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ABOUT COVER

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WJCCM mainly publishes articles reporting research results and findings obtained in the field of critical care medicine and covering a wide range of topics including acute kidney failure, acute respiratory distress syndrome and mechanical ventilation, application of bronchofiberscopy in critically ill patients, cardiopulmonary cerebral resuscitation, coagulant dysfunction, continuous renal replacement therapy, fluid resuscitation and tissue perfusion, hemodynamic monitoring and circulatory support, ICU management and treatment control, sedation and analgesia, severe infection, *etc*.

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MINIREVIEWS

Utilization of extracorporeal membrane oxygenation during the COVID-19 pandemic

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Abstract

The ongoing outbreak of severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2, or coronavirus disease 2019 (COVID-19)] was declared a pandemic by the World Health Organization on March 11, 2020. Worldwide, more than 65 million people have been infected with this SARS-CoV-2 virus, and over 1.5 million people have died due to the viral illness. Although a tremendous amount of medical progress has been made since its inception, there continues to be ongoing research regarding the pathophysiology, treatments, and vaccines. While a vast majority of those infected develop only mild to moderate symptoms, about 5% of people have severe forms of infection resulting in respiratory failure, myocarditis,

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septic shock, or multi-organ failure. Despite maximal cardiopulmonary support and invasive mechanical ventilation, mortality remains high. Extracorporeal membrane oxygenation (ECMO) remains a valid treatment option when maximal conventional strategies fail. Utilization of ECMO in the pandemic is challenging from both resource allocation and ethical standpoints. This article reviews the rationale behind its use, current status of utilization, and future considerations for ECMO in critically ill COVID-19 patients.

Key Words: Extracorporeal membrane oxygenation; COVID-19; Critical care; Acute respiratory distress syndrome; Shock; Research

Core Tip: This article aims to provide a review of the rationale for the use of extracorporeal membrane oxygenation (ECMO) in patients suffering from severe coronavirus disease 2019 (COVID-19) infection, including a discussion of current utilization practices, and ends with important future considerations for ECMO in critically ill COVID-19 patients as we progress during the current pandemic.

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INTRODUCTION

On December 31, 2019, the World Health Organization (WHO) was alerted of cases of pneumonia with an unknown etiology detected in Wuhan City, Hubei Provence, China. With rising fear of a potential endemic in the overpopulated city of Wuhan, Chinese national authorities along with the Wuhan Municipal Health Commission began a quest to identify all cases, amongst the 19 million occupants, as early as possible, as well as to trace potential sources through retrospective investigation. Initial investigations revealed the source of the first 27 confirmed cases of the novel coronavirus, severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2, coronavirus disease 2019 (COVID-19)], was the Huanan seafood market[1]. The market was immediately shut down, but the virus had already spread beyond what was anticipated. Not long after, reports of human-to-human transmission were documented and surrounding areas including Hong Kong, Taiwan and Macau took the drastic step of shutting down borders with their long-time allies.

Chinese scientists continued to study this unidentified pathogen until, finally, on the 7th of January 2020, the novel coronavirus was isolated from a single patient and gene sequencing was successfully performed and made available to the WHO five days later. This facilitated the ability for laboratories worldwide to produce diagnostic PCR tests to detect this new virus.

The novel coronavirus continued to spread to neighboring countries despite valiant efforts to subdue the spread. Today, COVID-19 has spread to over 200 countries, spread over six continents, infected over 65.8 million, and taken the lives of 1.5 million people worldwide to date[2]. On the 11th of March 2020, the WHO officially declared the COVID-19 outbreak a global pandemic, as what began as a simple case of viral pneumonia subsequently became one of the most devastating pandemics of the twenty-first century.

PATHOPHYSIOLOGY OF SARS-COV-2 VIRUS

The main method of person-person transmission of SARS-CoV-2 is by respiratory droplets, which is similar to the spread of influenza[3]. With droplet transmission, the

virus can be spread by coughing, sneezing, or conversing up to six feet away[3]. The virus has also been shown to be able to linger on surfaces for hours and in the air under experimental conditions[3]. Upon exposure to the virus, the incubation period has been shown to be within 14 d, with most cases presenting 4-5 d after exposure[3].

In order to fully comprehend the pathophysiology of SARS-CoV-2, the basic viral structure must first be understood. Coronaviruses, including SARS-CoV-2, are positive single stranded RNA viruses of approximately 30 kb in length[4]. They are composed of four main structural proteins: Membrane (M), spike (S), envelope (E) and nucleocapsid (N)[5]. The spike protein dictates host tropism and has been found to have an affinity to angiotensin converting enzyme-2 (ACE-2) receptors[5]. Epithelial cells in the lungs have a high concentration of ACE-2 receptors likely explaining the high incidence of respiratory symptoms associated with SARS-CoV-2[5]. Other organs with increased ACE-2 expression include the heart, ileum, kidneys and urinary bladder. Following virus binding to host cells *via* previously mentioned receptors, spike protein is cleaved and subsequently activated leading to irreversible membrane fusion[5]. After cell invasion, the positive stranded RNA released by the virus leads to the production of peptides and proteins by translation in the host, and RNA-dependent RNA polymerase which can further replicate viral RNA[5].

Based on degree of invasion and inflammatory response, symptoms can range from mild to severe respiratory distress and multiorgan failure[4]. Typically, initial symptoms are respiratory in nature given that the inhaled droplets easily invade lung epithelial cells expressing ACE-2 receptors. Surrounding the epithelial cells of the lungs are dendritic cells and macrophages, also known as antigen presenting cells, which present viral antigen to neighboring T-cells initiating a T-cell mediated response[4]. Cytotoxic T-cells (CD8+) play a role in killing the viral antigen while helper T-cells (CD4+) activate B-lymphocytes promoting antibody formation. However, with time, T-cell exhaustion is being observed in patients infected with SARS-CoV-2 which can partially explain clinical deterioration over time[4].

Activation of lymphocytes along with destruction of infected cells leads to the release of cytokines and inflammatory mediators, leading to what is commonly known as the cytokine storm[4]. The most important cytokines released include interleukins 6 and 8 (IL-6, IL-8). IL-6 interacts with the hypothalamus leading to high grade fever; IL-8 is a well-known chemoattractant for T-cells and neutrophils leading to an influx of inflammatory cells into the lungs, or other infected areas, and subsequent diffuse alveolar damage and pulmonary infiltration[4]. These cytokines can also cause vasodilation and increased vessel permeability that leads to hypoxemia, increased work of breathing, and acute respiratory distress syndrome (ARDS)[4]. This increased inflammatory response has also been found to cause significant endothelial damage, creating a hypercoagulable status with the end result ranging from capillary microthrombi to diffuse pulmonary emboli[4].

Unfortunately, the destructive effects of SARS-CoV-2 are not limited only to the pulmonary system. The inflammatory cascade it triggers can involve other organ systems as well, most prominently the cardiovascular system, as evidenced by increasing reports of myocarditis in the younger population[4]. This overwhelming inflammatory state can progress into critical disease, multiorgan failure, and eventually death. Most often, cytokine storm causes systemic vasodilation, which in turn leads to hemodynamic instability and suboptimal peripheral perfusion[4]. Compromised perfusion can cause renal failure, seen by elevation in blood urea nitrogen and creatinine, liver damage, noted by increased liver enzymes, myocardial infarction, and other organ dysfunction. Endothelial injury can also lead to prothrombotic states[4]. It is any combination of ARDS, multi-organ dysfunction from poor perfusion, hemodynamic cardiovascular collapse, and hypercoagulability that puts a patient at risk of shock and ultimately death[4] (Figure 1).

RATIONALE FOR USING EXTRACORPOREAL MEMBRANE OXYGENATION IN COVID-19 PATIENTS

Extracorporeal membrane oxygenation (ECMO) is often used as a last resort in patients with critical pulmonary or cardiovascular compromise, requiring mechanical support (Figure 2). It has various configurations based on the patient's initial requirement (pulmonary support, cardiovascular support, or both) and can be adjusted according to complication. Cardiac indications for ECMO include cardiogenic shock from a myocardial infarction, arrhythmia, pulmonary embolism, *etc.*, as well as post heart transplant, or as a bridge to longer term ventricular assist device (VAD)

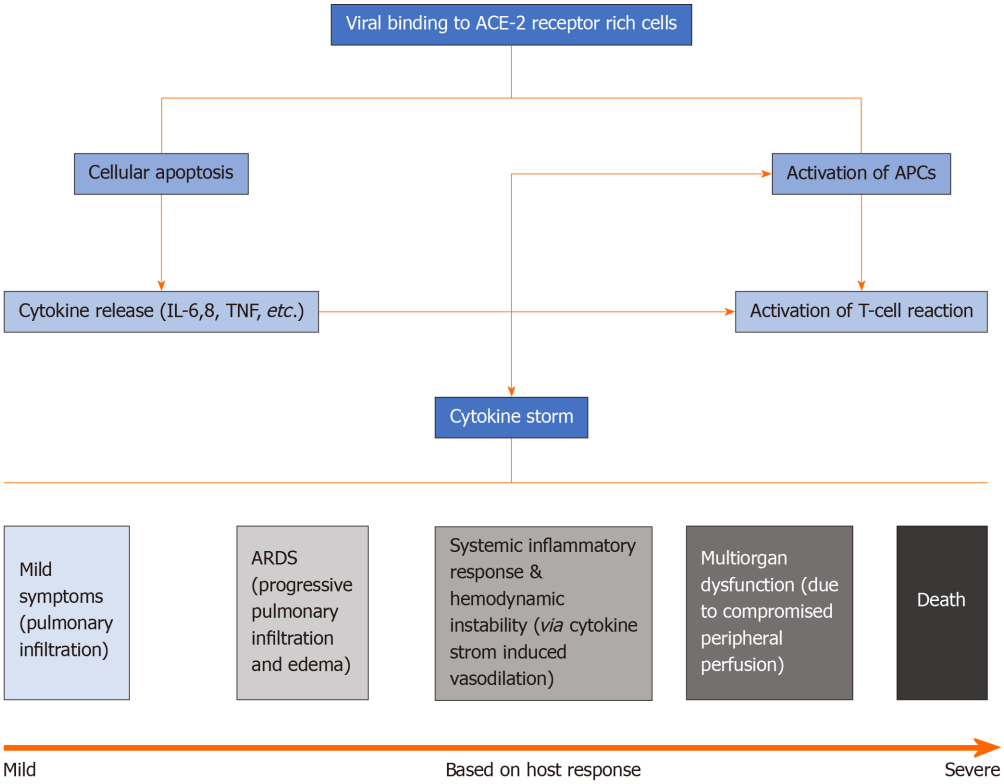

Figure 1 Pathophysiology of coronavirus disease 2019 infection. Viral binding and invasion of angiotensin converting enzyme 2 receptor-rich cells triggers destruction of infected cells with release of cytokines (mainly interleukin-6, interleukin-8 and tumor necrosis factor) and chemo-attractants, as well as activation of neighboring antigen presenting cells (APCs). Cytokine surge and APC activation triggers a T-cell mediated response and further release of cytokines. Activation of T-cells along with ongoing destruction of infected cells leads to cytokine storm. Symptoms developed range from mild respiratory symptoms to multiorgan failure and death based upon host response. ACE-2: Angiotensin converting enzyme 2; APCs: Antigen presenting cells; IL: Interleukin; TNF: Tumor necrosis factor; ARDS: Acute respiratory distress syndrome.

placement[6]. Respiratory indications for ECMO include ARDS secondary to pneumonia, aspiration, *etc.*, in addition to lung transplant (as a bridge before the procedure or after if evidence of graft failure), and pulmonary hemorrhage[6]. The potential for ECMO use in COVID-19 patients has been a topic of discussion recently. Previous success with ECMO in critically-ill patients diagnosed with Middle Eastern respiratory syndrome (MERS) encouraged physicians to try ECMO in an attempt to treat COVID-19 patients[7].

The most common clinical scenario in which patients with COVID-19 require ECMO is ARDS refractory to standard lung-protective ventilation and pronation[8,9]. In this situation, gas exchange is compromised given the underlying alveolar inflammation and edema; hence, patients require assistance with oxygenation. Veno-venous ECMO (V-V ECMO) is the modality used in such cases where blood is typically drained from a large peripheral vein, oxygenated *via* a synthetic lung, and returned to the circulation *via* a large peripheral vein[8]. Afterwards, newly oxygenated blood flows through the normal circulatory pathway to provide oxygenation to the remainder of the organ systems. With these ECMO settings, the native heart is required to function appropriately to ensure adequate blood distribution[8]. Initiation of ECMO in COVID-19 patients presents unique challenges as these patients are on maximal ventilatory support and are often in a prone position. Therefore, very specific criteria for ECMO initiation have been suggested: PaO_2/FiO_2 < 60 mmHg for > 6 h, PaO_2/FiO_2 < 50 mmHg for > 3 h or PCO_2 > 80 mmHg for > 6 h and arterial pH < 7.2[8].

In situations where the patient's cardiovascular function may be severely compromised in addition to respiratory compromise, such as in severe myocarditis, veno-arterial ECMO (V-A ECMO) is the optimal configuration used. In V-A ECMO, venous blood is drained, oxygenated *via* synthetic lung, then returned with force *via* a large peripheral artery towards the aorta. This increase in aortic blood flow enhances peripheral perfusion[10].

Superimposed sepsis or multi-organ dysfunction may develop in patients on V-V/V-A ECMO, requiring further calibration of ECMO settings to enhance cardiac output and support bodily functions. The main concept behind modifying V-V/V-A

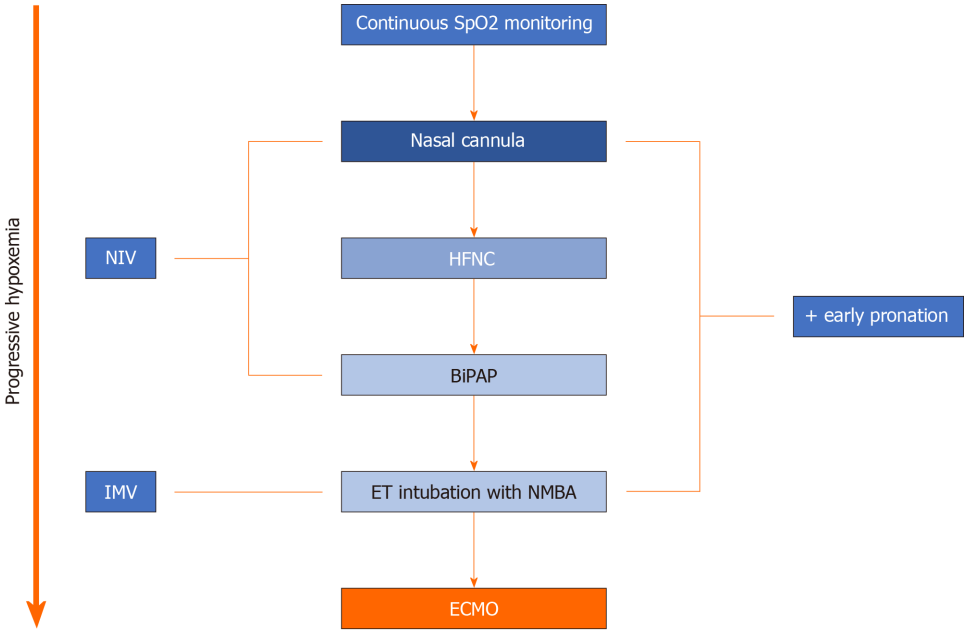

Figure 2 Respiratory management in coronavirus disease patients with pulmonary compromise. Extracorporeal membrane oxygenation is reserved as a final resort when all other noninvasive and invasive ventilation options fail. SpO_2: Saturation of oxygen *via* pulse oximetry; HFNC: High flow nasal cannula; BiPAP: Bilevel positive airway pressure; ET: Endotracheal; NMBA: Neuromuscular blockade agent; NIV: Noninvasive ventilation; IMV: Invasive mechanical ventilation; ECMO: Extracorporeal membrane oxygenation.

ECMO in such difficult circumstances is through the addition of an extra lumen, converting double lumen to triple lumen ECMO. The addition of this third lumen can help optimize settings based on a patient's requirements. For instance, if a patient on V-V ECMO (pulmonary support only) develops cardiac complications leading to compromise of cardiovascular function, the addition of an arterial output lumen, veno-venoarterial ECMO (V-VA ECMO), will allow for the addition of cardiac support to pre-existing pulmonary support[11]. In other circumstances, patients with both pulmonary and cardiovascular compromise may be inadequately oxygenating despite V-A ECMO; this is typically seen in larger patients or if a lumen with a small diameter is used[11]. The addition of a venous drainage lumen, venovenous-Arterial ECMO (VV-A ECMO), will allow more blood to be drained and oxygenated at a faster rate, thus improving oxygen supply[11]. Furthermore, it is not uncommon for patients on ECMO to develop acute kidney injuries within the first 48 h. The ECMO circuit itself can create an inflammatory reaction leading to capillary leak and subsequent pre-renal azotemia or even acute tubular necrosis[6]. In these instances, if pre-renal oliguria does not resolve after 72 h, continuous renal replacement therapy simultaneously with ECMO can be used to manage fluid status and maintain renal function[6]. Lastly, electrolytes and blood counts should be monitored very closely, as platelet consumption and potassium, magnesium, and phosphorous shifts have been observed in patients on ECMO and should be replaced accordingly[6].

Given the above, it would theoretically be rational to use ECMO for pulmonary and/or cardiovascular support in patients with COVID-19 refractory ARDS and certain other COVID-19-related complications; yet given the lack of clinical trials and prospective studies, questions regarding the true validity in the clinical setting remain unanswered. The two main factors that should be taken into consideration are its effectiveness and feasibility.

With regards to effectiveness, proof of ECMO success in patients with COVID-19 is scarce. Even prior to COVID-19, ECMO was shown to not lower 60-d mortality in patients with severe ARDS (from other non-COVID-19 conditions) *vs* other invasive ventilation techniques[9]. While trialing of ECMO in COVID-19 patients has increased during the pandemic, there are very limited reports of clinical outcomes. Furthermore, the handful of cases that have been published report inconsistent results. In a retrospective multicenter study by Ruan *et al*[12] that included 137 patients with COVID-19, seven patients required ECMO and there was 100% mortality despite ECMO use. These findings were supported by Yang *et al*[13] and Zhou *et al*[14], who reported 83% (5 out of 6) and 100% (3 out of 3) mortality rates in patients with COVID-19 who required ECMO at their respective centers. However, Wu *et al*[15] and Shen

et al[16] each reported one patient on ECMO who survived. Although there are not any other official publications regarding ECMO support, the Extracorporeal Life Support Organization (ELSO) is performing real-time tracking of all COVID-19 cases on ECMO worldwide, and there is currently insufficient data for the ELSO to recommend either for or against ECMO in patients with COVID-19[17].

With regards to feasibility, ECMO is complex, especially when designing a referral system. ECMO is expensive to incorporate, and there is a complexity of management associated with its use that requires an individually trained critical care team, often only available in highly specialized centers. In addition, increasing healthcare worker exposure with such a high-risk procedure, particularly with lack of clinical trial evidence to prove its efficacy, raises ethical concerns. Most smaller healthcare centers, both inside and outside of the United States, lack access to ECMO devices and the training required to operate them. Therefore, most authors are supportive of ECMO use in critically ill patients, but only in experienced centers with the necessary resources. For other less-equipped areas, ensuring availability of more basic equipment such as noninvasive and invasive mechanical ventilation with adequate direction for referral to centers with ECMO expertise is of higher priority, and is projected to save more lives in the current pandemic[18]. However, this approach comes at a cost to the critically ill that may benefit from ECMO in less-equipped areas, and is an ethical dilemma worth mentioning.

CURRENT UTILIZATION OF ECMO

Currently, the ELSO requires a set of guidelines to proceed with establishment of ECMO as a viable treatment option. These guidelines mandate ECMO be administered at a tertiary care center or greater with available facilities of a tertiary level Neonatal Intensive Care Unit, Pediatric Intensive Care Unit, and/or Adult Intensive Care Unit[17]. The location of service should also cover a geographic area that can provide a minimum of 6 ECMO patients per year[17]. The center should be actively participating in the ELSO registry[17]. The structure of the center should have a hierarchy including an ECMO program director, multiple associate directors assigned to a specific focus pertinent to ECMO care, an ECMO coordinator, and a multi-disciplinary team responsible for annual internal ECMO evaluation for quality improvement[17]. Every ECMO center should have its set of policies and procedures established with comprehensible indications and contraindications. Moreover, there should be distinct guidelines for clinical management, equipment maintenance, termination of therapy, and follow up of ECMO patients[17].

Currently, ECMO is used for respiratory support in 63% of cases, cardiac support in 29% of cases, and both in 8% of cases. The four categories that the ELSO registry considers in its recording of ECMO as it pertains to the pandemic are as follows: COVID-19 confirmed by testing, COVID-19 suspected but no testing confirmation, no clinical suspicion of COVID-19 (and no testing), and COVID-19 confirmed negative[17]. On June 26, 2020, the ELSO registry reported 1619 suspected or confirmed cases of COVID-19 patients on ECMO and specifically listed 1604 confirmed cases of COVID-19 patients on ECMO[17]. The discharged alive rate at 90 d from ECMO was reported at 541/975 patients (55%), and included discharges to rehabilitation facilities and long-term care facilities, indicating a possible lengthier recovery[17]. This rate is not far off from non-COVID-19 ARDS patients on ECMO, where 52% survived to hospital discharge[6]. For reference, in patients who require ECMO for cardiac support due to cardiac arrest or cardiogenic shock, survival rates range from only 20%-30% to hospital discharge[6]. The predominant form of ECMO utilized was VV, which was reported to be used 95% of the time. VA and other configurations were used in 5% cases. The utilization of ECMO as per various ELSO chapters can be seen in Figure 3, where North America demonstrated the highest use of ECMO followed by Europe[17].

SPECIAL CONSIDERATIONS FOR ECMO USE IN COVID-19 PATIENTS

COVID-19 related ARDS

The use of ECMO as a rescue therapy in patients with severe ARDS secondary to viral infections has been established in the literature for previous outbreaks of influenza A (H1N1) and SARS-MERS viruses. In a cohort of patients with H1N1-related ARDS, Noah *et al*[19] demonstrated a hospital mortality of 23.7% for ECMO treated patients *vs*

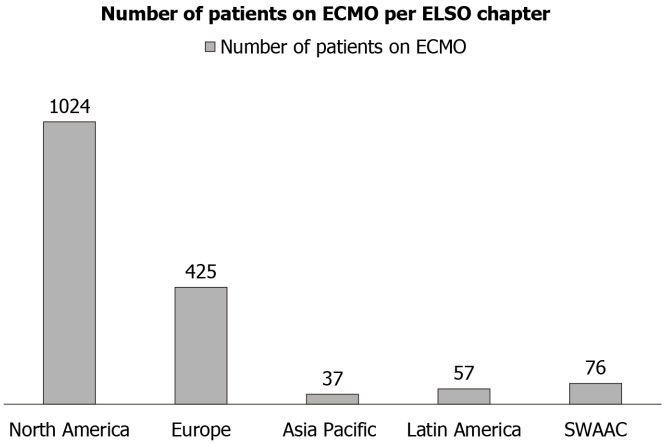

Figure 3 Utilization of extracorporeal membrane oxygenation. Various Extracorporeal Life Support Organization chapter uses were reported. Data reported was based on reports from June 26, 2020. ECMO: Extracorporeal membrane oxygenation; ELSO: Extracorporeal Life Support Organization.

52.5% for non-ECMO treated patients. Furthermore, in a retrospective study on MERS-related ARDS, lower mortality was appreciated in the ECMO-treated cohort (65%) compared to the non-ECMO-treated cohort (100%)[7]. There are no definite guidelines established for use of ECMO in COVID-19-related ARDS to-date. However, experience from previous outbreaks can be utilized to determine the guidelines for use of ECMO as a salvage therapy in patients with refractory hypoxemia. Table 1 further elaborates on the indications and contraindications for the use of ECMO in patients with COVID-19 related ARDS. Indications for ECMO use in a mechanically ventilated COVID-19 patient include a PaO_2/FiO_2 < 60 mmHg for > 6 h, PaO_2/FiO_2 < 50 mmHg for > 3 h, or a pH < 7.2 + $PaCO_2$ > 80 mmHg for > 6 h[9]. It is important to acknowledge ECMO with consideration of the extent to which the patient will benefit from treatment. Frequent reassessment of the hazard-to-risk ratio is a key factor in evaluation of patients undergoing treatment. In the case of no functional pulmonary or cardiac recovery after 21 d of treatment, an extensive discussion with family members should be made to discuss withdrawing ECMO support[20].

Shock patients with COVID-19

It has been observed that patients with underlying cardiac conditions can also develop cardiogenic and vasogenic shock with COVID-19 infections and can be temporarily managed with ECMO[21]. One 52-year-old male with a known history of congestive heart failure presented with COVID-19-related pneumonia[21]. He was initiated on levosimendan and norepinephrine for combined cardiogenic and vasogenic shock. Subsequently, a peripheral VAD was placed to attempt to mediate the cardiac component of the patient's shock. A VA ECMO arrangement was then utilized to treat the vasogenic component. The critical care team switched to VV ECMO once the shock resolved[21].

Long term use of ECMO and COVID-19 patients

The evidence for long term use of ECMO in COVID-19 patients varies. Zeng *et al*[22] reported 12 critically ill patients requiring ECMO, where half of them died from septic shock and multi-organ failure. However, Huette *et al*[23] reported outcomes from 12 patients on ECMO where 10 of 12 patients were weaned from ECMO, 9 patients were weaned from mechanical ventilation, and 8 patients were discharged from the hospital. Patients weaned from ECMO demonstrated an increase in their lymphocyte count and a decrease in their fibrinogen levels[23]. There was also an increase in the PaO_2/FiO_2 ratio in these patients[23]. A larger systematic review of 331 reported cases of COVID-19 patients receiving ECMO found a mortality rate of 46%[24].

FUTURE OF ECMO USE

ECMO centers

ECMO centers with COVID-19 patients should have special training for members of the ECMO team, regarding personal protective equipment and hospital infection

Table 1 Indications and contraindications for extracorporeal membrane oxygenation use in coronavirus disease 19 patients[17,19]

Indications
Refractory hypoxemia despite prone positioning and high PEEP
ARDS requiring vasoactive drugs due to COVID-19 (vasopressors)
Evidence of one organ failure with minimal co-morbidities
Contraindications
Multiple comorbidities
Immunocompromised status
Severe global developmental delay
Intracranial hemorrhage
Irreversible severe brain damage
Severe multiple organ failure
Mechanical ventilation for > 14 d before ECMO initiation

PEEP: Positive end expiratory pressure; ARDS: Acute respiratory distress syndrome; COVID-19: Coronavirus disease 19; ECMO: Extracorporeal membrane oxygenation.

control to contain spread of infection. The ECMO team should practice strict sterile technique along with respiratory droplet precautions including negative airflow isolation at the time of cannulation[25]. To restrict the exposures, the team should consist of a surgeon, an assistant, and a perfusionist[25]. The procedure should be performed in a negative pressure room[25]. The use of ultrasound can decrease the time taken to cannulate, therefore minimizing the risk of exposure[25]. Use of a bi-caval cannula can increase exposure time due to need for TEE and fluoroscopy[25]. To minimize patient contact, the patient can be positioned with the ECMO console facing a window to enable viewing of the control panel without entering the room[25]. Viral particles can disseminate through the gas-port of the membrane lung of the ECMO system. Evacuation of the exhaust port of the oxygenator and vigilance for the plasma leakage signs are measures which can help decrease the risk of spread of aerosols from the membrane lung[26].

Referral systems

There is a need to strengthen the patient referral systems to ECMO centers, including developing strict criteria that considers benefit *vs* futility of treatment for the patient[27]. This is important in determining the number of candidates that are eligible for ECMO. As patients are transferred to intensive care units (ICUs) for respiratory or other organ failure, there should ideally be guidelines that capture the status of the patient before treatment is futile, but in anticipation of failing traditional invasive ventilation. There should also be strict criteria to decide whether early transfer is appropriate for unpredictable or unclear disease progression[27]. Communication systems should be strong with respect to the availability of resources and personnel for ECMO cannulation[27]. A dedicated ECMO coordinator is instrumental for the success of such a collaboration[27].

An example of a regional framework system encouraging collaboration between remote areas and ECMO centers is discussed by Prekker *et al*[28]. The framework includes a dedicated ECMO officer overlooking referrals to five established ECMO centers in the state of Minnesota. In countries with expertise and resources, mobile ECMO teams are functional. These teams initiate ECMO on site and transfer the patients to a hospital within the region in less than 45 min[29].

Data collection registries and centralization

There should also be an effort to increase global participation in data collection registries, such as ELSO, to improve the exchange of expertise and local practices[27]. It has also been suggested that nationwide centralization of ECMO would make the governments more capable of fighting the COVID-19 crisis[30].

Research initiatives

As previously discussed, there is a need for additional research related to COVID-19 patients and ECMO. An example of one ongoing global research collaboration is the ECMOCARD trial. It is a prospective/retrospective multi-center short period incidence observational study of COVID-19 patients admitted to the ICU[31]. More than 30 centers in different ELSO member countries are participating and the authors plan to study the clinical characteristics and severity of ARDS in COVID-19 patients on ECMO, including the complications and survival rates[31].

More research is also needed to understand the synergism or lack thereof between ECMO and other COVID-19 therapies. Multiple studies reported the use of IV steroids, IV remdesivir, IV antibiotics, and even hydroxychloroquine in different combinations. However, there is still a lack of consensus as to which combinations are most effective in patients on ECMO with COVID-19 infection. Furthermore, there needs to be more research on the concomitant use of blood filters that remove cytokines from the blood in patients on ECMO[32]. It is unknown if this type of treatment can help with the increase in cytokine production seen in COVID-19 patients[32].

Ethical considerations

There are ethical dilemmas associated with the use of ECMO in COVID-19 patients. Some of the questions that need extensive discussion with consensus statements are how to define resource conservation during this time. In some practices, extracorporeal CPR is being discontinued for patients with refractory out-of-hospital cardiac arrest. There has also been a recent trend of postponing all procedures that might require post-op ECMO[28]. Another ethical dilemma is the lack of availability of ECMO in many parts of the country, and the harsh reality that some patients may not be able to benefit from this modality of treatment due to the lack of availability[28].

CONCLUSION

ECMO remains a valid treatment option for patients when other conventional treatment strategies fail. In patients diagnosed with COVID-19, therapy is guided largely from experience with previous coronavirus pandemics such as MERS. North America is the largest geographical region to utilize ECMO in the treatment of COVID-19, and it is without question necessary to have the personnel and infrastructure in place in order to safely treat patients with ECMO. In recent months, new literature continue to demonstrate more clear indications and contraindications for ECMO use, however, much research is still needed to demonstrate clear mortality benefit. Ethical dilemmas also need to be considered, such as ECMO use in the setting of CPR, and modes of expansion need to be examined in order to minimize the treatment availability gap between patients with access ECMO centers and those without access.

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ORIGINAL ARTICLE

Retrospective Study

Intensive care outcome of left main stem disease surgery: A single center three years' experience

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Abstract

BACKGROUND

Left main coronary artery (LMCA) supplies more than 80% of the left ventricle, and significant disease of this artery carries a high mortality unless intervened surgically. However, the influence of coronary artery bypass grafting (CABG) surgery on patients with LMCA disease on morbidity intensive care unit (ICU) outcomes needs to be explored. However, the impact of CABG surgery on the

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morbidity of the ICU population with LMCA disease is worth exploring.

AIM

To determine whether LMCA disease is a definitive risk factor of prolonged ICU stay as a primary outcome and early morbidity within the ICU stay as secondary outcome.

METHODS

Retrospective descriptive study with purposive sampling analyzing 399 patients who underwent isolated urgent or elective CABG. Patients were divided into 2 groups; those with LMCA disease as group 1 (75 patients) and those without LMCA disease as group 2 (324 patients). We correlated ICU outcome parameters including ICU length of stay, post-operative atrial fibrillation, acute kidney injury, re-exploration, perioperative myocardial infarction, post-operative bleeding in both groups.

RESULTS

Patients with LMCA disease had a significantly higher prevalence of diabetes (43.3% *vs* 29%, $P = 0.001$). However, we did not find a statistically significant difference with regards to ICU stay, or other morbidity and mortality outcome measures.

CONCLUSION

Post-operative performance of Patients with LMCA disease who underwent CABG were comparable to those without LMCA involvement. Diabetes was more prevalent in patients with LMCA disease. These findings may help in guiding decision making for future practice and stratifying the patients' care.

Key Words: Cardiac surgery; Critical care; Left main disease; Coronary graft; Outcome; Cardiac output

Core Tip: Post-operative performance of patients with left main coronary artery (LMCA) disease who underwent coronary artery bypass grafting were comparable to those without LMCA involvement.

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INTRODUCTION

Defining the intensive care unit (ICU) outcome predictors after cardiac surgery remains an optimum goal[1]. Prolonged ICU stay is associated with increased costs and adverse patient outcome[2]. Age, congestive cardiac failure, peripheral vascular disease, higher perioperative serum creatinine, and prior cardiac surgery had been identified by Hammermeister *et al*[3], as potential risk factors for adverse outcome after cardiac surgery. Although the risk of mortality after cardiac surgery has been identified in several studies through various scoring systems, there is a growing need to identify morbidity predictors and factors influencing the ICU length of stay in the cardiac surgery setting[4]. Time in blood glucose range[5], elevated perioperative troponin[6], and acute kidney injury (AKI) have been identified as individual risk factors for morbidity in cardiac surgery ICU[7].

The left main coronary artery (LMCA) supplies 80% of the blood demands of the left ventricle. Obstructive lesions of the LMCA carries high mortality with medical treatment[8], but improves markedly with surgical treatment[9]. Some authors do not

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consider LMCA occlusion as a risk for early and late mortality[10]. The challenges associated with LMS disease had been explored in previous work of El-Menyar *et al*[10] to include lesion location to outcome relation, subacute thrombosis potential, left ventricular function and patient comorbidities on overall outcome; and the risk-benefit ratio of coronary artery bypass graft surgery *vs* stenting. In a cross-sectional study conducted in Qatar, isolated LMCA obstruction was 4-fold higher in women, with high prevalence of distal and proximal lesions. The authors found that renal failure was independent predictor of left main stem (LMS) disease. The mortality over one-year was higher in patients with LMS disease[11].

To the best of our knowledge no previous studies have addressed the short-term morbidity based on the ICU outcome; hence LMS morbidity measures need to be explored further.

MATERIALS AND METHODS

Methods

This was a retrospective study conducted in Cardiothoracic Surgery Department, Heart Hospital, Hamad Medical Corporation, Qatar. The Heart Hospital is a tertiary cardiac care center and is currently performing over 350 cardiac surgeries annually. The study was conducted after approval of the local research committee of the institution review board (MRC-01-17-058). The review board waived the informed consent as this was a retrospective study. The patient data in the period from January 2015 to January 2018 were analyzed. We included all patients with isolated coronary artery bypass grafting (CABG). Patients with combined surgeries, were excluded. We screened 421 patients, and a total of 22 patients were excluded. Remaining 399 Patients were divided into 2 groups - those with LMCA disease as group 1 (75 patients) and those without LMCA disease, as group 2 (324 patients). They were then correlated with ICU outcome parameters.

The following set of data were analyzed and reported for all patients: Age, gender, past history of diabetes or hypertension, total anesthesia duration, time of cardiopulmonary bypass (CPB), time of aortic cross clamp (ACC), utilization of intra-aortic balloon pump (IABP), inotropes score, and Euro SCORE.

We had chosen the primary outcome variable to be the length of stay in the ICU (LOS_{ICU}), other variables collected included length of mechanical ventilation (LOV), and the length of stay in the hospital (LOS_{Hosp}), complications, including infections, AKI, post-operative atrial fibrillation (POAF), perioperative myocardial infarction (PMI), stroke, the need for veno-arterial extra corporeal membrane oxygenation (VA-ECMO) and early mortality within the hospital stay were reported for each patient. Dendrite Clinical Systems (London, United Kingdom) and (Cerner, United States) were used to retrieve data. In our institution we have a fast track approach in transferring patients to the step down, we transfer patients when they are off inotropes/vasopressors, no need for invasive or noninvasive ventilatory support, not requiring early kind of real replacement therapy, awake started pain medications, chest drain is our or minimal chest drain, and started oral medication.

Outcome definitions

The primary outcome was the LOS_{ICU}, the secondary outcomes were LOV, LOS_{Hosp}, complications, as POAF, AKI, PMI, infection, mortality within the hospital.

AKI was defined as an acute post-operative (within 48 h) reduction in kidney function, with absolute increase in the serum creatinine concentration of 0.3 mg/dL or greater (26.4 μmol/L), or an increase in serum creatinine of 1.5-fold from baseline) or dropping of urine volume to < 0.5 mL/kg/h for 6 h[12]. POAF is defined as a new onset of atrial fibrillation (AF) after cardiac surgery in patients who were in sinus rhythm before surgery and had no prior history of AF. Significant LMS disease was defined as a more than 50% narrowing of the lumen diameter as determined by angiography[13]. The vasoactive active inotrope score was calculated according to Gaies *et al*[14]. The LOV was defined according to our institute rule as the time from ICU admission to tracheal extubation. We define early mortality as mortality within the first 28 d within the hospital as per our organization rules. Bleeding events that mandate surgical re-exploration were also recorded. We defined PMI as post-operative rise of highly sensitive troponin T to level of 3466 ng/L associated with electrocardiographic, echocardiographic or angiographic evidence[6].

Statistical analysis

Normally distributed continuous variables were expressed as the mean ± SD. Skewed variables were presented as the median (interquartile range). The patients were divided into two groups according to the association of LMS disease. Continuous variables were compared using the Student' s *t*-test and the Mann Whitney *U* test, as found appropriate. Chi-square or Fisher's exact tests were used to compare categorical variables between the two groups. A significant association was defined by a *P* value ≤ 0.05 (two-tailed). Patients undergoing isolated CABG were included in the study and they were divided in two groups according to significant LMS disease. Group I: Patients without significant LMS disease (control group) and Group II: Patients with significant LMS disease (study group). Statistical analysis was performed using the SPSS software (version 22, Chicago, IL, United States).

RESULTS

Of the 421 patients screened, 399 patients were enrolled in this study; the remaining 22 patients met the exclusion criteria. The mean age was 51.9 ± 11.3 years. The rest of the baseline descriptive data are highlighted (Table 1). The predominant gender in this study were males, accounting for 245 patients (82.2%). The high prevalence of diabetes was noted in our study where 141 patients (47.3%) were diabetics. Patients were divided based on the association of LMS disease into 2 groups. Both groups were matched regarding the age, gender, association of hypertension, Euro score, baseline ejection fraction (EF), baseline creatinine and need for elective surgery (Table 2). We noted that diabetes was significantly more prevalent in LMS group (53% *vs* 44.4%, *P* = 0.05). The usage of IABP was significantly higher percentage among LMS group (*P* = 0.05).

There was no significant difference between both groups regarding inotropic and vasopressors demands. We did not encounter significant differences between the groups in terms of anesthesia, CPB and ACC times as well as number of grafts. The postoperative lengths of mechanical ventilation, ICU stay, and hospital stay did not show any significant differences between both groups (Table 3). Post-operative complications, including POAF, AKI, hospital-mortality, ventilator associated pneumonia, need for VA-ECMO, vasoactive inotrope score (VIS), re-admission to ICU, surgical re-exploration, major bleeding and PMI did not make significant differences between groups.

DISCUSSION

The salient findings of this work were: (1) The primary outcome which was the LOS_{ICU} was not different between the studied groups; (2) The secondary outcome measures did not show any significant differences; (3) Need for IABP support for LMS group was significantly higher than the group without LMS: and (4) Diabetes was more prevalent in patients with LMS.

To the best of our knowledge, this is the first study to address the ICU outcome of LMS disease after CABG. Chaitman *et al*[15] have highlighted the high morbidity and mortality of LMS disease and its frequent association with multi-vessel disease.

LMS disease patients comprised 18.7% of the patients in our study, compared with 30% in the Keogh *et al*[16] database. According to the guidelines of the American College of Cardiology/American Heart Association (ACC/AHA), CABG is a class I one recommendation for LMS stenosis in asymptomatic patients[17]. The most important coronary lesion in prognosis prediction is LMS, the latter is diagnosed in 5%-7% of patients who underwent coronary angiography[18]. The mortality in our LMS group was 2.7%. Conley and colleagues pointed to the contributing factors in LMS mortality to include age, diabetes, left ventricular function and dyslipidemia[19]. Su *et al*[20] in their review observed a mortality of 3.4% with conventional CABG in patients having LMS disease. Lower mortality in our series may be related to younger age.

In our study, patients with LMS disease were older and having higher prevalence of diabetes compared to those without LMS disease, but this did not attain statistical significance. Older patients may have more advanced form of CAD[21]. Usage of IABP was significantly higher in patients with LMS. In a meta-analysis of randomized controlled trials Rampersad *et al*[22] concluded that preoperative utilization of IABP

Table 1 Description of the studied group

Variable	*n*	Minimum	Maximum	mean ± SD
Age	399	18	79	51.9 ± 11.3
BMI (kg/m^2)	399	18.8	43.7	25.1 ± 7.1
Creatinine (μmol/L)	397	54.9	378.1	99.8 ± 55.8
EF%	388	18	65	45.8 ± 8.9
Additive Euro score	398	0	19	4.6 ± 3.1
CPB time (min)	393	0	377	118.1 ± 46.9
ACC time (min)	392	0	188	86.1 ± 38.7
Anesthesia time (min)	398	220	630	295.7 ± 71.2
VIS	398	0	29	6 ± 2.1
LOS_{ICU} (h)	397	26	320	65.9 ± 46.1
LOV (min)	397	190	17300	432 ± 65
LOS_{hosp} (d)	394	6	245	28.1 ± 12.9

BMI: Body mass index; EF: Ejection fraction; CPB: Cardiopulmonary bypass; ACC: Aortic cross clamp; WBCs: White blood cells; LOS_{ICU}: Length of stay in intensive care unit; LOV: Length of mechanical ventilation; LOS_{hosp}: Hospital length of stay; VIS: Vasoactive inotrope score.

Table 2 Demographic differences between both groups

Variable	Group I (LMS), 75 (%)	Group II (no LMS), 324 (%)	*P* value
Age	58.3 ± 11.8	55.19 ± 9.7	0.06
Gender (male)	62 (82.6)	264 (81.4)	0.34
Diabetes	39 (52)	144 (44.4)	0.05
Hypertension	32 (42.6)	144 (44.4)	0.13
Euro score	5.8 ± 3.9	5.0 ± 3.6	0.6
BMI	30.1 ± 6.3	27.9 ± 5.8	0.6
EF < 40	24 (32)	86 (26.5)	0.07
IABP	28 (37.3)	80 (24.6)	0.05
Elective surgery	45 (60)	224 (66.6)	0.5
Basal creatinine (μmol/L)	98.7 ± 46.5	94.7 ± 43.1	0.6

BMI: Body mass index; EF: Ejection fraction; IABP: Intra-aortic balloon pump; LMS: Left main stem.

reduced the early mortality in high-risk patients undergoing elective CABG. The IABP has been the most widely used mechanical circulatory support device. In cardiac surgery, the placement of the IABP was indicated when post-cardiotomy cardiogenic shock or mechanical complications appeared. Although preoperative IABP is frequently used by some clinicians in high-risk patients undergoing cardiac surgery, its effectiveness has not been confirmed[23].

In our study, patients with LMS had significantly more IABP utilization than the other group. IABP is the most commonly used mechanical circulatory device, and it is used in some centers as preoperative prophylaxis for high-risk CABG surgeries, although this practice is debatable[24]. In our study we followed an earlier study that supported the use of IABP preoperatively when 2 of the following factors were associated with LMS ejection fraction EF below 35%, re-do CABG, LMS stenosis more than 70%, unstable angina in the preoperative period[25]. Pilarczyk *et al*[26] mentioned that utilization of IABP in high risk patients could help the intra-operative hemodynamic management with trend towards clinical stability and better prognosis. The authors found that usage of IABP in the preoperative period could reduce ICU

Table 3 Main differences in both studied groups

Variable	Group I (LMS), 75 (%)	Group II (no LMS), 324 (%)	*P* value
Inotrops			
Dopamine, mean dose (μg/kg/min), mean ± SD	9 (12), 6.50 ± 3.10	31 (9.6), 7.23 ± 15.2	0.5, 0.34
Adrenaline, mean dose (μg/kg/min), mean ± SD	6 (8), 0.06 ± 0.01	27 (8.3), 0.05 ± 0.009	0.6, 0.8
Noradrenline, mean dose (μg/kg/min), mean ± SD	12 (16), 0.08 ± 0.01	43 (13.2), 0.07 ± 0.008	0.4, 0.7
Dobutamine, mean dose (μg/kg/min), mean ± SD	4 (5.3), 4.5 ± 1.4	11 (3.3), 3.9 ± 1.1	0.06, 0.09
Milrinone, mean dose (μg/kg/min), mean ± SD	3 (4), 0.56 ± 0.05	7 (2.1), 0.6 ± 0.04	0.9, 0.4
Intraoperative parameters			
CPB time (min)	139 ± 43	125 ± 69.6	0.6
ACC time (min)	87.1 ± 34	79.3 ± 30.1	0.9
Anesthesia time (min)	6.6 ± 1.4	6.5 ± 1.8	0.9
Grafts	3.1 ± 0.8	3.4 ± 1.01	0.7
Postoperative parameters			
LOV (min)	384.1 ± 123	375.1 ± 119	0.8
LOS_{ICU} (h)	65.9 ± 46.1	63.4 ± 43.9	0.6
LOS_{hosp} (d)	16.1 ± 4.2	14.7 ± 3.7	0.6
VIS	6.4 ± 2.6	6.1 ± 2.2	0.4
Post-operative outcome			
POAF	12 (16)	39 (12)	0.06
AKI	20 (26.7)	75 (23.1)	0.09
In-hospital-mortality	2 (2.7)	7 (2.1)	0.8
VAP	1 (1.3)	5 (1.5)	0.7
VA-ECMO	2 (2.7)	4 (1.2)	0.08
Re-admission ICU	2 (2.7)	8 (2.5)	0.8
Re-exploration	6 (8)	26 (8.6)	0.5
PMI	3 (4)	11 (3.3)	0.4

AKI: Acute kidney injury; CPB: Cardiopulmonary bypass; ACC: Aortic cross clamp; ECMO: Extracorporeal membrane oxygenation; LOV: Length of mechanical ventilation; LOS_{ICU}: Length of stay in intensive care unit; LOS_{hosp}: Hospital length of stay; POAF: Post-operative atrial fibrillation; VIS: Vasoactive inotrope score; VAP: Ventilator associated pneumonia.

and hospital lengths of stay as well as death within the hospital. Similarly, Christenson *et al*[25] found reduction in mortality, postoperative ICU and hospital stay with use of IABP. Our study is a retrospective data review. Our institutional preference is to insert IABP prophylactically after induction in patients with high risk LMCA disease. Takaro *et al*[27] mentioned that stenosis greater than 75% especially in the presence of left ventricular dysfunction is considered a high risk.

The assumption that LMS disease portends higher risk is due to the fact that 75% to 100% of myocardial territory is at risk when dominance of the left system is associated. Revascularization is recommended when more than 50% LMS disease is present, regardless of the symptoms or other ischemic association. CABG is recommended according to the American guidelines - when surgical bypass is feasible and SYNTAX score is more than 33, which define complexity of the multi-vessel disease[13]. The primary outcome in our study was the ICU length of stay, which was not significantly different in both groups (65.9 ± 4 6.1 *vs* 63.4 ± 43.9, $P = 0.6$). Many studies have showed LMS disease as a risk factor for surgery. In a systemic review over 172000 patients after cardiac surgery, the authors found LMS to be predictive of short-term adverse outcome[28].

In our study urgent procedures in the LMS group was 40%, which was not significantly different from patients without LMS 36.4% (Table 2). Sher-I-Murtaza *et al*[29] conducted a single center study and found the ICU length of stay to be higher in patients with LMS disease. The LMS population in this study was older and had more cases done on urgent basis. This was not the case in our study where both groups were matched regarding the age, Euro score and urgency. In our institution, LMS involvement alone does not warrant urgent surgical intervention. This probably has accounted for the difference in the ICU length of stay compared to Sher-I-Murtaza et al's[29] study.

According to the SYNTAX trial, the postoperative outcome is related to the burden of atherosclerosis of the native coronary vessels where percutaneous coronary revascularization strategy is adopted but not if CABG is applied[30]. In our study, the postoperative lengths of mechanical ventilation, ICU stay, and hospital stay did not show any significant differences between both groups (Table 3). Post-operative complications, including POAF, AKI, hospital-mortality, ventilator-associated pneumonia, need for VA-ECMO, re-admission to ICU, surgical re-exploration and PMI did not make significant differences between groups. The in-hospital mortality after CABG range from 1%-3% and its related to age, female gender, re-do surgery, low EF, degree of LMS stenosis and other coronary vessel involvement[31]. Mortality was equal in our studied groups, the low mortality in our patient population did not allow us to analyze the predictive factors beyond mortality. Both our groups were matched regarding the ACC, CPB, VIS, anesthesia time. Some authors refer the outcome to the type of cardioplegia used and the length of ACC[32]. All our patients underwent on-pump CABG, we used the same cardioplegia. Sher-I-Murtaza *et al*[29] reported worse outcome with LMS when compared to non LMS groups with regard to length of ventilation, mortality and need for inotropic support. This can be explained by the older age and the association of other lesions in their population while we operated on younger population. Blood consumption rate was not different among the two groups. This may be due to timely stoppage of antiplatelet therapy with appropriate bridging and use of antifibrinolytics in high risk patients.

Finally, we noted that diabetes was significantly more prevalent in LMS group (53% *vs* 44.4%, $P = 0.05$). Diabetes is known to increase the cardiovascular disease risk[33].

Study limitations: This study had the following limitations: (1) Being retrospective and conducted in a single center; (2) The revascularization strategy was based on the physician discretion; (3) Difficulty in doing long term follow up. Our study conclusions should be confirmed with larger randomized trials to better define mortality and morbidity variation in LMS patients in relation to the others; and (4) Low sample size.

CONCLUSION

Patients with LMS disease showed similar outcome as those without LMS in this study. Diabetes was more prevalent in patients with LMS. We observed that patients with LMS had significantly more IABP utilization. These findings may help in guiding decision making for future practice and stratifying the patients' care.

ARTICLE HIGHLIGHTS

Research background

Left main coronary artery (LMCA) supplies more than 80% of the left ventricle, and significant disease of this artery carries a high mortality unless intervened surgically. However, the influence of coronary artery bypass grafting (CABG) surgery on patients with LMCA disease on morbidity intensive care unit (ICU) outcomes needs to be explored.

Research motivation

However, the impact of CABG surgery on the morbidity of the ICU population with LMCA disease is worth exploring.

Research objectives

We aim at determining whether LMCA disease is a definitive risk factor of prolonged ICU stay as a primary outcome and early morbidity within the ICU stay as secondary

outcome.

Research methods

Retrospective descriptive study with purposive sampling analyzing 399 patients who underwent isolated urgent or elective CABG. Patients were divided into 2 groups; those with LMCA disease as group 1 (75 patients) and those without LMCA disease as group 2 (324 patients). We correlated ICU outcome parameters including ICU length of stay, post-operative atrial fibrillation, acute kidney injury, re-exploration, perioperative myocardial infarction, post-operative bleeding in both groups.

Research results

In this study, patients with LMCA disease had a significantly higher prevalence of diabetes (43.3% *vs* 29%, $P = 0.001$). However, we did not find a statistically significant difference with regards to ICU stay, or other morbidity and mortality outcome measures.

Research conclusions

Patients with left main stem (LMS) disease showed similar outcome as those without LMS in this study. Diabetes was more prevalent in patients with LMS. We observed that patients with LMS had significantly more intra-aortic balloon pump (IABP) utilization. These findings may help in guiding decision making for future practice and stratifying the patients' care.

Research perspectives

(1) The hospital length of stay did not differ between the studied groups with and without LMS disease; (2) The secondary outcome measures did not show any significant differences among the studied population; (3) Need for IABP support for LMS group was significantly higher than the group without LMS; and (4) Diabetes was more prevalent in patients with LMS.

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ORIGINAL ARTICLE

Prospective Study

Multicentered prospective investigator initiated study to evaluate the clinical outcomes with extracorporeal cytokine adsorption device (CytoSorb®) in patients with sepsis and septic shock

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Institutional review board statement: This study was

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Abstract

BACKGROUND

Sepsis is a severe clinical syndrome related to the host response to infection. The severity of infections is due to an activation cascade that will lead to an auto amplifying cytokine production: The cytokine storm. Hemoadsorption by CytoSorb® therapy is a new technology that helps to address the cytokine storm and to regain control over various inflammatory conditions.

AIM

To evaluate prospectively CytoSorb® therapy used as an adjunctive therapy along with standard of care in septic patients admitted to intensive care unit (ICU).

METHODS

This was a prospective, real time, investigator initiated, observational multicenter study conducted in patients admitted to the ICU with sepsis and septic shock. The improvement of mean arterial pressure and reduction of vasopressor needs were evaluated as primary outcome. The change in laboratory parameters, sepsis scores [acute physiology and chronic health evaluation (APACHE II) and sequential organ failure assessment (SOFA)] and vital parameters were considered as secondary outcome. The outcomes were also evaluated in the survivor and non-survivor group. Descriptive statistics were used; a P value < 0.05 was considered

to be statistically significant.

RESULTS

Overall, 45 patients aged ≥ 18 and ≤ 80 years were included; the majority were men (n = 31; 69.0%), with mean age 47.16 ± 14.11 years. Post CytoSorb® therapy, 26 patients survived and 3 patients were lost to follow-up. In the survivor group, the percentage dose reduction in vasopressor was norepinephrine (51.4%), epinephrine (69.4%) and vasopressin (13.9%). A reduction in interleukin-6 levels (52.3%) was observed in the survivor group. Platelet count improved to 30.1% (P = 0.2938), and total lung capacity count significantly reduced by 33% (P < 0.0001). Serum creatinine and serum lactate were reduced by 33.3% (P = 0.0190) and 39.4% (P = 0.0120), respectively. The mean APACHE II score was 25.46 ± 2.91 and SOFA scores was 12.90 ± 4.02 before initiation of CytoSorb® therapy, and they were reduced significantly post therapy (APACHE II 20.1 ± 2.47; P < 0.0001 and SOFA 9.04 ± 3.00; P = 0.0003) in the survivor group. The predicted mortality in our patient population before CytoSorb® therapy was 56.5%, and it was reduced to 48.8% (actual mortality) after CytoSorb® therapy. We reported 75% survival rate in patients given treatment in < 24 h of ICU admission and 68% survival rates in patients given treatment within 24-48 h of ICU admission. In the survivor group, the average number of days spent in the ICU was 4.44 ± 1.66 d; while in the non-survivor group, the average number of days spent in ICU was 8.5 ± 15.9 d. CytoSorb® therapy was safe and well tolerated with no adverse events reported.

CONCLUSION

CytoSorb® might be an effective adjuvant therapy in stabilizing sepsis and septic shock patients. However, it is advisable to start the therapy at an early stage (preferably within 24 h after onset of septic shock).

Key Words: Acute physiology and chronic health evaluation score; Hemadsorption; Sepsis; Sequential organ failure assessment score; Vasopressor

Core Tip: This prospective, real time, observational multicenter study was conducted in 45 patients with sepsis and septic shock. Post therapy, 26 patients survived and dose reduction in norepinephrine, epinephrine and vasopressin was 51.4%, 69.4% and 13.9%, respectively. Interleukin-6 level reduction was 52.3%, and platelet count improved significantly to 30.1%. Mean acute physiology and chronic health evaluation and sequential organ failure assessment scores were reduced significantly. Predicted mortality before CytoSorb® therapy was 56.5%, and mortality reduced to 48.8% after CytoSorb® therapy. The survival rate in patients given treatment in < 24 h of intensive care unit admission was 75% and 68% when given within 24-48 h of intensive care unit admission. CytoSorb® therapy was safe and well tolerated with no adverse events reported.

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INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection with a high mortality rate, ranging from 30%-50% or more[1]. Extracorporeal cytokine hemoadsorption attenuates the overwhelming inflammatory response in sepsis and helps in immunomodulation[1,2]. Septic shock is defined as

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sepsis with hyperlactataemia and concurrent hypotension[3,4]. In intensive care units (ICUs), sepsis is a leading cause of death and the 11th leading cause of death overall. In India, more than one million estimated new cases of sepsis are treated in ICUs each year, accounting for one out of every four patients in the ICUs. A recent study conducted by the Indian Society of Critical Care across 17 states of India in 4209 patients (the Indian intensive care case mix and practice patterns study) reported mortality as high as 46% in patients with septic shock and 42.2% overall in septic patients, compared with 17.8% mortality for ICU patients who did not develop sepsis[5].

The management of patients with septic shock includes early resuscitation with fluid and vasopressor therapy, support by mechanical ventilation, renal replacement therapy and appropriate antibiotic initiation[6]. An initial goal to treat patients with septic shock and sepsis is to maintain mean arterial pressure (MAP) and cardiac output. Patients who fail to respond to adequate fluid resuscitation are prescribed vasopressors [norepinephrine (NE), dopamine, epinephrine (E), vasopressin (V), phenylephrine] and inotropes (dobutamine, milrinone) in order to maintain hemodynamic parameters[7]. These agents help to maintain adequate blood pressure and organ perfusion. However, they can have substantial adverse effects like profound vasoconstriction, causing hypoperfusion and arrhythmic events[8]. Thus, their optimized use is crucial. CytoSorb® is an International Science Organization 10993 biocompatible device that is approved in the United States under International Science Organization 13485 certification. It is also approved as an extracorporeal cytokine adsorber in the European Union and marketed in 29 countries across the globe for all the indications that are associated with high cytokine levels[9-11]. It is a CE-approved hemoadsorption device designed to remove excess levels of inflammatory mediators like cytokines and other mid-molecular weight molecules through size selective removal and surface adsorption[12,13]. Unlike metabolic approaches to anti-inflammation, CytoSorb® is able to capture directly and reduce mid-molecular weight inflammatory mediators (approximately 10-60 kDa) in blood, including both pro- and anti-inflammatory cytokines, chemokines and bacterial exotoxins[14]. It is reported to work most effectively when treatment is initiated within 24 h of diagnosed sepsis[15]. As a result of adsorption of inflammatory metabolites like cytokines it is inferred that hemodynamic and metabolic stabilization will follow[16].

In addition to standard treatment, including renal replacement and cardiac support, recent studies showed promising results with the use of extracorporeal cytokine hemoadsorption therapy[17-20]. CytoSorb® therapy along with standard of care is also utilized in the treatment of allergic reactions, burn injuries, and liver and pulmonary failure. Other potential indications for use of CytoSorb® therapy are trauma, hemophagocytic lymphohistiocytosis, pancreatitis and rhabdomyolysis[21,22].

To date, scarce scientific evidence including few case series and randomized controlled trials are available on the use of CytoSorb® therapy[10,15]. An international registry of 22 countries on use of Cytosorb® therapy in 198 patients noted that sepsis was the most common indication for use of Cytosorb® therapy (n = 135) and reported improved interleukin (IL)-6 levels and improved actual mortality (AM, 65%) *vs* predicted mortality (PM, 78%) for these patients[10].

CytoSorb® has been used in India for several years. Therefore, the purpose of this prospective study was to collect data and evaluate the clinical outcomes with CytoSorb® therapy in patients with sepsis and septic shock.

MATERIALS AND METHODS

Study design

This was a prospective, real time, investigator initiated, observational, multicenter study conducted for 8 mo (including enrollment and completion) across four different tertiary care ICUs in India. The study protocol was approved by the local scientific and ethical committee. The study was conducted in compliance with the current International Council for Harmonization, Good clinical practice (ICH GCP), Schedule Y and Indian Council of Medical Research guidelines. A written informed consent was obtained from all the patients/relatives before initiating the therapy. The patients/caretakers received information about the usage, advantages and disadvantages of treatment.

Inclusion/exclusion criteria

We enrolled patients admitted in the ICU with sepsis and septic shock who were

initially managed for at least 6 h as recommended by the surviving sepsis guidelines[2]. Of these, we included those patients who had evidence of at least one new onset organ dysfunction during the course of sepsis.

Patients were excluded if: Diagnosed with septic shock for > 48 h; Had symptoms of uncontrolled hemorrhage in the last 24 h; Had more than three failed organs on presentation; Had received chemotherapy or radiation treatment within last 60 d; Diagnosed with chronic kidney disease stage 5 or end stage hepatic liver failure; Had a history of immunosuppressive disorders or admitted with acute coronary syndrome or life-threatening cardiac arrhythmia.

Study procedure

Before initiating the CytoSorb® therapy, the baseline patient data, including relevant demographic details, vital signs, clinical diagnosis, progression of clinical condition and laboratory parameters, were recorded in the case record form (CRF). To monitor the effects of CytoSorb therapy, all relevant parameters were recorded before and after the CytoSorb® treatment.

Primary outcomes

The following outcomes were considered as primary end points:

Change in vasopressor requirement: As per vasopressor or inotropic requirement, the MAP was targeted > 65 mmHg. Dose and number of drugs (*i.e.* NE, E and V) and change in MAP before and after CytoSorb® therapy were recorded.

Cytokine assay: Serum samples for multi cytokine assay (*i.e.* IL-1, IL-6) were collected pre-(baseline) and post-(after the last treatment) CytoSorb® therapy and analyzed in Syngene Lab (Bangalore, India). The post CytoSorb® samples were collected before disconnecting the device. Change in pre and post cytokine values were recorded in CRF.

Percentage reduction in vasopressor dose/cytokine level was calculated as (difference in average pre and average post vasopressor dose or cytokine level/average pre vasopressor dose or pre cytokine level dose) × 100. To monitor the vasopressor-MAP relationship, the MAP/NE ratio was used.

Secondary outcomes

Evaluation of laboratory parameters: We recorded the complete blood count and biochemistry test results both at baseline, during and at the completion of CytoSorb® therapy in the CRF. Change in laboratory parameter values for pre and post CytoSorb® therapy were evaluated.

Organ function

Acute physiology and chronic health evaluation (APACHE II) and Sequential organ failure assessment (SOFA) scores were recorded at baseline and post therapy. Vital parameters were recorded at baseline and on each day of CytoSorb® treatment. MAP, X–ray findings, ventilator requirement and oxygenation parameters (fraction of inspiration O_2, alveolar oxygen partial pressure, partial pressure of carbon dioxide) were also documented in CRF. At the end of treatment, change in pre and post therapy values were calculated. APACHE-II calculator was used as a severity score and mortality estimation tool[23].

Survival outcomes

Survival outcomes were determined on the basis of length of patients' stay in ICU (total number of days spent by the patient in ICU before, during and post CytoSorb® therapy) and mechanical ventilation/dialysis requirement (frequency at which the patients required mechanical ventilation and dialysis before and after the treatment).

Length of treatment

The duration of CytoSorb® treatment in hours and number of CytoSorb® devices used were decided as per the patient's condition and clinical outcomes. We used a minimum of two devices for each patient. Each day one CytoSorb® device was used for 8-12 h in hemodialysis machine or for maximum of 24 h in continuous renal replacement therapy machines.

Safety evaluation

Any event that was not expected due to the course of disease and concurrent

medications was recorded and evaluated.

Statistical analysis

A sample size calculation was not performed due to the exploratory character of the study. Data were primarily recorded in Microsoft Excel 2016. Data are summarized according to data distribution (normal or not-normal), and the appropriate parametric or non-parametric statistical tests were used to evaluate the difference in clinical outcomes and the change in clinical and laboratory parameters before and after CytoSorb® therapy. The level of significance was defined as $P < 0.05$.

RESULTS

Study population

A total of 45 patients aged ≥ 18 and ≤ 80 years were included in the study. Majority of the patients were men ($n = 31$; 69.0%) with mean age 47.16 ± 14.11 years. The mean age of women patients was 48.14 ± 19.04 years. Prior to CytoSorb® therapy, the percentage of patients who required mechanical ventilation and dialysis were 78% and 49%, respectively. The rest of the demographics are summarized in Table 1. Twenty-six patients (57.8%) survived the full course of CytoSorb® therapy, and 3 patients were lost to follow up.

Evaluation of primary outcomes

Vasopressor requirement: Table 2 shows the change in vasopressor drugs in the survivor group from the start after the termination of CytoSorb® therapy. Overall, before CytoSorb® therapy, 21 patients required NE, 4 patients were on E and 9 were on V. In general, there was a tendency of reduced need for vasopressors post CytoSorb® therapy, but it did not reach statistical significance. Amongst the patients in the non-survivor group, the use of vasopressor drugs increased or remained unchanged (data not shown).

Change in laboratory parameters in survivors (Table 3): Total lymphocyte count reduced significantly at the end of the therapy. Serum creatinine and lactate levels also reduced significantly. There was no other significant change in any of the investigated parameters (Table 3).

There was some reduction in the inflammatory marker levels for both IL-1 and IL-6, but it did not reach statistical significance (Table 4).

Change in vital parameters in survivors (Table 5): After CytoSorb® therapy, there was a 15.8% significant increase in MAP. Among non-survivors ($n = 19$) there was also a significant increase in MAP (from 69.56 ± 7.84 to 72.13 ± 13.2 mmHg, $P = 0.036$). Post CytoSorb® therapy, both heart rate and the Glasgow coma score improved significantly in the survivor group. The rest of the data for survivors are shown in Table 5.

Evaluation of secondary outcomes

Assessment of sepsis scores: Both APACHE II and SOFA scores were significantly reduced by the end of the treatment among survivors (Figure 1). Overall, there was a 20.7% reduction in APACHE II and 29.8% reduction in SOFA scores. In the non-survivor group, APACHE II scores increased from 26.5 ± 5.2 to 27.93 ± 5.2, and SOFA scores also increased from 13.56 ± 4.53 to 15.38 ± 4.29.

Predicted mortality: The PM before CytoSorb® therapy was 56.5% in the overall population; the actual mortality after CytoSorb® therapy was 48.8% (Figure 2).

Initiation of CytoSorb® therapy: In most patients, treatment was commenced between 24-48 h after ICU admission (Figure 3). Only 3 patients among survivors and 1 in non-survivors received therapy within < 24 h, and in 16 cases treatment was started > 48 h after ICU.

Overall, 50% ($n = 8$) of patients survived after 72 h of therapy. In the survivor group, the average number of days spent in ICU was 4.44 ± 1.66 d; while in the non-survivor group, it was 8.5 ± 15.9 d.

Evaluation of safety parameters: We could not observe any CytoSorb® related side effects or adverse events. There was no significant change in platelet or albumin levels (Table 3). Only 1 single patient showed clot formation in the device when used

Table 1 Baseline characteristics of all the patients before initiating the therapy

Baseline characteristics	Findings, mean ± SD
Age, yr	47.46 ± 15.56
Heart rate, beats/min	117 ± 22.05
MAP, mmHg	69.15 ± 9.19
GCS	9.04 ± 3.06
APACHE-II	25.46 ± 5.06
SOFA	12.90 ± 4.37
Leucocytes, μL	15311.44 ± 7140.54
Platelets, cells/mm^3	139153.48 ± 89467.72
S. Creatinine, mg/dL	2.74 ± 1.72
S. Lactate, mmoL/L	4.61 ± 2.87
$PaCO_2$	43.37 ± 18.22
PaO_2	94.02 ± 49.09
FiO_2	48.78 ± 43.28
PaO_2/FiO_2	118.6 ± 58.01

APACHE II: Acute physiology and chronic health evaluation; FiO2: Fraction of inspiration O_2; GCS: Glasgow coma scale; MAP: Mean arterial pressure; SD: Standard deviation; SOFA: Sequential organ failure assessment; $PaCO_2$: Partial pressure of carbon dioxide; PaO_2: Alveolar oxygen partial pressure.

Table 2 Percentage decrease in patients and vasopressor doses (survivors)

Vasopressor drug, μg/kg/min	Pre CytoSorb®, therapy patient number (*n*), dose (median)	Post CytoSorb® Therapy, patient number (*n*), dose (median)	% Decrease in dose	*P* value (dose)
Norepinephrine	21; 1	18; 0.45	43.3	0.160
Epinephrine	4; 0.055	1; 0.055	64.4	-
Vasopressin	9; 1.5	7; 1	15.4	0.816

without heparin due to the clinical condition of the patient, which led to the stoppage of the therapy when used for the second time. One patient was diagnosed with ventricular tachycardia and needed injection of amiodarone.

DISCUSSION

Various adjuvant therapies are included in current treatment modalities for controlling cytokine storm; immunoglobulin therapy, endotoxin-binding polymyxin B hemoperfusion, dialysis and plasma filtration, *etc.* The mortality rate still remains high with these techniques[24-26]. Direct hemoperfusion using a polymyxin B endotoxin-adsorbing column was studied in clinical trials (ABDOMIX Study). The study could not confirm its clinical efficacy due to the nephrotoxic effects of the technique and associated high risks of cartridge clotting resulting in acute blood loss in patients admitted in ICU[27]. Similarly, anti-IL-1RA, anti-IL-1β, anti-tumor necrosis factor-α and anti-lipopolysaccharide showed disappointing results in both preclinical and clinical trials, despite their ability to reduce significantly serum cytokine concentrations[28,29]. A recent Cochrane review reported low-quality evidence for high-volume hemofiltration in the treatment of critically ill patients with sepsis and suggested that more multicenter randomized controlled trials are required before these therapies can be recommended for routine use[12].

Extracorporeal cytokine adsorption is a recent adjuvant alternative introduced into clinical practice less than a decade ago. Its aim was to reduce cytokine storm by the bulk removal of mediators of inflammation. Later, this treatment was reported as safe

Table 3 Change in laboratory parameters for survivors

Parameters	Pre CytoSorb® therapy	Post CytoSorb® therapy	*P* value
Hb, g/dL	10.01 ± 2.20	9.28 ± 1.53	0.1830
HCT, %	29.74 ± 8.4	25.75 ± 7.67	0.0909
Leucocytes, µL	16724 ± 5425	11215 ± 3317	0.0001[1]
Platelets, cells/mm^3	139256 ± 88029	181203 ± 181381	0.2938
S. Creatinine, mg/dL	3.13 ± 1.92	2.08 ± 1.02	0.0190[1]
S. Lactate, mmol/L	4.75 ± 2.77	2.88 ± 2.39	0.0120[1]
SGOT, U/L	488.44 ± 1570.42	369.95 ± 1134.74	0.7661
SGPT, U/L	192.72 ± 298.99	145.90 ± 236.97	0.5503
BUN, mg/dL	76.21 ± 61.88	62.39 ± 52.28	0.4076
Bilirubin, mg/dL	9.91 ± 36.77	8.35 ± 31.36	0.8730
Sodium, mmol/L	134.38 ± 25.69	134.32 ± 6.20	0.9908
Potassium, mmol/L	3.98 ± 0.95	3.73 ± 1.05	0.3723
Albumin, g/L	2.65 ± 0.93	2.71 ± 0.95	0.8261
Arterial pH	7.35 ± 0.100	7.36 ± 0.105	0.7291
Bicarbonate	24.89 ± 10.71	24.75 ± 9.21	0.9599

[1]Significant value $P < 0.05$, all values are defined as mean ± SD.
BUN: Blood urea nitrogen; Hb: Hemoglobin; HCT: Hematocrit; SD: Standard deviation; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic-pyruvic transaminase.

Table 4 Cytokine assay results for survivors

Cytokine	Pre CytoSorb® therapy, mean ± SD	Post CytoSorb® therapy, mean ± SD	Percentage change	*P* value
IL1, pg/mL	10.74 ± 9.70	9.54 ± 9.66	11.11	0.5580
IL6, pg/mL	889.15 ± 1307.43	423.69 ± 1105.55	52.34	0.0792

IL: Interleukin.

Table 5 Change in vital parameters in survivors

Parameters	Survivor group		*P* value
	Pre CytoSorb® therapy, mean ± SD	Post CytoSorb® therapy, mean ± SD	
Heart rate, beats/min	118.57 ± 19.8	103.07 ± 19.38	0.0065[1]
MAP, mmHg	68.61 ± 9.62	79.42 ± 9.05	0.0001[1]
GCS	9.86 ± 2.34	12.20 ± 1.47	0.0001[1]
$PaCO_2$	43.32 ± 18.63	38.57 ± 11.66	0.2757
PaO_2/FiO_2	162.09 ± 82.99	161.20 ± 66.58	0.9704

[1]Significant *P* value < 0.05.
All values are defined as mean ± SD. FiO2: Fraction of inspiration O_2; GCS: Glasgow coma scale; MAP: Mean arterial pressure; $PaCO_2$: Partial pressure of carbon dioxide; PaO_2: Alveolar oxygen partial pressure; SD: Standard deviation.

and well-tolerated in more than 300 human treatments in very sick patients with the worst forms of sepsis and lung injury, and to date, the treatment has emerged as the safest in nearly 1500 human treatments overall[30]. Though published data suggest that using CytoSorb® in conjunction with standard care including mechanical ventilation and dialysis may decrease the level of pro-inflammatory cytokines and improve hemodynamics in sepsis and septic shock, high-quality data from clinical trials are not available yet[16].

The present study evaluated some aspects of the clinical outcomes with CytoSorb® device treatment along with current standard of care in management of sepsis and septic shock. We observed improved clinical outcomes of patients with septic shock in terms of reduced mortality as compared to predicted, improved hemodynamics as indicated by MAP, and reduced use of vasopressors and their doses.

We studied patients requiring increasing vasopressor dose to maintain MAP > 65 mmHg. In our study, MAP increased significantly during CytoSorb® therapy in both survivors and non-survivors. This improvement in MAP was accompanied by a non-significant reduction in vasopressor dose as also indicated by the increase in the MAP/NE ratio. These results are in accord with our previous study conducted in 10 ICU patients where an overall reduction in all the vasopressor drugs after CytoSorb® therapy was reported[31]. Of the nine patients who were given vasopressin, five were weaned off V, two had a reduced dose and two were on the same dose as before.

Our results were consistent with the results reported by a prospective single center study with 20 patients; wherein the CytoSorb® treatment included NE dose that was significantly reduced after 6 h (−0.4 μg/kg/min; $P = 0.03$) and 12 h (−0.6 μg/kg/min; $P = 0.001$). Shock reversal was achieved in 13 (65%) patients; 28 d survival was 45%. The study reported shock reversal in two-thirds of these patients after using CytoSorb® adsorption therapy[10]. The findings of our study are supported by some more recent case reports demonstrating that CytoSorb® might be an effective adjuvant therapy, decreasing vasopressor requirements and stabilizing hemodynamics of septic shock patients[15,31-35].

Cytokines play an important role in the pathophysiology of sepsis and other clinical conditions with systemic inflammation. An elevated circulating levels of pro-inflammatory cytokines causes dysregulation in immune response and results in multi organ failure causing prolonged ICU stay and high mortality in ICU patients[36,37]. Specifically, elevated serum IL-1 and IL-6 appear to correlate with sepsis severity and end-organ damage[38]. We performed a cytokine assay, and our results showed improved levels of IL-6 in survivor group.

In addition to all above parameters, our results showed significant reduction in laboratory parameters like total lung capacity count improved ($P < 0.00001$) and overall improvement in HR ($P = 0.0065$), Glasgow coma score ($P < 0.0001$) and other biomarkers like serum creatinine ($P = 0.0190$) and lactate ($P = 0.0120$). An insignificant improvement was seen in other parameters also (*i.e.* respiratory parameters, liver and kidney profile). There was significant reduction in the SOFA scores ($P = 0.0003$) in the survivor group. The current findings are well consistent with other published studies[33,39,40].

We also investigated the time of initiation of CytoSorb® (in less than 24 h or 48 h of admission in ICU). Although there was a tendency that survivors received therapy earlier compared to non-survivors, the numbers are very small to make firm conclusions regarding timing and outcome. Nevertheless, the tendency of this pattern provide some further support to those studies, which also reported that starting therapy within 24 h after the onset of septic shock is the most beneficial[16,24].

PM was 54% in survivor group and 60% in non-survivor group using acute APACHE II calculator[23]. However, the AM was 42%. Our findings are similar to those of Kogelmann *et al*[15] who used CytoSorb® as an adjunctive therapy in 26 critically ill patients with septic shock and in need of renal replacement therapy. They reported that AM was lower in the overall patient population than PM. The actual 28 d, ICU and hospital mortality was 61.54%, 73.08% and 80.77%, respectively. However, mortality as predicted by APACHE II score in the overall patient population was 89.9%. Another previously published study reported that hemoadsorption with CytoSorb® results in a decreased observed *vs* expected 28 d mortality in patients with septic shock, and the mean PM (based on SOFA) was 75% (95%CI: 71%-79%) while AM was found to be 48% (mean difference-27%, 95%CI: 38%-15%, $P < 0.001$)[11].

Regarding safety, our results provide further data that the therapy is safe, as we could not find any device related AE or laboratory deterioration. In fact, platelet count remained unchanged or rather slightly increased, rather than decreased. This is contrast with some other reports, where thrombocytopenia had been observed[41].

This study has certain limitations. The sample size is relatively small, several

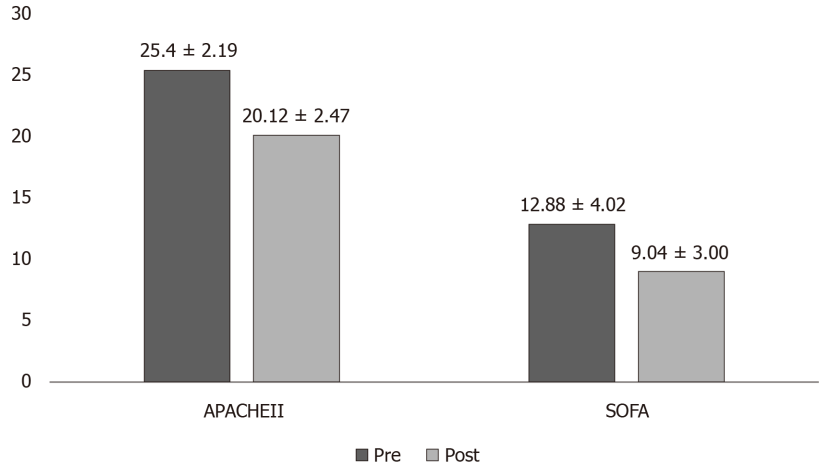

Figure 1 Sepsis scores in survivor group (pre and post Cytosorb® therapy). Significant *P* values obtained for both acute physiology and chronic health evaluation ($P < 0.0001$) and sequential organ failure assessment scores ($P = 0.0003$). APACHE II: acute physiology and chronic health evaluation; SOFA: Sequential organ failure assessment scores.

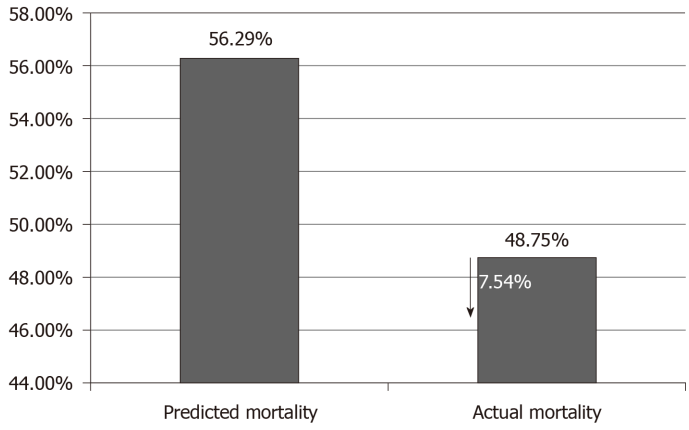

Figure 2 Predicted mortality *vs* actual mortality based on acute physiology and chronic health evaluation.

circumstances were not standardized and there was no control group. Detailed hemodynamic evaluation and conventionally used inflammatory markers, such as C-reactive protein or procalcitonin, were not measured. However, a very recent retrospective, propensity score matched study reported very positive results on around 100 patients without measuring inflammatory markers[11].

CONCLUSION

Overall, the current study showed improvement in hemodynamic stability and organ function and reduction in IL-6 levels. Our results provide further support to the notion that outcomes are better if cytokine adsorption (CytoSorb®) is initiated early after the onset of septic shock. We can also conclude that we could not find any treatment related AE. Further, studies should be performed to help us to identify the appropriate patient population and timing of therapy and also to test the positive results of retrospective and observational studies, just like the current results, in the setting of randomized clinical trials.

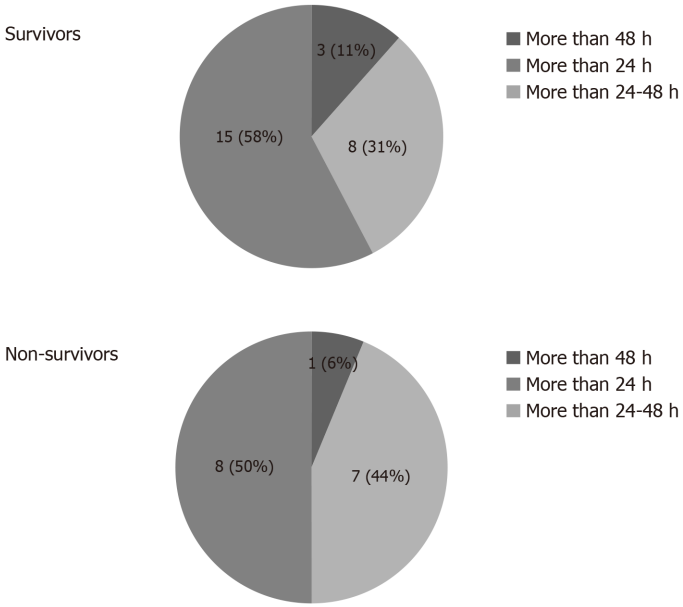

Figure 3 Time of initiation of CytoSorb® therapy in survivors and non-survivors.

ARTICLE HIGHLIGHTS

Research background

Sepsis is one of the oldest and most elusive syndromes in medicine, and yet it remains the most significant unmet medical need. In India, more than one million estimated new cases of sepsis are treated in intensive care units (ICUs) each year. CytoSorb® is an International Science Organization 10993 biocompatible device that is approved in the United States under International Science Organization 13485 certification. It is also approved as an extracorporeal cytokine adsorber in the European Union and marketed in 29 countries. In this study, clinical outcomes of patients with septic shock were assessed in terms of reduced mortality as compared to predicted, improved hemodynamics as indicated by mean arterial pressure (MAP) and reduced use of vasopressors and their doses.

Research motivation

Sepsis and septic shock is the leading cause of death among hospitalized patients. CytoSorb® therapy showed promising results in hyperinflammatory condition of critically ill septic patients. This study was conducted to evaluate clinical outcomes in these patients. This study will help clinicians to evaluate the use of CytoSorb® therapy for the patients considering clinical outcomes like MAP and use of vasopressors drugs.

Research objectives

The objective of the study was to evaluate CytoSorb® use as an adjunctive therapy along with the standard of care. The study showed improvement in hemodynamic stability and organ function and reduction in interleukin-6 levels.

Research methods

This was a prospective, real time, investigator initiated, observational multicenter study conducted in the patients admitted to the ICU with sepsis and septic shock. The improvement of MAP and reduction of vasopressor needs were evaluated as primary outcome. The change in laboratory parameters, sepsis scores [acute physiology and chronic health evaluation (APACHE II) and sequential organ failure assessment (SOFA)] and vital parameters were considered as secondary outcome. The outcomes were also evaluated in the survivor and non-survivor group. Descriptive statistics were used; a P value < 0.05 was considered to be statistically significant.

Research results

A total of 45 patients aged ≥ 18 and ≤ 80 years were included; a majority were men (n = 31; 69.0%) with mean age; 47.16 ± 14.11 years. Post CytoSorb® therapy, 26 patients

survived and 3 patients were lost to follow-up. In the survivor group, the percentage dose reduction in vasopressor was NE (51.4%), E (69.4%) and V (13.9%). A reduction in interleukin-6 levels (52.3%) was observed in the survivor group. Platelet count improved to 30.1% (P = 0.2938), total lung capacity count significantly reduced by 33% (P < 0.0001). Serum creatinine and serum lactate were reduced by 33.3% (P = 0.0190) and 39.4% (P = 0.0120), respectively. The mean APACHE II score was 25.46 ± 2.91, and SOFA scores was 12.90 ± 4.02 before initiation of CytoSorb® therapy and reduced significantly post therapy (APACHE II 20.1 ± 2.47; P < 0.0001 and SOFA 9.04 ± 3.00; P = 0.0003) in the survivor group. The predicted mortality in our patient population before CytoSorb® therapy was 56.5%, and it reduced to 48.8% (actual mortality) after CytoSorb® therapy. We reported 75% survival rate in patients given treatment in < 24 h of ICU admission and 68% survival rates in patients given treatment within 24-48 h of ICU admission. In the survivor group, the average number of days spent by patients in ICU was 4.44 ± 1.66 d; while in the non-survivor group, the average number of days spent by patients in ICU was 8.5 ± 15.9 d. CytoSorb® therapy was safe and well tolerated with no adverse events reported.

Research conclusions

Early initiation of CytoSorb® therapy significantly improves clinical outcomes.

Research perspectives

In the future, adding a standard of control group and conducting a study that is powered to compare the time of initiation of CytoSorb® therapy will be necessary.

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MINIREVIEWS

Acute cor pulmonale in patients with acute respiratory distress syndrome: A comprehensive review

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Abstract

Acute respiratory distress syndrome (ARDS)-related acute cor pulmonale (ACP) is found in 8%-50% of all patients with ARDS, and is associated with adverse hemodynamic and survival outcomes. ARDS-related ACP is an echocardiographic diagnosis marked by combined right ventricular dilatation and septal dyskinesia, which connote simultaneous diastolic (volume) and systolic (pressure) overload respectively. Risk factors include pneumonia, hypercapnia, hypoxemia, high airway pressures and concomitant pulmonary disease. Current evidence suggests that ARDS-related ACP is amenable to multimodal treatments including ventilator adjustment (aiming for arterial partial pressure of carbon dioxide < 60 mmHg, plateau pressure < 27 cmH_2O, driving pressure < 17 cmH_2O), prone positioning, fluid balance optimization and pharmacotherapy. Further research is required to elucidate the optimal frequency and duration of routine bedside echocardiography screening for ARDS-related ACP, to more clearly delineate the diagnostic role of transthoracic echocardiography relative to transesophageal echocardiography, and to validate current and novel therapies.

Key Words: Coronavirus; Critical care; Echocardiography; Hypertension; Pulmonary; Respiratory distress syndrome; Adult; Ventricular dysfunction; Right

Core Tip: Acute respiratory distress syndrome (ARDS)-related acute cor pulmonale (ACP) is associated with adverse hemodynamic and survival outcomes. It is an echocardiographic diagnosis marked by combined right ventricular dilatation and septal dyskinesia. Checking for ARDS-related ACP should be done in patients with ≥ 2 of 4 risk factors: Pneumonia, arterial partial pressure of oxygen-to-inspired oxygen fraction ratio < 150 mmHg, arterial partial pressure of carbon dioxide ≥ 48 mmHg, and

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driving pressure ≥ 18 cmH_2O. Treatments include ventilator adjustment (aiming for arterial partial pressure of carbon dioxide < 60 mmHg, plateau pressure < 27 cmH_2O, driving pressure < 17 cmH_2O), prone positioning, fluid balance optimization and pharmacotherapy.

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INTRODUCTION

For patients with acute respiratory distress syndrome (ARDS), concurrent acute cor pulmonale (ARDS-related ACP) is associated with adverse hemodynamic effects–and when severe–with a near doubling of mortality risk[1-4]. ARDS-related ACP is an echocardiographic diagnosis, which involves a dilated right ventricle with both systolic and diastolic dysfunction. As can be surmised, the greater the right ventricular dilatation, the more severe is the ACP, and the higher the risk of mortality.

The prevalence of ARDS-related ACP ranges from 8%-50% in various studies (Table 1)[1,2,4-10]. Given the current pandemic, special mention must be made about coronavirus disease 2019 (COVID-19). The first report of ACP in COVID-19 described five critically ill patients, with intracardiac thrombus being visualized on echocardiography in two patients[11]. Overall, it remains unknown if the prevalence of ACP differs significantly between COVID-19 and non-COVID-19 ARDS, though pulmonary embolism or pulmonary vascular thrombosis may predispose the former to ACP regardless of ARDS.

PATHOPHYSIOLOGY AND RISK FACTORS FOR ARDS-RELATED ACP

ARDS-related ACP occurs when right ventricular afterload increases acutely, leading to right ventricular systolic and diastolic dysfunction. Given the relatively stiff pericardial envelope, right ventricular diastolic dysfunction leads to right ventricular dilatation and leftward septal displacement, restricting the left ventricle (*i.e.*, ventricular interdependence). Consequently, ARDS-related ACP has been associated with adverse hemodynamic outcomes associated with both right and left ventricular dysfunction: Decreased stroke index, impairment of left ventricular diastolic function and compensatory tachycardia[5].

Normal right ventricular function depends on maintaining a low pulmonary vascular resistance. Any factor that increases pulmonary vascular resistance thus promotes ARDS-related ACP. ARDS itself, particularly when driven by pneumonia, can lead to endothelial dysfunction, microthrombi formation, vascular remodelling and occlusion of the pulmonary arterial bed. Among patients with ARDS, having more severe lung disease as measured by pulmonary dead space monitoring, may predict the risk of ACP[12]. Concomitant diseases that cause pulmonary vascular dysfunction can aggravate ARDS-related ACP. An example would be sickle cell disease, which can be complicated by pulmonary vasoconstriction (from hemolysis and nitric oxide scavenging) and vaso-occlusion (from fat embolism and *in situ* thrombosis)[10].

A potentially modifiable risk factor for ARDS-related ACP is hypercapnia[5], which causes pulmonary vasoconstriction, particularly when the arterial partial pressure of carbon dioxide exceeds 60 mmHg[7]. Hypercapnia can be particularly common in ARDS due to underlying ventilation-perfusion mismatch and the use of permissive hypercapnia. Another potential risk factor is hypoxemia, which causes hypoxic pulmonary vasoconstriction, though this is less well-demonstrated in clinical studies than for hypercapnia. Furthermore, positive pressure ventilation, high plateau pressure (especially if it exceeds 27 cmH_2O[4]), high driving pressure, and the use of positive end-expiratory pressure can increase pulmonary vascular resistance. Whether ACP predisposes ARDS patients to further harm by the high airway pressures in high-frequency oscillatory ventilation remains uncertain[3,13].

A combination of four risk factors have been used to risk stratify patients for ARDS-

Table 1 Definitions and prevalence of acute respiratory distress syndrome -related acute cor pulmonale

Ref.	Definition	Test	Prevalence
Vieillard-Baron *et al*[5] (2001)	Ratio of right ventricular end-diastolic area to left ventricular end-diastolic area in the long axis > 0.6 associated with septal dyskinesia in the short axis	TEE	19/75 (25%)
Jardin *et al*[4] (2007)	Ratio of right ventricular end-diastolic area to left ventricular end-diastolic area in the long axis > 0.6 associated with septal dyskinesia in the short axis	TEE	101/352 (29%)
Vieillard-Baron *et al*[6] (2007)	Ratio of right ventricular end-diastolic area to left ventricular end-diastolic area in the long axis > 0.6 associated with septal dyskinesia in the short axis	TEE	21/42 (50%)
Fichet *et al*[9] (2012)	Right ventricular dilatation was defined by a right ventricular end-diastolic area to left ventricular end-diastolic area ratio > 0.6 and reported as severe when ratio was ≥ 1 (apical four-chamber view). ACP was defined by right ventricular dilatation associated with septal dyskinesia observed in the short-axis view	TTE	ACP: 4/50 (8%); Severe ACP: 4/50 (8%)
Boissier *et al*[2] (2013)	Ratio of right ventricular end-diastolic area to left ventricular end-diastolic area in the long axis > 0.6 associated with septal dyskinesia in the short axis	TEE	49/226 (22%)
Lhéritier *et al*[7] (2013)	Association of right ventricular dilatation inthe long-axis view of the heart (ratio of right ventricular end-diastolic area to left ventricular end-diastolic area > 0.6) and a visually identified systolic paradoxical ventricular septal motion in the short-axis view of the heart	TEE	45/200 (23%)
Mekontso-Dessap *et al*[14] (2015)	Septal dyskinesia (in the short axis) with a dilated right ventricle (end-diastolic right/left ventricle area ratio > 0.6 in the long axis). Severe ACP defined as septal dyskinesia (in the short axis) with a dilated right ventricle (end-diastolic right/left ventricle area ratio ≥ 1 in the long axis)	TEE	ACP: 164/752 (22%); Severe ACP: 54/752 (7%)
Legras *et al*[8] (2015)	Association of right ventricular dilatation inthe long-axis view of the heart (ratio of right ventricular end-diastolic area to left ventricular end-diastolic area > 0.6) and a visually identified systolic paradoxical ventricular septal motion in the short-axis view of the heart	TEE	36/195 (18%)
Cecchini *et al*[10] (2016)	Dilated right ventricle (end-diastolic right ventricle/left ventricle area ratio > 0.6) associated with septal dyskinesia on the short-axis view	TEE or TTE	88/362 (24%)
See *et al*[1] (2017)	Severe ACP defined as right-to-left ventricular size (area) ratio ≥ 1 in end diastole at the papillary muscle level and interventricular septal straightening/paradoxical motion using the parasternal short axis view. NB. Apical four-chamber view was used as a secondary safeguard against false ACP determination, which did not occur	TTE	Only severe ACP reported: 66/234 (28%)

ACP: Acute cor pulmonale; ARDS: Acute respiratory distress syndrome; TEE: Transesophageal echocardiography; TTE: Transthoracic echocardiography.

related ACP: Pneumonia as a cause of ARDS, an arterial partial pressure of oxygen-to-inspired oxygen fraction (P/F) ratio < 150 mmHg, an arterial partial pressure of carbon dioxide 48 mmHg or greater, and a driving pressure 18 cmH2O or greater[14]. When two or more risk factors were present, the prevalence of ARDS-related ACP exceeded 20%, which led the authors to encourage routine echocardiography screening for such patients. Conversely, when fewer than two risk factors were present, the prevalence of ARDS-related ACP was 10% or less, and echocardiography can be done on demand.

DIAGNOSIS AND DEFINITION OF ARDS-RELATED ACP

The hallmark of ARDS-related ACP would be combined right ventricular dilatation and septal dyskinesia, which connote simultaneous diastolic (volume) and systolic (pressure) overload respectively. Without septal dyskinesia, the singular finding of right ventricular dilatation does not mean ACP. Serum-based biomarkers like cardiac troponin and pressure-based thresholds obtained *via* invasive pulmonary artery catheterization have not been useful for determining ACP[14], though B-type natriuretic peptide may be useful for risk stratification in the absence of left ventricular dysfunction[15].

In patients with ARDS, the presence of a dilated right ventricle does not automatically mean ARDS-related ACP. Two important differential diagnoses need to be considered: Pulmonary embolism and chronic right ventricular dilatation. Confident exclusion of pulmonary embolism requires either a low risk-adjusted d-dimer or a negative high-sensitivity test like computed tomography pulmonary angiography. Chronic right ventricular dilatation can be recognized by a right ventricular free wall diastolic thickness exceeding 9 mm (normal thickness < 5 mm)[16], which occurs *via* right ventricular remodelling. Such remodelling occurs in the context of gradual, rather than acute, elevation of pulmonary vascular resistance and development of pulmonary arterial hypertension *e.g.*, in patients with severe chronic

obstructive pulmonary disease and obesity-hypoventilation syndrome.

After excluding pulmonary embolism and chronic right ventricular dilatation, identification of ARDS-related ACP is by bedside ultrasound. The reference standard comprises transesophageal long axis and transgastric short axis views obtained by transesophageal echocardiography, with mean interobserver and intraobserver variability both under 10%[16]. ACP and severe ACP are defined as a ratio of right ventricular end-diastolic area to left ventricular end-diastolic area in the long axis being > 0.6 and ≥ 1 respectively, in combination with septal dyskinesia[14] (Table 1). An absolute threshold of right ventricular area to diagnose dilatation in ACP does not exist. To identify septal dyskinesia, short axis views are required to demonstrate a leftward shift of the septum in diastole. To determine right ventricular dilatation, comparative assessment of right and left ventricular areas in the long axis view can be achieved by standard measurements[16]. If one wishes to look for severe ACP, then eyeballing may suffice[1,17], and can be done in the short axis view[18]. Nonetheless, comparison of right and left ventricular areas could be of limited value if the left ventricle is chronically dilated due to valvular disease or cardiomyopathy[16].

As an alternative to transesophageal echocardiography, basic critical care echocardiography identification of ARDS-related severe ACP, *via* the transthoracic parasternal short axis view, can be achieved by trainees who have undergone as few as 30 practice scans[17]. Training requires few resources and can be facilitated by dyad (training in pairs) rather than individual training[18]. The transthoracic parasternal short axis view was chosen as the main view to assess the relative sizes of the right and left ventricles and to assess for septal straightening/paradoxical motion, as this view had a fixed landmark (papillary muscles) and was not prone to foreshortening or rotational error[1]. For severe ACP, since identification relies on a ratio of 1 between the right and left ventricle sizes, rapid visual comparison was possible without routine manual tracing of the endocardial borders. Meanwhile, the apical four-chamber view was used only as a secondary safeguard against false ACP determination, as it is prone to foreshortening or rotational error, and would lead to under-recognition of ACP.

For the identification of non-severe ACP, the sensitivity and specificity of transthoracic echocardiography were found to be 66% and 99% respectively, compared to transesophageal echocardiography[7]. The relatively low sensitivity of transthoracic echocardiography was ascribed to technical limitations for obtaining adequate images in critically ill patients with ARDS, and thus caution is needed when using transthoracic echocardiography to rule out ACP. Conversely, if image acquisition can be achieved (*e.g.* in non-obese patients), the very high specificity of transthoracic echocardiography means that it remains useful to rule in ACP.

MANAGEMENT OF ARDS-RELATED ACP

Fortunately, ARDS-related ACP is reversible and once reversed, ARDS-related ACP does not seem to elevate mortality risk[5]. While few randomized clinical trials for ARDS-related ACP therapy are available, several observational studies exist to guide clinical management (Table 2). Foremost in the treatment of ARDS-related ACP would be to minimize positive pressure. This can be achieved *via* reduction of tidal volume, reduction of positive end-expiratory pressure, or both. However, trade-offs exist. When tidal volume is too low despite increased respiratory rate, hypercapnia ensues, increasing pulmonary vasoconstriction. Avoiding an arterial partial pressure of carbon dioxide exceeding 60 mmHg[19] or 48 mmHg[20] have been proposed. Additionally, positive end-expiratory pressure should not be lowered if de-aeration and hypoxemia occurs.

Without resorting to extracorporeal membrane oxygenation or carbon dioxide removal, prone positioning can improve both hypercapnia and lung aeration of the dorsal segments. This can allow tidal volumes and positive end-expiratory pressure to be kept lower than what would have been possible in the supine position. In turn, prone positioning would mitigate ARDS-related ACP. Direct visualization of this effect was recently demonstrated in a patient with COVID-19 ARDS using real-time 3D transesophageal echocardiography[21]. During prone positioning, right ventricular end-diastolic volume decreased and paradoxical septal motion disappeared. And on reversion to supine positioning, acute cor pulmonale recurred.

Besides ventilatory strategies and prone positioning, fluid management should also be optimized to avoid hypervolemia, which would exacerbate right ventricular volume overload. Volume expansion should be stopped once ACP is recognized[22]. Pharmacologic therapy, based on physiology and yet to be widely demonstrated for

Table 2 Management options for acute respiratory distress syndrome-related acute cor pulmonale

Management option	Details	Best supporting evidence
Ventilator adjustment	Limit end-inspiratory plateau pressure to 30 cmH_2O. Target a tidal volume of 6-9 mL/kg. Positive end-expiratory pressure selected to improve oxygenation without requiring specific hemodynamic support, except for blood volume expansion	Observational study[5]
	Aim for partial pressure of carbon dioxide < 60 mmHg	Observational study[7]
	Aim for partial pressure of carbon dioxide < 48 mmHg	Observational study[14]
	Aim for plateau pressure < 27 cmH_2O	Observational study[4]
	Aim for driving pressure < 17 cmH_2O	Observational study[2]
Prone positioning	Ventilation in the prone position, especially for patients with refractory severe hypoxemia (P/F ratio < 100 mmHg)	Observational study[5,6,29]
Fluid balance optimization	Stop volume expansion	Expert opinion[22]
	Consider diuresis or fluid removal using hemofiltration	Expert opinion[28]
Pharmacotherapy	Pulmonary vasodilation using inhaled nitric oxide	Expert opinion[16]
	Pulmonary vasodilation using levosimendan	Pilot trial[23]
	Vasopressors to restore systemic blood pressure and to avoid right ventricular ischemia	Expert opinion[28]

ACP: Acute cor pulmonale; ARDS: Acute respiratory distress syndrome; P/F = Arterial partial pressure of oxygen/inspired oxygen fraction.

ARDS-related ACP, would be to use pulmonary vasodilators like inhaled nitric oxide[16] and levosimendan[23].

FUTURE DIRECTIONS

Future directions arising from animal experiments

Mechanical ventilation may contribute to the development of ACP *via* excessive pressure swings. In an experiment involving adult male Sprague-Dawley rats, Katira *et al*[24] induced acute right ventricular dilatation and ACP when the rats were exposed to high peak inspiratory airway pressure (45 cmH_2O) and zero positive end-expiratory pressure. In contrast, rats avoided ACP when they received the same peak inspiratory airway pressure and 10 cmH_2O of positive end-expiratory pressure. The postulated mechanism of ACP in this murine model is unclear, but it appears that positive end-expiratory pressure may mitigate repetitive lung strain, cyclic interruption/exaggeration of pulmonary blood flow and microvascular injury. Further work will be needed confirm this mechanism and to optimize the use of positive end-expiratory pressure for ACP management in humans.

Besides ventilator adjustments, animal data suggest that pharmacotherapy with Tris (hydroxymethyl) aminomethane (THAM), a pure proton acceptor, may be helpful to reduce ACP incidence or severity. When repeated lung lavage was used to create lung injury in piglets, administration of THAM buffered respiratory acidosis without generating carbon dioxide, and dampened the effect of arterial hypercarbia on pulmonary vasconstriction, compared to control animals which did not receive THAM[25]. Translational research would be needed to establish the same benefit in human patients at risk of ARDS-related ACP.

Further directions for clinical studies

Even though risk profiling of ARDS patients for ACP and bedside echocardiography are readily available, continuous monitoring for ACP can now only be achieved with single-use transesophageal echocardiography probes. It is unlikely that the latter can be justified for all patients with ARDS, and therefore, an optimal frequency and duration of routine bedside echocardiography screening for ARDS-related ACP needs to be defined[1]. Compared to transesophageal echocardiography, while transthoracic

echocardiography has limited sensitivity for ACP in general, studying the comparative accuracy and reliability for severe ACP would be interesting. Such comparison would also be clinically relevant given the wider availability and utilization of bedside transthoracic echocardiography compared to transesophageal echocardiography among intensivists.

Given the consistent evidence of ARDS-related ACP as an independent and modifiable risk factor for mortality from observational studies, future work should involve studies–including randomized trials if possible–to prevent the onset of ARDS-related ACP and to validate existing strategies to treat ARDS-related ACP. A promising novel therapy for ARDS-related ACP is veno-venous extracorporeal carbon dioxide removal, which corrects hypercapnia, allows low tidal volume ventilation and which appears to improve right ventricular function in a porcine model[26]. Beyond this proof-of-concept, human studies would be necessary as clinical effectiveness of extracorporeal therapy cannot be assured. For instance, among three patients with ARDS on veno-venous extracorporeal membrane oxygenation, ACP still developed. Pathophysiological mechanisms proposed included thromboembolic burden to the pulmonary vasculature, hypoxemia, acidosis, pathologic progression of ARDS, and chronic nonphysiologic flow to the right heart[27]. Finally, mechanical circulatory support devices like right ventricular assist devices and veno-arterial extracorporeal membrane oxygenation would help to unload the right ventricle[28]. Studies specific to ARDS-related ACP would be needed to delineate the appropriate use, timing and cost-effectiveness of these devices.

CONCLUSION

ARDS-related ACP is a prevalent and clinically important condition that leads to adverse hemodynamic and survival outcomes. Current evidence suggests that it is amenable to multimodal treatments including ventilator adjustment, prone positioning, fluid balance optimization and pharmacotherapy. However, more work is required to elucidate the optimal frequency and duration of routine bedside echocardiography screening for ARDS-related ACP, and to more clearly delineate the diagnostic role of transthoracic echocardiography. Prospective validation of current and novel therapies for ARDS-related ACP are awaited, especially *via* randomized controlled clinical trials.

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OPINION REVIEW

Inhaling muscle spray: A rising trend of abuse

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Abstract

Ethyl chloride was popular as an inhalant recreational drug in the 1980s. It is easily available in pharmacies as well as sold online as a topical anesthetic spray for pain relief. In recent times, its use is gaining popularity again among the youth as an inhalant drug due to its neuro-stimulatory effects. To avoid the risks associated with use of illegal drugs, and ease of availability of ethyl chloride without restrictions, there is a rising trend to use it as a "substitute" drug of abuse. In this paper, we try to highlight to the critical care and emergency physicians that majority of these cases present with predominant neurological symptoms, with occasional involvement of the cardiovascular system. The diagnosis of ethyl chloride poisoning is primarily clinical and supportive care is the mainstay of treatment, along with subsequent counseling. Ethyl chloride abuse should be considered as a differential diagnosis in young patients presenting with predominant neurological symptoms. Alongside raising public awareness, the manufacturers and retail distributors of these products have an important role to play in reducing the risk of abuse.

Key Words: Ethyl chloride; Abuse; Inhalant; Neurological; Recreational; Counselling

Core Tip: The purpose of this manuscript is to highlight to the critical care and emergency physicians regarding the rising trend of ethyl chloride spray as an inhalational drug of abuse, due to ease of availability as over-the-counter drug and its psychoactive effects. This manuscript emphasizes the need to consider ethyl chloride abuse in young patients presenting with predominant neurological symptoms. Also, raising public awareness and improving vigilance on the sale of these products will

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INTRODUCTION

Volatile substance abuse comprises of inhalation of volatile compounds such as glue, paints, sprays and fuels due to their psychoactive effects. Ethyl chloride was popular as an inhalant recreational drug in the 1980s. It is a colorless, flammable hydrocarbon with a strong ether-like odour[1]. It was originally used as a general anesthetic, but its use was subsequently discontinued considering its safety profile, unpleasant recovery phase and availability of newer superior agents[2]. It is used for cryoanalgesia to drain small abscesses and as a solvent and refrigerant in chemical industries. It is easily available in pharmacies as an over- the-counter topical anesthetic spray and also sold online for pain-relief from muscle spasm in athletes and also during tattoo and piercings. It rapidly evaporates due to its boiling point of 12 °C, and hence produces a cold sensation and feeling of pain relief[3]. In recent times, its use is gaining popularity again among the youth as an inhalant drug to "feel high".

DISCUSSION

Inhalants comprise of a broad range of volatile substances (Table 1). To avoid the risks associated with use of illegal drugs, and ease of availability of ethyl chloride without restrictions, there is a rising trend to use it as a "substitute" drug of abuse. The risk factors for potential abuse include male gender, low socio-economic status and middle-class youth.

People who "sniff" ethyl chloride inhale it directly from the container. During "huffing", it is sprayed over the clothes or on a towel, and the evaporating fumes are then inhaled through the nose and the mouth. Chronic abusers use "bagging" as they can inhale higher concentration of the chemical.

The pathophysiology of ethyl chloride neurotoxicity is secondary to its rapid absorption in the blood from the lungs. Also, being lipophilic, it gets concentrated in the brain with subsequent development of a range of central nervous system effects. Acute solvent exposure appears to produce N-methyl-D-aspartate receptor inhibition, as well as it increases α1β1 Gamma aminobutyric acid, α1 glycine and 5-hydroxy-tryptamine receptor activation[4].

They produce dose-related continuum of effects, ranging from motor excitation at low concentrations to central nervous system depression, seizures, coma and even cardiopulmonary arrest at higher concentrations. They can also sensitize the heart muscles and some people will develop fatal arrhythmias. The exact pharmacokinetics of ethyl chloride in humans is not known, but animal model studies suggest that its metabolism involves oxidation by cytochrome P-450 and NADPH- and O_2 dependant reaction to produce acetaldehyde. It may also undergo conjugation with glutathione *via* glutathione-*S*-transferase[1].

Majority of the cases have mild, short-lasting effects. The systemic effects of ethyl chloride are described in Table 2. Acute brief inhalation can result in feeling of drunkenness, euphoria, and hallucinations. Other acute effects include dizziness, confusion, impaired short-term memory, ataxia, lack of muscle coordination and even loss of consciousness[1,3]. Inhaling high dose of ethyl chloride has depressant effect on central nervous system. It is also used for chemsex[5]. Neurological symptoms secondary to chronic abuse result in ataxia, tremors, speech difficulties, decreased reflexes, hallucinations, involuntary eye movement/nystagmus and deranged liver function. It can also affect the cardiovascular system, predisposing the patient to various cardiac arrhythmias, like ventricular ectopy, atrio-ventricular conduction defects, brady-arrhythmias, and occasionally ventricular fibrillation or asystole leading to sudden cardiac death[6]. Data regarding severe toxicity secondary to ethyl chloride

Table 1 List of common volatile substances used as inhalants

Classification	Inhalant compounds
Aerosols	Spray paints; hairspray; deodorant; vegetable oil spray; fabric protector spray; shoe-shine spray
Organic solvents	Glue; paint thinner; gasoline; nail polish remover; dry-cleaning fluid; correction fluid
Gases	Anesthetics (*e.g.*, ether, chloroform, halothane, ethyl chloride, nitrous oxide); propane; butane (cigarette lighter fluid); refrigerants; whipped cream dispensers
Nitrites	Amyl nitrite; video head cleaner; room odorizer; leather cleaner; liquid aroma

Table 2 Systemic side-effects of ethyl chloride abuse

System involved	Effects
Neurological	Euphoria; visual hallucinations; confusion; dizziness; impaired short-term memory; ataxia; nystagmus; dysarthria; lack of muscle coordination; grand mal seizure; unconsciousness
Respiratory	Respiratory paralysis (rare)
Cardiovascular	Cardiac depression; sensitization to endogenous and exogenous epinephrine; ventricular tachycardia; ventricular fibrillation; asystole
Gastrointestinal	Abdominal cramps; nausea/vomiting
Hematological	Cyanosis
Hepatic	Hepatomegaly; transient deranged liver function test; elevated serum alanine aminotransferase
Ocular	Mild eye irritation
Dermal	Contact dermatitis (rare)

inhalation is rare, and few deaths have been reported till date. A patient developed cardiac arrhythmia along with neurological effects, subsequently leading to respiratory arrest[7].

The diagnosis of ethyl chloride poisoning is primarily clinical, based on history, including a detailed social history, and physical examination. There are no definite investigations to check the level of ethyl chloride in blood or urine. Supportive care is the mainstay of management. The initial management entails removal of the patient from ongoing exposure, which includes removing patient's clothes as they usually spray it on their own clothes for inhalation. Patients need to be monitored for cardiac arrhythmias and neurological depression. Usually the neurological effects are transient, and resolve quickly. There are no known antidotes or any specific means to enhance elimination. Most neurological symptoms completely resolve in about a week following cessation of its inhalation[8]. Physicians should consider concomitant ingestion of alcohol or other drugs of abuse in patients who do not regain consciousness or recover rapidly in the emergency department[9]. Few patients require supplemental oxygen, and those who are unconscious and/or develop respiratory depression will require advanced airway and ventilatory support. Patients should also be specifically evaluated for traumatic injuries, which otherwise can be overlooked[6].

Once the patient is medically stable, he/she must be referred for counseling and an outpatient psychiatric evaluation, as these patients are typically young, and frequently suffer from underlying social or behavioral problems.

Also, the manufacturers and retail distributors of these products have an important role to play in reducing the risk of abuse. Similar to health hazard labelling on cigarette packets, these aerosol sprays as well as other volatile substances should have a warning logo to raise awareness among the public. Pharmacies as well as online retailers can play their part by allowing purchase of a single ethyl chloride canister. Staff at pharmacies should be trained to identify customers who look suspicious of misusing this product.

CONCLUSION

Propensity for addiction and adverse effects of ethyl chloride are underappreciated

due to lack of awareness in public and healthcare professionals. We wish to raise awareness among the physicians regarding its rising trend of abuse as an inhalation agent, due to ease of availability and neuro-stimulatory effects. Ethyl chloride abuse should be considered as a differential diagnosis in young patients presenting with predominant neurological symptoms. Raising public awareness as well as improving vigilance on the sale of these products will help in reducing the burden of abuse.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Frequency of hepatic steatosis and its association with the pneumonia severity score on chest computed tomography in adult COVID-19 patients

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Abstract

BACKGROUND

Recent studies of the coronavirus disease 2019 (COVID-19) demonstrated that obesity is significantly associated with increased disease severity, clinical outcome, and mortality. The association between hepatic steatosis, which frequently accompanies obesity, and the pneumonia severity score (PSS) evaluated on computed tomography (CT), and the prevalence of steatosis in patients with COVID-19 remains to be elucidated.

AIM

To assess the frequency of hepatic steatosis in the chest CT of COVID-19 patients and its association with the PSS.

METHODS

The chest CT images of 485 patients who were admitted to the emergency department with suspected COVID-19 were retrospectively evaluated. The patients were divided into two groups as COVID-19-positive [CT- and reverse transcriptase-polymerase chain reaction (RT-PCR)-positive] and controls (CT- and RT-PCR-negative). The CT images of both groups were evaluated for PSS as the ratio of the volume of involved lung parenchyma to the total lung volume. Hepatic steatosis was defined as a liver attenuation value of ≤ 40 Hounsfield units (HU).

RESULTS

Of the 485 patients, 56.5% (n = 274) were defined as the COVID-19-positive group

study was retrospective in nature and no specific intervention is described in this article. The medical research center waived informed consent for this study.

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and 43.5% (n = 211) as the control group. The average age of the COVID-19-positive group was significantly higher than that of the control group (50.9 ± 10.9 years *vs* 40.4 ± 12.3 years, P < 0.001). The frequency of hepatic steatosis in the positive group was significantly higher compared with the control group (40.9% *vs* 19.4%, P < 0.001). The average hepatic attenuation values were significantly lower in the positive group compared with the control group (45.7 ± 11.4 HU *vs* 53.9 ± 15.9 HU, P < 0.001). Logistic regression analysis showed that after adjusting for age, hypertension, diabetes mellitus, overweight, and obesity there was almost a 2.2 times greater odds of hepatic steatosis in the COVID-19-positive group than in the controls (odds ratio 2.187; 95% confidence interval: 1.336-3.580, P < 0.001).

CONCLUSION

The prevalence of hepatic steatosis was significantly higher in COVID-19 patients compared with controls after adjustment for age and comorbidities. This finding can be easily assessed on chest CT images.

Key Words: Liver; Steatosis; COVID-19; Computed tomography; Pneumonia severity score

Core Tip: We evaluated the frequency of hepatic steatosis in the computed tomography (CT) of coronavirus disease 2019 (COVID-19) patients and its association with the pneumonia severity score (PSS). We retrospective evaluated the CTs of 485 patients with suspected COVID-19. Regression analysis showed that after adjusting for age and comorbidities there was almost a 2.2 times greater odds of hepatic steatosis in the COVID-19-positive group than in controls (odds ratio 2.187; 95% confidence interval: 1.336-3.580, P < 0.001). There was a positive correlation between hepatic steatosis and PSS. The study revealed a significantly higher prevalence of hepatic steatosis on CT in COVID-19 patients compared with controls.

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INTRODUCTION

An unknown infection that first appeared as a pneumonia cluster in Wuhan, China was later found to be caused by a new betacoronavirus species, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease was named coronavirus disease 2019 (COVID-19)[1,2]. The infection rapidly spread in Japan, South Korea, and Thailand. The World Health Organization (WHO) declared a Public Health Emergency of International Concern for COVID-19, evaluating its pandemic potential[3]. SARS-CoV-2, which causes severe acute respiratory syndrome, has resulted in the death of nearly two million people worldwide within the last year, and continues to pose serious concerns[4]. Risk factors associated with severe infection and mortality in COVID-19 include hypertension, severe obesity, chronic obstructive pulmonary disease, asthma, diabetes, cardiovascular disease, chronic kidney and liver disease, male gender, and advanced age[5,6]. Obesity has also been shown to be associated with progression to severe pneumonia associated with SARS-CoV-2 infection, need for hospitalization and mechanical ventilation because of acute respiratory failure, diffuse coagulopathy, and increased mortality risk[7]. In fact, morbid obesity has been identified as one of the most important risk factors in young adults with COVID-19[8]. Obesity is considered to play an important role in the pathogenesis of COVID-19 as it increases vulnerability to infections and adverse effects of the chronic inflammation of adipose tissue on the immune system resulting from metabolic dysfunction[9]. Nonalcoholic fatty liver disease (NAFLD) caused by

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ongoing metabolic abnormalities appears to be a potential risk factor for developing SARS-CoV-2 infection and its associated complications[10]. NAFLD is considered a hepatic manifestation of metabolic syndrome, including obesity, diabetes, dyslipidemia, and insulin resistance. The risk of severe COVID-19 can thus also be attributed to impaired liver function as a result of NAFLD[10]. In this study, we aimed to investigate the possible relationship between hepatic steatosis and COVID-19 infection severity based on computed tomography (CT) to evaluate liver attenuation, which is a non-invasive approach that can be used to identify the presence of hepatic steatosis during pulmonary CT examinations without any additional procedures.

MATERIALS AND METHODS

This retrospective study was approved by the Clinical Research Ethics Committee of Harran University (date: 07.12.2020 and session: 20). Informed consent was waived given the retrospective nature and characteristics of the study.

Study population

Between September 1, 2020 and October 1, 2020, 1216 patients who were admitted to the emergency department of our hospital with the suspicion and symptoms of COVID-19 and underwent both chest CT and the reverse transcriptase-polymerase chain reaction (RT-PCR) test were retrospectively evaluated. Patients with motion and image artifacts (*e.g.*, due to not holding the arms overhead), those with chronic liver disease findings, and those without nonenhanced CT images, which would affect the density of the liver, were excluded from the study.

Patients with a positive RT-PCR test and involvement compatible with COVID-19 on CT following the proposed reporting criteria for CT findings related to COVID-19 by the Radiological Society of North America[11] were included in the COVID-19-positive group. Those who were negative for the RT-PCR test and had no lung lesions on CT were included in the control group. To avoid possible false negative and false positive results associated with the PCR test, we used both CT and RT-PCR results when creating the control and COVID-19-positive groups. We also checked all chest CT images of the patients, as there may have been early false negative RT-PCR results. Those with CT findings that were typical, atypical, or indeterminate were excluded, and the remaining patients were considered ''negative''. According to these criteria, 62 patients were excluded from the control group. As a result, the study included a total of 485 consecutive presentations, of which 274 were COVID-19-positive (chest CT- and RT-PCR-positive) and 211 were COVID-19-negative controls (chest CT- and RT-PCR-negative). The flow diagram of the study population selection is shown in Figure 1.

CT image acquisition

The chest CT scan was performed in all patients with a 16-detector multi-slice CT device (Siemens Healthineers; Erlangen, Germany). The CT room and scanner were sanitized using standard cleaning procedures and approved disinfectants after each procedure. CT images were obtained at end inspiration during a single breath-hold without using intravenous contrast material. The main scanning parameters were: Tube voltage, 120 kV; tube current-time product, 50-350 mAs; pitch, 1.25; matrix, 512 × 512; slice thickness, 10 mm; and reconstructed slice thickness, 0.625-1.250 mm.

CT evaluation

Several methods have been described in the literature to determine hepatic steatosis on noncontrast CT, including a liver attenuation value of 10 Hounsfield units (HU) that was less than the spleen attenuation, absolute liver attenuation of < 40 HU, and a liver-to-spleen attenuation ratio of < 1. For steatosis, unenhanced CT has a sensitivity ranging from 43% to 95% and a specificity of 90%-100%[12,13]. In this study, two radiologists reviewed the CT images and obtained the HU attenuation values of the liver using circular regions of interest with an area of approximately 10 cm^2. The measurements were made at the level of the porta hepatis, avoiding the right hepatic lobe (segments 6 and 7), as well as vessels, calcifications, and biliary structures when possible (Figure 2). The chest CT images were evaluated by two thoracic radiologists with 8 and 9 yr of experience. They agreed on the results of each measurement and were blinded to the patient information. To prevent bias, the CT images were evaluated for steatosis in the abdominal window before the result of the RT-PCR test was known. Then, the lung window, with a center of −500 HU and a width of 1500 HU was examined for COVID-19 involvement. The RT-PCR test results were recorded

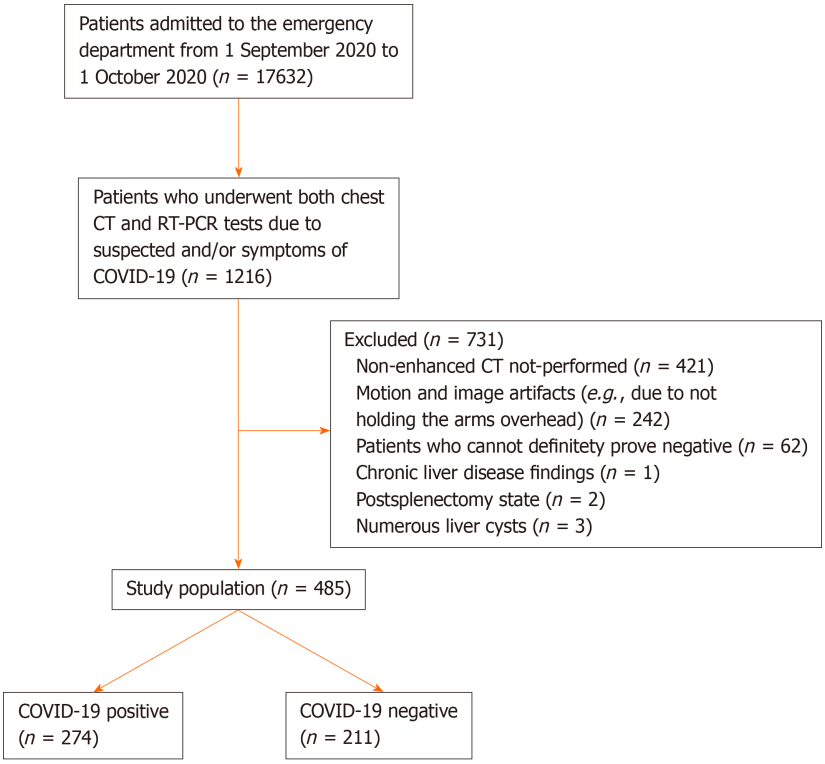

Figure 1 Flow diagram of the study population. COVID-19: Coronavirus disease; 2019; CT: Computed tomography; RT-PCR: Reverse transcription-polymerase chain reaction.

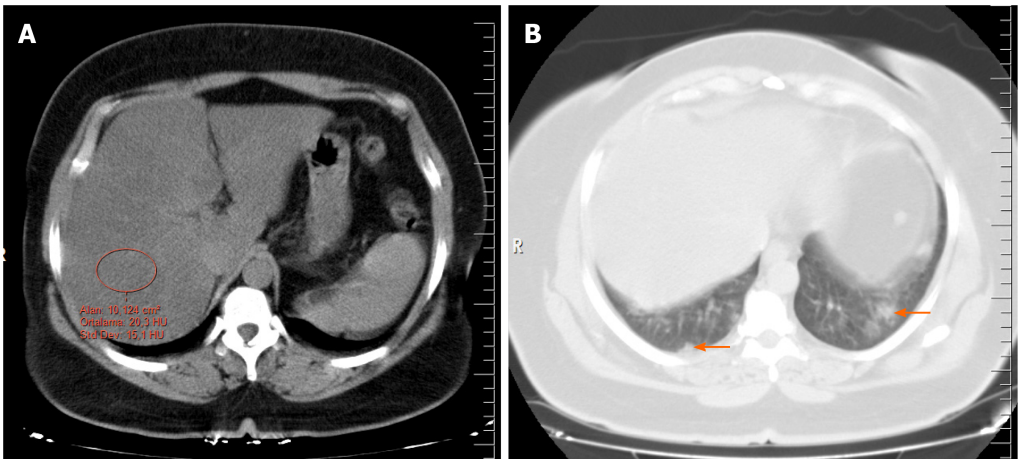

Figure 2 Noncontrast computed tomography of a patient with coronavirus disease 2019 accompanied by hepatic steatosis. A: The abdominal window shows the determination of the attenuation value with the measurement of a single region of interest (an area of approximately 10 cm^2) from the right liver lobe (segment 7); B: Lung window demonstrating lesions (orange arrows) compatible with coronavirus disease 2019.

after all the CT images were evaluated.

In this study, the definition of hepatic steatosis was accepted as a liver attenuation value of < 40 HU. Spleen attenuation values were not measured as the detection of steatosis by comparing the attenuation of the liver and spleen is more complex, requires more effort and time, and does not contribute to the diagnosis. All measurements were performed from a single section using the same method, which is supported by previous data showing that fat deposition in the liver is relatively homogeneous and most of the variation in the measurement of attenuation in that organ can be captured by measuring it in just one slice[14].

The COVID-19 pneumonia severity score (PSS), a semiquantitative method employed in previous studies, was used to measure the severity of lesions on chest CT[15,16]. First, the scope of the lesions in each lobe was estimated, and a score of 0 (none), 1 (affecting less than 5% of the lobe), 2 (affecting 5%-25% of the lobe), 3

(affecting 26%-49% of the lobe), 4 (affecting 50%-75% of the lobe), or 5 (affecting more than 75% of the lobe) was assigned. Second, the CT score was obtained by adding up the scores of the five lobes. For each patient, the CT score was in the range of 0 to 25.

Statistical analysis

Statistical analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, United States). Variables were divided into two groups, categorical and continuous. Frequency (percentage) values were used to report categorical variables, which were compared using the χ^2 test. means ± SD were used to compare continuous variables. The Kolmogorov-Smirnov test was used to determine whether continuous data were normally distributed. Normally distributed continuous variables were compared using Student's *t*-test, and continuous variables without normal distribution were compared using the Mann-Whitney *U*-test. Statistical significance was defined as a P value of < 0.05 for all comparisons. Binominal logistic regression analysis was performed with significant variables. Spearman's correlation was used to evaluate the relationships between continuous variables.

RESULTS

Of the 485 participants included in the study, 56.5% (n = 274) were included in the COVID-19-positive group and 43.5% (n = 211) in the control group. There was no significant difference between the COVID-19-positive and control groups in gender distribution (52.6% male, 47.4% female in the COVID-19-positive group and 53.6% male, 46.4% female in the control group; P = 0.450). The average age of the COVID-19-positive group was significantly higher than that of the control group (50.9 ± 10.9 years *vs* 40.4 ± 12.3 years, P < 0.001). The frequency of accompanying hepatic steatosis in the COVID-19-positive group was significantly higher compared with the control group (40.9% *vs* 19.4%, P < 0.001). The average hepatic attenuation value was significantly lower in the COVID-19-positive group compared with the control group (45.7 ± 11.4 HU *vs* 53.9 ± 15.9 HU, P < 0.001). The average PSS value of the COVID-19-positive group was 7.5 ± 3.4 (range: 2-18). The numbers of patients with obesity, overweight, diabetes mellitus, and hypertension were significantly higher in the COVID-19-positive group compared than in the control group (P = 0.001, P < 0.001, P = 0.003, and P < 0.001 respectively; Table 1).

Logistic regression analysis (Table 2) showed that after adjusting for age, hypertension, diabetes mellitus, overweight, and obesity there odds of hepatic steatosis was nearly 2.2 times greater in the COVID-19 positive group compared with the controls [odds ratio (OR) 2.187; 95% confidence interval (CI): 1.336-3.580, P < 0.001].

The characteristics of COVID-19 patients with and without the presence of hepatic steatosis are shown in Table 3. PSS was significantly higher in COVID-19 patients with hepatic steatosis than it was in those without steatosis (8.6 ± 3.5 *vs* 6.8 ± 3.2, P < 0.001). Similarly, obesity (25.0% *vs* 10.5%, P = 0.001), overweight (61.6% *vs* 40.6%, P < 0.001) and alcohol usage (3.6% *vs* 0%, P = 0.015) were significantly higher in those with hepatic steatosis.

The results of the correlation analyses are shown in Table 4. There was a weakly negative correlation between the hepatic attenuation value and PSS (r = −0.305, P < 0.001; Figure 3). There was a weakly positive correlation between PSS and age (r = 0.329, P < 0.001; Figure 4), and a weakly negative correlation was found between hepatic attenuation and age (r = −0.242, P < 0.001; Figure 5).

DISCUSSION

Following studies revealing the relationship between obesity and COVID-19[5,7], researchers focused on more specific issues related to metabolic disorders. A study suggested a possible association between hepatic steatosis and COVID-19 infection and showed that the frequency of this liver disorder was increased in COVID-19-positive patients[9]. That study, conducted in Brazil, included 316 patients (204 RT-PCR-positive; 112 RT-PCR-negative and chest CT-negative) who were evaluated retrospectively, the frequency of hepatic steatosis was found to be higher in the RT-PCR-positive group compared to the control group (31.9% *vs* 7.1%, P < 0.001)[9]. In this study, the CT results of 485 people (274 RT-PCR- and CT-positive and 211 RT-

Table 1 Comparison of patient variables in the coronavirus disease 2019-positive and control groups

		COVID-19$^+$, *n* = 274 (56.5%)	COVID-19$^-$, *n* = 211 (43.5%)	Total, *n* = 485	*P* value
Age (yr)		50.9 ± 10.9	40.4 ± 12.3	46.4 ± 12.7	< 0.001[c]
Male gender, *n* (%)		144 (52.6)	113 (53.6)	257 (53.0)	0.450
Hepatic steatosis, *n* (%)	Presence	112 (40.9)	41 (19.4)	153 (31.5)	< 0.001[c]
	Absence	162 (58.1)	170 (80.6)	332 (68.5)	
Liver's attenuation (HU)		45.7 ± 11.4	53.9 ± 15.9	49.3 ± 14.2	< 0.001[c]
Comorbidities					
Obesity (BMI ≥ 30 kg/m^2)		45 (16.4)	13 (6.2)	58 (12.0)	0.001[b]
Overweight (BMI 25–29.9 kg/m^2)		153 (55.8)	55 (26.1)	208 (42.9)	< 0.001[c]
Diabetes mellitus		68 (24.8)	29 (13.7)	97 (20.0)	0.003[b]
Hypertension		107 (39.1)	37 (17.5)	144 (29.7)	< 0.001[c]
Cardiac disease		36 (13.1)	23 (10.9)	59 (12.2)	0.455
Chronic lung disease		29 (10.6)	24 (13.7)	53 (10.9)	0.896
No comorbidity[1]		136 (49.6)	129 (61.1)	265 (54.6)	0.012[a]
Smoking history		57 (20.8)	56 (26.1)	112 (23.1)	0.110
Alcohol usage		4 (1.5)	4 (1.9)	8 (1.6)	0.709

[1]Includes obesity, overweight, diabetes mellitus, hypertension, smoking history, heart and lung diseases.
[a]*P* < 0.05.
[b]*P* < 0.01.
[c]*P* < 0.001.
BMI: Body mass index; COVID-19: Coronavirus disease 2019; HU: Hounsfield unit. Data are means ± SD or *n* (%).

Table 2 Binominal logistic regression analysis of statistically significant data in univariate analysis of patients with coronavirus disease 2019

Variable	OR	95%CI	*P*-value
Age	1.074	1.052-1.097	0.002[b]
Hepatic steatosis	2.187	1.336-3.580	< 0.001[c]
Obesity (BMI ≥ 30 kg/m^2)	4.810	2.269-10.195	0.001[b]
Overweight (BMI 25–29.9 kg/m^2)	3.573	2.181-5.853	< 0.001[c]
Diabetes mellitus	0.396	0.213-0.736	0.003[b]
Hypertension	1.455	0.867-2.442	0.156

[b]*P* < 0.01.
[c]*P* < 0.001.
BMI: Body mass index; CI: Confidence interval; OR: Odds ratio.

PCR- and CT-negative), also found a significantly higher frequency of hepatic steatosis in the COVID-19 group than in the control group [40.9% (112 of 274 patients) *vs* 19.4% (41 of 211 patients)]. In the previous study, the COVID-19-positive group had an almost 4.7 times higher probability of steatosis (OR: 4.698) compared with the controls. In our study, the odds were approximately 2.2 higher (OR: 2.187). The difference might be related to the greater prevalence of hepatic steatosis in Turkey. Unlike the Brazilian study, we evaluated comorbidities such as obesity, overweight, diabetes mellitus, and hypertension. The results of our study revealed that the incidence of hepatic steatosis remained increased in COVID-19 patients even after adjustment for age and comorbidities. In addition, in our study, the rates of hepatic steatosis in both the COVID-19 and control groups were higher than those of the Brazilian study, which may be related to nutritional, genetic or other regional differences. The prevalence of

Table 3 Comparison of patient variables in those with coronavirus disease 2019 and with or without hepatic steatosis

Variable	Steatosis$^+$, *n* = 112	Steatosis$^-$, *n* = 162	Total, *n* = 284	*P* value
Age (yr)	51.2 ± 9.2	50.7 ± 10.1	50.9 ± 10.9	0.321
Male gender, *n* (%)	65 (58.0)	79 (48.8)	144 (52.6)	0.131
Liver's attenuation, Hounsfield unit	34.2 ± 4.8	53.6 ± 7.2	45.7 ± 11.5	< 0.001[c]
Pneumonia severity score	8.6 ± 3.5	6.8 ± 3.2	7.5 ± 3.4	< 0.001[c]
Comorbidities				
Obesity (BMI ≥ 30 kg/m^2)	28 (25.0)	17 (10.5)	45 (16.4)	0.001[b]
Overweight (BMI 25-29.9 kg/m^2)	69 (61.6)	65 (40.6)	134 (48.9)	< 0.001[c]
Diabetes mellitus	33 (29.5)	35 (21.6)	68 (24.8)	0.139
Hypertension	42 (37.5)	65 (40.1)	107 (39.1)	0.662
Cardiac disease	13 (11.6)	23 (14.2)	36 (13.1)	0.533
Chronic lung disease	12 (10.7)	18 (11.1)	30 (10.9)	0.918
No comorbidity[1]	54 (48.2)	82 (50.6)	136 (49.6)	0.696
Smoking history	18 (16.1)	39 (24.1)	57 (20.8)	0.109
Alcohol usage	4 (3.6)	0 (0)	4 (1.5)	0.015[a]

[1]Includes obesity, overweight, diabetes mellitus, hypertension, smoking history, and heart and lung diseases.
[a]*P* < 0.05.
[b]*P* < 0.01.
[c]*P* < 0.001.
BMI: Body mass index. Data are means ± SD or *n* (%)

Table 4 Correlation between hepatic attenuation value, coronavirus disease 2019 pneumonia severity score, and age

		Liver attenuation value	Pneumonia severity score	Age
Liver attenuation value	*r*	1	−0.305[1]	0.242[1]
	P value		< 0.001[c]	< 0.001[c]
Pneumonia severity score	*r*	−0.305[1]	1	0.329[1]
	P value	< 0.001[c]		< 0.001[c]
Age	*r*	−0.242[1]	0.329[1]	1
	P value	< 0.001[c]	< 0.001[c]	

[1]Correlation is significant at the 0.01 level (2-tailed).
[c]*P* < 0.001.

NAFLD worldwide is estimated to be approximately 25%[17]. In a 2016 study conducted in Brazil in an age group similar to our study, a total of 800 people (561 women and 239 men) were examined, and the prevalence of steatosis was found to be 29.1% and higher in men than in women[18]. According to 2016 data published by WHO, Turkey is the country with the highest obesity prevalence (32.1%) in Europe[17]. A comprehensive review published in 2019, included studies reporting that the NAFLD prevalence in Turkey was between 47.9% and 54.4% in age groups similar to those in our study[17]. In a previous study conducted in our hospital population, it was found that men were most affected by NAFLD in the third and fourth decades of age[19]. Despite early studies reporting a higher risk of NAFLD in women, a large body of evidence now shows that the prevalence of NAFLD is higher in men than women, with gender-specific differences by age[20].

A systematic literature review of the association between NAFLD and severe COVID-19 regardless of obesity, which is considered the most important risk factor for both NAFLD and COVID-19, concluded that NAFLD might be a determining factor for severe COVID-19 even after adjusting for the presence of obesity (OR: 2.358, *P* <

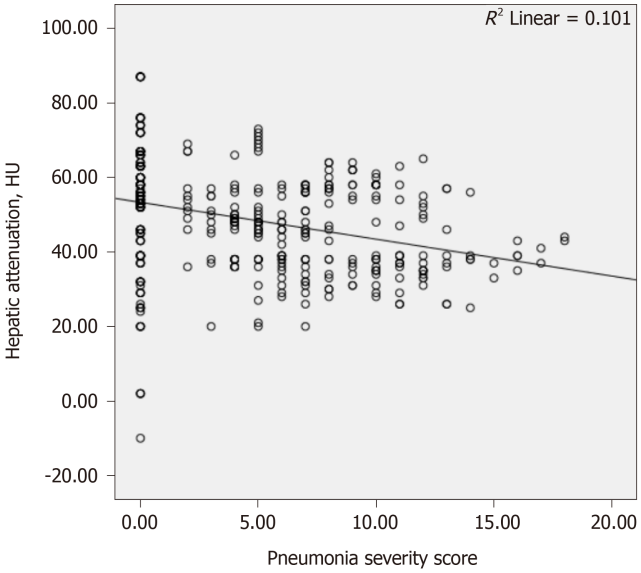

Figure 3 Scatter graph showing a negative correlation between the hepatic attenuation value and pneumonia severity score measured on computed tomography (Spearman's correlation coefficient, $r = -0.357$ and $P < 0.001$). The mean pneumonia severity score of the coronavirus disease 2019-positive group was 7.6 (4.2-11; minimum 2, maximum 18). HU: Hounsfield unit.

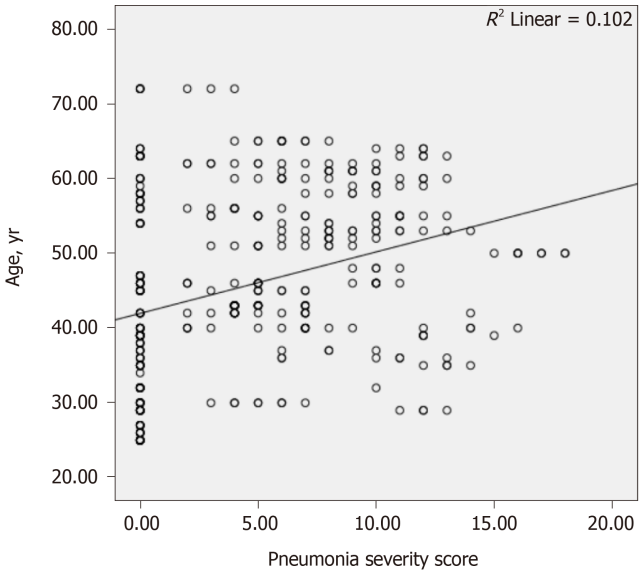

Figure 4 Scatter graph showing a positive correlation between age and the pneumonia severity score measured on computed tomography (Spearman's correlation coefficient, ($r = 0.371$ and $P < 0.001$).

0.001)[5]. However, a direct comparison and correlation analysis between hepatic steatosis and disease severity has not previously been published. In patients with COVID-19 requiring intensive care, new parameters such as invasive mechanical ventilation, nosocomial infections, acute respiratory distress syndrome, coagulopathy, and acute kidney injury are added to the main comorbidities, including male gender, advanced age, hypertension, coronary heart disease, chronic obstructive pulmonary disease, obesity, and chronic kidney disease, which further complicates the investigation of factors affecting disease progression[7,21,22]. In this study, we examined the relationship between PSS and hepatic steatosis in patients with symptomatic infection. We found that the PSS was significantly increased in COVID-19 patients with hepatic steatosis (8.6 ± 3.5 *vs* 6.8 ± 3.2, $P < 0.001$). That may indicate that comorbidities may accompany in patients with severe pneumonia. In addition, we showed a moderate correlation between hepatic steatosis with age and PSS. We consider that our results are the first data to directly demonstrate that relationship.

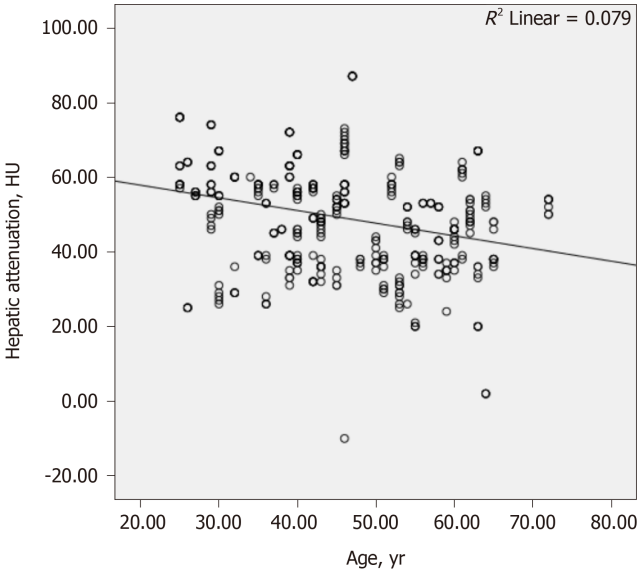

Figure 5 Scatter graph showing a negative correlation between the hepatic attenuation value and age (Spearman's correlation coefficient, $r = -0.303$ and $P < 0.001$). HU: Hounsfield unit.

According to the Centers for Disease Control and Prevention, having a chronic liver disease such as alcohol-related liver disease, NAFLD, and especially cirrhosis, can increase the risk of severe COVID-19[23]. In a retrospective study conducted in China including 202 COVID-19 patients, the prevalence of metabolic associated fatty liver disease (MAFLD) was 37.6%, and the risk of disease progression was increased in that group[24]. Various articles attempting to explain that possible relationship emphasize that MAFLD (defined as NAFLD in some articles) is a liver symptom of metabolic syndrome, is associated with chronic inflammation, and contributes to the interaction in the cytokine storm described in COVID-19 patients, causing disease progression, complications, and fatal consequences[9,10,24]. In support of those studies, we found that the radiological severity of pneumonia was higher in COVID-19 patients with steatosis that without steatosis. Our study, which investigated the relationship between hepatic steatosis and the severity of COVID-19 disease in patients according to tomographic criteria, provides valuable data to guide further study.

This study had several limitations. It was conducted retrospectively in a single tertiary university hospital, and all patients were from a single geographic region. The prevalence of hepatic steatosis may differ in different populations and regions. A strength of our study, is that to the best of our knowledge, it is the first to investigate the relationship between CT-assessed steatosis and PSS in adult COVID-19 patients.

CONCLUSION

The current study revealed a significantly higher prevalence of hepatic steatosis on CT in COVID-19 patients compared with controls after adjustment for age and comorbidities. In addition, it found a correlation between the severity of pneumonia measured on CT and liver density. Therefore, liver density measurement can be considered as a new parameter in the risk analysis of infected patients. This evaluation can be quickly and easily performed using already available CT data without the need for an additional examination. Further study is needed to confirm the presence of such an association after considering and minimizing multiple variables that can affect hepatic steatosis.

ARTICLE HIGHLIGHTS

Research background

Recent studies on coronavirus disease 2019 (COVID-19) demonstrated that obesity is significantly associated with increased disease severity, clinical outcome, and

mortality.

Research motivation

The association between hepatic steatosis, which frequently accompanies obesity, the pneumonia severity score (PSS) evaluated by computed tomography (CT), and the prevalence of steatosis in patients with COVID-19 remains to be elucidated.

Research objectives

The study objective was to assess the frequency of hepatic steatosis in the chest CT of COVID-19 patients and its association with the PSS.

Research methods

This was a retrospective study evaluating the CT of COVID-19 positive and negative patients in a tertiary hospital.

Research results

Of the 485 patients, 274 (56.5%) were defined as the COVID-19-positive group and 211 (43.5%) as the control group. The frequency of hepatic steatosis was significantly higher in the positive group than in the control group (40.9% *vs* 19.4%, $P < 0.001$). The average hepatic attenuation values were significantly lower in the positive group than in the control group (45.7 ± 11.4 HU *vs* 53.9 ± 15.9 HU, $P < 0.001$). Logistic regression analysis showed that after adjusting for age, hypertension, diabetes mellitus, overweight, and obesity there was almost a 2.2 times greater odds of hepatic steatosis in the COVID-19-positive group than in the controls (odds ratio 2.187; 95% confidence interval: 1.336-3.580, $P < 0.001$).

Research conclusions

The current study revealed a significantly higher prevalence of hepatic steatosis on CT in COVID-19 patients compared with controls after adjusting for age and comorbidities.

Research perspectives

Liver density and PSS can be easily examined on CT images of COVID-19 patients and the relationship between tomographic severity and steatosis can be evaluated.

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LETTER TO THE EDITOR

Patient–ventilator asynchrony in Saudi Arabia: Where we stand?

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Abstract

Patient–ventilator asynchrony in Saudi Arabia practices is common, and more emphasis on how to mitigate such a clinical problem is needed. This letter is intended to shed the light on the current national evidence of patient–ventilator asynchrony and how to step ahead for better patients' ventilation management.

Key Words: Ventilator; Asynchrony; Critical care; Saudi Arabia; Double triggering; Respiratory

Core Tip: Our Saudi national findings have questioned the effectiveness of the current education and training approaches on mechanical ventilation subject and its related management such as patient-ventilator asynchrony detection. Therefore, "keep calm and carry on strategy" is no longer effective; hence keep research with training and carry on strategy is indeed what we need to improve patient's outcomes.

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TO THE EDITOR

In acute and chronically ill patients, mechanical ventilation is used to improve oxygenation and reduce the load on respiratory muscles, ultimately preventing acute respiratory failure. The optimum interaction between the patient and the ventilator

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can help avoid unnecessary sedation, anxiety, discomfort, ventilator fighting events, diaphragm dysfunction and disuse atrophy, potentially cognitive changes, continued ventilation support and additional pulmonary complications[1,2]. Patient-ventilator asynchrony (PVA) is described as a lack of agreement between what is delivered from the ventilator and what patient's needs, which about 25% of those patients who ventilated for more than 24 h had a high rate of PVAs throughout the ventilation support. Indeed, when the incidence of PVAs is greater than 10%, the time interval of invasive ventilation support and the chance of developing tracheostomy are significantly increased[3].

The most common asynchronies in mechanical ventilation process are infective triggering, followed by double triggering, with slight variations between day and night[3,4]. For successful management, it is important to recognise the nature and triggers of the asynchrony. Several techniques were used to identify PVAs, including measurements of electrical diaphragm movement and oesophageal pressure. Such techniques are invasive, costly and require cumbersome equipment, which reduce their daily clinical practice usage[3,5,6]. A non-invasive and accurate method—namely, waveform analysis—would more certainly be effective for identifying and minimising PVAs[3]. However, it is no wonder that most critical care practitioners fail to manage interactions between patient and ventilator and even do not recognise common forms of PVAs[6].

Our recent work badged 'Saudi' in this area has included an attempt to use ventilator waveform analysis to detect common PVAs[7]. To assess the competence of intensive care clinicians to recognise different PVAs, Alqahtani *et al*[7] used a validated assessment approach. This tool included three videotapes for the most popular PVAs, such as auto-triggering. Remarkably, in critical care settings detection of PVAs were found low, with about 25% of PVAs being unnoticed by critical care practitioners. Only 10% of the respiratory therapists, nurses and physicians correctly detected all types, while only 22% correctly found two of these asynchronies. When we investigated the impact of previous training in mechanical ventilation on detection of PVAs, there were significant findings between trained and untrained clinicians. Those who were trained on ventilator waveforms analysis detected more asynchronies compared to not trained (identified three types 19% *vs* 3%, $P < 0.001$; identified two types, 30% *vs* 16%, $P = 0$ 0.001). In accordance with the literature, the present research also established prior training as an independent factor of the proper recognition of the PVAs[6,8]. Such factor is not only required in the detection of asynchronies but also in the management of all invasive and non-invasive ventilation modalities[4,9,10]. We did not find any correlation between years of experience and PVAs recognition. It seems that people with expertise may be overconfidence to their information and in effect, discourage them from honing their skills in the detection to PVAs. Double-triggering was commonly detected among clinicians, which about 49% of the clinicians correctly identified, indicating how easy to identify it. The positive effects of female gender were also associated, which we found female gender as an independent and significant factor to better identify two or more PVAs (odd ratio 1.93; 1.07-3.49). Altogether, though, all clinicians showed a poor level of PVA detection. Such findings could be attributed to the lack of adequate training in mechanical ventilation. Adequate education and training are vital in reducing failures and in alleviating otherwise non-invasive and invasive mechanical ventilation complications[10,11]. All things considered, establishing a clinical audit at intensive care level would improve patient care and outcomes.

The clinical and research implications of our findings are crucial. They confirm that the primary and only modifiable factor to help in the proper recognition of PVAs is prior training on ventilator graphics, irrespective of expertise. This will help to advise hospital policymakers as to create PVA identification policies and provide systematic PVA management guidance. To improve the capacity to identify PVAs further, each hospital can perform more regular training and guidance on ventilator graphics for all critical care clinicians who handle patients with mechanical ventilation. In future studies, the experience and application of PVAs should be investigated before and after education and training sessions to assess the short and long-standing impact on outcomes. Our result has questioned the effectiveness of the current education and training approaches on mechanical ventilation subject and its related management such as PVAs detection. Therefore, "keep calm and carry on strategy" is no longer effective; hence keep research with training and carry on strategy is indeed what we need to improve patient's outcomes.

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AIMS AND SCOPE

The primary aim of the *World Journal of Critical Care Medicine* (*WJCCM*, *World J Crit Care Med*) is to provide scholars and readers from various fields of critical care medicine with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCCM mainly publishes articles reporting research results and findings obtained in the field of critical care medicine and covering a wide range of topics including acute kidney failure, acute respiratory distress syndrome and mechanical ventilation, application of bronchofiberscopy in critically ill patients, cardiopulmonary cerebral resuscitation, coagulant dysfunction, continuous renal replacement therapy, fluid resuscitation and tissue perfusion, hemodynamic monitoring and circulatory support, ICU management and treatment control, sedation and analgesia, severe infection, *etc*.

INDEXING/ABSTRACTING

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EDITORIAL

New Year's greeting and overview of *World Journal of Critical Care Medicine* in 2021

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Abstract

As editors of *World Journal of Critical Care Medicine* (*WJCCM*), it is our great pleasure to take this opportunity to wish all our authors, subscribers, readers, Editorial Board members, independent expert referees, and staff of the Editorial Office a Very Happy New Year. On behalf of the Editorial Team, we would like to express our gratitude to all authors who have contributed their valuable manuscripts and to the independent referees and our subscribers and readers for their continuous support, dedication, and encouragement. The excellent team effort by our editorial board members and staff of the Editorial Office allowed *WJCCM* to advance remarkably in 2020. In the future, the Baishideng Publishing Group and *WJCCM*'s editorial board will continue to increase their communication and collaboration, both internally and involving our external contributors, in order to promote our collective impact on the field of Critical Care Medicine even further.

Key Words: Acknowledgments; Editorial members; *World Journal of Critical Care Medicine*; Baishideng Publishing Group; Journal development

Core Tip: As editors of the *World Journal of Critical Care Medicine* (*WJCCM*) and in view of the achievements of this journal in 2020, we take this opportunity to wish all our authors, subscribers, readers, Editorial Board members, independent expert referees, and staff of the Editorial Office a Very Happy New Year and express our gratitude to your collective and individual contributions and support. In the future, the Baishideng Publishing Group and the *WJCCM*'s editorial board will continue to work to strengthen further communication and cooperation within the field of critical care medicine and emergency medicine, while simultaneously promoting the development

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of *WJCCM* to a new level.

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INTRODUCTION

First of all, we, on behalf of all editors of the Baishideng Publishing Group (BPG), extend our sincere gratitude to you for your contributions to the *World Journal of Critical Care Medicine* (*WJCCM*) in 2020. We wish you a Happy New Year!

In 2020, BPG routinely published 47 open-access journals, including 46 English-language journals and 1 Chinese-language journal. Our successes were accomplished through the collective dedicated efforts of BPG staff and Editorial Board Members, such as yourself. BPG's Editorial Board Members number 3136, and Peer Reviewers number 29039.

ACADEMIC INFLUENCE OF *WJCCM*

As one of the key developing journals of BPG, *WJCCM* was founded in 2012 as a high-quality, online, open-access, single-blind, peer-reviewed journal published by the Baishideng Publishing Group[1]. The journal has a total of 31 official editorial board members[2], and their country distribution is shown in Figure 1. *WJCCM* mainly publishes articles reporting research results obtained in the field of critical care medicine and covering a wide range of topics, including acute kidney failure, acute respiratory distress syndrome and mechanical ventilation, application of bronchofiberscopy in critically ill patients, cardiopulmonary cerebral resuscitation, coagulant dysfunction, continuous renal replacement therapy, fluid resuscitation and tissue perfusion, hemodynamic monitoring and circulatory support, intensive care unit management and treatment control, infection and anti-infection treatment, rational nutrition and immunomodulation in critically ill patients, sedation and analgesia, severe infection, and shock and multiple organ dysfunction syndrome. While we are celebrating *WJCCM*'s 9-year anniversary, we are very proud to share with you that since its launch, *WJCCM* has published 155 articles (Figure 2). Among these, the total cites is 1738, and the average cites per article is 11.21 (Figure 3). The current number of total visits to the *WJCCM* homepage is about 370000, of which 20.6% of those visits have been from the United States, 17.7% from Bosnia and Herzegovina, and 9.6% from China. The specific traffic data and download statistics are shown in Figure 4A and B. The *WJCCM* is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure, China Science and Technology Journal, and Superstar Journals databases[2]. BPG will be submitting an application to Clarivate Analytics in 2022, with anticipation of it being abstracted and indexed in the Science Citation Index Expanded.

In 2020, *WJCCM* received a total of 23 manuscripts from authors around the world for consideration of publication and published nine articles[3]. The distribution of published manuscripts by type is shown in Figure 5. The distribution of authors of published articles by country/territory is shown in Figure 6.

In the last month of 2020, we received 68 manuscripts for consideration for publication in 2021 following successful completion of peer-review. The specific types and number of manuscripts received are shown in Figure 7A and B. As a global academic journal in critical care medicine, our authors hail from various countries and regions, reflecting a diversified contribution to the field that is embodied within an optimized platform to promote worldwide medical research sharing and exchange.

All the good achievements that were made in the past year are inseparable from the dedication of our authors, subscribers, readers, Editorial Board members, independent expert referees, and staff of the *WJCCM*'s Editorial Office. To date, *WJCCM* has 31 official editorial board members. We hope that each *WJCCM* Editorial Board Member will continue to conduct high-quality peer reviews for *WJCCM* in 2021 and support

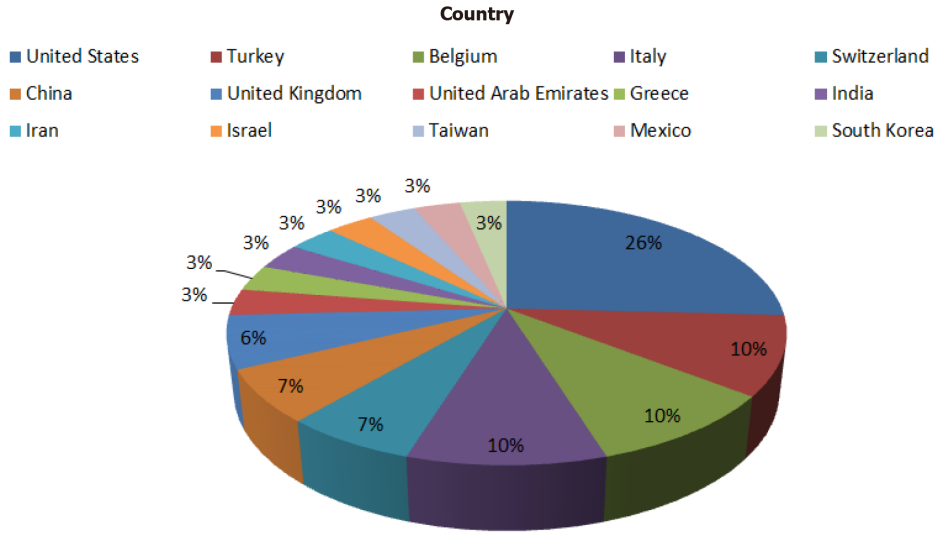

Figure 1 Distribution of Editorial Board members' countries for *World Journal of Critical Care Medicine*.

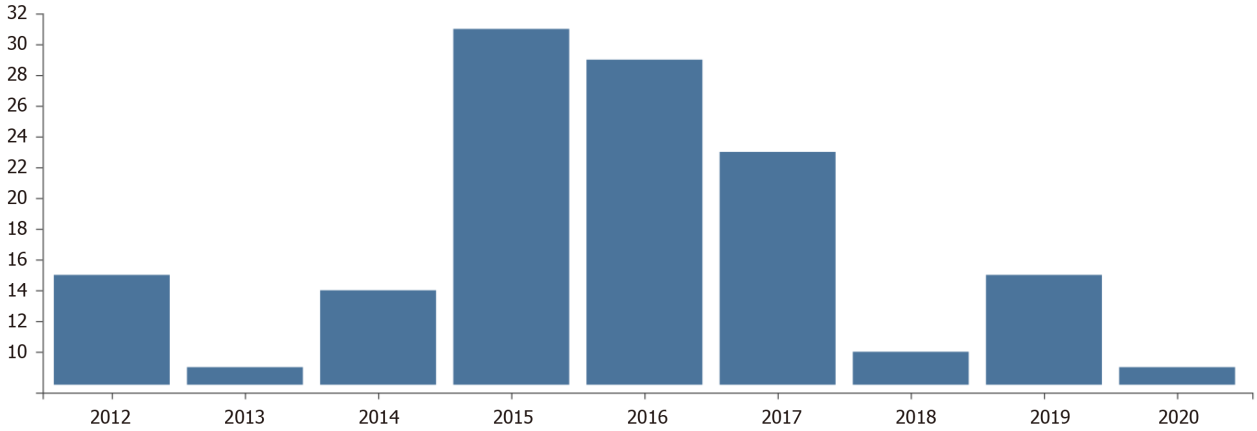

Figure 2 Analysis of the number of articles published since 2012.

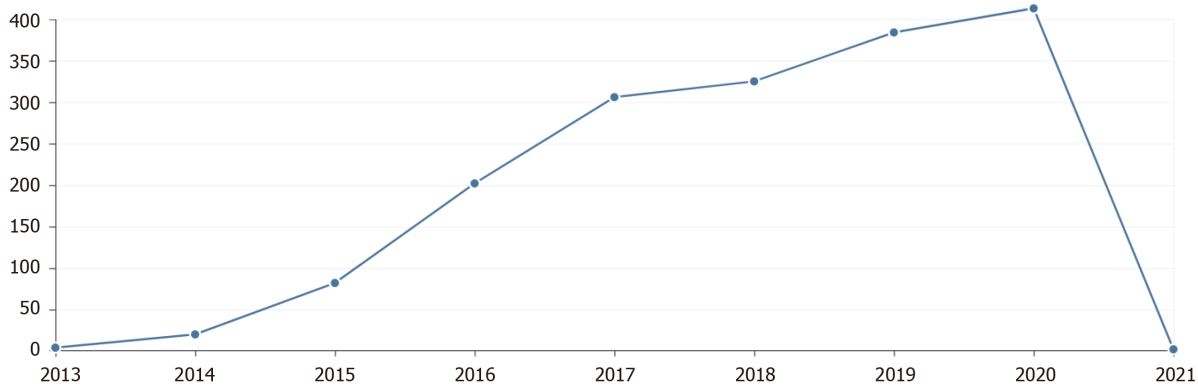

Figure 3 According to the year of publication, the citation frequency of the article.

WJCCM's mission of publishing high-quality articles that will make substantive contributions to the development of basic medical and clinical research. Meanwhile, we hope that every expert in the field of critical care medicine will contribute more articles to support our efforts towards that end. We look forward to more outstanding experts and scholars actively applying to become members of our editorial department. As always, all peer review experts are urged to review each manuscript in a timely

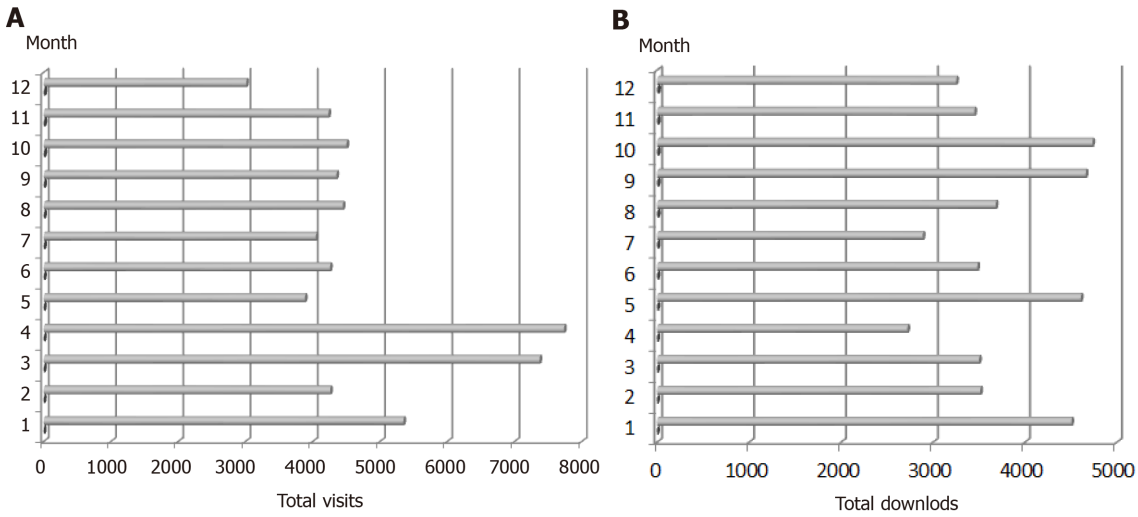

Figure 4 Number of total visits to the *World Journal of Critical Care Medicine* homepage and number of total downloads to the *World Journal of Critical Care Medicine* articles in 2020. A: Total visits; B: Total downloads.

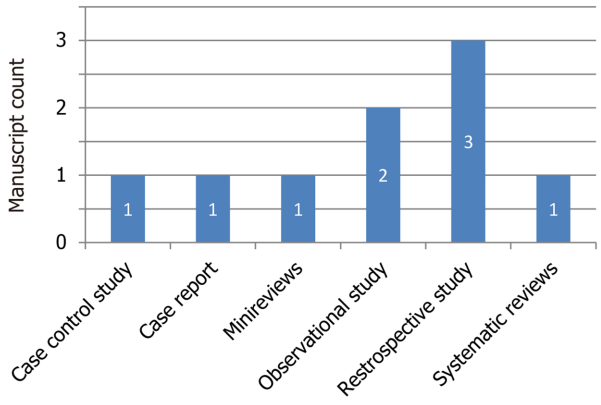

Figure 5 Column type distribution of manuscripts published in *World Journal of Critical Care Medicine* in 2020.

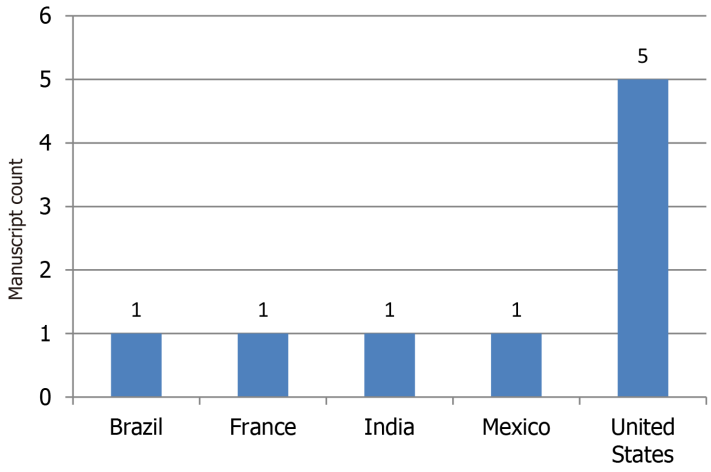

Figure 6 Distribution of authors' countries for the manuscripts published in *World Journal of Critical Care Medicine* in 2020.

manner.

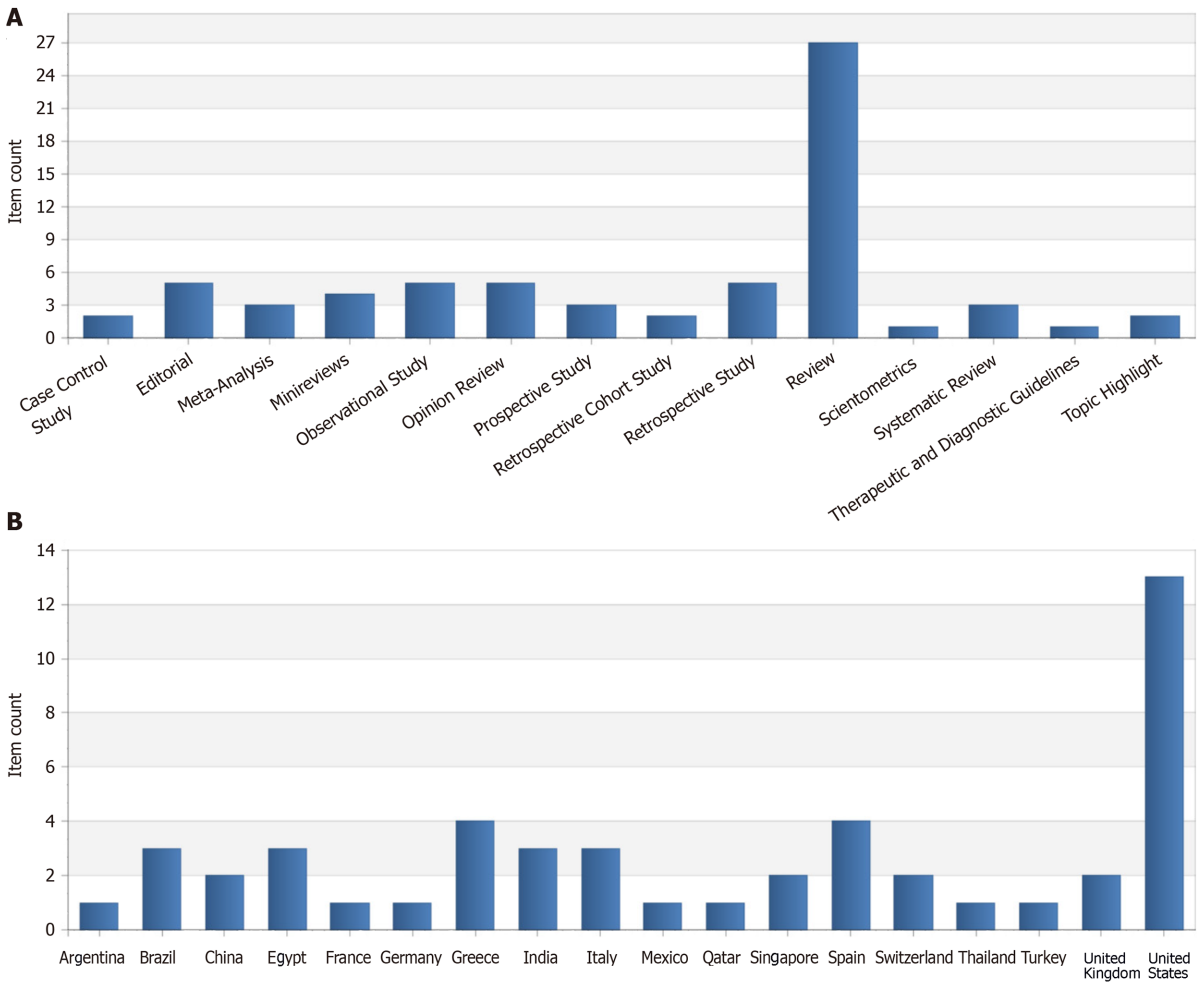

Figure 7 Bibliographic data for articles received by the *World Journal of Orthopedics* in the last month of 2020. A: Article types; B: Authors' countries.

CONCLUSION

It is with your great support that we expect to be more productive and to be able to raise the academic rank of *WJCCM* even higher in order to achieve these goals, we appreciate the continuous support and submissions from authors and the dedicated efforts and expertise by our invited reviewers, many of who also serve on our editorial board. The Editors-in-Chief will continue to strive to work with the journal's Editorial Office staff to make the manuscript submission process as simple as possible and to ensure efficient communication with the authors, providing professional support and answering their questions. Ultimately, we will remain open to any suggestions that could improve *WJCCM*'s operation and publication. Please feel free to contact us (editorialoffice@wjgnet.com) if any question on your personal submission arises or you have any suggestions.

Once again, on behalf of *WJCCM*, we wish you and your families the best for the New Year.

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2 **Baishideng Publishing Group**. Editorial Board Members. Available from: https://www.wjgnet.com/2220-3141/editorialboard.htm
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REVIEW

Sepsis: Evidence-based pathogenesis and treatment

Jay Pravda

ORCID number: Jay Pravda 0000-0001-5737-5506.

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Country/Territory of origin: United States

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Grade A (Excellent): 0

Grade B (Very good): 0

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Abstract

Sepsis can develop during the body's response to a critical illness leading to multiple organ failure, irreversible shock, and death. Sepsis has been vexing health care providers for centuries due to its insidious onset, generalized metabolic dysfunction, and lack of specific therapy. A common factor underlying sepsis is the characteristic hypermetabolic response as the body ramps up every physiological system in its fight against the underlying critical illness. A hypermetabolic response requires supraphysiological amounts of energy, which is mostly supplied *via* oxidative phosphorylation generated ATP. A by-product of oxidative phosphorylation is hydrogen peroxide (H_2O_2), a toxic, membrane-permeable oxidizing agent that is produced in far greater amounts during a hypermetabolic state. Continued production of mitochondrial H_2O_2 can overwhelm cellular reductive (antioxidant) capacity leading to a build-up within cells and eventual diffusion into the bloodstream. H_2O_2 is a metabolic poison that can inhibit enzyme systems leading to organ failure, microangiopathic dysfunction, and irreversible septic shock. The toxic effects of H_2O_2 mirror the clinical and laboratory abnormalities observed in sepsis, and toxic levels of blood H_2O_2 have been reported in patients with septic shock. This review provides evidence to support a causal role for H_2O_2 in the pathogenesis of sepsis, and an evidence-based therapeutic intervention to reduce H_2O_2 levels in the body and restore redox homeostasis, which is necessary for normal organ function and vascular responsiveness.

Key Words: Sepsis; Septic shock; Redox homeostasis; Thiosulfate; Hydrogen peroxide

Core Tip: Sepsis mortality remains unacceptably high because there is no specific treatment to prevent or reverse the multiple organ failure and refractory hypotension that develops in this condition. An evidence-based analysis suggests that impaired

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systemic redox homeostasis caused by the toxic accumulation of hydrogen peroxide has a causal role in the pathogenesis of this often fatal illness. The data imply that restoration of redox homeostasis by therapeutic reduction of hydrogen peroxide will significantly reduce the morbidity and mortality associated with sepsis. A therapeutic intervention to reduce systemic levels of hydrogen peroxide is presented.

Citation: Pravda J. Sepsis: Evidence-based pathogenesis and treatment. *World J Crit Care Med* 2021; 10(4): 66-80
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INTRODUCTION

Medicine has made fantastic strides over the past century. Our intricate knowledge of disease has been spearheaded by amazing advances in laboratory techniques that allow us to identify and instigate changes at the molecular level. This has led to an explosion of data accompanied by a detailed insight into pathological processes that perpetuate disease states leading to the identification of potential therapeutic targets, which can be exploited for new and more effective therapeutic interventions. However, while laboratory research is an extremely useful tool to obtain a pathophysiological snapshot of disease it cannot, on its own, identify the pathogenesis, and for some diseases, a creative theoretical approach is the only way to get "upstream" where novel insights may shed light on difficult clinical problems.

A prime example is sepsis, a systemic process with a high fatality rate that ultimately leads to microangiopathic dysfunction, refractory hypotension, multiple organ failure, and death. Worldwide, someone dies of sepsis every 3 s with 20% of global deaths being sepsis-related for a total of 11 million deaths annually and growing. Sepsis is thought to be a hyper-immune response to infection[1]. But in over 40% of sepsis cases there is no identifiable infectious agent, and culture positivity is not independently associated with mortality in sepsis[2-6]. These observations suggest that infection can be sufficient but is not absolutely necessary for sepsis to develop. It also suggests an endogenous process that is common to both infectious and non-infectious conditions (*i.e.*, multiple body trauma, pancreatitis, post-surgery, *etc.*), which is set in motion, ultimately leading to sepsis. Finally, the profound immunosuppression occurring during sepsis[7] suggests a non-immune contemporaneous process as the proximate causal factor in the development of the sepsis syndrome. This raises the consideration that the immune system is failing for the same reason other organs fail.

From a metabolic perspective, there is evidence of impaired mitochondrial oxygen utilization in sepsis despite normal oxygen tension[4,8-10]. This suggests a mitochondrial-derived agent capable of interfering with oxygen utilization by inhibiting substrate oxidation during the tricarboxylic acid (Krebs) cycle or oxidative phosphorylation. The close association of hyperlactatemia with adverse sepsis outcomes despite the absence of tissue hypoxia or impaired tissue oxygenation provides further evidence that implicates impairment of mitochondrial oxidative metabolism as discussed in more detail below[11,12].

The identification of mitochondrial abnormalities in sepsis focuses attention on bioenergetics and suggests that the common link between infectious and non-infectious origins of sepsis is not an immune response but a hypermetabolic state that sends mitochondrial metabolism into “overdrive” causing dysfunction of vital intramitochondrial bioenergetic processes. This reduces the problem of sepsis to the identification of a mitochondrial-generated molecule whose production is scaled up during hypermetabolism and is capable of inhibiting enzymes in the Krebs cycle and/or the electron transport chain (ETC). This is likely to be a small molecule that is normally eliminated within mitochondria since most people do not develop sepsis during a clinical hypermetabolic response.

A prime element that fulfills these theoretical requirements is hydrogen peroxide (H_2O_2), a small, cell-membrane permeable highly toxic oxidizing agent that is produced within mitochondria as a result of electron transport chain auto-oxidation [13]. H_2O_2 must be immediately eliminated to prevent cell damage and is removed by

the following series of reactions (Figure 1)[14-16].

Studies have shown that blood H_2O_2 is significantly elevated in human sepsis and septic shock with values reported up to 558 μmol/L, which is over 100 times the normal upper limit of 5 μmol/L and over ten times 50 μmol/L upper limit at which H_2O_2 becomes cytotoxic[17-19]. Certain cell populations, such as lymphocytes, undergo apoptosis at H_2O_2 exposure of less than 1 μmol/L, which can lead to significant lymphopenia and immunosuppression[19,20]. Normal intracellular H_2O_2 levels are in the picomolar range[19,21]. Thus, septic blood has over a million times greater H_2O_2 concentration than normal cells resulting in the potential for significant systemic cellular cytotoxicity which can disrupt metabolic pathways and organ function.

Other clinical abnormalities observed in sepsis such as hypotension, coagulopathy, encephalopathy, microangiopathic and cardiac dysfunction, erythrocyte rigidity, methemoglobinemia, glutathione depletion, mitochondrial damage, and lymphocyte apoptosis are also documented adverse effects of H_2O_2, all of which contribute to multiple organ failure and lymphocytopenia observed in sepsis[22-25].

But where does all this H_2O_2 come from? Although leukocytes such as neutrophils can produce large amounts of H_2O_2 during the respiratory burst[26], the profound immunosuppression[7,27-30] during advanced stages of sepsis suggests a significant non-immune contribution to the persistently elevated blood H_2O_2 levels observed in advanced sepsis and septic shock. Significant depletion of tissue glutathione in muscle, lung, and erythrocytes in addition to plasma thiol depletion (albumin cys34) suggests these tissues have become H_2O_2 generators contributing to elevated blood H_2O_2 in sepsis patients[22,31,32].

The production of mitochondrial H_2O_2 depends upon the rate of electron transfer through the ETC. The higher the electron transfer rate the greater the production of H_2O_2. Studies in isolated mitochondria have shown an exponential increase in reactive oxygen species (*i.e.*, H_2O_2) at strongly polarized levels of mitochondrial membrane potential[33], which can occur in hypermetabolic critically ill patients. Other studies in mice have shown that mitochondrial H_2O_2 will increase up to 15x the normal rate during state-3 (maximal) respiration[34]. The clinical correlate of state-3 respiration is a hypermetabolic state, which is characterized by tachycardia, tachypnea, leukocytosis, high fever, and significantly enhanced protein biosynthesis. These are the cardinal elements that define the systemic inflammatory response syndrome (SIRS), which accompanies sepsis. This implies that a clinical hypermetabolic response is accompanied by supraphysiological increases in ETC-generated H_2O_2 and is the common factor linking infectious and non-infectious sepsis.

Due to the limited amount of mitochondrial glutathione available for H_2O_2 neutralization in addition to high basal levels of mitochondrial H_2O_2, a sustained hypermetabolic response can overwhelm cellular reductive (antioxidant) capacity resulting in un-neutralized H_2O_2 leaking out of cells and into the bloodstream with a subsequent rise in blood H_2O_2 reaching toxic levels[35-40].

H_2O_2 is a metabolic poison and the data suggest that sepsis is due to an endogenous H_2O_2 poisoning secondary to the oxidative damage inflicted by this highly toxic oxidizing agent. Since H_2O_2 is permeable through cell membranes, elevated blood H_2O_2 indicates systemic reductive depletion, which perpetuates the production of H_2O_2 [41]. Toxic levels of H_2O_2 will disrupt cellular function in all body organs, which can lead to multiple organ failure and microvascular dysfunction. Any cell undergoing a hypermetabolic response can deplete its reductive capacity and contribute to total body H_2O_2 load.

A potential cause and effect relationship between H_2O_2 and sepsis has likely remained obscure because a hypermetabolic state, which generates H_2O_2, is a confounding factor in the relationship between infection and sepsis (Figure 2)[42-51].

Based on the data, H_2O_2 is also an intervening variable in the setting of critical illness-associated sepsis (Figure 3)[52-55]. Intervening variables have an important role in therapy as they are mechanistically "closer" to the final effect and can serve as a therapeutic target. The observation that culture-positive sepsis patients on appropriate antibiotics still die suggests an additional factor independent of infection that exerts a significant influence on the clinical outcome of sepsis[5]. In this scenario, the H_2O_2 induced tissue damage and metabolic dysfunction (the effect) is too severe and can no longer be reversed by treating the infection (the exposure) with antibiotics. As an intervening variable with a postulated causal role in sepsis, H_2O_2 explains why culture positivity is not independently associated with mortality in sepsis[5] since the data supports H_2O_2 (and not infection per se) as the proximal causal agent in sepsis.

Figure 1 Krebs cycle derived reducing equivalents (NADH, FADH2) donate electrons that are processed by the electron transport chain during oxidative phosphorylation. Up to 5% of electrons (e^-) will normally escape the electron transport chain (ETC) into the mitochondrial matrix (electron leakage)[14-16]. These electrons combine with molecular oxygen (O_2) to form superoxide anion radical (O_2^-), which is metabolized by superoxide dismutase (SOD) to hydrogen peroxide (H_2O_2) that in turn is converted to glutathione disulfide (GS-SG) and water *via* glutathione peroxidase (GPX) and its reducing co-factor glutathione (GSH). Critical illness hypermetabolic states increase ETC activity leading to enhanced electron leakage and far greater H_2O_2 formation, which can deplete cellular GSH resulting in a build-up of H_2O_2 in cells and blood causing bioenergetic dysfunction and organ failure.

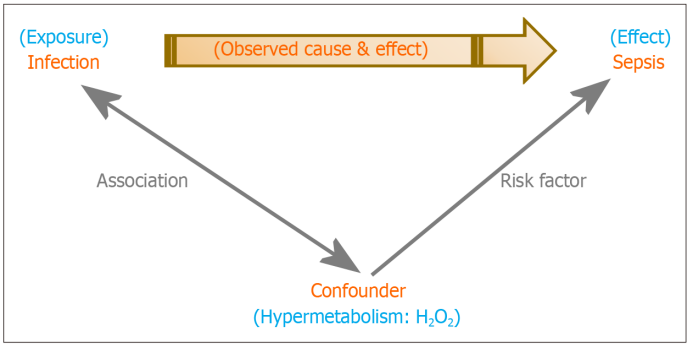

Figure 2 Confounding in Sepsis: The hypermetabolic state that accompanies a critical illness is a con-founding factor in the relationship between systemic infection (exposure) and sepsis (effect). Hypermetabolism generates large amounts of hydrogen peroxide (H_2O_2), which is both a risk factor for the development of sepsis and is bilaterally associated (double arrow) with infection. Systemic infection triggers a hypermetabolic state accompanied by greatly amplified generation of H_2O_2, but non-infectious critical illness can also generate large amounts of H_2O_2 due to the accompanying hypermetabolic state. High levels of blood H_2O_2 can cause systemic lymphocyte apoptosis leading to significant lymphocytopenia, which predisposes to infection. Thus, systemic build-up of H_2O_2 can lead to sepsis. This can occur after an infectious or non-infectious insult. In the latter instance, infection may develop as a result of H_2O_2 induced systemic lymphocyte apoptosis and subsequent lymphocytopenia.

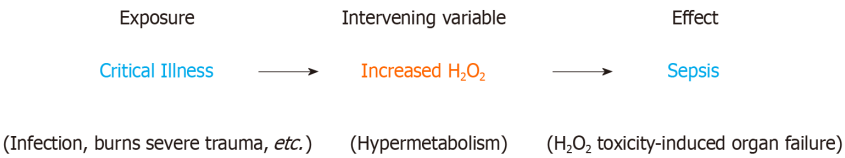

Figure 3 Sepsis and intervening variables: Hydrogen peroxide is an intervening variable between a critical illness (exposure), which triggers a systemic hypermetabolic response, and sepsis (effect). Hypermetabolism, characterized by the systemic inflammatory response syndrome, is the clinical manifestation of supraphysiological cellular H_2O_2 production. This will eventually lead to reductive depletion and sepsis (H_2O_2 toxicity, bioenergetic organ failure) if allowed to persist. Prolonged critical illness (hypermetabolism) and dietary restriction severely limit the body's ability to re-establish and maintain redox homeostasis. Under these circumstances, direct acting reducing equivalents must be supplied to the patient to aid in neutralizing excess H_2O_2. A hypermetabolic response to critical illness or injury may continue for years after hospital discharge and contribute to increased inpatient and post-discharge morbidity and mortality (chronic critical illness and post sepsis syndrome respectively)[52-55].

All hypermetabolic states (infectious and non-infectious), have the potential of generating excess H_2O_2, which can accumulate to toxic levels leading to bioenergetic organ failure and sepsis. The relationship between exposure (infection) and con-founder (H_2O_2) is bilateral because systemic infections cause a hypermetabolic state that can elevate blood H_2O_2 but non-infectious hypermetabolic states (*i.e.*, burns, multiple body trauma) can generate sufficient H_2O_2 leading to generalized lymphocyte apoptosis and profound lymphocytopenia, which can lead to infection. Serial negative blood cultures can eventually turn positive because of this phenomenon. In other words, infections can increase blood H_2O_2 but a primary non-infectious increase in blood H_2O_2 can eventually lead to infection, reinforcing the widely held view that sepsis is always due to infection. In the latter case, infection is the result of H_2O_2 induced lymphocytopenia (Figure 4).

Studies have shown that certain antibiotics can cause mitochondrial dysfunction accompanied by a significant production of H_2O_2[46]. This implies that patients must have sufficient residual reductive capacity to deal with the oxidative stress imposed by antibiotic treatment, underscoring the critical need to begin antibiotics along with

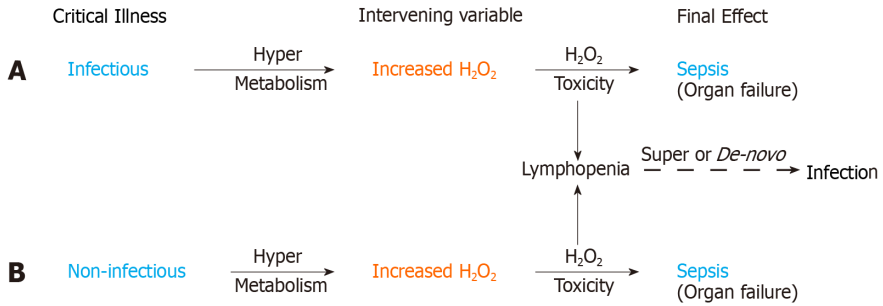

Figure 4 H_2O_2 induced immune system failure. Sequences 4A and 4B illustrate the common hypermetabolic response in infectious and non-infectious critical illness leading to H_2O_2 toxicity induced organ failure and sepsis. Lymphocytes are highly sensitive to H_2O_2 induced apoptosis. Lymphopenia is thus a manifestation of H_2O_2 induced immune system failure secondary to a hypermetabolic response in both infectious and non-infectious critical illness. H_2O_2 induced lymphopenia will predispose to de-novo infection in otherwise sterile critical illness and may cause a super-infection in patients on appropriate antibiotics. H_2O_2 toxicity and/or super-infection may contribute to sepsis mortality despite appropriate antibiotics.

reductive therapy as early as possible during the course of infection-associated sepsis. Reductive therapy encompasses any treatment that increases reductive (antioxidant) capacity, *i.e.*, glutathione, protein thiols, *etc.* The purpose of which (in sepsis) is to augment the patient's reductive (antioxidant) capacity to neutralize H_2O_2.

For the patient, the clinical benefits of limiting exposure to H_2O_2 go beyond discharge from the hospital because H_2O_2 can damage mitochondrial DNA. Mitochondrial DNA (mtDNA) is highly vulnerable to H_2O_2 induced oxidative damage due to the proximity of mtDNA to the electron transport chain, both of which reside on the matrix side of the inner mitochondrial membrane. Exposure of mtDNA to H_2O_2 will inflict base mutations and nucleotide mispairing that upon transcription result in the incorporation of mutated protein subunits into the electron transport chain (ETC). Mutated ETC components interfere with electron transport resulting in augmented electron leakage with increased H^2O^2 generation[47-52]. This establishes a self-amplifying vicious cycle with ever greater production of H_2O_2 and mtDNA damage, which can lead to prolonged metabolic and bioenergetic dysfunction in sepsis survivors and contribute to the post-sepsis syndrome.

H_2O_2 induced impaired redox homeostasis as a primary mechanism of disease is a novel pathogenesis that is supported by experimental evidence and is grounded in fundamental concepts of redox biology, redox biochemistry, and bioenergetics. Similar to electrolyte balance and acid/base buffering systems, redox homeostasis is a vital homeostatic mechanism required for normal cellular function and should be assessed in all critically ill patients.

CLINICAL MANIFESTATIONS OF H2O2 INDUCED OXIDATIVE STRESS

Since most H_2O_2 is a product of mitochondrial electron transport chain activity, clinical manifestations of H_2O_2 begin with its effects on cellular metabolism. Indeed, with almost 40% of all cellular reactions being redox reactions[53], the potential for H_2O_2 induced oxidative impairment of cellular metabolism and bioenergetics cannot be overstated, especially since blood H_2O_2 levels reported in sepsis exceed cellular cytotoxic tolerances by several-fold[17]. The mechanisms of H_2O_2 toxicity mirror the clinical manifestations of sepsis and include:

Hyperlactatemia

Elevated blood lactate is common among patients with sepsis and is associated with significantly greater mortality[12]. Toxic levels of H_2O_2 can inhibit enzymes in the Krebs cycle and electron transport chain leading to hyperlactatemia and bioenergetic failure characteristic of advanced sepsis[54-59]. H_2O_2 increases cellular lactate by interrupting mitochondrial oxidative energy flux (directional oxidation), which is needed to maintain the proton motive force (electrochemical proton gradient) that fuels pyruvate import into the mitochondrial matrix[60,61]. Studies have shown that H_2O_2 inhibits a variety of enzymes including enzymes within the Krebs' cycle such as aconitase, alpha-ketoglutarate dehydrogenase, and Succinate Dehydrogenase[55-57, 62].

Once inhibited, the Krebs cycle can no longer supply sufficient reducing equivalents (NADH, $FADH_2$) needed to sustain the mitochondrial proton gradient. Diminished Krebs cycle supplied reducing equivalents can decrease (and eventually collapse) the mitochondrial proton gradient. This will impair the proton motive force needed for pyruvate translocase in the inner mitochondrial membrane to transport pyruvate into mitochondria in symport with a proton[60,61]. The end result is increased cytosolic pyruvate and subsequent conversion to lactate with resulting hyperlactatemia[11]. Thus, in sepsis, hyperlactatemia can be a manifestation of H_2O_2 toxicity, in which case the reduction of serum lactate alone has no effect on the outcome of sepsis[63,64].

The effect of a dysfunctional Krebs cycle on serum lactate levels can be seen with the inherited deficiency of alpha-ketoglutarate dehydrogenase, which is associated with severe congenital hyperlactatemia[65]. Under these circumstances, increasing inspired oxygen will not lower serum lactate since the problem is with the diminished supply of electrons to the electron transport chain, which collapses the proton gradient dissipating the proton motive force, and not the availability of oxygen.

Studies have shown substantial lactate production from the lungs of patients with septic shock[66]. Hypoperfusion or hypoxia is highly unlikely given that the lungs are continuously bathed in oxygen and receive the entire cardiac output. However, when combined with other studies showing decreased lung glutathione in sepsis, H_2O_2 toxicity is a strong possibility. Therapeutic removal of H_2O_2 (discussed below) can contribute to the normalization of bioenergetic function and serum lactate.

It's worth noting that the mitochondrial proton motive force fuels both ATP synthase and nicotinamide nucleotide transhydrogenase both of which are located in the inner mitochondrial membrane. The former is needed to synthesize ATP while the latter is required to generate mitochondrial NADPH, a critical source of reducing equivalents for the regeneration of mitochondrial glutathione needed to neutralize H_2O_2[13]. Thus, sepsis-associated hyperlactatemia may signal a compromised proton motive force and the start of a vicious cycle leading to increased H_2O_2 induced oxidative stress and bioenergetic failure.

Anemia

A common feature during the progression of sepsis is anemia. Several factors can contribute to the development of sepsis-associated anemia however, sepsis per se is independently associated with the development of anemia, and healthy erythrocytes exposed to plasma from sepsis patients undergo eryptosis[67,68]. H_2O_2 induced oxidative stress initiates erythrocyte suicidal cell death known as eryptosis leading to cell shrinkage and clearance from the blood[68-71]. Thus, H_2O_2 initiated eryptosis may contribute to sepsis-related anemia.

Hypocalcemia

Low serum calcium is a common finding in patients with sepsis and critical illness, with reported prevalence rates of up to 80%[72]. Hypocalcemia may be due to one or more of various causes[73]. However, during sepsis, calcium is shifted into red blood cells with significant increases in erythrocyte calcium of more than twice the control

value[74]. Given that about 85% of all cells in the body are red blood cells, this shift may significantly contribute to sepsis-associated hypocalcemia[75]. Erythrocytes exposed to oxidative stress (*i.e.*, H_2O_2) activate calcium-permeable cation channels leading to calcium entry into the cell[71]. Significantly increased lymphocyte calcium has also been reported in sepsis[76]. This suggests that the elevated blood H_2O_2 reported in sepsis may cause a more generalize intracellular shift of calcium.

Shock

Sepsis-associated hemodynamic instability can progress to septic shock, which carries a high mortality. Oxidative stress due to H_2O_2 exposure causes extensive cytoskeletal disruption to endothelial cells leading to significant endothelial retraction and microangiopathic dysfunction[22]. The net effect of microvascular H_2O_2 exposure is microangiopathic dysfunction, impaired vasomotor responsiveness, barrier disruption with edema formation, and irreversible hypotension (septic shock)[22,77]. Studies have reported hypotension in an animal model after intravenous administration of H_2O_2 [25].

Immunosuppression

Sepsis patients develop profound immunosuppression that begins within days after the onset of sepsis[7,28,30]. Lymphocytes are extremely sensitive to H_2O_2 induced apoptosis, which occurs at H_2O_2 concentrations of less than 1 μmol/L[19,20]. Studies report blood H_2O_2 concentrations in sepsis of up to 558 μmol/L, which is over 500 times the concentration of H_2O_2 needed to cause lymphocyte apoptosis[17-19]. The ability of high blood H_2O_2 concentrations to cause generalized lymphocyte apoptosis explains the profound immunosuppression observed in sepsis patients.

Respiratory failure

Sepsis-associated acute respiratory distress syndrome (ARDS) is a serious complication of sepsis that carries a high mortality. It is characterized by increased permeability of pulmonary capillary endothelial and epithelial cells. The increased vascular permeability leads to diffuse capillary leak, pulmonary edema, and eventual wet lung, which triggers the secondary development of pathological features[78,79]. Studies have demonstrated that low dose H_2O_2 can increase pulmonary vascular bed permeability and capillary filtration[80-83]. This suggests that the high levels of H_2O_2 reported in the blood of sepsis patients may have a causal role in the initiation of ARDS.

Acute kidney injury

Sepsis-associated acute kidney injury (S-AKI) is a life-threatening complication that develops in up to two-thirds of patients with sepsis or septic shock, which in half of the patients develops before seeking medical attention[84]. Once thought to be a consequence of cellular hypoxia leading to acute tubular necrosis, it is now recognized that S-AKI can occur in the setting of normal or increased renal blood flow[84]. Studies suggest a critical role for microcirculatory dysfunction, which is present in every vital organ in animal models and humans with sepsis[84-86]. When combined with studies showing a decreased substrate flux through the Krebs cycle in mice kidneys after the induction of experimental sepsis[87], these effects mirror the known toxic effects of H_2O_2, among which is microangiopathic dysfunction and Krebs cycle enzymatic inhibition[22]. In support of a role for H_2O_2 in S-AKI, studies of experimental murine sepsis employing Mito-TEMPO, a mitochondrially targeted reducing agent (antioxidant) active against H_2O_2, significantly increased renal microcirculation, glomerular filtration rate, and ATP synthesis[88,89].

The renal endothelium is highly vulnerable to oxidative stress with agents such as H_2O_2, a highly toxic oxidizing agent that can diffuse across cell membranes to impair critical signaling and regulatory function required for microvascular function[90]. Other studies report significant cytotoxicity in human tubular epithelial cells exposed to 100 μmol/L H_2O_2, while 200 μmol/L exposure caused mitochondrial cytochrome-C translocation to the cytoplasm in addition to significant intracellular increases in H_2O_2. These concentrations are within the range reported for blood H_2O_2 in sepsis patients of up to 558 μmol/L[17,91]. H_2O_2 can inhibit various enzymes involved in oxidative metabolism including Krebs cycle enzymes, ATP synthase, and nucleotide (ADP-ATP) translocase[55-57,92]. The resulting inhibition in mitochondrial oxidative flux may contribute to the increased glycolytic production of lactate by proximal tubule cells observed during sepsis[93]. Increased glycolysis would revert to oxidative phosphorylation when H_2O_2 induced inhibition of mitochondrial oxidative metabolism

is resolved. Lastly, rat renal artery infusion of 70 mmol/L H_2O_2 (140x that found in human sepsis blood) is reported to cause massive proteinuria without electron microscopic ultrastructural glomerular abnormalities[94]. This is consistent with the minimal postmortem histological findings in human S-AKI[84,86]. This suggests that renal exposure to blood H_2O_2 levels observed in human sepsis may cause cellular dysfunction without overt signs of cellular damage.

Coagulopathy

Disseminated intravascular coagulation (DIC) is a life-threatening complication frequently encountered in sepsis that is characterized by the systemic activation of the coagulation system leading to microvascular thrombosis, and potentially life-threatening hemorrhage due to consumption of platelets and coagulation factors[95]. DIC can originate from damage to the microvasculature, which triggers the extrinsic coagulation cascade[96]. H_2O_2 can cause microvascular injury by peroxidation of endothelial cell membranes, which triggers the expression of tissue factor and subsequent systemic activation of the extrinsic coagulation pathway leading to DIC [97-99]. Intravenous administration of H_2O_2 is reported to have resulted in fatal sepsis and DIC, underscoring the role of H_2O_2 induced oxidative stress in both of these conditions[100].

On a more fundamental level, the endothelium is critically involved in preventing inappropriate coagulation by maintaining barrier function and producing several endogenous anticoagulants[101]. The elevated levels of blood H_2O_2 reported in sepsis can permeate endothelial cells throughout the body causing substantial oxidative stress accompanied by profound disruption in both form and function[77,102]. Studies have reported significant endothelial dysfunction that is associated with mortality and severity of coagulopathy[101]. H_2O_2 induced endothelial dysfunction can explain why anticoagulants fail to show a survival benefit in sepsis-induced DIC[103] since these agents fail to restore endothelial redox homeostasis.

Encephalopathy

Sepsis-associated encephalopathy (SAE) is a diffuse cerebral dysfunction ranging from lethargy and lack of concentration to personality changes, delirium, and coma that occurs secondary to sepsis in the absence of direct central nervous system (CNS) infection. SAE affects up to 70% of sepsis patients and is associated with higher mortality and poorer long term outcomes with half of surviving patients suffering from long-term cognitive defects[104,105]. The brain is highly sensitive to H_2O_2 induced oxidative damage and dysfunction, and studies report dose-dependent cytotoxicity starting at H_2O_2 exposures of 10 μmol/L[106]. Encephalopathy is reported to occur after the accidental ingestion of H_2O_2[107]. Encephalopathy was also reported after intravenous administration of H_2O_2 for alternative medicine therapy[100].

H_2O_2 is diffusible through cell membranes which facilitates its diffusion into the central nervous system where it can disrupt neuronal and synaptic function. Studies have shown that H_2O_2 can alter neuron membrane properties and impair synaptic transmission leading to hyperexcitability and epileptiform activity[108,109]. This is notable because epileptic seizures can be a manifestation of SAE. Other studies have demonstrated bioenergetic impairment with decreased ATP biosynthesis and utilization in neurons exposed to H_2O_2[110,111]. H_2O_2 has also been reported to alter rat hippocampal synaptic plasticity, which can negatively impact long-term potentiation, learning, and memory[112]. Thus, the presence of elevated levels of blood H_2O_2 in sepsis can have acute and chronic effects on brain function and cognition.

TREATMENT

Sepsis is a life-threatening medical emergency that can precipitously evolve into hemodynamic instability, septic shock, and death. Thus it may not be possible or prudent to wait for a blood H_2O_2 level if clinical signs of H_2O_2 toxicity are present. Additionally, it takes some time before free H_2O_2 can accumulate in the bloodstream given the multiple layers of reductive (antioxidant) defense systems that mitochondrial H_2O_2 must traverse on its way to the intravascular compartment including mitochondrial and cytoplasmic glutathione followed by interstitial albumin whose cys34 amino acid can react with H_2O_2 (60% of total albumin) and ultimately serum albumin (40% of total albumin) and red blood cell reductive (glutathione) capacity [13]. During the time it takes to reach the blood stream and build-up, toxic levels of

intracellular H_2O_2 can inhibit critical cellular bioenergetic reactions leading to compromised bioenergetic function. This was demonstrated in ulcerative colitis, an inflammatory bowel disease, in which a primary increase in colonic epithelial H_2O_2, thought to have a causal role in this disease, resulted in impaired beta-oxidation due to H_2O_2 inhibition of mitochondrial thiolase, the last enzyme in the beta-oxidation cascade[113].

Within this context, the data support the critical need for reduction of systemic H_2O_2 in sepsis to prevent bioenergetic organ failure and restore microcirculatory function. Restoration of redox homeostasis by the elimination of excess H_2O_2 must accompany other therapeutic interventions to optimize clinical responsiveness and outcome. Sodium thiosulfate (STS) is a direct-acting reducing agent that can neutralize H_2O_2 upon contact.

STS is approved for use in cyanide poisoning with a recommended dose of 12.5 g over slow IV infusion (10 to 20 min) in adults and 250 mg/kg in children[114]. Similar dosing regimens can be considered in sepsis. Repeat dosing can be guided by clinical status, blood reducing capacity (glutathione, plasma thiols), and blood H_2O_2 levels. The general chemical reaction for the reduction of H_2O_2 with sodium thiosulfate yields sodium trithionate, sodium sulfate, and water[115].

$2Na_2S_2O_3 + 4H_2O_2 \rightarrow Na_2S_3O_6 + Na_2SO_4 + 4H_2O$

The rationale underlying STS administration in sepsis is to reduce blood H_2O_2 to normal (less than 30 μmol/L) in order to allow intracellular H_2O_2 to diffuse down its concentration gradient into the systemic circulation where it can be neutralized by STS. STS is generally well tolerated and is an accepted therapy for cisplatin toxicity and renal failure associated calciphylaxis (25 g three times weekly)[116,117]. High dose STS (up to 16 g per M^2 surface area, repeated after 4 h) is reported to be well tolerated in children under 12 years of age[118].

STS is reported to replenish intracellular glutathione, which will aid in the removal of intracellular H_2O_2 and restoration of redox homeostasis[119,120]. Decreasing serum lactate indicates that H_2O_2-induced Krebs cycle inhibition and bioenergetic dysfunction are being reversed. Restoration of vascular responsiveness by STS may cause extant vasopressor measures to have an unanticipated amplified effect. Thus, STS administration in critically ill patients should be accompanied by close patient monitoring. Finally, if STS therapy proves to be successful in the treatment of sepsis then treatment with STS should be considered in all critically ill (hypermetabolic) patients in order to restore depleted systemic reducing equivalents before blood H_2O_2 becomes toxically elevated.

Specific treatment considerations

ARDS: Inhaled STS may have a beneficial effect to neutralize H_2O_2 that has diffused through the alveolar-capillary membrane causing oxidant damage in the alveolar space.

S-AKI: Primary prevention of S-AKI is not possible in all patients because most patients developing S-AKI already have it at presentation. Administration of STS should be considered when patients first seek medical care to initiate primary or secondary prevention.

The evidence supports the use of STS as a specific therapeutic agent for the treatment of sepsis and its associated complications. Given the high mortality, significant societal burden, and absence of a safe and effective treatment for this deadly condition, clinical studies are urgently needed to determine the effectiveness of STS for the treatment of sepsis.

CONCLUSION

The mortality in sepsis is unacceptably high because there is no specific therapy to treat the sepsis syndrome. H_2O_2 toxicity mirrors the clinical and laboratory abnormalities observed in sepsis, and toxic levels of blood H_2O_2 have been reported in this condition. This and other data implicate H_2O_2 as the causal factor in the pathogenesis of sepsis, which predictably develops accompanied by systemic depletion of reducing equivalents (*i.e.*, glutathione) needed for the reduction (neutralization) of metabolically generated H_2O_2. Once the body's reductive (antioxidant) capacity is depleted, H_2O_2 will continue to be generated and flood the system.

Prolonged supraphysiological production of H_2O_2 generated by electron transport chain hyperactivity during a hypermetabolic state (such as sepsis) can overwhelm

cellular reductive systems leading to H_2O_2 accumulation within tissues and blood. H_2O_2 is a highly toxic membrane-permeable metabolic poison that can cause severe bioenergetic dysfunction and cellular damage if allowed to accumulate. Continued exposure can lead to the collapse of systemic redox homeostasis, proton motive force dissipation, organ failure, microvascular dysfunction, and fatal septic shock. Reduction of blood H_2O_2 is paramount in order to prevent H_2O_2 toxicity from irreversibly shutting down cellular metabolism.

The data support the use of sodium thiosulfate as a systemic reducing agent with the goal of restoring redox homeostasis by neutralizing excess systemic H_2O_2. Prophylactic use of sodium thiosulfate in all critically ill (hypermetabolic) patients should be considered before irreversible H_2O_2 induced bioenergetic failure and microvascular dysfunction develop.

Based on the data, the missing critical intervention to improve patient outcomes and reduce mortality in patients with sepsis and septic shock is the normalization of systemic redox homeostasis. The addition of specialists in redox medicine to the team providing care to critically ill patients can contribute to achieving this heretofore elusive goal.

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REVIEW

What we learned in the past year in managing our COVID-19 patients in intensive care units?

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Abstract

Coronavirus disease 2019 is a pandemic, was first recognized at Wuhan province, China in December 2019. The disease spread quickly across the globe, spreading stealthily from human to human through both symptomatic and asymptomatic individuals. A multisystem disease which appears to primarily spread *via* bio aerosols, it has exhibited a wide clinical spectrum involving multiple organ systems with the respiratory system pathology being the prime cause of morbidity and mortality. Initially unleashing a huge destructive trail at Wuhan China, Lombardy Italy and New York City, it has now spread to all parts of the globe and has actively thrived and mutated into new forms. Health care systems and Governments responded initially with panic, with containment measures giving way to mitigation strategies. The global medical and scientific community has come together and responded to this huge challenge. Professional medical societies quickly laid out "expert" guidelines which were conservative in their approach. Many drugs were re formulated and tested quickly with the help of national and international collaborative groups, helping carve out effective treatment strategies and help build a good scientific foundation for evidence-based medicine. Out of the darkness of chaos, we now have an orderly approach to manage this disease both from a public health preventive and therapeutic standpoint. With preventive measures such as masking and social distancing to the development of highly effective and potent vaccines, the public health success of such measures has been tempered by behavioral responses and resource mobilization. From a therapy standpoint, we now have drugs that were promising but now proven ineffective, and those that are effective when given early during viral pathogenesis or later when immune dysregulation has established, and the goal is to help reign in the destructive cascade. It has been a fascinating journey

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for mankind and our work here recapitulates the evolution of various aspects of critical care and other inpatient practices which continue to evolve.

Key Words: COVID-19; Respiratory support; Renal replacement therapy; Extracorporeal membrane oxygenator; Medications; Therapeutics

Core Tip: Severe acute respiratory syndrome coronavirus 2 transmission and the inpatient therapeutic management of coronavirus disease 2019 has been subject of immense research in the past one year. Our knowledge and understanding of the virus and the treatment of the disease continue to evolve. We attempt to summarize the progress made in a concise but comprehensive manner along with our insights into future directions.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first reported and widely believed to have originated at Wuhan in the Hubei province, China in late December 2019[1]. It started as a Zoonotic disease and gained a foothold in human population by person-to-person transmission, having evolved into a destructive pandemic infecting more than 100 million people and has caused more than 2.2 Million deaths till date[1,2].

A member of Beta coronaviruses, which includes SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV) which have caused localized epidemics in the Asian continent, the SARS-CoV-2 rapidly spread across the globe and has now survived and evolved with mutants due to its ability to stealthily spread by airborne transmission, ability to survive in varying environmental conditions, causing asymptomatic or mild infection in humans with transmission characterized by the ability to infect early on during the prodromal phase of illness, aided generously by "super spreaders"[1,3,4].

The management of the disease has evolved with early conservative guidelines from experts to evidence-based recommendations which continue to evolve every day touching all aspects of care from the use of respiratory assist devices, medication including repurposed drugs, novel and controversial therapies as well as delivery of our critical care services. Here we attempt to capture some of these changes and present the current state of evidence of some of these therapies and services used in the management of COVID-19[5].

INFECTIVITY AND TRANSMISSION CHARACTERISTICS

Since the beginning of the pandemic SARS-CoV-2 duration of shedding, infectivity, and mechanism of transmission of infection have been very keenly studied as they have practical implications. We now have better knowledge and understanding of these characteristics. The viral RNA has been detected by reverse transcriptase-polymerase chain reaction testing from the upper respiratory tract for a mean of 17 d with a maximal duration of 83 d. Likewise, from the lower respiratory tract, the viral RNA has been detected for a mean duration of 17.2 d with a maximal duration of only 35 d. However more importantly the live virus has not been cultured beyond the 9th day of symptom in any study to date. Hence the maximal infectivity is likely in the first week from symptom onset and tapers off subsequently[6].

Respiratory transmission is now considered the predominant mode of infection. Droplets are large particles typically more than 5 microns which are heavier and drop within 6 feet, whereas aerosols are smaller than 5 microns and post evaporation remain suspended like pollens in the air having the ability to travel longer distances [7]. Our current understanding is that the virus is shed as particles across a wide range of sizes[8,9]. A longer duration, closer proximity, forced exhalation of air from a patient with high viral load is now considered necessary for cross-infection to occur with SARS-CoV-2[8]. Logically a "full high-level barrier protection" with Personal Protective Equipment (PPE), N95 mask & Negative pressure room may therefore be necessary when managing a highly symptomatic patient who is excessively coughing, is on high flow oxygen, noninvasive ventilation (NIV), Mechanical ventilator, is undergoing Bronchoscopy or has a Tracheostomy. In all these situations, a large amount of air is being mobilized across the mucosa covered with the virus, enhancing the possibility of viral aerosolization & infection[8]. In fact if the combination of "full barrier precautions" and adherence to clinical practice guidelines are strict, then the likelihood of infection with SARS-CoV-2 in clinical care areas for staff is substantially reduced or insignificant[10].

The role of respiratory assist devices and maneuvers in the pandemic

COVID-19 is a disease that affects multiple organ systems but primarily and disproportionately affects the Respiratory system. Early in the pandemic stemming from the Chinese experience, COVID-19 patients were intubated early when needing more than 5-6 L/min oxygen to avoid aerosolization of SARS-CoV-2 infection to staff and due to the anticipation, that these patients would deteriorate rapidly with the attendant risk of substantial hypoxia during intubation. However it is now apparent that such aggressive measures are not warranted as it places substantial burden on the need for critical care resources[11]. Although not proven to be causative, the early surge of COVID-19 cases in New York city and Italy in early 2020 was notable for very high mortality noted in intubated patients[12,13].

Adult respiratory distress syndrome (ARDS) is the dominant respiratory clinical syndrome seen in COVID-19 patients[13,14] with histopathology primarily characterized by diffuse alveolar damage very similar to SARS-CoV-1 and MERS-CoV infections[15]. ARDS related lung injury and Respiratory mechanics in COVID-19 appear to be similar to non-COVID-19 ARDS; nevertheless substantial controversy exists regarding management in literature which is intriguing and is addressed in our discussion[11,13,14].

Oxygen supplementation and NIV

It is generally accepted that low flow oxygen with a simple face mask or Cannula is used for supplemental oxygen as the first line of support when SaO_2 is less than 88%. The next line of oxygen supplementation is through high flow nasal cannula (HFNC). It provides oxygen at a very high flow rates (40-80 L/min). This oxygen also is heated and humidified to simulate physiological conditions in the airway promoting patient comfort and tolerance[16]. HFNC is essentially a flow generator helping with mucociliary clearance in the airway and improves the Ventilatory function of the lung by providing low levels of functional "Positive end expiratory Pressure (PEEP)" in the respiratory tract[17]. A type 1 surgical mask can substantially reduce particulate aerosol contamination from nasal devices when placed over them[18]. The dispersion of aerosolized particles is higher than a simple mask for HFNC but much less when compared to NIV in simulated experiments[19,20].

NIV such as continuous positive airway pressure (CPAP) and Bi-level alveolar positive airway pressure (BIPAP) are the next line which provides pressure targeted ventilation. CPAP has traditionally been used in acute cardiogenic pulmonary edema by increasing functional residual capacity and therefore oxygenation and compliance. BIPAP in addition to the latter has also been used in acute exacerbation of the chronic obstructive pulmonary disease for counterbalancing inner PEEP with external PEEP and decreasing work of breathing by acting as an inhalation assist device[17]. Both modes of NIV have been traditionally used in obstructive sleep apnea and obesity hypoventilation syndrome[21]. CPAP and BIPAP must be used with a full-face mask to decrease the risk of aerosolization. BIPAP can also be used with a helmet mask (mostly available in Europe). They have been shown to have an acceptable level of aerosolization which can be further attenuated with the help of a well-fitting helmet mask[22].

In general, HFNC is preferred over NIV. HFNC is much more comfortable for the patient as it allows for speech, eating/drinking as well as comfort[17]. But NIV may be preferred in patients who have acute chronic obstructive pulmonary disease (COPD)

exacerbation with hypercarbia, acute pulmonary edema and those who have sleep disordered breathing.

Evidence from non-COVID-19 literature for HFNC and NIV

In the FLORAL trial involving hypercpaneic patients with acute hypoxemic respiratory failure, HFNC was shown to decrease intubation rate which was statistically significant in a sub-group of patients with $Pao_2/Fio_2 < 200$ when compared to non-rebreather mask (≥ 10 L/min) or NIV. Mortality also favored the HFNC group at 90 d when compared to the other two groups in this study[23].

In another study, HFNC was non-inferior to NIV for preventing reintubation and post-extubation respiratory failure in high-risk adults[24].

In another randomised controlled trial involving high-risk adults, the combined use of HFNC and NIV prevented more extubation failures than HFNC alone[25] suggesting that the two modalities can complement each other.

In the LUNG SAFE study, about 15% of ARDS patients were treated with NIV. Failure of NIV was increasingly common with increasing severity of ARDS but mortality was especially higher in patients who had Pao_2/Fio_2 lower than 150 mmHg [26] and hence should be avoided in this subgroup of Moderate to Severe ARDS Patients.

In a systematic review and meta-analysis involving 25 studies and 3804 patients, the use of both helmet and face mask NIV was associated with decreased mortality and endotracheal intubation compared to standard oxygen therapy[27]. However, in sensitivity analysis excluding studies which included COPD exacerbation and congestive heart failure exacerbation, the observed benefit on mortality was not noted. The beneficial effect on mortality was also less certain with patients who had severe ARDS.

Evidence from COVID-19 literature for HFNC and NIV

Good quality data is lacking but some moderate sized retrospective observational studies have been published.

In Lombardy Italy, about 350 of 3988 patients with COVID-19 Pneumonia were treated with NIV, of which 50 percent required intubation. The mortality of the latter group was similar to patients who were intubated on admission to the intensive care units (ICU)[28].

In one published Italian retrospective observational study of 670 patients, the rate of intubation and adjusted mortality did not vary in patients who were treated with High flow oxygen, CPAP and BIPAP[29].

In a study of 110 patients who received non-invasive ventilation *via* helmet for two days, followed by the high flow nasal oxygen therapy or high flow oxygen alone, there was no difference in the ventilator free days at 28 d between NIV and high flow, but patient in the helmet NIV group had decrease in intubation and mechanical ventilation free days, with the *P* value of 0.03[30].

In a systematic review and meta-analysis of non-randomized cohort studies involving about 1897 critically ill patients, there was no statistically detectable difference on all-cause mortality between patients undergoing intubation without *vs* with a prior trial of HFNC/NIV [eight studies, 1128 deaths; 48.9% *vs* 42.5%; risk ratio (RR) 1.11, 95% confidence interval (CI): 0.99-1.25, $P = 0.08$][31].

Monitoring of patients on HFNC and NIV

Patients need to be carefully monitored when on supplemental oxygen devices like high flow or NIV. Intubation should not be withheld when appropriate criteria are met. It is estimated that about 20%-25% of patients can avoid intubation and help preserve Critical resources during the pandemic[17]. Further evidence is needed.

Early vs late intubation

The concept of early *vs* late intubation in COVID-19 pneumonia is controversial which has elicited a fascinating Pros-Con debate[32,33].

Early on, some professional organizations like the Royal College of Anesthetists & Intensive Care Society recommended early intubation to prevent the risk of high environmental contamination with other oxygenation and ventilatory adjuncts like NIV/HFNC[32].Others like the Society of Critical Care Medicine recommended careful monitoring with NIV/HFNC and intubation when the latter failed[34].

A failed NIV followed by intubation can be associated with an increased risk of complications during intubation like hypotension, desaturation, and aspiration with associated increased risk of mortality[35]. While some studies in non-COVID-19

hypoxemic respiratory failure show increased mortality with delayed intubation[35,36] others in COVID-19 hypoxemic respiratory failure showed no such increased mortality[13].

Proponents of early mechanical ventilation emphasize the possibility of "Patient self-inflicted Lung injury (P-SILI) "in the non-intubated critically ill patient with acute hypoxemic respiratory failure which is a collective term for the high minute ventilation, a high respiratory drive of the ARDS patient worsening the preexisting lung injury with increased vascular permeability along with local and global lung over distension[37]. P-SILI in a spontaneously breathing patient is akin to ventilator-induced lung injury in a mechanically ventilated patient[33] and is caused by high pleural pressures and trans pulmonary pressure swings. Lung protective ventilatory strategies using mechanical ventilation along with deep sedation and/or neuromuscular paralysis can prevent P-SILI[37,38]. The endotracheal tube helps gain good control over an unstable airway and regulate oxygen, pressure, and volume[39].

Opponents of early and liberal Mechanical ventilation offer many valid reasons. The concept of P-SILI is relatively new and the evidence supporting it is not very robust [33]. Mechanical ventilation brings along with it a host of complications like delirium secondary to sedation, hemodynamic instability secondary to decreased sympathetic drive and positive pressure ventilation, increased risk of infection, immobilization with increased risk of thromboembolism, neuromuscular paralysis, post-intensive care syndrome with its attendant physical and neurocognitive dysfunction[32]. Intubation and mechanical ventilation are associated with one of the highest risks of aerosolization[40] and for the patient, there is risk of procedure related hypotension, hypoxemia, cardiac arrest, and other complications[41]. During a pandemic conserving critical resources and their judicious use is important and intubating every patient with hypoxemic respiratory failure is going to be unethical[42,43].

No randomized control studies have been published on this topic. The definition of early *vs* late intubation is variable across studies. A few small single-center retrospective studies have reported variable outcomes for delayed *vs* early endotracheal intubation[44-47] with one study reporting worser mortality outcomes for delayed intubation and other three being equivocal.

In a systematic review and meta-analysis of non-randomized cohort studies involving about 9000 critically ill patients compared early (less than 24 h after ICU admission) *vs* late (more than 24 h after ICU admission) intubation found no difference in all-cause mortality(3981 deaths; 45.4% *vs* 39.1%; RR 1.07, 95%CI: 0.99-1.15, $P = 0.08$), duration of mechanical ventilation (1892 patients; MD - 0.58 d, 95%CI: 3.06-1.89 d, $P = 0.65$), ICU length of stay and renal replacement therapy (RRT)[31].

Due to limited data, the question apart from some lively, elegant and animated discussions between experts is probably unsettled[33,48].

Nebulization

SARS-CoV-2 virus transmission occurs predominantly through close contact, poor ventilated environment in a susceptible host *via* droplets/aerosols and less likely through fomites[6,7,9].Transmission *via* bio aerosols from medical procedures like Nebulization and Tracheostomy has been a very valid concern as discussed earlier[49].

As *per* the Global initiative for asthma & The Australian National Asthma Council, the recommendation is to use nebulization therapy only if unavoidable[50,51]. On the contrary, the British National Institute of Health Care and Excellence recommends that patients with COVID-19 can continue using nebulization therapy[52]. Such contrary guidelines and recommendations have sowed doubts in the minds of patients and professional health care practitioners. It is indicative of the fact that the evidence base for these contrary recommendations is not very strong.

Although a continuation of inhalational treatment for chronic respiratory diseases has been universally recommended[51], the optimal mode is less certain. Inhalers have been recommended as they seem to generate fewer aerosols, the drug is contained in the container and less likely to be contaminated by infectious particles, and they also have a low emitted dose[49]. However, either *via* normal exhalation or cough (determined by drug formulation characteristics) induced by the inhaled medication, inhalers can produce exhaled bio aerosols and hence they do not seem to be superior to nebulizer therapy[49].

Theoretically, nebulizer therapy produces an aerosol of the medication in the nebulizer container and hence should not produce infected aerosols unless the container or medication gets contaminated[49]. An aerosol droplet coming in contact with an infected mucous membrane, like in the lung stops being airborne and hence is no longer an aerosol[53]. Hence good hygiene precautions undertaken while using the nebulizer and while loading the medication should prevent the spread of infection by

aerosolization[49,53]. Besides, other precautions to prevent bio aerosolization have been proposed such as the use of viral filters in the circuit of nebulizers/ventilators, use of vibratory mesh nebulizers which separate medication from patient interface including circuits, and good provider/patient hygiene and using mouthpiece with handheld devices[53]. Universally full barrier precautions as discussed earlier should be practiced to limit infection.

Bronchoscopy

At the beginning of the pandemic, many Pulmonary/Bronchology societies made recommendations for COVID-19, but were limited by generalizations, lack of exhaustiveness, and clear guidance was not available due to the novelty of the disease; extrapolation from previous coronavirus pandemics was required[54]. Almost all societies recommended deferring bronchoscopy in non-urgent cases, observing full barrier precautions when performing bronchoscopies, restricting the number of personnel who could be participating in the procedure, limit aerosol producing procedures like nebulization, use of atomizers and jet ventilation[55]. Peri procedurally recommendations included using sedation (or even paralytics when feasible) to avoid coughing, avoiding high flow and high shearing maneuvers, all intended to limit aerosolization. Flexible bronchoscopy is encouraged and rigid bronchoscopy is discouraged with post-procedure recommendations lacking consensus[54]. To avoid cross-contamination or accidental transmission, single-use flexible bronchoscopes are encouraged[54].The patient can wear a mask and a slot can be made for introducing the bronchoscope[54,55].

Certain acceptable indications for bronchoscopy in COVID-19 times include but not exhaustively, symptomatic airway stenosis, symptomatic hemoptysis, migrated stent, therapeutic aspiration of obstructive symptomatic secretions or masses, diagnosis of secondary infections in intubated COVID-19 patients, diagnosis of cancer, and diagnosis of infection in immunocompromised patients[55].

In a single-center, where 241 bronchoscopies were performed on 107 COVID-19 patients, 54 patients (50.5%) had Broncho Alveolar Lavage (BAL) with 35 patients (65%) demonstrating a positive culture. About 1/3rd of intubated patients required bronchoscopy presumably due to thickened white gelatinous secretions (likely due to heated air with less humidification as was recommended by guidelines) or bloody secretions due to high use of anticoagulants. BAL cultures were more likely to be positive (65%) compared to tracheal cultures (45%). 6% of BAL cultures also grew a second organism. The study showed a high rate of secondary infection in COVID-19 patients above and beyond that was diagnosed with tracheal cultures, indicating that under treatment may be driving higher mortality[56].

In another single-center series of 93 intubated patients, 101 bronchoscopies were performed which did not show increased secondary infection when compared to non-covid ventilator associated pneumonia[57].

In general, bronchoscopy has not shown any definitive increase in transmission when proper precautions have been observed[56,57].

Tracheostomy

Tracheostomy has been widely used across the globe for COVID-19 management. Initially, expert guidelines were made available which were very conservative in their recommendations but now we have better evidence to guide our decisions[58]. Certain pertinent issues concerned with Tracheostomy are addressed here.

The Indications for tracheostomy have traditionally not been well defined, dependent on multiple factors and individual circumstances[59]. In the current COVID-19 times, tracheostomies have been performed early (less than 7 to 10 d after intubation) and for very liberal indications with critical care resource utilization as a goal commensurate with principles of "Disaster management"[60-62]. However, guidelines based on several critical considerations including virology of transmission and infectiousness of the patient recommended the timing to be past 10 d and when patients show clinical improvement[59]. This is because it is difficult to predict the clinical trajectory of ARDS patients with COVID-19. After the patient has navigated the first few days of Critical illness and shown clinical improvement, but anticipate prolonged mechanical ventilation, with reasonable pulmonary reserves, the FiO_2 less than 40% and PEEP less than 8, then tracheostomy can be considered[59,60,63,64]. Given that there are advantages and disadvantages to both early and late tracheostomy, and with relatively proven non-inferiority, the timing of tracheostomy like in non-COVID-19 patients has to be individualized[61,63]. In practice, a systematic review and meta-analysis encompassing 462 COVID-19 patients revealed that 250 patients (71.5%) received tracheostomy 14 d after intubation, which is consistent with

conventional practice[65].

Tracheostomy can be performed by the "open or surgical" method in the operating room or by "Percutaneous dilatation" at the patient bedside. Initially, the recommendation was to use the "Open or Surgical" method to minimize exposure to bio aerosol which is potentially more with the percutaneous method[59,64]. However, with diligent and appropriate use of "Full barrier" precautions including PPE with or without a negative pressure room, the increased risk to healthcare personnel has not materialized and the emphasis is now to optimally use available resources as both methods have been proven to be safe[59,62,64,65]. In a pooled analysis of 3060 tracheostomies, 55.7% were created by the open method and 43.4% were created by the percutaneous method[65].

Post-procedural management guidelines suggest to limit staff exposure to bio aerosols have been published and it has been demonstrated that this can be implemented successfully by training new staff members unfamiliar with tracheostomy care, thereby helping free critical ICU resources when necessary[59,62,64].

Post tracheostomy outcome data in COVID-19 patients are now available. In a pooled analysis, of 2890 mechanically ventilated patients 54.9% were reported to have been successfully weaned, of 2628 patients 34.9% were successfully decannulated, and of 2980 patients 513 patients (13.1%) had died[65].

Overall tracheostomy in COVID-19 patients has evolved from the early time of guidelines recommending "abundant caution" to now practice and outcomes which seem to be more consistent with "regular order".

Convalescent plasma and monoclonal antibody

Convalescent plasma has been used to treat many infectious diseases in the past like Influenza, MERS-CoV, Ebola Virus, Influenza, *etc.*, but efficacy and evidence are not firmly established[66,67]. The goal of such passive immunization is to neutralize the infectious organism with the help of naturally formed and passively transferred antibodies[66]. Novel neutralizing monoclonal antibodies (nabs) and nano antibodies have also come into play during the coronavirus pandemic[68].

SARS-CoV-2 virus enters the cell *via* the angiotensin-converting enzyme 2 (ACE2) receptors on the respiratory and gastrointestinal tract epithelium. The SARS–CoV-2 virus has an outer "S" glycoprotein, with S1 and S2 subunits. The S1 subunit has a receptor binding domain along with receptor binding motif, the latter attaches to the ACE2 receptor in the host, and there is a conformational change in the S protein leading to S2 fusing with the host cell wall membrane followed by internalization of the virus into the host cell. The SARS-CoV-2 antibody in the convalescent plasma/nabs can halt the virus from multiplying and establishing a foothold in the host by interfering with receptor attachment, inhibiting wall fusion after attachment, and preventing uncoating of the virus once inside the cytoplasm[68,69].

With COVID-19, convalescent plasma has been widely used from the early days of the pandemic on a compassionate basis with regulatory approval[70]. However; results from various studies have been inconsistent.

Analysis of large observational data and different Randomized control studies show that when plasma with low SARS-CoV-2 antibody titer or when used later in the disease trajectory or both results in lack of survival benefit, does not halt the progression of the disease or help with stabilization of symptoms[70-72]. COVID-19 patients with moderate to severe ARDS, especially intubated patients do not derive any benefit from convalescent plasma[70-73].

On the contrary, when the plasma has high antibody titer, and patients receive early on at symptom onset in the community or even during early hospitalization when patients have mild to moderate disease, it results in better survival, disease stabilization and halts the progression of the disease[70,73,74].

As *per* Food and Drug Administration (FDA), high titter convalescent plasma corresponds to a neutralizing antibody titer of ≥ 250 in the Broad Institute's neutralizing antibody assay, a signal-to-cutoff of ≥ 12 in the Ortho VITROS immunoglobulin G (IgG) assay, or a level of ≥ 1:2880 in the Mount Sinai COVID-19 ELISA IgG Antibody Test[75].

The role of passive immunization with convalescent plasma or Neutralizing antibodies is to inhibit viral replication early in the disease when the host does not have sufficient antibodies of its own. Once the infection is established, native antibodies are formed and inflammatory processes are at work, at which point the passively transfused antibodies are not helpful[76].

Similarly neutralizing Monoclonal antibodies like Bamlanivimab were found to help reduce viral load, and hospitalization in recently diagnosed mild to moderate COVID-19 disease as outpatient especially in patients with co-morbidities across age groups,

especially in elderly, but not useful in hospitalized severely ill COVID-19 patients[77]. In the yet to be published Blaze-2 trial, Bamlanivimab used as a prophylaxis in nursing home and assisted care home residents were found to decrease symptoms and even have a survival advantage when compared to placebo[78]. And although peer review is pending, this appears to be a promising therapy when used in high-risk patients either as prophylaxis or early disease complementing the huge anticipated benefit of vaccine administration on a large scale.

The FDA has updated its Emergency use authorization on February 4, 2021 and now limits the use of high titer COVID-19 convalescent plasma only for the treatment of hospitalized patients with COVID-19 early in the disease course and to those hospitalized patients who have impaired humoral immunity and cannot produce an adequate antibody response[79].

The recovery trial has reported its findings in a preprint article on the use of high titer convalescent plasma in hospitalized patients which is yet to be peer reviewed [80]. 5795 patients were randomly allocated to receive convalescent plasma and 5763 to usual care alone. There was no significant difference in 28-d mortality between the two groups: 1398 (24%) of 5795 patients allocated convalescent plasma and 1408 (24%) of 5763 patients allocated usual care died within 28 d (RR 1.00; 95%CI: 0.93-1.07; $P = 0.93$). Similarly there was no change in the proportion of patients discharged from hospital, progression of patients not on mechanical ventilation towards intubation, successful cessation from mechanical ventilation or need for RRT. However, the mean number of days from symptom onset was 9, and therefore likely the plasma was not used early enough in the disease course.

Glucocorticoids

Glucocorticoids are one of the oldest, well known, inexpensive, immunomodulatory agents with wide ranging immunosuppressive, anti-inflammatory and anti-allergic effect. They also have a multitude of adverse effects as well[81]. It was therefore natural to test their effectiveness as a therapeutic agent for COVID-19, and although some of the earlier studies did not show any benefit, the "RECOVERY Trial" was the earliest well conducted randomized sontrol trial that showed survival benefit in severely ill patients needing supplemental oxygen and ventilation[82]. The latter study showed that there was mortality benefit with use of dexamethasone.

A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care[77].

Overall 17 percent relative reduction in mortality (22.9 *vs* 25.7 percent, RR 0.83, 95%CI: 0.75-0.93),

Patients on invasive mechanical ventilation or (ECMO) at baseline–36 percent relative reduction (29.3 *vs* 41.4 percent, RR 0.64, 95%CI: 0.51-0.81). Age-adjusted analysis suggested a 12.3 percent absolute mortality reduction.

Patients on noninvasive oxygen therapy (including NIV) at baseline–18 percent relative reduction (23.3 *vs* 26.2 percent, RR 0.82, 95%CI: 0.72-0.94). Age-adjusted analysis suggested a 4.1 percent absolute mortality reduction.

Currently as *per* a pooled meta-analysis, the use of glucocorticoids is estimated to cause 31 fewer deaths *per* 1000 [odds ratio (OR) 0.87, 95%CI: 0.77 to 0.98; risk difference 31 fewer *per* 1000, 95%CI: 55 fewer to 5 fewer], risk of mechanical ventilation is reduced by 28 *per* 1000 (OR 0.73, 0.58 to 0.92; risk difference 28 fewer *per* 1000, 45 fewer to 9 fewer), and duration of hospital stay is reduced by almost 1 d (mean difference -0.99 d, -1.36 to -0.64), all results estimated to be of moderate certainty[83].

With this the use of glucocorticoids became well established as standard of care for the treatment of severely ill COVID-19 patients needing supplemental oxygen and or ventilation. This has been followed by the question whether the standard 6 milligram Dexamethasone *per* day therapy which was used in the RECOVERY TRIAL is sufficient a dose or if there is an incremental benefit by dose increase? Also, another pertinent question is whether there is any benefit of targeting any other specific immune pathways.

While Randomized control data involving the inhibition of complement C5 inhibitor, raviluzumab has not been shown to be of benefit as *per* preliminary unpublished data[84], the role of Interleukin-6 inhibitor, tocilizumab has been quite intriguing.

Tocilizumab

Tocilizumab is an interleukin 6 receptor antagonist monoclonal antibody that has been used to treat patients with COVID-19 respiratory and organ failure targeting a key step in inflammatory mediated damage[68]. Early treatment data in observational and randomized control studies, not involving many critically ill patients and without

Glucocorticoid use showed that Tocilizumab was safe but did not have any significant Clinical outcomes[85-87]. There were six small trials which did not show any significant benefit from Tocilizumab[88]. However, data from "STOP COVID"-a large observational study and "REMAP CAP"-A well designed open label international randomized control study consisting of 803 patients, suggest that "the early use of Tocilizumab on entry to ICU" may have important survival and other outcome benefits in the short term which was not seen in less sick patients studied in randomized control trials outside the ICU[85-87,89]. This was especially noted in patients who had ICU admission within 3 d of symptom onset[89] or had evidence of organ failure on admission to ICU[87]. Participants in the Randomized, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) study also had a relatively larger proportion of patients on glucocorticoids (more than 80%) compared to other studies[86,87]. In "REMAP-CAP" Tocilizumab (n = 353) and Sarilumab (n = 48) each reduced in-hospital mortality compared with standard of care (28 and 22 *vs* 36 percent; OR for hospital survival 1.64, 95%CI: 1.14-2.35 for Tocilizumab and 2.01, 95%CI: 1.18-4.1 for Sarilumab).

The Tocilizumab arm of RECOVERY TRIAL reported preliminary results which are undergoing peer review[88]. This was an open label randomized placebo-controlled trial in which 82% patients took glucocorticoids like dexamethasone. 2022 patients received tocilizumab and 2094 received standard of care. To be eligible for randomization, patients with COVID-19 were to have hypoxia (SpO_2 < 92%) and C-reactive protein more than 75 mg/dL.

Of 596 (29%) patients in the Tocilizumab group and 694 (33%) patients in the usual care group died (RR 0.86; 95%CI: 0.77-0.96; P = 0.007) at 28 d, an absolute difference of 4%. This translates into Numbers Needed to Treat for saving one life of 25.

Tocilizumab also increased the probability of being discharged alive within 28 d from 47% to 54% (RR 1.23, 95%CI: 1.12-1.34, P < 0.0001).

Among patients not on invasive mechanical ventilation when entered into the trial, Tocilizumab significantly reduced the chance of progressing to invasive mechanical ventilation or death from 38% to 33% (RR 0.85, 95%CI: 0.78-0.93, P = 0.0005).

Allocation to Tocilizumab reduced the use of all forms of dialysis (5% *vs* 7%, RR 0.75, 95%CI: 0.59-0.96, P = 0.02).

Tocilizumab did not have any effect on the chance of successful cessation of invasive mechanical ventilation.

These benefits were seen in all patient subgroups, including those requiring oxygen *via* a simple face mask through to those requiring mechanical ventilators in an intensive care unit.

Tocilizumab is estimated to reduce the relative risk of death by 14% and reduced the time spent in hospital by 5 d when used for patients on oxygen and in addition to the corticosteroid dexamethasone[90].

Taken together data from all 8 trials, use of tocilizumab was associated with 13% proportional reduction in 28-d mortality (death RR 0.87, 95%CI: 0.79-0.96, P = 0.005). It is noteworthy that these mortality benefits were noted in the RECOVERY TRIAL only in patients receiving concomitant steroids.

In summary, it appears that in severely ill COVID-19 patients with hypoxia accompanied by hyper inflammatory state, the early concomitant use of glucocorticoids and Tocilizumab improves outcomes including survival, organ support and progression of disease, suggesting additive or synergistic effect with these two agents.

This beneficial data appears to be quite specific for Tocilizumab, as the numbers of patients with Sarilumab in REMAP-CAP study were few. Trials involving Sarilumab are in progress and results are expected in the future[88].

The United Kingdom government and Center for disease control have expeditiously approved the use of Tocilizumab based on data from REMAP-CAP and RECOVERY TRIALS[90,91]. Other government and Professional societies are expected to update their guidelines soon as well.

Remdesivir

Remdesivir is an inhibitor of "viral RNA dependent RNA polymerase" which inhibits SARS-COV-2 *in vitro*[92] but has not been shown to decrease viral load when compared to placebo[93]. It has been studied extensively in clinical trials and the findings are summarized below.

The outcome data has been measured using the multipoint ordinal scale with each number denoting a particular "clinical status" and the changes are measured and reported accordingly[92-94].

In the international, multicentric auditory consonant trigram test-1 study conducted by the National Institute of Allergy and Infectious Diseases and others, 541 patients were assigned to Remdesivir and 521 to placebo in a double-blind placebo-controlled trial; the study drug was given intravenously for 10 d. A significant number of patients had severe disease with SpO_2 less than 94% by definition and requiring supplemental oxygen. It reported a primary outcome of improved median recovery time of 10 d compared to 15 d with placebo. There was a trend to improvement in mortality which was not statistically significant, 11.4% and 15.2% in two groups, respectively [hazard ratio (HR) 0.73; 95%CI: 0.52-1.03] by day 29. In sub-group analysis, there was mortality benefit noted in patients who were on simple low flow oxygen, (HR 0.30; 95%CI: 0.14-0.64). Remdesivir also showed shorter hospital length of stay, reduced disease progression, and lesser utilization of respiratory assist devices like oxygen, invasive mechanical ventilation, and ECMO[92].

In the World health organization led SOLIDARITY trial[95], which was conducted at multiple sites in 30 countries, 11330 adults underwent randomization. Death occurred in 301 of 2743 patients receiving Remdesivir and in 303 of 2708 receiving its control (RR 0.95; 95%CI: 0.81-1.11; $P = 0.50$) showing no survival benefit. In this study which had good adherence, Remdesivir was given intravenously for 10 d. Remdesivir did not reduce the incidence of new ventilation.

In another randomized control trial, for patients with moderate clinical disease (Pulmonary infiltrates with SpO_2 more than 94% by definition); Remdesivir did not demonstrate any difference in clinical status when compared to placebo after a 10-d course. Interestingly, the same study showed improvement in clinical status after a 5-d course. The study was confounded by open-label design and imbalances with co-therapy and therefore the significance is unknown[96].

Other randomized control trials did not show any difference in clinical status outcome between a 5 and a 10-d course of Remdesivir[33,34] and the drug is generally safe with no significant adverse effects[92,94,96,97].

Barcitinib, an oral selective Janus kinase inhibitor 1 and 2 inhibitors impair cell entry of the SARS-CoV-2 virus and inhibits cellular signaling pathway. It has been tested in RCT in combination with Remdesivir and compared to placebo it has improved median time to recovery by 1 d (RR for recovery, 1.16; 95%CI: 1.01-1.32; $P = 0.03$). At 15 d, time to recovery favors the drug combination. In sicker patients who are on NIV or high flow oxygen the time to recovery was 10 d compared to 18 d. (RR for recovery, 1.51; 95%CI: 1.10-2.08). However, given the lack of efficacy for survival, in practice, it can be used with Remdesivir, when steroids are contraindicated[98].

In summary in patients with severe disease (SpO_2 less than 94% with pulmonary infiltrates) and risk of the hyper inflammatory response, Remdesivir may help improve time to clinical recovery and reduce duration of hospitalization, but does not improve survival[92-94,99-101]. It is likely not very helpful or may have very modest benefits in patients who have mild to moderate disease (Pulmonary infiltrates with SpO_2 more than 94%)[34,96,100]. As *per* a meta-analysis, it may help to reduce the need for ventilation but the effect may not be large. It may help to reduce serious adverse events and may aid with some recovery. For non-ventilated patients, a 5 d course compared to 10 d course results in reduced costs, more benefits and less harm[101].

With lack of improvement in survival, the soft benefit of improvement in clinical status, the need to be given by intravenous infusion often as an inpatient over 5 d, lack of cost effectiveness and an endless number of patients with this pandemic, remdesivir is not an optimal answer where the treatment needs to be inexpensive, scalable and equitable[99,101,102]. However since it does reduce time to clinical recovery and reduces duration of hospitalization among survivors, it can help free up inpatient resources in a pandemic and hence gets approval from FDA and Infectious disease society of America[101,103].

Hydroxychloroquine

It is an immunomodulatory drug that has been used extensively in rheumatological disorders. It was repurposed for use in COVID-19 patients and many governments around the world including the United States allowed emergency authorization for its use. Its mechanism of action appears to be by inhibiting glycosylation of ACE2 receptors and increasing the pH of endosomes, in effect preventing virus entry into the cells[104,105].

Many studies have been performed with or without concomitant use of azithromycin compared to placebo after initial case reports and non-randomized studies showed efficacy for the drug against SARS-CoV-2[104]. However, none of the randomized control trials, systematic reviews, and meta-analyses, with or without Azithromycin has shown any benefit for Hydroxychloroquine with regards to survival

[92,104,105]. Likewise, there is no benefit with regards to the length of hospitalization, virological cure rate, clinical status score based on a multipoint ordinal scale, need for mechanical ventilation, and radiological improvement[92,104,105]. There was concern over QT prolongation due to both hydroxychloroquine and azithromycin having those properties as well as concern for the possibility of other side effects without much proven benefit as noted before[104,106]. Currently, both these drugs are not used for COVID-19.

ECMO and COVID-19

ECMO is a resource-intensive therapy that has been used when conventional critical care management has failed to help the patient[107]. It has been used in previous pandemics like pandemic influenza A with variable success[108].

It is recommended by experts that ECMO be offered only at experienced centers that have adequate manpower and material resources as well as expertise in managing them, as every aspect of its care from patient selection, maintenance and liberation is highly specialized and nuanced[107]. In fact when regions are under crises level of care amid a surge of cases, then it may be difficult to offer highly resource-intensive therapies like ECMO[107].

The indications, contraindications, and general principles of ECMO care in COVID-19 remain the same[107] with some finer changes to approach and management. It is preferred that aerosolization of the virus is limited and hence transportation is restricted. Cannulation is best performed at the bedside in the ICU. Tracheostomy which is often performed to help lighten sedation and facilitate decannulation needs to be restricted. All personnel need to observe full barrier precautions[107]. Nevertheless, there is evidence that tracheostomy can be safely managed with standard full barrier precautions as mentioned elsewhere in this article and likely guidelines may change. The patient may not be able to be prone due to cannula and likewise, mobilization may be restricted[107].

Patients with COVID-19 often require deep sedation due to various factors and hence post ECMO delirium may need more supportive ICU care or discharge to specialized rehabilitation centers[107,109]. Veno venous ECMO is the most commonly used ECMO for respiratory failure and outcomes are better with this modality compared to veno arterial ECMO which is used only when concomitant circulatory support is necessary[107,109]. Given the high incidence of thrombosis in COVID-19, therapeutic anticoagulation keeping activated partial thromboplastin time 1.5 to 2.5 times normal is recommended often bordering on the higher side[107] to prevent clot formation in the oxygenator and other parts of the circuit.

Initially reports suggested poor outcomes with ECMO[110] with mortality in the range of 80%-100% but subsequently, a report from the Extracorporeal Life Support Organization registry which included only experienced centers suggested that the 90-d mortality in more than 1000 carefully selected patients was about 40% and this compares reasonably well with non-COVID-19 patients, indicating that when patient selection is optimal and with the application of best principles of standardized care, the outcomes can be optimal in COVID-19[109].

RRT

RRT is a term that denotes a process of replacing the non-endocrine function of the kidney in acute or chronic kidney injury/disease encompassing filtration across the permeable membrane, exchange of solute and electrolytes along with the removal of fluid[111]. There are different modalities which include standard intermittent hemodialysis (IHD), continuous RRT (CRRT), prolonged intermittent RRT (PIRRT), and peritoneal dialysis[112]. CRRT or its variates are preferred in critically ill patients due to their superior ability for fluid removal, causing less hemodynamic instability and consistent metabolic control[112]. It also provides for predictable dosing of medication in renal failure. However, CRRT is not superior to IHD when it comes to survival or Renal recovery[112].

CRRT functions by way of three different mechanisms namely convection, diffusion, and adsorption by the filtering membrane[113]. Different modalities or techniques which employ one of these machines are used such as simple diffusion (continuous venovenous hemodialysis), convection (continuous venovenous hemofiltration), or a combination of both (continuous venovenous hemodiafiltration)[114]. No one technique is superior to the other overall and employing any of them is a matter of availability, patient characteristics, and clinician judgment or preference[114]. Timing of RRT, whether early or late after diagnosis of acute kidney injury (AKI) and establishing indication for RRT has been an important question for many well-conducted clinical trials, largely demonstrating equivocal outcomes[113].

There is a paucity of COVID-19 data for RRT. Recommendations from guidelines have essentially been an extension from the non-COVID-19 population with emphasis on limiting staff exposure and optimal utilization of resources during the pandemic [114]. Full standard barrier precautions for staff taking care of ICU patients are recommended[114]. CRRT is ideal for ICU patients which can be managed by ICU nurses but if limited PIRRT can be used which will optimize resource utilization[114]. IHD consumes more specialized resources and equipment along with a dedicated dialysis nurse in full attendance for the duration of the session and is, therefore, less preferred[112]. Access to CRRT is essential with the right internal jugular vein being preferred especially if proning followed by femoral access, left internal jugular vein, and subclavian veins[112].

COVID-19 has been recognized as a prothrombotic disease having consequences for filter life, and as such regional citrate anticoagulation can be used if already in use in the institution. The latter should not be started if such practices are not already in vogue[113,115]. Systemic anticoagulation with low molecular weight heparin or Ultra fractionated heparin or other agents may be necessary to prolong the life of the circuit but specific evidence-based anticoagulation protocols are lacking in the literature [116]. Extracorporeal blood purification with RRT has been proposed as a therapeutic strategy to remove cytokines and other biological immune mediators to improve clinical outcomes. However, evidence for such therapies is currently lacking and is recommended only in the context of clinical trials[116,117].

In a systematic review of COVID-19 patients with AKI, involving 51 studies and 21531 patients, the incidence of AKI was found to be 12.3%. Patients with transplants had a higher rate of AKI at 38.9% (290 patients) and 39% in ICU patients (565 patients). Patients who did not survive had higher rates of AKI at 42% (1745 patients)[118].

RRT use was reported in 39 studies involving 17,664 patients. With overall use of 5.4% with higher rates noted in 16.3% in ICU patients (776 patients), and 15.6% in transplant patients (117 patients)[118]. AKI was more common in studies from North America, followed by Europe, and was least noted in China[118]. There is increasing evidence that both AKI and the need for RRT are important factors influencing survival in COVID-19 patients[112].

CONCLUSION

It was Sir William Osler who inspired by Thomas Carlisle said, "It is not our goal to see what lies dimly in the distance but to do what lies at hand".

The COVID-19 pandemic has continued to teach us many important medical, social, political, economic, and humane lessons at a huge cost. Early on with a limited understanding of the virus, its transmission, spread in the community and the medical management of the disease, our response as a global community was reactive, guided by abundant caution. Medical practices and literature consisted of non-peer-reviewed articles, case reports, and case series consisting of incomplete and non-standardized data resulting in approaches and clinical management which were not scientifically sound, exposing patients to potentially nonbeneficial or even harmful treatment strategies[119,120].

Organized efforts to develop sound epidemiological, demographic, and evidence-based data resulted in governmental organizations (*e.g.*, United Kingdom based Recovery trial), international trial networks (*e.g.*, REMAP-CAP), The Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study COVID-19 Registry and others who were well-positioned to rapidly deploy pragmatic trials, design data collection networks to meet data analytic needs in response to the COVID-19 pandemic[119,120].

As evident from our review, the application of sound scientific evidence-based management principles distilled from decades of research in the past, with some accommodations in practices specific to the SARS-CoV-2, mitigation strategies, along with the careful implementation of disaster management principles in times of surge have resulted in better and superior outcomes. This is borne out by the fact that although outcomes have varied highly between centers[121], they have generally improved with time[122], especially when health care delivery systems are not stressed due to surge[123]. This is evident by one organization's meticulous and highly diligent efforts to manage the pandemic by way of standardized, protocolized management principles accommodating new information as well as providing room for research opportunities[124]. This along with rapid large-scale effective immunization provides us hope to get back our lives and business back to normal

soon.

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MINIREVIEWS

Glucocorticoid and mineralocorticoid receptor expression in critical illness: A narrative review

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Abstract

The glucocorticoid receptor (GCR) and the mineralocorticoid receptor (MR) are members of the steroid receptor superfamily of hormone-dependent transcription factors. The receptors are structurally and functionally related. They are localized in the cytosol and translocate into the nucleus after ligand binding. GCRs and MRs can be co-expressed within the same cell, and it is believed that the balance in GCR and MR expression is crucial for homeostasis and plays a key role in normal adaptation. In critical illness, the hypothalamic-pituitary-adrenal axis is activated, and as a consequence, serum cortisol concentrations are high. However, a number of patients exhibit relatively low cortisol levels for the degree of illness severity. Glucocorticoid (GC) actions are facilitated by GCR, whose dysfunction leads to GC tissue resistance. The MR is unique in this family in that it binds to both aldosterone and cortisol. Endogenous GCs play a critical role in controlling inflammatory responses in critical illness. Intracellular GC concentrations can differ greatly from blood levels due to the action of the two 11β-hydroxysteroid dehydrogenase isozymes, type 1 and type 2. 11β-hydroxysteroid dehydrogenases interconvert endogenous active cortisol and intrinsically inert cortisone. The degree of expression of the two isozymes has the potential to dramatically influence local GC availability within cells and tissues. In this review, we will explore the clinical studies that aimed to elucidate the role of MR and GCR expression in the inflammatory response seen in critical illness.

Key Words: Mineralocorticoid receptor; Glucocorticoid receptor, Critical illness; 11beta-hydroxysteroid dehydrogenase; Aldosterone; Cortisol

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Core Tip: Endogenous glucocorticoids (GCs) play a critical role in controlling inflammatory responses in critical illness. Intracellular GC concentrations can differ greatly due to the action of the two 11β-hydroxysteroid dehydrogenase isozymes. The degree of expression of the two isozymes has the potential to dramatically influence local GC availability. The GC receptor and the mineralocorticoid receptor are members of the steroid receptor superfamily of hormone-dependent transcription factors. The study of the mineralocorticoid receptor and GC receptor expression and function in the inflammatory response seen in critical illness might aid in identifying the patients who will benefit from exogenous corticosteroid administration.

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INTRODUCTION

The glucocorticoid receptor (GCR) and the mineralocorticoid receptor (MR) are members of the steroid receptor superfamily of hormone-dependent transcription factors. The receptors are structurally and functionally related. They are localized in the cytosol and translocate into the nucleus after ligand binding. GCRs and MRs can be co-expressed within the same cell, and it is believed that the balance in GCR and MR expression is crucial for homeostasis and plays a key role in normal adaptation.

In critical illness, the hypothalamic-pituitary-adrenal (HPA) axis is activated, and as a consequence, serum cortisol concentrations are high. However, in a number of patients cortisol levels are relatively low for their illness severity. Glucocorticoid (GC) actions are mediated by GCR, whose dysfunction leads to GC tissue resistance. The MR is unique in this family in that it binds to both aldosterone and cortisol.

Endogenous GCs play a critical role in controlling inflammatory responses in critical illness. Intracellular GC concentrations may be greatly different compared to blood levels due to the action of the 11β-hydroxysteroid dehydrogenase (11β-HSD) isozymes, type 1 and type 2. 11β-HSDs interconvert endogenous active cortisol and intrinsically inert cortisone. The degree of expression of the two isozymes has the potential to dramatically influence local GC availability within cells and tissues.

GCR

During critical illness the HPA axis is activated, resulting in increased serum adrenocorticotropic hormone and cortisol concentrations[1-4]. However, a subset of patients present with low serum cortisol levels despite their illness severity[5,6]. Critical illness-related corticosteroid insufficiency (CIRCI) is characterized by the organism's inability to produce adequate cortisol or tissue resistance to its actions, or both[7].

Sepsis and septic shock are the most common causes of mortality in critically-ill patients. GCs, the end-products of the HPA axis, have been used for over 40 years in the treatment of sepsis. The Surviving Sepsis Campaign Guidelines 2016 recommended hydrocortisone administration when despite adequate fluid resuscitation and vasopressor therapy, the hemodynamic stability in septic shock cannot be restored[8]. However, not all patients benefit from their administration, and as yet the patients who would benefit from their use cannot be accurately identified[9-12].

Cortisol signaling is mediated by GCR, a ubiquitous intracellular receptor protein. Alternative splicing of the primary transcript gives rise to two highly homologous GCR isoforms[13]. GCR-α is the functionally active receptor; once it binds to cortisol, the receptor-cortisol complex translocates from the cytosol to the nucleus. In the nucleus, the complex exerts transcriptional activation or repression by directly binding to genes that contain GC responsive elements[14], resulting in the inhibition of the

inflammatory response[15,16]. On the contrary, the function of GCR-β has not been well-explored. It is known to suppress GCR-α activity and is unable to bind both natural and synthetic ligands[17-19]. Figure 1 diagrammatically represents cortisol signaling *via* GCR.

The Sepsis-3 guidelines suggest the use of hydrocortisone in septic shock patients who are resistant to fluid administration and vasoactive agents[20]. Not all patients respond to this therapy, suggesting the existence of GC resistance. GC resistance is defined as the inability of GCs to exert their effects on target tissues[21]. It is characterized by decreased sensitivity of immune cells to GCs, which under normal conditions terminate the inflammatory response[22]. Therefore, it becomes apparent that apart from cortisol levels, how tissues respond to cortisol is as important. It has been suggested that the extent of cortisol's effect might be analogous to GCR expression, subtype and affinity in a specific target cell[23]. Such an example is the increased expression of *GCR-β* in certain tissues in inflammatory diseases, which has been associated with decreased sensitivity to GCs[24].

GC resistance may be a consequence of decreased *GCR* expression, GCR affinity for the ligand, nuclear translocation and DNA binding or may be due to altered transcription factor interaction. Most data on GC resistance in critical illness originates from experimental models involving sepsis-induced injury[25-29]. Essentially these studies have shown downregulation of *GCR-a* and induction of *GCR-β* expression[30-33].

Human clinical studies in critically-ill patients have mostly investigated cortisol availability, while only a few have explored the role of GCR. GC resistance has been described in a cohort of septic patients, demonstrating reduced *GCR-a* and elevated *GCR-β* expression levels in septic patients compared to healthy subjects; these results suggest that treatment with steroids might aggravate GC resistance in patients with increased GCR-β levels[34]. A transient, increased *GCR-β* expression has been reported in sepsis; moreover, the septic patients' sera could induce GC resistance *in vitro*[35]. Another study reported reduced *GCR-a* expression levels in sepsis[36], and diminished GCR protein levels have also been described in various organs during sepsis[37]. A decreased number of GCR-α and increased GCR-β receptors has been shown in heart and liver biopsies in the context of sepsis[25]. It has been shown that in septic shock, *GCR* expression increased, while GCR binding capacity decreased, proposing that it is the decreased GCR binding capacity and not the number of receptors that interferes with the response to exogenous or endogenous GCs[38]. In contrast, GCR number and affinity in septic patients did not differ from control subjects, suggesting that GCs could be effective in the hemodynamic compensatory phase of sepsis[39]. Increased *GCR-a* expression has been shown in the acute phase of sepsis, questioning the need for exogenous steroids at this phase[40]. Only one study has demonstrated downregulation of cortisol binding in critically-ill, ventilated patients[41]. Finally, our group was able to demonstrate that critically-ill steroid-free patients have a highly variable expression of both GCR isoforms in peripheral polymorphonuclear cells. Moreover, *GCR* expression and HPA axis function undergo a biphasic response during acute or subacute critical illness; this dissociation of reduced *GCR* expression and elevated cortisol might imply an abnormal stress response[42,43].

In coronavirus disease 2019 (COVID-19), results from the RECOVERY trial suggested significant benefits of steroid administration in critically-ill COVID-19 patients[44]. Specifically, the trial demonstrated that dexamethasone reduced mortality risk by 17%. A study in noncritically-ill COVID-19 patients showed that the HPA axis was activated. Patients exhibited an increase in cortisol, which was significantly higher than in those without COVID-19 infection, and these cortisol levels were associated with higher mortality rates[43]. Another study found that cortisol levels were lower in critically-ill COVID-19 patients compared to critically-ill non-COVID-19 patients[45]. In fact, nearly 70% of the COVID-19 critically-ill patients had plasma cortisol concentrations < 10 μg/dL, meeting CIRCI criteria. However, so far, data on COVID-19 and *GCR-a* expression are lacking.

Ascorbic acid (vitamin C) levels are depleted in critically-ill patients. This vitamin has been shown to play a crucial role in HPA axis function. The adrenal glands contain very high concentrations of ascorbic acid and use it to synthesize cortisol[46]. At the cellular level, vitamin C works synergistically with corticosteroids by restoring GCR function. Specifically, ascorbic acid reverses GCR oxidation, restoring GC-responsiveness in oxidant conditions. The end result is increased GC availability and GCR-α activation[47].

Overall, it seems that during critical illness *GCR* expression is independently regulated. This might explain the different responses seen in patients to exogenously administered steroids or endogenously secreted cortisol. Apart from *GCR* expression,

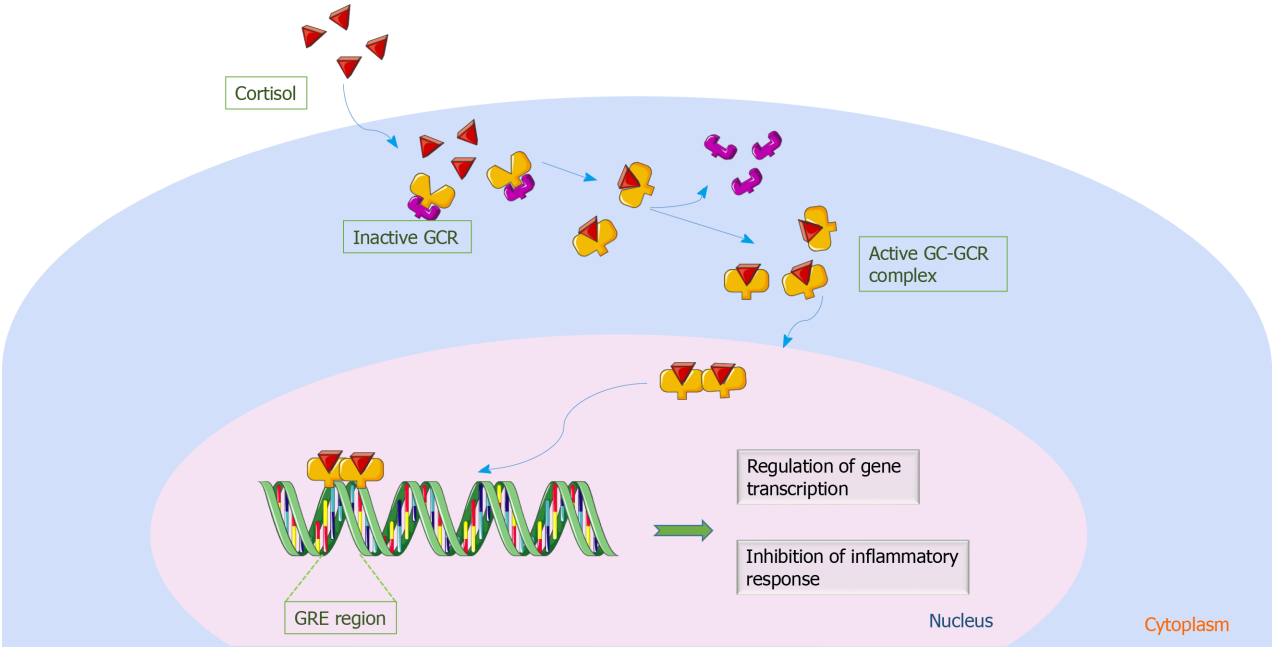

Figure 1 Cortisol signaling through the glucocorticoid receptor. Cortisol signaling is mediated by a ubiquitous intracellular receptor protein, the glucocorticoidreceptor (GCR). Once it binds to cortisol, the receptor-cortisol complex translocates from the cytosol to the nucleus. In the nucleus, the complex exerts transcriptional activation or repression by directly binding to genes that contain glucocorticoid (GC) responsive elements (GREs), resulting in the inhibition of the inflammatory response. GC-GCR: Cortisol-glucocorticoid receptor complex.

the role of post-translational modifications, GCR complex components and the efficiency of nuclear translocation of the GCR complex should be the focus of future clinical studies.

MR

The MR is, along with the GCR, a member of the steroid receptor superfamily of hormone-dependent transcription factors. The receptors are structurally and functionally related. Similar to GCR, MR is also localized in the cytosol and translocates into the nucleus after ligand binding. In the nucleus, the ligand-receptor complex recognizes specific DNA regions and activates target gene expression[48]. While GCR is relatively ubiquitously expressed and exclusively binds GCs, the MR shows a more restricted expression pattern, and can bind both aldosterone and cortisol. MR is mostly expressed in epithelial cells of renal distal tubules, colon, sweat and salivary glands, and is implicated in sodium reabsorption, water homeostasis and potassium secretion[49]. The classical ligand for MR is aldosterone, the main mineralocorticoid steroid hormone, through activation of the renin-angiotensin system. Aldosterone is the principal regulator of salt and water balance but can also act on nonepithelial sites, contributing significantly to cardiovascular disease[50].

Hyperreninemic hypoaldosteronism may occur during critical illness and has been associated with a greater proinflammatory status, a higher degree of acute organ failure, and worse prognosis. It has been attributed to impaired adrenal response to increasing renin levels[51-53]. The recent demonstration of the reduced mortality in septic shock patients treated with adjunctive GCs combined with fludrocortisone[9], and the effectiveness of angiotensin II in treating vasodilatory shock[54] has renewed interest in the role of the MR in critical illness[55].

The MR, originally thought to be expressed only in kidneys, is now known to have a wider distribution. At the organ level, it is expressed in heart, vessels, brain, and adipose tissue[56]. MR signaling induces inflammation, oxidative stress, and fibrosis/remodeling, thereby causing tissue and organ damage, particularly in the heart and vessels[49]. Furthermore, clinical studies have reported a beneficial outcome of MR antagonism in patients with cardiovascular diseases, mainly due to the prevention of inflammatory damage[57]. At the cellular level, MR is expressed in vascular cells, adipocytes, and immune cells[58]. This inflammatory involvement of MR and aldosterone in cardiovascular diseases suggests an association with immune

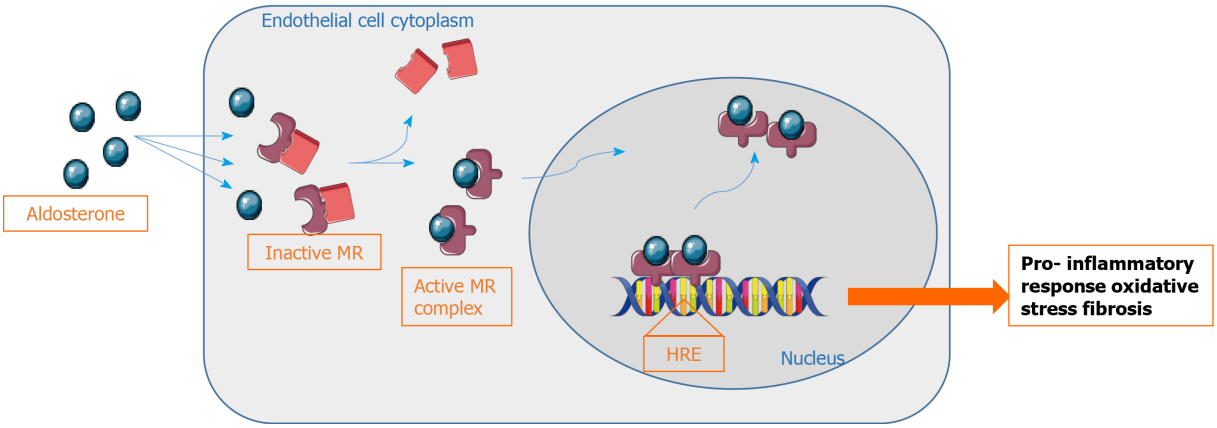

Figure 2 Mineralocorticoid signaling. The mineralocorticoid receptor is localized in the cytosol and translocates into the nucleus after ligand binding. In the nucleus, the aldosterone-mineralocorticoid receptor (MR) complex recognizes specific DNA regions, and activates target gene expression. MR signaling induces inflammation, oxidative stress, and fibrosis/remodeling, thereby causing tissue and organ damage. HRE: Hormone response element.

system changes. It has been consistently reported that aldosterone stimulation promotes proinflammatory responses[59,60]. In human leukocytes, MR expression has been shown in CD34+ hematopoietic progenitor cells, in peripheral blood T and B lymphocytes, macrophages, dendritic cells, and neutrophils[61]. In macrophages, lymphocytes and dendritic cells, MR signaling induces proinflammatory responses[62, 63]. The MR antagonist, spironolactone, was shown to have anti-inflammatory effects on cultured human peripheral blood mononuclear cells isolated from healthy subjects. Furthermore, angiotensin II induced aldosterone synthesis and enhanced cytokine production through an MR-dependent mechanism in human peripheral blood mononuclear cells[64,65]. In Figure 2, MR signaling is depicted.

11β-HSD

Both the innate and adaptive immune responses depend on the adhesion and migration of leukocytes across endothelial cells towards the inflamed site, where they protect against invading pathogens and repair damaged tissue. At the inflamed site, neutrophils undergo constitutive apoptosis to be removed from the inflammatory environment. Normally, acute inflammation rapidly resolves. However, failure to rapidly remove apoptotic neutrophils prolongs the inflammatory response. As mentioned above, endogenous GCs play a critical role in controlling inflammatory responses. Although GCs have an immunosuppressive effect on immune cells, they exert contradictory effects on neutrophils. At the inflamed sites they exert an anti-inflammatory effect by blunting neutrophil priming, whereas they increase circulating neutrophil count by delaying their apoptosis[66]. In circumstances of uncontrolled inflammation, polymorphonuclear cells can become detrimental by causing tissue injury and organ damage in critical illness[67].

Intracellular GC concentrations may vary compared to blood levels due to the action of the two 11β-HSD isozymes. 11β-HSD interconverts endogenous active cortisol and inert cortisone, which does not bind to GCR[68]. 11β-HSD2 (encoded by the *HSD11B2* gene) inactivates GCs, while 11β-HSD1 (encoded by *HSD11B1*) regenerates active GCs from inert keto forms, and hence modulates GC-regulated functions. Moreover, 11β-HSD1 is widely expressed in tissues that express high levels of GCR, suggesting that 11β-HSD1 modulates ligand access to GCR-α[68]. The degree of expression of these two isozymes may drastically affect local GC availability within individual cells and tissues.

11β-HSD1 is widely distributed, with its expression being highest in the liver, but is also expressed in adipose tissue, vessels, brain, and immune cells. In immune cells, 11β-HSD1 is primarily expressed in macrophages and lymphocytes, especially during inflammation[56,62,69]. 11β-HSD1 activates functionally inert GC precursors (cortisone) to active GCs (cortisol) within target tissues, and amplifies local GC actions. 11β-HSD2, except being expressed in the classical aldosterone-target tissues, is also expressed in the pancreas and the reproductive system[68]. 11β-HSD2 protects the MR from illicit occupancy by cortisol by inactivating cortisol within cells.

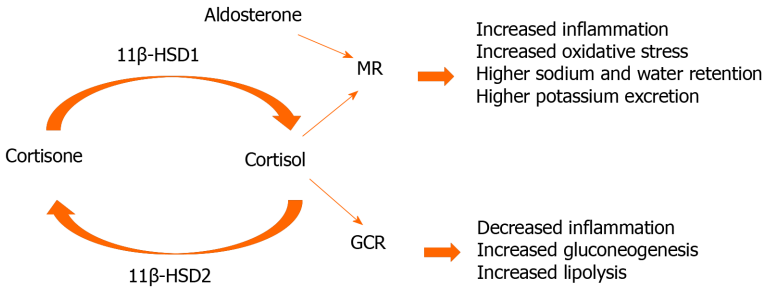

Figure 3 Glucocorticoid and mineralocorticoid receptor function, and the role of 11β-dehydrogenase isozymes. The ubiquitous glucocorticoid receptor (GCR) binds exclusively to cortisol, whereas the mineralocorticoid receptor (MR) is a receptor with equal affinity for mineralocorticoids and glucocorticoids. In epithelial tissues, MR activation leads to the expression of proteins regulating ionic and water transports, resulting in the reabsorption of sodium, and as a consequence an increase in extracellular volume, increase in blood pressure, and excretion of potassium to maintain a normal salt concentration in the body. The MR is activated by aldosterone and cortisol. Target cells for aldosterone express the enzyme 11β-dehydrogenase (11β-HSD) 2 that has no effect on aldosterone, but converts cortisol to cortisone, which has only a very weak affinity for the MR In essence, this enzyme "protects" the cell from cortisol and allows aldosterone to act appropriately. 11β-HSD1 activates functionally inert cortisone to active cortisol within target tissues and amplifies local glucocorticoid actions.

Aldosterone and cortisol bind the MR and have a similar affinity for the MR. The binding of cortisol or aldosterone to the MR results in different cellular responses[55]. Under physiological conditions, plasma cortisol levels are 100 × higher than aldosterone levels, and most MRs are occupied by GCs. The 11β-HSD enzymes regulate whether cortisol or aldosterone will bind to the MR. 11β-HSD type 2 metabolizes cortisol to inactive cortisone. Cortisone is unable to bind or activate the MR, and aldosterone occupies the MR. When 11β-HSD2 is not present or not functional, the ligand binding site on the MR is occupied by cortisol.

11β-HSD2 is mainly expressed in the classical aldosterone (mineralocorticoid)-target tissues, including the distal nephron, sweat and salivary glands, and colonic epithelium. 11β-HSD1 catalyzes the regeneration of active GCs, particularly in GC-target tissues, where it amplifies GC actions. *In vitro*, colocalization of the two enzymes within a cell results in their reciprocal regulation to minimize simultaneous expression [68]. Figure 3 diagrammatically shows the interplay between the corticoid receptors, their ligands and the 11β-HSD isozymes.

Although the immunosuppressive and anti-inflammatory activities of GCs are well documented, the expression of 11β-HSD enzymes in immune cells, and in particular polymorphonuclear cells, is not well understood. Overall, an anti-inflammatory role for 11β-HSD1 has been proposed in leukocytes, while studies have suggested that 11β-HSD2 is not expressed in these cells[70]. In human T-lymphoblastic leukemia cells, both 11β-HSD2 expression and reciprocal regulation of 11β-HSD1 and 11β-HSD2 have been shown to be associated with GC resistance[71,72].

Data for tissue resistance to GC activity are limited in critical illness. Indirect evidence suggesting altered tissue 11β-HSD activity comes from studies that found increased plasma cortisol:cortisone ratio in critically-ill septic and trauma patients[73, 74]. A recent study showed that in septic shock patients, sensitivity to GCs does not appear to be mediated by changes in the expression of the 11β-HSD2 isozyme[75]. Whether the reciprocal change in 11β-HSD1/11β-HSD2 is part of an adaptive response to inflammation or contributes to GC resistance remains to be established.

CONCLUSION

Studies on the expression of GCR, MR, 11β-HSD1 and 11β-HSD2 in critically-ill patients may allow a better understanding of homeostatic regulations of GCR and MR.

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MINIREVIEWS

Predictive modeling in neurocritical care using causal artificial intelligence

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Abstract

Artificial intelligence (AI) and digital twin models of various systems have long been used in industry to test products quickly and efficiently. Use of digital twins in clinical medicine caught attention with the development of Archimedes, an AI model of diabetes, in 2003. More recently, AI models have been applied to the fields of cardiology, endocrinology, and undergraduate medical education. The use of digital twins and AI thus far has focused mainly on chronic disease management, their application in the field of critical care medicine remains much less explored. In neurocritical care, current AI technology focuses on interpreting electroencephalography, monitoring intracranial pressure, and prognosticating outcomes. AI models have been developed to interpret electroencephalograms by helping to annotate the tracings, detecting seizures, and identifying brain activation in unresponsive patients. In this mini-review we describe the challenges and opportunities in building an actionable AI model pertinent to neurocritical care that can be used to educate the newer generation of clinicians and augment clinical decision making.

Key Words: Artificial intelligence; Digital twin; Critical care; Neurology; Causal artificial

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Core Tip: The modern clinical environment is increasingly surrounded by data. The existing literature is sparse concerning the creation of a "digital twin" artificial intelligence (AI) model as a tool for education and potentially clinical decision making in the neurologic intensive care unit setting. This mini review will give readers an introduction to applications of AI inside and outside of healthcare, the idea of the "digital twin" as a model of disease, how AI has been applied in neurocritical care, and methodology for building a neurocritical care digital twin AI model that is based on a solid understanding of underlying pathophysiology.

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INTRODUCTION

The National Academy of Medicine released a report in 2010 highlighting recommendations with regards to what the United States Department of Health and Human Services can do to improve population health[1]. One of the suggested approaches in the report highlighted that the biological and environmental causes of poor health are complex and inter-related. Computer simulation models and other novel analytical tools such as artificial intelligence (AI) can potentially elucidate these relationships and help us better understand the underlying pathophysiology. The main pre-requisite for such models is that they should be built on the foundation of plausible biological and physiological understanding and algorithms.

In a world increasingly surrounded by data, digital twins have been used in everything from wind turbines to cities to spacecraft to model processes and preempt problems[2]. The European Union has even been attempting to create a digital twin model of planet earth to better forecast weather and predict climate change[3]. It would not be unreasonable to think that these technological advances could be applied to the field of healthcare as well. With the recent rise of electronic medical records, more sophisticated monitoring, and molecular biology in healthcare, digital twin technology provides a unique opportunity to personalize medicine to the level of the individual patient[4]. Digital twins are able to integrate vast amounts of data to create digital replicas of the physical environment and acts as models that are able to inform clinical decision making in an actionable way[5].

There is a need to evaluate the status of research on the use of simulation applications by various medical and surgical specialties to identify and recommend areas of research wherein there is a significant knowledge gap. This urgency is further compounded by the issue that medical errors are one of the leading causes of death in the United States[6]. Whether the use of simulation models by expert clinicians (or trainees) will improve the overall patient outcomes in clinical practice remains a challenging research question. Yet, it would be unquestionably helpful to test medical decisions in an "in silico" environment before attempting our treatment strategies on real patients. Such a testing environment would be especially useful to evaluate management decisions of uncertain benefit the patients.

WHAT IS A DIGITAL TWIN?

Digital twins are a concept from engineering whereby digital models of a system are built to allow testing of products more efficiently and economically[2]. The development of the use of a "Twin AI" for predictive modeling in health care first caught attention in 2003 with the Archimedes project, which sought to model the

complicated management of diabetes and was validated to 18 different trials involving diabetes with a very high correlation despite the fact that the trial data was not used to develop the model[7]. These new digital twin AI models are able to integrate the various demographic and individual-specific factors that complicate diabetes management on a level that the human brain cannot[8]. In addition to proving an accurate predictive model at the population level, Archimedes has also been shown to make accurate predictions for individuals[9]. The high accuracy of prediction and fidelity of the model led to its use in in-silico clinical trials, thereby saving crucial time, millions of dollars and most importantly shielding patients from being exposed to harm from interventions that may or may not have been beneficial[8,10].

In clinical practice, the concept of digital twins has also been applied to the fields of cardiology and endocrinology[11-13]. In cardiology, a few digital twin models have recently been developed to allow clinicians to provide precise care tailored to the patient by considering inter-individual variability and integrating the wide spectrum of biologic, environmental, and lifestyle data that influence cardiovascular outcomes. However, there is still much work to be done before these models become common in clinical practice[12]. Additionally, AI has been used to create large-scale synthetic data for training of other machine learning algorithms[14]. In Endocrinology, an AI model of the pancreas has been developed for use in the critical care setting to manage patients' glucose levels[13].

In the field of undergraduate medical education, programs that utilize an AI model of physiology, such as justphysiology and sycamore, have recently been incorporated in curricula[15]. These simulations afford the benefits of providing a safe practice environment for trainees, exposing students to a range of pathology that is not restricted to the available patient population, and getting students to engage actively with the underlying physiological principles involved in chronic disease management. While these models are based on solid mathematical models of human physiology, they are focused on chronic disease management rather than the acute pathology seen in critical care units and are unable to adapt to prospective data from real-time patients.

Digital twin AI models can be developed as "associative models" (mostly data driven) or "actionable models" (based on causal inference). Associative models are built using retrospective electronic health record data, which is more readily available. Utilizing a database of 703782 patients, Tomašev *et al*[16] created an associative AI model that was able to predict 55.8% of inpatient acute kidney injury events at 48 h. While these models are great at providing prognostic information, they do not offer information on the effects of different interventions on patient care. Additionally, these models are purely data-driven and do not consider the underlying physiology or causal pathways of disease in their development. The clinical utility of these models is limited by the lack of precision and underperformance in the clinical setting. In comparison, actionable AI models (or, as we have previously coined them, "Causal AI" models) are developed with explicit consideration of causal pathways, providing greater clinical utility in predicting the outcome of a given intervention as well as providing clinicians a better understanding of how the AI model is reaching its conclusions[17,18].

AI APPLICATIONS IN NEUROCRITICAL CARE

While digital twin models have been developed and tested for use in the fields of diabetes, cardiology, and sepsis management, this model has not yet been tested in the neurocritical care (NCC) unit. Yet, the NCC unit is an optimal place to develop "Twin AI" model. Within the NCC unit, there is a large need to integrate vast amounts of data including intracranial pressure, electroencephalography, hemodynamics, ventilation parameters, body temperature, and fluid balance, along with the neurological exam to allow neurointensivists to make time-sensitive and impactful decisions for patient care[19,20]. Use of AI to augment clinical decision making also has the potential to reduce costs and improve access to quality care for patients in areas where the expertise of a NCC physician is not readily available[21].

In NCC, current AI technology focuses on interpreting electroencephalography, monitoring intracranial pressure (ICP), and prognosticating outcomes[22]. AI models have been developed to interpret electroencephalograms by helping to annotate the tracings, detecting seizures, and identifying brain activation in unresponsive patients [23-26]. More specific models have been developed to analyze waveforms of ICP to detect artifact in ICP measurements, predict future ICP levels, determine which

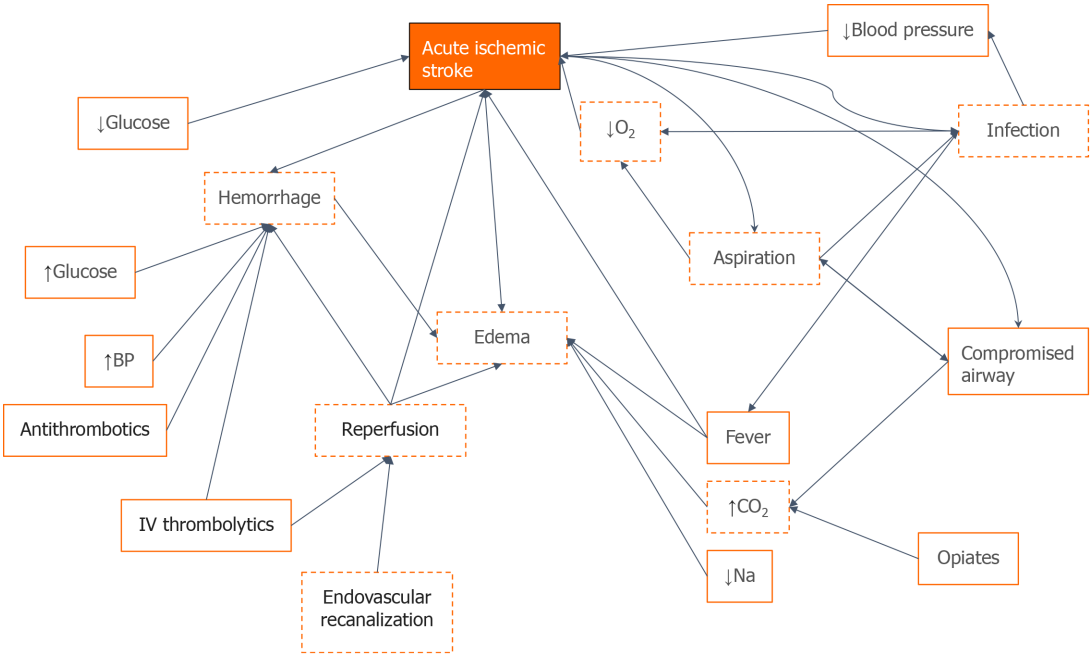

Figure 1 A directed acyclic graph for stroke patients that link concepts through Bayesian networks built from an underlying understanding of disease processes. Orange boxes represent concepts, orange solid lines represent actionable factors, dashed red lines represent semi-actionable factors, arrows represent Bayesian connections between different variables. O_2: Oxygen; CO_2; Carbon dioxide; BP: Blood pressure; Na: Sodium.

patients are at risk of increased ICP, and prognosticate mortality[27-30]. AI models are able to provide prognostic information for patients with subarachnoid hemorrhage, traumatic brain injury, or who are at risk for health-care associated ventriculitis and meningitis[31-33]. In the European Union, technologies such as Avert-IT have been developed for use in the critical unit to predict hypotensive events in patients with traumatic brain injury[34]. Still, to our knowledge, a model that integrates all the measures available in the NCC unit to create a broad digital twin model of the patient does not yet exist.

Having a digital twin model that can accurately replicate patient physiology in the NCC environment would have distinct advantages. Such a model would allow training physicians to sharpen their clinical decision making and provide opportunities to trial different treatments without ever risking patient safety. Preliminary results of a digital twin model used to predict response to treatments in patients in the intensive care unit with sepsis within the first 24 h have shown that creating such a model is possible[18].

A similar approach should be feasible for neurocritical diseases and illustrations of how these models could be conceptually built for application in NCC are shown in Figures 1 and 2. In applying this model to a patient with ischemic stroke, for example, factors such as blood pressure, glucose levels, securing an airway, and giving anticoagulation, thrombolytics, or opiate medication are all actionable factors that can be input into the AI model. These actions will affect certain semi-actionable factors and the overarching concept in the digital twin AI model such as hemorrhage, edema, aspiration, and, ultimately, ischemic stroke, all connected by Bayesian networks. Similar models such as this will be built for other disease states within the NCC unit as well. With this digital twin of the patient, trainees will be able to test different interventions and get real-time feedback on the effects of their intervention without ever having to worry about potential harm to the actual patient.

UTILITY IN MEDICAL EDUCATION

The central purpose of medical education, learning and assessment is to optimize patient care, avoid harm to the patients, and improve the cognitive skills of practitioners and learners alike. Continual learning and retooling are a vital aspect of practicing medicine. A major concern in healthcare and medical education is that initial training must be provided with minimal risk to patients. Moreover, maintenance of skills among busy physicians practicing in the community is an ever-

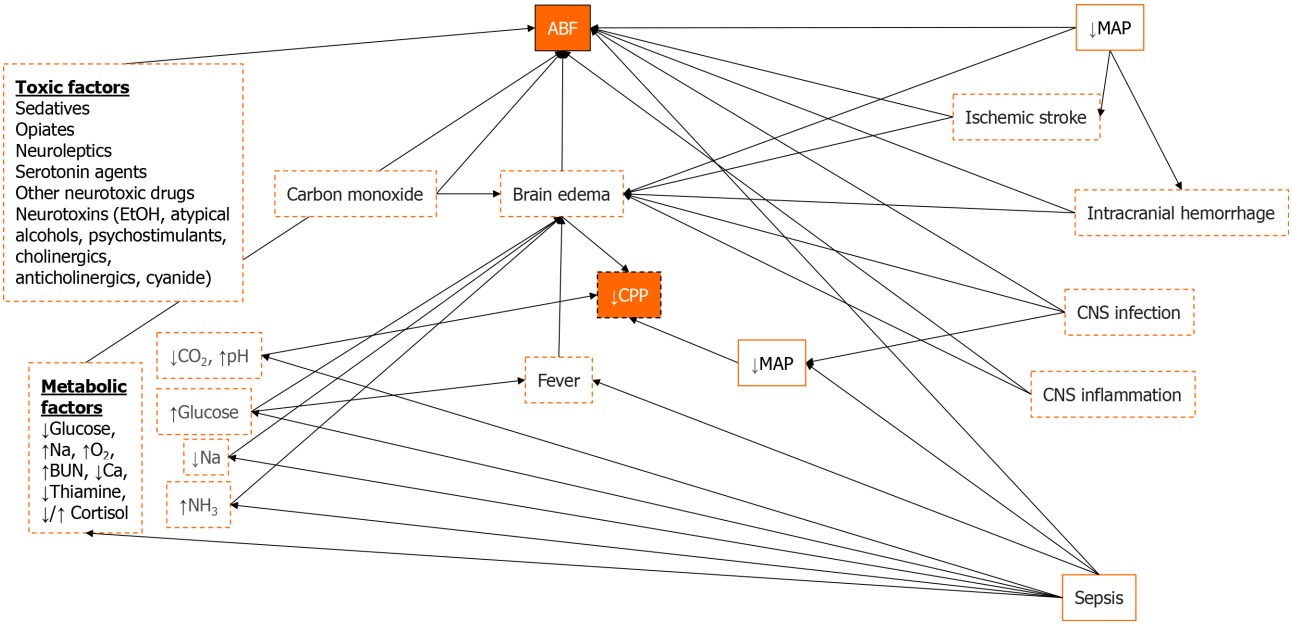

Figure 2 A directed acyclic graph for acute brain failure that links concepts through Bayesian networks built from an underlying understanding of disease processes. Orange boxes represent concepts, orange solid lines represent actionable factors, dashed red lines represent semi-actionable factors, arrows represent Bayesian connections between different variables. MAP: Mean arterial pressure; CPP: Cerebral perfusion pressure; NH_3: Ammonium; Na: Sodium; BUN: Blood urea nitrogen; Ca: Calcium; O_2: Oxygen; ABF: Acute brain failure; CNS: Central nervous system.

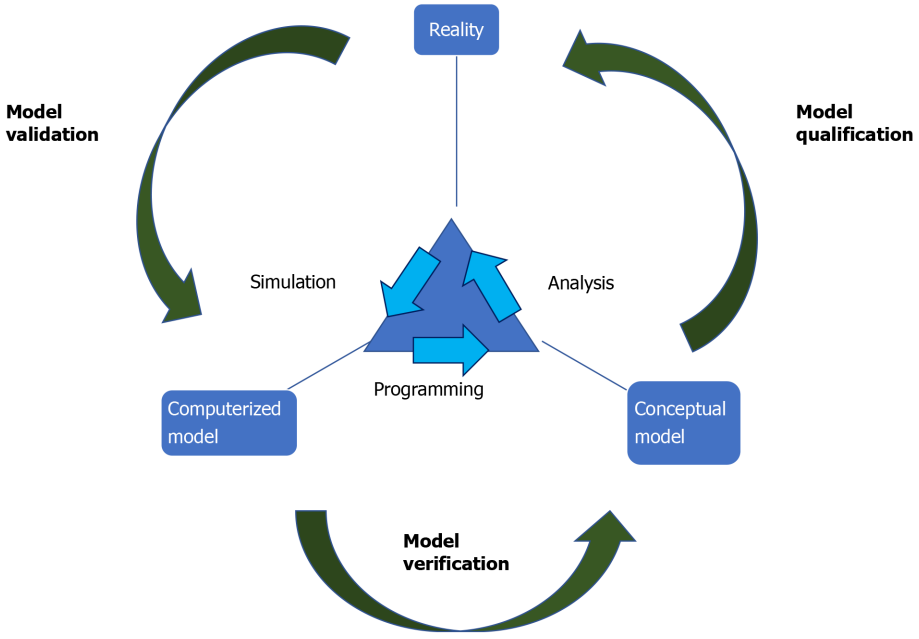

Figure 3 Accurate verification and validation of the model using the iterative steps of programming, simulation, and analysis[39].

growing concern.

The utilization of a virtual environment to enhance the procedural performance through simulation is not a new concept. High-fidelity simulators are now a prerequisite for gaining proficiency in endoscopic, laparoscopic, and robotic surgery [35]. With the advent of minimally invasive surgical procedures, it became evident that there is a dire need for skill acquisition outside the operating theater before attempting a similar procedure on real patients[36]. Despite the compelling evidence in various areas of clinical medicine, the world of critical care medicine has lagged in providing a well-equipped platform for cognitive training and skill acquisition in the virtual environment.

Creating an "in-silico" model or a "digital twin" allows learning, cognitive skill acquisition and refinement in an environment that does not expose patients to the risk of uncertain interventions and offers the ability to test the cognitive domains of decision making in real time with rapid assessment and perceptible metrics. We envision creating such an educational tool with potential refinement to a level that it can be used as a digital twin to assess the effect of an intervention in the virtual environment without exposing actual patients to risk. Early in the medical education program, even low fidelity patient presentations can be a good fit for assessment purposes if appropriately matched for the level of learner and educational level. The digital twin AI model can not only be used for medical education but can also be utilized for summative assessment where the cognitive competency of the critical care trainees can be assessed in an objective manner to determine if he/she can be graduated to the next level.

BUILDING THE AI MODEL–CHALLENGES AND ETHICAL CONSIDERATIONS

AI model should be constructed in such a way that they augment, rather than attempt to replace, the clinician's judgment[37]. Transparent AI models based on our understanding of pathophysiology are more likely to be trusted, and consequently implemented into practice, by clinicians than "black-box" AI models that reach their conclusions through multiple layers of neural networks. Actionable AI models should therefore be based on sound biology and should aim to replicate real-life disease processes.

Building these models starts with directed acyclic graphs (DAGs). DAGs are diagrams that connect concepts (defined as variables) through Bayesian networks that represent the probabilistic relationship between those concepts (Figures 1 and 2). These DAGs, built from an understanding of underlying pathophysiology and in collaboration with content experts act as a base for the development of the AI model. Expert knowledge is necessary to develop the rules that will connect the variables (*i.e.*, what would be expected to happen to the connected variables after a certain change in one of them). To avoid bias, we intend to gain expert consensus on our rules using DELPHI method, an iterative process of surveying experts that seeks to integrate knowledge about a specific field, before constructing the AI models. These DAGs are then converted into statements that can then be transformed into code and incorporated into the AI model. Once the model is developed, it will be prospectively validated by comparing its predictions to the actual clinical findings in real patients, the irreplaceable gold standard for any AI application to health care. This process will go through multiple cycle or iterations of computer modeling (programming), comparing the performance of the digital twin in an "in-silico" environment (simulation) and gathering of qualitative and quantitative data to improve the performance of the model (analysis) (Figure 3). This process was piloted in our feasibility study for the digital twin of critically ill sepsis patients[18].

While a digital twin model in healthcare could lead to a more accurate, individualized model of health and diseased states, this new technology also brings with it ethical questions, such as who will have access to this new technology, how this technology may lead to a deemphasizing of patient autonomy in favor of algorithms, and how compiling large amounts of health data may lead to identification of trends that may justify future divisiveness and segregation[38]. In creating any new AI technology, we must be cognizant of the ethical and safety implications of the new technology and ensure that any new AI model acts to augment rather than supersede clinician judgement. Like any nascent technology, AI models can be initially erroneous or insufficiently accurate; validation is therefore essential for their refinement and must always be conducted before their implementation.

CONCLUSION

While digital twin models have been established in the fields of cardiology, endocrinology, and undergraduate medical education, a validated model has not yet been adopted to training and clinical practice in the field of NCC. We propose to develop actionable digital twin models based on an understanding of the underlying pathophysiology of disease to train future physicians and potentially inform clinical

decision making in the complex environment of NCC.

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ORIGINAL ARTICLE

Retrospective Study

Emergency service results of central venous catheters: Single center, 1042 patients, 10-year experience

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Abstract

BACKGROUND

Central venous catheterization is currently an important procedure in critical care. Central catheterization has important advantages in many clinical situations. It can also lead to different complications such as infection, hemorrhage, and thrombosis. It is important to investigate critically ill patients undergoing catheterization.

AIM

To evaluate the characteristics, such as hospitalization, demographic characteristics, post-catheterization complications, and mortality relationships, of patients in whom a central venous catheter was placed in the emergency room.

METHODS

A total of 1042 patients over the age of 18 who presented to the emergency department between January 2005 and December 2015 were analyzed retrospectively. The patients were divided into three groups, jugular, subclavian, and femoral, according to the area where the catheter was inserted. Complications related to catheterization were determined as pneumothorax, guidewire problems, bleeding, catheter site infection, arterial intervention, and sepsis. Considering the treatment follow-up of the patients, three groups were formed as outpatient treatment, hospitalization, and death.

RESULTS

The mean age of the patients was 60.99 ± 19.85 years; 423 (40.6%) of them were women. Hospitalization time was 11.89 ± 16.38 d. There was a significant correlation between the inserted catheters with gender (P = 0.009) and hospitalization time (P = 0.040). Also, blood glucose, blood urea nitrogen, creatinine, and

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serum potassium values among the biochemical values of the patients who were catheterized were significant. A significant association was observed in the analysis of patients with complications that develop according to the catheter region (P = 0.001) and the outcome stage (P = 0.001). In receiver operating characteristic curve analysis of hospitalization time and mortality area under curve was 0.575, the 95% confidence interval was 0.496-0.653, the sensitivity was 71%, and the specificity was 89% (P = 0.040).

CONCLUSION

Catheter location and length of stay are important risk factors for catheter-borne infections. Because the risk of infection was lower than other catheters, jugular catheters should be preferred at entry points, and preventive measures should be taken by monitoring patients closely to reduce hospitalization infections.

Key Words: Emergency service; Central venous catheter; Complications; Infection; Mortality

Core Tip: A total of 1042 patients were included in this retrospective study. All central venous catheters were inserted in the emergency room. This study included 10 years of experience in our emergency department. In receiver operating characteristic curve analysis of hospitalization time and mortality, sensitivity was 71%, and specificity was 89% (P = 0.040). Complications in the subclavian vein and femoral vein were observed more frequently in the long term. Jugular vein catheterization can be preferred primarily due to the difficulties in application and due to the low number of complications.

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INTRODUCTION

Emergency services are dynamic clinics where acute and emergency aspects of diseases and injuries affecting patients of all age groups are prevented. Resuscitation, primary care, diagnosis, and treatment of emergency cases are performed. Due to the nature of acute illnesses and injuries and their independence from each other, when they will come to emergency services and their number cannot be predicted[1]. Acute procedures should be done as soon as possible in terms of the density, variety, and patient circulation of emergency services.

Intravenous applications in emergency rooms act as a lifeline in saving the life of the patient. For this reason, the process must be done quickly and safely. In a study conducted on patients with penetrating injuries in the emergency department, timely and effective intravenous interventions were reported to increase survival rates[2].

Central venous catheterization (CVC) is an important intervention that is widely used today. Emergency services have a large variety of patient populations where central venous interventions are frequently applied. CVC is necessary for the use of vasoactive or irritant drugs, in insufficient peripheral intravenous routes, rapid infusion of intravenous fluids, parenteral alimentation, frequent therapeutic plasmapheresis, and transvenous pacemaker placement. In addition, CVC is used for hemodialysis and hemodynamic monitoring during major surgery[3].

A central venous catheter is to be placed percutaneously. The main routes of catheterization are the internal jugular vein (IJV), subclavian vein (SCV), and femoral vein (FV). The placement of a catheter in the IJV is gaining in popularity and is preferred in children[4]. Various complications may develop in CVC, such as pneumothorax, hemothorax, venous thrombosis, vertebral and cervical artery injuries, artery puncture, bleeding, arrhythmia, catheter dysfunction such as catheter blockage or

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catheter breakage, infection, cardiac tamponade, respiratory tract obstruction, and chylothorax[5,6].

Each catheter region to be used has its advantages and disadvantages. IJV catheterization is often used in intensive care units on mechanically ventilated comatose patients. SCV catheterization is not preferred in these patients due to the risk of sudden pneumothorax[7]. The most important disadvantage of IJV catheterization is the difficulty of detecting the skin and restricting neck movements. The risk of pneumothorax, hemothorax, and vena cava superior injury is much less. At the same time, the development of thrombosis and narrowing of the IJV is much less due to the lack of catheter angulation, which is monitored in the SCV[8].

The aim of this study was to analyze the different catheter insertion sites, diagnoses, complications, length of hospitalization, catheter-related local infection, and bacteremia in terms of morbidity and mortality in patients who were followed up in the emergency service.

MATERIALS AND METHODS

Study design and population

In this retrospective study, 1042 patients over 18-years-old who were admitted to the emergency room between January 2005 and December 2015 were analyzed. CVC was implanted in patients whose general condition was poor, whose vascular access could not be opened in the emergency room, who needed dialysis and fluid resuscitation, who suffered traffic accidents, falls, burns, malignancy, or acute and chronic renal failure, and who needed blood or cardiopulmonary resuscitation. The exclusion criteria were applied to all patients with severe bleeding diathesis and an indication other than infection in the area where the catheter was to be placed. All patients were divided into three groups: jugular, subclavian, and femoral according to the area of the catheter placed. These catheters were divided into right and left. Seven groups were formed according to complications after catheterization: pneumothorax, guidewire problems, bleeding, catheter location infection, arterial interference, sepsis, and no complications. Patients who were planned to have a catheter application were divided into subgroups according to their diagnosis. The subgroups were renal diseases (acute and chronic renal failure), respiratory diseases (asthma, chronic obstructive pulmonary diseases, pulmonary embolism), endocrine diseases (hypoglycemia, diabetic ketoacidosis, hyperosmolar coma, thyroid crises), multiple organ failure, gastrointestinal bleeding and perforations, cerebrovascular diseases (cerebrovascular infarcts, intraparenchymal hemorrhages, epidural and subdural hemorrhages, cerebral edema, subarachnoid hemorrhages), trauma to the thorax (thoracic open injury, severe pneumothoraces, severe lung parenchymal injuries), traffic accidents (inside and outside the vehicle), malignancies in poor general condition, life-threatening gunshot injuries, cardiac diseases (myocardial infarction, heart failure, cardiac tamponade, cardiomyopathies), cardiovascular diseases (aortic dissection and aneurysms), severe injuries as a result of falls, second and third-degree burns with a large surface area, extremity amputation, penetrating-cutting tool injuries, and cardiopulmonary resuscitation. It could be done in more groups, but the most common diagnoses requiring catheter indication were included in the emergency department.

Sixteen groups were also identified according to the services where catheterized patients were hospitalized. These services were emergency services, infectious diseases, general internal medicine, nephrology, gastroenterology, intensive care unit, cardiology, neurosurgery, thoracic surgery, chest diseases, general surgery, cardiovascular surgery, neurosurgery, plastic surgery, burn unit, and neurology services.

Patients were observed from hospitalization until discharge. Outpatients were followed up retrospectively with an automation system for 3 mo after they were discharged, and those who did not come to the hospital were questioned by phone. Diagnoses, admission dates, contact information, demographic, clinical, and laboratory data are included in the registry system of our hospital. As a result, all patients were reached *via* call and/or hospital records.

Central venous catheter

Kits prepared for central venous catheter application in the emergency department were used. Components of these kits included: The needle included an injector to allow passage of the guidewire, double or triple catheter, guidewire, plastic sheath in which the guidewire was placed, dilator, 3/0 silk sharp needle suture, and scalpel. A

central venous catheter procedure was performed under local anesthesia. The patient was placed in the supine position. The jugular vein catheter was positioned with the head slightly down. For the SCV catheter, the arms were extended to the sides parallel to the body. For the FV catheter, the legs were kept open at a certain angle. During the procedure, the patient was monitored, and heart rhythm was followed. The sterility of the area where the catheter will be applied was provided with 10% povidone-iodine. Lidocaine was used for local anesthesia. The Seldinger technique was used for central venous catheter application[9]. Main lines of central venous catheter application after anesthesia was achieved included: (1) sterilizing the procedure area; (2) proper positioning of the thick needle to which the guidewire will be sent; (3) inserting the guidewire into the vein lumen by applying slight negative pressure; (4) advancing the guidewire into the vein lumen; (5) dilating the path through which the catheter will pass; (6) inserting the catheter into the vein with the help of a guidewire; (7) adequate progression and fixation of the catheter in the vein; and (8) closing in a sterile manner. Lung radiography and ultrasonography were performed for central venous catheter complications.

Catheter-related infection was determined according to the "Centers for Disease Control" criteria[10]. Catheter tip colonization was accepted if more than 15 colony-forming units microorganisms were produced from the catheter tip. Local signs for catheter-induced local infection (induration, edema, heat increase, purulent yeast arrival) and the reproduction of microorganisms in catheter tip culture were noted.

Criteria used in determining the location of the central venous catheter

In the emergency department, ultrasonography was not commonly used until 2018. For this reason, none of the 1042 patients could be subjected to catheter placement accompanied by ultrasonography. Accompanied by ultrasonography, we were unable to learn about complications that may occur as a result of catheter placement. But for catheter placement, all patients were applied with some criteria. These criteria are as follow.

Jugular catheters: Elderly, cachectic, superficial vein structure, lack of coagulopathy barrier, lack of local wound infection, low risk of pneumothorax, rapid venous return, and direct compression in bleeding. Right or left catheter placement was performed according to the current condition of the patient and the experience of the clinician.

Subclavian catheters: Obesity, the dressing was comfortable, the placement procedure was possible while ensuring airway control, there was no local infection, no coagulopathy, and the right or left catheter was placed according to the experience of the clinician.

Femoral catheters: Fast intervention with high success rate, no local infection, no coagulopathy, no division during cardiopulmonary resuscitation and/or intubation, no risk of pneumothorax, no Trendelenburg position, cachectic patients and according to the experience of the clinician, right or left catheters were placed. However, due to the current location of the inguinal region, jugular or subclavian catheters were preferred more because of the high risk of infection, although sterility was taken into consideration.

Laboratory design: Hemogram and biochemical blood samples of the patients were taken at the emergency service. Hemogram was measured using Sysmex DI-60 CBC Analyzer (Istanbul, Turkey). Biochemistry was analyzed by Beckman Coulter Automated AU-680 (Beckman Coulter, Inc., Fullerton, CA, United States). Hemogram and biochemistry results were studied between 45-60 min.

Statistical analysis

The data obtained from the study were analyzed with the SPSS 20 (SPSS Inc., Chicago, IL, United States) package program. Kolmogorov-Smirnov test was performed while investigating the normal distributions of the variables. Descriptive statistics were presented as mean ± SD or median (minimum-maximum) for continuous variables and as the number of cases and percentage (%) for nominal variables. When examining the differences between groups, Mann-Whitney *U* and Kruskal-Wallis H tests were used because the variables did not come from the normal distribution. ^{2} analysis was used when examining the relationships between groups of nominal variables. Receiver operating characteristic curve analysis was performed to predict the development of mortality. While interpreting the results, values below the significance level of 0.05 were considered statistically significant.

RESULTS

The mean age of the patients was 60.99 ± 19.85 years (minimum 18-maximum 99); 423 (40.6%) of them were women. The mean age of jugular vein catheter patients was 60.74 ± 20.20 years, and 339 (40%) were female. The mean age of SCV catheter patients was 59.66 ± 19.17 years, and 42 (27.3%) were female. The mean age of FV catheter patients was 63.67 ± 18.57 years and 42 (42%) were women. Hospitalization time was 11.89 ± 16.38 d. The patients who were catheterized were not statistically significant with age ($P = 0.939$), but there was a significant correlation with gender ($P = 0.009$) and hospitalization time ($P = 0.040$). Also, blood glucose, blood urea nitrogen, creatinine, and serum potassium were statistically significant from the biochemical values of the patients who were catheterized. The relationship with other biochemical values could not be determined. Among the hemogram parameters, it was statistically significant with hemoglobin and mean corpuscular hemoglobin concentration, and no correlation was found with other values (Table 1).

In the analysis of the patients by catheter site, gender ($P = 0.004$), developing complications ($P = 0.009$), and final decision stage ($P = 0.001$) were statistically significant. While 174 (16.7%) of all patients were treated on an outpatient basis, 783 (75.1%) of them were found to be cured, and 85 (8.2%) died ($P = 0.001$, Table 2).

In the analysis of patients with their diagnosis according to the catheterized region, in general, the right IJV catheter was inserted most often. In addition, the right FV in multiple organ failure, the left SCV in chest injuries, burns, piercing-cutting tool injuries, and cardiopulmonary resuscitation, and the right SCV in cardiovascular diseases were the most common catheter-inserted vein (Table 3).

The analysis of the patients according to the services they received while hospitalized after being catheterized is shown in Table 4.

In receiver operating characteristic curve analysis of hospitalization time and mortality, the area under curve was 0.575, the 95% confidence interval was 0.496-0.653, the sensitivity was 71%, and the specificity was 89% ($P = 0.001$) (Figure 1).

DISCUSSION

Intravenous catheters, one of the indispensable tools in modern medical practices, are applied for specific purposes and can be used for a long time. Although central venous catheters provide great benefits for patients, they also cause significant mortality and morbidity due to both mechanical and infectious complications[11,12]. In emergencies and critical patient follow-up, CVC is often needed. However, there are important points to be considered in CVC. First of all, it should be preferred to use a central vein with a large flow rate and high current. For this purpose, percutaneous IJV, SCV, and FV are used in CVC[4]. Right IJV is preferred primarily because of its straight connection with the superior vena cava and its short distance to the right atrium[7]. Left IJV should be the next choice because it reaches the superior vena cava by angulation twice, and catheterization is technically difficult. If there are coagulation and bleeding disorders, SCV catheterization is high risk, and in these cases, extrathoracic veins such as IJV or FV should be used[3,7,8]. Mickley[8] stated that the right IJV should be used if possible for central venous interventions and hemodialysis catheters. Central vein catheterization is a generally accepted protocol using the original Seldinger technique[9]. The Seldinger technique was used in all cases, and the rules of asepsis were adhered to. Right IJV was observed in 56.7% of the cases, left IJV in 14.8%, right SCV in 6.5%, left SCV in 8.4%, right FV in 7.4%, and left FV in 6.1%.

CVC can cause some complications. Early complications include arterial puncture, development of hematoma, nerve injury, pneumothorax, hemothorax, difficulty in cannulation, and arrhythmia. No complications were observed in 92.9% of our patients, most of whom had IJV intervention. In addition to expected complications such as pneumothorax and hemothorax, complications such as brachial plexus injury due to SCV catheterization or massive retroperitoneal hemorrhage due to femoral catheterization can be seen[13,14]. Pneumothorax was seen in 4 (0.4%) cases, one right subclavian and three left subclavian cases. All of these patients were cachectic and in poor general condition. Catheter dysfunction is caused by catheter malposition, catheter kinking, or catheter compression[15,16]. Bending and breaking of the guidewire in the vein was detected in a total of 2 (0.2%) patients, one in the left SCV and the other in the right FV. In preventing early catheter dysfunction, IJV catheterization may be an advantage in priority. In total, 8 (0.8%) of the patients had bleeding, 30 patients (2.9%) had artery puncture, 1 patient had hematoma, and 2 patients had

Table 1 Basal and laboratory features of the inserted catheters

Catheter area inserted					
	All patients, *n* = 1042, mean ± SD	**Jugular, *n* = 743, mean ± SD**	**Subclavian, *n* = 155, mean ± SD**	**Femoral, *n* = 144, mean ± SD**	***P* value**
Baseline characteristics					
Age, yr	60.99 ± 19.85	60.74 ± 20.20	59.66 ± 19.17	63.67 ± 18.57	0.939
Sex, female/male	423/619	339/449	42/112	42/58	**0.009**
Hospitalization time	11.89 ± 16.38	12.50 ± 16.03	11.00 ± 20.08	9.73 ± 13.39	**0.040**
Laboratory finding					
Biochemistry					
BS, mg/dL	139.45 ± 101.56	145.21 ± 112.63	120.35 ± 55.74	130.30 ± 72.49	0.008
BUN, mg/dL	42.77 ± 41.29	51.11 ± 44.40	19.65 ± 13.91	24.58 ± 26.42	0.001
Creatinine, mg/dL	2.62 ± 2.89	3.20 ± 3.14	0.99 ± 0.68	1.37 ± 1.68	0.001
TBIL, mg/dL	0.87 ± 0.84	0.82 ± 0.63	0.80 ± 0.88	1.22 ± 1.43	0.485
AST, mg/dL	37.65 ± 47.22	32.56 ± 25.60	40.04 ± 60.05	61.38 ± 90.77	0.508
ALT, mg/dL	35.81 ± 49.37	30.31 ± 26.18	38.58 ± 67.59	61.21 ± 91.95	0.710
ALP, mg/dL	108.57 ± 64.10	104.95 ± 56.71	104.66 ± 59.33	131.48 ± 93.90	0.569
Na, mmol/L	138.61 ± 5.38	138.68 ± 5.33	138.22 ± 5.07	138.68 ± 5.96	0.125
K, mmol/L	5.00 ± 1.03	5.13 ± 1.10	5.07 ± 0.71	4.79 ± 0.70	0.027
Cl, mmol/L	100.23 ± 6.23	100.18 ± 6.11	100.41 ± 6.95	100.29 ± 6.04	0.778
Amylase	89.98 ± 49.88	87.93 ± 47.66	91.64 ± 53.25	98.78 ± 56.30	0.419
CRP, mg/dL	4.44 ± 8.12	3.53 ± 5.14	4.32 ± 7.65	9.26 ± 15.90	0.925
Hemogram					
WBC, × 10^3/UL	10.57 ± 4.51	10.26 ± 3.59	10.32 ± 4.05	12.49 ± 7.72	0.228
Hb, g/dL	13.77 ± 2.07	13.63 ± 2.12	14.09 ± 1.77	14.16 ± 1.98	0.017
Hct, %	42.17 ± 6.62	42.07 ± 6.78	42.23 ± 5.80	42.62 ± 6.65	0.737
MCV, fL	87.74 ± 6.29	87.71 ± 6.42	87.45 ± 6.18	88.24 ± 5.70	0.927
MCH, pg	29.37 ± 2.36	29.30 ± 2.41	29.48 ± 2.29	29.67 ± 2.20	0.905
MCHC, g/dL	33.25 ± 1.36	33.19 ± 1.37	33.47 ± 1.29	33.29 ± 1.36	0.002
RDW, %	14.69 ± 1.73	14.74 ± 1.79	14.45 ± 1.50	14.66 ± 1.61	0.082
PLT, × 103/μL	248.22 ± 80.14	248.71 ± 76.33	256.88 ± 76.01	236.42 ± 100.38	0.073
MPV, fL	8.48 ± 1.01	8.54 ± 1.03	8.33 ± 1.06	8.34 ± 0.86	0.085

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase test; AST: Aspartate aminotransferase test; BS: Blood sugar; BUN: Blood urea nitrogen; Cl: Chlorine; CRP: C-reactive protein; Hb: Hemoglobin; Hct: Hematocrit; K: Potassium; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; MCV: Mean corpuscular volume; MPV: Mean platelet volume; Na: Sodium; PLT: Platelet; RDW: Red cell distribution width; SD: Standard deviation; TBIL: Total bilirubin; WBC: White blood cell.

difficulty catheterizing. In similar studies, the incidence of carotid artery puncture was reported between 2.0%-9.9% during catheterization of IJV[5]. Most of the difficulties in arterial puncture and cannulation observed in our catheterization-related cases were obesity, short neck, elderly, and poor general condition as the main cause of these early complications.

During jugular catheterization, complications such as Horner Syndrome, arrhythmia, and cardiac tamponade have been reported, as well as the development of carotid-jugular arteriovenous fistula due to carotid puncture[17,18]. In a total of 4 (0.4%) cases, no other complications were observed except arrhythmia. It is recommended to monitor the patient during the jugular site catheterization and to take a chest radiograph after the application[19]. Both examinations are routinely performed

Table 2 Analysis of the inserted catheter area according to gender, complication, and final situation

	Catheter area inserted						Total, *n* (%)	*P* value
	R jugular, *n* (%)	L jugular, *n* (%)	R subclavian, *n* (%)	L subclavian, *n* (%)	R femoral, *n* (%)	L femoral, *n* (%)		
Gender								
Female	248 (42.0)	73 (47.4)	20 (29.4)	23 (26.1)	30 (39.0)	29 (45.3)	423 (40.6)	0.009
Male	343 (58.0)	81 (52.6)	48 (70.6)	65 (73.9)	47 (61.0)	35 (54.7)	619 (59.4)	
Complication								
No	583 (98.6)	149 (96.8)	63 (92.6)	75 (85.2)	49 (63.6)	46 (71.9)	965 (92.6)	0.001
Pntx	0	0	1 (1.5)	3 (3.4)	0	0	4 (0.4)	
GW	0	0	0	0	1 (1.3)	1 (1.6)	2 (0.2)	
Bleeding	2 (0.3)	0	0	4 (4.5)	1 (1.3)	1 (1.6)	8 (0.8)	
WI	2 (0.3)	1 (0.6)	1 (1.5)	1 (1.1)	2 (2.6)	6 (9.4)	13 (1.2)	
AI	4 (0.7)	4 (2.6)	2 (2.9)	3 (3.4)	11 (14.3)	3 (4.7)	27 (2.6)	
Sepsis	0	0	1 (1.5)	2 (2.3)	13 (16.9)	7 (10.9)	23 (2.2)	
Decision								
OPT	104 (17.6)	28 (18.2)	12 (17.6)	14 (15.9)	9 (11.7)	7 (10.7)	174 (16.7)	0.001
DWH	484 (81.9)	121 (78.6)	46 (67.6)	58 (63.6)	35 (45.5)	41 (64.1)	783 (75.1)	
Mortality	3 (0.5)	5 (3.2)	10 (14.7)	18 (20.5)	33 (42.9)	16 (25.0)	85 (8.2)	
Total	591 (100)	154 (100)	68 (100)	88 (100)	77 (100)	64 (100)	1042 (100)	

AI: Arterial intervention; DWH: Discharged with healing; GW: Guide wire; L: Left; Pntx: Pneumothorax; OPT: Outpatient treatment; R: Right; WI: Wound infection.

in our cases. Also, in cases with arrhythmia, the guidewire was withdrawn to a certain extent, the procedure was interrupted, and major complications were prevented.

The average staying time of temporary catheters should not exceed 3-4 wk for IJV and SCV catheters and 2 wk for femoral catheters[5]. The average length of stay in our study did not exceed 2 wk. The length of stay of the catheter is associated with both thrombotic complications and the risk of infection[20].

In the study of Cook *et al*[21], it was stated that changing catheters at short intervals did not decrease the frequency of colonization and infection. Because catheter insertion is a traumatic procedure and there is a risk that asepsis conditions may deteriorate during catheter insertion, installing a new catheter in itself poses a risk of catheter-related infection. It is known that there is a directly proportional relationship between catheter insertion time and catheter colonization and catheter-related infection[22,23]. Chen *et al*[24] found that the stay of the catheter for more than 7 d was significant in terms of catheter-related infection.

Infections developing in CVC for various reasons lead to very serious complications including patient mortality[25]. Early infection is associated with contamination during catheter insertion, skin infection, or catheter pathway infection. Late infection is often accompanied by endoluminal catheter contamination[26]. Two types of infections are observed: local infection and systemic infections. *Staphylococcus aureus* (*S. aureus)* and *S. epidermiditis* are the most common microorganisms isolated during catheter-related bacteremia. This risk increases in the presence of wound infection. The risk of infection is higher with FV catheters than with SCV and IJV catheters[27]. In our study, wound infection due to catheters was detected in 13 (1.2%) cases. Localized infection findings were observed in 8 (0.7%) FV, 3 (0.3%) IJV, and 2 (0.2%) SCV. Although *S. aureus* and *S. epidermiditis* grew in the samples taken from the wound site, there was no growth in the samples taken from the catheter tip. Blood cultures were not routinely sent from the patients. We think that there was no growth in the catheter tip cultures, care for sterility while inserting the catheter, careful and regular dressing of the insertion site, and not using the catheters for more than 3 wk.

Table 3 Analysis of inserted catheter sites according to diseases

Diagnosis	Catheter area inserted						Total, *n* (%)
	R jugular, *n* (%)	L jugular, *n* (%)	R subclavian, *n* (%)	L subclavian, *n* (%)	R femoral, *n* (%)	L femoral, *n* (%)	
Renal diseases	228 (38.5)	43 (27.9)	1 (1.5)	2 (2.3)	6 (7.8)	5 (7.8)	285 (27.3)
Respiratory diseases	45 (7.6)	8 (5.1)	3 (4.4)	3 (3.4)	16 (20.8)	6 (9.4)	81 (7.8)
Endocrine diseases	34 (5.8)	7 (4.5)	1 (1.5)	0	4 (5.2)	0	46 (4.4)
Multiple organ insufficiency	0	0	1 (1.5)	2 (2.3)	12 (15.6)	7 (10.9)	22 (2.1)
Gastrointestinal system bleeding	56 (9.5)	12 (7.8)	2 (2.9)	0	0	3 (4.7)	73 (7.0)
Gastrointestinal system perforations	27 (4.6)	2 (1.3)	2 (2.9)	0	5 (6.5)	1 (1.6)	37 (3.6)
Cerebrovascular diseases	61 (10.3)	16 (10.4)	0	1 (1.1)	4 (5.2)	3 (4.7)	85 (8.2)
Thoracic traumas	1 (0.2)	0	7 (10.3)	14 (15.9)	0	0	22 (2.1)
Traffic accidents	12 (2.0)	7 (4.5)	1 (1.5)	2 (2.3)	0	0	22 (2.1)
Malignancies	30 (5.1)	7 (4.5)	4 (5.9)	1 (1.1)	4 (5.2)	4 (6.3)	50 (4.8)
Firearm injury	5 (0.8)	3 (1.9)	3 (4.4)	4 (4.5)	1 (1.3)	1 (1.6)	17 (1.6)
Cardiac diseases	39 (6.6)	22 (14.3)	1 (1.5)	1 (1.1)	5 (6.5)	13 (20.3)	81 (7.8)
Cardiovascular diseases	1 (0.2)	2 (1.3)	3 (4.4)	3 (3.4)	6 (7.8)	0	15 (1.4)
Falls	26 (4.4)	15 (9.7)	12 (17.6)	7 (8.0)	3 (3.9)	6 (9.4)	69 (6.6)
Burns	22 (3.7)	9 (5.8)	18 (26.5)	27 (30.7)	8 (10.4)	12 (18.8)	96 (9.2)
Amputation	1 (0.2)	1 (0.6)	0	2 (2.3)	0	0	4 (0.4)
Penetrating tool injury	3 (0.5)	0	8 (11.8)	11 (12.5)	1 (1.3)	1 (1.6)	24 (2.3)
Cardiopulmonary resuscitation	0	0	1 (1.5)	8 (9.1)	2 (2.6)	2 (3.1)	13 (1.2)
Total	591 (100)	154 (100)	68 (100)	88 (100)	77 (100)	64 (100)	1042 (100)

L: Left; R: Right.

Blot *et al*[28] found that *S. aureus*, coagulase negative *Staphylococcus*, and *Pseudomonas aeruginosa* were the most frequently isolated agents in catheter-related infections and catheter colonization. Chen *et al*[24] often isolated Gram-positive cocci and yeasts in cases of catheter-related infection. In the study of Yapar *et al*[29], 14 of 97 patients using long-term CVC had a catheter-related infection, 28.5% of the agents were coagulase negative *Staphylococcus*, 21.4% *S. aureus*, 21.4% *Acinetobacter* species, and 14.5% *Klebsiella pneumoniae*. It has been reported that 7.1% are *Pseudomonas* species, and 7.1% are *Escherichia coli*. Although catheter-related blood infections vary according to the size of the hospital, the unit, and the type of catheter, studies have reported that it ranges between 2.5% and 14.5%[25]. In our study, sepsis developed due to infection in 23 (2.2%) patients. Most of these patients were detected in 13 (1.2%) cases in the right FV and 7 (0.7%) cases in the left FV. All of these cases consisted of obese, poor general condition, and intensive care patients. In 6 (0.6%) of these blood culture cases, *S. aureus*, 3 (0.3%) coagulase negative *Staphylococcus*, 2 (0.2%) *Pseudomonas aeruginosa*, 3 (0.3%) *Acinetobacter* species, 7 (0.7%) *Escherichia coli*, and 2 (0.2%) Gram-positive cocci were found to reproduce. While 174 (16.7%) of all patients were treated on an outpatient basis, 783 (75.1%) of them were found to be cured, and 85 (8.2%) died. The reason for the high mortality rate is that the general condition of patients with catheters inserted is poor, the coma score is low, and most patients need care.

CONCLUSION

CVC is an indispensable application especially for emergency services and brings with

Table 4 Analysis of the inserted catheter areas according to the services where the patients were hospitalized

Hospital services	Catheter area inserted						Total, *n* (%)
	R jugular, *n* (%)	L jugular, *n* (%)	R subclavian, *n* (%)	L subclavian, *n* (%)	R femoral, *n* (%)	L femoral, *n* (%)	
Emergency department	94 (15.9)	27 (17.5)	12 (17.6)	14 (15.9)	10 (13.0)	10 (15.6)	167 (16)
Infectious diseases service	11 (1.9)	2 (1.3)	1 (1.5)	1 (1.1)	3 (3.9)	4 (6.3)	22 (2.1)
General internal medicine service	173 (29.3)	45 (29.2)	5 (7.4)	1 (1.1)	9 (11.7)	8 (12.5)	241 (23.1)
Nephrology service	99 (16.8)	21 (13.6)	0	3 (3.4)	7 (9.1)	5 (7.8)	135 (13)
Gastroenterology service	29 (4.9)	7 (4.5)	0	0	0	2 (3.1)	38 (3.6)
Intensive care unit	40 (6.8)	10 (6.5)	13 (19.1)	17 (19.3)	31 (40.3)	20 (31.3)	131 (12.6)
Cardiology service	12 (2.0)	3 (1.9)	1 (1.5)	2 (2.3)	1 (1.3)	1 (1.6)	20 (1.9)
Brain surgery service	24 (4.1)	7 (4.5)	5 (7.4)	7 (8.0)	2 (2.6)	3 (4.7)	48 (4.6)
Thoracic surgery service	4 (0.7)	4 (2.6)	6 (8.8)	13 (14.8)	4 (5.2)	2 (3.1)	33 (3.2)
Chest diseases service	18 (3.0)	7 (4.5)	0	1 (1.1)	1 (1.3)	1 (1.6)	28 (2.7)
General surgery service	46 (7.8)	3 (1.9)	8 (11.8)	9 (10.2)	7 (9.1)	4 (6.3)	77 (7.4)
Cardiovascular surgery service	10 (1.7)	0	7 (10.3)	10 (11.4)	1 (1.3)	1 (1.6)	29 (2.8)
Orthopedics and traumatology service	10 (1.7)	13 (8.4)	10 (14.7)	6 (6.8)	0	2 (3.1)	41 (3.9)
Plastic and reconstructive surgery service	4 (0.7)	2 (1.3)	0	4 (4.5)	0	1 (1.6)	11 (1.1)
Neurology service	17 (2.9)	3 (1.9)	0	0	1 (1.3)	0	21 (2.0)
Total	591 (100)	154 (100)	68 (100)	88 (100)	77 (100)	64 (100)	1042 (100)

L: Left; R: Right.

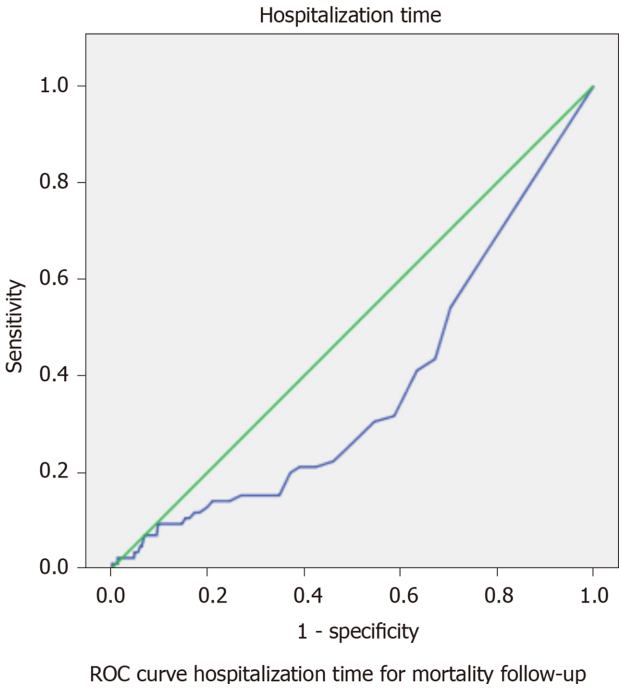

Figure 1 Mortality analysis of hospitalization time. ROC: Receiver operating characteristic.

it the risk of many complications. Complications in the subclavian and FVs are more common in long-term use. Jugular vein catheterization can be preferred primarily due to the difficulties in application and the low number of complications. In addition, prevention of risk factors with infection control policies and measures developed can significantly reduce catheter-related infection rates.

ARTICLE HIGHLIGHTS

Research background

Risk assessment in patients with a central venous catheter is necessary to prevent some unwanted consequences associated with invasive procedures.

Research motivation

The impact on the clinical, morbidity, and mortality of patients with central venous catheters in the emergency room population is worth investigating.

Research objectives

We aimed to determine whether there is a definite risk factor in short-term emergency room stay as the primary outcome of patients with central venous catheters and as a secondary outcome whether there is long-term morbidity and mortality at the time of hospitalization.

Research methods

In this study, 1042 patients who were admitted to the emergency department between 2005 and 2015 were analyzed, retrospectively. The patients in whom a central venous catheter was placed in the study were divided into three groups as jugular, subclavian, and femoral. Complications, diagnosis, and hospital stay after catheter insertion were evaluated.

Research results

The mean age of the patients was 60.99 ± 19.85 years; 423 (40.6%) of them were women. Hospitalization time was 11.89 ± 16.38 d. The mean age of the patients with jugular catheters was 60.74 ± 20.20 years, and 339 (40%) of them were women. The mean age of subclavian catheter patients was 59.66 ± 19.17 years, and 42 (27.3%) of them were women. In femoral catheters, the mean age was 63.67 ± 18.57 years, and 42 (42%) were women. There was a significant relationship between the inserted catheters with gender (P = 0.009) and hospitalization time (P = 0.040). , the biochemical values of the placed catheters were statistically significant with blood glucose, blood urea nitrogen, creatinine, and serum potassium. A significant association was observed in the analysis of patients according to complications (P = 0.001) and outcome stage (P = 0.001). While 174 (16.7%) of all patients were treated on an outpatient basis, 783 (75.1%) of them were found to be cured, and 85 (8.2%) died. In receiver operating characteristic curve analysis of hospitalization time and mortality, the area under curve was 0.575, the 95% confidence interval was 0.496-0.653, the sensitivity was 71%, and the specificity was 89% (P = 0.040).

Research conclusions

The jugular vein is safer and more comfortable for patient compliance between central venous catheters. Femoral vein catheters are at higher risk for infection. Changing central catheters frequently does not reduce the risk of infection and complications.

Research perspectives

Subclavian catheters have a high risk of hemopneumothorax in cachectic patients. Jugular catheters are safe. However, it is not preferred due to the discomfort of the patients and the limited neck movements. It is difficult to attach a jugular catheter to short and obese patients. Also, artery puncture is common. Femoral catheters are the group with the highest infection rate.

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SYSTEMATIC REVIEWS

SARS-CoV-2 (COVID-19), viral load and clinical outcomes; lessons learned one year into the pandemic: A systematic review

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Abstract

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections is diagnosed *via* real time reverse transcriptase polymerase chain reaction (RT-PCR) and reported as a binary assessment of the test being positive or negative. High SARS-CoV-2 viral load is an independent predictor of disease severity and mortality. Quantitative RT-PCR may be useful in predicting the clinical course and prognosis of patients diagnosed with coronavirus disease 2019 (COVID-19).

AIM

To identify whether quantitative SARS-CoV-2 viral load assay correlates with clinical outcome in COVID-19 infections.

METHODS

A systematic literature search was undertaken for a period between December 30, 2019 to December 31, 2020 in PubMed/MEDLINE using combination of terms "COVID-19, SARS-CoV-2, Ct values, Log_{10} copies, quantitative viral load, viral dynamics, kinetics, association with severity, sepsis, mortality and infectiousness''. After screening 990 manuscripts, a total of 60 manuscripts which met the inclusion criteria were identified. Data on age, number of patients, sample sites, RT-PCR targets, disease severity, intensive care unit admission, mortality and conclusions of the studies was extracted, organized and is analyzed.

RESULTS

At present there is no Food and Drug Administration Emergency Use Authorization for quantitative viral load assay in the current pandemic. The intent of this research is to identify whether quantitative SARS-CoV-2 viral load assay correlates with severity of infection and mortality? High SARS-CoV-2 viral load was found to be an independent predictor of disease severity and mortality in majority of studies, and may be useful in COVID-19 infection in susceptible individuals such as elderly, patients with co-existing medical illness such as diabetes, heart diseases and immunosuppressed. High viral load is also associated

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with elevated levels of TNF-α, IFN-γ, IL-2, IL-4, IL-6, IL-10 and C reactive protein contributing to a hyper-inflammatory state and severe infection. However there is a wide heterogeneity in fluid samples and different phases of the disease and these data should be interpreted with caution and considered only as trends.

CONCLUSION

Our observations support the hypothesis of reporting quantitative RT-PCR in SARS-CoV-2 infection. It may serve as a guiding principle for therapy and infection control policies for current and future pandemics.

Key Words: COVID-19; SARS-CoV-2; Viral load; Severe sepsis; Dynamics; Mortality

Core Tip: High viral load in Coronavirus-2 infections is an independent predictor of disease severity, mortality and prognosis. However there is a wide heterogeneity in fluid samples at different phases of the disease and data should be interpreted with caution. In aggregate, observations support the hypothesis of checking and reporting viral load by quantitative real time reverse transcriptase polymerase chain reaction, instead of binary assessment of a test being positive or negative. Longitudinal analysis with viral loads should be conducted for interpretation of outcome data. This may be the guiding principle for therapy and infection control policies for future pandemics.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic and associated mortality continues to rise and spread unabated in United States and worldwide. Coronavirus disease 2019 (COVID-19) infection is diagnosed *via* real time reverse transcriptase polymerase chain reaction (RT-PCR). However this assessment is qualitative and reported as a binary positive or a negative test. There is an urgent need to identify high risk patients early in the course of the illness, which includes rapid testing. Quantitative viral load may provide valuable assessment in risk stratification and may assist with early implementation of therapy in susceptible populations such as elderly, immunosuppressed patients with comorbidities.

Quantitative viral RNA load as determined by qRT-PCR assay and reported as cycle threshold (Ct < 38) value and/or $\log_{10}$ (viral copies/mL) from respiratory or blood specimens is a critical factor in diagnosing SARS-CoV-2 virus infection[1-60]. In addition, viral load dynamics in body fluids such as plasma, serum, urine, feces is emerging as a factor in determination of severe inflammation, infectiousness and transmissibility of COVID-19[1-60].

Similar association of high viral load along with age, comorbidities and elevated mortality were also demonstrated during the previous SARS-CoV, pandemic in Hong Kong in the year 2003 and MERS-CoV pandemic in middle east in 2012[61-64].

At present there is no Food and Drug Administration (FDA) Emergency Use Authorization issued for quantitative viral load assay in the current pandemic[59]. The intent of this research is to identify whether quantitative SARS-CoV-2 viral load assay correlates with clinical outcomes, particularly if there is any correlation with severity of infection and mortality? This a correlation study and does not imply causation. The author qualitatively examined the available data from different manuscripts to find patterns and generate a hypothesis for future research. These may assist clinicians; epidemiologist and health care policy makers develop strategies to improve care in COVID-19 sepsis.

MATERIALS AND METHODS

A systematic literature search was undertaken in PubMed/MEDLINE using combination of terms "COVID-19, SARS-CoV-2, Ct values, Log_{10} copies, quantitative viral load, viral dynamics, kinetics, severity of symptoms, sepsis, mortality'' for a period between December 30, 2019 to December 31, 2020. Review of manuscripts was performed according to principles outlined in Cochrane handbook. Figure 1 (PRISMA flow diagram).

Due to an explosion of COVID-19 related research and manuscripts, search was limited to adult (> 18 years) human subjects and published in English language journals. All data is retrospective, de-identified and conforms to the ethical principles in "Declaration of Helsinki". Manuscripts from preprint non-peer reviewed servers, review articles and individual case reports were excluded. After screening 990 manuscripts, a total of 60 manuscripts which met the inclusion criteria were identified. Data on age, number of patients, sample sites, RT-PCR targets, disease severity, intensive care unit (ICU) admission, mortality and conclusions of the studies was extracted, organized and presented (Table 1). Other relevant articles with relevant information on viral load assessment and mortality, severity and infectiousness and transmission were also included for discussion purposes. During the course of the pandemic in the year 2020, the author followed the PubMed literature on the research question and carefully tracked and evaluated the consistency and quality of the published articles to ensure credibility, reliability, transferability and reduce the risk of bias. The full text of selected articles was fully read, and the key findings were extracted. To establish reliability the author recorded the data in a table and updated assessment of the results. The use of the tables for recording manuscripts provided this researcher with a chance to evaluate the results of the data provided in each manuscript and follow the trends in this topic. The table also helped in construction of concise conclusions of the data. The table is transparent and reproducible and may be useful for other researchers to follow upon.

Due to a high heterogeneity in patient population, data from different countries, different methods in sampling, comorbidities, and different parameters used, the content was analyzed and is summarized using qualitative (descriptive) terms. Data with P value (< 0.05) was considered statistically significant.

RESULTS

Sixty manuscripts met the inclusion criteria with our research question, and are summarized[1-60]. Twenty eight manuscripts (46%) were reported from China[1,2,4-13,15,17,20-22,25,26,29,32,36,38,39,42,43,52,54], Eight (13%) studies from United States [27,28,30,35,40,53,59,60], Four (6%) were from France[3,33,37,56] and South Korea[19,31,34,50], Three (5%) from Spain[48,57,58], Two (3%) were from Italy[18,24] and Germany[14,41] and One manuscript (2%) was from Switzerland[16], Hong Kong[23], Sweden[44], Norway[45], Israel[49], Greece[55], Japan[47], Turkey[46], Brazil[51] (Table 1).

A total of 10514 patients were pooled from all reported studies. Quantitative RT-PCR and viral dynamics are reported in samples obtained from nasopharyngeal and oropharyngeal swabs, saliva, sputum, bronchial/tracheal lavage, feces, plasma/serum and urine samples. All studies had initial COVID-19 diagnosed on upper respiratory samples. Subsequent quantitative viral load was obtained and described from various other specimens and body fluids.

RT-PCR targets of SARS-CoV-2 virus included the following genes: *ORF1* (open reading frame), *N* (Nucleocapsid), *E* (Envelope), *RdRp* (RNA dep RNA polymerase), *5'UTR* (5'untranslated region). Forty-three studies (70%) reported viral kinetics in Ct values and 18 (30%) reported it as Log_{10} copies/mL values.

Association between viral load and disease severity

Thirty-six studies (7222 patients) demonstrated a significant association between pharyngeal viral load at onset of symptoms with severity of COVID -19 and ICU care [4-9,13,15,17-20,24,26,27,29,30,32,33,36-38,41,42,44,45,48,49,51-56,58,59]. The majority of these studies reported highest viral load at onset of symptoms.

Most studies consistently defined severity of illness and sepsis as: Respiratory rate ≥ 30 beats/min, resting-state oxygen saturation ≤ 93%, arterial partial pressure of oxygen/oxygen concentration ≤ 300 mm Hg or mechanical ventilation, shock, or multiple organ failure requiring care in ICU[4,8,29,65].

Table 1 Manuscript evaluating quantitative viral load assay and coronavirus disease 2019 outcomes. Sixty manuscripts meet the inclusion criteria

Ref./country	Number of patients	Age (yr)	Sampled sites	Quantitative viral load reported as Ct values or Log_{10} copies /mL /*RTPCR* gene target	Correlation with severity of sepsis	Correlation with mortality	*P* value	Merits of the study/key points
He *et al*[1], China	94	Median 47 yr	Nasopharynx	Ct values/; N gene	Not reported	Not reported	NR	Highest viral load at pre-symptomatic stage and infectiousness peaks before symptom onset.
Xu *et al*[2], China	51	Median 37 yr	Nasopharynx, BAL, Anal swab	Ct values/; ORF1ab and N gene	No	No	> 0.05	The quantitative viral load and infectiousness may be the similar for primary (imported form epicenter) and secondary and tertiary exposed group of patients but decrease rapidly (in 14 d) in tertiary patients.
Lescure *et al*[3], France	5	Median 46 yr	Nasopharynx, Stool, Plasma	Log_{10}copies/mL; RdRp-IP1 gene, E gene	No	Inadequate sample size	NR	Presymptomatic patients may have a high viral load and be highly infectious.
Liu *et al*[4], China	76	Median 50 yr	Nasopharynx	Ct values; Gene not reported	Yes	No	< 0.005	Patients with severe COVID-19 have a higher mean viral load (60 times higher) and long shedding period.
To *et al*[5], China	23	Median 62 yr	Oropharynx	Log_{10}copies/mL/; RdRp gene	Yes	Not reported	0.56	Peak viral load occurs at onset of symptoms and is correlated with increasing age and severity although not statistically significant.
Shen *et al*[6], China	5	Median 60 yr	Nasopharynx	Ct values; Gene not reported	Yes	No	NR	Patients with severe sepsis and high quantitative viral load benefit from convalescent plasma. The viral load became negative in all 5 patients in 12 d with clinical improvement.
Duan *et al*[7], China	10	Median 52.5 yr	Nasopharynx	Ct values; ORF1ab and N gene	Yes	No	< 0.001	Resolution of severe sepsis and negative viral load with convalescent plasma infusion.
Chen *et al*[8], China	48	Median 63 yr	Oropharynx. serum	Ct values; ORF1ab and N gene	Yes	Yes	< 0.001	Serum viremia and viral load associated with severity and poor prognosis. High RNAaemia is associated with elevated IL-6 levels.
Pan *et al*[9], China	82	Not reported	Oropharynx. Sputum, Stool	Log_{10}copies/mL; N gene	Yes	Yes	NR	Viral load is high on presentation. Stool samples may turn positive later in the disease.
Cao *et al*[10], China	199	Median 58 yr	Oropharynx	Log_{10}copies/mL; N and E gene	Not reported	No	NR	Lopinavir-Ritonavir did not aid with clinical improvement, reduce mortality or reduce the viral loads.
Wang *et al*[11], China	237	Median 65 yr	Oropharynx, Sputum	Log_{10}copies/mL; Gene not reported	Not reported	Not reported	NR	Remdesivir group does not decrease viral load compared to control group, however it may have faster time to clinical improvement.
Zou *et al*[12], China	18	Median 59 yr	Nasopharynx, Oropharynx	Ct values; ORF1b	Not reported	Not reported	NR	High viral load begins in the presymptomatic period and may suggest high infectivity.
Wang *et al*[13], China	23	Median 56 yr	Nasopharynx, Oropharynx, sputum, fecal, urine, plasma	Ct values; RdRp and N gene	Yes	None	< 0.001	High viral load and shedding from multiple tissues occurs for a prolonged period in severe cases. Feces remains positive for a prolonged time.
Wölfel *et al*[14], Germany	9	Not reported	Oropharynx, Sputum, stool, serum, urine	Log_{10}copies/mL; RdRp and E gene	No	No	NR	High viral load begins in the presymptomatic period and may continue beyond 10 d after symptoms ensue suggest high infectivity. No positivity in stool, urine or serum. All cases were with mild symptoms.
Zheng *et al*[15],	96	Median	Nasopharynx,	Ct values and Log_{10}copies/mL;	Yes	Not reported	0.03	High respiratory viral load associated with disease severity and serum

China		55 yr	Oropharynx, sputum, fecal, urine, plasma	ORF1ab				positivity and stool shedding occurs later and persists for a longer period.
Baggio *et al*[16], Swiss	352 adults, 53 children	Mean 36.5 yr	Nasopharynx	Log_{10}copies/mL; ORF1ab and E gene	Not reported	Not reported	NR	Children and adults can have same variation of viral loads, but risk of transmission and lower susceptibility in children may have other contributing factors.
Shi *et al*[17], China	114	Median 43.5yr	Oropharynx, serum	Log_{10}copies/mL; N gene	Yes	Not reported	< 0.001	High viral loads associated with severe sepsis in female patients.
Clementi *et al*[18], Italy	200	Mean 64 yr	Nasopharynx	Ct values; ORF1ab and E gene	Yes	Not reported	0.08	Higher viral loads associated with older age group and severity of sepsis.
Kwon *et al*[19], Korea	31	Mean 50 yr	Nasopharynx	Ct values; RdRp and N gene	Yes	None	0.093	High viral loads correlated with elevated cytokine profile and severity of sepsis.
Yu *et al*[20], China	92	Mean 55 yr	Sputum	Ct values/N and ORF1b	Yes	No	0.017	Higher baseline sputum viral load on admission is associated with severe disease.
Liu *et al*[21], China	31	Median 58 yr	Nasopharynx, sputum	Ct values; ORF1ab and N gene	Not reported	Not reported	NR	Viral load is higher in deep sputum samples and have a higher shedding and transmission capacity.
Zhou *et al*[22], China	31	Median 41 yr	Nasopharynx	Ct values; ORF1ab and N gene	No	No	NR	Asymptomatic patients have high viral loads and continue viral shedding and transmission.
Cheung *et al*[23], Hong Kong	59	Median 58.5 yr	Stool	Log_{10}copies/mL; Gene not reported	No	No	= 0.019	Stool viral loads are higher in patients with diarrhea and may persist after negative respiratory specimens.
Azzi *et al*[24], Italy	25	Mean 61.5 yr	Saliva	Ct values; 5'UTR	Yes	Not reported	= 0.04	High salivary viral loads may be associated with severe disease and may persist after the negative respiratory specimens. High viral load associated with high serum LDH suggestive of tissue damage.
Chen *et al*[25], China	22	Median 36.5 yr	Saliva, feces, Oropharynx	Ct values; ORF1ab and N gene	No	No	NR	Sputum and stool viral load remains positive after pharyngeal samples turn negative. Indicating the infectivity may persist after negative pharyngeal samples.
Huang *et al*[26], China	16	Median 59.5 yr	Nasopharynx, sputum, tracheal aspirates, fecal, urine, plasma	Ct values; N gene	Yes	No	< 0.01	In severe cases higher viral load is demonstrated in deep sputum and tracheal aspirates compared to upper respiratory tract specimens.
Pujadas *et al*[27], United States	1145	Mean 64.6 yr	Nasopharynx	Log_{10}copies/mL; RdRp and N gene	Yes	Yes	= 0.003	High viral load is an independent predictor of mortality.
Arons *et al*[28], United States	57	Mean 75 yr	Nasopharynx, Oropharynx	Ct values; N1 and N2	No	Not reported	NR	High viral loads demonstrated in presymptomatic, asymptomatic cases, favoring high transmissibility in close knit nursing home population.
Huang *et al*[29], China	308	Median 63 yr	Nasopharynx, Oropharynx	Ct values; ORF1ab	Yes	Yes	< 0.001	High viral load associated with critical disease and mortality. Sputum samples have higher viral loads.
Magleby *et al*[30], United States	678	Median 69 yr	Nasopharynx,	Ct values; ORF1b and E gene	Yes	Yes	< 0.001	High viral load is an independent risk factor for severe sepsis, intubation and death.
Park *et al*[31], Korea	46	Median 26 yr	Nasopharynx, Oropharynx, sputum ,	Ct values; RdRp, N and E gene	No	No	NR	High fecal viral load and shedding, follows and persists after respiratory symptoms resolve for up to 50 d.

			Stool					
Yu *et al*[32], China	76	Median 40 yr	Nasopharynx, Oropharynx, sputum, urine, plasma	Ct values; ORF1b and N gene	Yes	None	< 0.001	Digital droplet PCR is superior for patients with high suspicion but negative RTPCR. High viral load correlated with risk for progression and disease activity.
Blot *et al*[33], France	14	Median 67 yr	Broncho-alveolar fluid	Log_{10}copies/mL; RdRp	Yes	Not reported	= 0.013	Higher viral load associated with worse sepsis related organ failure (SOFA) scores.
Kim *et al*[34], Korea	13	Median 30 yr	Nasopharynx	Ct values; RdRp and E gene	No	No	NR	Patient with mild or asymptomatic infections are infectious before symptoms appear and 14 d of isolation may be sufficient in asymptomatic carriers.
Argyropoulos *et al*[35], United States	205	Median 60 yr	Nasopharynx	Log_{10}copies/mL; RdRp and N gene	Decreased	Decreased	< 0.001	Study shows inverse correlation of high viral load with duration, severity of sepsis and no correlation with survival.
Xu *et al*[36], China	85	Median 56 yr	Nasopharynx, Oropharynx, serum	Ct values; ORF1b and N gene	Yes	Yes	< 0.001	Detection of high serum viral load in the serum increases the severity of organ damage, sepsis and mortality.
Veyer *et al*[37], France	58	Median 55.1 yr	Plasma	Log_{10}copies/mL; ORF1b and N gene	Yes	Yes	= 0.036	Detection of high Viral load in the serum increases the severity of sepsis and mortality.
Lin *et al*[38], China	217	Median 50 yr	Nasopharynx, Oropharynx, anal	Ct values; ORF1b and N gene	Yes	No	= 0.006	Anal viral load remains positive longer and is correlated with severity of sepsis and ICU admission.
Wang *et al*[39], China	275	Median 49 yr	Oropharynx	Ct values; ORF1b and N gene	No	No	= 0.824	Similar viral loads between severe and mild cases, no correlation of viral load to ICU admission, severity or mortality.
Kimball *et al*[40], United States	23	Mean 80.7 yr	Nasopharynx, Oropharynx	Ct values; N1, N2 genes	No	No	= 0.3	High viral loads in unrecognized asymptomatic and presymptomatic patients may contribute to infectiousness and transmission.
Schwierzeck *et al*[41] ,Germany	12	Not reported	Nasopharynx	Ct values; E and RdRp genes	Yes	No	= 0.007	High viral load, 200 times greater in symptomatic patients compared to asymptomatic patients.
Xia *et al*[42], China	10	Mean 56.5 yr	Nasopharynx	Ct values; ORF1ab and N gene	Yes	No	NR	Higher viral load associated with severe symptoms and increased neutrophil/lymphocyte ratio.
Huang *et al*[43], China	41	Median 49 yr	Nasopharynx, Oropharynx, sputum, BAL	Ct values; 5'UTR	No	No	No	Patients with high viral load with RNAeamia had severe infection, elevated cytokine levels, and mortality but not statistically significant.
Hagman *et al*[44], Sweden	167	Median 63	Nasopharynx, Oropharynx, sputum, Blood	Ct values; E, RdRp, ORF1 genes	Yes	Yes	P < 0.05	Viral RNAemia on admission was associated with eight fold increased risk of in hospital death.
Prebensen *et al*[45], Norway	123	Median 64	Nasopharynx, Oropharynx, sputum, Blood	Ct values for respiratory specimens; Log_{10}copies/mL for plasma samples; E gene	Yes	Yes	< 0.001	Higher viral loads associated with ICU admission and death.
Hasanoglu *et al*[46], Turkey	60	Mean 32	Nasopharynx, Oropharynx, sputum, urine, Blood, rectal	Ct values; RdRp gene	Decreased	Decreased	= 0.0141	Viral loads in younger asymptomatic patients were significantly higher compared to elderly, symptomatic patients.
Kawasuji *et al*[47], Japan	28	Median 45	Nasopharynx	Log_{10}copies/mL; N gene	No	No	= 0.015	High admission nasopharyngeal viral load associated with increased risk of transmission.

Bermejo-Martin *et al*[48], Spain	250	Median 66	Nasopharynx, Oropharynx, sputum, urine, Blood, rectal	Log_{10}copies/mL; N gene	Yes	Yes	< 0.001	Increased serum viral load associated with increased severity, mortality and dysregulated host response.
Shlomai *et al*[49], Israel	170	Median 62	Nasopharynx	Ct values; N gene	Yes	Yes	< 0.0001	Increased hypoxemia, severity and eight fold increase in mortality.
Ra *et al*[50], Korea	213	Median 25	Nasopharynx	CT value; E, N, RdRp gene	No	No	None	Comparable viral load in asymptomatic and symptomatic patients, asymptomatic patients contribute to ongoing transmission.
Faico-Filho *et al*[51], Brazil	875	Median 48	Nasopharynx	Ct value; N gene	Yes	Yes	< 0.0001	Admission nasopharyngeal viral load was independently associated with increased mortality.
Chen *et al*[52], China	52	Median 62	Blood, oropharynx	Log_{10}copies/mL; ORF1ab	Yes	Yes	< 0.001	Increased RNAemia associated with severity, markers of inflammation and mortality.
Fajnzylber *et al*[53], United States	88	Median 57	Nasopharynx, Oropharynx, sputum, Blood	Log_{10}copies/mL; N gene	Yes	Yes	= 0.009	Increased viremia associated with severity, progression and mortality.
Zhou *et al*[54], China	195	Median 66	Oropharynx	Ct value; N gene, ORF1ab	Yes	Yes	< 0.005	High viral load associated with multi organ failure and death.
Maltezou *et al*[55], Greece	1122	Mean 46	Nasopharynx, Oropharynx	CT value; E, RdRp gene	Yes	Yes	< 0.05	High viral load correlated with intubation and in hospital mortality.
Bitker *et al*[56], France	129	Median 69	Nasopharynx, Oropharynx, sputum	Ct value; ORF1ab	Yes	Yes	< 0.05	High viral load associated with increased mortality.
Carrasquer *et al*[57], Spain	169	Median 67	Nasopharynx	Ct value; E, N gene, ORF1ab	No	No	= 0.029	High viral load statistically not associated with in hospital mortality.
de la Calle *et al*[58], Spain	455	Mean 64	Nasopharynx	Ct value; N gene	Yes	Yes	= 0.022	High viral load associated with respiratory failure, and 30 d mortality.
Bryan *et al*[59], United States	109	Mean 65	Nasopharynx	Ct value; N gene	Yes	Yes	= 0.01	The high nasopharyngeal viral load on admission was independently associated with greater mortality.
Choudhuri *et al*[60], United States	1044	Mean 65	Nasopharynx	Ct value; ORF1ab	No	Yes	< 0.001	High viral load is an independent predictor of increased mortality.

Data on country of origin, age, number of patients, sample sites, real time reverse transcriptase polymerase chain reaction targets, correlation with sepsis and mortality and key conclusions. NR: Not reported; ORF: Open reading frame; E: Envelope; N: Nucleocapsid; 5'UTR: 5 prime untranslated; RdRp: RNA dependent RNA polymerase; Ct: Cycle threshold; SOFA: Sequential organ failure assessment; ICU: Intensive care unit; COVID-19: Coronavirus disease 2019.

There is variation observed in kinetics, tissue distribution and antibody response between mild and severe infections. Wang *et al*[13] analyzed a cohort of 12 severe and 11 mildly ill patients and demonstrated a significant difference in the initial nasopharyngeal peak viral load ($P < 0.001$) between two groups. Subsequent prolonged viral shedding in other body fluids and stool occurred with detectable viral load for up to 40 d (days) in severely ill compared to 15 d in mildly ill group. Viral RNA was detected from respiratory tract, stool, plasma and urine samples in the

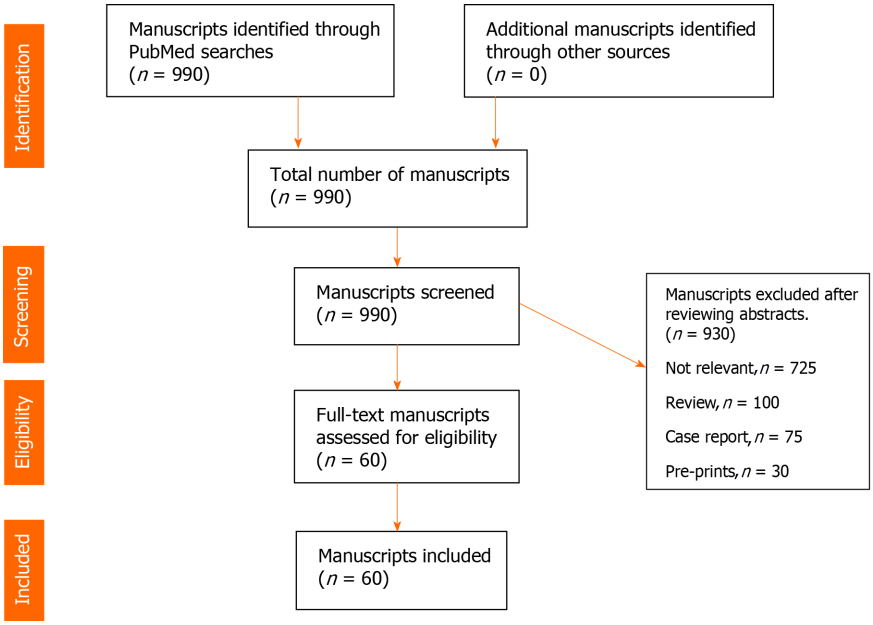

Figure 1 PRISMA flow diagram.

severe group. Mildly ill patients had viral shedding restricted to respiratory tract and no virus was detected 10 d after onset of symptoms[13].

Yu *et al*[20] analyzed their cohort of 92 patients and observed that high viral load in baseline sputum samples was linearly associated with severity and risk of disease progression ($P < 0.017$).

Another cohort of 96 patients with mild and severe infections demonstrated similar viral kinetics. Respiratory viral load remained elevated in the severe group up to the third and fourth week after disease onset, compared to milder group where viral load peaked in the second week followed by a decline. Subsequent viral detection in serum samples was also higher in patients with severe disease than in patients with mild disease (45% *vs* 27%, $P < 0.03$)[15].

In general nasopharyngeal viral levels remained high in severe group and, begin to decrease after 14 d of symptom onset[4,15,65]. Subsequently, samples from other sites may also test positive for the virus. For example, viral load from stool samples were found to peak during the third and fourth weeks after disease onset and continue to remain positive during convalescence[9,13,15,19,25,31]. Some studies also reported presence of high viral load in stool up to 50 d after onset of COVID-19 symptoms[31, 38].

Significance of viral load in stool remains unclear, whether it represents a true infection or residual viral nucleic acid and not transmissible live virus. Gastrointestinal epithelium also expresses angiotensin-converting enzyme II (ACE-2) receptors. Infection of gastrointestinal (GI) tract may occur primarily from swallowed nasopharyngeal secretions or due to dissemination to GI tract from viremia[23]. Eighteen studies (5479 patients) demonstrated a statistically significant (P value < 0.005) association between higher viral load in different samples and severity of disease[4,7,8,13,17,27,29,30,32,36,45,48,49,51,52,54-56].

Liu *et al*[4] analyzed their cohort of 46 mild and 30 severely ill patients with elevated nasopharyngeal viral load and demonstrated an association with severity. Viral load was 60 times higher in severe cases and with severe clinical outcomes ($P < 0.005$). Mild cases had viral clearance, with 90% of patients testing negative after 10 d. In contrast, all severe cases had persistently elevated viral load beyond 10 d of symptoms were elderly and required ICU care.

In a cohort of patients on dialysis, Schwierzeck *et al*[41] also demonstrated a similar association with severity. Ct values of symptomatic cases were significantly lower compared to asymptomatic cases (22.55, 29.94, respectively, $P = 0.007$), indicating approximately 200-fold higher viral load[41]. Similarly other authors from their cohorts from different countries Bermejo-Martin *et al*[48]; Spain, Shlomai *et al*[49]; Israel, Chen *et al*[52]; China, Zhou *et al*[54]; China, Maltezou *et al*[55]; Greece have demonstrated a statistically significant association between admission high viral load and intubation, ICU care and multi-organ dysfunction.

Collectively these data from different cohort of patients suggests that severe COVID-19 patients with a high viral load correlate with higher risk for severe infection with ICU admission and multi-organ dysfunction. Factors common to these cohorts was increased age, and active preexisting medical co-morbidities.

Association between viral load and inflammatory markers

Higher viral load on admission samples were also associated with elevated levels of IL-6, cytokines, lactate dehydrogenase (LDH), lymphopenia and elevated neutrophil/lymphocyte ratio; indicative of poor sequential organ failure assessment (SOFA) scores and associated with hyper-inflammatory state contributing to the severity of sepsis[8,19,24,29,33,36,37,42,48,49,52,65,66].

In a cohort of 48 patients, Chen *et al*[8] reported an association between high viral load in serum with elevated Il-6 Levels (≥ 100 pg/mL) and cytokine storm in critical compared to mildly ill patients ($P < 0.001$). These patients had a higher incidence of multi-organ failure and mortality.

Similarly Xia *et al*[42] in their cohort of 10 patients with severe illness and elevated nasopharyngeal viral load reported severe lymphopenia with CD4+ lymphocyte counts as low as 61 cells/uL (reference value: 355-1213 cells/μL). Neutrophil to lymphocyte ratio was also elevated in this group.

Liu *et al*[65] reported their cohort of 46 patients with severe illness and elevated nasopharyngeal viral load. $CD4^+$ and $CD8^+$T lymphocyte count displayed a linear negative correlation ($P < 0.001$) with high viral count; and positively correlated with IL-2R, prothrombin time, lactate dehydrogenase, and hypersensitive troponin T ($P = 0.002$, $P = 0.009$, and $P < 0.001$, respectively). Also elevated, were levels of inflammatory factors, IL-2R, IL-6, IL-8 Levels in the severe compared to mild group ($P = 0.022$, 0.026, and 0.012, respectively)[65].

Blot *et al*[33] in their series of 14 patients demonstrated a positive correlation of high nasopharyngeal viral load on admission with risk of hypoxemia, increased oxygen requirements and SOFA score in respiratory distress syndrome patients ($P = 0.013$). Similar association with increase in severity of sepsis, organ damage and mortality was also reported by Xu *et al*[36].

Lucas *et al*[66] in their series of 113 patients with COVID-19 patients demonstrated an overall increase in cells of innate lineage and a reduction in T lymphocytic cell counts. High viral load correlated significantly with levels of IFNα, IFNγ, TNF and tumor necrosis factor-related apoptosis-inducing ligand. Chemokines responsible for monocyte recruitment correlated significantly with viral load in severe disease. Inflammasome associated cytokines were also elevated, including IL-1α, IL-1β, IL-6, IL-18 and TNF[66].

Similarly Han *et al*[67] in their series of 60 critical patients demonstrated high levels of cytokines TNF-α, IFN-γ, IL-2, IL-4, IL-6, IL-10 and C reactive protein (CRP). Serum IL-6 and IL-10 Levels were significantly higher in critically ill compared to moderately ill group. The levels of IL-10 positively correlated with CRP ($r = 0.41$, $P < 0.01$)[67].

Collectively these studies provide evidence that high viral load may be a surrogate marker for predicting inflammation and severity in COVID-19 infection.

Association between viral load and mortality

Subgroup analysis of 20 studies (7183 patients) demonstrated an association of admission viral load with in hospital mortality[8,9,27,29,30,36,37,45,46,48,49,51-56,58-60]. Majority of patients in this category were older (median > 65 years) and with medical comorbidities[8,9,29,30,33,36,37,45,46,48,49,58-60]. High admission viral load was an independent risk factor for in hospital mortality ($P < 0.005$)[8,27,29,30,36,46,48,49,51,52,54,59,60].

Pujadas *et al*[27] demonstrated an association of viral load as an independent predictor of mortality in a cohort of 1145 hospitalized patients. Mean $\log_{10}$ viral loads significantly differed between patients who survived [$n = 807$; mean $\log_{10}$ viral load 5.2 copies/mL (SD 3)] *vs* those who succumbed [$n = 338$; 6.4 copies/mL (SD2.7)]. Cox proportional hazards model was adjusted for age, sex, asthma, atrial fibrillation, coronary artery disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes, heart failure, hypertension, stroke, and race. The results demonstrate a significant independent association between viral load and mortality [hazard ratio 1.07 [95% confidence interval (CI): 1.03–1.11), $P = 0.0014$], and 7% increase in hazard for each log transformed copy/mL. Univariate survival analysis also demonstrated a significant difference in survival probability between high and with low viral load ($P = 0.0003$), with a mean follow-up of 13 d and a maximum follow-up of 67 d[27].

Magleby *et al*[30] in their cohort of 678 patients demonstrated that higher viral load was associated with increased age, comorbidities, smoking status, and recent chemotherapy. Mortality was highest, 35.0% in the high viral (Ct < 25; n = 220) followed by 17.6% in the medium viral (Ct 25-30; n = 216) and 6.2% with a low viral load (Ct > 30; n = 242; P < 0.001). The need for mechanical ventilation was also highest in the high viral (29.1%), compared to medium (20.8%) and low viral load (14.9%; P < 0.001) group. High viral load was independently associated with mortality [adjusted odds ratio (OR) 6.05; 95%CI: 2.92-12.52; P < 0.001] and intubation (adjusted OR 2.73; 95%CI: 1.68-4.44; P < 0.001) in multivariate models.

Similarly Huang *et al*[29] in their analysis of 308 patients demonstrated a high viral load associated with in-hospital mortality in (6/16) of critical patients, while no mortality was observed in the low viral load group (P < 0.0001). High viral load was associated with myocardial damage, elevated troponins, coagulopathy, abnormal liver and renal functions. Elevated IL-6, LDH, and elevated neutrophil counts and reduced CD4+, CD8+ lymphocytes were noted in deceased patients P < 0.0001)[29].

In a cohort of 109 patients Bryan *et al*[59] demonstrated high viral load on admission was associated with a significantly increased 30-d mortality (OR, 4.20; 95%CI, 1.62–10.86. Their data suggested that a CT value of 22 may serve as a useful discrete cutoff for significant viral replication that is associated with mortality[59].

In a cohort of 1044 patients, Choudhuri *et al*[60] demonstrated a statistical correlation of Ct value at admission was higher for survivors (28.6, SD = 5.8) compared to non-survivors (24.8, SD = 6.0, P < 0.001). After adjusting for age, gender, body mass index, hypertension and diabetes, increased cycle threshold was associated with decreased odds of in-hospital mortality (0.91, CI: 0.89-0.94, P < 0.001)[60].

Collectively these multiple cohort of patients from different studies shows a trend of the association of high viral load and mortality in hospitalized patients.

Association between viral load and infectivity, transmission and antibodies to SARS-CoV-2

Although not statistically significant, 20 studies (1857 patients) indicated the importance of high viral load dynamics with infectiousness and transmissibility (P > 0.05-0.53)[1-3,10-12,14,16,21,22,23,25,28,31,34,39,40,43,47,50].

Association between viral load and infectivity remains unclear, but earlier peak in viral load in SARS-CoV-2 infection suggests that infectivity may be higher earlier in the course than would be expected based on the SARS model[5,62,63].

Subgroup analysis suggests these patients are younger and had milder disease and may be highly infectious and transmit virus to the population given their asymptomatic or presymptomatic nature of illness. These studies shed light on high viral load and its association with infectivity and transmissibility. Highest respiratory viral load was noted at pre-symptomatic stage and infectiousness peaked before symptom onset [1,2,3,5,12,14,16,22,34,40,47,50].

He *et al*[1] demonstrated an infectiousness profile on 77 infector–infected transmission pairs. Highest viral load in oropharynx at the time of symptom onset correlated with infectiousness. Presymptomatic transmission was 44% (95%CI, 30%–57%) whereas infectiousness started at 12.3 d (95%CI, 5.9-17 d) before symptom onset and peaked at onset (95%CI: –0.9 to 0.9 d). They estimated that proportion of presymptomatic transmission was 37%-48%[1].

Xu *et al*[2] reported on 51 symptomatic patients, demonstrating transmission from primary (patients who visited the epicenter, Wuhan), to secondary (patients who came into contact with primary) and tertiary (patients who came into contact with only secondary cases). Their findings suggested incubation period in tertiary group was longer compared to primary and secondary groups (both P < 0.05). Ct values detected in tertiary were similar to those for the imported and secondary patients at the time of admission (both P > 0.05). For tertiary group, the viral load was undetectable in half of patients (52.63%) on day 7 and in all patients on day 14. One third of patients in imported and secondary groups remained positive on day 14 after admission. They concluded that infectivity of SARS-CoV-2 may gradually decrease in tertiary patients [2]. This study emphasizes that early quarantine and lock down measures may have mitigated the spread of disease in countries that enforced it strictly. The reason for decrease in infectivity from secondary to tertiary exposed patient remains unclear. Although speculative, this may be due to reduced quantitative viral load transmitted and other strict mask and quarantine measures[2,44].

Some reports demonstrated an association of high viral load and risk of transmission in a closed knit population[28,40]. In a cohort of 80 patients including both health care workers and nursing home residents from COVID-19 outbreak in Washington State, high viral load in unrecognized asymptomatic and presymptomatic

patients contributed to infectiousness and transmission. Although the mortality was high in these patients, it did not correlate statistically with the viral load[28]. Similarly Kimball *et al*[40] analyzed their cohort of 23 patients from a long term care facility. Ten (43%) had symptoms on testing, and 13 (57%) were asymptomatic. Seven days after testing, 10 of these 13 previously asymptomatic residents had developed symptoms and were inferred as presymptomatic at time of testing. The Ct values indicated large quantities of viral RNA in asymptomatic, presymptomatic, and symptomatic residents, suggesting potential for transmission regardless of symptoms[40].

There are at present limits to our understanding and evidence in determining infectiousness and the risk of transmissibility. As described earlier, there is evidence of ongoing viral shedding in various body fluids after symptom resolution in COVID infection and may be prolonged, especially in stool samples compared to respiratory secretions (P < 0.001-0.5)[9,13,15,19,25,31,38,67]. Currently there is no reported evidence of fecal –oral transmission. Further the severity of illness also appears to extend the duration of viral shedding. However, based on current data, there is no convincing evidence that duration of shedding correlates with duration of infectivity. The viral nucleic acid detected in various body fluids later in the course of infection may represent non-viable fragments of virions.

Wölfel *et al*[14] demonstrated that live virus can be cultured from respiratory samples in patients with positive SARS-CoV-2 RT-PCR. However, the percentage of positive cultures declined and no live virus was successfully isolated after day 8 from symptom onset despite ongoing high quantitative viral load. Additionally, virus could not be isolated from samples less than 10^5 copies/mL. However a caveat with this cohort was that patients had mild symptoms and were young and middle aged adults. This emphasizes the point that elevated high viral load in convalescing patients may be suggestive but not a definitive factor in infectiousness and transmissibility[14].

There is evidence that children are susceptible to SARS-CoV-2 infection, but frequently do not have symptoms, raising possibility that children could be facilitators of viral transmission. Reports comparing viral kinetics in adults and pediatric patients have demonstrated that children, adolescents and adults can have same variation of viral load, but higher risk of transmission and asymptomatic illness in children may have other contributing factors[16,47,50].

The immune responses of the host to COVID-19 and its relation to infectivity and transmission remain unclear and data is emerging[5,13,59,68,69]. Most patients seroconvert by day 15 after symptom onset and Anti-SARS-CoV-2-NP or anti-SARS-CoV-2-RBD IgG levels correlate with virus neutralization[5]. While risk of transmission after symptom resolution and the presence of antibodies may be lower, it cannot be ruled out with available evidence[1-3,5]. Transmission by asymptomatic or minimally symptomatic individuals also appears likely and highlights the importance of contact tracing and isolation of exposed individuals, especially as transmission potential may be maximal early in course of infection as depicted in the nursing home cohort[28,40]. In their large series of 100 patients Li *et al*[68] demonstrated specific anti SARS-CoV-2 (IgM, IgG, IgA) antibodies to S-1, N, and RBD viral proteins in the serum within two weeks after onset and reached a peak in 17 d and maintained high levels up to 50 d post infection.

Fourati *et al*[69] demonstrated an inverse relationship of lower serum titer of neutralizing antibodies (anti-S1 Ig A and Ig G) with elevated nasopharyngeal viral load and severe COVID-19 sepsis. This may indicate an inability to clear infection and have a deleterious impact on survival. Patients who were alive at 28 d displayed higher titers of anti-S1 Ig A and Ig G on admission compared to those who succumbed [69]. Similar observation was demonstrated by Bryan *et al*[59]; this study demonstrated that detection of anti-SARS-CoV-2 nucleocapsid IgG is associated with lower viral loads in patients. They concluded that high viral loads almost never coexist with SARS-CoV-2 sera-positivity and suggest that persons with anti-SARS-CoV-2 antibodies on admission have reduced 30-d all-cause mortality[59]. Both these studies may suggest that presence of antibody titers on admission, coupled with molecular testing, may be particularly prognostic factor, helpful to assess the disease course for high risk patients who cannot provide a clinical history[59,69]. The mechanism may be due to lower host humoral immune response in the elderly patients with comorbidities.

The heterogeneity of the non-respiratory specimen's limits its significance in explaining the risk of transmission and no correlation can be inferred. Further research is needed. In addition it is also important to determine viability of virus outside the respiratory and gastrointestinal tract at different stages of infection in both asymptomatic and symptomatic individuals. This will improve understanding of transmission risk and allow greater certainty around guidelines for appropriate

contact tracing and quarantine periods[70].

DISCUSSION

SARS-CoV-2 is diagnosed based on nucleic acid test, detecting viral RNA. We briefly discuss the relevance of diagnostics in the context of our research question. Laboratories have set up their RT-PCR techniques with primers and probes and protocols, algorithms following guidelines from United States FDA and Center for Disease Control and Prevention (CDC) and World Health Organization[71]. A reference, limit of detection range is set by each laboratory based on reaction system and amplification conditions, specified according to manufacturer's specifications[72]. These tests are high throughput and have high sensitivities and specificity. Bisoffi *et al* [73] demonstrated that nucleic acid tests have highest performance with 91.8% sensitivity, 100% specificity, 100% PPV (positive predictive value) and 97.4% negative predictive value). Some variation may exist in considering single gene targets. *S* and *RdRp* genes had highest sensitivity (94.1%) at their institution[73]. Factors that may affect sensitivity of tests are duration of illness, site of specimen collection, and viral load. Some authors have reported that false negative rates may occur in up to 30% tests[71]. However, at present there is no clear advantage of choosing one particular gene over another as long as the sample acquisition, preparation and device operations are performed by trained personnel and laboratories[70,71].

Viral load is the quantity of viral RNA in a given volume expressed as infectious particles per milliliter. This is also expressed as Log_{10} copies /mL or Ct value. Ct value represents the number of amplification cycles needed for a target gene to exceed a threshold detection level. It is inversely related to viral load; lower the value of Ct, higher the viral load[3,5,12,70,71]. For SARS-CoV-2 the test results are considered positive when multiple genes had a Ct value less than 38. If only one of target gene had a Ct value of < 38, it is reported as a single test positive[32]. Fung *et al*[74] compared the limit of detection for various assays and reported it to be between 85-499 copies/mL for CDC assays and 74 copies/mL with other commercial high-throughput laboratory analyzers. Digital droplet PCR is another technique useful in situations with a high suspicion of infection but a low viral load or a negative test. This test has an advantage of absolute quantification and higher sensitivity in viral RNA detection especially in low viral load samples[32,75].

Strengths and limitations of this manuscript

This study is a large pooled, qualitative content analysis of 60 manuscripts with a cohort of 10514 patients' from different cohorts and countries evaluating patterns of quantitative viral load in predicting disease severity, mortality, risk of infectiousness, transmissibility, and prognosis in patients with COVID-19. The author presents the relative merits and discusses the objective data presented in these studies. This a correlation study and does not imply causation.

However, there are certain limitations in this study. Since there is a high heterogeneity of samples and data in the majority of these manuscripts, the content analysis is qualitative (narrative) and these data should be interpreted with caution and considered only as trends. Differences in distribution of age, sex, definition of disease severity, and other confounding variables such as medical comorbidities, different virologic tests and heterogeneous samples may contribute to different clinical outcomes. For instance very few studies adjusted their statistic models for the other medical morbidities which could have increased the risk for morbidity and mortality [4,6,7,15,19,27,30]. The majority of these studies are on hospitalized patients which has a potential bias of analyzing the more severely ill amongst the overall infected population. Further variations of ACE 2 receptors and expression in various tissues in different ethnic populations may play a role in virulence and transmissibility of this virus[76]. A viral nucleic acid load from a particular sample assay may not represent an exact systemic viral load in the body; further viral load may also not represent viable virions and may be falsely misleading. In addition there is no consistent trajectory of why certain samples test positive with high virus loads and others do not. Another important point to consider is that, majority of studies is from one country: China and from a few medical centers around the epicenter of outbreak, possibly leading to overlapping of population data in reported manuscripts. Other limiting factors may include the testing protocol and standards, set for RT-PCR targets vary between different laboratories[68-70]. Finally there is always a possibility of observer (author bias) which is to be considered.

Although majority of studies showed a positive association between a high viral load and mortality there were three studies with (434 patients) suggestive of an inverse correlation between the two. Argyropoulos *et al*[35] in their report on 205 patients demonstrated an inverse correlation of admission nasopharyngeal viral load with duration, severity of sepsis and no correlation with survival ($P < 0.001$). The reason for low mortality in this study is unclear. One possible explanation could be due to the fact that viral loads detected from nasopharyngeal samples were obtained at a later time point in the disease course. As we have described earlier, that SARS-CoV-2 viral load peaks earlier in the infection followed by cytokine storm and hyper-inflammation when the innate immune system is unable to control the initial viral replication [61]. At these later times points the viral replication may start to defervesce but the multi-organ dysfunction is secondary to systemic hyper-inflammatory response. Similarly Hasanoglu *et al*[46] on their cohort of 60 patients demonstrated an inverse relationship of high viral load with mortality; however their study had a mean age of 32 signifying a younger age group, where mortality is lower compared to older patients. Another group of 169 patients, reported from Spain by Carrasquer *et al*[57] demonstrated no statistical association of high viral load with in hospital mortality when adjusted to age, gender and serum cardiac troponin levels. The conclusions from this study suggested myocardial damage with medical comorbidities as the cause for increased mortality in susceptible population and not high viral loads.

Why is quantitative viral assay important?

Although infection and inflammation begins with the respiratory tract, it also involves extra pulmonary organs[77]. Isolation of viral nucleic acid in multiple tissues, blood and body secretions are indicative of systemic spread and are indicative of severe infection. Evidence from these manuscripts suggests that high viral load occurs in respiratory tract samples during presymptomatic period and peaks at the onset of symptoms and gradually declines over the next one to three weeks[1,2,3,5,9,12,14,16,22,34,40]. Increased viral load in respiratory tract represents active viral replication and a surrogate marker for predicting severity[28,32,37,61]. This is in contrast to previous SARS-CoV epidemic in 2003 where the peak viral load occurred during second week after symptoms appeared and was positively correlated with increased mortality[5,62,63]. This fact explains the increased infectivity and rapid transmission of SARS-CoV-2 compared to previous SARS-CoV epidemic[5]. Along with comorbidities, assessment of viral load from nasopharynx or sputum may determine the risk of severity of sepsis in symptomatic, hospitalized elderly patients[4,5,18]. High viral load is also associated with elevated cytokine, lymphopenia *i.e.,* markers for inflammation and portends poor prognosis[8,24,33,36,37,42,52,65,66]. Early determination of viral load also has therapeutic benefits, such as administration of convalescent plasma, neutralizing antibodies, antiviral medicines and corticosteroids in susceptible elderly patients[6,7,11].

SARS-CoV-2 pandemic continues to spread unabated in United States and worldwide. This is particularly evident after the end of lock down and social distancing measures with increased mobility of the population. A report from a reference laboratory evaluated 29713 de-identified samples from respiratory tract. 14.9% of samples tested positive. Highest positivity rate was identified in males born between1964-1974. Patients between ages of 11-25 had highest viral load (> 10 Log_{10} copies/mL). The clinical symptoms or outcomes of these patients were not known. This study demonstrates that high viral load in younger group may be an important risk factor for infectivity and transmission in a community, regardless of their symptom status[78].

COVID -19 infections in younger asymptomatic patients, with high viral load may fare well due to their robust physiologic reserve. However, they are at highest risk for transmitting the disease and are called super spreaders. These infections generally appear asymptomatic or milder in younger population, but elderly patients bear the brunt of severe infection, hospitalization and mortality[61,62].

CONCLUSION

High SARS-CoV-2 viral load was found to be an independent predictor of disease severity and mortality in high proportion of studies, and may be useful in predicting the clinical course and prognosis of patients with COVID-19. However there is a wide heterogeneity in fluid samples and different phases of the disease and these data should be interpreted with caution and only considered as trends. In aggregate, these

observations support the hypothesis of checking and reporting viral load by quantitative RT-PCR, instead of binary assessment of a test being positive or negative.

ARTICLE HIGHLIGHTS

Research background

High viral load has an implication in the clinical outcomes in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. At present there is no Food and Drug Administration Emergency Use Authorization for quantitative viral load assay in the current pandemic. Currently the coronavirus disease 2019 (COVID-19) tests are reported as a binary assessment of either positive or negative test.

Research motivation

The intent of this research is to identify whether quantitative SARS-CoV-2 viral load assay correlates with severity of infection and mortality?

Research objectives

To assess high viral load and its association with the severity, mortality, infectiousness in COVID-19 infections.

Research methods

A systematic literature search was undertaken for a period between December 30, 2019 to December 31, 2020 in PubMed/MEDLINE using combination of terms "COVID-19, SARS-CoV-2, Ct values, Log_{10} copies, quantitative viral load, viral dynamics, kinetics, association with severity, sepsis, mortality and infectiousness''. Data on age, number of patients, sample sites, real time reverse transcriptase polymerase chain reaction (RT-PCR) targets, disease severity, intensive care unit admission, mortality and conclusions of the studies was extracted, organized and is analyzed.

Research results

High SARS-CoV-2 viral load was found to be an independent predictor of disease severity and mortality in high proportion of studies, and may be useful in predicting the clinical course and prognosis of patients with COVID-19.

Research conclusions

There is a wide heterogeneity in fluid samples and different phases of the disease and these data should be interpreted with caution and only considered as trends. In aggregate, these observations support the hypothesis of checking and reporting viral load by quantitative RT-PCR, instead of binary assessment of a test being positive or negative.

Research perspectives

In future, longitudinal studies with viral load should be monitored and analyzed, so it can be considered in interpretation of outcome data. It may also be a guiding principle for therapy and infection control policies for current and future pandemics.

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META-ANALYSIS

COVID-19 and resuscitation: La tournée of traditional Chinese medicine?

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Abstract

BACKGROUND

As it has been established in previous publications of the author, the current extra-hospital statistics referring to cardiopulmonary resuscitation (CPR) are far from being minimally satisfactory (14%-17% success). Since the appearance of acquired immune deficiency syndrome, its application has been increasingly undermined as other subsequent pandemics (H1N1, Ebola, coronavirus disease 2019) seriously infringing lay rescuers intervention during classical CPR steps (mouth-to-mouth ventilation), forcing to modify vital support protocols. Both KI-1 Yong quan and PC-9 Zhong chong alternative rescue maneuvers could come to aid those victims of impending death situation due to both cardiac arrest or stroke, upgrading current survival rates of said unfortunate patients.

AIM

To validate a complementary resuscitation maneuver originated in Chinese Medicine knowledge, carefully integrated into international CPR protocols [*World Journal of Critical Care Medicine* (*WJCCM*), August 2013].

METHODS

The model to verify its statistical validity of quoted research was the Retrospective Cohort Study, which redeems the "semiotic paradigm" that gave rise to medical semiotics. Its value strives in the differential detail if the deceased patients are considered the control group instead of the patients that may be deceased. Thus, combining the semiotic paradigm with the Retrospective Cohort Study allows us to manage the collateral potential lethal effects of the random process in cases of extreme emergencies.

RESULTS

The statistic results provided by the methodological analysis of this work were previously published in *WJCCM* August 2013, ISSN 2220-3141). In a total of 89 patients in which the Yong quan maneuver was tested, 75 survived and 14 died.

manuscript

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Country/Territory of origin: Argentina

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In order to compare this data with the percentages of survivors in the other maneuvers, we stipulate the assumption that if 89 patients are the 100% of the sample, how many patients would survive if the survival rate is 6.4% in CPR, 30% in defibrillation and 48% in CPR + defibrillation. By this way we obtained the approximate values of patients that would survive when applying these classical resuscitation maneuvers. Then we obtained the format of the tables to perform the exact Fisher test with the help of a statistical processor; the consequent result in a valuation of $P < 0.0001$ was considered "extremely statistically significant".

CONCLUSION

The author herein provides a methodological–statistical analysis of such contribution which does not imply any cost at all and could even help prevent the withdrawal of classical CPR practices.

Key Words: COVID-19; Cardiopulmonary resuscitation protocol; Contingency measures; KI-1 Yong quan resuscitation maneuver; Pandemic

Core Tip: Against current pandemic scenario, the author analyzes the possible difficulties that could occur on essential life support protocols as cardiopulmonary resuscitation (CPR). As happened with the previous H1N1 pandemic, from when it was decided to postpone the "kiss to life" (mouth ventilation) giving priority to the precordial massage, coronavirus disease 2019 global situation could drastically reduce survival rates due to CPR and life-support protocols. For this reason, the author insists on an additional complementary resuscitation maneuver from Traditional Chinese Medicine - already published by the *World Journal of Critical Care Medicine* in Beijing in August 2013, in order to improve the rescue success in sudden death and out-of-hospital cardiac arrest.

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INTRODUCTION

The cardiopulmonary resuscitation (CPR) maneuver can be considered to constitute the most important medical act that exists in universal medicine. Both in the East and in the West, its medical significance acquired such importance that even those who are not practicing physicians or involved otherwise in Medical or Health Sciences manage to be authorized once they have been instructed in the "chain of events" incorporated into the life support protocol sequences[1].

Following the American Heart Association, the CPR aims - understood as the reversal of clinical death - are to preserve life, restore health and limit disabilities, although such benefits can, in fact, only be achieved by a limited number of victims, whose dispositions and pathologies are more often than not totally unknown to the eventual rescuers, whose mission, in turn, is to save them from such a dire situation[2,3].

According to World Health Organization (WHO), more than 23% of all causes of death are due to cardiovascular factors. If to that percentage we add up that of cerebrovascular diseases, the total surpasses 30% of all existing causes of death. For this reason, by the end of 2020, beyond this gloomy pandemic crisis that affects us, the number of deaths due to cardiac arrest could reach a staggering 30000000 deaths per year[4]. Taking a current example, the results of the extrahospital rescues only reaches the meager figure of 6.5% with precordial massage and of 17%, when defibrillation is used. If the total death toll during World War II was estimated to be around 50,000,000 along the course of four years of devastation, it should not be difficult for us to consider that we are facing a true sanitary catastrophe[4,5].

MATERIALS AND METHODS

Materials

KI-1 Yong quan acupuncture point location: KI-1 Yong quan is located in the sole of each foot, in the place where it makes its plantar flexion. Dividing a line that runs all across the foot´s sole, the point is found at the junction between the anterior and the middle third of the plantar fascia level at its deepest position (see Figures 1 and 2)[1,4,5].

Physiological functions of KI-1 Yong quan point: According to chapter 5 of the *Ling Shu*, KI-1 Yong quan is considered the Tsing-well point of the kidney meridian and the "root" of the *Shao Yin* level (conformed by kidneys and heart). Said quotation explains by itself the remarkable influence of KI-1 Yong quan overall cardiac physiology[1,5]. It is the vortex where the Terrestrial Qi ascends into our bodies for nurture the *zhang*, mostly in that organs placed in the upper part of the torso that maintain the essential vital functions due to their continuous function (heart and lungs).

Moreover, KI-1 Yong quan is the main place for the ascending Yin Qi from the earth into our bodies. Therefore, this kind of energy will nurture the *zhang*, especially those organs placed at the highest (Yang) part of the torso, essential due to their vital function which cannot be interrupted: heart and lungs, providing them Yang Qi for a perfect biological equilibrium[1,4,5].

Topographic anatomy of PC-9 Zhong chong acupuncture point: Traditionally, this point is located at the tip of the middle finger, mostly to bleed it under emergency conditions. Rather curiously, that finger is also known in Spanish has "*cordial*" or "*heart finger*", showing a nominative association with its anatomic-functional value between it and the organ it protects[4].

Physiological Functions of PC-9 Zhong chong: PC-9 Zhong chong is the Tsing-well point of the "Heart Protector" or Pericardium meridian. As such, it is a Heart stimulating source that explains the therapeutic possibility of alleviating cardiovascular conditions. Its effect enables PC-9 to restore the cardiac pacemaker by direct stimulation over the sinoauricular node (vide infra Figure 3).

Scientific validation of PC-9 Zhong chong in bilateral double amputees as well as healthy volunteers has been successful for applying as supplementary resuscitation maneuver equivalent as the KI-1 Yong quan praxis[4].

Next, a formalized protocol project was submitted to *World Journal of Critical Care Medicine* in 2016 in order to integrate said acupunctural points into the CPR sequence.

Stages of the The International Liaison Committee on Resuscitation - CPR sequence ("chain")

See below Figure 4: (1) Prior to the application of chest massage: Assess the victim's state of consciousness and lung-heart failure; (2) Seek help (call 911), and/or apply KI-1 Yong quan/PC-9 Zhong chong in situations in which it is impossible to start the The International Liaison Committee on Resuscitation (ILCOR) protocol: If the victim is trapped in a car crash, an overturned car, a landslide, or there is a massive number of victims or a catastrophe; or Delayed CPR due to physical barriers to execute chest massage or exhausted rescuers due to catastrophic number of victims, *etc*[5]; (3) During chest compression: during the precordial massage, KI-1 Yong quan could be simultaneously stimulated by a third rescuer in the sole of the victim's foot[5]; (4) During defibrillator application: prior to the electric shock, activate KI-1 Yong quan through placing needles in both soles before defibrillation (or at PC-9 Zhong chong if the patient is a bilateral amputee)[1,5]; and (5) Unsuccessful basic and advanced CPR: KI-1 Yong quan and PC-9 Zhong chong stimulation become the "golden standard" for reverting legal clinical death[5].

In a very interesting paper, Bester and Kodish[6] address the issue in a crucial way providing a moral justification for CPR application. Undoubtedly, there should be no need to gauge the value of taking this decisive action during impending-life situations. The clinical version of Bester and Kodish[6] makes it clear that they abide by the moral imperative of rescue, except for very specific situations, called "Do Not Resuscitate" orders, in force in many countries, although there is no such provision in Argentina.

Methodological statistical approach – KI-1 Yong quan maneuver benefit

Randomness principle always request to minimize uncertainty[5,7].

In spite of what has been stated, comprehending that we might not eventually be able to solve every single question, we have given statistical priority to prove the following affirmation proposed between two hypotheses: Ho (null hypothesis): its

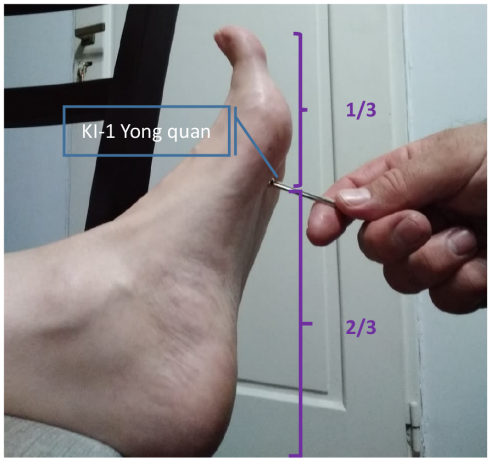

Figure 1 KI-1 Yong quan resuscitation maneuver: Side view.

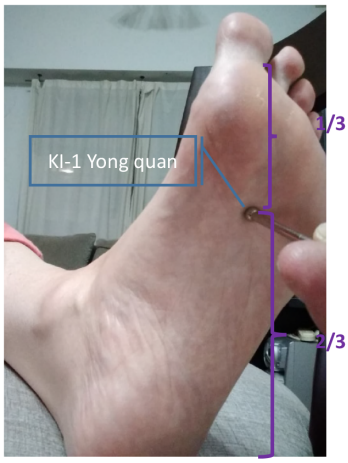

Figure 2 KI-1 Yong quan resuscitation maneuver: Front view.

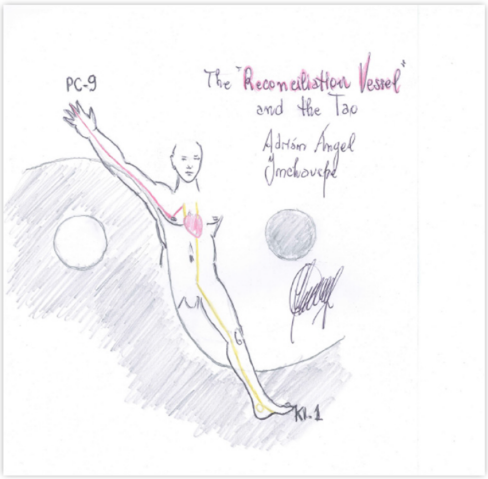

Figure 3 The reconciliation vessel and the Tao.

affirmation determines the lack of association between the variables under study; Ha (alternative hypothesis): its affirmation implies some degree of relationship between said variables[5,7].

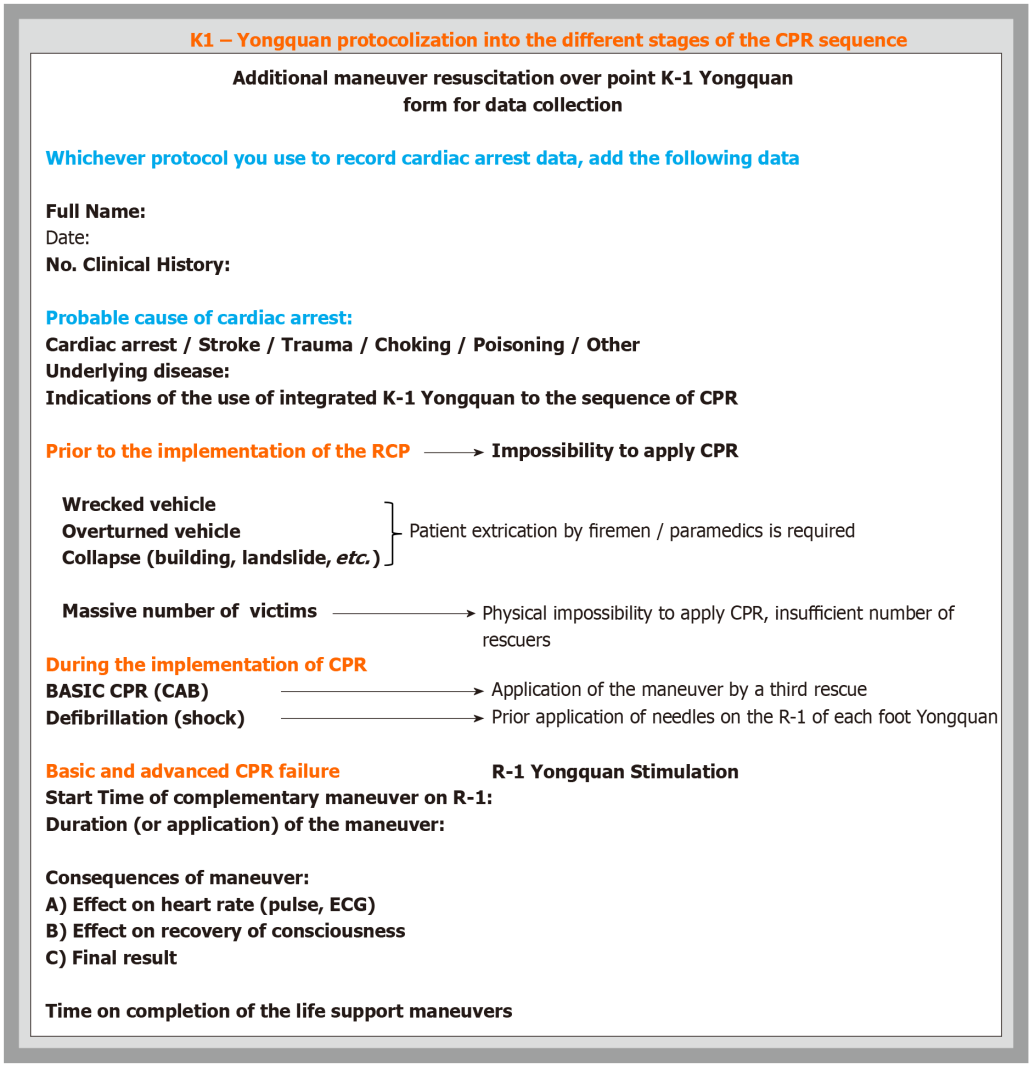

Figure 4 KI-1 Yong quan Protocol integrated to International Liaison Committee on Resuscitation: Cardiopulmonary resuscitation "Action chain". Citation: Inchauspe AA. Drawing the Yongquan protocol into the different stages of the cardiopulmonary resuscitation sequence. *World J Crit Care Med* 2013; 2: 17-20. Copyright © The Author(s) 2013. Published by Baishideng Publishing Group Inc[5].

We first compared the group assisted by CPR precordial massage (6.5% response) and those rescued by KI-1 Yong quan resuscitation maneuver (84.84% response):

$|PA - PB| = |0.064 - 0.85| = 0.786 < SE\ (0.05) \times 1.96 = 0.098$.

This fact theoretically proves that KI-1 Yong quan resuscitation method success does not depend on fate.

Afterwards, we compared the use of CPR defibrillation (48% response) against the KI-1 Yong quan resuscitation maneuver (84.84% response):

$|PA - PB| = |0.48 - 0.84| = 0.36 < SE\ (0.0076) \times 1.96 = 0.0148)$.

Thus, $[PA' - PB] = 0.36$.

Quoted analysis also proves to be statistically significant, favoring the KI-1 Yong quan resuscitation maneuver by means of this comparative analysis[5,7].

If we consider the control group conformed by the already deceased people instead of the patients that prospectively may be deceased, thus the Retrospective Cohort Study will safely solve this "*statistical issue*", allowing us to manage potential lethal effects, thus eliminating the fateful impairment found in random contingency, mostly in these cases under extreme emergency situation[5,7].

RESULTS

As to its statistical verification, several sequences of survival rates were presented, the first 7 of which were published in Health (2015), the 8th one in the *World Journal of Critical Care Medicine* (2016) and the 9th and last sampling, at the Health Care Summit

Congress in Dublin (June 2018) (see below Figure 5).

About the last ninth statistic, from a total of 89 patients in which KI-1 Yong quan maneuver was tested, 75 victims survived and 14 died. In order to compare this data with the percentages of survivors in the other rescue protocols, we assume that if 89 patients represent the 100% of the sample, how many patients would survive if the successful CPR rate would be 6.4% after chest massage (see Figure 6); 30% post-defibrillation (see Figure 7) or 48% that kept alive after CPR +defibrillation carried out jointly (see Figure 8).

So we then obtained the approximate values of victims that would survive when applying these resuscitation maneuvers in round figures in order to facilitate calculations. From the total of patients (89 cases), we subtracted the survivors to obtained the mortality rates[7].

The Graph Pad site showed a two-tailed *P* value, recommending us to analyze the sample with dichotomous variables so as to obtain more reliable deductions (for a more detailed mathematical explanation, please refer to "*Yongquan Maneuver´s Oddysey: Current Validation Of Its Significance Of P Through The Fisher's Exact Test For Dichotomous Variables*", published by Acta Scientific Paediatrics[7].

Thus we then obtained the format of the tables to perform the exact Fisher test, solved by a statistic mathematical processor; the results were located at the side of each table. As we can see, the Fisher exact test obtained a statistic valuation of $P < 0.0001$, considering quoted outcome as "extremely statistically significant"[7].

DISCUSSION

As was shown when stating Randomness in this problem - that means, under such extremely emergency situation - the control group would not only not benefit from a second chance of survival during imminent death, but also such therapeutic discrimination would also imply a fatal, collateral or unwanted results for the members of that group, doomed by this investigation model[4].

Regarding adding the complementary maneuver on KI-1 Yong quan / PC-9 Zhong chong into the classic CPR protocol, what has previously been stated contrasts with the essence of that principle. If data on fatal contingency is previously known in a study in which patients will be randomly discarded, such methodology will clearly impair them of the KI-1 maneuver benefit in case of basic and advanced CPR failure.

Random non-intervention practiced on such a group would inevitably lead to a most serious ethical problem as not providing adequate assistance to those patients who have been "sorted out".

As stated in Article 32 of *the Declaration of Helsinki VI on Ethical Human Rights* should not be forgotten when it states that "*In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, reestablishing health or alleviating suffering*"[8].

Although it is true that the article refers to informed consent, it is understood that these are not cases of extreme urgency, where the essential criterion of saving life acquires paramount significance.

Now let's ethically confront this right to life with the autonomy rights to which several Western countries refer, in order to evaluate priorities when determining the importance of individual opinion and its impact on rescue efforts at a global level.

The principle of patient autonomy

Patient autonomy is generally ethically respected. However, in Argentina in the case of CPR, the rescuer's criteria prevail, refusing to leave the victim without help. Said right requires a patient who can consent or refuse CPR, but without deterioration from depression, neuropsychiatric medication, or co-occurring illnesses. In any case, despite the fact that this right remains in force in many countries, a Research Ethics Committee must first assess the real possibility of restoring the patient's health[9].

Advance directives and living wills

Advance directive expresses a person's last wishes, or preferences regarding his or her end-of-life care; in many cases, questionably limiting the CPR rescue.

Quoted item is conformed by the directions from patients to physicians about the provision of medical care during a terminal illness course or when confronted with the impossibility to make proper decisions. It constitutes a clear evidence of the patient's

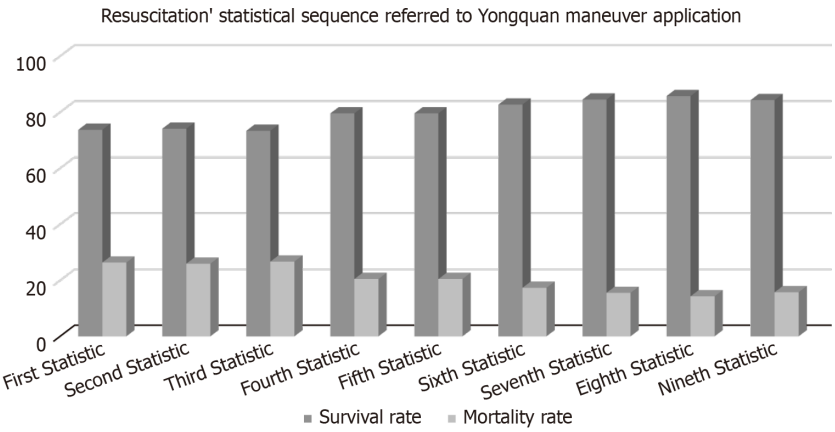

Figure 5 Statistical Sequence Referred to KI-1 Yong quan maneuver application (referred above). Citation: Inchauspe AA, Inchauspe M. "Yongquan Maneuver´s Odyssey: Current Validation of Its Significance of P Through the Fisher's Exact Test for Dichotomous Variables". *Acta Scientific Paediatrics* 2019; 2: 53-60. Copyright ©The Author(s) 2013. Published by Acta Scientific Paediatrics[7].

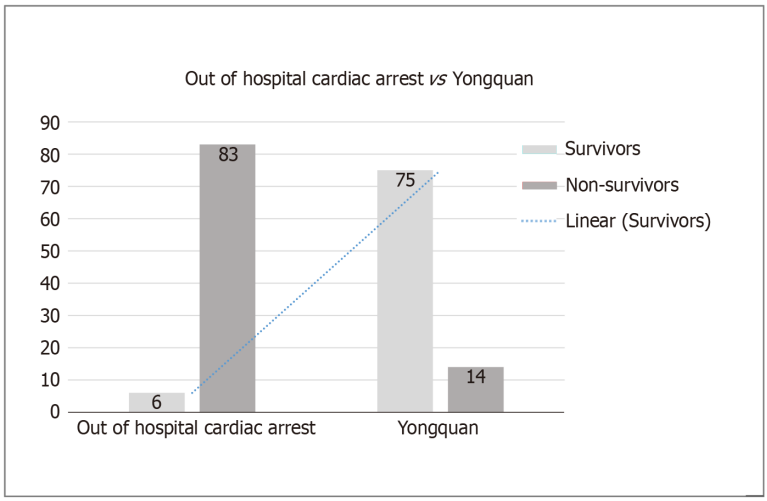

Figure 6 Out of Hospital Cardiac Arrest vs. Yong quan Survivors' tendency. Citation: Inchauspe AA, Inchauspe M. "Yongquan Maneuver´s Odyssey: Current Validation of Its Significance of P Through the Fisher's Exact Test for Dichotomous Variables". *Acta Scientific Paediatrics* 2019; 2: 53-60. Copyright ©The Author(s) 2013. Published by Acta Scientific Paediatrics[7].

wishes and can be legally enforced[9].

In Argentina, life is an immanent right that does not only depend exclusively on patients. Neither the victims nor rescuers can change the legal consensus of CPR protocols in an emergency state.

CPR suspension would only be considered in those terminal conditions determined in outdoors trauma triage score (slaughter, traumatic hemicorporectomy, massive loss of brain mass)[10] or indoors hospitals, so a Bioethical Committee can carefully study each particular case in order to suggest vital support suspension due to irreversible suffering conditions.

Despite the above-mentioned "*non-resuscitation orders*" based on the law in force of each country, the KI-1 Yong quan resuscitation maneuver would be useful as long as it is promptly applied, with the following considerations: (1) Currently, according to WHO, 23% of overall causes death result by cardiovascular origin[11]; (2) If we sum up the 7.6% of cerebrovascular casualties, we reach an average of 30% of overall causes of death[5,7]; (3) PC-9 Zhong Chong's proposal on the protocol involving Chinese acupuncture points has a dual purpose: The first and most important is the inclusion of those individuals who suffered bilateral amputation, which in this way could benefit greatly from the stimulation of this alternative point before the failure of the basic and/or advanced CPR; and The second is to have another stimulation alternative that provides an additional opportunity to rescue patients in a situation of imminent death due to sudden death or cardiac arrest[4,5,7].

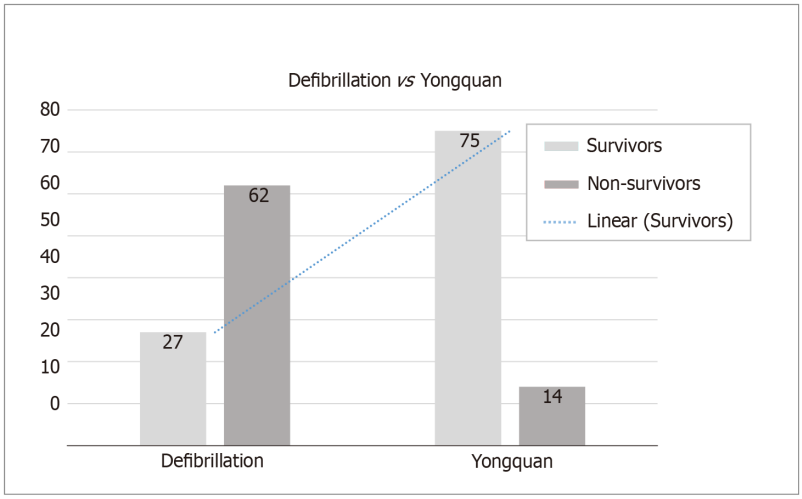

Figure 7 Defibrillation *vs* Yong quan Survivors' tendency. Citation: Inchauspe AA, Inchauspe M. "Yongquan Maneuver´s Odyssey: Current Validation of Its Significance of P Through the Fisher's Exact Test for Dichotomous Variables". *Acta Scientific Paediatrics* 2019; 2: 53-60. Copyright ©The Author(s) 2013. Published by Acta Scientific Paediatrics[7].

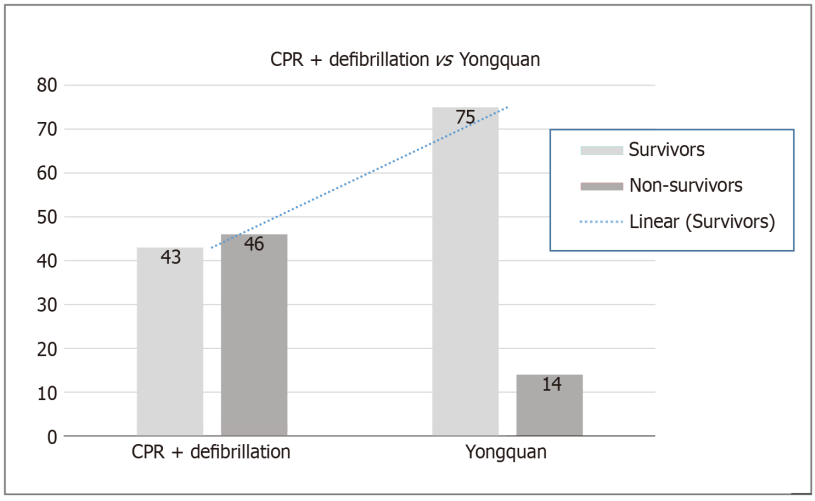

Figure 8 Cardiopulmonary resuscitation + defibrillation *vs* Yong quan Survivors' tendency. CPR: cardiopulmonary resuscitation. Citation: Inchauspe AA, Inchauspe M. "Yongquan Maneuver´s Odyssey: Current Validation of Its Significance of P Through the Fisher's Exact Test for Dichotomous Variables". *Acta Scientific Paediatrics* 2019; 2: 53-60. Copyright ©The Author(s) 2013. Published by Acta Scientific Paediatrics[7].

We must remember that diabetes affects almost 10% of the world's population, increasing the risk of cardiovascular and cerebrovascular diseases from 50% to 80% in these patients[11]. Consequently, every three seconds, a diabetic foot is amputated in the world[5,7].

In Argentina, two people per hour (that is, 54 per day and more than 20000 per year) will experience sudden death; the global annual average attributed solely to sudden death ranges from 5 to 6 million victims[7].

In infants, the sudden death mortality is over 35.2 deaths per 100000 live births in 2018 (Figure 9). Again, these children lack true capacity to accept or reject any vital protocol to decide the life-saving benefit provided by the CPR protocol[12].

Plausible solution to the dilemma of applying the CPR protocol with or without prior informed consent:

We have analyzed this particular situation with the Research Ethics Committee of the Province of Buenos Aires, in order to settle the dilemma in face of the always surprising and unexpected appearance of a sudden death scenario.

Given that the patient under these conditions is clearly unable to decide the application of this universal protocol, a possible solution emerged upon scientific consensus once the life support protocol and its modifications had been accepted by

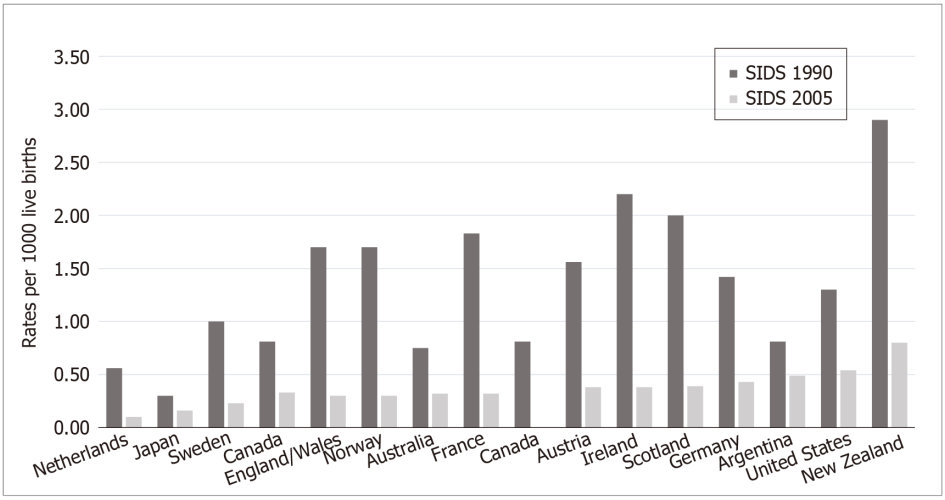

Figure 9 International sudden infant death syndrome rates, ordered from lowest to highest sudden infant death syndrome rates, National Center for Education in Maternal and Child Health – Georgetown University. SIDS: Sudden infant death syndrome.

the Committee of Scientific Research or Regional Bioethics One acceptable solution lies in spreading through local/regional mass media (also adding social networks) the future establishment of the protocol in question. The media diffusion of said novelty should be applied only for some hospitals in the area, leaving citizens with their free decision where to turn in case of extreme need. Likewise, it will be clarified that the health emergency services will also apply said life support scheme within their area of influence.

The information will remain valid for at least one week on the mass media networks. In this way, it is possible to comply with the objective of informing the population of the future intervention with the CPR modality agreed by the experts of the region.

Research committees must be very efficient while organizing educational programs and developing hospital guidelines. Again, ethical and moral dimensions of such decision should pay special attention not to transfer an even more serious offence to the rescue group: That of abandoning the patient[5,7,9,11].

CONCLUSION

In my country there exists so far no “Do Not Resuscitate” order; consequently, any evasion of the application of CPR in a condition of cardiac arrest shall be interpreted as “abandonment of the patient”; and the life support maintenance time – as long as it has arrived in time at the scene, maintaining suitable oxygen saturation – shall not be less than 45 minutes of rescue, before considering it failed.

The contribution of the complementary maneuver on the KI-1 Yong quan and /or PC-9 Zhong chong acupuncture points is neither intended to replace nor to interrupt the CPR international protocol, but to provide an alternative way of upgrading heart stoppage survival rates when the ILCOR-CPR protocol has failed.

Cotler[9] states very well that in his work “The” do not resuscitate "order; clinical and ethical rationale and implications” that the provision of CPR and do-not-resuscitate orders (DNRs) raises a current legal controversy regarding the need to obtain consented permission during a crucial moment to act efficiently during such a critical situation. Although patients' values or previous determinations are relevant, particularly those related to unwanted reasons to deny CPR rescuers decisions concerning CPR often must be made within seconds, most of the time without knowing patients´ directives[13].

On the other hand, those conditions that could presuppose the denial of the initiation of CPR (terminal illnesses, “therapeutic fierceness”, *etc.*) imply a deep knowledge of the philosophical controversy they pose, which may not necessarily be within the reach of most of the usual rescuers, be them firefighters or security personnel, professors or teachers, relatives, friends or unknown laypersons who learned life support protocols. Compliance under the spirit of a CPR protocol must not

carry responsibilities that exceed the compassion, self-denial or altruism of citizens who offered to save a fellow´s life.

Futility means that purposes cannot be achieved. Therefore, the underlying philosophy for providing CPR without waiting for any consent as an emergency outdoors procedure could be a source of controversial vulnerability for rescues today. Failure to guarantee free action of rescue team members would inevitably lead CPR Protocol to a futile fate[13].

In a cardiac arrest situation, time-pressure urges any rescue team to achieve its mission; and my particular opinion is that currently–far from universalizing a practice that has been shown to save millions of lives–the goals of treatment are subjected to conflicts from judicial companies, always attentive to finding those altruistic citizens and health professionals who cared to properly teach and learn the CPR on suspects of violating individual human rights.

As was well stated by Cotler[9], CPR is predicated on the assumption that life is sacred, as well as the efforts to maintain it, so that CPR will be successful. This seems to be really consistent with his belief that allowing someone to die is harm[13]. To establish a prognostic doubt of this universal practice –accessible to both health professionals such as doctors, paramedics, civil defense security personnel as well as lay Samaritans or relatives– will result in an unfair insecurity for potential rescuers, undermining the overall results of CPR application against the possibility of legal or financial threatening for them. Saving a life through CPR implies an altruistic, humanely ethical and disinterested practice in order to provide our fellow human beings with a new opportunity to live. It does not seem appropriate to subject professionals or volunteers to the menace of such a contingency.

It is my conviction that proposing a regional information plan prior to the application of CPR protocols would allow their consensual determinations of DNR orders in those countries in which these are in force, avoiding any dangerous restrictions that may hinder such a valuable resuscitation practice for those who need it most.

ARTICLE HIGHLIGHTS

Research background

Regarding KI-1 Yong quan application as a cardiopulmonary resuscitation (CPR) revival point, divulgation was not limited to actuarial cardiac results, but KI-1 Yong quan function as a brain protector in both traumatic and vascular brain injury situations should be included. Needless to say, all patients subjected to the stimulation of KI-1 Yong quan by cardiac arrest were neurologically classified with 3 points on the Glasgow Scale. Likewise, the validation of this CPR complementary rescue maneuver, deepening its significance of certainty respect to current techniques and protocols still in force. The difference obtained was also confirmed to be statistically significant, adding to this analysis the F-test for dichotomous variables; thus, all the statistical validations demonstrated once more the relevant certainty before other methods currently used instead of KI-1 Yong quan maneuver. Maybe such assertion led the Chinese to conclude that both KI-1 Yong quan and PC-9 Zhong chong acupuncture points had the ability to "reset" the vital signs that are absent, as a battery that would provide us with a source of alternative vital energy if our own existence is under severe danger.

Research motivation

The current figures produced by the COVID-19 pandemic and its respective mutations are close to 125000000 infected and 3000000 deaths. Faced with such a panorama, it is evident that the application of life support protocols in the extra-hospital setting is hardly exceeding 6.4%. Even those not specialized in the subject can easily realize that the survival results are extremely poor. The success of CPR - an authorized medical maneuver in laypersons properly prepared for it - depends crucially on the application of such a protocol by the general population to improve survival rates. Consequently, the main reason for this work is to offer an alternative available to the public worldwide and to help resolve the current success figures in CPR without risk of contagion.

Research objectives

The clear objectives already exposed are upgrade current survival rates in global CPR

thanks to the aid of this complementary resuscitation maneuver. On the other hand, there is a genuine intention of the author to relocate Traditional Chinese Medicine within the global context of existing therapeutic possibilities in emergency situations. The work justifies - after an uninterrupted investigation of the author for almost 40 years - that Chinese Medicine can deservedly share its place with Western Medicine in CPR protocols globally. Let us remember that CPR is the only authorized medical practice in those laypeople duly authorized to exercise said practice.

Research methods

As to its statistical verification, several sequences of survival rates were presented, the first 7 of which were published in Health (2015), the 8th one in the *World Journal of Critical Care Medicine* (2016) and the 9th and last sampling, at the Health Care Summit Congress in Dublin (2018). Its value actually strives in the differential detail if the deceased patients group is considered the control group instead of the patients that may be deceased group. Thus, the possibility of combining the indiciary or semiotic paradigm with the Retrospective Cohort Study allows us to manage potential lethal effects which are collateral to the random process in cases of extreme emergencies.

Research results

Strictly speaking, with 14 deaths out of 89 cases after applying this complementary rescue praxis has proven that its extra-hospital survival rates are 8 times higher than the best out-of-hospital survival rates (84.27% success).

Research conclusions

The KI-1 Yong quan complementary resuscitation maneuver, systematized since 1987, has been consistently performed in sudden death and cardiac arrest conditions as a final resource upon both basic and advanced CPR failure. After almost thirty years of experience, the author herein provides a reasoned survival bio-energetic circuit based on a detailed methodological–statistical analysis of the Wondrous Vessels (Qi jing ba mai) participating in it. The divulgation of K-1 emergency therapeutic possibilities looks for its inclusion into Critical Care Protocols, in order to upgrade survival rates in both cardiac arrest and stroke victims worldwide.

Research perspectives

Close to a total of 125000000 infections and 3000000 deaths in the world, the author believes that it is appropriate to urgently submit to medical science this easy-to-apply KI-1 Yong quan/PC- 9 Zhong chong resuscitation maneuver as a contingency measure in the face of such a catastrophe global that involves zero cost. Even without a pandemic, it is estimated that after 2020 the number of deaths from cardiac arrest and sudden death could reach 30000000 deaths per year, a figure equivalent to suffering the genocide of 50 Hiroshima bombs or 126 tsunamis Indonesia-like.

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OPINION REVIEW

Medical students as disaster volunteers: A strategy for improving emergency department surge response in times of crisis

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Abstract

Disasters resulting in mass casualty incidents can rapidly overwhelm the Emergency Department (ED). To address critical manpower needs in the ED's disaster response, medical student involvement has been advocated. Duke-National University of Singapore Medical School is in proximity to Singapore General Hospital and represents an untapped manpower resource. With appropriate training and integration into ED disaster workflows, medical students can be leveraged upon as qualified manpower. This review provides a snapshot of the conceptualization and setting up of the Disaster Volunteer Corps – a programme where medical students were recruited to receive regular training and assessment from emergency physicians on disaster response principles to fulfil specific roles during a crisis, while working as part of a team under supervision. We discuss overall strategy and benefits to stakeholders, emphasizing the close symbiotic relationship between academia and healthcare services.

Key Words: Disaster medicine; Disaster response; Medical students; Volunteers; Medical education

Core Tip: The Disaster Volunteer Corps provides a unique way of teaching medical students disaster medicine principles in a hands-on experiential format, while simultaneously enhancing operational readiness of the hospital in times of disaster. This model of collaboration between university education and healthcare services provides a feasible model of structured volunteerism.

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INTRODUCTION

Disasters can occur with little warning and produce mass casualties that quickly overwhelm an Emergency Department's (ED) capacity. In many parts of the world, EDs operate at close to maximum capacity daily, and strategies are thus needed to cope with a sudden increase in patient load. Disaster contingency plans of many hospitals involve the shunting of existing non emergent operations staff and healthcare workers to areas of need such as the ED, operating theatres, disaster wards, and other supporting services. Despite these measures, considerable time is needed for staff redeployment and there exists a critical manpower shortfall in the initial hours following a mass casualty incident.

In the literature, there have been a multitude of recommendations made for the improvement of ED surge capacity[1,2]. These range from strategies to recognise an impending surge, resource utilisation during a surge, new workflows and processes, and of note to this review, the role of additional staff in the form of medical students to augment ED surge capacity. As many medical schools are built beside hospitals, the EDs of these hospitals thus have a ready and available manpower resource that can be quickly activated in an emergency. Due to the flexible nature of day-to-day responsibilities for medical students as compared to physicians and nurses working on the wards, medical students could potentially respond rapidly to the ED within minutes of activation. They can be task trained to fulfil specific roles, working under supervision and as part of a team. It is notable from previous disasters that medical students were eager and enthusiastic to contribute in times of crisis, but were often held back by their perceived lack of experience and feelings of inadequacy[3-6]. Indeed, a recent study noted that medical students were capable of carrying out disaster triage with equal parity to emergency physicians[7,8]. Students were also made 'runners' within the hospital during a crisis, a role they could play well due their familiarity with the hospital layout and equipment location[9]. With proper training, coordination, and integration with ED workflow, medical students can thus be a huge asset in disaster management at the ED.

Several disaster training programmes aimed at medical students have been published in literature, with varying training approaches. Duration of the courses ranges from one day to four weeks, comprising both didactic lectures and practical training[10]. To the best of our knowledge, there has been no reported studies where medical students were formally inducted as volunteers attached to an Emergency Department, with staggered training over the entire duration of their medical school career.

This review provides a snapshot of the conceptualization and setting up of the Disaster Volunteer Corps (DVC) program at Duke-National University of Singapore (Duke-NUS) Medical School, a novel approach of formally engaging medical students as disaster volunteers while supplementing the medical curriculum. We discuss overall strategy and benefits to stakeholders, emphasizing the close symbiotic relationship between academia and healthcare services.

DVC OBJECTIVE AND AIMS

The overall objective of the DVC is to recruit, train, and retain keen medical students in different areas of disaster management, who can be reliably activated in the event of an emergency to serve as skilled manpower support.

The specific aims of the DVC are threefold: (1) Educational aim: The educational aim is for the training of medical students in the core competencies needed to support disaster operations in the ED; (2) Institutional aim: To strengthen the surge capacity of the ED, by having a pool of trained, competent, and trusted volunteers that can be rapidly mobilized; and (3) National aim: The national aim of the DVC is achieved through the training of medical students, to improve the community response to terror

and crisis. This is in line with the Singapore government's strategy of a robust community response to threats and disasters[11].

SETTING AND STAKEHOLDER BUY-IN

Singapore General Hospital (SGH) is the largest tertiary care hospital in Singapore, with approximately 350 patients presenting each day to the ED. Duke-NUS Medical School, SGH's affiliated medical university, is located in proximity to the ED (400 meters away) and has a cohort of approximately 250 students. For most days of the week, medical students undertake their clinical rotations in the wards, clinics, and operating theatres of SGH.

The DVC represents a tripartite partnership between major stakeholders of SGH, Duke-NUS Medical School, and the Students' Council of Duke-NUS Medical School. The proposal to involve medical students as disaster volunteers in a formal capacity involved ensuring that the goals of the DVC aligned with each stakeholder's agenda.

In keeping with Duke-NUS Medical School's agenda for student education, the DVC curriculum was designed to complement traditional medical education. As most medical schools do not teach much in the way of disaster medicine, the DVC seeks to plug this gap, enhancing medical education in a practical and hands-on approach. Duke-NUS Medical School was thus supportive of the DVC as it was in keeping with its objective of education and service to the community. The emergency planning committee and senior management of SGH recognized and appreciated the potential contributions of student volunteers and supported training by providing manpower and resources for the DVC. From the medical student perspective, the program offered an opportunity for formal disaster training to be equipped with skill sets which would allow them to contribute practically and productively in a real-world crisis. They would also be integrated into ED disaster planning and operations as an asset. The proposal for the DVC was thus warmly received among the medical student population.

FORMAL CONCEPTION AND OPERATIONALISATION

A formal agreement between SGH and Duke-NUS Medical School for the participation of its students was achieved. Students of the DVC could take their leave amidst their clinical duties (*e.g.*, ward round, clinic) if they were activated in a true disaster. Medical liability and insurance were also extended by Duke-NUS Medical School to students participating in official DVC activities. Tasks in which students could participate in were agreed upon, and for which they were trained for as per the curriculum (Table 1).

The DVC pilot program was officially launched in 2019 with ten medical student volunteers. Scheduled training sessions were held once every three months, with students task trained for specific disaster roles (Table 1). Core faculty involved in training were emergency physicians with subspecialty fellowships in disaster medicine, prehospital medicine, and toxicology, and who were actively involved in the hospital's disaster planning and response committee. This allowed for added realism in the DVC trainings. Contributions were made also from other specialities including nursing, security, and allied health.

The DVC curriculum was composed of modular courses (Figures 1-3), with assessment to ensure competency of volunteers[12]. The modular concept for training was adopted as it allowed better flexibility for medical students to acquire specific skillsets and competencies over time while giving better control to hospital emergency response planners to achieve a targeted readiness level and facilitating deployment decisions for students in specific roles as part of the hospitals' disaster response team. Each module consisted of a didactic lecture giving broad overview of disaster response plans followed by specific task training based on unique assigned roles and culminated in a summary disaster simulation exercise for better appreciation of coordination and workflow as part of the hospital's disaster response team. Assessments to ensure competency for the specific task included multiple choice questions, quizzes, and objective structured clinical examinations. Feedback on each training session was sought so as to improve training for subsequent batches of students. A train-the-trainer approach was adopted, where medical students who had completed a module would assist ED faculty in the training of subsequent batches of students. This leverages on peer learning and teaching pedagogy, promotes ownership

Table 1 Disaster Volunteer Corps curriculum: Training modules

Module	Duration	Workshop
1	7 h	Introduction and disaster medicine principles; HAZMAT decontamination course
2	7 h	Disaster field responder course; Disaster first aid course
3	7 h	Bioterrorism and pandemic responder course; Radiation responder course
4	7 h	Psychological first aider course; Introduction to hospital disaster operations

HAZMAT: Hazardous material.

Figure 1 Disaster first aider course. A: Application of pressure dressing to stop bleeding; B: Arm sling for fractures.

of knowledge, and allows for program scalability. On a practical level, records of students who have underwent training are kept which would allow trainers to tap on these students to assist them and subsequently carry out training sessions independently. A call-tree activation process synchronized with the hospital's disaster activation plans was implemented for DVC activation in times of crisis.

In addition to the scheduled training sessions, the DVC was also invited to participate in a hospital wide disaster simulation exercise as an observer, with plans for enhanced participation as the DVC matures. Through the DVC program and with exposure to disaster simulation exercises, we aim to enable the deployment of student volunteers during crisis situations in defined roles according to their competency, working under general supervision of team leaders.

Figure 2 Disaster field responder course. A: Teaching Disaster Volunteer Corps students how to apply principles of disaster triage in the field; B: Bioterrorism and pandemic preparedness course: Donning of the powered air purifying respirator; C: Radiation responder course: Use of Radiation Survey Meters to detect radiation contamination; D: Psychological first aider course: Coaching students on how to counsel psychological casualties.

Figure 3 Hospital Decontamination Station first responder course. A: Disaster Volunteer Corps (DVC) students decontaminate 'casualties' from a chemical incident; B: DVC students with staff and hazmat instructors.

KEY ADVANTAGES AND CHALLENGES

The critical shortage of skilled manpower during a disaster is to be anticipated. Although there may be large numbers of good Samaritans who would volunteer their services during a crisis, the specific skills required in these individuals are often lacking and at best questionable, making deployment decisions difficult. There is also

difficulty in ensuring ED security in the context of accepting help from individuals whose motives may not be apparent at the outset. Considering these issues, medical students who are often already in the hospital on clinical attachment and can be trained to fulfil specific roles in times of disaster[13], represent an untapped manpower resource that can be harnessed to augment the ED's surge capacity.

The involvement of medical students in disaster operation, however, is not without its challenges. Although the practical hands-on approach adopted by the DVC gives medical students an advantage in appreciating the complexities of dealing with disasters, there are several contentious issues related to their actual deployment in times of disaster. Concerns include exposure to psychological trauma, medical student safety, and the medicolegal aspects of caring for patients in such situations[14-16]. It is therefore important for the level of involvement and specific roles of students to be agreed upon by all stakeholders to prevent misunderstanding, ensure safety of the students, and maximise their assistance in times of disaster. The decision making and actions required in crisis situations are made even more difficult with the limited resources available[17]. These are challenges faced by healthcare workers with extensive experience and training and would be compounded for medical students with limited experience and knowledge. Critical decisions on the need for performing interventions such as field amputations and surgical procedures should thus be left to qualified physicians, with medical students best placed to render aid under supervision on predetermined tasks. Discussions should also be had about the psychological impact of working in disaster environments, with possible exposure to grievous injuries and suffering, the ethics of providing care in extreme situations, reasons for withholding treatment in certain conditions, triage intentions with the aim of benefiting the majority, and palliative care for the unsalvageable[18-20].

The potential contribution of medical students in crisis conditions are manifold[21], and training of students to fulfil specific roles with clearly defined objectives would be beneficial for ED surge capacity. The participation of well trained, motivated, and readily available volunteers would be invaluable in ED disaster management.

CONCLUSION

The DVC provides a unique way of teaching medical students disaster medicine principles in a hands-on experiential format, while simultaneously enhancing the operational readiness of the hospital and ED in times of disaster. This model of close collaboration between university education and healthcare services provides a feasible model of structured volunteerism that could be replicated in other similar settings.

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REVIEW

Orosomucoid-like protein 3, rhinovirus and asthma

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Abstract

The genetic variants of orosomucoid-like protein 3 (*ORMDL3*) gene are associated with highly significant increases in the number of human rhinovirus (HRV)-induced wheezing episodes in children. Recent investigations have been focused on the mechanisms of *ORMDL3* in rhinovirus infection for asthma and asthma exacerbations. *ORMDL3* not only regulates major human rhinovirus receptor intercellular adhesion molecule 1 expression, but also plays pivotal roles in viral infection through metabolisms of ceramide and sphingosine-1-phosphate, endoplasmic reticulum (ER) stress, ER-Golgi interface and glycolysis. Research on the roles of *ORMDL3* in HRV infection will lead us to identify new biomarkers and novel therapeutic targets in childhood asthma and viral induced asthma exacerbations.

Key Words: Asthma; Intercellular adhesion molecule 1; Orosomucoid-like protein 3; Rhinovirus infection; Sphingolipids

Core tip: Orosomucoid-like protein 3 (*ORMDL3*) gene has been identified to have a strong association with childhood asthma. The gene has also been found to link with human rhinovirus (HRV) infection in children. ORMDL3 mediates HRV infection through regulating expression of HRV receptor intercellular adhesion molecule 1, metabolisms of ceramide and sphingosine-1-phosphate, endoplasmic reticulum (ER) stress, ER-Golgi interface and glycolysis.

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INTRODUCTION

Asthma is one of the major health and economic burdens in the world. It is a syndrome characterised by airway inflammation and intermittent symptoms of wheeze and shortness of breath. The combinations of genetic and environment factors cause the disease[1]. The disease has a high prevalence as well as a chronic relapsing course. Acute asthma exacerbations are the major cause of high morbidity and mortality whilst severe asthma remains difficult to treat.

In 2007, single nucleotide polymorphisms (SNPs) flanking *ORMDL3* gene on chromosome 17 were found to be highly associated with asthma in a genome-wide association study[2]. This association has subsequently been replicated in many studies, including a multi-ancestry global meta-analysis[3]. The locus has also been found to be associated with many asthma related traits. Expression quantitative trait loci analysis revealed that SNPs in the locus regulate transcript levels of potential asthma genes[4]. The locus is associated with eosinophil account in blood and fractional exhaled nitric oxide levels[5]. *ORMDL3* locus is now considered as the major predisposing factor for childhood-onset asthma. Children with enhanced transcription genotypes at *ORMDL3* locus have been found to have significant increases in the number of wheezing illnesses. Early symptomatic human rhinovirus (HRV) infection is a risk factor for subsequent asthma, and the infection causes nearly two thirds of childhood asthma exacerbations[6]. The genetic variants on chromosome 17q21 and early environmental tobacco smoke exposure enhance the association between early respiratory infection and early-onset asthma. Individuals who were homozygous for the risk alleles at the *ORMDL3*-associated SNPs had a greater than twofold difference in the association between early viral infection and asthma[7].

The symptoms of virial respiratory infection are most caused by rhinoviruses[8]. More than twenty years ago, as the development of molecule techniques of identifying pathogens, rhinoviruses were found to be the major virus types in mild and severe wheezing illness in all age groups of children, but particularly over one year of age[9]. The most common symptoms for HRV infection include rhinorrhea, sore throat, nasal congestion, sneezing, cough, and headache[10]. HRV infection is also the major cause for exacerbations of chronic obstructive pulmonary disease (COPD) and cystic fibrosis [11,12]. In this review, I will update the recent developments for research on potential mechanisms that *ORMDL3* regulates HRV infection in asthma. I will also discuss the research strategies to identify novel therapeutic targets for HRV infection in human airway diseases.

HRVS

HRVs were identified in the 1950s for exploring the causes of the common cold[13,14] and are positive-sense, single-stranded-RNA (ssRNA) viruses with approximate 7200 base pairs. The viruses belong to the family *Picornaviridae* and the genus enterovirus. The genome consists of a single gene whose translated a protein peptide. The protein peptide then is cleaved by protease to 11 proteins[15]. Among them, four proteins including VP1, VP2, VP3, and VP4 consist the viral capsid encasing the RNA genome, while the rest are non-structural proteins (2A, 2B, 2C, 3A, 3B, 3C, 3D) for functioning in viral replication and assembly[11].

SEROTYPES AND PHYLOGENETICS OF HRVS

Serotypes are defined as groups within a single species of microorganisms that share distinctive surface structures. The four capsid proteins of HRVs provide the virion an icosahedral structure, with a canyon in VP1 of attachment to cell surface receptors. More than 90% of known HRV serotypes are classified as major group, utilizing the cell surface receptor intercellular adhesion molecule 1 (ICAM1), while the minor group HRVs attach cells *via* the low-density lipoprotein receptor (LDLR). Some of the major-group HRVs can use heparan sulphate as an additional receptor for cell attachment and entrance[16-18]. More than 100 serotypes of HRVs were discovered and the

diversities of serotypes of HRVs make the specific vaccine against the virus infection very difficult to create.

Phylogenetics is the study of the evolutionary relatedness among organisms. Molecular phylogenetics applies sequence data to infer these relationships. Based on sequence, phylogenetic sequence HRVs are classified into three species, HRV-A, HRV-B and HRV-C. HRV-A (containing 77 serotypes) and HRV-B (containing 30 serotypes) species can be cultured in normal cells culture[19]. HRV-C strains do not grow in standard cell culture although the genomic organization of HRV-C strains is similar to that of HRV-A and HRV-B. At least 50 different types of HRV-C have been identified [20,21]. In 2011, HRV-C was found to grow in sinus mucosal tissue, and the species used a distinct cell attachment mechanism[22]. It was then identified that HRV-C entrance of cells by cadherin related family member 3 (CDHR3) receptor[23].

RECEPTORS FOR HRVS

ICAM1

ICAM1 is a cell surface ligand for the lymphocyte function antigen 1 adhesion receptor [24,25]. It was cloned and sequenced in 1988[26]. ICAM1 is a 90 kD inducible surface glycoprotein. It promotes adhesion in immunological and inflammatory reactions. In 1989, ICAM1 was then found as a receptor for HRVs major group entrance to the cell by using ICAM1 monoclonal antibody blocking the cytopathic effect in HeLa cells[27]. It binds to integrins of CD11a/CD18, or CD11b/CD18 and it is a prominent molecule in leukocyte trafficking, immunological synapse formation, and cellular immune responses[28]. ICAM1 is expressed on essentially all leukocyte subsets, epithelial cells, endothelial cells, fibroblasts, platelets and others[29]. For most cell types under non-inflammatory conditions, ICAM1 expression is constitutively low, it is detectable only on endothelial cells[30,31]. On the condition of stimulations of IL-1β, TNF-α, IFN-γ and other cytokines, ICAM1 can increase expression in a cytokine- and cell-specific manner [28,32]. Soluble ICAM1 can be detectable in the plasma and it increases in patients with various inflammatory conditions. HRVs upregulate membrane-bound ICAM1 expression *via* a NFKB-dependent mechanism[33] and downregulate the release of soluble ICAM1[34]. ICAM1 upregulation was also founded *in vivo* on nasal epithelial cells in an experimental HRV39 infection of healthy volunteers[35].

LDLR

LDLR family members were identified as the receptors for minor group rhinoviruses, that consists of only 12 known HRV-A types. The members are evolutionarily ancient proteins that are expressed on the surface of many cell types[36]. The LDLR family includes at least three members that can bind and internalize HRV as the LDLR, the LDLR related protein and the very low density lipoprotein receptor. Receptors in this family are recognized by the presence of several structural modules and overall similar domain arrangements. The structural characters include ligand-binding repeats, epidermal growth factor precursor repeats, a single transmembrane domain, β -propeller modules and a relatively short cytoplasmic tail[37]. LDLR uptakes its natural ligand, cholesterol-carrying lipoprotein particles by endocytosis, and their release upon delivery to the low pH milieu of the endosome[38]. The cytoplasmic tail of the LDLR family members contains specific motifs that can interact with a number of cytoplasmic adaptor and scaffold proteins to mediate signal transduction[37].

CDHR3

CDHR3 is a member of cadherin superfamily of transmembrane glycoproteins. The biological function remains unclear. Other members of this family such as desmosomal cadherins and classical cadherins are responsible for communications between identical cells through calcium-dependent interactions. Protocadherins are involved in neuronal plasticity and tissue development[39]. Cadherins are the major components of adherens junctions and desmosomes and also have other functions including signalling and mechanical transduction[40].

OTHER RECEPTORS

Some major-group HRVs also use heparan sulphate as an additional receptor[11]. Airway epithelial cells infected by HRV can detect and respond to the virus *via* toll-

like receptors (TLRs) to activate signalling pathways and generate pro-inflammatory cytokines and type I interferons[41]. The HRV6 capsid was found to be recognized *via* TLR2. With HRV6 ssRNA internalization, the virus genome is recognized by endosomally located TLR7 and TLR8[42].

HRV INFECTION AND RESPIRATORY DISEASES

HRVs not only are highly associated with asthma, COPD and cystic fibrosis, the viruses also have been found to cause upper respiratory infection including common cold, acute otitis media and rhinosinusitis. They can be responsible for lower respiratory infection including coup, bronchiolitis, community-acquires pneumonia. Based on antigenic cross-reactivity in serum neutralization tests, clinical isolates of HRV-A and HRV-B identified by 1987[43] were classified into 100 serotypes. More recently isolated A and B types were assigned solely on sequence identity criteria[44], HRV-A and HRV-C isolates are more virulent in infants, and are more likely to cause exacerbations of childhood asthma compared to HRV-B[45,46]. HRVs cause respiratory illness throughout the world and throughout the year. Longitudinal studies of the epidemiology and clinical features reported a peak incidence of HRV infection in the early fall and a smaller peak in the spring[47]. HRVs are the most common cause of respiratory viral illness during the spring, summer, and fall months. Infections with influenza virus and RSV predominate in the winter[11]. Not like other respiratory viruses, such as influenza virus and respiratory syncytial virus that cause cytopathology of the upper respiratory tract; for HRV infection, the epithelial cell lining and borders remained structurally intact although the cells were sloughed[48]. However, HRVs can still cause damage of epithelial cell barrier function[49], which can facilitate the transmigration of bacteria and exposing basolateral epithelial cell receptors such as TLRs[50]. Direct infection of the lower airway or the stimulation of inflammatory, immunological, or neurogenic mechanisms are the mechanisms of low airway dysfunction or diseases. Impaired innate and acquired immune responses for Th1 responses were found in asthma patients[51,52]. Epidermal growth factor (EGF) promotes viral replication by suppressing antiviral related immune mediators and has prominent role of EGF in the immune response to HRVs[53]. There are currently no approved antiviral therapies for HRVs, and treatments majorly are supportive.

ORMDL3 AND HRV INFECTION

After the association of the polymorphism of *ORMDL3* and asthma has been established[2,54], the subsequent research found it was linked to the frequency of rhinoviral wheezing illness and then subsequent development of childhood asthma [6]. Inhalation allergen could induce a significant increase in levels of expression of *ORMDL3* in airway epithelium and in macrophages in an allergen-induced mouse model[55]. The research on the roles of *ORMDL3* in HRV infection just begun and most results were from mouse models and cellular models. In a transgenic mice that express increased levels of human *ORMDL3* showed that *ORMDL3* contributes to antiviral defence to HRV infection through pathways that may include interferons (IFNα, IFNβ, IFNλ), OAS, and RNAse L[56]. In a human epithelial cell model, *ORMDL3* was found to be required in supporting HRV replication *via* SPT inhibition [57]. Human *ORMDL3* is a trans-membrane protein anchoring in the endoplasmic reticulum (ER). The ER is the site responsible for protein folding, storage of calcium and synthesis of lipids. ER stress can reduce the capacity for protein folding and thereby regulate cellular responses to inflammation. *ORMDL3* facilitates the unfolded protein response to cellular stress by influencing ER calcium ATPase and ER-mediated Ca^{2+} flux[58]. It interacts with the serine SPT enzyme complex in sphingolipid synthesis especially for ceramide and sphingosine-1-phosphate (S1P) levels[59]. *ORMDL3* could work in multiple pathways in regulating HRV infection[60].

THE POTENTIAL REGULTATING MECHANISMS OF *ORMDL3* FOR HRV INFECTION

Regulating ICAM1 expression levels

To explore the roles of *ORMDL3* in epithelial cells, our lab established *ORMDL3* knockdown and *ORMDL3* over-expression immortalised epithelial cell lines and human primary bronchial epithelial cells. Knockdown of *ORMDL3* led to a steroid-independent reduction of both IL8 and IL6 release and reduced ER stress after stimulation of IL1β. Global gene expression analysis revealed that knockdown of *ORMDL3* resulted in the reduction of expression of genes regulating host-pathogen interactions, stress responses and ubiquitination. Metabolomic analyses showed that knockdown led to changes in levels of metabolites integral to glycolysis. Additionally, knockdown increased concentrations of the immune mediators such as ceramides. The multiple effects of *ORMDL3* in cellular inflammation are consistent with its substantial genetic influence on childhood asthma. Of particular interest is that *ORMDL3* knockdown strongly reduced expression of the HRV receptor ICAM1 during the inflammatory response[61]. In an eosinophil *ORMDL3* knockdown experiment, a significant reduction in adhesion of *ORMDL3*-siRNA-treated eosinophils to ICAM1 was noted compared to control-siRNA-treated cell, and *ORMDL3* regulates eosinophil trafficking, recruitment[62]. The results indicate *ORMDL3* can regulate ICAM1 expression level, then influence HRV infection in human epithelial cells and immune cells.

Regulating ER stress

ORMDL3 is a protein anchored on the ER of the cell. The ER in eukaryotes is the site of protein folding as well as the site for synthesis of lipids and sterols and the storage of free calcium. Stresses on ER can therefore lead to an imbalance between the capacity for protein folding and the demand. It is linked to cellular responses to inflammation. ER stress happens when the capacity of the ER to fold proteins becomes saturated. ER stress induces the evolutionarily conserved signalling pathways, defined as the unfolded protein response, which compromises the stimulus and then determines whether the cell die or survives. It may be caused by factors that impair protein glycosylation, disulphide bond formation, mutations or overexpression. We previously experiments showed *ORMDL3* was a regulator of ER stress in mouse and in cellular models[61,63]. There are three signal transduction pathways for ER stress, including protein kinase RNA-like ER kinase (PERK), activating transcription factor 6 (ATF6) and inositol-requiring enzyme 1 (IRE1)[64]. Both non-structural protein 2B and HRV16 can induce an ER stress response through the PERK and ATF6 pathways[65]. Different viruses can modulate these mechanisms to escape the host immune response to their advantages[66].

Regulating sphingolipids metabolism

ORMDL3 was first identified as a regulator for *de nove* synthesis of sphingolipids in cells[59]. Sphingolipids are amphipathic molecules derived from sphingosine. Ceramides are the central molecules of sphingolipids metabolism. Sphingosine phosphorylation leads to S1P. S1P and ceramides mediate cell proliferation, survival, apoptosis, differentiation and cell-cycle arrest[67,68]. Ceramide-rich platforms affect signalling cascades in immune cells, including activation of B cells, bacterial pathogen infection. S1P drives the differentiation of immune cells, inducing changes in their phenotypes and regulating production of eicosanoids and inflammatory cytokines [69]. Clinical studies showed that sphingosines and ceramide were increased in asthmatic airways[70]. Sphingolipid pathways offer many opportunities for pharmacologic intervention and investigations of anti-inflammatory effects have been centred on S1P[69]. Importantly, modulating sphingolipids is known to affect ICAM1 expression in epithelial cells (keratinocytes)[71] so that the ICAM1/sphingolipid axis may provide novel prevention strategies for viral-induced childhood asthma. Ceramide levels were greatly affected by the expression of *ORMDL3* in mouse model [72,73] and in airway epithelial cells[61]. Decreased sphingolipid synthesis was found in children with 17q21 asthma–risk genotype[74]. Ceramides activate protein phosphatase 2 to cause endothelial dysfunction[75]. Ceramides suppress the electron transport chain to induce production of reactive oxygen species in mitochondria[76]. Imbalance of ceramides and impaired TLR4-mediated autophagy were reported in an *ORMDL3*-overexpressing mouse model[77]. S1P receptors inhibition was found to be critical for immunomodulation. S1P can directly suppress TLR mediated immune response from T cells. S1P extracellular actions are mediated by its interaction with a

family of five specific G-protein-coupled receptors, $S1P_1$-$S1P_5$[78]. Ceramide kinase and sphingosine kinases control many aspects of cell physiology, including inflammatory response and cell survival[79]. S1P was found to be important in immunoglobulin E-mediated mast cell migration and degranulation[80], allergic asthma, and secretion of inflammatory cytokines[81]. In allergic models of asthma, S1P and ceramide are important signalling molecules for airway hyperreactivity, mast cell activation, and inflammation[82].

Regulating ER-Golgi interface

Golgi apparatus is a cell organelle that facilities process and package proteins and lipid molecules to be exported from the cell. Infection of human epithelial cells with several rhinovirus strains triggers a rapid activation of the acid sphingomyelinase. The activity of the acid sphingomyelinase results in the formation of ceramide in the cell membrane. Acid sphingomyelinase is also a key molecule for the infection of human cells with rhinoviruses[83,84]. The ability of replicating picornaviruses to influence the function of the secretory pathway has important implications for host defence. Individual non-structural protein B2 and HRV16 can both fragment the Golgi apparatus and block secretion, whereas viral infection fragments the Golgi apparatus without blocking secretion[84]. HRV uses a phosphatidylinositol 4-phosphate/cholesterol counter-current for the formation of replication compartments at the ER-Golgi interface[85]. *ORMDL3* regulates ER stress and lipid membrane synthesis and that could directly influence ER-Golgi interface to response HRV infection.

Regulating glycolysis

Glycolysis is a cytoplasmic pathway that breaks down glucose into two three-carbon compounds and generates energy. Glucose is trapped by phosphorylation, with the assistance of the enzyme hexokinase. Glycolysis is one of major energy-yielding pathways that glucose is converted into pyruvate in the glycolytic process[86]. Recent research showed that IL-1β/inhibitory κB kinase ε signalling plays an important role in house dust mite-induced glycolysis[87]. Aerobic glycolysis is increased in asthma, which promotes T cell activation. Inhibition of aerobic glycolysis blocks T cell activation in asthma[88]. Lactic acid (LA), pyruvic acid (PA) and LA/PA are increased in the process. Increased glycolysis and anaerobic respiratory muscle glycolysis during airways obstruction may be important in these changes[89]. The early asthmatic response has been found to be associated with calcium binding, glycolysis and mitochondria activity in rats[90]. Glycolysis of target cells was found as an intrinsic host factor that determines the extent of norovirus replication[91]. *ORMDL3* deficient epithelial cells showed abnormality of glycolysis[61] and that can regulate HRV replication in cytoplasm.

The possible regulating mechanisms of *ORMDL3* for HRV infection were listed in the Table 1.

THE POTENTIAL THERAPEUTIC TARGETS FOR HRV INFECTION

Targeting ORMDL3/ICAM1 and sphingolipid pathways

Many compounds work in the *ORMDL3*/ICAM1 and sphingolipid pathways. Myriocin is the potent inhibitor of SPT, the rate-limiting enzyme of first step in sphingosine biosynthesis. Recent research showed that SPT activity was increased by house dust mite exposure and that *de novo* sphingolipids synthesis can be effectively inhibited by myriocin both *in vitro* and *in vivo*[92]. Fumonisin B1 has a structural similarity to the cellular sphingolipids, and this similarity can disturb the metabolism of sphingolipids by inhibiting the enzyme ceramide synthase[93]. Fumonisin B1 can attenuate nitrotyrosine formation and oxidative/nitrosative stress, epithelial cell apoptosis, and airway inflammation to improve histopathological abnormalities[94]. Tamoxifen inhibits ceramide glycosylation[95]. Tamoxifen treatment in horses with induced acute pulmonary inflammation promoted early apoptosis of blood and BALF neutrophils, reduction in BALF neutrophils[96]. Fingolimod is an FDA approved immunomodulatory drug for treating multiple sclerosis by down regulating S1P receptor[97]. FTY72 acts as a high-affinity agonist at the G protein-coupled sphingosine 1-phosphate receptor-1 (S1P1) on thymocytes and lymphocytes to induce aberrant internalization of the receptor[98]. There are numerus inhibitors in sphingolipid and ceramide synthesis pathways[99,100], investigating these inhibitors provide the potential therapeutic tools to influence HRV infection. HRV-induced inflammatory responses are inhibited by phosphatidylserine containing liposomes[41].

Table 1 Orosomucoid-like protein 3 roles in regulating human rhinovirus infection

Regulating molecules and processes	The roles in human rhinovirus infection	Ref.
ICAM1	*ORMDL3* regulates ICAM1 expression for influencing HRV adhesion and entrance and viral load	[56,61,62]
ER stress	*ORMDL3* regulates ER stress and the ER stress can induce PERK and IRE1 pathways that affect HRV infection	[61,63,65]
Ceramide and S1P	*ORMDL3* regulates ceramide and S1P levels. S1P and ceramide are responsible for cell survival, proliferation, apoptosis, differentiation and cell-cycle arrest; they also affect ICAM1 expression	[55,61,71,72,77]
ER-Golgi interface	HRV can both fragment the Golgi apparatus and block secretion. *ORMDL3* regulates ER-Golgi interface through ER stress and sphingolipid metabolism	[61,84,85]
Glycolysis	*ORMDL3* regulates glycolysis. Glycolysis can determine the extent of replication of HRVs in cells	[61,91]

ICAM1: Intercellular adhesion molecule 1; *ORMDL3*: Orosomucoid-like protein 3; HRV: Human rhinovirus; ER: Endoplasmic reticulum; S1P: Sphingosine-1-phosphate.

Research models of epithelial cells and finding new targets for HRV infection

Research models to investigate interactions between human host (genetic) and environmental factors are underdeveloped. These interactions are very important for chronic respiratory diseases such as asthma. We now know that airway microorganisms play important roles in health and in chronic respiratory diseases, but how the host and microorganisms function remain unclear. The airway epithelium has previously been investigated with monolayer models, where undifferentiated epithelial cells are grown underneath culture media. Cells that are grown at an air liquid interface (ALI) can be fully differentiated. ALI becomes a realistic and efficient tool to study cell-cell interaction studies following exposure to aerosolized or gaseous form of air pollutants[101], bacteria[102] and virus[103]. Primary bronchial epithelial cells cultured at ALI leads to differentiate into respiratory epithelium consisting of goblet cells, ciliated cells, basal cells and club cells. ALI culture system is also considered as a feasible approach to implement the "3R principle"-replacement, reduction, Recently epithelial ALI culture was successfully applied with HRV infection [104]. ALI cultures contain more epithelial components and are closer to normal human airways. In a further development, three-dimensional (3D) cultured lung tissues known as spheroids[105] other cell types such as fibroblasts are included. 3D culture with epithelial cells could help to provide highly predictive drug tests for patient-specific conditions in the near future[106]. The advantages of the ALI and 3D human lung spheroid models for interaction study are listed in Table 2. Importantly, ALI and 3D human lung spheroid models can be co-cultured with microorganisms relevant to asthma. These models provide an alternative of animal research and will reduce the use of animals in experiments as animal model for genetic modify are complicated procedures and time-consuming. Genetic animal model usually takes many generations of breeding and screening. For example, we identified *DPP10* as a novel gene underlies asthma in 2003[107], we created a *Dpp10* mutagenesis mouse tool and finally finished functional studies in 2018[108]. The use of genetic modified epithelial cells such as specific gene knockout cells not only provides a powerful platform to study the interaction between gene and environment but also to identify the novel therapeutic targets such as for HRV infection.

CONCLUSION

ORMDL3 emerged as a key molecule to regulate HRV infection in human respiratory epithelial cells. It influences the expression of HRV receptor ICAM1, the ER stress pathway, ceramide and S1P metabolism, ER-Golgi interface and glycolysis process. ORDM3/ICAM1 and sphingolipid metabolism provide novel therapeutic targets for HRV infection. Epithelial models with ALI and other 3D cultures will have prominent roles to identify the druggable molecules for clinical treatment of asthma, COPD, cystic fibrosis and other respiratory conditions induced by HRVs.

Table 2 The models for studying interaction of host and environmental factors

The available models	Advantages	Disadvantages
Monolayer cell models	Simplistic model; Easy to culture within short times	Cells underneath the medium, no connection to other types of cells and no tight junctions; Non-optimal physiologic response; The growth kinetics of bacteria, fungal or virus on monolayer are known to be different from human body
Air liquid interface model	Polarized differentiated airway epithelium containing ciliated epithelial cells, basal cells and mucus producing cells, mimicking human epithelium; It can be co-cultured with pathogens; Respiratory virus is known to show similar replication kinetics as in human body	
3D human lung spheroid model	3D multicellular spheroids are small, tightly bound cellular aggregates that tend to form when cells are maintained under non-adherent conditions; Other cell types such as fibroblasts can be incorporated and can be co-cultured with pathogens	
Animal models	*In vivo*	Have ethical issues and many results cannot be replicated in human studies; High cost; Time consuming, not applicable to high-throughput studies

3D: Three-dimensional.

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MINIREVIEWS

Role of proning and positive end-expiratory pressure in COVID-19

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Abstract

The novel coronavirus, which was declared a pandemic by the World Health Organization in early 2020 has brought with itself major morbidity and mortality. It has increased hospital occupancy, heralded economic turmoil, and the rapid transmission and community spread have added to the burden of the virus. Most of the patients are admitted to the intensive care unit (ICU) for acute hypoxic respiratory failure often secondary to acute respiratory distress syndrome (ARDS). Based on the limited data available, there have been different opinions about the respiratory mechanics of the ARDS caused by coronavirus disease 2019 (COVID-19). Our article provides an insight into COVID-19 pathophysiology and how it differs from typical ARDS. Based on these differences, our article explains the different approach to ventilation in COVID-19 ARDS compared to typical ARDS. We critically analyze the role of positive end-expiratory pressure (PEEP) and proning in the ICU patients. Through the limited data and clinical experience are available, we believe that early proning in COVID-19 patients improves oxygenation and optimal PEEP should be titrated based on individual lung compliance.

Key Words: COVID-19; Acute respiratory distress syndrome; Positive end-expiratory pressure; Proning; Ventilation management; Acute respiratory distress syndrome; Intensive care unit

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Core Tip: Optimizing and titrating the positive end-expiratory pressure (PEEP) in acute respiratory distress syndrome (ARDS) patients has been studied widely in the critical care world. However, the ARDS caused by coronavirus disease 2019 (COVID-19) possesses a challenge due to relatively preserved compliance in the early phase of this disease and questions the guidelines which have been long established. Proning, though tedious and cumbersome, which has been traditionally proved to improve oxygenation and survival benefits in ARDS patients has been extensively applied in COVID-19 patients. This article critically analyzes the role of PEEP and proning in COVID-19 patients.

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INTRODUCTION

As of February 2021, coronavirus disease 2019 (COVID-19) has accounted for over 3 million deaths worldwide and over 500000 deaths in the United States alone according to the World Health Organization[1]. In a study done in New York City, including 5700 hospitalized COVID-19 patients, 14.2% of patients required intensive care unit (ICU), and 90% of the patient admitted to the ICU were mechanically ventilated[2]. In a small study done with 245 patients, 20% of hospitalized COVID-19 patients were triaged to the ICU secondary to worsening respiratory failure and acute respiratory distress syndrome (ARDS)[3]. Timing of intubation has been a matter of debate for years but given the pandemic, it is more important now than ever to evaluate the risk and benefits associated with early or late intubation. While the early intubation strategy was used in the earlier phases of the pandemic, it was found that early intubation is associated with higher mortality, and the decision to mechanically ventilate the patient should be made cautiously for each patient[4]. Given the high burden of the ICU admission and mechanical ventilation associated with COVID-19 infection, it is imperative to understand the underlying respiratory mechanics related to ARDS and to critically review the application of traditional ventilation management on this novel disease.

ARDS is defined as new or worsening non-cardiogenic respiratory failure with PaO_2 to FiO_2 ratio less than 300 and presence of bilateral infiltrates on the imaging occurring within 1 wk of original clinical insult as mentioned in Table 1. ARDS severity can be further categorized based on the PaO_2/FiO_2 ratio (P/F ratio), where severity is significantly associated with mortality as shown in Table 2[5].

The basic etiology for ARDS includes non-cardiogenic pulmonary edema, shunt-related hypoxemia, and reduced aeration of lungs thus contributing to decreased lung compliance. Management of ARDS as outlined by ARDSnet protocol includes low tidal volume, optimizing PEEP for plateau pressure less than 30, prone positioning[6].

Optimizing PEEP by titrating it, increases pressure at the end of expiration and keeps the damaged alveoli open to facilitate ventilation. Low tidal volume decreases transpulmonary pressure and decreases the risk for ventilator-induced lung injury. Some studies have shown driving pressure as a predictor of mortality in ARDS patients[7]. Driving pressure is measured by subtracting the PEEP from the plateau pressure, which can also be expressed as the ratio of tidal volume and respiratory system compliance. Prone positioning enhances oxygen saturation by improving the ventilation-perfusion ratio by redistributing the blood flow to the better-ventilated lung units.

COVID-19 PATHOPHYSIOLOGY

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, positive-stranded RNA virus. The virus has a great affinity for human angiotensin-converting enzyme (ACE)-2 receptors, which are expressed mainly on Type II

Table 1 Acute respiratory distress syndrome definition

ARDS definition	
Onset	Within 1 wk of a known clinical insult or new or worsening respiratory symptoms
Chest imaging	Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules on either Chest X-ray or computed X-ray tomography scan
Origin of edema	Respiratory failure not fully explained by heart failure or fluid overload; Need objective assessment (*e.g.*, echocardiogram) to exclude hydrostatic edema if no risk factors present
Oxygenation	PaO_2/FiO_2 ratio < 300 with PEEP > 5 cm/H_2O

ARDS: Acute respiratory distress syndrome; PEEP: Positive end-expiratory pressure.

Table 2 Acute respiratory distress syndrome severity and associated mortality

PaO_2/FiO_2 ratio (with PEEP > 5 cm/H_2O)	ARDS severity	Mortality (95%CI)
200-300	Mild	27% (24-30)
100-200	Moderate	32% (29-34)
< 100	Severe	45% (42-48)

PEEP: Positive end-expiratory pressure; ARDS: Acute respiratory distress syndrome; CI: Confidence interval.

pneumocytes but also upper respiratory tract epithelial cells, vascular endothelium, and small intestine enterocytes. Viral infection results in excessive immune response leading to a cytokine storm and thus resulting in systemic inflammatory syndrome and multiorgan failure. It is also believed that viral infection also results in endothelial dysfunction, increased thrombin formation, thus stimulating a hypercoagulable state and thrombosis. This in turn causes thrombosis of the pulmonary vasculature, leading to hypoxic respiratory failure. The exact patho-physiology is yet to be described[8].

Histopathological study of lungs affected by SARS-CoV-2 as compared to H1N1 and SARS provides further insight into the pathophysiology underlying this disease. Histopathologically, acute lung injury includes diffuse alveolar damage (DAD), acute fibrinous and organizing pneumonia (AFOP), and organizing pneumonia (OP).

Diffuse alveolar damage is the most common pattern seen in typical ARDS patients, which is the most severe form of acute lung injury. It is caused by alveolar and endothelial cell damage causing fluid and cellular exudation and disruption of the blood-air barrier. DAD is divided into three phases: (1) Acute exudative phase: It occurs within 1 wk of the injury. It is characterized by damage to the alveolar wall causing hyaline membrane formation, edema, and alveolar membrane thickening. Vascular thrombosis and microthrombi are also frequently seen in DAD, even in absence of a systemic hypercoagulable state as a result of local inflammation. Angiographic studies done on typical ARDS patients have also shown the presence of thrombosis in its early phase. Chest imaging within 24 h to 48 h may be normal. Computed-tomography (CT) of the chest in acute phase of ARDS after 48 h commonly shows bilateral diffused patchy opacity with ventro-dorsal gradient of density predominant in dependent area (Figure 1A)[9]. Bilateral ground-glass opacity (Figure 1B) and crazy paving pattern can also be found in early phase (Figure 1C); (2) Subacute organizing phase or proliferative phase: It occurs 1 wk after the initial pulmonary injury and is characterized by fibrin organization, fibroblast migration, and collagen secretion. intra-alveolar hyaline membrane gets organized into fibrotic tissue. Reactive atypical changes in type II pneumocytes and squamous metaplasia is also noted. Some DAD resolves after this phase, whereas others progress to the chronic fibrotic phase. Diffuse coarse reticular opacity can be found on chest imaging in this phase (Figure 2A)[9]; and (3) Chronic fibrotic phase: It occurs weeks to months after the initial injury and is characterized by progressive architectural remodeling and interstitial fibrosis. CT chest typically reveals persistent ground-glass densities and coarse reticulations (Figure 2B)[9]. DAD is considered as the pathognomonic histological feature of ARDS. It can be present in isolation or in combination with AFOP and/or OP.

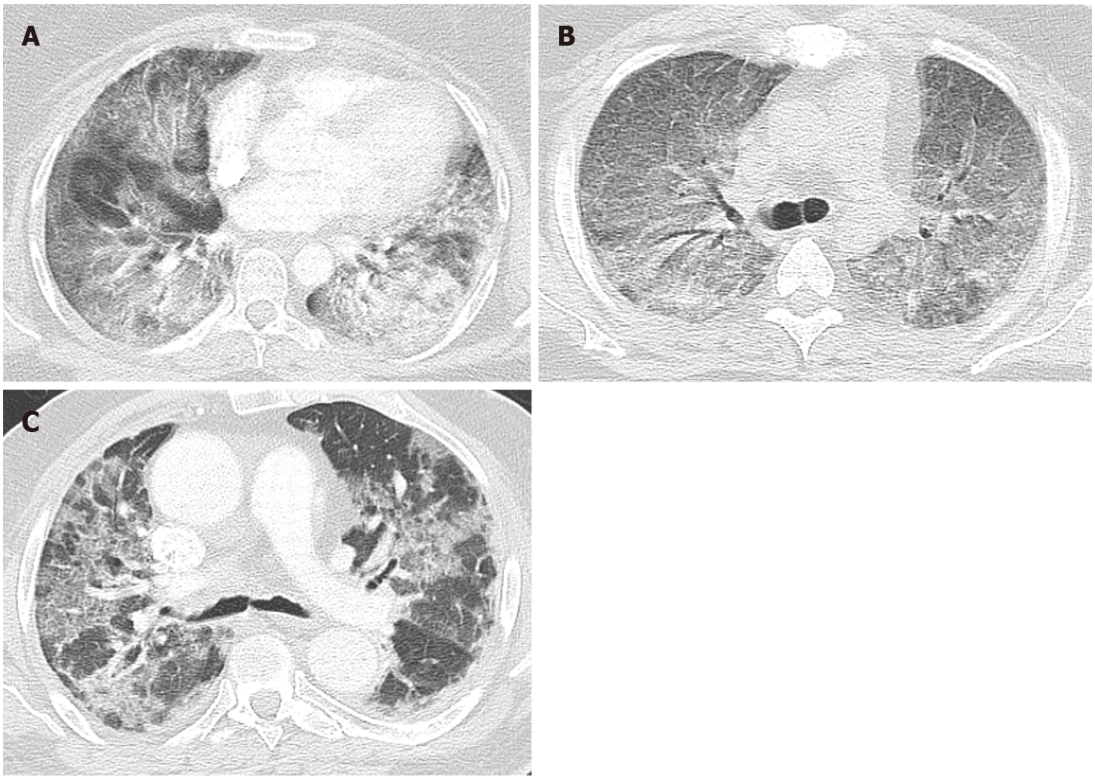

Figure 1 Computed tomography of the chest in acute exudative phase of acute respiratory distress syndrome in coronavirus disease 2019 patients. A: Bilateral diffused patchy density with ventro-dorsal gradient of density; B: Bilateral ground-glass opacity; C: Crazy-paving pattern.

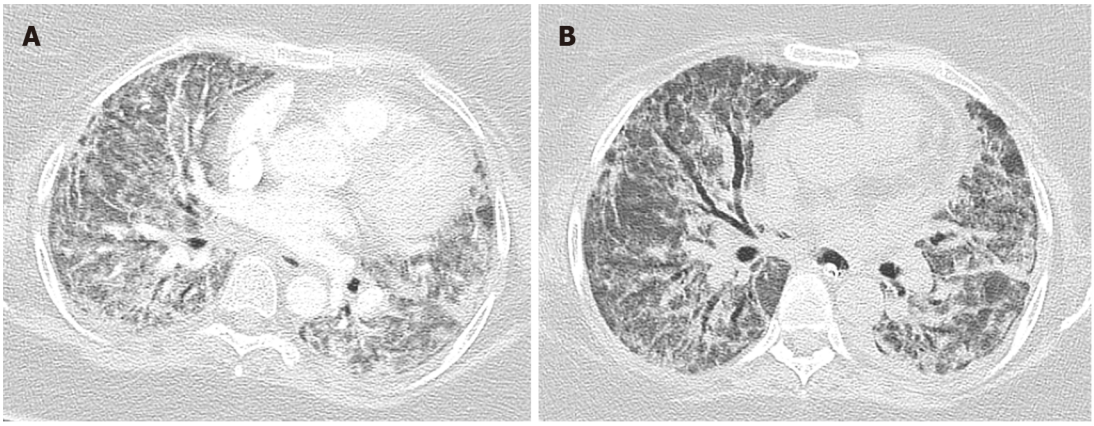

Figure 2 Computed tomography of the chest proliferative and fibrotic phase. A: Bilateral reticulations in proliferative phase; B: Bilateral fibrotic change in fibrotic phase.

AFOP is characterized by fibrin balls in alveoli with organization caused by fibroblast migration and collagen secretion. It can be seen along with DAD. OP can also be seen either in isolation or with DAD or AFOP. It is characterized by intraluminal tufts of fibroblasts and immature collagen tissue in alveolar ducts and distal airspaces.

A study showed that early SARS-CoV-2 is associated with diffuse alveolar damage characterized by vascular congestion, intra-alveolar edema, patchy inflammatory cellular infiltration but hyaline membrane formation is not prominent. Hyaline thrombi were found in the blood vessels. Whereas late stage of SARS-CoV-2 infection has a combination of diffuse alveolar damage and microvascular damages resulting in fibrinous exudation characteristic of AFOP[10].

A study was conducted to find the difference in lung histopathology in patients affected by SARS, 2009-H1N1 Influenza and SARS-CoV-2. It revealed that the early phase of ARDS affecting the lungs including DAD, AFOP, organizing fibrosis, end-stage fibrosis, and superimposed pneumonia are equally distributed amongst the three

causative factors. However, microthrombi and pulmonary thrombosis are more commonly seen in lungs affected by SARS and SARS-CoV-2 viruses as shown in Table 3[11].

COVID-19 PHENOTYPES

Though COVID-19 meets the ARDS criteria based on the Berlin definition, it differs in the way that COVID ARDS has severe hypoxemia with near-normal respiratory system compliance. Gattinoni *et al*[12] postulated the different phenotypes of COVID pneumonia requiring different approaches to the management.

COVID ARDS can be divided into early phase L type pneumonia and late phase H type pneumonia: (1) L type is characterized by low-weight lungs with low elastance and preserved compliance. These lungs have low recruitability as the amount of non-aerated lung is less. These patients are characterized to be less dyspneic with near-normal compliance. Gattinoni postulated the hypothesis of pulmonary vasoplegia causing hypoxemia. However, various other theories are postulated including damage to the ACE-2 receptors and upregulation of ACE-1 receptors resulting in uneven pulmonary vasoconstriction and hypoxemia; and (2) H type is characterized by high weight lungs with high elastance and decreased compliance. These lungs have increased recruitability due to extensively collapsed lungs. These patients fit into the characteristic feature of ARDS. Hypoxemia is caused by systemic inflammatory syndrome causing alveolar damage.

These phenotypes are a topic of debate as many scholars postulate that these phenotypes are a mere progression of ARDS in which L type is consistent with mild ARDS and H type is consistent with severe ARDS. Gattinoni described these phenotypes based on the study of 16 patients with COVID-19 showing significantly normal compliance and increased shunt fraction compared to typical ARDS patients. However, there have been multiple follow-up studies showing the presence of similar mechanics in the typical ARDS patients with near-normal respiratory system compliance in mild ARDS[13]. The study done in New York amongst 257 patients showed that the baseline respiratory mechanics was comparable to the typical ARDS patients. Per the study, 25% of the patients enrolled did have compliance greater than 38 mL/cm H_2O, however, such heterogeneity is also seen in typical ARDS patients [13]. Lower compliance in COVID ARDS has also been seen in smaller studies from Seattle and Boston with median compliances of 29 and 35 respectively[14,15]. Another study showed the heterogeneity amongst compliance and dissociation between respiratory compliance system and hypoxemia in non-COVID ARDS patients. Amongst 1117 ARDS patients, one out of eight patients had preserved compliance whereas three out of four patients had poor respiratory compliance. The study showed that of the patients with preserved compliance, 43% had moderate to severe ARDS with P/F ratio < 150. It also showed an increase in mortality associated with patients with lower respiratory compliance[16]. Thus, the different phenotypes proposed by Gattinoni *et al*[12] requires further investigation to know whether it is characteristic of typical ARDS or is mainly applicable to COVID ARDS.

While as per Gattinoni *et al*[12], silent hypoxemia is caused by near-normal respiratory compliance, Tobin *et al*[17] believe that silent hypoxemia is secondary to underlying following physiological mechanisms.

Per Tobin *et al*[17], dyspnea is caused by stimulation of respiratory centers which are oversensitive to $PaCO_2$ whereas a decrease in PaO_2 from 90 mmHg to 60 mmHg results in no stimulation, and also a drop in PaO_2 less than 60 mmHg results in dyspnea in only half of the subjects. Thus, response to hypoxia is influenced by $PaCO_2$. Studies have shown blunted response to hypoxia in elderly and diabetic patients.

The shift of oxygen dissociation curve brought in by increased temperature seen in COVID-19 patients results in a decreased level of saturation even at higher PaO_2. Given the carotid bodies are sensitive to PaO_2 and not oxygen saturation, the chemoreceptors are not activated, resulting in silent hypoxia. Oxygen saturation measured by pulse oximetry is less reliable once saturation drops below 80%, and the true saturation measured by arterial-blood gas could be 10% higher than that measured by pulse oximetry.

Thus, given the differing thoughts for the underlying physiology, the management approach of the two experts differs widely as shown in Table 4[18,19]. While Gattinoni *et al*[12] believes in early intubation and mechanical ventilation to prevent patient-self-induced lung injury, Tobin *et al*[17] believe intubation is a rescue maneuver reserved

Table 3 Histopathological features of 2009 H1N1, severe acute respiratory syndrome and severe acute respiratory syndrome coronavirus 2

Virus	Number of patients	Diffuse alveolar damage, *n* (%)	AFOP, *n* (%)	Organizing fibrosis, *n* (%)	End-stage fibrosis, *n* (%)	Superimposed pneumonia, *n* (%)	Microthrombi, *n* (%)	Pulmonary thrombosis, *n* (%)
2009 H1N1	287	90	0.30	40	3	30	24	6
SARS	64	98	9	47	6	31	58	28
SARS-CoV-2	171	88	4	52	1	32	57	15

AFOP: Acute fibrinous and organizing pneumonia; SARS: Severe acute respiratory syndrome; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Table 4 Different views of Gattinoni *et al*[12] and Tobin *et al*[17]

Gattinoni *et al*[12]	Tobin *et al*[17]
Silent hypoxemia is caused by vasoplegia which increases the respiratory drive and increases the tidal volume, causing negative intrathoracic pressure. Dyspnea is not endorsed in the setting of near-normal respiratory compliance	Silent hypoxemia is caused by underlying physiologic mechanism such as fever causing right shift of oxygen dissociation curve, unreliability of pulse oximeter at SaO_2 < 80% and decreased chemoreceptor response to PaO_2 < 60 mmHg with normocapnia
Increased tidal volume causing progressive increase in negative intrathoracic pressure results in P-SILI	P-SILI needs further research and increase in tidal volume is not associated with requiring intubation, whereas, underlying critical condition leads to intubation
Esophageal manometric measurement of work of breathing is crucial to determine the inspiratory efforts of the patient. Esophageal pressure > 15 is associated with increased risk of lung injury and patient should be intubated as early as possible	No data available to support the arbitrary measurement of esophageal pressure as an indication of intubation. Also, insertion of esophageal balloon in dyspneic COVID-19 patients increases the risk for intubation
Early intubation is advised along with esophageal manometric measurement of work of breathing	Less liberal use of intubation and mechanical ventilation. Should be used when hypoxia is accompanied with increased work of breathing and severe respiratory distress
Spontaneous breathing trials should be implemented only at the end of the weaning process as strong spontaneous efforts raise oxygen demand, edema and P-SILI	Weaning and spontaneous breathing trial should be initiated as early as 24 h after initial intubation

P-SILI: Patient-self-induced lung injury; COVID-19: Coronavirus disease 2019.

for hypoxic patients in severe respiratory distress.

ROLE OF PEEP IN COVID-19 ARDS

PEEP applies pressure to the lung during exhalation, thereby, decreasing atelectasis and improving ventilation-perfusion (VQ) mismatch. In general, patients are typically maintained at the PEEP of 5 because it is thought to mimic physiological conditions. PEEP is titrated based on driving pressure and the PEEP-FiO_2 table provided by ARDSnetwork guidelines[20]. If a patient requires higher FiO_2, increasing the PEEP further improves the oxygen saturation and thereby, allows to lower the FiO_2 to safer levels (< 0.60). PEEP can also be titrated by measuring transpulmonary pressure with the help of esophageal manometry or by studying the pressure-flow curve on the ventilator[21].

Optimal PEEP is PEEP that maximizes potential benefit (better oxygenation and less atelectrauma) and minimizes potential harm (hemodynamic compromise, volutrauma, and increased dead space). Excessive PEEP can decrease venous return and thus, reducing cardiac output and resulting in hemodynamic compromise. It can also increase volutrauma if excessive PEEP is applied and theoretically can cause VQ mismatch by creating physiologic dead space by improving ventilation and decreased perfusion. Thus, optimal PEEP is essential in managing ventilation in patients with acute respiratory distress syndrome[22].

Higher PEEP does not significantly improve the oxygen in all hypoxic patients. Presumably, PEEP helps only if there are atelectatic lung units that can be recruited. Studies in typical ARDS have also shown that increasing the PEEP in "non-recruitable" lungs results in a further decrease in P/F ratio whereas, in patients with "recruitable" lungs results in improving oxygenation.

Multiple small studies are available that discuss the effects of higher *vs* lower PEEP on oxygenation and compliance in COVID patients. A study of 14 mechanically ventilated patients showed that a decrease in PEEP resulted in an increase in lung compliance and a decrease in dead space ventilation in 13 out of 14 patients whereas in 1 patient it showed an increase in respiratory compliance with an increase in PEEP [23]. Another study done in Greece including 17 mechanically ventilated patients within 2-3 d of intubation, showed a decrease in PEEP by 25%-30% increasing the respiratory compliance and a decrease in hypercapnia with no change in P/F ratio [24]. A study matched 30 patients of COVID ARDS with typical ARDS patients and showed the difference in respiratory mechanics at PEEP of 5 and 15. There was a significant increase in the P/F ratio with an increase in PEEP in both COVID ARDS and typical ARDS with no significant change in compliance at either of the PEEP level. In COVID-19 patients, lung recruitment was independent of the oxygenation and respiratory mechanic changes due to PEEP[25]. Some studies used recruitment to inflation ratio (R/I) which is defined as the ratio between the compliance of recruited lung to that of the respiratory system, as a measure of recruitability. R/I ratio of > 0.5 suggested more potential for lung recruitment with respect to lung inflation. In a small study involving 12 mechanically ventilated patients, lower PEEP was used in poorly recruitable lungs whereas higher PEEP was applied to patients with highly recruitable lungs, however, the difference in respiratory mechanics with different values of PEEP was not studied further[26]. Beloncle *et al*[27] in a study of 25 patients divided into highly and poorly recruitable lungs based on R/I ratio showed there was no difference in respiratory compliance at PEEP of 5 cm and 15 cm/H_2O in both the group of patients, whereas the recruited lung volume was significantly higher at PEEP of 15 compared to a PEEP of 5 in patients with highly recruitable lungs compared to those with poor recruitability. The study also revealed that the P/F ratio was significantly higher at PEEP of 15 cm/H_2O in patients with higher recruitability as compared to a PEEP of 5, however, no difference in the P/F ratio with a change in PEEP was noticed in the lower recruitability group. In a small study with 19 typical ARDS patients (non-COVID), 9 patients were recruitable where oxygenation improved with high PEEP, whereas the other 10 patients did not show significant improvement in oxygen saturation with high PEEP[28]. Similar findings with the heterogeneity in the respiratory system compliance have been found in the COVID ARDS, though the presence of higher compliance is seen more in COVID ARDS which might be consistent with mild ARDS.

Thus, we believe that COVID ARDS though has higher compliance, PEEP should be optimized and individualized for each patient based on titration according to FiO_2 or esophageal manometry.

ROLE OF PRONING IN COVID ARDS

Effects of proning

Mechanisms by which proning improves oxygenation are still debated. In ARDS patients, dorsal lung units are involved more with relative sparing of ventral lung units. However, due to gravitational force, perfusion is better in the dorsal lung units compared to the ventral units. Proning helps redistribution of the blood flow, thus causing the well-aerated ventral units to have more perfusion[29]. Similarly, proning also improves ventilation in the dorsal lung units, thus improving ventilation-perfusion match. Proning also encourages the drainage of secretion from the lungs. Though proning improves oxygenation, its effect tends to decrease over time and not all patients respond to proning. Traditionally, in ARDS, proning has been shown to improve oxygenation in multiple studies, however, only the PROSEVA trial has shown survival benefits[30]. PROSEVA study included ARDS patients with a P/F ratio < 150, who were prone for >16 h/d for an average of 4 d. Study showed 16% mortality with prone positioning compared to 33% mortality in supine positioning (*P* value < 0.001).

Evidence of proning in COVID-19

In hypoxic respiratory failure caused by COVID-19, proning has been extensively

applied in both non-intubated awake patients and intubated patients[31]. Though many studies are available, the sample size of each study is very limited[32]. Multiple studies showed that early proning in non-intubated awake patients improves oxygenation and results in the prevention of intubation. A study revealed that early awake proning combined with high flow nasal cannula in 10 COVID-19 patients in China resulted in the prevention of intubation[33], though the study is limited by the sample size. At baseline, these patients' PF ratio varied from 89 to 200, thus, having a varied spectrum of diseased patients, and patients were prone for 16 h/d or less as tolerated. After prone positioning, median $PaCO_2$ increased slightly whereas P/F ratio was significantly elevated[32]. Another study showed that early proning in non-intubated patients improves oxygen saturation and decreases respiratory rate. This study also showed a 90-d mortality benefit in prone patients compared to patients who were not prone amongst 60 patients with severe hypoxia secondary to COVID infection[34]. Various other studies including non-intubated, awake patients showed improvement in oxygenation and improved respiratory comfort. Caputo *et al*[35] revealed that self proning improved oxygen saturation from 84% to 94% in all 50 ED patients included and avoided intubation in 76% of the patients. The remaining 24% of patients showed no significant improvement in oxygenation and required intubation within 24 h of admission. Elharrar *et al*[36], included 24 awake, non-intubated patients, of which only 63% tolerated proning for > 3 h and of which improvement of oxygenation was seen in 25% of the patients, but oxygenation returned to baseline on supination. In Italy, Sartini *et al*[37] showed that in 15 non-intubated, awake patients on non-invasive ventilation, early proning showed significant improvement in oxygenation during pronation whereas 80% had sustained improvement even after pronation, whereas 6% worsened after pronation. All the patients had a significant decrease in respiratory rate both during and after pronation. Coppo *et al*[38] revealed that of 56 included patients, 47 patients could tolerate proning, of which all the patients had significant improvement in oxygenation immediately after proning whereas improved oxygenation was maintained in only 50% of patients after resupination. A few of the relevant studies are shown in Table 5.

Thus, all the studies did show the improvement in oxygenation, however, are limited by the sample size and not all studies showed whether the improvement in oxygenation was sustained. Evidence for the effect on long-term outcomes and endpoints, such as mortality and rate of intubation is lacking. The conclusion is made mainly from case series and case reports, rather than clinical trials. Thus, the low quality of evidence available in support of awake proning needs to be critically analyzed and further researched.

Amongst the ventilated patients with typical and COVID-19 ARDS, proning has been shown to improve oxygenation. Of the 42 intubated patients of COVID-19 ARDS, proning showed initial improvement in oxygenation and P/F ratio. Mortality amongst these patients was 21.4% similar to the PROSEVA study[39]. In another study, among 31 patients who underwent prone ventilation, the P/F ratio increased from a median of 150 mmHg in the supine position to 232 mmHg in the prone position and compliance increased from 33 cm/H_2O to 36 cm/H_2O. The P/F ratio and compliance were maintained 72 h after initial prone ventilation[15]. In the earlier studies done in China, early prone ventilation amongst 29 patients was significantly associated with improved prognosis and improved oxygenation after 7 d of proning[40].

Adverse effects of proning

Proning is not without its complication. Venous stasis can lead to facial and ocular edema, whereas arm extension can lead to brachial plexus neuropathy[41]. Pressure ulcers and pressure necrosis are also common in prone positioning. Thus, additional support should be applied at pressure points such as shoulder, face, and anterior pelvis and frequent repositioning are necessary. Mechanical complications such as device displacement, including dislodging of the endotracheal tube and central lines are also commonly seen in the prone position. In some patients, hemodynamic compromise or oxygen desaturation may also occur. A Specialized prone team consisting of 3-5 members should be employed in each hospital and special attention should be paid to the endotracheal tube and central lines.

Though proning has been shown to improve oxygenation in each study, the technical difficulties associated with it are cumbersome. In the event of a cardiac arrest in a prone patient, even with the help of the expert team, it takes at least 5 min to resupinate the patient and with the risk of displacement of the endotracheal tube. Disconnection of the central lines and injury to staff and/or patients can occur. Prone cardiopulmonary resuscitation (CPR) has been used previously in neurosurgical patients where turning the patients would result in neural damage. During prone

Table 5 Studies on awake proning in coronavirus disease 2019

Ref.	Study sample	Percentage of patients prone, *n* (%)	Improvement in oxygenation amongst prone (percentage of patients), *n* (%)
Caputo *et al*[35]	50	100 (50)	76
Elharrar *et al* [36]	24	63 (15)	25
Sartini *et al*[37]	15	100 (15)	80
Xu *et al*[33]	10	100 (10)	100
Coppo *et al*[38]	56	84 (47)	100

CPR, chest compressions are applied over the scapula or thoracic spine with or without counter-pressure on the sternum. Defibrillation can also be done by placing the defibrillator pads on specific locations among the prone patients[42]. Newer methods to do prone CPR, echocardiogram, central line placement have been adopted to accommodate proning as a therapeutic intervention. In our clinical experience, even bronchoscopy can be done in the prone positioning.

Contraindications of proning

Proning is contraindicated in patients with a spinal fracture, whereas it is relatively contraindicated in patients with long bone fractures, increased intracranial pressure, and an open abdomen. Massive obesity should not be considered as a contraindication [43].

LIMITATION

This review is limited by the small number of studies available to provide adequate evidence. Sample size of all these studies is also very small, limiting our conclusion. Thus, we encourage large randomized study to help provide more concrete information on approaching the ventilation for COVID-19 patients.

CONCLUSION

For patients suffering from COVID-19, early proning is an inexpensive therapeutic intervention to improve oxygenation. In patients with ARDS secondary to COVID-19, PEEP should be titrated individually based on the compliance of the respiratory system and proning should still be encouraged given drastic improvement in oxygenation. Further randomized clinical trials are suggested among the COVID patients to address these important clinical issues.

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MINIREVIEWS

Incremental value of compression ultrasound sonography in the emergency department

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Abstract

The quick evaluation of venous thromboembolism is a key point of modern medicine since the delayed diagnosis is associated with a worse prognosis. Venous ultrasound (VU) is a sensitive and rapidly performed test in cases of suspected deep venous thrombosis. Various protocols have been proposed for its execution, such as the study of the whole deep venous circulation of the lower limb or the analysis of the femoral-popliteal area. The aim is to detect a vessel thrombus and the most sensitive element is the non-compressibility with the probe. Initially, the thrombus is hypoechogenic and adherent to the vessel; later, it tends to organize and recanalize. Usually, in the early stages, the risk of embolism is higher. The role of studying the iliac axis and calf veins is still uncertain. VU is not useful for assessing response to anticoagulation therapy and it is unclear whether the persistence of thrombotic abnormalities can guide on a possible prolongation of therapy.

Key Words: Compression ultrasound; Deep venous thrombosis; Venous ultrasound; Venous thromboembolism; Critical care ultrasonography

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Core Tip: Venous ultrasound represents an important weapon for emergency setting care. Nevertheless, several different protocols present in the literature could create confusion. In this review our goal is to define a practical and clear guide to support the physician in rapid deep venous thrombosis diagnosis and correct management.

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INTRODUCTION

Thrombus formation is a pathological phenomenon caused by an inappropriate hemostatic response; many different factors are involved, often favored in blood stasis points such as venous valves. A major theory delineating the pathogenesis of venous thromboembolism (VTE), often called Virchow's triad, states that VTE occurs as a result of alterations in blood flow, in vascular endothelial injury and in blood constituents. Blood clots could leave these sides to enter the bloodstream, reaching right heart chambers and pulmonary circulation. Rarely, in the presence of patent foramen ovale with right-to-left shunt, there may be systemic embolism. Hence, deep venous thrombosis (DVT) and pulmonary embolism (PE) are two sides of the same coin; about 50% of patients with proximal DVT is affected by an asymptomatic PE, as well as 80% of PEs suffers DVT (often asymptomatic)[1]. DVT may be distal, interesting tibial-peroneal district, or proximal, that affects femoral-popliteal veins; proximal DVT is more frequently related to PE.

DVT is the third most common cardiovascular disease, following heart attack and ischemic stroke[2] (DVT incidence: 150/100000/year, PE incidence: 60-70/100000/year). According to Cohen *et al*[3], based on 6 EU countries data (Italy, Spain, France, Germany, United Kingdom and Sweden), EP-related death rate was 12%[3].

DVT should be suspected in patients presenting with leg swelling, pain or erythema; usually symptoms are unilateral calf-related if isolated distal DVT, whole-leg related if proximal DVT[4]. Many patients are asymptomatic. Although uncommon, it is important to identify patients with phlegmasia cerulea dolens, that ranges from phlegmasia alba dolens to venous gangrene, because it should be considered for more aggressive management[5]. PE has a wide variety of presenting features, ranging from no symptoms to shock or sudden death. The most common presenting symptom is dyspnea, followed by chest pain (classically pleuritic) and cough. Chronic thromboembolic pulmonary hypertension has been estimated to occur in 4.8% (95%CI: 2.3-9.6) of patients who survive a PE[6].

The most used predictive score of DVT is Wells Score[7] (Table 1), more accurate than revised Geneva score in PE suspected patients[8-10]. It predicts an increasing incidence of PE with major probability classes ("low" if ≤ 0 points to "high" ≥ 3 points)[11]. PE incidence ranged from 1%-13% in low probability level (Wells score < 2), 28%-58.3% in medium probability level (Wells score 2-6), and 58.1%-93% in high probability level (Wells score > 6). The sensitivity ranged from 63.8%-79.3%, and the specificity ranged from 48.8%-90.0%.

Quick diagnosis of DVT/PE represents a fundamental weapon for modern medicine. The early detection of DVT is crucial to reduce the risk of thromboembolism in the critical patient, thus reducing the related morbidity and mortality. A delayed diagnosis of PE has poor outcomes, ranges from shock to hospital death[12]: Therefore, the 30 d mortality rate exceeds 3% in patients with DVT who are not anticoagulated, and this mortality risk increases 10-fold in patients who develop PE.

The most diffused vascular diagnostic tools are: (1) Phlebography: Gold standard, not widely used for its invasiveness; (2) Computed tomography (CT) angiogram: Utilized for PE and proximal districts (pelvic, iliac, caval); (3) Magnetic resonance imaging angiogram: Utility comparable to CT angiogram; and (4) Echocolordoppler: The most employed instrumental methodic for quick diagnosis and screening of pathology (limited just in the most peripheral venous tracts).

Table 1 Wells' score

Features	Score, points
Active cancer (in treatment or treated in the last 6 mo or under palliative care)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremity	1
Bedridden recently > 3 d or major surgery within 12 wk	1
Localized tenderness along the deep venous system	1
Entire leg swollen	1
Calf swelling > 3 cm compared to the other leg	1
Pitting edema, confined to symptomatic leg	1
Collateral (nonvaricose) superficial veins present	1
Previously documented DVT	1
Alternative diagnosis to DVT as likely or more likely	-2

DVT: Deep venous thrombosis.

Therefore, we realized a review of clinical studies comparing outcomes of patients with a history of DVT subjected to different managements. We achieved this by doing formal searches of the electronic database MEDLINE (source PubMed) and the Cochrane Controlled Clinical Trials Register Database. About 40 studies were selected from 1989 to 2017, by a combination of medical subject headings including the following terms: Compression ultrasound (CUS), DVT, venous ultrasound (VU) and VTE. References from reviews and selected articles were also examined for potentially relevant citations. Our analysis was restricted to the trials that focused on the comparison between different existing diagnostic protocols, with a special focus on emergency department experiences.

VU

VU is the commonest methodic used for DVT assessment. Many different protocols have been proposed, thus incrementing the confusing about its management. The study of deep veins is performed with high-frequency linear probes (5-7.5 MHz) or a sector probe, when the limb is particularly large-sized (Figure 1). Specifically, evaluation of the femoral veins should be done with the lower limb in extra-rotation, while other veins are studied in supine position with flexed knee. CUS with Doppler is the choice diagnostic test in patients with suspected DVT and the sensitivity and specificity of proximal CUS is greater than 95% (Figure 2). However, proximal CUS suffers from limitations[13]: (1) Calf vein thrombus, that are harder to assess than proximal veins; and (2) Iliac veins thrombus, that cannot be assessed for compressibility and thus these veins should be assessed with venography.

Pretest evaluation

First step in DVT assessment is probability estimation according to Wells Score[14]. In case of low pretest probability, a negative D-Dimer can rule out DVT without the need for ultrasound confirmation. If, conversely, pretest probability by Wells Score is high, VU is recommended[15,16] (Figure 3). Therefore, the role of D-Dimer in this diagnostic process is limited: it is a degradation product of cross-linked fibrin and it is elevated in nearly all patients with acute DVT (high sensitivity), but it is non-specific since high levels are found in many other conditions (*i.e.* malignancy, sepsis, recent surgery or trauma, pregnancy, renal failure).

Protocols

Complete doppler ultrasound: Is the preferred one and it includes bilateral compressions from inguinal ligament, passing through calf veins, to ankle (compressions are separated by 2 cm intervals); it also provides for bilateral common femoral and popliteal vein color doppler images and spectral doppler waveforms, in order to verify possible asymmetries[17,18]. CUS false positivity in calf evaluation is

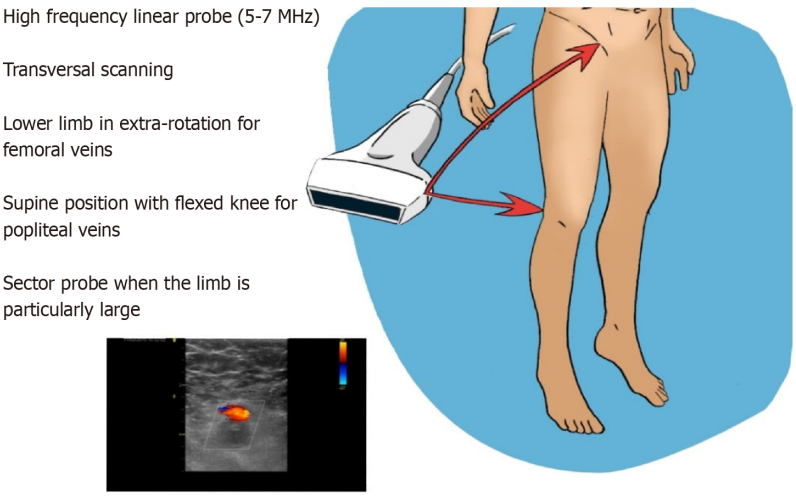

Figure 1 Study optimization.

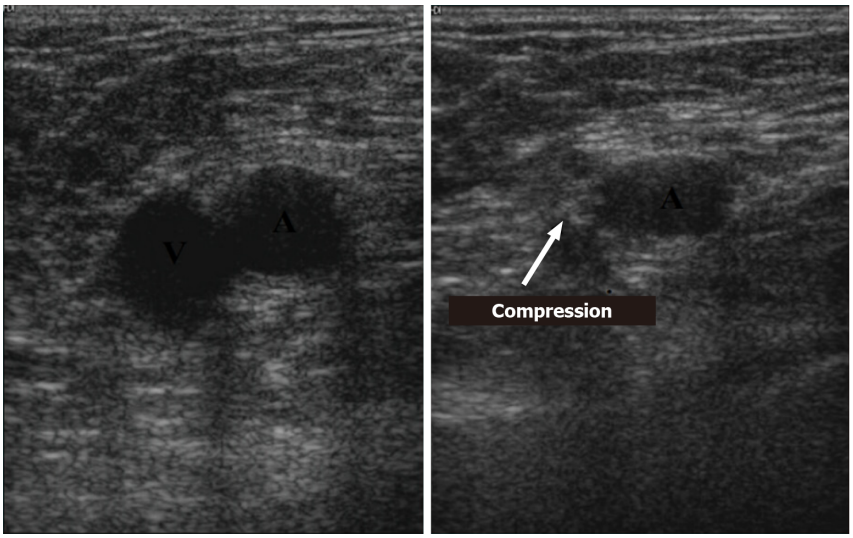

Figure 2 Compression ultrasound example.

extremely uncommon (its specificity in calf district reaches about 97.8%)[19], and the risk of excessive treatment related to calf DVTs represents the principal argument against this protocol. Calf assessment may also provide alternative findings, like musculoskeletal abnormalities[20]. Prospective studies have demonstrated that lack of compressibility of a vein with the ultrasound probe is the most sensitive (> 95%) and specific (> 95%) sonographic sign for proximal vein thrombosis. The addition of color flow Doppler does not improve the sensitivity but can provide supportive evidence of thrombus and help to identify calf veins. Variation of venous size with the Valsalva maneuver has a low sensitivity and specificity for the diagnosis and is no longer performed in many centers[21-24]. In case of negative result, the risk of DVT after 3 mo is estimated about 0.57% (95%CI, 0.25%–0.89%) (Figure 4)[25].

Extended compression ultrasound: This protocol is a point-of-care examination that consists of compressions from thigh to knee and is principally utilized when complete doppler ultrasound (CDUS) is not quickly viable[26]. However, if it results negative, a confirmatory CDUS after 5-7 d is recommended, in order to exclude calf involvement (evaluating to start anticoagulation if this is not possible)[27-30]. (Figure 4).

Two-region ultrasound: The compressions are limited to femoral and popliteal areas. As in extended compression ultrasound (ECUS), also in this case a negative response should be followed by a CDUS examination 5-7 d later, because both the previous two protocols do not comprehend calf veins[27,31,32]. D-Dimer after a negative ECUS or two-region ultrasound does not affect the follow-up unless it results negative[33]

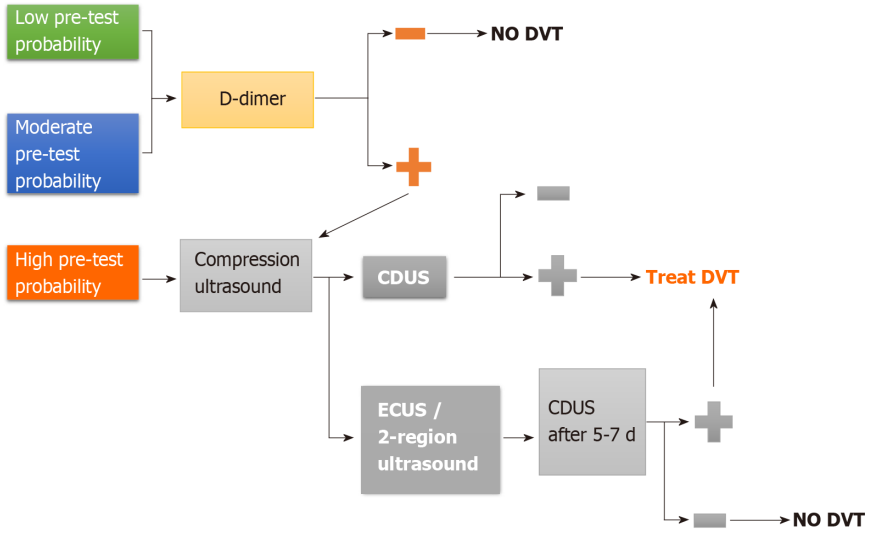

Figure 3 Pretest evaluation algorithm. CDUS: Complete doppler ultrasound; DVT: Deep venous thrombosis; ECUS: Extended compression ultrasound.

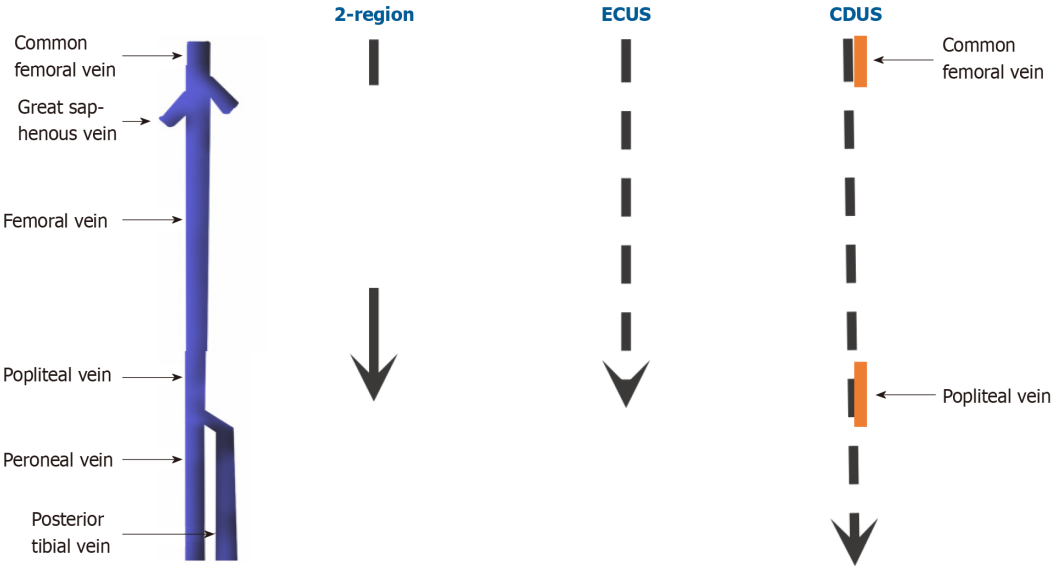

Figure 4 Different protocols. Dotted arrows correspond to ultrasound scans separated by 2 cm intervals. Yellow segments instead represent doppler points. CDUS: Complete doppler ultrasound; ECUS: Extended compression ultrasound; 2-region: Two-region ultrasound.

(Figure 4).

Thrombosis sides and related approach

The management of DVT is also related to its side, in particular two sides are more controversial (Figure 5): (1) Ileocaval: Being in a blind side for ultrasound sonography, it could be underdiagnosed. Nevertheless, although a normal CUS could be present, asymmetrical or continuous femoral doppler waveforms or whole-leg swelling may indicate an upstream impediment. In these cases, it is reasonable to think about pelvic ultrasound, CT or magnetic resonance venography to rule out this possibility. It has been estimated that this side is involved in 1.6% of DVTs[34]. Because the accuracy of duplex ultrasound for ileocaval DVT is not established, the threshold for CT or magnetic resonance venography should be low; (2) Calf veins: Even if calf district examination is just included in CDUS protocol, calf involvement management is subject to debate. If the physician chooses a wait-and-see approach without treating, it is recommended to repeat ultrasound at 1 wk. If new scan shows proximal progression, then start anticoagulation (progression occurs in 9%-21.4% of cases and is usually associated to symptoms perseverance or exacerbation)[35]; if instead clot remains stable, you should scan again at 2 wk. If thrombus is not more observable at 1

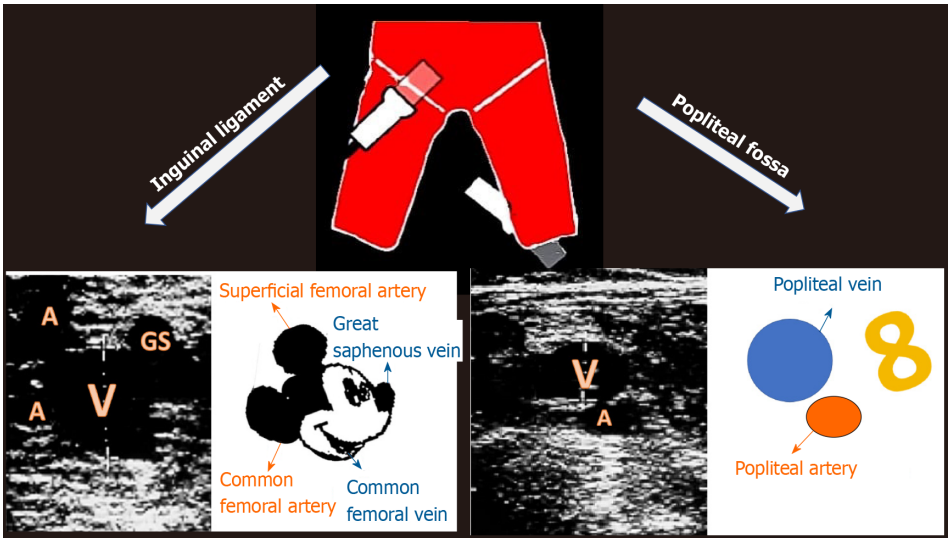

Figure 5 Reference points and respective sonogram images. A: Artery; GS: Great saphenous vein; V: vein.

wk or does not show significant evolution at 2 wk, or if you have begun treating, you can stop its follow-up. You could consider a new assessment in case of therapeutic changes[35,36]. More investigations will be needed to clarify prevalence and risk factors of progression in non-anticoagulated calf thromboses[37]. It is important to point out that short calf areas of non-compressibility are not significative[38], further scans or D-dimer may supply in these cases, although positive D-dimer has demonstrated to be not discriminatory[39]. Moreover, presence of calf DVT could be important in risk stratification about different fields like chronic venous insufficiency, mortality and cancer diagnosis or recurrent DVT occurrence[40,41]. The current American College of Radiology/American Institute of Ultrasound in Medicine/Society of Radiologists in Ultrasound guidelines include selective calf imaging for the subset of patients with calf symptoms not explained by the proximal scan; and (3) Upper limbs: Old statistics referred an incidence of upper limbs thrombosis about 2%-3%, mainly in young patients and in right arm, especially after hard physical effort or in thoracic outlet syndrome.

Thrombus types and classification

The thrombus evolution is characterized by several phases, each with different embolic risk: (1) Early stage (1-6 d): Clot shows hypoechoic structure and low adherence to vessel walls; (2) 2nd stage (7-14 d): Inhomogeneous structure with alternation of echogenic and hypo/an-echoic areas; and (3) 3rd and 4th stage (> 14 d): Organization and recanalization phases: Flow appearance inside thrombus to color doppler.

The first two phases have the highest PE risk.

Basing on echogenic characteristics and appearance of thrombus, we can classify lesions as follows (Table 2): (1) Acute Venous thrombosis: Noncompressible, but the clot is not stiff and gets deformed under probe push; thrombus presents a regular profile, and the respective vein is dilated; (2) Chronic post-thrombotic change: It shows residual findings after an acute venous thrombosis. In this case clot is noncompressible, fixed and resists to pressure deformation; moreover, its profile is often non-uniform, as well as non-uniform and thickened could look vessel wall after thrombus incorporation or recanalization, while vein does not present dilated rather its caliber may be reduced (scarring setting). Sometimes it is associated to thick adhesions (synechiae), as effect of retraction forces exerted by thrombotic material, and less often to calcification sides. Echogenicity does not reflect how old thrombus is[42]. It is important to keep in mind that this persisting lesion is not a thrombus and anticoagulation therapy is not required in this case[43]; (3) Subacute thrombus: This term shouldn't be commonly used since it refers to a typical and unusual situation in which ultrasound shows a change in acute thrombus aspect few weeks apart, not includable in chronic post thrombotic change definition. These changes should occur no later than 6 mo after clot formations[44,45] (thrombus usually progresses or heals within 6 mo from its generation); (4) Scarring: It is a process that can follow a not completely recovered acute thrombosis, due to fibroblasts action on thrombus and consequent

Table 2 Lesion types

Lesion definition	Characteristics
Acute thrombus	Noncompressible; deformable under probe push; regular profile; dilated vein
Subacute thrombus	Change in acute thrombus aspect few weeks apart, not includable in chronic post-thrombotic change definition (no later than 6 mo after clot formation)
Chronic post-thrombotic change	Noncompressible; resists to pressure deformation; non-uniform profile; reduced/normal vein caliber

fibrosis with its effects on wall thickening and synechiae production. It can determine an uncomplete stenosis which could endure for years[44,46]. Scarring has to be more correctly considered part of "chronic post thrombotic change" definition; (5) Indeterminate (equivocal): Definition utilized when it is not possible to clearly classify the lesion; (6) and Recurrent DVT: It is a thrombus formation on a chronic post thrombotic change region or a new acute venous thrombosis in a patient with a former thrombosis episode in same or contralateral leg[47-50]. It is a quite common eventuality[49], especially in patients with scarring lesions[51]. It could be not easy to recognize a new acute thrombus occurring in a chronic post thrombotic change zone [47,51,52]. Various criteria have been advanced to support diagnosis, in particular increments in compressed vein size > 4 mm or in D-dimer values, while no modifications in ultrasound scans at 1-3 d and at 7-10 d as exclusion criterion; however, their efficiency is still not clear[35,47,53-55]. Magnetic resonance also has been considered to assist differential diagnosis of recurrent DVTs from simple scars[55].

Serial scanning or D-dimer may be helpful in cases where the ultrasound does not detect clear new abnormalities, or the findings are difficult to interpret. Equivocal ultrasound findings may require serial imaging after 1-3 and 7-10 d to determine if there are any acute changes that would indicate recurrent DVT. D-dimer may also be helpful to establish if recurrent DVT is present.

FOLLOW-UP

During anticoagulant therapy, ultrasound follow up is not necessary. For example, in the early stages of treatment, there may be minimal progression of thrombotic material, but this is not an indication to change anticoagulant or to insert a caval filter. Therefore, to evaluate "response" of venous clot to therapy does not alter treatment [36,56,57].

Ultrasound at the end of treatment may be helpful to get a clear picture of the venous district for future assessment[54].

It is unclear whether the persistence of thrombotic abnormalities can guide on a possible prolongation of anticoagulant therapy. Further studies will be needed to define the correlation between residual risk and therapy[58].

A separate mention deserves isolated distal DVT, that-as stated above-sometimes resolves or does not extend proximally without treatment and is associated with less severe complications. Thus, routine use of whole leg ultrasonography has the potential to lead to the diagnosis of DVT that does not necessarily need to be treated. Data on distal DVT remain unclear. It is not yet known who patients are at risk and how long any anticoagulation therapy should be[59].

CONCLUSION

DVT is an often-misrecognized pathology that can cause serious clinical conditions, such as PE. Actually, ultrasound evaluation of the lower venous district can give essential information for a rapid diagnosis, especially in conditions of hemodynamic instability or when second level examinations are not readily available. Hence, compressive ultrasonography is one of the most effective tools in the emergency department in the hand of physicians. It is a non-invasive, low-cost diagnostic methodology that does not expose the patient to ionizing radiation; therefore, it is a rapid examination that should be part of the diagnostic flow chart for PE.

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MINIREVIEWS

Point-of-care ultrasound in a pandemic: Practical guidance in COVID-19 units

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has stretched our healthcare system to the brink, highlighting the importance of efficient resource utilization without compromising healthcare provider safety. While advanced imaging is a great resource for diagnostic purposes, the risk of contamination and infection transmission is high and requires extensive logistical planning for intrahospital patient transport, healthcare provider safety, and post-imaging decontamination. This dilemma has necessitated the transition to more bedside imaging. More so than ever, during the current pandemic, the clinical utility and importance of point-of-care ultrasound (POCUS) cannot be overstressed. It allows for safe and efficient beside procedural guidance and provides front line providers with valuable diagnostic information that can be acted upon in real-time for immediate clinical decision-making. The authors have been routinely using POCUS for the management of COVID-19 patients both in the emergency department and in intensive care units turned into "COVID-units." In this article, we review the nuances of using POCUS in a pandemic situation and maximizing diagnostic output from this bedside technology. Additionally, we review various methods and diagnostic uses of POCUS which can replace conventional imaging and bridge current literature and common clinical practices in critically ill patients. We discuss practical guidance and pertinent review of the literature for the most relevant procedural and diagnostic guidance of respiratory illness, hemodynamic decompensation, renal failure, and gastrointestinal disorders experienced by many patients admitted to COVID-units.

Key Words: COVID-19; SARS-CoV-2; Point-of-care ultrasound; COVID-intensive care units; COVID-unit; Critical care; Decontamination; Pandemic; Imaging in COVID-19; Point-of-care ultrasound in a pandemic

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Core Tip: In the current coronavirus disease 2019 (COVID-19) pandemic, advanced imaging is a great resource for diagnostic purposes but the risk of contamination and intra-hospital infection transmission is high and requires extensive logistical planning for intrahospital patient transport, healthcare provider safety, and post-imaging decontamination. Point-of-care ultrasonography is a reliable and resourceful tool for bedside diagnosis and clinical assessment. We discuss practical guidance and pertinent review of the literature for the most relevant procedural and diagnostic guidance of respiratory illness, hemodynamic decompensation, renal failure, and gastrointestinal disorders experienced by many patients admitted to COVID-units.

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INTRODUCTION

The novel coronavirus disease of 2019 (COVID-19) has led to over two million deaths till date. Given 4.6 per 100000 patients with COVID-19 pneumonia require hospitalization, and 9%-11% of these requiring intensive care units (ICU) care, diagnostic imaging will likely be necessary during their hospitalization. Some conventional imaging modalities, such as computed tomography (CT), carry high sensitivity and specificity for diagnoses. However, there are logistical concerns associated with isolation, intra-hospital transport, time and person-power expenditure, as well as risk for healthcare exposures. They also require a labor-intensive decontamination process of the imaging location and the intra-hospital pathway. This has caused most institutions to shift toward reliance on point-of-care imaging. The American College of Radiology and Radiological Society of North America have established guidelines for preparedness and decontamination of imaging equipment for special pathogen units such as COVID-units[1]. The challenge of using imaging equipment lies in protecting caregivers and preventing disease transmission. Additionally, it requires maneuvering a portable X-ray machine in and out of isolation rooms ("hot zones"), double-bagging of X-ray detectors with impermeable plastic sheets, and often multiple caregivers protected by personal protective equipment (PPE). The process of efficient and safe decontamination can be time-consuming and requires an investment of substantial resources and regular training of technicians.

Instead, point-of-care ultrasound (POCUS) can replace X-rays and CTs in many situations and thus mitigate logistical problems associated with large equipment for radiography. Numerous studies have reported the accuracy and non-inferiority of POCUS compared to conventional imaging for clinical diagnosis and decision-making [2]. Moreover, POCUS has become a standard part of the critical care medicine training curriculum and is recommended by several international society guidelines for the care of critically ill patients[3-8]. Its use has also been highlighted in epidemics, specifically the Ebola epidemic, where it proved as a useful clinical tool in patient care [9].

The goal of this article is to provide readers with an understanding of how to best use POCUS for acutely ill patients during the time of a pandemic, where resources are stretched thin and routine imaging studies such as X-rays and CT scans occur with diminished frequency due to logistical constraints. Using real-time ultrasound images from our COVID-19 patients, we want to highlight those POCUS techniques that can rapidly replace conventional imaging modalities during this COVID pandemic, offer instruction on performance, and provide an evidence-based anchor *via* reference literature.

General considerations with POCUS in COVID-units

A few general considerations with POCUS in COVID-units.

Dedicated ultrasound and location: In COVID-units hosting multiple patients, it is essential to have an ultrasound machine dedicated strictly to that unit. The machine should be stored at a specified location for easy retrieval during emergent use[10].

Bundling of ultrasound examinations with patient care: Given the logistics of donning and doffing PPE and ultrasound machine decontamination, along with risks to healthcare workers, ultrasound examinations should be bundled with other patient care-related activities when possible.

Ultrasound machine and probe decontamination: Although easier to clean compared to large X-ray machines, ultrasound machines used on COVID-19 patients still need to be thoroughly disinfected according to institutional protocols. Thoroughly wipe down with a probe-friendly Environmental Protection Agency-approved disinfectant wipe for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the transducer probes, screen, keypad, wires, and plug before bringing it outside the patient's room, to prevent contamination of "warm" and "cold zones"[11]. We advocate for cleaning the machine before leaving the patient's room, and once again immediately outside the patient room thereafter, as argued by other authors[12]. Despite cohorting of COVID-19 patients, disinfecting ultrasound machines in between patient care is paramount to protect healthcare workers from potential occupational exposure. An ultrasound probe cover should be used for sterile procedures to prevent nosocomial infection to the patients and also maintain a barrier for the machine from bodily fluids[13]. Consider individual ultrasound gel packets to prevent cross-contamination as well as ultrasound machine covers for more easily wipeable decontamination surface[14].

Ultraportable ultrasound devices: Handheld pocket ultrasounds are commonly being used in emergency departments, and ICUs and can be ideal for pandemic situations. Regular probe covers can be used for a handheld device with the decontamination process similar to that used for cart-based machines after use.

Training: Care must be taken to ensure that providers using POCUS are sufficiently trained, credentialed as relevant, and that appropriate supervision is provided institutionally. This becomes relevant, particularly where providers are being repurposed for clinical duties outside their prior scope of practice. Simulation-based training in using and decontaminating ultrasound devices can help providers to become accustomed to institutional procedures and protocols[15].

Saving images and documentation: It is important to save images obtained on POCUS to the patient charts using picture archiving and communication system or digital imaging and communications in medicine for review and interpretation by other care providers and consultants on the team[11]. A brief procedure note can be documented in the patient chart highlighting the findings on the POCUS examination along with pictures of highlighted findings if possible. Saving images and documenting reports are important, as they provide accessible records and allows for comparison through serial imaging. In order to minimize contact time and exposure risk, it is imperative to focus only on the acquisition of quality images while in the patient's room with the ability to interpret outside the room subsequently.

Overview of diagnostic utility of POCUS

POCUS has been increasingly utilized for both, procedural guidance and bedside diagnosis of a multitude of conditions. Table 1 lists many of these applications, which are summarized below.

Procedural guidance

POCUS has been found to improve first attempt success in many procedures needed in a COVID-unit.

Endotracheal intubation

One of the most common reasons for admission to a COVID-unit is acute hypoxemic respiratory failure requiring invasive mechanical ventilation. During the COVID-19 outbreak, many hospitals have protocols for direct invasive mechanical ventilation, opting against non-invasive positive pressure ventilation to reduce the risk of aerosolized exposure[16,17]. A chest radiograph (CXR) to confirm the correct placement of the endotracheal tube (ETT) is often performed after intubation. Instead, ultrasonography can be used to confirm successful ETT placement. The advantages of POCUS are its easy availability, high specificity, speed of detection, safety (without

Table 1 Various applications of point-of-care ultrasound in a coronavirus disease 2019-units

Point of care ultrasound in COVID-units	
Procedural guidance	Endotracheal intubation
	Peripheral intravenous access
	Central venous access
	Gastric tube placement
	Thoracentesis
	Paracentesis
	Lumbar puncture
Airways and lung	Pleural effusions
	Patchy B-lines and rugged pleural surface
	Consolidations
	Atelectasis
	Pneumothorax
Shock physiology	Fluid responsiveness
	Stroke volume assessment
	Pericardial effusion
	Right ventricular function
	Tricuspid annular planar systolic excursion
	Shunt physiology with agitated saline
	Deep vein thrombosis
Abdomen and hepatobiliary	Ascites
	Small bowel obstruction
	Acute cholecystitis
	Acute cholangitis
	Pancreatic evaluation
	Aortic evaluation
Genitourinary	Acute kidney injury
	Hydronephrosis
	Renal stones
	Renal vascular resistive indices for volume overload
Neurovascular	Optic nerve sheath diameter

COVID-19: Coronavirus disease 2019.

radiation exposure), and ease of repeat imaging. A high-frequency linear probe is used to ultrasound the neck during or after the endotracheal intubation. With the probe placed in a transverse position at the base of the neck, the trachea appears as a round hypoechoic structure in the center of the neck with a reverberation artifact and hypoechoic shadow. If the probe is moved slightly to the left of the trachea, the esophagus appears as a thick-walled collapsed structure with the hypoechoic center just posterior to the trachea. As the ETT passes through the trachea, one can visualize fluttering in the trachea as immediate confirmation of endotracheal intubation. This is known as the "Snowstorm sign"[18]. On successful endotracheal intubation, the widening of the vocal cord with a hyperechoic circular tube in the trachea with an acoustic shadow beneath it is seen. This is known as a "Bullet Sign"[18] (Figure 1). In the event of esophageal intubation, the tube will be visualized in the esophagus and gives the impression of a second trachea. This is known as the "double-track sign"

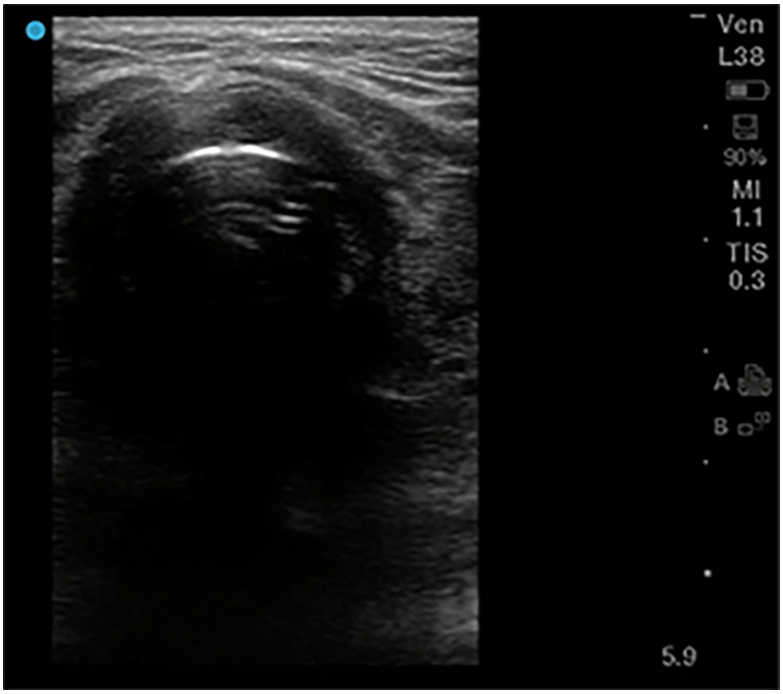

Figure 1 Endotracheal intubation. High frequency 5-10 MHz linear probe with probe marker facing toward patients' right side, placed at base of neck midline just superior to suprasternal notch. "Bullet sign" of proper endotracheal intubation seen here, with hyperechoic air-mucosal interface and posterior shadowing.

[19]. The accuracy of linear-probe ultrasound for successful intubation is 98%[20]. Once the successful endotracheal intubation is performed, mainstem bronchus intubation can be ruled out by performing a lung ultrasound using a linear high-frequency probe with a sensitivity of 98.7% and specificity of 97.1%[21]. In tracheal intubations, bilateral lung sliding should be visualized on POCUS. In the case of right mainstem bronchus intubation, the left contralateral lung exam will not demonstrate lung sliding due to absent lung ventilation. Cardiac pulsations, visualized on the pleural surface (lung pulse) can help differentiate main stem intubation from a pneumothorax[22] (Video 1). Once identified, the ETT can be retracted by a few centimeters during simultaneous ultrasound visualization of left lung to assess for lung sliding, which confirms correct placement of ETT.

Peripheral venous access

A high-frequency linear probe can be used to place peripheral venous access swiftly if superficial veins are not identified on a physical exam. Ideally, a superficial vein that is 3 mm to 10 mm beneath the skin is visualized in transverse and longitudinal axis with an ultrasound. This allows the provider to gauge the path of the vein and decide the length of the intravenous catheter to use. A color Doppler can be utilized to differentiate an artery from a vein when in doubt. The success rate of ultrasound-guided peripheral venous access is 81% compared to 70% in the control group with palpation/visualization approach. It also reduces the number of attempts and time to achieve a venous access[23,24].

Arterial access

Arterial access is often required in patients requiring vasopressor therapy and invasive mechanical ventilation for close hemodynamic monitoring and frequent arterial blood gases. The radial artery is the most common site utilized for arterial line placement. Using POCUS, first-pass success can be improved by up to 71%[25]. Since the vessel and the catheter tip can be directly visualized in real-time during the procedure, the chances of complications are lower compared to palpation method[26]. POCUS also offers superiority in deeper located arteries decreasing serious complications and improving the first-pass success.

Central venous access and confirmation

There are several advantages of having central venous access in patients admitted to a COVID-ICU. It reduces the number of venous punctures for frequent blood draws, allows for hemodynamic monitoring, and consistent access for sedation and vasoactive

medications. Standard of care is for central venous line (CVL) placement to be performed under direct ultrasonographic visualization as its use reduces complications and improves first-pass success when conducted by trained personnel[27]. Real-time POCUS can be utilized to visualize and capture the image of the guide-wire in the intended central vessel during the procedure. Once the CVL is placed, an agitated saline bolus can identify correct placement by finding immediate microbubbles in the right atrium on the subcostal cardiac view (also known as rapid atrial swirl sign) (Video 2)[28]. The same probe can be utilized post-procedure to ensure lung sliding and rule out procedure-related pneumothorax. A prospective study identified correct CVL placement using POCUS with a sensitivity of 86.8% and a specificity of 100%[29]. They found that the median time to POCUS completion for confirmation of line placement was 16 min compared to 32 min for a CXR[29]. This time difference is further accentuated in COVID-units, given the intricate process of PPE and decontamination needs with X-ray machines.

Gastric tube placement

Patients admitted to COVID-units are often intubated for mechanical ventilation and require nutrition *via* an enteral feeding tube. Gastric tube placement is generally a safe procedure, but in rare instances, complications such as bronchial placement, pneumothorax, pneumonia, tracheal or esophageal injury can occur[30]. Typically, a CXR is required for confirmation of the tube placement in the stomach. However, in COVID-units, this can be time- and resource-consuming. Instead, a POCUS can be used to identify the correct placement of a gastric tube with a 91%-98% sensitivity and 67%-100% specificity using a two-point approach[31,32]. Using a micro-convex (2-4 Hz) probe or a small footprint high-frequency linear probe (5-10 MHz), the trachea and esophagus are visualized in the suprasternal notch. A gastric tube appears as a hyperechoic circular structure within the esophagus, posterior to the trachea with an acoustic shadow below it. Once confirmed, using a low-frequency probe (2-5 MHz the curvilinear probe or 1-5 MHz phased array probe) in the epigastric region angling towards the left subcostal region, the gastric tube can be identified as a hyperechoic line within the stomach (Figure 2). It is important to note that in an air-filled stomach, visualization of the gastric tube may be difficult. Attaching the tube to suction before performing the POCUS examination can increase the diagnostic yield.

DIAGNOSTIC POCUS

Lungs

Studies have demonstrated that a CT scan of the chest is 86% sensitive in making a clinical diagnosis of COVID-19[33]. Typical findings include peripheral based patchy ground-glass opacities with increasing lung involvement with the severity of illness [34]. Pleural effusions, cavitary lesions, nodules, and mediastinal lymphadenopathy are uncommon in COVID-19[34,35]. POCUS can better characterize COVID-19 Lung disease, and lung ultrasound patterns have been described[36]. A multiple-point lung examination with ultrasound can be a quick and efficient way to demonstrate patchy B-lines with interspersed normal lung parenchyma in early disease (Figure 3). Subsequently, subpleural consolidation with bronchograms can also be appreciated. Lung ultrasonography can also help in identifying early disease even before symptom onset[35] (Video 3).

Ultrasound is superior to CXR in assessing for pleural effusions[37]. Development of secondary bacterial pneumonia and parapneumonic loculated effusions can be seen on POCUS and can guide if draining is required (Video 4). Early literature from China suggests an incidence of pneumothorax in SARS-CoV-2 to be 2% compared to 25% in SARS-CoV-1[38,39]. However, the incidence may be much higher based on our experience and multiple reported cases in the literature[40,41]. A sudden hemodynamic decompensation with acute hypoxemia in an otherwise stable intubated patient should raise suspicion for a pneumothorax that may need prompt identification and intervention. Identifying a lung point in the absence of B-lines and lung sliding can quickly identify a pneumothorax and help decide on early intervention with chest tube placement and decompression[42] (Video 5). The M-mode can be used to observe lung pulse and "sandy-beach" appearance of healthy lungs to reasonably exclude the possibility of a pneumothorax[42] (Video 6, Figure 4). Since most COVID-19 patients present with severe CXR and require prolonged mechanical ventilation, POCUS can be used to assess diaphragm atrophy and chances of liberation from the ventilator. While several methods of examining the diaphragm exist, the easiest

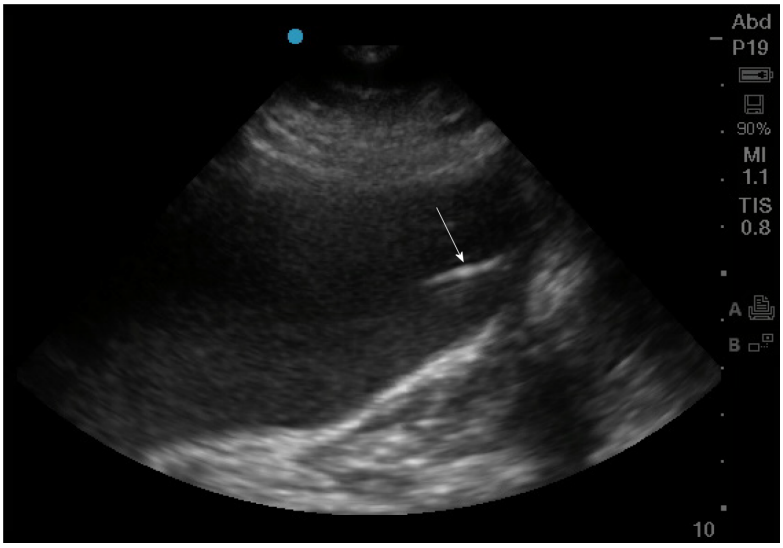

Figure 2 Gastric enteral tube placement. Phased array probe (1-5 MHz) in "Abdominal" preset with probe marker facing cephalad placed in left mid-clavicular subcostal location. The stomach here is distended with hypoechoic fluid, and inside it can be seen a linear hyperechoic density representing the gastric enteral tube (arrow).

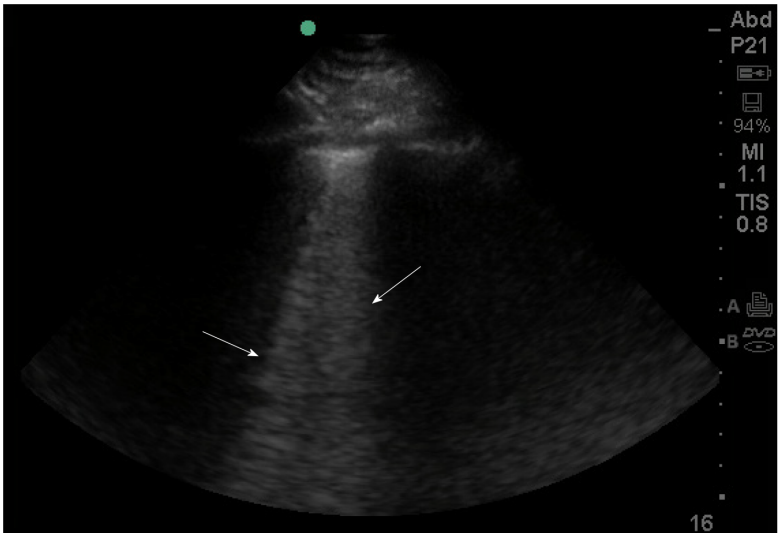

Figure 3 B-lines on lung ultrasound. Phased array probe (1-5 MHz) with probe marker facing cephalad placed in an intercostal space. B lines (denoted by arrows), are well-defined comet-tail, vertical hyperechoic artifacts arising from the pleural line that obliterate normal A-lines, and descend to the bottom of the screen. Multiple B-lines in an interspace indicates an interstitial syndrome, where there are increased air-fluid interfaces creating this artifact.

methods include assessing diaphragmatic thickness in anterior subcostal space using curvilinear low-frequency probe and M-mode to assess the amplitude of diaphragmatic excursion and the velocity of the contraction[43]. The normal thickness of the diaphragm is 22-28 mm[44]. The thickness of less than 20 mm may suggest the presence of diaphragmatic atrophy[45].

Cardiac

Cardiac ultrasound is an excellent tool to assess for global and regional wall motion of the cardiac chambers, pericardial, valvular pathology, right ventricular dysfunction, volume responsiveness, and to differentiate etiologies of shock. American Society of Echocardiography recently published a statement on POCUS use in COVID-19 patients, with a recommended protocol for relevant cardiac views[11].

Often assessment of volume status in COVID-19 patients is pertinent but challenging. Several methods have been used for volume status assessment with varying limitations[46]. In mechanically ventilated patients who are not breathing spontaneously, measuring the distensibility of the inferior vena cava (IVC) can help assess volume status (Figure 5). More importantly, the respiratory variation in IVC

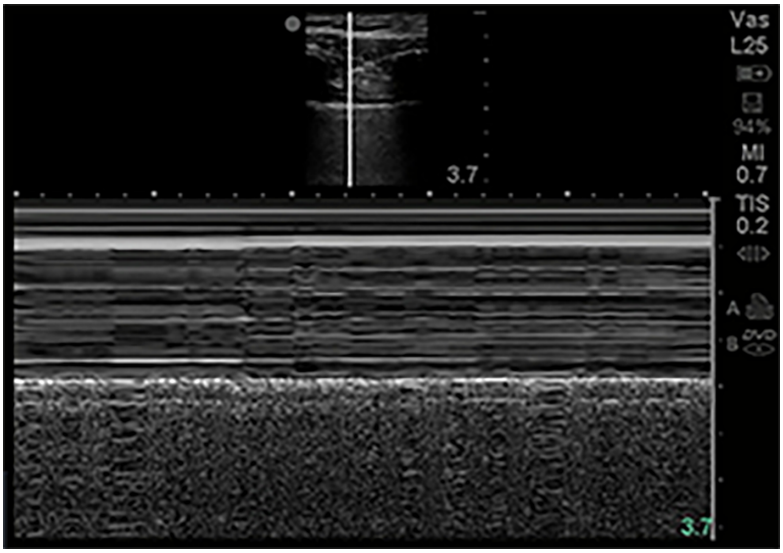

Figure 4 M-Mode normal lung. M-mode of normal lung demonstrates linear shadows from soft tissue followed by granular deeper shadows commonly described as "Sandy-beach sign".

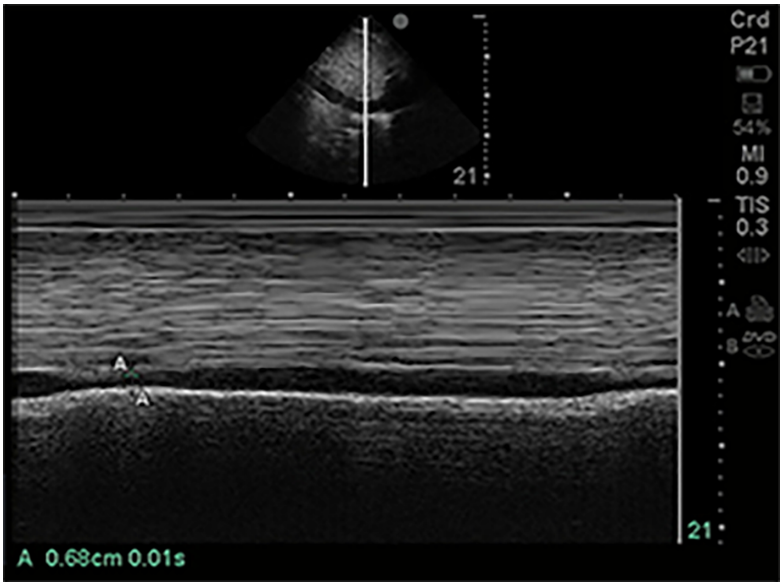

Figure 5 Inferior vena cava size in M-mode. Of 1-5 MHz phased array probe with probe marker facing cephalad, subcostal location, inferior vena cava (IVC) visualized in sagittal plane. M-mode line centered on IVC just inferior to hepatic vein inflow. IVC measured in this M-mode image at 1.70 cm maximally and 0.68 cm minimally.

diameter (known as ΔIVC) can predict fluid responsiveness in mechanically ventilated patients with a sensitivity of 76% and specificity of 86% according to a meta-analysis [47]. Vignon *et al*[48] assessed various parameters, including variation in superior vena cava (SVC) using transesophageal ultrasonography, variation in IVC, and change in left ventricular outflow tract (LVOT) velocity using pulsed-wave doppler for fluid responsiveness. While SVC variation had the best specificity (84%) in predicting fluid responsiveness, variation in IVC diameter (greater than 8%) had a specificity of 70%. It is imperative to note that patients IVC variability may not be accurate in spontaneously breathing patients experiencing significant dyspnea as it can lead to significant variation in intrathoracic pressures and IVC diameter[49]. Variation in IVC diameter, coupled with lung and cardiac ultrasound exams can be helpful for clinical decision-making about volume status. A hyperdynamic left ventricle (LV) may suggest underfilling and need for intravascular volume resuscitation[50]. For a more accurate assessment, an M-mode can be used in the parasternal short-axis across the LV to assess papillary muscle apposition[50].

For providers trained in advanced critical care echocardiography, the use of spectral Doppler can help assess stroke volume and cardiac output[51]. In the parasternal long-axis view, the LVOT diameter can be measured to estimate LVOT area[51] (Figure 6). Using a pulsed wave Doppler, the LVOT velocity time integral (VTI) can be calculated in a five-chamber apical cardiac view (Figure 7). This estimates the distance traveled by blood in one heartbeat. Multiplying the LVOT VTI by the LVOT area equals the stroke volume for each cardiac contraction (Figure 8)[51,52]. If the stroke volume or cardiac output is reduced, depending on the clinical picture, it could result in the initiation of inotropy or volume resuscitation. The key is for repeated measurement of stroke volume/cardiac output with any given intervention.

Another utility of cardiac ultrasound is to assess the etiology of the shock state. The presence of a large pericardial effusion with right ventricular and atrial wall collapse may suggest tamponade physiology. A large, dilated right ventricle (RV) with hypokinetic longitudinal walls and hyperkinetic apex may suggest RV outflow obstruction secondary to pulmonary embolism (PE). However, severe hypoxemia with pulmonary vasoconstriction can be seen in COVID-19, and so the presence of a dilated RV may not be specific for a PE and should correlate clinically (Video 7). Using M-mode, tricuspid annular planar systolic excursion can be obtained to estimate RV function in these cases[53] (Figure 9). Although, in cases of negative findings or normal RV function, PE cannot be ruled out as it has a low negative predictive value.

POCUS can also be used to investigate the hypoxemia of unclear etiology. A contrast study can be performed at the bedside by injecting agitated sterile saline *via* a three-way stopcock to look for an intracardiac or intrapulmonary shunt. The appearance of agitated saline bubbles in the LV within three heartbeats suggests an intracardiac shunt, while after five beats may suggest intrapulmonary shunt (late-appearance)[54,55].

Vascular

The risk of venous thromboembolism in COVID-19 has been reported in 25%-31% of COVID-19 patients[56,57] (Video 8). Increasing D-dimer, PT, or aPTT independently predicts the risk of venous thrombus embolism in these patients, thus necessitating assessment for deep vein thrombosis and PE[56-58]. For diagnostic accuracy, a high frequency, the linear probe can be used to assess deep veins of the lower extremities for evidence of thromboembolism[59] (Video 9). Evaluation of two regions (common femoral vein from the bifurcation with the greater saphenous vein to the bifurcation of superficial and deep femoral veins distally, and the popliteal vein) on both legs can be performed rapidly using compression ultrasonography.

Genitourinary

Acute kidney injury (AKI) is a common complication in critically ill patients with COVID-19[60]. Direct viral tropism, cytokine storming, rhabdomyolysis, and acute tubular necrosis (ATN) have been hypothesized as causes of AKI in COVID-19, similar to Ebola or SARS-CoV-1[60-63].

Gray-scale ultrasonography with a low frequency (2-5 MHz) curvilinear probe can be used to assess renal anatomy[64] (Figure 10). In states of hypoperfusion, the kidney appears hypoechoic. In contrast, kidneys appear hyperechoic in ATN secondary to rhabdomyolysis due to myoglobin deposits in the renal tubules[64]. Color Doppler can be utilized to evaluate lobar vessels and can provide information regarding flow states and underlying pathology. The vessels are poorly visible in poor perfusion states and may also indicate poor splanchnic perfusion. In these COVID-19 patients with renal failure, malfunction of a urinary catheter, particularly given duration of the length of indwelling placement, may go unnoticed and misinterpreted as acute kidney injury and anuria. Anechoic bladder volume can be easily seen qualitatively and measured quantitatively on POCUS to help rule out urinary retention and urinary catheter malfunction[65].

Abdominal

Gastrointestinal symptoms in COVID-19 patients are common on presentation as well as complications from hospitalization[66,67]. COVID-19 patients are particularly at risk for bowel hypomotility due to opiates and paralytics[67]. POCUS can be utilized as a diagnostic tool to identify the etiology of the abdominal symptoms in these patients. Using a curvilinear low-frequency probe, paralytic ileus can be identified as both small and large intestinal dilation and bowel wall thickening. A random movement instead of unidirectional flow of spot echogenic material can be seen in fluid-filled bowel, suggesting a downstream bowel obstruction. If the probe is kept

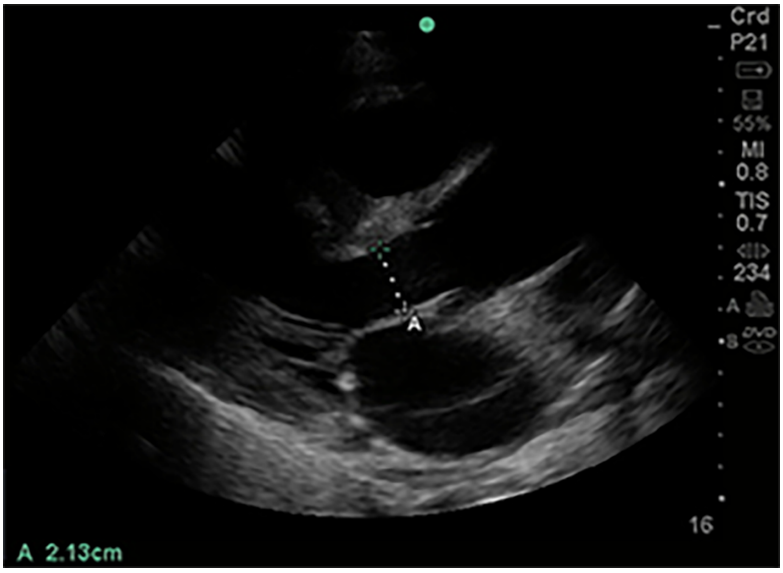

Figure 6 Left ventricular outflow tract diameter parasternal long axis view. Of 1-5 MHz phased array probe with probe marker facing patient's right shoulder, parasternal long axis view. Left ventricular outflow tract diameter measured during mid-systole, inner edge to inner edge, from septal endocardium to anterior mitral leaflet, in order to calculate cross-sectional area (πr^2).

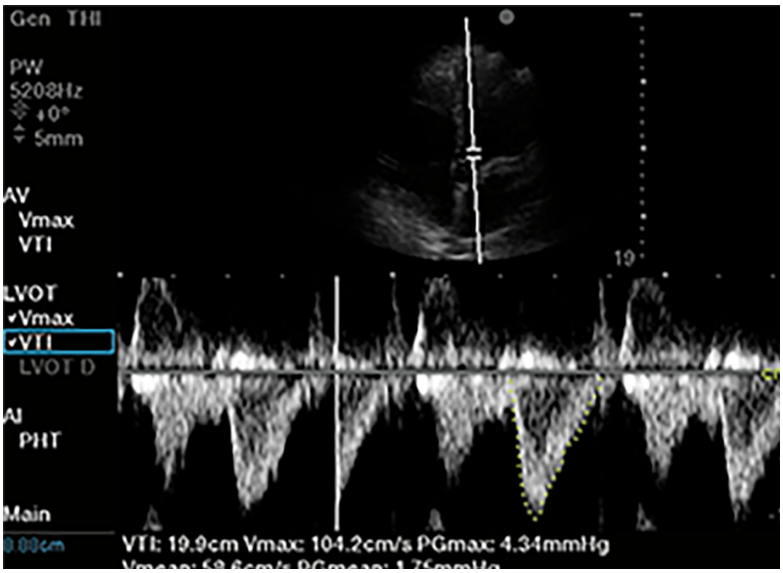

Figure 7 Left ventricular outflow tract velocity time integral. Of 1-5 MHz phased array probe, apical 5 chamber view. Pulsed wave doppler selected, with sample volume placed 5 mm proximal to aortic valve in center of the left ventricular outflow tract. Notice narrow signal with rapid upstroke in velocities, with end-systolic click terminating flow signal. In this case traced velocity time integral was 19.9 cm.

LVOT area (A)=πr^2; where r is the radius of LVOT (r = LVOT diameter ÷ 2)
Stroke volume (SV) = LVOT area × VTI
Cardiac output (CO)= Stroke volume × Heart rate

Figure 8 Formula to calculate stroke volume and cardiac output using pulsed wave doppler. LVOT: Left ventricular outflow tract; VTI: Velocity time integral.

still to observe the bowel, one can identify the sedimentation of intestinal content and "pearl-string" like a pattern of gas in the bowel[68]. Distended proximal bowel with collapsed distal bowel can help differentiate mechanical obstruction from paralytic ileus. Studies have demonstrated a sensitivity of 94%-100% and a specificity of 81%-100% for the lung ultrasound in diagnosing small bowel obstruction outperforming plain radiography (sensitivity of 77% and specificity of 50%)[69,70].

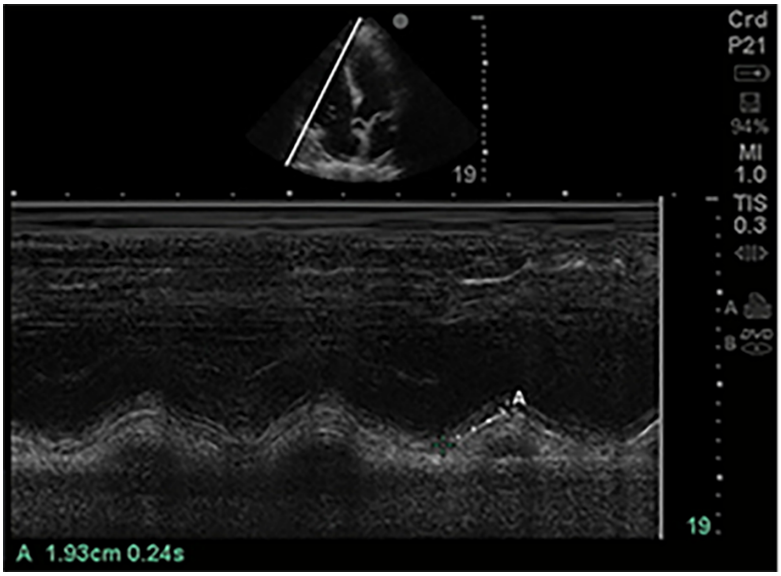

Figure 9 Tricuspid annular planar systolic excursion (tricuspid annular plane systolic excursion). Phased array probe (1-5 MHz) in "Cardiac" preset, placed in apical 4 chamber view. M-mode line is placed across the lateral tricuspid annulus to assess longitudinal contraction of the right ventricle (RV) free wall, a regional surrogate for RV function. The tricuspid annular planar systolic excursion of this patient was 1.93 cm which is low normal.

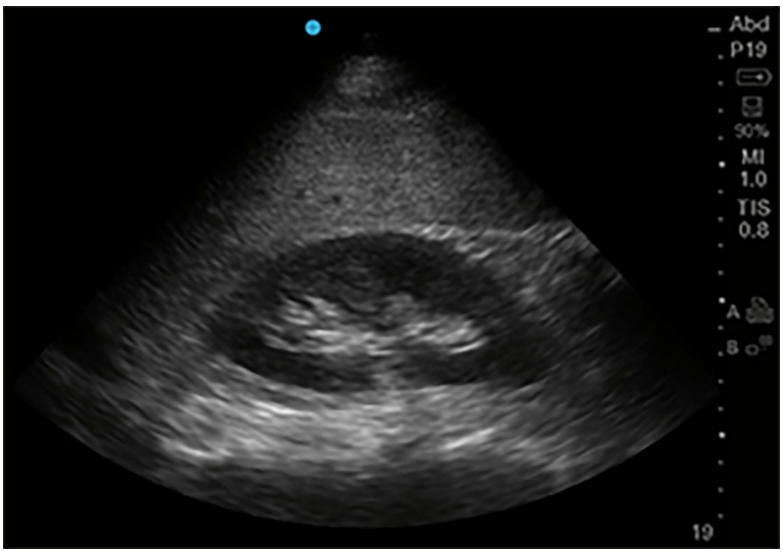

Figure 10 Kidney in its Longitudinal axis. Phased array probe (1-5 MHz) in "Abdominal" preset placed with probe marker facing cephalad in right mid-axillary location. In this normal ultrasound, the liver serves as an acoustic window, under which can be seen the thin hyperechoic kidney capsule, the hypoechoic parenchymal cortex, and the central hyperechoic renal sinus.

Ascites can also be identified easily on POCUS. Assessment of Morrison's pouch (hepatorenal recess), the splenorenal recess, and the pelvis for fluid collection is a common approach[71] (Video 10). The ideal site for paracentesis can be identified with the largest fluid pocket and least bowel presence. Color Doppler can be used *via* a linear high-frequency probe to look for abdominal wall vessels to prevent abdominal sheath hematomas and bleeding during paracentesis[71].

Neurologic

Many patients with COVID-19 suffer neurologic complications, and CT imaging of the head can be logistically challenging[72]. Ultrasound has been used as a non-invasive tool to identify elevated intracranial pressures by measuring optic nerve sheath diameter (ONSD)[73]. A high-frequency linear probe can be used to measure the optic nerve sheath diameter at 3 mm beyond the globe, where the contrast is maximum (Figure 11). Since the sensitivity of ONSD greater than 5 mm for intracranial hypertension is 100%, it serves as a useful screening tool for altered mental status in

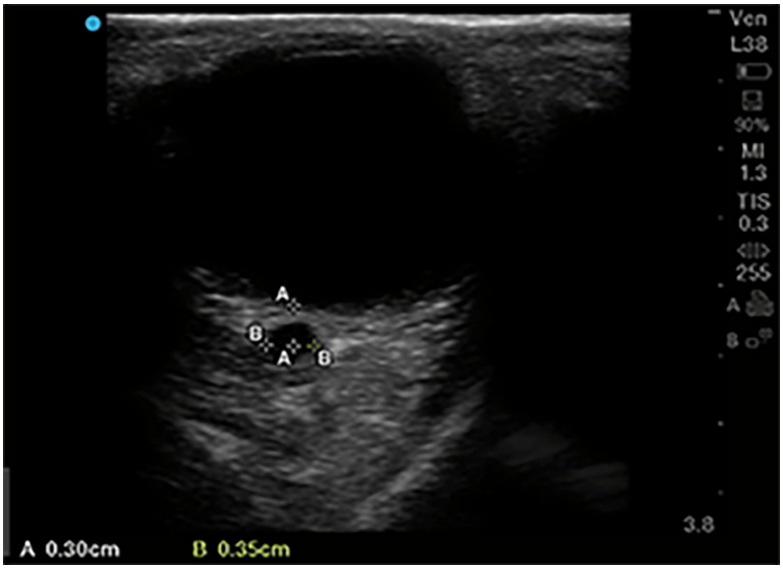

Figure 11 Optic nerve sheath diameter. High frequency 5-10 MHz linear probe in "Ophthalmic" or "Venous" preset with probe gently placed on upper eyelid in horizontal plane. Diameter of optic nerve is measured in transverse dimension, 3 mm posterior to where optic nerve enters the globe. In this patient optic nerve sheath diameter is measured at 3.5 mm.

the emergency d and outperforms ophthalmoscopic evidence of papilledema, which can take 12 h to develop[74-76].

Limitations

There are several limitations to the use of POCUS in the critical care setting. It requires expertise in general ultrasound knowledge, image acquisition skills, image interpretation skills, and the ability to integrate that information with other data appropriately to make clinical decisions affecting patient care. Certain clinical situations, such as obesity, high PEEP ventilation, bowel gas, and overlying catheters and wires, may interfere with the acquisition of good images. POCUS also requires sufficient experience and confidence to know when imaging is inadequate for interpretation and instead requires a formal sonogram or another imaging modality such as an X-ray or a CT scan.

CONCLUSION

In summary, we noticed a practice gap between literature on critical care ultrasonography and clinical practices commonly employed by many intensivists due to easily available conventional imaging modalities. In the setting of a pandemic, however, conventional imaging modalities become resource limited; therefore, we highlight how POCUS can fill this need in a timely, repetitive and evidence-based manner.

POCUS is an excellent tool for use in COVID-units as it provides essential bedside clinical information reliably and cost-effectively while maintaining patient and provider safety without the need for radiation exposure or arduous decontamination. Its use can improve first-pass success and reduce complications with bedside procedures. Simulation-based training sessions can prepare healthcare providers to utilize this tool efficiently in COVID-units, though obtaining proficiency in some applications requires substantial hands-on experience[77]. Where feasible, handheld POCUS devices can be assigned to each isolation room to prevent the spread of the pathogen and improve patient care. While the use of POCUS in the inpatient setting is continually increasing, provider proficiency and experience must also continuously improve. In a contained situation where limited exposure to healthcare providers is recommended, POCUS can be a useful diagnostic tool and allow for a complete assessment of the patient, as highlighted in this article. Further imaging can be considered if POCUS is unrevealing or non-specific, but it is certain to reduce the requirement of advanced imaging. It is essential to acknowledge the advantages and limitations of POCUS for its appropriate application in COVID-units.

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ORIGINAL ARTICLE

Case Control Study

Trends of central line-associated bloodstream infections in the intensive care unit in the Kingdom of Bahrain: Four years' experience

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Institutional review board statement: We performed to study according to the latest version of Helsinki's Declaration. The Research and Ethics Committee at the Ministry of Health, Kingdom of Bahrain, approved the study.

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Abstract

BACKGROUND

The central venous line is an essential component in monitoring and managing critically ill patients. However, it poses patients with increased risks of severe infections with a higher probability of morbidity and mortality.

AIM

To define the trends of the rates of central line-associated bloodstream infections (CLABSI) over four years, its predicted risk factors, aetiology, and the antimicrobial susceptibility of the isolated pathogens.

METHODS
The study was a prospective case-control study, performed according to the guidelines of the Center for Disease Control surveillance methodology for CLABSI in patients admitted to the adult intensive care unit (ICU) and auditing the implementation of its prevention bundle.

RESULTS
Thirty-four CLABSI identified over the study period, giving an average CLABSI rate of 3.2/1000 central line days. The infection's time trend displayed significant reductions over time concomitantly with the CLABSI prevention bundle's reinforcement from 4.7/1000 central line days at the beginning of 2016 to 1.4/1000 central line days by 2018. The most frequently identified pathogens causing CLABSI in our ICU were gram-negative organisms (59%). The most common offending organisms were *Acinetobacter*, *Enterococcus*, and *Staphylococcus epidermidis*, each of them accounted for 5 cases (15%). Multidrug-resistant organisms contributed to 56% of CLABSI. Its rate was higher when using femoral access and longer hospitalisation duration, especially in the ICU. Insertion of the central line in the non-ICU setting was another identified risk factor.

CONCLUSION
Implementing the prevention bundles reduced CLABSI significantly in our ICU. Implementing the CLABSI prevention bundle is crucial to maintain a substantial reduction in the CLABSI rate in the ICU setting.

Key Words: Bloodstream infection; Central line; Intensive Care Unit; Microbiology; Prevention bundle; Kingdom of Bahrain

Core Tip: The study aimed to define the trends of the rates of central line-associated bloodstream infections (CLABSI) over four years, its predicted risk factors, aetiology, and the antimicrobial susceptibility of the isolated pathogens. We found that implementing the prevention bundles reduced CLABSI significantly in our intensive care unit (ICU). Therefore, implementing and reinforcing the CLABSI prevention bundle are crucial to substantially reducing the CLABSI rate in the ICU setting.

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INTRODUCTION

The central venous line is an essential component in monitoring and managing critically ill patients. However, it poses patients with increased risks of severe infections with a higher probability of morbidity and mortality. The presence of bacteraemia initiated by the intravenous catheter is the hallmark of catheter-related bloodstream infection (BSI). Central line-associated BSIs (CLABSIs) are BSI developed in patients with central venous catheters in which there is no other apparent secondary source for bacteraemia. It is one of the most common, fatal, and costly side effects of central venous catheterisation and is one of the most frequent causes of nosocomial infections[1].

CLABSI has wide variable rates in different parts of the world, even in other institutes and units in the same country[2-5]. This rate depends on many factors such as the unit crowdedness, the scope of service provided, the ratio of the nursing staff to the patients, the staff adherence to the recommended infection control measures, and the availability of resources needed for implementing these measures[6].

STROBE statement.

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The International benchmark of the National Health Safety Network (NHSN) reported a pooled CLABSI rate of 1.25/1000 central line days[7]; while the International Nosocomial Infection Control Consortium (INICC) reported pooled data from the developing countries with a CLABSI rate of 4.1 per 1000 central line-days[8]. Recently, regional studies from Arabian Gulf countries reported an average of 3.1/1000 central line days in 2017[9]. On the other hand, resource-limited countries like India reported a much higher rate of CLABSI in the range of 10-40/1000 central line days[10].

Due to the relatively high incidence of CLABSI in Arabian Gulf countries, it is crucial to prevent these infections. Many previous studies proved that most cases of CLABSI are preventable through implementing an evidence-based prevention bundle. This prevention consists of a group of elements during the insertion of the central line insertion and its maintenance. Decreasing the catheter-related infection rates can be achieved in most intensive care units (ICUs) through periodic education programs complemented by auditing and regular surveillance of the CLABSI rate[6].

According to the best of our knowledge, there is no previous published data about the rate of CLABSI in Bahrain. Therefore, the current study aimed to determine the rate of CLABSI in ICUs in Salmaniya Medical Complex (SMC), the main tertiary care hospital in Bahrain. We also sought to define the risk factors for CLABSI acquisition and define the microbiological profile of central line-related bacteraemia to map its antimicrobial susceptibility. This microbiologic and antimicrobial susceptibility mapping help select the appropriate empirical antibiotics therapy for clinically suspected CLABSI before laboratory identification of the causative organism, especially among critically ill patients in the ICU where early administration of appropriate antimicrobial treatment is crucial and lifesaving.

MATERIALS AND METHODS

Design and setting

The study was a prospective observational case-control study, done over four years (from January 2015 till December 2018); in the adult ICU at Salmaniya Medical Complex (SMC). SMC is the main governmental tertiary-care hospital in the Kingdom of Bahrain with a 1200 bed capacity. The unit has 22 fully equipped single intensive care rooms staffed by trained nurses with a 1:1 nurse-patient ratio.

We implemented a comprehensive CLABSI prevention program in our ICU in 2016; to reduce the CLABSI rate to a level comparable to the United States NHSN rate benchmark[11]. The program included intensive education of ICU staff about CLABSI prevention bundle elements for both insertion and maintenance; regular auditing of the practice in the unit by the infection control liaison nurse (dedicated ICU nurse staff who received intensive training in the infection control with reserved hours for infection control work); and close monitoring of CLABSI rate, with periodic feedback from/to the ICU staff.

CLABSI prevention bundle for insertion included optimizing the hand hygiene before insertion, maximizing the sterile barrier precaution at insertion (full sterile body precaution for insertor including cap, mask, sterile gown, and gloves), optimal selection of the catheter insertion site, full patient body draping, proper chlorhexidine skin preparation at the insertion site. In addition, the CLABSI Prevention bundle for line care and maintenance included daily reviewing of central line necessity, optimizing the hand hygiene requirements, proper scrubbing of the hub before each use with an appropriate antiseptic, limiting accessing the catheters only with sterile devices, stressing dressing changes under complete aseptic technique using sterile gloves, and proper periodic replacement of dressings (dry gauze dressings every two days/transparent dressings every seven days)[12].

Study population

The study included all the patients (≥ 14 years) admitted to the adult ICU in SMC and needed placement of a central line for one or more days, during four years between January 2015 to December 2018. There were no exclusion criteria. We defined the cases as patients who developed CALBSI after 48 h from their admission to ICU. The control group was ICU patients who had central line insertion without the development of CLABSI. CLABSI was diagnosed -according to NHSN definition- as a laboratory-confirmed BSI. We also identified an eligible primary BSI causing organism, and a suitable central line was present on the laboratory-confirmed BSI date of the event (LCBI DOE) or the day before[11]. We defined the underlying medical or surgical

conditions by proper history taking, thorough clinical examination, and the needed investigations as appropriate.

Data collection

We collected the data prospectively through the unit's daily round by the ICU infection control liaison nurse. The nurse observed all central line catheterized inpatients using a particular surveillance form. The form recorded specific demographic data like age, gender, underlying diseases, hospital admission date, date of ICU admission, clinical diagnosis, and the patient outcome (death or discharge). It also included the date of insertion of the central line, the type of central line, its location, and the number of its lumens. Cases with suspected CLABSI were further referred for evaluation by the infection control team. The team included a clinical microbiologist and infectious diseases physician to finalize the cases if they fulfilled all the required clinical and microbiological criteria to diagnose CALBSI as per the NHSN definition[11].

The infection control liaison nurse collected the data about ICU staff's adherence (doctors and nurses) to the recommended CLABSI prevention bundle, using the standardized audit checklist for line insertion and maintenance. The checklist included the prevention bundle elements mentioned above. These data were collected during the observational rounds in the unit twice per week. We got a minimum of 120 observations for maintenance elements per month; and included the insertion checklist for all the lines inserted in the unit. We compared the prospective data collected for the three years (from January 2016 to December 2018) to the retrospective data collected from the same unit during the one year before implementing the comprehensive CLABSI prevention program (during the 2015 year).

Bacterial identification and antibacterial susceptibility testing

We used the traditional culture and biochemical characteristics of the isolates for proper bacterial identification. In addition, we standardized the antimicrobial susceptibility testing according to the Clinical and Laboratory Standards Institute[13]. According to the multi-drug resistance (MDR) classification system, MDR strains have resistance to 3 or more classes of antimicrobial agents[14].

Statistical analysis

We collected and tabulated the data using the electronic health system, then analysing it using the statistical software SPSS version 24 (IBM Corp, Chicago, IL, United States). We calculated the descriptive statistics of demographic variables, including frequencies, percentages, means, and ranges. To calculate the incidence rate of CLABSI as events per 1000 catheter-day, we divided the total number of patients with CLABSI/total number of catheter days during the year of the study, then multiply by 1000. The compliance to prevention bundle (average overall compliance to central line insertion and maintenance prevention elements) was calculated by dividing the number of compliant elements over the number of observed elements then multiply by 100. The Research and Ethics Committee at the Ministry of Health, Kingdom of Bahrain, approved the study. We did not collect consent, as the study was observational.

RESULTS

The study included all patients admitted to ICU during the study period between 2015 and 2018. During the study period, there were 3323 patients with 1634 central line insertions. We documented 34 CLABSI cases, with an average rate of 3.2/1000 central line days (the rate was 4.7/1000 at the beginning of 2015 dropped to 1.4/1000 central line days by the end of 2018 (Figure 1). Table 1 showed the demographics data, the clinical characteristics, and the potential risk factors for the CLABSI cases, in addition to the control group (catheterized patients without CLABSIs). About 71% of the patients who developed CLABSI had medical and while 29% had surgical conditions (71%), with a mean age of 63.6 years; twenty were male (59%). In addition, patients with CLABSI were relatively older than the control group (median age of 63.6 years *vs* 52.6 years, respectively). However, there was no significant difference between the CLABSI cases and the control group in age, gender, or the type of admission (medical *vs* surgical). All the patients admitted to the ICU and needed central lines had temporary, non-tunnelled, with more than one-lumen type of central lines.

Table 1 Univariate analysis of risk factors for central line-associated bloodstream infections

Potential risk factor		CLABSI cases, *n* = 34, *n* (%)	Control, *n* = 1600, *n* (%)	*P* value[1]
Age	< 50 yr	11 (32)	672 (42)	0.13
	> 50 yr	23 (68)	928 (58)	
Gender	Male	20 (59)	880 (55)	0.32
	Female	14 (41)	720 (45)	
Primary clinical diagnosis	Medical	24 (71)	1056 (66)	2.88
	Surgical	10 (29)	544 (34)	
Catheter insertion site	Subclavian	4 (11)	496 (31)	< 0.05
	Jugular	10 (30)	464 (29)	
	Femoral	20 (59)	640 (40)	
ICU time interval from ICU admission till line insertion	< 5 d	19 (56)	1408 (88)	< 0.05
	> 5 d	15 (44)	192 (12)	
Location of central line insertion	ICU	20 (59)	1216 (76)	< 0.05
	Non-ICU	14 (41)	384 (24)	
Length of duration central line	< 1 wk	11 (32)	1438 (90)	< 0.001
	> 1 wk	23 (68)	162 (10)	
Death		15 (44)	432 (27)	< 0.01
A live discharge		19 (54)	1168 (73)	< 0.01

[1]Using Chi-squared test.
ICU: Intensive care unit; CLABSI: Central line-associated bloodstream infections.

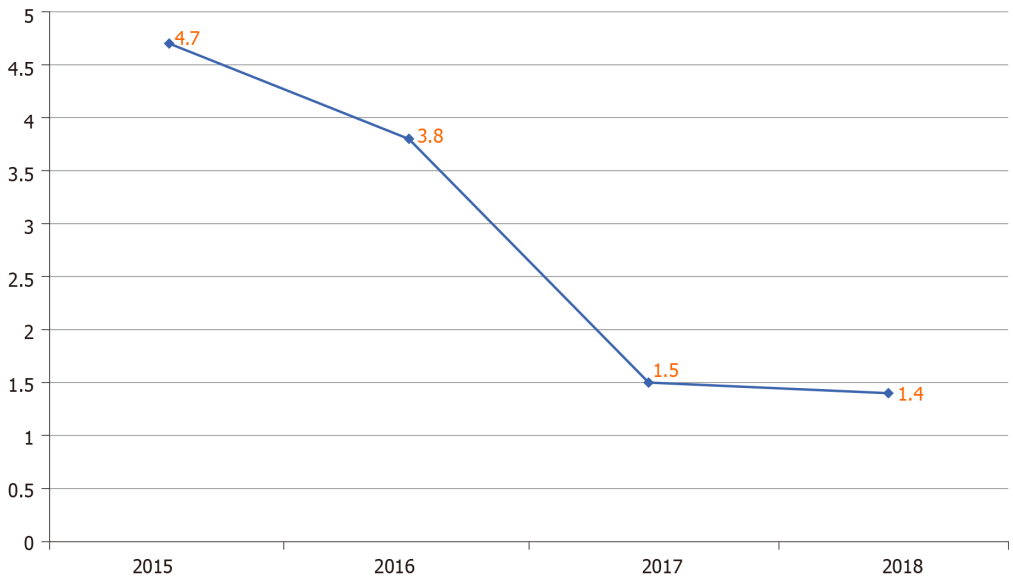

Figure 1 Rates of central line-associated bloodstream infection in intensive care unit (2015-2018).

The table also showed that CLABSI developed on average on day 15th after the central line's insertion. All infected central line had triple lumens and non-tunnelled. The most common insertion site was femoral (59% of all CLABSI and 3% of all femoral-inserted central lines), followed by the jugular vein (30% of all CLABSI and 2.1% of jugular vein-inserted central lines). Most of the infected central lines were inserted inside the ICU (59%), while the remaining were inserted in the emergency room ($P < 0.05$). Patients who developed CLABSI had a significantly longer median duration of stay in the ICU before placement of the central lines (7.6 d *vs* 2.8 d with $P <$

0.05). In addition, they had a higher proportion of catheter placement in the femoral vein (59% *vs* 40% with $P < 0.05$), especially with inserting the central line outside the ICU setting (41% *vs* 24% with $P < 0.05$) than with the control group. The patients who developed CLABSI had a significantly longer central line insertion duration than those who did not develop CLABSI ($P < 0.001$). Patients who developed CLABSI had a substantially higher mortality rate than the control group (44% *vs* 27%, $P < 0.01$).

Table 2 showed the microbiological causes of CLABSI. Gram-negative bacteria were the most common organisms isolated from CLABSI (56%), followed by gram-positive bacteria (41%). Candida was isolated from 3% of the isolates. The gram-positive coagulase-negative *Staphylococcus* (18%) were the most common organisms isolated, followed by the gram-negative *Acinetobacter* (15%), gram-positive *Enterococci* (15%), *Pseudomonas* (12%), *Escherichia* (12%), *Klebsiella* (9%), and *Staphylococcus aureus* (6%). We observed MDR organisms in 59% (20/34) of all CLABSI cases (gram-positive and gram-negative organisms).

Table 3 showed the antibiotic sensitivity pattern for the common gram-positive organisms causing CLABSI in the current study. Their sensitivity rate to both Linezolid and Daptomycin was 100%. *Staphylococcus aureus* and Coagulase-negative *Staphylococci* were 100% sensitive to vancomycin. Table 3 also showed other antibiotics sensitivities for common gram-positive organisms. We showed the antibiotic sensitivity pattern for the common gram-negative organisms causing CLABSI in the current study in Table 4. Effective of Colistin was present in all the four main strains of the isolates. *Pseudomonas aeruginosa* had 100% sensitivity to piperacillin-tazobactam, ceftazidime, cefepime, meropenem, ciprofloxacin, gentamicin, and amikacin. *Acinetobacter baumannii* isolates had a high level of resistance. Three out of the five isolates (60%) were MDR and resistant to most tested antibiotics. However, all *Acinetobacter baumannii* isolates were sensitive to colistin (100% sensitivity). Three out of the four *Escherichia coli (E. coli)* isolates (75%) were MDR; one was *ESBL* producers (25%), and two were CRE (50%). *Klebsiella pneumoniae* isolates also had a high resistance level; two out of the three isolates (66%) were CRE. However, all *Klebsiella pneumoniae* isolates (100%) retain their sensitivity to colistin.

Compliance to prevention bundle

Figure 2 showed the overall compliance with the CLABSI prevention bundle for central line insertion. It showed significant improvement throughout the study period. This improvement was related to the enhancement of adherence to the optimum selection of the anatomical insertion site. Compliance was deficient (45%) at the beginning of the study in 2016 due to a lack of experience in inserting the central line in the subclavian or internal jugular by the ICU residents covering the duty. Therefore, training the ICU residents to optimize the insertion site improved adherence to the proper selection of insertion sites to reach 83% by the end of 2018. Figure 3 showed the overall compliance with the CLABSI prevention bundle for the care and maintenance of the central lines. It showed the overall improvement during the study period, predominantly the appropriate dressing replacement and hub scrub practice, which accomplished through reinforcement of the practice by the observing infection control liaison nurse.

DISCUSSION

CLABSIs result in many preventable deaths each year with a high financial cost and load on the healthcare system. Nevertheless, these infections are preventable. Therefore, implementing a prevention program is of paramount importance. After we implemented the CLABSIs prevention program, the rate of CLABSI in our ICU decreased from 4.7/1000 central-catheter days at baseline (at the beginning of implementing the CLABSI prevention program) to 1.4/1000 central catheter-days at the end of the study. This achieved rate is comparable to the international benchmark of NHSN, with its reported median CLABSI rates of 1.25/1000 central-catheter days [7]. Many previous studies showed a similar reduction of CLABSI by reinforcing the CLABSI prevention program[15-18]. For example, a promising report published by Al Abdulla illustrated a significant decline of CLABSI from 6 per 1000 central line days during 2011 to 0.3 per 1000 central line days in 2016 in ICU among one of the major teaching hospitals in Saudi Arabia[19].

The current study revealed many factors that increased the risk of CLABSI. The rate of CLABSI in our ICU increased when using femoral access. It also increased with the hospitalization duration before the ICU admission and the longer ICU admission

Table 2 The microbiological causes of central line-associated bloodstream infections

Organism	Number (percentage out of total 34), *n* (%)	MDR organism, *n* (%)
Gram negative bacteria		
Acinetobacter	5 (15)	3 MDR[1] (60)
Escherichia coli	4 (12)	1 ESBL (25) 2 CRE (50)
Pseudomonas	4 (12)	2 CRP (50)
Klebsiella	3 (8)	2 CRE (66)
Morganella	1 (3)	
Serratia	1 (3)	
Stenotrophomonas maltophilia	1 (3)	
Total gram negative	19 (56)	10 (53)
Gram positive bacteria		
Enterococcus	5 (15)	3 VRE (60)
Coagulase negative *Staphylococcus*	6 (18)	6 MRCONS (100)
Staphylococcus aureus	2 (5)	1MRSA (50)
Streptococcus viridans	1 (3)	
Total gram positive	14 (41)	10 (71)
Candida species	1 (3)	
Total	34 (100)	20/34 (59)

[1]Multi-drug resistance: Resistant to > 3 classes of antimicrobial.
CRE: Carbapenem resistant enterobacteriasae; ESBL: Extended spectrum B lactamase producer; CRP: Carbapenem resistant pseudomonas; VRE: Vancomycin resistant enterococcus; MRCONS: Methicillin resistant coagulase negative staphylococcus; MRSA: Methicillin resistant staphylococcus aureus; MDR: Multi-drug resistance.

Table 3 Antibiotics sensitivity percentage of the common gram-positive causative organisms for central line-associated bloodstream infections in our study

Antibiotic	*Staphylococcus aureus*, *n* (%) = 2 (5)	Coagulase negative *Staphylococcus*, *n* (%) = 6 (18)	*Enterococcus*, *n* (%) = 5 (15)
Penicillin	0/2 (0)	0/6 (0)	1/5 (20)
Ampicillin			1/5 (20)
Erythromycin	1/2 (50)	0/6 (0)	0/5 (0)
Clinamycin	1/2 (50)	3/6 (50)	
Trimethoprim sulphamethoxazole	1/2 (50)	1/6 (16)	
Vancomycin	2/2 (100)	6/6 (100)	2/5 (40)
Cloxacillin	1/2 (50)	0/6 (0)	
Tetracycline	1/2 (50)	3/6 (50)	
Linazolid	2/2 (100)	6/6 (100)	5/5 (100)
Daptomycin	2/2 (100)	6/6 (100)	5/5 (100)

duration before the central line's insertion. The site of insertion also affects the risk of CLABSI. The risk increased when the line insertion setting was outside the ICU, such as the Emergency Room, which commonly happened if there is a long waiting time before transferring the patient to the ICU.

The insertion site is a significant risk factor to develop CLABSI. Previously published data showed an increased risk of developing infectious complications when

Table 4 Antibiotics sensitivity percentage of the common gram-negative causative organisms for central line-associated bloodstream infections in our study

Antimicrobial agent	*Acinetobacter baumanii*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Klebsiella*
	n (%) = 5 (15)	*n* (%) = 4 (12)	*n* (%) = 4 (12)	*n* (%) = 3 (9)
Piperacillin tazobactam	2/5 (40)	4/4 (100)		
Ceftriaxone			1/4 (25)	1/3 (33)
Ceftazidime	2/5 (40)	4/4 (100)	1/4 (25)	1/3 (33)
Cefipime	2/5 (40)	4/4 (100)	1/4 (25)	1/3 (33)
Merpenem	2/5 (40)	4/4 (100)	2/4 (50)	1/3 (33)
Imipenem	2/5 (40)	2/4 (50)	2/4 (50)	1/3 (33)
Ciprofloxacin	2/5 (40)	4/4 (100)	1/4 (25)	1/3 (33)
Gentamicin	2/5 (40)	4/4 (100)	1/4 (25)	1/3 (33)
Amikacin	2/5 (40)	4/4 (100)	1/4 (25)	1/3 (33)
Colistin	5/5 (100)	4/4 (100)	4/4 (100)	3/3 (100)

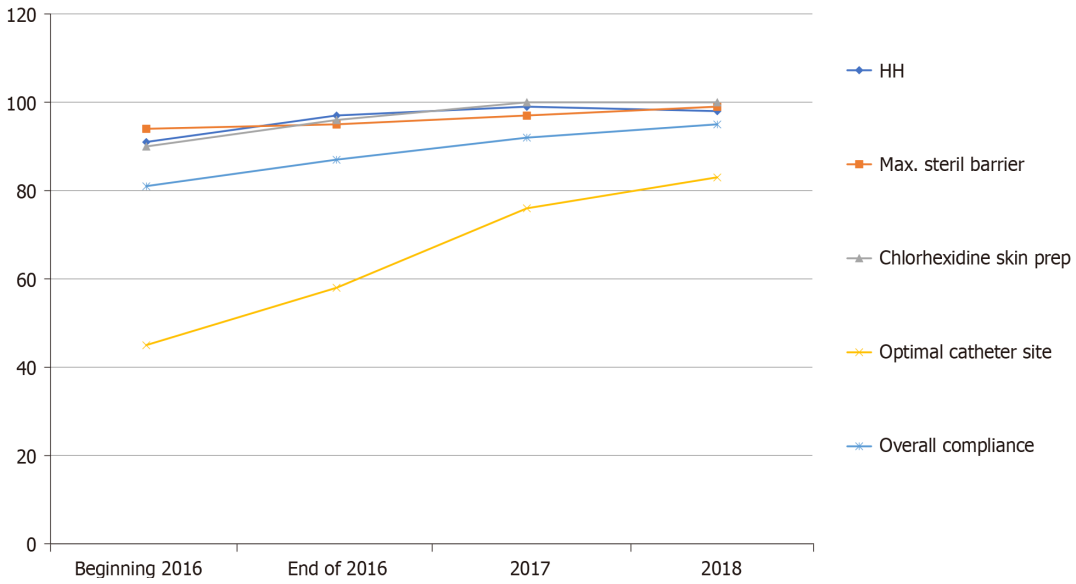

Figure 2 Compliance to central line-associated bloodstream infection prevention bundle for insertion.

using femoral access, consistent with our finding[20-22]. Accordingly, we should avoid the femoral access site as much as possible to avoid increasing the rates of CLABSI and thrombotic events compared to subclavian and internal jugular sites. The subclavian site is associated with the lowest rate of CLABSI, as observed in the current study and other studies. Nevertheless, occasionally, it is difficult to use the subclavian and internal jugular sites due to coagulopathies or anatomical difficulties such as distorting anatomical features[23]. In the current study, the duration of central line insertion longer than a week was also a significant risk factor to develop CLABSI. This finding agreed with Baier *et al*[24], who found that central line insertion duration for more than eight days was a significant risk factor to develop CLABSI.

In the current study, the microbial profile showed a predominance of the gram-negative bacteria (56%), with a high percentage of the MDR strains. Similar data obtained from previously published studies worldwide illustrated the change in the gram-negative carriage's global tendency rather than the gram-positive. These observations were greatly accentuated in the ICU setting due to the high exposure to nosocomial microorganisms[25-29]. Addressing the bacterial profile and the prevalence of MDR bacteria causing CLABSI in patients admitted to ICUs and their antimicrobial resistance profile may help the physicians make a rapid management decision and start the most proper antibiotics until the result of bacterial culture and

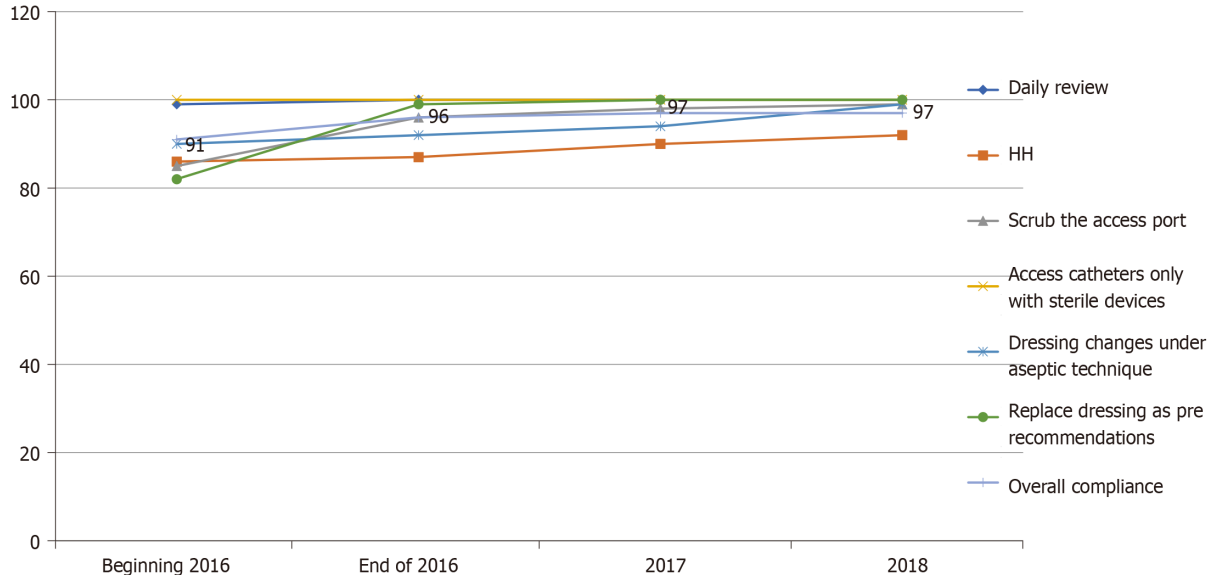

Figure 3 Compliance to central line-associated bloodstream infection prevention bundle for care and maintenance (2015-2018).

antibiotic sensitivity pattern becomes available.

Limitations

The current study had certain limitations. We conducted the survey in a single centre in Bahrain. Consequently, the results cannot be generalized to other public or private hospital settings. We did not address the patients' clinical details, which could be a critical risk factor to develop CLABSI. However, despite the study's limitations, it can provide the clinicians with valuable data concerning the incidence rates and the prevalence of CLABSI in Bahrain, reflecting the rest Arabian Gulf region's status.

CONCLUSION

Given such a promising trend of reducing CLABSI in our ICU through reinforcement of the unit's prevention program, we believe that it is possible to achieve lower CLABSI rates. To attain such desired outcomes, we need to reinforce the ICU doctors to select the optimal site to insert the central line, avoid the femoral access, and reinforce the central line's insertion inside the ICU only by a trained ICU physician. As the microbial profile of CLABSI in our ICU showed a predominance of the gram-negative bacteria with a significant proportion of MDR organisms, we advise using broad-spectrum gram-negative coverage (in addition to gram-positive) as part of the empirical antibiotics therapy in patients with suspected CLABSI.

ARTICLE HIGHLIGHTS

Research background

The central venous line is an essential component in monitoring and managing critically ill patients. Central line-associated bloodstream infection (CLABSI) are BSIs developed in patients with central venous catheters. The presence of these infections is associated with a higher risk of morbidity and mortality.

Research motivation

Because we do not have enough data about the rate of CLABSI and the causative organisms in the Kingdom of Bahrain, we would like to estimate the magnitude of the problem in our intensive care units (ICUs). Knowing the microbial profile of CLABSI in our ICU help proper use of the empirical antibiotics therapy in patients with suspected CLABSI.

Research objectives
The study aimed to define the trends of the rates of CLABSI over four years, its predicted risk factors, aetiology, and the antimicrobial susceptibility of the isolated pathogens

Research methods
The study was a prospective case-control study, performed according to the guidelines of the Center for Disease Control surveillance methodology for CLABSI in patients admitted to the adult ICU and auditing the implementation of its prevention bundle.

Research results
Thirty-four CLABSI identified over the study period, giving an average CLABSI rate of 3.2/1000 central line days. The infection's time trend displayed significant reductions over time concomitantly with the CLABSI prevention bundle's reinforcement from 4.7/1000 central line days at the beginning of 2016 to 1.4/1000 central line days by 2018. The most frequently identified pathogens causing CLABSI in our ICU were Gram-negative organisms (59%). The most common offending organisms were *Acinetobacter*, *Enterococcus*, and *Staphylococcus epidermidis*, each of them accounted for 5 cases (15%). Multidrug-resistant organisms contributed to 56% of CLABSI. Its rate was higher when using femoral access and longer hospitalisation duration, especially in the ICU. Insertion of the central line in the non-ICU setting was another identified risk factor.

Research conclusions
Implementing the prevention bundles reduced CLABSI significantly in our ICU. Reinforcing CLABSI prevention bundle implementation is crucial to substantially reducing the CLABSI rate in the ICU setting.

Research perspectives
We need to study the mechanism of bacterial resistance among patients infected with CLABSI. We also need to study viral coinfection and its effects on morbidity and mortality. We should compare our data with the data from other countries to generalize the obtained results.

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ORIGINAL ARTICLE

Observational Study

Reduced exercise capacity and self-perceived health status in high-risk patients undergoing lung resection

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Author contributions: Valenza MC was the guarantor and designed the study; Cabrera-Martos I, Rodríguez-Torres J and López-López L participated in the acquisition, analysis and interpretation of the data and drafted the initial manuscript; Quero-Valenzuela F and Cahalin LP revised the article critically for important intellectual content.

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Abstract

BACKGROUND

Lung resection represents the main curative treatment modality of non-small cell lung cancer. Patients with high-risk to develop postoperative pulmonary complications have been classified as "high-risk patients." Characterizing this population could be important to improve their approach and rehabilitation.

AIM

To identify the differences between high and low-risk patients in exercise capacity and self-perceived health status after hospitalization.

METHODS

A longitudinal observational prospective cohort study was carried out. Patients undergoing lung resection were recruited from the "Hospital Virgen de las Nieves" (Granada) and divided into two groups according to the risk profile criteria (age ≥ 70 years, forced expiratory volume in 1 s ≤ 70% predicted, carbon monoxide diffusion capacity ≤ 70% predicted or scheduled pneumonectomy). Outcomes included were exercise capacity (Fatigue Severity Scale, Unsupported Upper-Limb Exercise, handgrip dynamometry, Five Sit-to-stand test, and quadriceps hand-held dynamometry) and patient-reported outcome (Euroqol-5 dimensions 5 Levels Visual Analogue Scale).

RESULTS

In total, 115 participants were included in the study and divided into three groups: high-risk, low-risk and control group. At discharge high-risk patients

Data sharing statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to their containing information could compromise the privacy of research participants.

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presented a poorer exercise capacity and a worse self-perceived health status ($P < 0.05$). One month after discharge patients in the high-risk group maintained these differences compared to the other groups.

CONCLUSION

Our results show a poorer recovery in high-risk patients at discharge and 1 mo after surgery, with lower self-perceived health status and a poorer upper and lower limb exercise capacity. These results are important in the rehabilitation field.

Key Words: Non-small cell lung cancer; Exercise tolerance; health status; Patient-reported outcomes; Postoperative quality of life; Exercise test

Core Tip: Lung cancer is the leading cause of cancer death among men and the second among women worldwide. A revolutionary change in this approach is being witnessed with less invasive techniques. However, it is still associated with a high incidence of postoperative pulmonary complications, which could lead to a reduced exercise capacity. Patients with higher risk to develop postoperative pulmonary complications have been classified as "high-risk patients," and they could present a lower exercise capacity and self-perceived health status.

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INTRODUCTION

Lung cancer is the leading cause of cancer death among men and the second among women worldwide. Non-small cell lung cancer represents 80% of all lung cancer cases, and lung resection still represents the main curative treatment modality[1].

In the last years, a revolutionary change in this approach is being witnessed[2] with less invasive techniques. However, it is still associated with a high incidence of postoperative pulmonary complications (PPCs), particularly common in patients with comorbid conditions and elderly individuals[2,3]. PPCs include (1) respiratory failure, (2) pneumonia, (3) atelectasis requiring bronchoscopy, (4) myocardial infarction, and (5) arrhythmias requiring intravenous treatment. Patients with a higher risk to develop PPCs have been classified as "high-risk patients," and many authors have focused specifically on the approach for these patients. Besides being a clinical marker for decreased survival[3], PPCs have been associated with a longer length of hospital stay and a negative influence on the patient's ability to resume usual daily physical activity [3].

Lung cancer patients are known to frequently exhibit poor exercise capacity, low physical activity levels and an impaired health-related quality of life that can be further aggravated after lung resection surgery[4]. Pulmonary resection causes a decrease in the lung volume, which is linked to the pain related to the chest wall, the respiratory muscle injury and the loss of muscle strength caused by bed rest, resulting in a disturbance of cardiopulmonary function and can lead to this postoperative exercise limitation. Exercise capacity has been associated with PPCs, showing a lower VO_2max or a major extent of lung tissue resection in patients with PPC after curative lung resection[5]. However, other factors could affect exercise capacity like quadriceps weakness[6], illness perception[7], depressive symptoms or quality of life[8]. Moreover, we have not found specific studies based on the upper and lower limb evaluation. Functional exercise testing offers an opportunity to objectively measure patients' exercise capacities, to identify exercise limitations that would otherwise remain undetected and to identify self-perceived capacity[9]. Moreover, the survivor's

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perception of functional capacity and health status provides important information beyond objective pulmonary function testing. Despite this, we have not found studies about functional exercise limitation in these patients depending on their risk profile.

To stratify patients undergoing lung resection could be important to improve the specific rehabilitation programs and targeting these patients. Therefore, the aim of this study was to identify the differences between high and low-risk patients in exercise capacity and self-perceived health status at discharge and in the following month.

MATERIALS AND METHODS

Study population and data collection

A longitudinal observational prospective cohort study has been carried out. Patients undergoing lung resection were recruited from the Thoracic Surgery Service of the "Hospital XXX" (XXX) between April 2017 and July 2018. They had to be between 18 and 80-years-old, and they were informed about the study purpose. Patients were excluded if they presented with cognitive impairment, mental instability, orthopedic pathologies that limited the test performance or neurologic pathologies. Informed consent was obtained from all individual participants included in the study. The study protocol was reviewed and approved by the XXX Ethics Committee (XXX). The STROBE guideline was followed during the course of the research[10].

Group assignment

Lung resection patients were divided into two groups according to the risk profile criteria[11]. High risk was defined as one or more of the following: age ≥ 70 years, forced expiratory volume in 1 s ≤ 70% predicted, carbon monoxide diffusion capacity ≤ 70% predicted or scheduled pneumonectomy. The maximum and minimal age of both lung resection groups were used to calculate the age range where control group should be included.

Outcome measures

Data collecting was performed before lung resection, at discharge and 1 mo after surgery, always by the same investigators previously trained and blinded to the patient's allocation. All patients followed a similar recovery pathway: after lung surgery, patients remained in the resuscitation unit 24 h and followed a similar analgesic treatment during their hospital stay, with non-steroidal anti-inflammatories. A normalized interview and an initial assessment were carried out when inclusion criteria were confirmed. Some data were collected from the medical history: anthropometric data, comorbidities (Charlson comorbidities index)[12] and operative duration. Respiratory capacity was assessed by spirometry[13] and anxiety and depression through the Hospital Anxiety and Depression Scale[14].

Main outcomes included were exercise capacity and self-perceived health status.

Exercise capacity

Exercise capacity included the self-perceived fatigue and a lower and upper limb evaluation.

To evaluate the fatigue severity, the Fatigue Severity Scale was used. The Fatigue Severity Scale[15] was developed to measure the impact of disabling fatigue on daily functioning. The instrument consists of nine items, and the total score ranges between 9 and 63. A higher score indicates more self-perceived fatigue. Minimal clinically important difference (MCID) for Fatigue Severity Scale has been reported to be 20.2.

Lower limb assessment: A hand-held dynamometer (Lafayette Manual Muscle Testing System, model 01163, Lafayette, IN, United States) was used to assess the lower limbs[16]. The test was performed with the patient seated with his/her knees and hips flexed at 90°. Resistance was applied to the anterior tibia during 5 s of maximal muscle contraction. Three trials were done in the dominant leg, and the highest value in Newton was selected for the analysis. An MCID of 46 Newton has been established.

The Five Sit-to-Stand Test (5STS) has been previously used to evaluate exercise tolerance in respiratory patients[17]. It was performed with standard height (46 cm) chair without armrests. Participants were asked to stand up all the way and sit down landing firmly, as fast as possible, five times without using the arms, and the time taken was recorded as the participant's score. The self-perceived dyspnea and lower limb fatigue were recorded, previously and after the test, using the modified version

Table 1 Baseline characteristics of the groups

		Low-risk group, *n* = 39	High-risk group, *n* = 44	Control group, *n* = 32	*F*
Age in yr		52.18 (13.91)	69.91 (7.97)	48.44 (13.57)	37.171[a,c]
Sex, % males		31.88	42.03	26.09	0.704
BMI		27.08 (5.02)	26.50 (4.56)	26.08 (4.42)	0.405
Length of hospital stay		6.56 (1.82)	6.95 (2.03)	-	0.362
Charlson index		4.10 (2.38)	4.93 (2.43)	1.38 (1.60)	22.861[b,c]
Operation duration in min		208.79 (86.34)	208.81 (52.29)	-	0.999
Surgical procedure, %VATS		74.5	72.4	-	0.722
Spirometric parameters	FEV_1	2.71 (0.83)	1.60 (0.50)	2.88 (0.86)	18.301[a,c]
	FVC	3.57 (1.02)	2.5 (1.05)	3.59 (0.92)	8.605[a,c]
HADS	Anxiety	3.95 (2.71)	4.64 (2.95)	2.38 (2.94)	5.866[b,c]
	Depression	0.92 (1.49)	4.36 (3.84)	0.31 (0.78)	28.964[a,b,c]
	Total	4.87 (3.34)	9 (5.65)	2.69 (3.59)	20.253[a,b,c]

Variables are expressed as mean (SD) or percentage.

[a]Significant differences between low-risk and high-risk groups.

[b]Significant differences between low-risk group and control group.

[c]Significant differences between high-risk group and control group. BMI: Body mass index; FEV_1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; HADS: Hospital Anxiety and Depression Scale; VATS: Video-assisted thoracic surgery.

of the Borg Scale[18]. The MCID for the 5STS has been reported to be 5 s.

Upper limb assessment: Handgrip strength is a reliable marker of peripheral muscle strength[19]. A handgrip dynamometer (TEC-60; Productos Técnicos, EE.UU.) was used to do three in the dominant hand, and the peak force in Newton was recorded. A difference of 49 Newtons has been established as the MCID.

The unsupported upper-limb exercise (UULEX) test is an incremental test developed by Takahashi *et al*[20] to measure peak unsupported arm exercise capacity. The subjects need to move a bar from their lap to the highest level they can reach until exhaustion. The total score was the total duration of the test in seconds. The self-perceived dyspnea and lower limb fatigue were recorded using the modified version of the Borg Scale[18]. The MCID for Borg scores was set at 1 score.

Patient-reported outcome

The Euroqol-5dimensions 5 Levels (EQ-5D-5L) was used to evaluate the general health status. The questionnaire comprises two parts. The first section includes five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each with five levels (no problem, slight problems, moderate problems, severe problems and extreme problems), and the result is an index. A value of 1 indicates full health and a value of less than zero indicates a quality of life worse than death. The second part includes a Visual Analogue Scale [EQ-5D-5L visual analogue scale (VAS)], which records the responder's self-evaluated health between 0 (the worst imaginable health) and 100 (the best imaginable health)[21]. The MCID for the EQ-5D-5L index ranges from 0.05 and for the EQ-5D-5L VAS has been reported to be 8 points.

Statistical analysis

Statistical power calculation (GPower version 3.1.9.2 for Windows) was performed at the conception stage utilizing expected differences in the primary endpoint (EQ-5D-5L VAS) based on our previous pilot study in related subjects that employed similar methodology (unpublished). This suggested that a sample size of 30 in each group will have 80% power to detect a probability of 0.5. To allow for a generous safety margin, we decided to aim for approximately 35 patients in each study group.

Statistical Package SPSS version 20.0 (International Business Machines, Armonk, NY: http://www-01.ibm.com/support/docview.wss?uid=swg21476197) was used to analyze the data obtained. Descriptive statistics (mean ± SD) or percentages (%) were used to describe sample baseline characteristics. The Kolmogorov–Smirnov test was

Table 2 Exercise capacity and self-perceived health status before lung resection

		Low-risk group, *n* = 35	High-risk group, *n* = 40	Control group, *n* = 32	*F*
Exercise capacity					
FSS		19.72 (12.99)	28 (19.49)	9.00	16.469 1[a,b,c,1]
Lower limb assessment					
Hand-held dynamometry		107.24 (51.59)	112.31 (47.99)	213.01 (60.58)	43.669 1[b,c,1]
5STS	Dyspnea baseline	0.41 (1.33)	0.32 (1.12)	0	1.478
	LL fatigue baseline	0.36 (1.20)	1.23 (2.38)	0	5.829 1[a,c,1]
	Time	12.43 (4.49)	18.23 (14.27)	9.87 (2.66)	8.202 1[a,b,c,1]
	Dyspnea post-test	1.03 (1.98)	0.86 (1.79)	0	4.098[b,c]
	LL fatigue post-test	0.72 (1.57)	1.77 (2.94)	0	7.297 1[a,b,c,1]
Upper limb assessment					
Handgrip dynamometry		329.46 (93.08)	291.57 (117.29)	380 (79.31)	7.178 1[b,c,1]
UULEX test	Dyspnea baseline	0.44 (1.50)	0.38 (1.03)	0	1.64[c]
	UL Fatigue baseline	1.00 (1.59)	1.13 (1.82)	0	6.322 1[b,c,1]
	Time	442.50 (230.69)	187.50 (201.80)	555.00 (124.75)	23.245 1[a,b,c,1]
	Dyspnea post-test	2.19 (2.54)	0.88 (1.59)	0.25 (0.98)	7.439 1[b,1]
	UL Fatigue post-test	6.56 (2.19)	6.38 (2.19)	5.50 (2.66)	1.283
Self-perceived health status					
EQ-5D-5L VAS		86.81 (16.99)	66.23 (22.94)	94.69 (4.91)	23.147 1[a,c,1]
EQ-5D-5L index		1.00	0.76 (0.43)	1.00	11.238[a,b,c]

Variables are expressed as mean (SD).
[a]Significant differences between low-risk and high-risk groups.
[b]Significant differences between low-risk group and control group.
[c]Significant differences between high-risk group and control group.
[1]Global *P* value adjusted by multiplicity. 5STS: Five sit-to-stand test; EQ-5D-5L: Euroqol 5 dimensions 5 levels; FSS: Fatigue severity scale; LL: Lower limb; UL: Upper limb; UULEX: Unsupported upper-limb exercise; VAS: Visual analogue scale.

performed to assess continuous data normality, prior to statistical analysis. Normally distributed baseline demographic variables were compared by analysis of variance (ANOVA). The one-way ANOVA was used for baseline data. For each outcome measure, a three (high-risk, low-risk, control) × two (admission and discharge or discharge and follow-up) mixed ANOVA was performed. If the three × two ANOVA showed a significant interaction for each variable, then Bonferroni's post hoc test was used to identify the specific mean differences. A 95% confidence interval was used for statistical analysis. A *P* value of less than 0.05 was considered statistically significant. Global *P* values were adjusted for multiplicity with the Bonferroni method.

RESULTS

A total of 115 participants were deemed eligible and accepted to participate in this study. The distribution of participants is shown in Figure 1. Baseline characteristics of the sample are described in Table 1.

Significant differences were found in age between high-risk and the other groups. The low-risk and high-risk groups presented a similar length of hospital stay (P = 0.320) and Charlson index. Surgical procedures were similar in both groups, with most of them undergoing video-assisted thoracic surgery (74.5% *vs* 72.4%). As expected, forced expiratory volume in 1 s and forced vital capacity presented significant differences between low and high-risk groups (P < 0.05). Hospital Anxiety and Depression Scale presented poorer scores in the high-risk group.

Table 3 Exercise capacity and self-perceived health status differences at discharge among and between groups

		Low-risk group, *n* = 29			High-risk group, *n* = 36			Control group, *n* = 32			*F*
		Mean change	95%CI	*P* value among groups	Mean change	95%CI	*P* value among groups	Mean change	95%CI	*P* value among groups	
Exercise capacity											
FSS		-4.17 (16.76)	(-10.02, 1.67)	0.156	-8.00 (18.56)	(-14.10, -1.90)	0.012	0	-	1	21.735 1[a,b,c,1]
Lower limb assessment											
Hand-held dynamometry		7.20 (24.49)	(2.11, 16.52)	< 0.001	22.94 (31.12)	(12.41, 33.47)	< 0.001	-0.05 (0.85)	(-0.35, 0.25)	0.729	15.8 1[b,c,1]
5STS test	Dyspnea baseline	-0.64 (1.45)	(-1.15, -0.12)	0.017	-1.05 (2.14)	(-1.75, -0.35)	0.004	0	-	1	4.122 1[b,c,1]
	LL fatigue baseline	-0.30 (1.28)	(-0.76, 0.15)	0.186	-0.42 (1.81)	(-1.02, 0.17)	0.160	0	-	1	8.735 1[a,b,c]
	Time	-3.30 (7.28)	(-5.88, -0.72)	0.014	-7.84 (11.39)	(-11.58, -4.09)	< 0.001	-0.06 (0.50)	(-0.24, 0.13)	0.531	14.818 1[a,b,c,1]
	Dyspnea post-test	-0.91 (2.02)	(-1.63, -0.19)	0.015[1]	-2.74 (2.92)	(-3.69, -1.78)	< 0.001	0	-	1	20.128 1[a,b,c,1]
	LL fatigue post-test	-0.42 (2.00)	(-1.13, -0.28)	0.008[1]	-1.74 (2.77)	(-2.65, -0.83)	< 0.001	0	-	1	23.570 1[a,b,c,1]
Upper limb assessment											
Handgrip dynamometry		34.14 (46.47)	(16.46, 51.81)	0.124	28.05 (40.84)	(14.24, 41.87)	< 0.001	15.28 (64.29)	(-7.89, 38.46)	0.188	7.663 1[b,c,1]
UULEX test	Dyspnea baseline	-1.62 (2.78)	(-3.10, -0.14)	0.034[1]	-2.00 (2.15)	(-3.24, -0.76)	0.004	0	-	1	11.262 1[b,c,1]
	UL fatigue baseline	-0.75 (2.74)	(-2.21, 0.71)	0.292	-4.29 (3.27)	(-6.17, -2.39)	< 0.001	0	-	1	37.713 1[a,b,c,1]
	Time	202.50 (204.20)	(93.68, 311.31)	0.002	145.70 (232.63)	(11.39, 280.03)	0.036	-3.75 (40.14)	(-18.22, 10.72)	0.601	86.717 1[a,b,c,1]
	Dyspnea post-test	-1.87 (3.44)	(-3.71, -0.04)	0.046	-2.29 (2.05)	(-3.47, -1.10)	0.001	0	-	1	17.854 1[b,c,1]
	UL fatigue post-test	0 (3.40)	(-1.81, 1.81)	1	-1.71 (2.05)	(-2.90, -0.53)	0.008	0	-	1	9.688 1[a,c,1]
Self-perceived health status											
EQ-5D-5L VAS		14.35 (20.48)	(3.82, 24.88)	0.011	11.10 (22.07)	(0.77, 21.43)	0.037	-0.50 (2.64)	(-1.45, 0.45)	0.292	38.091 1[a,b,c,1]
EQ-5D-5L index		0.14 (0.35)	(0.07,0.21)	< 0.001	0.28 (0.46)	(0.11, 0.46)	0.003	0	-	1	9.686 1[a,c,1]

Variables are expressed as mean (SD).

[a]Significant differences between low-risk and high-risk groups.

[b]Significant differences between low-risk group and control group.

[c]Significant differences between high-risk group and control group.

[1]Global *P* value adjusted by multiplicity. 5STS: Five sit to stand test; CI: Confidence interval; EQ-5D-5L: Euroqol 5 dimensions 5 levels; FSS: Fatigue severity scale; LL: Lower limb; UL: Upper limb; UULEX: Unsupported upper-limb exercise; VAS: Visual analogue scale.

Exercise capacity and self-perceived health status scores before lung resection are presented in Table 2.

Significant differences were found in fatigue severity and lower limb and upper limb strength between groups. The 5STS and UULEX also presented significant differences between groups, with poorer results in the high-risk group. A significant poorer self-perceived health status was shown in the high-risk group.

Exercise capacity and self-perceived health status differences at discharge among and between groups are presented in Table 3.

The high-risk group presented a significant increase in the fatigue severity at discharge ($P = 0.012$) and a poorer strength ($P < 0.001$). In the 5STS test, the high-risk group obtained significantly poorer results than the other groups, with a significant clinical difference in dyspnea and time. In the UULEX, both resection groups presented a significant statistical and clinical increase in the dyspnea levels ($P < 0.05$). However, only the high-risk group presented a significant increase in upper limb fatigue pretest ($P < 0.001$). The time reached in the UULEX was lower in both groups at discharge ($P < 0.05$), and a significant increase in upper limb fatigue and dyspnea post-test were found in the high-risk group ($P < 0.05$). The EQ-5D-5L VAS and index decreased in both groups after the intervention ($P < 0.05$), and it was clinically relevant in the high-risk group, which also presented significant differences in the between groups analysis.

Exercise capacity and self-perceived health status differences 1 mo after discharge, among and between groups are presented in Table 4.

Fatigue improved in the high and low-risk groups. However, the increase was not statistically or clinically significant ($P > 0.05$). The high-risk group presented poorer results in the 5STS and in the UULEX. The high-risk group increased, statistically and clinically significant, ($P = 0.004$), and the low-risk groups reduced ($P = 0.024$) the dyspnea. The EQ-5D-5L VAS and index improved significantly in the low-risk group ($P = 0.015$), with an improvement that clinically relevant. Significant differences were found between groups in the EQ-5D-5L VAS.

DISCUSSION

The aim of this study was to identify the differences between high and low-risk patients in exercise capacity and self-perceived health status at discharge and in the following month. Moreover, to compare the results with a control group is important to know if this population will reach the normative values of a similar population. Our findings show a poorer recovery in high-risk patients, with more self-perceived fatigue, a lower self-perceived health status and a poorer upper and lower limb exercise capacity. These results represent an advance in the field of rehabilitation because it allows the design of specific rehabilitation programs for each risk group.

The sample of subjects included in this study was representative of the general population undergoing lung resection, with similar sociodemographic characteristics [22].

Our results have shown significant differences in self-perceived fatigue between both surgery groups, with a higher score in the high-risk group. The occurrence of fatigue has been described following elective surgery as a negative predictor for the functional recovery[23]. Patients with persistent deficits in muscle performance will be more rapidly fatigued following motor tasks and will probably report higher levels of self-perceived fatigue. There are several possible mechanisms involved in fatigue, one of which is the release of proinflammatory cytokines by the tumor and its microenvironment. Our lung resection patients improved their fatigue level 1 mo after surgery. However, the results do not reach the control group scores. A vicious cycle may thereby be created in which these individuals avoid engaging in physical activity, further reducing their cardiorespiratory fitness and increasing their fatigability.

Our study shows poorer results in lower limb exercise capacity in the high-risk group. Similar studies[24] have shown that after lung resection surgery patients experience a decrease in maximal exercise tolerance during the first month after the intervention. This observed impairment in exercise tolerance has been reported to be induced by the cancer treatment or associated immobility; however, previous studies have suggested that deficits in exercise tolerance are likely to be apparent before surgery[24]. This aspect goes in line with our study, which suggests that exercise capacity could be determined prior to the intervention by the risk profile patient. This is important because some patients may regard immediate postoperative complications as an acceptable risk but are not prepared to accept significant postoperative

Table 4 Exercise capacity and self-perceived health status differences, 1 mo after discharge, among and between groups

		Low-risk group, *n* = 29			High-risk group, *n* = 36			Control group, *n* = 32			*F*
		Mean change	95%CI	*P* value, among groups	Mean change	95%CI	*P* value among groups	Mean change	95%CI	*P* value among groups	
Exercise capacity											
FSS		2.84 (16.33)	(-3.90, 9.58)	0.393	2.50 (14.78)	(-3.74, 8.74)	0.416	0	-	1	18.606 1[b,c,1]
Lower limb assessment											
Hand-held dynamometry		-15.56 (31.54)	(-32.37, 1.24)	0.067	-18.57 (27.73)	(-34.58, -2.56)	0.026	0.01 (9.61)	(-2.29, 4.64)	0.494	23.129 1[b,c,1]
5STS test	Dyspnea baseline	0.69 (1.98)	(-0.00, 1.39)	0.051	0.37 (2.26)	(-0.37, 1.11)	0.321	0	-	1	4.152[c]
	LL fatigue baseline	0 (2.15)	(-0.76, 0.76)	1	0.21 (1.49)	(-0.28, 0.70)	0.390	0	-	1	7.650 1[b,c,1]
	Time	1.75 (8.08)	(-1.10, 4.62)	0.221	3.95 (14.58)	(-0.84, 8.74)	0.104	-0.01 (0.57)	(-0.21, 0.20)	0.931	18.333 1[a,b,c,1]
	Dyspnea post-test	1.12 (1.87)	(0.46, 1.78)	0.002	0.68 (1.47)	(0.20, 1.17)	0.007[1]	0	-	1	26.453 1[a,b,c,1]
	LL fatigue post-test	0.39 (1.54)	(-0.15, 0.94)	0.151	0.11 (2.27)	(-0.64, 0.85)	0.777	0	-	1	47.483 1[a,b,c,1]
Upper limb assessment											
Handgrip dynamometry		3.80 (58.47)	(-28.58, 36.18)	0.805	3.21 (69.72)	(-37.04, 43.47)	0.866	-16.24 (64.27)	(-39.42, 6.93)	0.163	15.494 1[b,c,1]
UULEX test	Dyspnea baseline	1.06 (3.29)	(-0.69, 2.82)	0.217	-0.60 (2.87)	(-2.66, 1.46)	0.526	0	-	1	54.082 1[a,b,c,1]
	UL fatigue baseline	0.94 (3.02)	(-0.67, 2.55)	0.234	0 (3.27)	(-2.34, 2.34)	1	0	-	1	194.932 1[a,b,c,1]
	Time	-225.00 (191.62)	(-327.11, -122.89)	< 0.001	-240.00 (187.62)	(-374.00, -105.00)	0.003	7.50 (80.28)	(-21.44, 36.44)	0.601	19.744 1[a,b,c,1]
	Dyspnea post-test	2.18 (2.61)	(0.79, 3.58)	0.004	-2.40 (2.79)	(-4.40, -0.39)	0.024	0.13 (0.49)	(-0.05, 0.30)	0.161	133.723 1[a,b,c,1]
	UL fatigue post-test	0.94 (2.32)	-0.30 (2.17)	0.127	0 (1.76)	(-1.26, 1.26)	1	-0.19 (0.90)	(-0.51, 0.14)	0.245	8.777 1[a,c,1]
Self-perceived health status											
EQ-5D-5L VAS		-19.58 (23.59)	(-34.57, -4.59)	0.015	-3.33 (14.03)	(-12.25, 5.58)	0.428	-2.81 (13.68)	(-7.74, 2.12)	0.254	42.089 1[a,c,1]
EQ-5D-5L index		-0.07 (0.35)	(-0.15, 0.01)	0.057	-0.22 (0.65)	(-0.54, 0.99)	0.163	0	-	1	0.789

Variables are expressed as mean (SD).

[a]Significant differences between low-risk and high-risk groups.

[b]Significant differences between low-risk group and control group.

[c]Significant differences between high-risk group and control group.

[1]Global *P* value adjusted by multiplicity. 5STS: Five sit to stand test; CI: Confidence interval; EQ-5D-5L: Euroqol 5 dimensions 5 levels; FSS: Fatigue severity scale; LL: Lower limb; UL: Upper limb; UULEX: Unsupported upper-limb exercise; VAS: Visual analogue scale.

functional disability[25].

Similar to our study, Cavalheri *et al*[26] assessed exercise capacity using the 6 min walking test in a cross-sectional study of lung cancer survivors and found that compared to age and gender-matched healthy controls there were statistically significant differences in exercise capacity. These results are similar to ours. However, they did not include a self-perceived report of dyspnea and fatigue levels, which gives us valuable information about how the patient feels their capacity or a risk profile differentiation. Benzo *et al*[27], in a meta-analysis, found a lower exercise capacity in patients who develop clinically relevant complications after curative lung resection. However, they only used the levels of VO_2max without taking into account self-perceived exercise limitations. In the same line, Snowden *et al*[28] analyzed a sample of 116 major elective surgery patients and showed that patients with a higher frequency of PPCs had a much reduced level of preoperative cardiorespiratory reserve when compared with those with fewer complications.

Concerning upper limbs, our study has shown that high-risk patients present a poorer exercise capacity after lung resection. Upper limb exercise capacity plays an important role in many basic and instrumental activities of daily living and may provide unique information about upper extremity endurance not reflected in the field-based walking tests. Previous studies in similar populations have found an upper limb impairment in patients after breast cancer or cardiac surgery[29], showing decreased functionality and exercise capacity after surgery, similar to our results. However, and despite its importance, we have not found studies about UL exercise capacity after lung resection.

Finally, our results have displayed poorer self-perceived health status in the high-risk group, even 1 mo after discharge. Self-perceived health status is an important variable that rarely has been measured, but it is of tremendous significance, particularly when treating high-risk operable patients[30]. What patients fear most is to be left physically and mentally handicapped and not be able to resume an acceptable daily lifestyle[25]. In line with our study, previous research has shown that more complex resections, such as pneumonectomy, are associated with worse postoperative quality of life[25]. Brunelli *et al*[31] also stated that lung resection patients presented reduced quality of life values compared with the general population. However, they considered that high-risk patients had a postoperative quality of life scores similar to those observed in younger and fitter patients, which contrasts with our results. Nevertheless, the authors explained that the patients who dropped-out could have changed the results, and it should be taken into account when interpreting the results.

Our study has some limitations that have to be reported. First, the 1 mo follow-up is not enough to verify if symptom burden and exercise limitation are maintained over time. However, we have based our study design on previous studies that use the same follow-up, and in the consideration that early recovery of patients is essential to improve their quality of life. Secondly, a specific assessment of respiratory function could be included to get an objective measure of lung tissue. However, we have considered that self-perceived exercise capacity could be more important to carry out daily activities. Third, the inclusion of some comorbidities such as chronic obstructive pulmonary disease, which could affect the assessment, were not included. However, we have based our study design on previous studies, which also did not include them [22].

CONCLUSION

Our results show a poorer recovery in high-risk patients at discharge and 1 mo after surgery, with more self-perceived fatigue, lower self-perceived health status and a poorer upper and lower limb exercise capacity. Moreover, none of the groups undergoing surgery reached the results of the control group. These results represent an advance in the field of rehabilitation because it allows the design of specific rehabilitation programs for each group of patients.

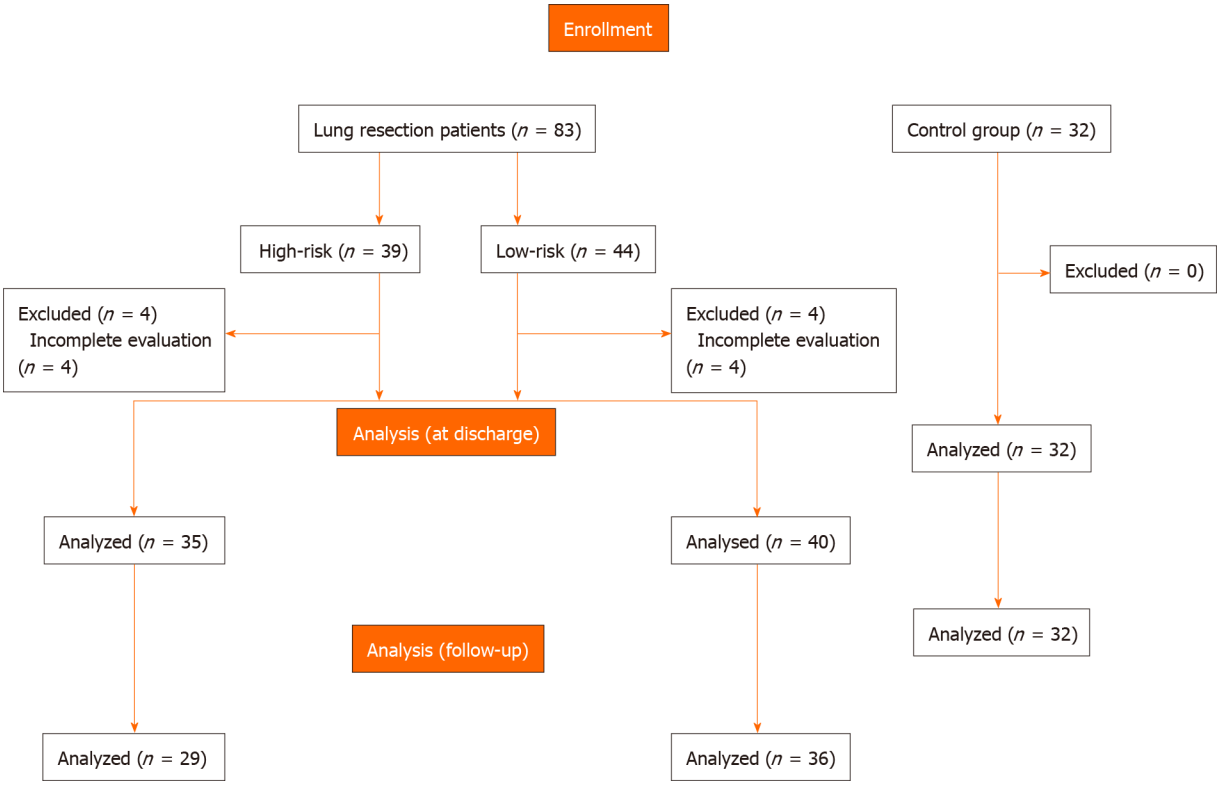

Figure 1 Consort flow diagram of participants.

ARTICLE HIGHLIGHTS

Research background

Lung cancer resection still produces a high incidence of postoperative pulmonary complications. High-risk lung cancer patients are more likely to have postoperative pulmonary complications. Exercise capacity and functionality is affected in lung cancer patients after hospitalization.

Research motivation

High-risk patients present more complications after hospitalization. Upper and lower limb exercise capacity could be affected in these patients.

Research objectives

To determine if there are differences between high and low-risk patients in exercise capacity. To identify differences in self-perceived health status depending on the risk of developing postoperative pulmonary complications at discharge and 1 mo after hospitalization.

Research methods

This was an observational prospective cohort study conducted between April 2017 and July 2018. Inclusion criteria included: to be between 18-years-old and 80-years-old and to be informed about the study purpose. Patients were divided into two groups according to the risk profile criteria. Outcome measures included: Fatigue Severity Scale, dynamometry, 5 Sit-to-Stand Test, unsupported upper-limb exercise, Euroqol-5 dimensions 5 levels.

Research results

Fatigue severity was higher in the high-risk group at discharge. Upper and lower limb exercise capacity presented poorer results in the high-risk group at discharge. Self-perceived health status also presented significant differences between groups. One month after hospitalization, all differences remained.

Research conclusions

High-risk patients present a poor recovery at discharge and 1 mo after hospitalization. More fatigue and a poorer exercise capacity were found in this group. Both groups undergoing lung resection did not reach control group levels even 1 mo after hospitalization.

Research perspectives

The approach of lung cancer patients should be different depending on the risk profile. Future studies are needed to research the differences between high and low-risk patients in a longer term. Future studies should include objective measures to identify these differences.

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ORIGINAL ARTICLE

Observational Study

Retrospective analysis of anti-inflammatory therapies during the first wave of COVID-19 at a community hospital

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Institutional review board statement: The study was approved by the Community Medical Center Institutional

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Abstract

BACKGROUND

Our understanding of the severe acute respiratory syndrome coronavirus 2 has evolved since the first reported cases in December 2019, and a greater emphasis has been placed on the hyper-inflammatory response in severely ill patients. The

Review Board (IRB # 20-005).

Informed consent statement: Informed consent was waived by the Community Medical Center Institutional Review Board as the study was deemed minimal risk to participants due to its retrospective nature and de-identified results.

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purpose of this study was to determine risk factors for mortality and the impact of anti-inflammatory therapies on survival.

AIM

To determine the impact of various therapies on outcomes in severe coronavirus disease 2019 patients with a focus on anti-inflammatory and immune-modulating agents.

METHODS

A retrospective analysis was conducted on 261 patients admitted or transferred to the intensive care unit in two community hospitals between March 12, 2020 and June 17, 2020. Totally 167 patients received glucocorticoid (GC) therapy. Seventy-three patients received GC alone, 94 received GC and tocilizumab, 28 received tocilizumab monotherapy, and 66 received no anti-inflammatory therapy.

RESULTS

Patient survival was associated with GC use, either alone or with tocilizumab, and decreased vasopressor requirements. Delayed administration of GC was found to decrease the survival benefit of GC therapy. No difference in survival was found with varying anticoagulant doses, convalescent plasma, tocilizumab monotherapy; prone ventilation, hydroxychloroquine, azithromycin, or intravenous ascorbic acid use.

CONCLUSION

This analysis demonstrated the survival benefit associated with anti-inflammatory therapy of GC, with or without tocilizumab, with the combination providing the most benefit. More studies are needed to assess the optimal timing of anti-inflammatory therapy initiation.

Key Words: COVID-19; Corticosteroids; Intensive care unit; Methylprednisolone; Tociluzimab; Anti-inflammatory

Core Tip: Anti-inflammatory therapy with glucocorticoids (including methylprednisolone) and combination treatment with tocilizumab and glucocorticoids improve survival in critically ill patients with coronavirus disease 2019. Dual inhibition of the NFK-β therapy with glucocorticoid and inhibition of the interleukin-6 pathway with tocilizumab may offer greater survival benefits.

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INTRODUCTION

In late December 2019, patients in Wuhan, China began presenting to hospitals with a viral pneumonia of unknown origin characterized by a clinical syndrome comprising of cough and dyspnea[1,2]. While there was a wide range of severity, the disease could lead to respiratory failure and death. Caused by the coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), this disease state was named the coronavirus disease 2019 (COVID-19). Following rapid international spread, the World Health Organization upgraded the outbreak to a pandemic, the first pandemic since the 2009 H1N1 outbreak[3]. As of January 29, 2021, the disease has over 100 million cases confirmed infections and over 2 million confirmed deaths[4]. Our understanding of the disease state has continued to evolve as well. While the high mortality rate was

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originally thought to be closely related to acute respiratory distress syndrome (ARDS), newer evidence has shown additional potential causes[5]. Severely ill patients may have a hyper immune response, leading to dysregulated and excessive cytokine release which can lead to multiple-organ failure[6]. Patients have been found to enter a hypercoagulable state, leading to increased risk of thrombosis and strokes[7,8]. Our better understanding and continued research has led to rapid changes in treatment recommendations for COVID-19.

Treatment for COVID-19 has been rapidly evolving as new evidence emerges. Therapies have focused on antivirals (*e.g.*, remdesivir, favipiravir), anti-inflammatory medications (dexamethasone, methylprednisolone), antibodies (convalescent plasma), immunotherapy (tocilizumab, anakinra, sarilumab), anticoagulation (heparin), vitamin therapy (ascorbic acid, vitamin D), different modalities of respiratory support, and other novel therapies (hydroxychloroquine, melatonin, famotidine)[9]. Remdesivir, an antiviral therapy, was the first approved therapy to treat COVID-19 in hospitalized patients aged 12 and older weighing at least 40 kg. Remdesivir shows in-vitro activity against SARS-CoV-2 as well as a quicker time to recovery in hospitalized COVID-19 patients[10-13].

Immune based therapies have theoretical benefits in the cytokine storm phase of the disease. Corticosteroids have been employed due to their potent anti-inflammatory and immunomodulatory effects. Dexamethasone showed favorable clinical results in COVID-19 in the RECOVERY trial, demonstrating a lower 28-d mortality in patients receiving invasive mechanical ventilation or oxygen alone[14]. Patients who did not require supplemental oxygen did not benefit from the addition of dexamethasone. A meta-analysis of 7 randomized controlled trials that included hydrocortisone, methylprednisolone, and dexamethasone showed lower 28-d all-cause mortality, however the majority of data came from the RECOVERY trial[15]. The METCOVID trial was a parallel, double-blind, placebo-controlled, randomized clinical trial which compared methylprednisolone *vs* placebo in hospitalized patients with COVID-19[16]. The primary endpoint of 28 d mortality was not different between groups, however a post-hoc analysis of the data demonstrated that patients > 60 years old who received methylprednisolone did have decreased 28 d mortality.

Some concerns remain over using corticosteroids to treat COVID-19. Data from other novel coronavirus infectious, namely Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) show a negative effect on virus clearance with steroid use[17,18]. Liu *et al*[19] showed negative effects of corticosteroids in COVID-19 including increased 28-d mortality and delayed viral clearance in a large multicenter retrospective analysis. Methylprednisolone made up the majority (96.8%) of the steroids used.

Tocilizumab is a monoclonal antibody which competitively inhibits the action of interleukin-6 (IL-6), a pro-inflammatory cytokine which correlates with disease severity in COVID-19[20,21]. Tocilizumab has shown mixed results in randomized clinical trials. Earlier trials used tocilizumab as mostly monotherapy with low utilization of corticosteroids and failed to show efficacy[22-25]. Later trials, such the REMAP CAP and RECOVERY trials, utilized corticosteroids in greater numbers due to the release of the RECOVERY trial data on dexamethasone, and showed decreased mortality with tocilizumab[26,27]. The RECOVERY trial included only patients with C-reactive protein (CRP) > 75 mg/L, while the REMAP CAP trial did not specify a CRP threshold for inclusion, but found the strongest effect in the subgroup with highest CRP.

MATERIALS AND METHODS

Study population and data collection

To determine risk factors for mortality and the impact of anti-inflammatory therapy on survival in patients critically ill from COVID-19 we conducted a retrospective analysis of 261 consecutive patients admitted or transferred to the intensive care unit (ICU) of two community hospitals from March 12th to June 17th 2020. The study was approved by the Community Medical Center Institutional Review Board (IRB # 20-005). Inclusion criteria were the following: confirmed diagnosis of SARS-CoV-2 (COVID-19) by a positive PCR test and signs and symptoms of COVID-19 infection, age greater than 18. The study baseline was the time of hospital admission. In terms of ICU management, patients received standard of care therapy. Management and timing of ventilator support, employment of ARDS net ventilator strategies, antibiotic use, antiviral therapy, use of anticoagulation, initiation of vasopressors, use of convalescent

plasma, glucocorticoid (GC) therapy (defined as GC use for greater than 48 h), and use of tocilizumab was determined by the ICU physician and consultants.

Patient demographics, comorbidities, clinical and outcome variables were obtained from the electronic medical record and entered into a de-identified database. Measurements included arterial blood gas, routine metabolic chemistries, CRP, D-Dimer, IL-6, ferritin, complete blood count with differential, and all variables necessary to calculate the Sequential Organ Failure Assessment (SOFA) score on admission. Other collected data included the day of admission, date of ICU transfer, date of death, length of vasopressor usage, days on mechanical ventilation, partial pressure of oxygen to fraction inspired of oxygen (PaO_2/FIO_2) ratio, time to initiation of GC therapy, time to ICU transfer, use of therapeutic agents [azithromycin, hydroxychloroquine, convalescent plasma, use of heparin (low molecular weight or unfractionated either as prophylaxis or full anticoagulant therapy), and use of tocilizumab].

Acute kidney injury (AKI) was defined based on kidney disease: Improving Global Outcomes criteria; namely, an increase in serum creatinine (SCr) > 0.3 mg/dL or a level > 1.5 times the baseline value SCr by ≥ 0.3 mg/dL, within 48 h. Where SCr at baseline is unknown and there is no documented history of chronic kidney disease baseline SCr was arbitrarily assigned a value of 1 mg/dL[28]. Timing and indication for the initiation of renal replacement therapy were determined by the consulting nephrologist.

Ethics statement

All procedures performed in the study were in accordance with the 1964 Helsinki declaration and its later amendments. Patients' data were kept confidential, and no patients' identifiers were included in data files handled for the purposes of this study.

Data analysis

The major outcome evaluated was hospital survival for patients admitted or transferred to the ICU during the index admission. Employing Cox proportional hazards model we performed a risk factor analyses for in-hospital survival. Secondly, we evaluated the impact of anti-inflammatory therapy on patient survival.

Summary statistics were computed for the survivors, non-survivors, and treatment groups. Four treatment groups were evaluated: All patients who received GC therapy, GC therapy alone, tocilizumab + GC therapy, tocilizumab alone, and standard treatment alone (no anti-inflammatory therapy). The use of subcutaneous heparin (fractionated or unfractionated), use of convalescent plasma, azithromycin, hydroxychloroquine, antibiotic therapy, and vasopressor use were included as standard therapy. Due to our previous use of intravenous ascorbic acid (IVAA) in sepsis, IVAA use was evaluated as an adjunct treatment modality. We performed both univariate and multivariate analyses. Continuous variables were expressed as median with interquartile ranges, and compared by the Student's *t*-test or the Wilcoxon rank-sum test as appropriate. Multiple comparisons were analyzed with Kruskal Wallis ANOVA or Bonferroni correction when indicated. Categorical values were compared with Pearson's chi-squared test and Fisher's exact test when indicated. Kaplan Meir survival curves with log-rank test analysis and Cox proportional hazards analysis were employed to compare factors associated with survival and to compare treatment groups. Variables that were significant by univariate analysis at $P < 0.05$ were candidates for multivariate analysis. Multivariate Cox proportional hazards with forward variable selection was performed to determine variables independently predictive of survival and for comparing anti-inflammatory therapy groups with standard care.

As there was the possibility of factors influencing the use of corticosteroids, a logistic regression analysis was implemented to create a propensity score for corticosteroid use. A propensity score was generated employing the following factors; age, sex, race, the diagnosis of chronic obstructive pulmonary disease (COPD), need for mechanical ventilation, and PaO_2/FiO_2 ratio on admission. Cox proportional hazards analysis with time to corticosteroid administration as a time-dependent covariate was employed to compare survival among groups. Survival analysis was performed with propensity score adjusted multivariate Cox proportional hazards analysis. Finally, we repeated Cox proportional hazards analysis with both propensity score adjustment and with time to corticosteroid administration as a time-dependent covariate.

RESULTS

Patient characteristics

From March 12, 2020 to June 17, 2020, 261 patients with COVID-19 were admitted to the ICU. There were 94 patients (36%) admitted directly to the ICU and 167 (64%) patients who were initially admitted to non-ICU COVID units then later transferred to ICU. During these four months, hospital mortality for ICU patients was 64% (167 patients). On univariate analysis, there was no significant difference in mortality between those directly admitted to ICU 59 (62%) *vs* transferred to ICU 108 (64%), (P = 0.74, odds ratio 0.92, 95% confidence interval 0.54-1.55). The median time to transfer to ICU was 3 d [interquartile range (IQR) 1-5]. In those patients not initially admitted to ICU, there was no statistically significant difference in time to ICU transfer between survivors and non-survivors median time 2 d (IQR 1-5) *vs* 3 d IQR (1-6) (P = 0.11). There was a statistically significant difference in SOFA scores in patients admitted to the ICU in comparison to those admitted to COVID-19 units [6 (IQR 3-10) *vs* 3.5 (IQR 2-5) P < 0.001]. The median age was 69 years (IQR 61-80), 60% of patients were greater than 65 years and 30% were older than 77, 129 patients (48%), were Caucasian and 158 (60%) were males. The majority of patients (n = 178, 68%) had or developed severe respiratory failure requiring mechanical ventilation, and 39 (15%) required hemodialysis. Of note 167 patients received corticosteroids; either hydrocortisone 100mg every 8 h (n = 12, 7%) or methylprednisolone 40mg every 12 h (n = 155, 92%). A total of 73 patients received GC alone, 94 received both tocilizumab and GC, 28 were on tocilizumab therapy alone, and 66 patients did not receive anti-inflammatory therapy. The dose of tocilizumab employed was 8 mg/kg.

Univariate analysis: Predictors of survival and treatment

Patient characteristics are described in Table 1. Univariate predictors of decreased survival included the need for mechanical ventilation, AKI, Caucasian race, male sex, older age, lower total lymphocyte count, higher neutrophil/lymphocyte ratio, and a greater degree of respiratory failure manifested by a lower PaO_2/FIO_2 ratio. Therapeutic and pharmacologic interventions are described in Table 2. Survival analysis employing univariate Cox proportional hazards analysis revealed patient survival was associated with use all patients receiving GC (GC alone and GC + tocilizumab), GC use alone, less use of vasopressors, and combination therapy with tocilizumab with GC (Table 3). It is pertinent to note that there was no statistically significant difference in survival with the use of anticoagulant doses of heparin, subcutaneous heparin, convalescent plasma, tocilizumab alone, prone ventilation, IVAA, hydroxychloroquine, or azithromycin use. All patients who received remdesivir expired (n = 6, 3%). As anticipated non-survivors demonstrated a higher degree of elevated inflammatory and pro-thrombotic markers interleukin-6 at 48 h, D-Dimer at 24 h and 48 h respectively (Table 4).

Multivariate analysis/Cox proportional hazards analysis

To identify independent predictors of survival, we performed multivariate Cox proportional hazards analysis with stepwise forward variable selection which revealed the following as independent predictors of decreased survival: increased age, male sex, and a requirement for vasopressors. GC use including those patients receiving GC alone and those receiving GC + tocilizumab was associated with survival (Table 5). Kaplan Meier survival analysis curves Kaplan Meier curve for GC treatment (GC alone and GC + tocilizimab) is represented in Figure 1 (GC use, log rank test P < 0.001).

As there was the possibility of factors influencing the use of GC, a logistic regression analysis was implemented to create a propensity score for GC use. A propensity score was generated employing the following factors; age, sex, race, the diagnosis of COPD, need for mechanical ventilation, and PaO_2/FIO_2 ratio on admission (Table 1 and Supplementary Figure 1). In order to confirm that anti-inflammatory therapy influenced survival we next repeated a propensity score adjusted Cox proportional hazards analysis with stepwise forward variable selection including GC alone, tocilizumab + GC, tocilizimab alone, and standard treatment. The model revealed independent predictors of decreased survival remained unchanged, conversely both GC alone and GC + tociluzimab were associated with survival (Table 6). The Kaplan Meier comparing all treatment groups is represented in Figure 2A (log rank test P < 0.001). Separate Kaplan Meier comparing each group and standard care are represented in Figure 2B (GC and standard of care, log rank P = 0.002), and Figure 2C (tocilizumab + GC and standard care, log rank P = 0.016), and Figure 2D (tocilizumab alone and standard care, log rank P = 0.061).

Table 1 Coronavirus disease 2019 patients admitted to intensive care unit characteristics of survivors and non-survivors, *n* (%)

	Non-survivor (*n* = 167)	Survivor (*n* = 94)	*P* value	OR	95%CI
Age	71 (61, 82)	61 (62, 78)	0.011		
Race (Caucasian)	89 (75)	40 (56)	0.007	2.37	1.27-4.40
BMI	29 (23, 34)	28 (24, 32)	0.49		
Sex (male)	75 (70)	83 (53)	0.01	0.49	0.29-0.84
Diabetes	31 (29)	53 (34)	0.3	1.26	0.75-2.2
CHF	13 (12)	21 (14)	0.7	1.1	0.66 – 2.4
CAD	24 (29)	41 (27)	0.41	1.2	0.7-2.2
COPD	38 (23)	23 (30)	0.75	0.9	0.5-1.6
CKD	11 (10)	21 (17)	0.1	1.85	0.87-3.83
HTN	54 (51)	91 (59)	0.16	1.4	0.86-2.3
AKI	87 (52)	30 (32)	0.002	2.3	1.21-2.5
Mechanical ventilation	134 (80)	44 (47)	< 0.001	4.7	2.7-8.3
Hemodialysis	29 (18)	10 (11)	0.13	1.8	0.3-3.9
Neutrophils × 10^9/L	7.3 (4, 10)	7.8 (5.1, 13)	0.97		
Lymphocytes	0.7 (0.5, 1.2)	0.9 (0.6, 1.6)	0.011		
Neutrophil/lymphocyte	10 (6, 18)	7.5 (4, 14)	0.017		
SCr (mg/dL)	1.2 (0.9, 1.9)	1.2 (0.8, 1.8)	0.49		
Plts (× 10^9 /L)	230 (162, 310)	236 (182, 302)	0.27		
Tbili (mg/dL)	0.5 (0.4, 0.8)	0.5 (0.4, 0.8)	0.65		
SOFA admit	5 (3, 9)	4 (2, 6)	0.095		
PaO_2/FIO_2	190 (76, 285)	232 (123, 307)	0.039		
PaO_2	68 (52, 116)	66 (48-112)	0.083		
FIO2	1 (0.45, 1)	1 (0.96, 1)	0.12		

OR: Odds ratio; CI: Confidence interval; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; CHF: Congestive heart failure; AKI: Acute kidney injury; HD: Hemodialysis; tBili: Total bilirubin; Plts: Platelets INR: International normalized ratio. PaO_2 /FiO_2: Partial pressure of oxygen/inspired concentration of oxygen ratio; SOFA: Sequential Organ Failure Assessment; BMI: Body mass index; SCr: Serum creatinine.

In order to adjust for time of GC administration, we employed a propensity score adjusted Cox proportional hazards analysis adjusting GC administration as a time dependent covariate, which revealed independent predictors of decreased survival were: increased age, male sex, and a requirement for vasopressors. GC use including those patients receiving GC alone and those receiving GC + tocilizimab was associated with survival. Conversely, the addition of GC as the time adjusted covariate was associated with a significant decrease in survival and negatively impacted the survival impact of GC treatment suggesting that later initiation of GC is associated with a negative impact on survival (Table 7). The analysis was repeated comparing all treatment groups which revealed the same independent predictors of decreased survival were the following: Increased age, male sex, and a requirement for vasopressors. The groups receiving GC alone and those receiving GC + tocilizumab were associated with survival (Table 8).

Cox proportional hazards analysis adjusted for differences among groups

Among treatment groups, there were significant differences in baseline characteristics observed on univariate analysis (Table 6). In order to adjust for these differences, we repeated the previous Cox proportional hazards analysis model incorporating SOFA score, baseline SCr, FiO2, history of coronary artery disease, and CRP at 24, and all previous variables analyzed on previous Cox models. The propensity score adjusted Cox proportional hazards model with GC as a time dependent covariate demonstrated

Table 2 Pharmacologic and therapeutic interventions in coronavirus disease 2019 intensive care unit patients, *n* (%)

	Non-survivor (*n* = 167)	Survivor (*n* = 94)	*P* value	OR	95%CI
GC (all patients)[1]	99 (59)	68 (72)	0.035	0.55	0.32-0.96
Vasopressors	124 (74)	35 (37)	< 0.001	4.8	2.8-8.4
IV Ascorbic acid	100 (59)	54 (57)	0.7	1.1	0.66-1.84
Hydroxychloroquine	128 (78)	69 (75)	0.57	1.2	0.65-2.1
Azithromycin	65 (40)	25 (26)	0.06	1.69	0.97-2.9
Heparin therapeutic dose	80 (48)	51 (54)	0.32	0.77	0.46-1.3
Heparin prophylaxis dose	58 (35)	32 (34)	0.91	1.03	0.6-1.75
Convalescent plasma	44 (26)	27 (29)	0.68	0.88	0.5-1.56
Remdesivir	6 (3)	0 (0)			
Prone positioning	52 (31)	32 (35)	0.91	1.03	0.6-1.75
Tocilizumab	20 (12)	8 (8.5)	0.55	1.28	0.56-2.9
GC only	44 (26)	29 (30)	0.47	0.8	0.48-1.4
GC + tocilizumab	55 (32)	39 (40)	0.16	0.68	0.4-1.15

[1]Treatment stratified as total patients receiving glucocorticoid (GC) therapy (GC alone and GC + tocilizumab).
GC: Glucocorticoid; OR: Odds ratio; CI: Confidence interval; IV: Intravenous.

Table 3 Univariate Cox proportional hazards survival analysis of pharmacological and therapeutic interventions in coronavirus disease 2019 intensive care unit patients

	B	SE	*P* value	HR	95%CI
GC (all patients)	-0.84	0.16	< 0.001	0.45	0.38-0.61
Vasopressors	0.039	35	0.027	1.4	1.05-2.1
IV ascorbic acid	0.1	0.15	0.49	1.1	0.91-1.5
Hydroxychloroquine	-0.58	0.36	0.1	0.56	0.27-1.14
Azithromycin	0.25	28	0.39	1.3	0.72-2.3
Heparin therapeutic dose	0.15	0.35	0.67	1.16	0.51-2.31
Heparin prophylaxis dose	-0.27	0.3	0.35	0.76	0.48-1.3
Convalescent plasma	0.29	1	0.77	1.3	0.72-9.8
Remdesivir	6 (3)	0			
Prone positioning	0.36	0.52	0.44	1.43	0.51-1.4
Tocilizumab	-0.48	0.27	0.08	0.61	0.36-1.06
GC only	-0.75	0.21	0.001	0.47	0.18-0.41
GC + tocilizumab	-1.3	0.21	<0.001	0.27	0.4-1.15

HR: Hazard ratio; CI: Confidence interval; GC: Glucocorticoids; IV: Intravenous.

that older age, higher SOFA score, and higher baseline SCr were associated with poor outcomes while the combination of tocilizumab and GC was associated with increased survival (Table 7).

DISCUSSION

During the first wave of the pandemic patients requiring admission to the ICU were associated with a mortality of 30%-70%[29-33]. The requirement for mechanical

Table 4 Inflammatory markers in coronavirus disease 2019 survivors and non-survivors

	Non-survivors (*n* = 167)	Survivors (*n* = 94)	*P* value
IL-6 day 1 (pg/mL)	112 (70, 137)	100 (70, 135)	0.34
IL-6 day 2	415 (139, 476)	350 (78, 423)	0.016
D-dimer day 1 (ng/mL)	1125 (647, 2434)	991 (513, 2196)	0.04
D-dimer day 2	849 (604, 1210)	1140 (646, 2263)	0.03
CRP day 1 (mg/L)	117 (89, 159)	113 (96, 149)	0.9
CRP day 2	107 (81, 154)	117 (88, 167)	0.62
Ferritin day 1 (ng/mL)	931 (593, 1367)	960 (609, 1395)	0.51
Ferritin day 2	822 (447, 1432)	1053 (712, 2057)	0.05

IL-6: Interleukin 6, CRP: C-reactive protein.

Table 5 Unadjusted Cox proportional hazards analysis of independent predictors of survival in intensive care unit patients with coronavirus disease 2019

	B	SE	*P* value	HR	95%CI
Age	0.031	0.007	< 0.001	1.032	1.02-1.05
Sex (male)	0.39	0.2	0.046	1.48	1.008-2.2
Vasopressors	0.485	0.2	0.016	1.62	1.095-2.4
GC administration (all patients)[1]	-0.61	0.19	0.002	0.54	0.37-0.79

[1]Treatment stratified as total patients receiving GC therapy (GC alone and GC + tocilizumab).
HR: Hazard ratio; CI: Confidence interval; GC: Glucocorticoids.

Table 6 Propensity score adjusted Cox proportional hazards analysis of independent predictors of survival in intensive care unit patients with coronavirus disease 2019

	B	SE	*P* value	HR	95%CI
Age	0.03	0.007	< 0.001	1.031	1.02-1.05
Sex (male)	0.41	0.2	0.038	1.51	1.022-2.22
Vasopressors	0.47	0.23	0.019	1.6	1.081-2.37
GC + Tocilizumab	-0.78	0.22	0.001	0.46	0.29-0.72
GC only	-0.44	0.22	0.048	0.65	0.42-0.99

SE: Standard error; HR: Hazard ratio; CI: Confidence interval; GC: Glucocorticoids; IV: Intravenous.

ventilation is associated with the highest mortality[30-32,34]. One observational study from Wuhan Du *et al*[30] reported that all 52 patients admitted to the ICU expired during the index hospitalization. In the present study, mortality was consistent with previously reported studies particularly, due to the large percentage of patients requiring mechanical ventilation[30-32,35]. Similarly, we demonstrate that male sex, advancing age, and requirements for vasopressor support were independent predictors of decreased survival[32,36]. Similar to experiences in Wuhan, patients not initially admitted to ICU had significant organ dysfunction with a median SOFA score of 3[30].

The geographical area that the hospitals in the current study services represent one of the largest Medicare populations in the country. Thus overall, the current study represents treatment in an older group of patients and patients requiring mechanical ventilation when compared to the RECOVERY trial and the Northwell COVID-19 treatment consortium[14,37]. The results of the current study demonstrating improved

Table 7 Propensity score adjusted (glucocorticoids as a time-adjusted covariate) Cox proportional hazards analysis of independent predictors of survival in intensive care unit patients with coronavirus disease 2019

	B	SE	*P* value	HR	95%CI
Time adjusted GC	2.5	1.01	0.014	12.9	1.06-87.5
Age	0.03	0.007	< 0.001	1.03	1.01-1.04
Sex (male)	0.4	0.2	0.05	1.5	1-2.17
Vasopressors	0.51	0.2	0.01	1.66	1.12-2.4
GC (all patients)[1]	-2.94	1.01	0.004	0.05	0.007-0.36

[1]Treatment stratified as total patients receiving glucocorticoids (GC) therapy (GC alone and GC + tocilizumab).
SE: Standard error; HR: Hazard ratio; CI: Confidence interval; GC: Glucocorticoids.

Table 8 Propensity score adjusted (glucocorticoids as a time adjusted covariate) Cox proportional hazards analysis of independent predictors of survival in intensive care unit patients with all treatment groups added into the model

	B	SE	*P* value	HR	95%CI
Time adjusted GC	2.5	1.01	0.015	12	1.62-85
Age	0.03	0.007	< 0.001	1.03	1.01-1.04
Sex (male)	0.4	0.2	0.04	1.5	1.01-2.2
Vasopressors	0.5	0.2	0.01	1.66	1.12-2.45
GC + tocilizumab	-3.07	1.02	0.003	0.046	0.006-0.46
GC (only)	-2.77	1.02	0.007	0.06	0.008-0.46

SE: Standard error; HR: Hazard ratio; CI: Confidence interval; GC: Glucocorticoids.

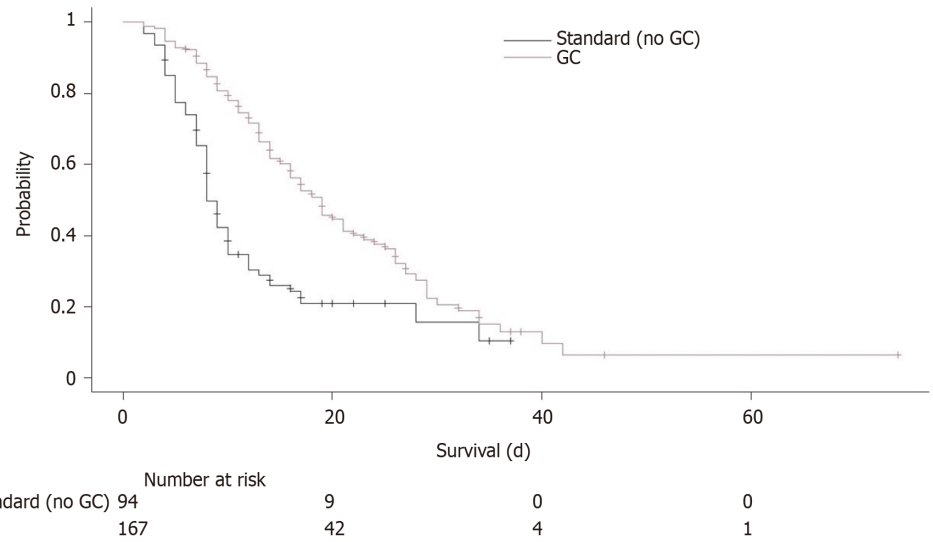

Figure 1 Kaplan Meier survival curve demonstrating increased survival in all patients who received glucocorticoid (red line) *vs* no glucocorticoid therapy (black line) log-rank test *P* < 0.001.

survival in patients receiving anti-inflammatory should be viewed with this context in mind.

A dysregulated immune response resulting in a hyper-inflammatory state is a hallmark of COVID-19 patients who develop severe progressive respiratory failure and multi-organ dysfunction[38]. A small percentage of these patients have clinical characteristics and laboratory parameters similar to macrophage activation syndrome or cytokine storm seen in H1N1 influenza and CAR-T therapy[39-42]. Although many

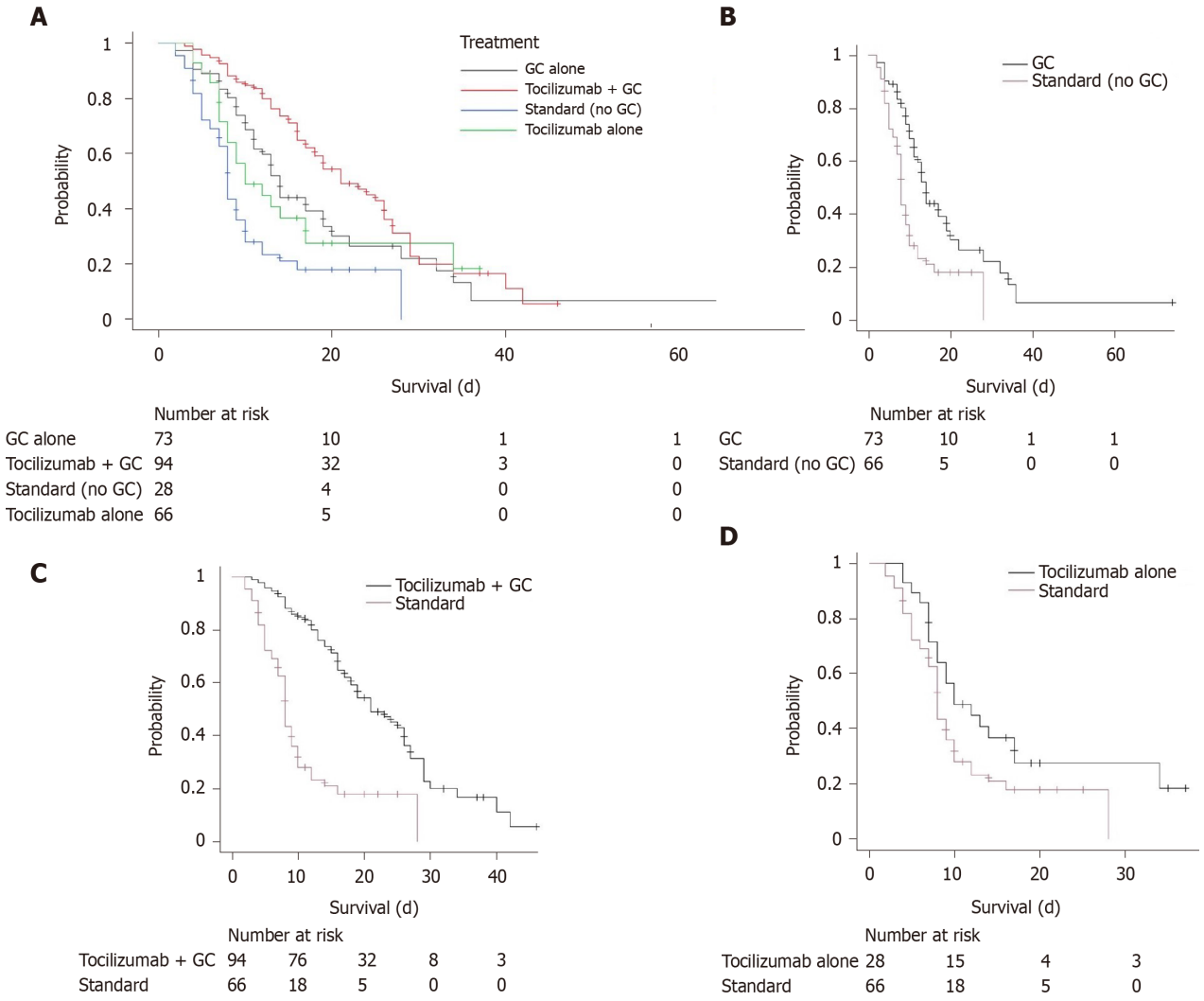

Figure 2 Kaplan Meier survival curve. A: Kaplan Meier survival curve demonstrating increased survival differences in groups receiving tocilizimab + glucocorticoid (GC) (red line), GC alone (black line), tocilizumab alone (green line), and standard treatment (blue line), log rank test with Bonferroni adjustment, $P < 0.001$; B: Kaplan Meier survival curve comparing groups GC alone (black line), and standard treatment (red line) log rank test, $P < 0.001$; C: Kaplan Meier survival curve comparing groups tocilizumab + GC (black line), and standard treatment (red line) log rank test, $P = 0.016$; D: Kaplan Meier survival curve comparing groups tocilizumab (black line), and standard treatment (red line) log rank test, $P = 0.062$.

pro-inflammatory cytokines are elevated in patients with severe COVID -19 infection, there is mounting evidence that increased pro-inflammatory cytokine signatures of IL-6 and TNF-α correlate with severity of disease and increased mortality[38,43,44]. Thus, from therapeutic standpoint therapies that inhibit the NFK-β pathway and IL-6 make GC and tocilizumab prime therapeutic candidates[37-38].

During the first wave of the pandemic, the use of anti-inflammatory therapy may have been predicted by understanding the pathophysiology of cytokine storms observed in CAR-T and in previous influenza viruses, experience in ARDS, and by some who believed the evidence supported the use of GC in viral pneumonia[22,45-47]. Long *et al*[48] reported improvement in mortality outcomes in 5327 patients with SARS associated with MERS in those patients receiving GC therapy. Likewise, Li *et al*[49] reported improved mortality outcomes in patients hospitalized with A(H1N1)pdm09 influenza[46,48-50]. In March 2020, Wu reported an observational study of 84 patients revealing reduced mortality risk in patients with ARDS risk receiving methylprednisone[50].

Prior to the RECOVERY trial, the use of GC in the treatment of severe COVID-19 was considered controversial and potentially harmful as treatment possibly could increase and prolong viral shedding. To some degree treatment with GC is still not without controversy[16,51]. Towards the end of the third wave, there has been increasing evidence from randomized controlled trials and observational studies that GC therapy improves survival in severe COVID-19, and the use of GC in low to moderate dosing is not associated with increased viral shedding[14,15,51,52]. To date,

the use of anti-cytokine therapy mainly with anti-IL-6 treatment with tocilizumab has yielded mixed results[53-55].

In many infections, it is not the pathogen that determines the virulence of the disease. Instead, it is the host response to the pathogen that causes tissue injury, delayed healing, morbidity, and mortality. COVID-19 associated respiratory failure is a cehost response hyper-inflammatory pulmonary disease driven by macrophages and hyper-cytokinemia[54-56]. Of note, most patients with SARS-CoV-2 infection are mild or completely asymptomatic, with only a minority progressing to severe illness[54]. In the setting of mild or asymptomatic disease, there is an appropriate release of antiviral interferons, clearance of viral debris by phagocytosis, and a controlled innate immune response followed by the development of adaptive immunity[54,56,57]. However, there is an impaired release of interferons and an abnormal innate immune response associated with excessive hyper-inflammatory response in the small subset of patients progressing to severe disease[57]. Although SARS-CoV-2 viral cytopathic effect on the epithelial cells of the respiratory tract has been demonstrated, investigators have found it challenging to retrieve live virus during the severe symptomatic pulmonary phase of the disease despite clinical evidence of tissue injury and damage[58]. The positive response of anti-inflammatory and immunomodulatory agents in severe SARS-CoV-2 infection underscores the dysregulated hyper-inflammatory host response responsible for the tissue damage and virulence of severe COVID-19.

Although in the present study elevated body mass index did not significantly correlate with mortality, hyper-nutrition (sarcopenic obesity) is a known risk factor for developing severe COVID-19 disease and mortality[59]. Due to increased expression of the angiotensin converting enzyme-2 receptor, adipose tissue is a target for SARS-CoV-2 infection, adipose tissue function as an endocrine organ which results in a pro-inflammatory state, activation of NOD-, LRR-, and pyrin domain-containing protein 3 inflammasome and release of pro-inflammatory cytokines[60-63]. In addition, increase adipose tissue increases circulating TNF-α and IL-6[61]. Furthermore, obesity is associated with CD-4 T-cell exhaustion and decreases in anti-inflammatory cytokines IL-10 and IL-4[61,64,65]. Thus hyper-nutrition obesity sarcopenic patients are at higher risk for acquiring infection and developing the inflammatory immune dysregulation observed in severe COVID-19 disease[61,65].

Unfortunately, the current study did not investigate the presence gastrointestinal (GI) manifestation of severe COVID-19 disease. Further studies are needed to explore the possible organ crosstalk between the pulmonary and GI systems as the GI tract is both a driver of inflammation and a potential infectious source[66].

In the current study, we demonstrated the survival benefit of anti-inflammatory therapy employing several Cox proportional hazard models. Firstly, univariate analysis of therapy revealed survival benefit in all patients receiving GC treatment and tocilizumab + GC treatment while tocilizumab alone offered no survival benefit. Unadjusted multivariate analysis, propensity score adjusted Cox proportional hazard with and without GC use as a time-adjusted covariate supported survival benefits observed in the univariate analysis. Cox proportional hazards with GC therapy as a time dependent covariate suggest that earlier treatment with GC offers a greater survival benefit. After adjusting for differences among patient groups, combination therapy with tocilizumab + GC remained associated with increased patient survival. Overall combination therapy with tociluzimab + GC offered the greatest survival benefit.

The strengths of the current study are it represents a real world scenario in the treatment of critically ill patients in a predominantly older population with COVID-19 during the first wave of the pandemic when there was a paucity of randomized controlled evidence guiding therapy. Study limitations include the retrospective nature of the study and the difficulty in adjusting for confounding due to multiple interventions involved.

CONCLUSION

Anti-inflammatory therapy with GC and combination treatment with tocilizumab and GC improve survival in critically ill patients with COVID-19. Dual inhibition of the NFK-β therapy with GC and inhibition of the Il-6 pathway with tocilizumab may offer greater survival benefits. It is pertinent to note that monotherapy with tocilizumab alone was not associated with an increase in survival. Further prospective studies investigating combination anti-inflammatory therapy and timing of initiation of therapy are needed.

ARTICLE HIGHLIGHTS

Research background

Anti-inflammatory therapies have been the focus of treatment for severe hospitalized coronavirus disease 2019 (COVID-19) patients. Mixed literature has led to multiple approaches to providing these immune-modulating agents to calm the host response which has been shown to cause severe illness. Our study provides a retrospective evaluation of treatment provided to ICU-admitted COVID-19 patients and their outcomes.

Research motivation

Corticosteroids have clearly been the mainstay of treatment for hypoxic COVID-19 patients, but there has been debate on the best approach for additional anti-inflammatory therapies. Studies surrounding tocilizumab have previously shown mixed results complicated by a changing treatment regimen as we learned more about the disease process.

Research objectives

The objective of this evaluation was to evaluate treatment provided to severe COVID-19 patients early in the pandemic at our institution and provide additional guidance on any regimens which were associated with improvement in patient outcomes. What was clear after our assessment was that anti-inflammatory therapies using corticosteroids, potentially in combination with tocilizumab, could provide the best outcomes for our patients.

Research methods

Two hundred and sixty-one patients admitted to two community hospital intensive care units for severe COVID-19 were retrospectively analyzed for risk factors for mortality using propensity matched scoring.

Research results

Patient survival was associated with corticosteroid use, with or without tocilizumab. Timing of administration of corticosteroids was an important factor which determined patient outcomes with delays leading to decreased survival. No differences were found with use of anticoagulation, convalescent plasma, tocilizumab monotherapy, prone ventilation, hydroxychloroquine, azithromycin, or intravenous ascorbic acid use.

Research conclusions

Anti-inflammatory therapy with corticosteroids with or without tocilizumab was associated with the best outcomes in our cohort of severe COVID-19 patients.

Research perspectives

More trials are needed based on the appropriate dose, timing, and duration of corticosteroids in COVID-19. The benefit of tocilizumab and corticosteroids as combination treatment also needs to be explored further in randomized trials.

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SYSTEMATIC REVIEWS

Neutrophil kinetics and function after major trauma: A systematic review

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Abstract

BACKGROUND

Immune dysfunction following major traumatic injury is complex and strongly associated with significant morbidity and mortality through the development of multiple organ dysfunction syndrome (MODS), persistent inflammation, immunosuppression, and catabolism syndrome and sepsis. Neutrophils are thought to be a pivotal mediator in the development of immune dysfunction.

AIM

To provide a review with a systematic approach of the recent literature describing neutrophil kinetics and functional changes after major trauma in humans and discuss hypotheses as to the mechanisms of the observed neutrophil dysfunction in this setting.

METHODS

Medline, Embase and PubMed were searched on January 15, 2021. Papers were screened by two reviewers and those included had their reference list hand searched for additional papers of interest. Inclusion criteria were adults > 18 years old, with an injury severity score > 12 requiring admission to an intensive care unit. Papers that analysed major trauma patients as a subgroup were included.

RESULTS

Of 107 papers screened, 48 were included in the review. Data were heterogeneous

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and most studies had a moderate to significant risk of bias owing to their observational nature and small sample sizes. Key findings included a persistently elevated neutrophil count, stereotyped alterations in cell-surface markers of activation, and the elaboration of heterogeneous and immunosuppressive populations of cells in the circulation. Some of these changes correlate with clinical outcomes such as MODS and secondary infection. Neutrophil phenotype remains a promising avenue for the development of predictive markers for immune dysfunction.

CONCLUSION
Understanding of neutrophil phenotypes after traumatic injury is expanding. A greater emphasis on incorporating functional and clinically significant markers, greater uniformity in study design and assessment of extravasated neutrophils may facilitate risk stratification in patients affected by major trauma.

Key Words: Neutrophils; Multiple trauma; Immunophenotypes; Inflammation; Systemic inflammatory response syndrome; Intensive care units

Core Tip: Major trauma results in complex immune dysfunction, with dysregulated pro- and anti-inflammatory processes presenting as clinical syndromes such as acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS). This review examines the role of neutrophils in immune dysfunction following major trauma requiring admission to the intensive care unit, with a focus on the kinetics of the neutrophil immunophenotype and how this correlates with clinical outcomes. This review also proposes new hypotheses as to the mechanisms of complications of immune dysfunction, including ARDS and MODS.

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INTRODUCTION

Major traumatic injury precipitates a complex disease process, with multiple physiological and immunological stressors spanning from the moment of injury to well after discharge. Despite improvements in addressing the acute causes of morbidity and mortality, the WHO reports that trauma still accounts for 10% of all deaths globally[1]. In Australia, trauma ranks as the third highest area of health care spending, at a cost of $8.9 billion in the 2015-2016 financial year[2]. A significant portion of this expenditure is associated with extended intensive care unit (ICU) admissions complicated by syndromes of immune dysfunction, including: multiple organ dysfunction syndrome (MODS), acute respiratory distress syndrome (ARDS), persistent inflammation, immunosuppression and catabolism syndrome, sepsis, and hospital associated infections[3-7].

Neutrophils are one of the key components of the innate immune response and are suspected to be one of the main effector cells involved in MODS and sepsis following major trauma[4]. Neutrophil phenotype provides a unique snapshot of the immune response to trauma, as it represents the functional culmination of the complex cellular milieu observed in severe, systemic inflammation[8,9]. Trauma is a 'sterile' inflammatory process, with neutrophils being activated by products of cellular damage and necrosis, known as danger associated molecular patterns (DAMPs), rather than bacterial products[10]. Important DAMPs released in trauma include high mobility group box 1, mitochondrial nucleic acids, and cell free DNA (cfDNA)[6,10].

In response to DAMPs, neutrophils transition from resting to either a primed or activated phenotype, accompanied by changes in both cell surface markers and functional status[6,11-14]. Following priming and activation, there is initially

significantly increased release of neutrophil antimicrobial products, including reactive oxygen species (ROS), cytokines, heparin binding protein, elastase, and neutrophil-derived cfDNA known as neutrophil extracellular traps (NETs), contributing to a systemic inflammatory response syndrome (SIRS)[6,12-17].

Clinically, this may be followed or accompanied by a period of decreased immune activity resulting in an increased risk of infectious complications. This period has been labelled the compensatory anti-inflammatory response syndrome (CARS)[4]. Immunologically, this period is characterised by neutrophil dysfunction, hypo-responsiveness to subsequent stimuli and active immunosuppression[1,18]. Whilst CARS was initially thought to follow SIRS, there is evidence to suggest that the underlying mechanisms to both SIRS and CARS are activated at the same point early after trauma[1,16,19].

Despite their key role, to our knowledge there are currently no systematic reviews describing neutrophil immunophenotype in adults affected by major trauma. This review aims to describe the extant literature on neutrophil immunophenotype over time in adults admitted to the ICU with major trauma, with a focus on markers that may predict complications related to immune dysfunction during the ICU admission. It also aims to generate hypotheses as to the mechanisms behind MODS and sepsis, and areas for future research.

MATERIALS AND METHODS

This review was conducted in accordance with the protocol available in the Supplementary materials. All study types (*e.g.*, cohort, case-control, randomized controlled trials) were eligible for inclusion providing patient inclusion/exclusion criteria were met and an assessment of neutrophil function or kinetics was performed. Inclusion criteria were: English language, adult human (aged > 18 years) population with an injury severity score (ISS) > 12 implying major trauma[20], who required admission to an ICU. Exclusion criteria were a publication date prior to 1990 (to provide an assessment of the relatively recent literature) and conditions which influence the immune phenotype, namely pregnancy, haematological malignancy and immunosuppression.

The Medline Ovid, PubMed and Embase databases were searched on January 15, 2021. We used the following search terms to search the above databases: trauma or major trauma, neutrophil, innate immunity, activation, function, dysfunction, immunophenotype, intensive care, critical care or illness. The complete search strategies used for each database are shown in the Supplementary materials. Results were then filtered by date (> 1990), human adults and English language. Both reviews and primary studies were initially included, with the review papers hand searched for further relevant studies which were subsequently screened.

Study eligibility was assessed by 2 independent reviewers (LF and AW) in a blinded manner using online Covidence software[21]. Disagreements between reviewers were resolved by consensus. Data on the studied patient population and assessment of neutrophil function or kinetics was extracted by the same reviewers and recorded in Table 1. Bias was estimated for included studies but was not a barrier for inclusion given the nature of the literature (predominantly small observational studies with heterogenous outcome measures and moderate-high risk of bias). Data were analysed qualitatively, and summary statements produced for key findings in the literature. Meta-analysis was not performed owing to the heterogeneity in outcome measures used in included studies.

RESULTS

Two hundred and twenty five papers were identified using the search strategy outlined above and in the Supplementary materials. Following removal of duplicates, 83 articles remained. A further 24 papers were identified through hand-searching reference lists, resulting in 107 articles having titles and abstracts screened for relevance, of which 30 studies were excluded as irrelevant. Only primary studies were summarised in this review. Review papers were included but were used to identify further relevant primary studies only.

The full text review resulted in the exclusion of 29 papers. Main reasons for exclusion were: not specifically reporting neutrophil phenotypes (n = 12) or patients not meeting eligibility criteria, either due to age or ISS (n = 9). In total, 48 manuscripts were included in this review. This information is summarised in the PRISMA diagram

Table 1 A summary of papers included in the review

Title of paper	Ref.	Year published	Number of patients recruited	Average ISS	Average age	Samples collected (time post injury)	Location of study	Major outcomes
Postinjury neutrophil priming and activation states: therapeutic challenges	Botha *et al*[12]	1994	10	N/A	N/A	3 h, 6 h, 12 h, 24 h, 48 h, 72 h, 96 h	United States	Functional states of NADP H, primed 6-24 h, unprimable > 48 h
Postinjury neutrophil priming and activation: an early vulnerable window	Botha *et al*[14]	1995	17	26.7	26.7	3 h, 6 h, 12 h, 24 h, 48 h, 72 h	United States	Priming occurs < 24 h after injury, but cells are resistant to priming 48 h after trauma
Early Neutrophil Sequestration after Injury: A Pathogenic Mechanism for Multiple Organ Failure	Botha *et al*[25]	1995	33	27.7	29.1	3 h, 6 h, 12 h, 24 h	United States	Neutrophil kinetics and CD11b expression suggest end organ sequestration predisposing to MODS
Base deficit after major trauma directly relates to neutrophil CD11b expression: a proposed mechanism of shock-induced organ injury	Botha *et al*[27]	1997	17	26.7	26	3 h, 6 h, 12 h, 24 h, 48 h, 72 h, 96 h, 120 h	United States	Kinetics of neutrophilia, CD11b, CD18 and CD11a
Major injury induces increased production of IL10 in human granulocyte fractions	Koller *et al*[49]	1998	15	28	36	Daily between days 3-10	Germany	Neutrophils from trauma patients produce IL-10
The effects of trauma and sepsis on soluble L-selectin and cell surface expression on L-selectin and CD11b on leukocytes	Maekawa *et al* [32]	1998	20	20.1	45.6	ADM, every 30 min up to 4 h, every 3h up to 24 h, every 6 h up to 120 h	Japan	Neutrophil L selectin and CD11b both increase immediately and more slowly out to 24 h post trauma in ISS > 16 but not in ISS < 16
Polymorphonuclear Neutrophil Chemiluminescence in Whole blood from Blunt Trauma Patients with Multiple Injuries	Brown *et al*[56]	1999	12	36.4	49.5	< 24 h	United States	CR3a is a marker of neutrophil priming and is upregulated in trauma
Neutrophils are primed for cytotoxicity and resist apoptosis in injured patients at risk of for multiple organ failure	Biffl *et al*[13]	1999	12	22.6	N/A	Daily for 5 d	United States	Neutrophil apoptosis is delayed in trauma patients
Preferential Loss of CXCR-2 Receptor Expression and Function in Patients Who Have Undergone Trauma	Quaid *et al*[35]	1999	20	19	35	One sample within 24 h	United States	CXCR-2 expression and function are downregulated in severely injured patients
Superoxide production of neutrophils after severe injury: Impact of subsequent surgery and sepsis	Shih *et al*[57]	1999	18	26.2	41.6	1 d, 3 d, 7 d	Taiwan	Neutrophil superoxide production after trauma is initially increased but is then decreased in those who go on to develop multiorgan failure at day 7
Early role of neutrophil L-selectin in posttraumatic acute lung injury	Rainer *et al*[29]	2000	147	[1]	[1]	On admission to ED	Hong Kong	Total leukocyte and neutrophil counts, expression of L-selectin, and the ratio of neutrophil to plasma L-selectin increased with injury and were highest in those who developed acute lung injury (ALI). Soluble L-selectin decreased with injury severity and was lowest in those who developed ALI
Early Trauma polymorphonuclear neutrophil responses to chemokines are associated with development of sepsis, pneumonia and organ	Adams *et al*[34]	2001	15	34	36	12 h	United States	High CXCR2 activity correlated with ARDS. Low CXCR2 activity correlated with sepsis

failure								
Decreased leukotriene release from neutrophils after severe trauma: role of immature cells	Koller *et al*[40]	2001	15	35	35	1 sample, between 3-14 d	Germany	Neutrophils secrete less leukotrienes following trauma
Prospective study of neutrophil chemokine responses in trauma patients at risk for pneumonia	Tarlowe *et al*[36]	2005	32	27.4	35.1	ADM, 3 d, 7 d	United States	Prospectively assessed CXCR function and expression in neutrophils from trauma patients at high risk for pneumonia and their matched volunteer controls. CXCR2-specific calcium flux and chemotaxis were desensitized by injury, returning toward normal after 1 wk. CXCR1 responses were relatively maintained
Neutrophil priming for elastase release in adult blunt trauma patients	Bhatia *et al*[15]	2006	10	29.3	40.3	ADM, 24 h, 3 d, 5 d	United Kingdom	Neutrophils release more elastase after trauma
Aberrant regulation of polymorphonuclear phagocyte responsiveness in multi-trauma patients	Hietbrink *et al*[30]	2006	13	21	40	ADM, 3 d, 5 d, 7 d	Netherlands	Priming markers low in first week. Decreased responsiveness to fMLP with increased ISS
Neutrophil-derived circulating free DNA: a potential prognostic marker for posttraumatic development of inflammatory second hit and sepsis	Margraf *et al*[58]	2008	37	31.6	45	ADM, daily for 10 d	Germany	Kinetics of NET formation, 3 patterns of kinetics
Early expression changes of complement regulatory proteins and C5a receptor (CD88) on leukocytes after multiple injury in humans	Amara *et al*[39]	2010	12	48	38	4 h, 12 h, 24 h, 120 h, 240 h after trauma	Germany	Complement regulators and CD88 on neutrophils are significantly altered following trauma. CD55 is elevated, shows decreased expression
Nature of Myeloid Cells Expressing Arginase 1 in Peripheral Blood After Trauma	Bryk *et al*[45]	2010	10	18.63	43.7	< 24 h, 3-7 d, 14-21 d	United States	MDSCs derived from major trauma patients show increased arginase activity, allowing modulation of T cell responses
Divergent adaptive and innate immunological responses are observed in humans following blunt trauma	Kasten *et al*[11]	2010	22	22.8	36.3	1 sample, between 24-96 h	United States	CD11b kinetics, lipid rafts, phosphorylated Akt increased in trauma
A genomic storm in critically injured humans	Xiao *et al*[19]	2011	167	31.3	34	< 12 h, 1 d, 4 d, 7 d, 14 d, 21 d, 28 d	United States	Genomics of response to trauma, anti- and pro-inflammatory mechanisms activated simultaneously
A subset of neutrophils in human systemic inflammation inhibits T cell responses through Mac-1	Pillay *et al*[33]	2011	N/A	N/A	N/A	N/A	Netherlands	ROS-induced immunosuppressive CD16bright/CD62L dim neutrophil population first isolated
Kinetics of the innate immune response after trauma: implications for the development of late onset sepsis	Hietbrink *et al*[8]	2012	36	24.2	45	3-12 h, daily for 10 d	Netherlands	Kinetics of neutrophilia, CRP, IL-6, CD11b, FcγRII, CXCR1, respiratory burst, CD88
Molecular mechanisms underlying delayed apoptosis in neutrophils from multiple trauma patients with and without sepsis	Paunel-Görgülü *et al*[59]	2012	24	46.7	41.7	Routinely until 10 d	Germany	Neutrophil apoptosis is reduced after trauma and patients undergoing a post-trauma course complicated by sepsis exhibit different expression of pro- and anti-apoptotic regulators
Increased MerTK expression in circulating innate immune cells of patients with septic shock	Guignant *et al*[60]	2013	51	38	35	24-48 h	France	TAM receptors are differentially upregulated in sepsis and trauma
IL33-mediated ILC2 activation and neutrophil	Xu *et al*[48]	2017	472	20.2	N/A	ADM, < 24 h, daily	United States	IL33 kinetics, neutrophils produce IL-5

IL5 production in the lung response after severe trauma: A reverse translation study from a human cohort to a mouse trauma model						for 7 d		
Prehospital immune responses and development of multiple organ dysfunction syndrome following traumatic injury: a prospective cohort study	Hazeldine *et al* [23]	2017	89	24	41	< 1 h after trauma, 4-12 h, 24-48 h	United States	Early kinetics of neutrophil phenotype, including neutrophilia, cytokines, NETs, CD11b, and CD16/CD62L subsets
Early decreased neutrophil responsiveness is related to late onset sepsis in multitrauma patients: An international cohort study	Groeneveld *et al* [31]	2017	109	1	1	On arrival	Netherlands, South Africa	Reduced fMLP responsiveness in a cohort study at early time points and in association with septic shock
Heparin-binding protein as a biomarker of post-injury sepsis in trauma patients	Halldorsdottir *et al*[28]	2018	97	33	47	1 d, 3 d, 5 d	Sweden	HBP is a marker of neutrophil activation and correlates with ISS
A rise in neutrophil size precedes organ dysfunction after trauma	Hesselink *et al* [26]	2018	81	1	1	ADM, 6 h, 12 h, 24 h, 48 h	Netherlands	In patients who developed organ failure a significant increase in neutrophil count, size and complexity, and a decrease in lobularity were seen after trauma
Neutrophil-derived long noncoding RNA IL-7R predicts development of multiple organ dysfunction syndrome in patients with trauma	Jin *et al*[55]	2020	60	23.5	51.5	ADM	China	Neutrophil derived lnc-IL7R negatively correlates with MODS and mortality
New automated analysis to monitor neutrophil function point-of-care in the intensive care unit after trauma	Hesselink *et al* [5]	2020	15	33	1	<12 h, 3 d, 6 d, 10 d, 15 d	Netherlands	Patterns of phagosomal acidification correlate with infection, neutrophil CD16/CD62L subsets
Point-of-Care analysis of neutrophil phenotypes: A first step toward immune-based precision medicine in the Trauma ICU	Spijkerman *et al* [24]	2020	32	N/A	N/A	ADM to trauma bay	Netherlands	CD16/CD62L neutrophil subtype correlates with infection
Olfactomedin 4 Positive Neutrophils are Upregulated Following Hemorrhagic Shock	Kassam *et al*[61]	2020	56	N/A	41.5	ADM, 3 d, 7 d	United States	Increased OLFM4+ neutrophil fraction after blunt trauma associated with increased ICU length of stay, ventilator days
Current Concepts of the inflammatory response after major trauma – an update	Giannoudis[18]	2003	Review Paper	2	2	2	United Kingdom	Malignant SIRS can develop into MODS or ARDS, however main effect of trauma on neutrophils is suppressive
Trauma: The role of the innate immune system	Hietbrink *et al* [4]	2006	Review Paper	2	2	2	Netherlands	Neutrophils are the main effector cells leading to MODS, an overactive SIRS can lead to CARS/MARS
The systemic inflammatory response induced by trauma is reflected by multiple phenotypes of blood neutrophils	Pillay *et al*[3]	2007	Review Paper	2	2	2	Netherlands	Description of cell surface markers and their role in normal neutrophil function and in trauma
Postinjury immune monitoring: can multiple organ failure be predicted?	Visser *et al*[46]	2008	Review Paper	2	2	2	Netherlands	Excessive neutrophilia in the hours post trauma increase risk of MODS and mortality. Severity of the initial SIRS causes the depth of immunosuppression
Trauma equals danger – damage control by the immune system	Stoecklein *et al* [62]	2012	Review Paper	2	2	2	United States	Trauma induces immunosuppression, characterised clinically as CARS or MARS (mixed antagonist response syndrome)
The impact of trauma on neutrophil function	Hazeldine *et al* [16]	2014	Review Paper	2	2	2	United Kingdom	Sequestration of neutrophils in organs may lead to ARDS, whilst leaving the circulation open to infection

The systemic immune response to trauma: an overview of pathophysiology and treatment	Lord *et al*[17]	2014	Review Paper	[2]	[2]	[2]	United Kingdom	Heightened SIRS suppresses immune responses resulting in inflammation and cellular immunoparalysis, contradictory accumulation in organs causes organ dysfunction
Assessing the Immune Status of critically ill trauma patients by flow cytometry	Kuethe *et al*[63]	2014	Review Paper	[2]	[2]	[2]	United States	CD66b and CD11b are selective markers for neutrophils when expressed together. Neutrophils differentially regulate cell surface markers based on activation
The role of neutrophils in immune dysfunction during severe inflammation	Leliefeld *et al* [42]	2016	Review Paper	[2]	[2]	[2]	Netherlands	NETosis occurs in response to IL-8, TNFα and LPS, under the control of NADPH oxidase. Massive neutrophil release from the bone marrow may result in exhaustion
Neutrophils in critical illness	McDonald[64]	2018	Review Paper	[2]	[2]	[2]	Canada	TREM-1 may assist in differentiating sterile from septic SIRS, as TREM-1 only upregulates in sepsis
Innate Immunity in the Persistent Inflammation, Immunosuppression and Catabolism Syndrome and its implications for therapy	Horiguchi *et al* [6]	2018	Review paper	[2]	[2]	[2]	United States	Major DAMPs in trauma include HMGB1, mtDNA, ATP and cfDNA. Result in neutrophils releasing IL-6, TNFα, IFNγ, and ROS. Neutrophils exist in resting, primed and active states
Danger signals in the ICU	Schenck *et al* [10]	2018	Review Paper	[2]	[2]	[2]	United States	mtDNA is a main DAMP in trauma due to similarities to bacterial DNA. Early neutrophil chemotaxis is DAMP dependent
Neutrophil heterogeneity and its role in infectious complications after severe trauma	Hesselink *et al* [9]	2019	Review Paper	[2]	[2]	[2]	Netherlands	Activated neutrophils leave the blood, leaving dysfunctional neutrophils behind. Analysis of low density neutrophils, CD16/CD62L subtypes
Does neutrophil phenotype predict the survival of trauma patients?	Mortaz *et al*[1]	2019	Review Paper	[2]	[2]	[2]	Iran	CD11b is considered a marker of poor prognosis, increased CXCR2 relates to risk of ARDS. Understanding phenotype could allow use as a predictive tool

[1]Trauma cohorts divided into subgroups, full group statistics not available.

[2]Review article.

N/A: Not available; ADM: Admission; HMGB1: High mobility group box 1; mtDNA: Mitochondrial nucleic acids; cfDNA: Cell free DNA.

(Figure 1)[22].

A summary of the results and each study's patient demographics, including average age, ISS, and frequency of samples, is included in Table 1. Multiple changes to neutrophil phenotype were noted, and these changes can be broadly classified into physical parameters, cell surface markers, and changes in neutrophil function.

Physical parameters

Neutrophil count: There were eight papers that assessed changes in neutrophil count over time. In most cases these studies compared neutrophil counts in trauma patients to a control population, however the control samples only originate from one time point, from non-matched control volunteers, potentially introducing bias. There were also discrepancies in the number of samples collected, and the window in which samples could be collected at each time point. Lack of standardisation in data collection make it difficult to compare studies quantitatively.

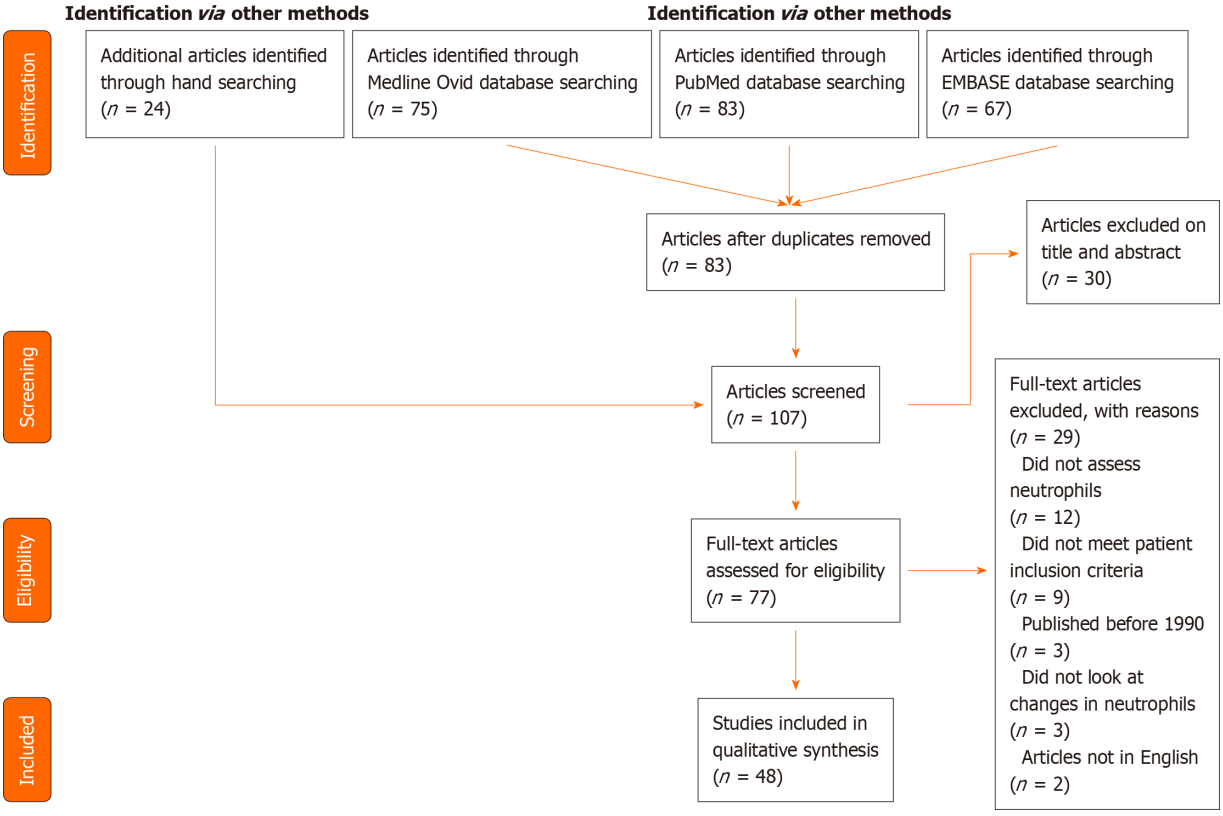

Figure 1 PRISMA diagram summarising included studies. Further characteristics of each study are available in Table 1.

Neutrophilia is the first and most easily assessable change following trauma, driven by endogenous cortisol and catecholamine release promoting neutrophil demargination from the vasculature and accelerated migration from the bone marrow [23,24]. As well as being one of the first events following trauma, neutrophilia is prolonged, with reports of neutrophil counts being 2- to 5-times higher in trauma patients out to 5 d compared to healthy controls, and remaining significantly elevated out to 10 d post-trauma[8,11]. Neutrophils make up more than 80% of the total white cell count for at least 5 d following trauma[25], demonstrating their critical role in the immune response post injury.

Peak neutrophilia occurs soon after injury, with maximum neutrophil counts usually being detected 3 h after trauma[25-27]. Indeed, Hazeldine and colleagues collected blood samples in the prehospital setting and showed that leucocytosis began within minutes of trauma and persisted for days[23].

Circulating neutrophil counts in patients with major trauma followed reproducible trends. Counts tended to drop from the initial peak between 6-24 h[25-27], but remained higher than controls. Multiple studies showed a further drop in neutrophil count between days 3 and 5, followed by a rebound to levels seen in the 6-24 h phase [8,23,25,28] (see Figure 2A for schematic).

Neutrophil size: There was one paper identified which discussed changes in neutrophil size. This was a recent paper by Hesselink and colleagues published in 2019 [26]. Neutrophil size is a recent marker of neutrophil activation and has been shown to be a good early predictor for MODS, with increased neutrophil size on admission to the emergency department correlating with the development of organ dysfunction later in the disease course[26].

In all patients, neutrophil size trended upward over the first 48 h following trauma [26]. In patients who developed MODS, there was a significant increase in neutrophil size relative to both healthy controls and to trauma patients who didn't develop MODS[26]. Though not routinely reported, neutrophil size is an easily assessable parameter as it is calculated during routine full blood examinations with differentials [26].

Cell surface markers

CD11b: There were ten papers analysing changes in CD11b. These papers faced

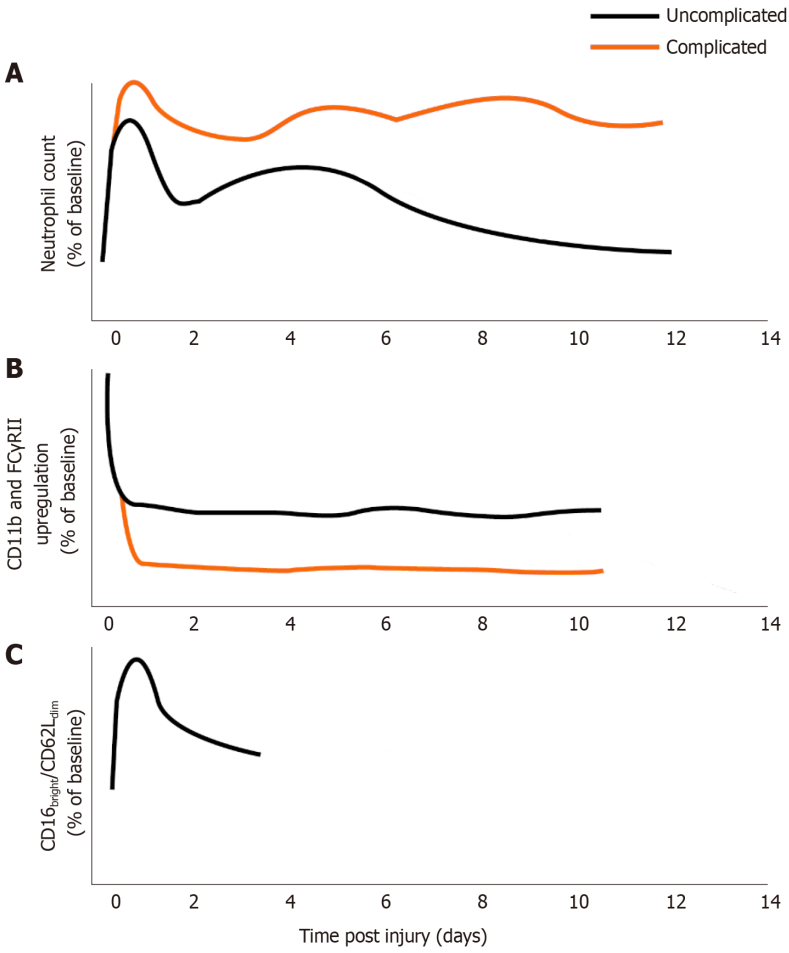

Figure 2 Schematical representation of neutrophil changes over time following major trauma, differentiated by complicated or uncomplicated clinical course. Complicated course indicates subsequent sepsis or multiple organ dysfunction, where evidence exists in the literature. A: Neutrophil number post injury relative to pre-injury/control levels; B: Neutrophil responsiveness (CD11b or FC Gamma receptor II upregulation in response to fMLP) following injury relative to control; C: Immunosuppressive $CD16^{bright}/CD62L^{dim}$ neutrophils as percentage of total neutrophils relative to control. No data exist for the presence of these cells more than 4 d after trauma or in complicated/uncomplicated courses.

similar challenges to those looking at neutrophil count – there are major discrepancies in methodology between papers, with large variations in the window for sample collection at time points which could have significant impacts on the resulting data. These papers generally compare results to a non-standardised control sample which is collected at only one time point.

CD11b is a component of the β2 integrin receptor MAC-1, which is involved in neutrophil adhesion to the endothelial wall during extravasation[29]. It also plays a significant role in phagocytosis and the respiratory burst, and is a well-documented marker of neutrophil activation[16,29].

Expression of CD11b increases within minutes of trauma, implying neutrophils become activated early after injury[23]. Most studies show CD11b is significantly increased relative to healthy controls in the first 12 h[8,11,14,23,25,30]. In some studies, this difference was maintained up to 10 d post trauma[8].

In general, CD11b tended to peak early after injury, usually within the first 6-12 h. This was followed by a trough from 24-48 h[8,14,23,25], before rising again and remaining at elevated levels after 48 h[8].

There is conflicting data on whether CD11b correlates with clinical markers. Botha *et al*[25] reported that expression at 12 h correlated negatively with base deficit (a marker of tissue ischaemia and reperfusion injury severity) and neutrophil count; this was hypothesised to represent extravasation of activated neutrophils into damaged tissues. Hietbrink *et al*[4,30] reported that an ISS >16 was associated with increased CD11b expression, whereas Spijkerman *et al*[24] reported that absolute levels of CD11b did not have value in predicting which patients would develop infection.

However, CD11b upregulation following stimulation with fMLP (N-Formylmethionyl-leucyl-phenylalanine, a potent neutrophil activator) shows improved value as

a predictive marker. At all timepoints, the fold-increase in CD11b after exposure to fMLP is decreased in trauma patients relative to healthy controls, and is particularly low on day 2 post trauma[8,23,24,30]. fMLP-induced CD11b expression was significantly lower in patients who developed infection and correlated with increased ISS[24,30]. A similar phenomenon of hypo-responsiveness has been observed with FC Gamma receptor II (FCγRII, CD32) upregulation, which has also been shown to correlate with development of infectious complications[8,31] (Figure 2B). Thus, assessment of surface marker changes in response to stimuli may be more predictive of immune dysfunction than expression of cell surface markers alone.

CD62L: Six papers analysed the expression of CD62L in neutrophils following major trauma. CD62L is a lectin involved in the rolling interactions with endothelium during extravasation[3,23]. It is shed on activation of the neutrophil to allow increased mobility into the tissues, and can therefore be used as a marker of extravasation as well as neutrophil activation[3,4,9,16].

Earlier studies demonstrated an apparent reduction in neutrophil CD62L expression accompanied by a rise in soluble L-selectin in plasma associated with severity of injury and development of complications[29,32]. More recent studies have supported these findings, specifically that traumatic injury correlates with a reduction in CD62L expression; this is consistent with the hypothesis that systemic inflammation leads to generalised neutrophil priming and the presence of a $CD16^{bright}/CD62L^{dim}$ subtype in the circulation (see below)[23,33]. Although the absolute number of CD62L molecules on neutrophils is decreased following trauma[16], it has been shown that trauma-derived neutrophils show significantly reduced shedding of CD62L when stimulated *in vitro* up to 72 h after trauma[23].

CXCR2 (CD182): Seven papers included analysis of the kinetics and function of CXCR2 following trauma. The quality of these studies varied (some included matched control groups whereas others did not) however results were broadly consistent and are discussed below.

CXCR2 is a chemokine receptor which responds to IL-8, allowing chemotaxis to sites of inflammation[3,8,34]. A change in surface expression of CXCR4 to CXCR2 is a critical step in allowing neutrophil efflux from the bone marrow (discussed further below)[35]. CXCR2 expression is easily downregulated following interactions with IL-8, and re-expression is delayed by up to 24 h[11,35]. CXCR2 is elevated within the first hour post-trauma, with decreased expression from 3 h onwards[23,36]. CXCR2 expression has been correlated with outcomes, with evidence suggesting that significantly increased CXCR2 responses to GRO-α (a CXCR2-specific ligand) correlated with ARDS, and significantly decreased responses correlated with sepsis [34]. Importantly, in this study there was no significant difference observed in CXCR2 expression between trauma patients who didn't develop complications and healthy controls[34], suggesting that CXCR2 could be used as a predictive tool for the development of complication post injury. Conversely, CXCR1 has been assessed several times and does not appear to change over time following trauma, nor correlate with clinical outcomes[34,36].

C5aR1 (CD88): The receptor for the complement anaphylatoxin C5a (C5aR1 or CD88) under physiological circumstances serves to drive important neutrophil antimicrobial responses such as chemotaxis and ROS production[37]. In severe inflammation such as multiple trauma, massive activation of the complement system occurs[38]. Amara and colleagues demonstrated changes in multiple complement regulatory proteins immediately after trauma, including a reduction in CD88 expression on neutrophils and an inverse association with ISS[39].

Neutrophil subsets, maturity and immunosuppression

Neutrophil heterogeneity is marked after trauma, though the functional implications of identified differences in circulating cells, as well as their relationship to cellular developmental stages remains under investigation. In healthy controls, the circulating neutrophil population is almost exclusively composed of mature segmented cells with lobular nuclei[40]. Following trauma there is a rapid increase in the number of immature neutrophils in the blood stream. This occurs in part due to emergency granulopoiesis, a G-CSF induced acceleration of neutrophil production and release accompanied by a diversion of other cell lineages toward neutrophil development, as reviewed elsewhere[41].

Another factor driving a circulating neutrophilia is the CXCR4/CXCL12 axis. During development in the bone marrow immature neutrophils express CXCR4 (chemokine receptor 4), which responds to the high levels of CXCL12 (chemokine

ligand 12) in the bone marrow, causing the cells to remain in-situ[42]. Trauma results in disruption of the CXCR4/CXCL12 balance, allowing neutrophils to enter the circulation and resulting in a heterogenous neutrophil population in terms of maturity and function[35]. One method of assessing cellular maturity is the complexity and lobularity of nuclei; immature cells have a less lobulated nucleus and thus are often referred to as 'band cells' which can represent up to 98% of circulating neutrophils in conditions of severe stress such as major trauma or septic shock[35]. It has been reported that the average lobularity (and therefore maturity) of neutrophils in the circulation trends downwards over the first 48 h after trauma[26].

Combining marker expression has allowed the subtyping of neutrophils based on CD16 and CD62L expression. The differential expression and corresponding intensity of the signal detected on flow cytometry give rise to the terms 'bright' and 'dim'. Seven papers included discussions on neutrophils categorised using this process.

Under homeostatic circumstances, a homogenous population of $CD16^{bright}/CD62L^{bright}$ neutrophils exists[33]. However, in the first 12 h after trauma they account for less than 40% of the neutrophil population[5]. By day 3, they have increased and stabilised at approximately 80% of neutrophils in circulation[5].

In contrast, the hypersegmented $CD16^{bright}/CD62L^{dim}$ subtype exhibits an immunosuppressive phenotype[33]. Proteomic analysis suggests they are not simply more mature neutrophils, but rather a completely separate subtype[43]. These cells produce ROS to suppress lymphocytes similarly to myeloid-derived suppressor cells (MDSCs)[36]. They show adequate phagocytosis but dysfunctional phagolysosomal acidification[31], potentially resulting in neutrophils being able to phagocytose but not kill pathogens and thus allowing the neutrophils to act as a method of transport around the body and into the tissues[9]. Whilst they make up less than 20% of the total circulating neutrophil population following trauma, they are significantly elevated compared to controls within minutes of trauma and remain elevated up to 72 h later[5,23]. To our knowledge, no associations with organ dysfunction or secondary sepsis have yet been demonstrated (Figure 2C).

A third subset ($CD16^{dim}/CD62L^{bright}$) of neutrophils comprise half of the neutrophil population up to 12 h after trauma. From day 3 onwards their percentage in the circulation rapidly decreases until they comprise less than 10% of the circulating neutrophil population[5,24]. These cells possess a band shaped nucleus, indicating they are likely immature neutrophils released from the bone marrow[17,42]. Despite their immaturity, these cells appear to have adequate phagosomal acidification compared to the other subtypes discussed[5].

Another neutrophil subtype described in autoimmunity, neoplasia and sepsis are low density neutrophils (LDNs), so named due to their isolation from the peripheral blood mononuclear cell fraction of centrifuged blood samples rather than the polymorphonuclear cell fraction, indicating a lower physical density than expected of neutrophils[9]. This population of cells is in itself heterogeneous, demonstrating different phenotypes in different disease states and has been reviewed elsewhere[44]. Low density neutrophils are much less investigated in the context of major trauma, with our review of the literature yielding a single publication which showed LDNs found in the PBMC layer displayed evidence of an activated phenotype and significant arginase activity, known to suppress T-cell function[45].

DISCUSSION

Immature neutrophils predominate in the circulation following trauma

Neutrophil count is readily available from routine blood work and remains significantly elevated for a prolonged period after trauma. This increase in neutrophil count is associated with a relative decrease in $CD16^{bright}/CD62L^{bright}$ neutrophils and an increase in $CD16^{dim}/CD62L^{bright}$ neutrophils, which are thought to be immature due to early release from the bone marrow[5,9,16,23,24]. This evidence is supported by the observation that the average lobularity of neutrophils in the circulation decreases over the first 48 h, implying an increasing proportion of less mature neutrophils in the blood[26].

This increase in the proportion of immature neutrophils in the bloodstream may be due not only to influx of developing neutrophils from the bone marrow, but also due to extravasation of more mature, activated neutrophils into the end organs[25,27]. This extravasation of highly activated cells may result in collateral tissue damage and predispose to MODS[16,17,27,46]. The extravasation of neutrophils may explain the observed reduction in neutrophil count over the first 6-24 h. A correlation has been

identified between the magnitude of the neutrophil count, the steepness of the decrement at 12 h and the development of organ dysfunction, which may make this an attractive avenue of investigation for prognostication in this patient group[27,46].

Extravasation of activated neutrophils may leave the circulation susceptible to infection

A reduction in lobularity accompanied the drop in neutrophil count between days 3 and 5 post injury, correlating with changes in activation markers such as CD62L and fMLP-induced CD11b expression (see "Results" section). There are several potential reasons for this phenomenon. One is that the lifespan of a circulating neutrophil in trauma is 3 to 5 d, however it takes 7 d for the bone marrow to produce new neutrophils leading to a potential gap in neutrophil supply and demand between days 4-7[1,8,13]. Whilst it is tempting to accept this explanation, differences in lifespan are unlikely to solely account for the observed reduction in circulating neutrophil count, especially given the phenomenon of emergency granulopoiesis[41].

Another theory is that activated neutrophils extravasate into tissues, leaving behind potentially immature or hypofunctional neutrophils with defects in activation, chemotaxis[9,27,30] and antimicrobial functions[23], consistent with our work in broader critically ill cohorts at risk of secondary infection[7,47]. This hypothesis would be supported by the observation that CD11b, a marker of activation and key regulator of extravasation, initially peaks within 6 h of injury before decreasing at the same time the neutrophil count and average lobularity decrease[8,25-27], indicating activated cells have extravasated. The observed decrease in CXCR2 expression after 3 h may indicate that cells expressing high levels of CXCR2 have already extravasated into the tissues[16,23]. The remaining cells in circulation may be ineffective at clearing infection, predisposing to bacteraemia and sepsis[9,12,27,30]. Further, the average lobularity of neutrophils dropped faster in patients who later developed organ dysfunction[26], consistent with the hypothesis that more mature cytotoxic neutrophils moved into the tissues and were replaced with less mature cells from the bone marrow.

Extravasation of activated neutrophils could be complicated by changes in the inflammatory state around this time. Day 5 is typically when the anti-inflammatory response starts to dominate, accompanied by a rise in the immunosuppressive cytokines IL-5 and IL-10, and the emergence of heterogeneous and immunosuppressive neutrophils[9,16,42,48,49]. The massive complement activation and reduced CD88 expression following trauma (see above) may also play a part, as reduced CD88 expression has been associated with nosocomial infection[7] and defective neutrophil antimicrobial function in general critically ill cohorts[47]. Thus, the neutrophils that remain in circulation may show suppressed activity partly due to the increased anti-inflammatory signalling in the bloodstream.

Deficient circulatory immunity due to one or more of bone marrow exhaustion, intrinsically hypofunctional neutrophils or active immunosuppression may allow for haematogenous seeding of bacteria into multiple organs filled with primed and activated neutrophils. This may act as a 'second hit', resulting in a secondary SIRS response causing organ dysfunction and sepsis if the infection is not controlled. These changes are summarised in Figure 3 below.

Limitations

This study has several limitations, relating to both the search strategy and biases within the primary studies. Firstly, the studies reviewed are limited in that they study circulating neutrophils, which although pragmatic may not represent the phenotypes and activity of neutrophils sequestered in the tissue[13].

There are also limitations relating to observational studies. Monitoring neutrophils over extended periods of time makes it difficult to account for confounding variables such as patient comorbidities, and most of the studies done in this area use a pool of control samples rather than individually matched controls.

There does not appear to be a consensus on methodology across studies when it comes to frequency of sample collections and the time window in which samples can be collected. This makes quantitative meta-analysis of these data difficult, as some studies collected every 30-60 min after trauma whereas other studies only collected one sample every 3-5 d.

This review was limited in scope, so that not all markers of neutrophil dysfunction could be discussed. However, this allowed for a focussed review of clinically relevant markers that show the most promise and had the most literature available for analysis. Furthermore, this review focussed specifically on the neutrophil, and whilst an

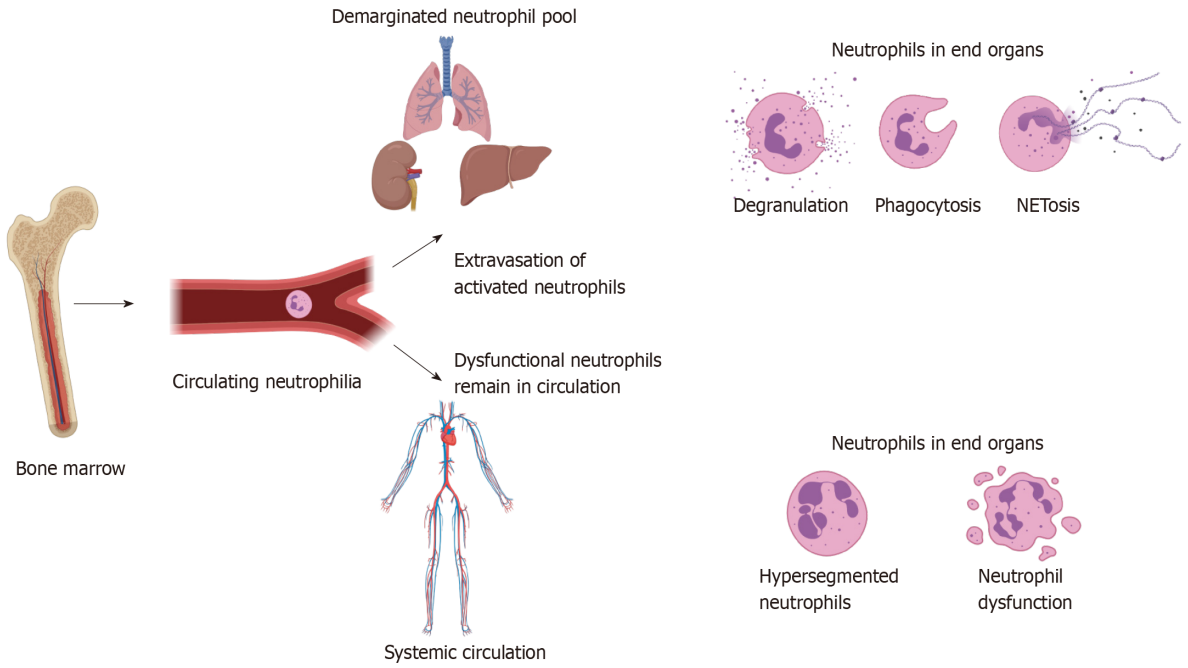

Figure 3 Neutrophil extravasation and resultant immune dysfunction. Tissue damage caused by injury leads to danger associated molecular pattern, catecholamine and corticosteroid release, which result in neutrophil egress from the bone marrow, as well as increased production through emergency granulopoiesis. This leads to a circulating neutrophilia and altered phenotypes of circulating neutrophils as discussed in text. It is hypothesised that hyperinflammatory cells expressing high levels of adhesion markers transmigrate into the demarginated pool in the lungs, spleen, liver and other end organs, where they may cause further inflammation through NETosis, degranulation and phagocytosis, leading to organ dysfunction. The loss of these highly inflammatory cells from the circulation leads to remaining neutrophils being dysfunctional, predisposing the individual to immune failure and secondary infection. Figure produced using Biorender.

important cell type in this clinical context, one cell type is clearly not the only determinant of immune function and clinical outcome. The original search strategy allowed for focused results however this may have also limited the number of papers found. To address this, three databases were searched and the reference lists of selected papers were hand searched to ensure seminal papers had been identified.

Implications and future research

This review has several implications for clinicians working with major trauma patients in the ICU. A major finding of this review is that there are several markers of neutrophil function which can be assessed with a simple blood sample, and many of these markers have predictive value for risk stratifying trauma patients at risk of immune dysfunction. Current tools used to categorise major trauma fail to adequately distinguish the various phenotypes seen in major trauma patients, and one of the major outcomes of this work may be the identification of immunological signatures which can be used to allow individualised tailored care.

This paper proposes several avenues for future research. Firstly, one issue encountered in applying neutrophil markers to clinical outcomes in trauma is that only individual markers have been assessed for predictive value. The immune system is complex and following trauma the system is dynamic and overlapping; as such, a single marker is unlikely to provide insight into the complexity of the overlapping SIRS and CARS responses[3]. Therefore, the authors suggest developing a clinical tool which combines multiple phenotypic markers, in a similar way to the APACHE-II or SOFA tools for measuring and classifying critical illness. This tool may encompass values such as the ratio of neutrophils at 3h:12h, neutrophil lobularity, fMLP-induced CD11b/FCγRIII expression, CXCR2, and the relative proportions of neutrophil CD16/CD62L subtypes. Combining these values may have better prognostic capability than the single values alone, and allow for the identification of specific subcategories of trauma patients that may benefit from specific clinical interventions, as has been reported for ARDS[50,51]. Recently published work related to COVID-19 has demonstrated the utility of this approach and may inform subsequent research in the trauma context[52].

A second area would be to develop techniques that allow the phenotyping of extravasated neutrophils. There has been some success in analysing neutrophils obtained from broncho-alveolar lavage in patients with ARDS, however it would be

interesting to analyse samples from other end organs in trauma patients to determine if the phenotypes of the neutrophils in these organs match the phenotypes seen in circulation, or diverge in a way we would expect. Characterisation of neutrophils that have moved back into circulation from the tissues (reverse transmigration) may allow for less invasive analysis of these cells[53,54]. Thirdly, the expanding utility of -omic profiling may allow for more in depth analysis of the genomic and proteomic changes that precede phenotypic variability, potentially allowing for risk stratification even earlier following trauma[19,55].

CONCLUSION

The immunophenotype of neutrophils isolated from patients with major trauma differs significantly from healthy controls and varies over the course of intensive care admission. Several of these changes are correlated with adverse outcomes, including organ dysfunction and secondary sepsis.

This review aimed to provide an overview of the extant literature and characterise key aspects of neutrophil immunophenotype in trauma, with special attention to factors which may hold prognostic value for patients with severe trauma. Key findings included a persistently elevated neutrophil count, stereotyped alterations in cell-surface markers of activation and the elaboration of heterogeneous and immunosuppressive populations of cells in the circulation. Many of these changes may be driven by extravasation of highly activated neutrophils into the peripheral tissues, predisposing to organ dysfunction and leaving the circulating compartment hypofunctional and less able to respond to infectious challenges. Future research may benefit from comprehensive combinations of phenotypic and functional markers, as well as interrogation of cells that have extravasated into tissues. These promising initial findings combined with further research may allow clinicians to better risk-stratify their patients.

ARTICLE HIGHLIGHTS

Research background

Neutrophils play an important role in immune dysfunction after major traumatic injury and alterations in this cell type are associated with the development of complications including organ failure and secondary infection. The kinetics of neutrophil dysfunction in the context of trauma is not completely understood and may have important implications for therapy.

Research motivation

Developing a granular and nuanced understanding of neutrophil kinetics and changes after trauma is necessary if key associations with disease and therapeutic targets are to be identified.

Research objectives

This review aimed to provide an overview of established aspects of neutrophil immunophenotypes in trauma, with special attention to factors which may hold prognostic value.

Research methods

This study was a systematic review of the PubMed, Ovid Medline and Embase databases for all papers on neutrophil kinetics or function after major trauma (injury severity score > 12) in adults (≥ 18 years) since 1990.

Research results

Key findings include a notable increase in immature ($CD16^{dim}$/$CD62L^{bright}$) neutrophils poorly responsive to subsequent bacterial stimuli which may confer susceptibility to bacteraemia. Highly inflammatory neutrophils which express adhesion markers and chemoattractant receptors such as CD11b and CXCR2 extravasate into end organs where they may damage host tissues and cause organ dysfunction.

Research conclusions

Neutrophil dysfunction after major trauma is complex and changes over time. Several stereotyped changes have been observed in multiple studies, as discussed above. Immunophenotyping of multiple cell types combined with clinical and laboratory data may yield endotypes likely to respond to different therapies.

Research perspectives

Areas of ongoing research include integration of multiple markers of immune dysfunction, enrichment strategies for clinical trials of immunomodulatory agents and the assessment of live cells in tissues rather than the circulation.

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SYSTEMATIC REVIEWS

Elderly adults with COVID-19 admitted to intensive care unit: A narrative review

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Abstract

BACKGROUND

In the context of the Coronavirus disease 2019 (COVID-19) pandemic, it has been reported that elderly patients are particularly at risk of developing severe illness and exhibiting increased mortality. While many studies on hospitalized elderly patients with COVID-19 have been published, limited information is available on the characteristics and clinical outcomes of those elderly patients admitted to intensive care unit (ICU).

AIM

To review the available evidence of the clinical data of elderly patients admitted to the ICU due to COVID-19.

METHODS

We searched for published articles available in English literature to identify those studies conducted in critically ill patients admitted to the ICU due to COVID-19, either exclusively designed for the elderly or for the whole ICU population with COVID-19, provided that analyses according to the patients' age had been conducted.

RESULTS

Only one study exclusively focusing on critically ill elderly patients admitted to the ICU due to COVID-19 was found. Eighteen additional studies involving 17011 ICU patients and providing information for elderly patients as a subset of the whole study population have also been included in the present review article. Among the whole patient population, included in these studies, 8310 patients were older than 65 years of age and 2630 patients were older than 70 years.

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Clinical manifestations were similar for all patients; however, compared to younger ones, they suffered from more comorbidities and showed a varied, albeit high mortality.

CONCLUSION

In summary, at present, although elderly patients constitute a considerable proportion of critically ill patients admitted to the ICU due to severe COVID-19, studies providing specific information are limited. The evidence so far suggests that advanced age and comorbidities are associated with worse clinical outcome. Future studies exclusively designed for this vulnerable group are needed.

Key Words: SARS-CoV-2; COVID-19; Elderly; Critically ill; Intensive care unit mortality; Respiratory failure

Core Tip: Coronavirus disease 2019 (COVID-19) affects people of all ages; however, the risk for severe illness increases with age, with older adults being at highest risk. While many studies with regard to COVID-19 impact on elderly patients have been carried out, the information on characteristics and clinical outcome of critically ill elderly patients admitted to the intensive care unit (ICU) due to COVID-19 is scarce. Studies exclusively designed for these patients are limited. Data derived from these studies and additionally from studies analyzing critically ill elderly patients as a subset of the whole ICU population with COVID-19, support that advanced age along with comorbidities are associated with worse clinical outcome.

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INTRODUCTION

December 2019 was marked by the emergence of coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)[1]. First detected in Wuhan, China, this infectious disease has spread rapidly worldwide, and it was declared a global pandemic by the World Health Organization on March 11, 2020[2].

The major clinical complication in patients with COVID-19 is respiratory failure and acute respiratory distress syndrome (ARDS) followed by sepsis, septic shock and multi-organ failure. The disease affects people of all ages; however, the incidence and the severity of COVID-19 consistently rises with increasing age[3-12]. Even if a completely understood pathophysiological mechanism for the severity of COVID-19 infection in the elderly has not been described, two major axes play a cornerstone role, multimorbidity such as hypertension, cardiovascular disease, diabetes, chronic respiratory and chronic kidney disease[13,14] as well as changes and dysregulation affecting organ systems of older adults. Specifically, changes affecting the immune system, processes known as immunosenescence and inflammaging[15-17] and anatomical and functional decline of the respiratory system[18], have been proposed to contribute to a more severe course of infection at advanced age. Furthermore, Santesmasses *et al*[19], have recently indicated an age-related increased ACE2 gene expression, which encodes the cell entry receptor for SARS-CoV-2, with increased levels of ACE2 protein in older individuals, highlighting that advanced age represents a major risk factor for disease severity.

A consequence of the increased incidence and severity of COVID-19 infection among elderly populations compared with younger adults is that the former will often need advanced medical care[20]. This fact, combined with the ongoing global population ageing[21], highlights the burden that this particular age group with severe

COVID-19 infection puts on healthcare systems worldwide.

According to the available evidence, elderly patients are at an apparent increased risk of adverse outcome[22-27]. The mortality within older patient population could probably be further compounded by shortages of ICU beds and/or access to mechanical ventilatory support[28]. Indeed, in the context of COVID-19 pandemic, age and co-morbidities have been used as selection criteria to triage patients for ICU admission in order to prioritize the younger ones[29,30]. On the other hand, it could be suggested that in no overwhelmed ICU capacity, access to ICU for elderly patients with COVID-19 may be preserved and possibly could contribute to survival of severe forms of COVID-19.

Therefore, given the significant proportion of elderly patients putting pressure on health care systems, understanding the course of COVID-19 in this specific population is considered of major importance. The aim of this review is to present the existing literature and to provide a summary of the current evidence concerning characteristics and outcomes of elderly patients admitted to the ICU due to COVID-19, useful for the better management of this vulnerable population in the future.

MATERIALS AND METHODS

The search of the published medical literature was conducted across PubMed and Google Scholar databases using the keywords "COVID-19", "SARS-CoV-2", "critical care", "intensive care", "ICU", "mechanical ventilation", "elderly", "older patients", "death", "mortality", in order to find studies reporting characteristics and clinical outcome of critically ill elderly patients with laboratory- confirmed COVID-19 admitted to ICU, published in 2020 and in the early 2021. The last literature search was conducted on May 20, 2021. Only articles published in English were included; no limitations were applied to study design or country of origin. We also searched the reference lists of relevant articles to identify further articles. Studies were considered eligible if they included elderly patients with COVID-19 either exclusively or as a group among the whole study ICU population. Studies that did not analyse separately the subset of elderly patients were excluded.

The following data were extracted: first author, year of publication, country of origin, sample size of patients with COVID-19, mean or median age, number of elderly patients, number of deaths in each age group. Since there is no universally accepted age cut-off defining "elderly"[31], we followed each study's definition as it was used by the authors.

Our initial search did not identify studies exclusively designed for critically ill elderly patients with COVID -19 admitted to the ICU. Thus, we included those studies that provided separate data for elderly patients, as a subgroup, in the analyses of the whole study ICU population with COVID-19. However, during the revision process of the present review article, two additional studies have been recently released; therefore they have been added to the present review[32,33].

RESULTS

Description of the studies

Finally, a total of 19 studies fulfilling the inclusion criteria were included involving 18210 critically ill patients admitted to the ICU due to COVID-19. The proportion of elderly patients included in the whole studies population was considerable: 10646 patients were older than 60, 8310 patients older than 65 and 2630 patients older than 70 years of age. Table 1 lists the summary characteristics of the included studies. Five studies were conducted in China, three studies in the United States, one in Canada, one in Australia, one in Kuwait and eight in Europe (Italy, Germany, Sweden, the United Kingdom and the Netherlands). As the duration of mechanical ventilation and recovery from COVID-19 are often quite prolonged procedures, several articles included a substantial number of patients who were still in the ICU at the end of data collection.

Presence of comorbidities

In the large cohort study by Grasselli *et al*[23], including 1591 patients with COVID-19 admitted to ICUs of the Lombardy Region, Italy, 363 patients (23%) were older than 71 years. All patients older than 80 and 76% older than 60 had at least one comorbidity.

Table 1 Critically ill coronavirus disease-2019 elderly patients, included in observational clinical studies conducted in intensive care units

Ref.	Country	Median age, yr	Sample size / No. of the elderly admitted to the ICU (proportion, %)	ICU mortality, No. of deaths (%), all ages	ICU mortality of the elderly, No. of deaths and proportion (%)	Comments
Yang *et al*[8], *Lancet Respir Med*	China	59.7[1]	52 / 27 ≥ 60 yr (52)	32 (61.5)	20/27 (74.1) (≥ 60 yr)	-
Grasselli *et al* [23], *JAMA*	Italy	63	1591 / 961 ≥ 61 yr (60.4)	405 (60.3)	322/436 (73.9) (≥ 61 yr)	525/961 elderly patients still in ICU; 920/1591 patients (all ages) still in ICU
Richardson *et al* [24], *JAMA*	United States	N/A	1281 / 613 ≥ 65 yr (47.8)	291 (78)	182/200 (91) (≥ 65 yr)	413/613 patients ≥ 65 yr old still in hospital; 908/1281 patients (all ages) still in hospital
Bhatraju *et al*[49], *NEJM*	United States	64[1]	24 / N/A	12 (57.1)	62 (≥ 65 yr)	3 patients remained intubated at the end of the study
Karagiannidis *et al*[52], *Lancet Respir Med*	Germany	71	1727 / 1305 ≥ 60 yr (75.5)535, 70-79 yr; 388, ≥ 80 yr	906 (53)	174/382 (46), 60-69 yr; 335/535 (63), 70-79 yr; 280/388 (72), ≥ 80 yr	ICU deaths in elderly with invasive and non-invasive mechanical ventilation are reported
Yu *et al*[47], *Crit Care*	China	64	226 / 149 ≥61 yr (65.9)	87 (41.2)	62/140 (44) (≥ 61 yr)	9/149 elderly patients still in hospital; 15/226 patients (all ages) still in hospital
Shi *et al*[34], *Clin Lab Anal*	China	59.4[1]	161 / 83 ≥ 60 yr (51.5)	50 (39)	36 (60-74 yr)24.24 (> 74 yr)	Further comparison analysis revealed that no difference was found among the following age group patients: ≤ 44, 45-59, 60-74, and ≥ 75 yr; 33/161 still in hospital- N/A if they were in ICU or in hospital's ward
Burrell *et al*[35], *MJA*	Australia	63.5	200 / 123 ≥ 60 yr (61.5); 97 ≥ 65 yr (48.5)	30 (15)	28/123 (22.8) (≥60 yr); 25/97 (25.8) (≥ 65 yr)	6/200 patients still in hospital wards
Aleva *et al*[36], *J Crit Care*	The Netherlands	65[1]	50 / 30 ≥ 65 yr (60)	13 (32)	10/30 (33) (≥ 65 yr)	All survivors successfully discharged from the hospital
Mitra *et al*[37], *CMAJ*	Canada	69	117 / 76 ≥ 65 yr (64.9)	18 (17.1)	16/69 (23) (≥ 65 yr)	7/76 elderly patients still in ICU; 12/69 elderly patients still hospitalized; 12/117 patients (all ages) still in ICU
Alshukry *et al* [38], *PLoS One*	Kuwait	47	82 / 25 > 60 yr (30.4)	60 (73.1)	17/25 (68) (> 60 yr)	-
Larsson *et al*[39], *Acta Anesthesiol Scand*	Sweden	59	260 / 110 ≥ 60 yr (42.3); 28 ≥ 70 yr (10.7)	60 (30.3)	37/81 (45.7) (≥ 60 yr)	29/110 elderly patients still in ICU; 62/260 patients (all ages) still in ICU
Wang *et al*[42], *AJRCCM*	China	60	344 / 194 ≥ 60 yr (56.4)	133 (38.7)	101/194 (52.1) (≥ 60 yr)	-
Auld *et al*[46], *Crit Care Med*	United States	64	217 / 106 ≥ 65 yr (48.8)	62 (29.7)	45/103 (44) (≥ 65 yr)	3/106 elderly patients still in ICU; 8/217 patients (all ages) still in ICU
Xu *et al*[48], *Crit Care*	China		239 / 112 ≥ 65 yr (46.9)	147 (61.5)	82/112 (73.2) (≥ 65 yr)	-
Thomson *et al* [50], *PLoS One*	United Kingdom	62	156 / 89 ≥ 60 yr (57)	38 (24.3)	31/89 (34.8) (≥ 60 yr)	-
Nachtigall *et al* [51], *Clin Microbiol Infect*	Germany	73	399 / 318 ≥ 60 yr (79.6)	109 (27.3)	102/318 (32) (≥ 60 yr)	-
Guillon *et al*[32], *Intensive Care Med*	France	N/A	9885 / 5126 ≥ 65 yr (51.9); 480 ≥ 80 yr (4.9)	2914 (29.5)	1986/5126 (38.7) (≥ 65 yr); 300/480 (62.5) (≥ 80 yr)	-
Dres *et al*[33], *Ann Intensive Care*	France, Switzerland, Belgium	74	1199 / 639 70-74 yr (53.3); 367 75-79 yr (30.6); 193 > 80 yr (16.1)	549 (45.8)	247/639 (38.7) (70-74 yr); 173/367 (47.1) (75-79 yr); 129/193 (66.8) (> 80 yr)	All patients were ≥ 70 yr old

[1]mean value. ICU: Intensive care unit; N/A: Not available.

Hypertension was the most common, followed by diabetes, hypercholesterolemia, ca

Similarly, in the large study of 5700 hospitalized patients with COVID-19 in the United States, including a subgroup of 373 ICU patients, older persons and those with pre-existing hypertension and/or diabetes were highly prevalent[24]. Other chronic conditions, such as smoking, malignancy, chronic kidney disease and chronic liver disease were less reported elsewhere[34-36]. In another study by Mitra *et al*[37] in critically ill patients with COVID-19 admitted to ICU, the majority were older than 65 and 73.5% of patients had at least one medical comorbidity. Seventeen (94.4%) out of the 18 patients who died (with a median age of 75 years), had at least one comorbid disease[37]. In addition, Burrell *et al*[35], have shown that the number of comorbidities was associated with increased risk of ICU admission, need for mechanical ventilation or death. Similarly, older patients with comorbidities and ARDS were found at increased risk of death[8,38], though such an association was not observed elsewhere [36,39].

Clinical features

Based on the data collected from the selected studies, fever, cough, and shortness of breath were the most commonly developed symptoms among patients with COVID-19, including older adults[40]. Compared to younger patients, older ones more frequently presented shortness of breath; a factor related to dismal prognosis[41,42]. Other clinical manifestations in the elderly included fatigue, myalgia, nasal congestion, sore throat, diarrhea, nausea, anorexia, headache, and dizziness[43-45]. Other atypical presentations of the infection in elderly patients included absence or low-grade fever [36], abdominal pain and delirium[16,45]. Interestingly, in the cohort study of Kennedy *et al*[43], delirium symptoms, such as impaired consciousness, disorientation and inattention were found to be among the most common clinical manifestations in patients aged over 65. Additionally, 37% of patients presented delirium in the absence of fever or shortness of breath, while delirium was correlated with adverse clinical outcomes, including ICU admission or even death[43].

Mechanical ventilation

Among the 19 included studies, only seven report on mechanical ventilation use in older individuals. In the study by Grasselli *et al*[23], the majority (89%) of elderly patients admitted to the ICU received invasive mechanical ventilation with high levels of positive end expiratory pressure (PEEP). There was need for higher fraction of inspired oxygen (FiO_2) in the group aged ≥ 64 years compared to the group aged ≤ 63 years (70% *vs* 60% respectively, $P = 0.006$); the ratio of the partial pressure of oxygen in arterial blood (Pao_2) to Fio_2 was higher in the younger patients compared to older ones (163 *vs* 156, $P = 0.02$). In addition, patients with hypertension were significantly older and had higher PEEP levels and lower PaO_2/FiO_2 compared with patients without hypertension[23].

In the studies by Auld *et al*[46], Yu *et al*[47] and Richardson *et al*[24], the proportion of elderly patients requiring mechanical ventilation was 52%, 89% and 91% respectively. In the large study by Richardson *et al*[24], which included 5700 patients hospitalized with COVID-19 in the New York City area, 373 patients (14.2%) were admitted to the ICU and 320 (12.2%) of them received invasive mechanical ventilation. An intriguing find was that older and frailer patients were less likely to receive ventilatory support compared to younger ones (< 65 years old); however, it could be attributed, at least in part, to incomplete outcome data, since 413 out of 613 patients were still hospitalized at the study end.

Clinical outcome

Usually, mortality rates were calculated based on the number of patients who had an outcome or had been discharged from the ICU, thus, excluding patients who were still in ICU. In all studies without exception, older patients with COVID-19 admitted to the ICU had a higher mortality rate compared to younger patients. In the study by Yang *et al*[8], 20 out of 27 (74.1%) patients ≥ 60 years old died. Similarly, in the study by Xu *et al*[48], among 112 critically ill patients ≥ 65 years old, mortality rate was 73.2 %. Alshukry *et al*[38], in their study included 82 patients admitted to the ICU; 17 out of 25 (68%) patients ≥ 60 years old died, while Bhatraju *et al*[49] reported similar mortality rates in patients ≥ 65 years (62%). Other studies, namely those by Auld *et al*[46], Yu *et al*[47], and Larsson *et al*[39], which included, 106, 149 and 110 elderly patients respectively, among the whole ICU study population, reported mortality rates of 44%, 44% and 45.7% respectively. Comparable mortality rates were reported by Shi *et al* [34], 36%, Burrell *et al*[35], 25.8%, Aleva *et al*[36], 33% and Mitra *et al*[37], 23%, though, not all patients had reached an outcome at the study end. Finally, Thomson *et al*[50], in 89 patients ≥ 60 years old admitted to the ICU with COVID-19 reported a mortality

rate of 31.3%.

In accordance with the aforementioned observational small-scale studies, large studies have reported similar findings. Indicatively, in the study by Richardson *et al* [24] mortality rates for those who received mechanical ventilation in the 18-to-65 and older-than-65 age groups were 76.4% and 97.2%, respectively. Mortality rate for those in the 18-to-65 and older-than-65 years age groups who did not receive mechanical ventilation was 1.98% and 26.6%, respectively.

In the earlier study by Wang *et al*[42], which included 344 patients admitted to ICU due to COVID-19, older patients (> 60 years) with comorbidities were at dramatically increased risk of death, having a mortality of 75.9% (101/194), whereas a 24.1% mortality was observed in patients ≤ 60 years old. A lower mortality of 32% has been recently reported by Nachtigall *et al*[51], who analyzed 318 critically ill patients ≥ 60 years old with COVID-19 in German ICUs.

In the large retrospective analysis by Grasselli *et al*[23], older age was, among others, an independent risk factor associated with increased mortality. Specifically, 322 out of 436 (73.9%) ICU patients over 60 years of age died. Again, as commented above, a considerable number of patients (525 out of the 1521 study patients) were still in the ICU at the end of the study. Possibly for the same reason, the reported mortality of 91% among older patients in the study by Richardson *et al*[24], may have been overestimated, as it was calculated only for 413 out of 613 patients ≥ 65 years old who were either discharged alive or died by the end of the study.

The German nationwide cohort study by Karagiannidis *et al*[52] comprised 1727 mechanically ventilated patients, 75.5% of them aged ≥60 years. The mortality rate of 60.5% in this age group was remarkably higher compared to the observed mortality rate of 28% in the 18-to-59 age group. Further stratifying elderly patients (≥ 60 years) by age (60-69, 70-79, ≥ 80 years old), the risk for death increased with each successive age group (46%, 63%, 72% respectively). Moreover, comparison between mechanically ventilated patients and non-ventilated ones revealed that the latter presented significantly lower mortality rates regardless of age (1% and 22.5% in the 18-to-59 and ≥ 60-age group respectively).

Finally, two recently published large-scale studies by Guillon *et al*[32] and Dres *et al* [33], the latter focusing exclusively on elderly patients over 70 years old, demonstrated similar results with reported mortality rates 38.7% in patients ≥ 65 years and 45.8% in patients ≥ 70 years, respectively. Moreover, both studies showed that elderly patients over 80 years old were remarkably more susceptible to death (62.5% and 66.8%) compared to young- and middle-old patients.

DISCUSSION

Despite the large number of COVID-19- related publications, and despite the impact of COVID-19 on the elderly population, we found only a limited number of relevant studies being conducted in ICU, providing evidence on characteristics, clinical course and outcomes of critically ill elderly patients with COVID-19. In most of the studies, elderly patients comprised a substantial proportion of the study population, ranging approximately from 30.4% to 79.6%, indicating, thus, the high burden of advanced age on ICU beds capacity.

Although limited evidence on elderly patients in the ICU setting is available, accumulating observational data show a varied, albeit high mortality. This variability could partially be explained by management heterogeneity of these patients, the diversity in sample size and the incomplete outcome data due to rapid publication of results, while a substantial number of these patients were still in the ICU or the hospital at the time their outcome was evaluated. Another factor possibly influencing the reported mortality is a trend towards improvement of the disease clinical outcome. During the initial surge of the pandemic, reports of critically ill COVID-19 patients in China, Italy and the United States have reported a high mortality, whereas recent analyses are reassuring that ICU mortality is lower than earlier reports suggested[53]. Similarly, according to a systematic review and metanalysis of patients with severe COVID-19, the overall estimate for the reported case fatality rate was 45% (95%CI, 38%-52%); nevertheless, significant variability was observed by age, among other parameters[54]. Specifically, the reported case fatality ratio was higher in older patients and in early pandemic epicenters, which may have been influenced by limited ICU resources.

Two recent studies confirm the evolution of clinical outcome over time in adults with COVID-19-related critical illness admitted to ICU. The first study shows that

among patients with COVID-19–related critical illness admitted to ICUs in the United States, mortality seemed to decrease over time despite stable patient characteristics [55]. According to the second study, among more than 4000 critically ill patients with COVID-19 admitted to ICUs located at central Europe, 90 d mortality decreased from 42% to 25% over the study period. Although detailed information on elderly population is not provided in this study, mortality was higher in older patients as well as in those with diabetes, obesity and severe ARDS[56]. Probably, more studies are necessary to confirm these results and to investigate the causal mechanisms in the elderly subset of patients.

The impact of age on mortality of critically ill patients has been already demonstrated in earlier studies in the pre-COVID-19 era[57-60]. However, important factors, such as severity of acute illness, comorbidities, as well as functional status of very old patients before ICU admission might be of more importance for the prognosis than age alone[61]. Similarly, according to a recent metanalysis, in the context of COVID-19, age-related comorbidities seem to have a more important effect than age itself; though this metanalysis refers to the whole population of hospitalized elderly patients with COVID-19 and not exclusively to those admitted to the ICU[62]. A currently ongoing clinical trial (ClinicalTrials.gov identifier NCT04321265) has planned to study the outcome of elderly ICU patients (≥ 70 years) suffering from COVID-19 using a multi-centre and multi-national approach.

Clinical manifestation of the disease was common in all age groups, however, quite often, elderly patients seem to present insidious symptom onset, as low-grade fever or altered mental status with confusion or delirium, indicating the necessity for increased suspicion by clinicians for prompt diagnosis and appropriate interventions. Notably, dyspnea as presenting symptom in older individuals seemed to correlate with dismal prognosis, at least according to one study[42]. Regarding comorbidities, as they are more likely to occur in adults ≥ 60 years old, and as advanced age is associated with immune system dysfunction, a possible correlation between the particular high risk for severe disease of elderly population and the pre-existing diseases may be explained. Specifically, the majority of studies indicated hypertension, diabetes, COPD and obesity as the most commonly identified diseases, which could predict poor prognosis.

Although in some studies the type of ventilatory support, *i.e.*, invasive or non-invasive, in elderly patients is not clear, mechanical ventilation was associated with high mortality. As limited data is available on ventilation strategies used in elderly ICU patients with COVID-19, further research is needed as more comprehensive clinical insights concerning ICU treatment strategies in this population may be offered, in order to improve survival.

CONCLUSION

In this narrative review we summarize the current evidence for the characteristics and outcomes of elderly patients admitted to the ICU due to COVID-19. The cumulative data so far show that severe COVID-19 has a direct health impact on the elderly population, putting that at increased risk of mortality. Until effective treatments emerge, supportive care, including appropriate ventilator support for the acute respiratory failure along with co-morbidities clinical management, should be followed in the ICU so that survival of elderly patients with severe form of COVID-19 be improved. To this end, future studies exclusively designed for this vulnerable group are absolutely necessary.

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease-2019 (COVID-19) affects people of all ages; however, in particular the elderly is at higher risk of severe illness.

Research motivation

Although many studies on elderly adults with COVID-19 admitted to hospital wards have been published, the information on characteristics and clinical outcome of critically ill elderly patients admitted to the intensive care unit (ICU) due to COVID-19 is limited.

Research objectives

To provide information about clinical features and outcomes of elderly critically ill patients admitted to the ICU due to COVID-19, by carrying out a review of the existing literature.

Research methods

PubMed and Google Scholar databases were searched up to May 20, 2021, while reference lists were explored for relevant articles, to identify studies either focusing on this patient population or studies in which age-stratified results were reported.

Research results

A total of 19 studies, involving 10646 patients older than 60, 8310 patients older than 65 and 2630 patients older than 70 years of age, were included. Only one study exclusively focusing on critically ill elderly patients admitted to the ICU due to COVID-19 was found. Although clinical manifestations were similar for all ICU patients, compared to younger ones, elderly patients suffered from more comorbidities and showed a varied, albeit high mortality, up to 91%.

Research conclusions

Studies exclusively designed for elderly ICU population with COVID-19 are currently limited. The current evidence suggests that elderly patients admitted to the ICU with COVID-19 are at increased risk of death.

Research perspectives

Future studies focused on elderly patients admitted to the ICU due to COVID-19 are worthwhile.

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META-ANALYSIS

Clinical benefits of corticosteroid administration during adult cardiopulmonary resuscitation: A systemic review and meta-analysis

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Abstract

BACKGROUND

The clinical benefits of steroid administration during cardiac arrest remain unclear. Several studies reported that patients who received steroids after achieving a return of spontaneous circulation (ROSC) had better outcomes, but few studies have investigated the benefits of steroid administration during resuscitation. We hypothesized that administration of steroid during cardiac arrest would be associated with better clinical outcomes in adults with cardiac arrest.

AIM

To investigate the effect of steroid administration during cardiac arrest and the outcomes of resuscitation.

METHODS

We included studies of participants older than 18 years of age who experienced cardiac arrest and included at least one arm that received corticosteroids during cardiac arrest. A literature search of PubMed and Embase on 31 January 2021 retrieved placebo-controlled studies without limitation for type, location, and initial presenting rhythm of cardiac arrest. The study outcomes were reported by odds ratios (ORs) compared with placebo. The primary outcome was survival rate at hospital discharge. Secondary outcomes included a sustained ROSC, survival rate at hospital admission, and neurological outcome at hospital discharge.

RESULTS

Six studies including 146262 participants were selected for analysis. The risk of bias ranged from low to high for randomized-controlled trials (RCTs) and low (for non-RCTs). Steroid administration was associated with increased survival at hospital discharge [OR: 3.51, 95% confidence interval (CI): 1.98-6.20, $P < 0.001$], and steroid administration during cardiac arrest was associated with both an increased rate of sustained ROSC (OR: 1.81, 95%CI: 1.91-4.02, $P < 0.001$) and a favorable neurological outcome at hospital discharge (OR: 3.02, 95%CI: 1.26-7.24,

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P = 0.01).

CONCLUSION
Steroid administration during cardiac arrest was associated with better outcomes of resuscitation. Further study of the use of steroid in the selected circumstances are warranted.

Key Words: Steroid; Cardiac arrest; Survival; Systematic review; Meta-analysis

Core Tip: Several studies have demonstrated that patients who receive steroids after achieving a return of spontaneous circulation (ROSC) had better outcomes. Few studies have investigated steroid administration during resuscitation, and the results are not clear. We conducted a systematic review and meta-analysis of the clinical benefits of steroids during cardiac arrest. The analysis included six studies and found that steroid administration during cardiac arrest was associated with better outcomes of resuscitation, including survival rate at hospital discharge, sustained ROSC, and favorable neurological outcome at hospital discharge.

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INTRODUCTION

Cardiac arrest is an important public health problem worldwide. In the United States, cardiac arrest accounts for around 320000 to 360000 deaths each year[1,2]. A study in the United States reported a rate of return of spontaneous circulation (ROSC) of up to 72%[3]. Nevertheless, the reported global outcomes of 30% for ROSC, 8% survival at hospital discharge, 11% 1-mo survival, and 7.7% 1-year survival are quite different[4]. Improving the overall survival of cardiac arrest depends on multiple factors, including type of initial presenting rhythm, bystander cardiopulmonary resuscitation (*i.e.*, CPR), the witnesses present, and interventions during and after resuscitation[5-7].

Previous studies have demonstrated that patients who receive hydrocortisone or methylprednisolone after achieving ROSC had improved survival after cardiac arrest [7-9]. On the other hand, studies of corticosteroid administration during resuscitation are few and unclear[10,11]. A randomized-controlled trial (RCT) by Mentzelopoulos *et al*[9] found that a combination of vasopressin, steroid, and epinephrine administered during resuscitation and with post-resuscitation shock resulted in improved survival at hospital discharge with a favorable neurological outcome. However, Tsai *et al*[11] reported that administration of hydrocortisone during cardiac arrest was associated with an improved ROSC rate in out-of-hospital cardiac arrest (referred to as OHCA) patients but was not associated with increased survival at hospital discharge. For that reason, we conducted an up-to-date systematic review and meta-analysis to investigate the effect of steroid administration during cardiac arrest and on the outcomes of resuscitation, including survival rate at hospital discharge, sustained ROSC, survival at hospital admission, and neurological outcomes at discharge.

MATERIALS AND METHODS

Protocol

This systematic review and meta-analysis was prepared following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (*i.e.*, PRISMA) statement guidelines[12]. The protocol was prospectively registered with PROSPERO international prospective register of systematic reviews in health and social care (ID:

CRD42021227093).

Search strategy and inclusion criteria

Two authors independently searched two standard databases, PubMed and Embase, from their inception until 31 January 2021, without language restriction. The search words "steroid," "glucocorticoid," "methylprednisolone," "dexamethasone," "cardiac arrest," "cardiopulmonary resuscitation," "heart arrest," and "cardiopulmonary arrest" were the Medical Subject Headings used, in combination and with various spellings and endings. We also searched relevant reviews and their references to identify additional eligible studies. In addition, we searched for any unpublished trials registered on the "clinicaltrials.gov" Internet site.

The selection criteria were: (1) Inclusion of adults ≥ 18 years of age with cardiac arrest, regardless of initial presenting rhythm and location (*i.e.*, inpatient or out-of-hospital); (2) At least one arm having received a corticosteroid during cardiac arrest; (3) Reporting of one of the following, sustained ROSC defined as not requiring CPR for a consecutive 15 min[9] or 20 min[7] or longer, survival at hospital admission, survival at hospital discharge, and neurological outcome at discharge. We excluded animal studies, studies without a control group (*e.g.*, case reports, case series), and review articles. Two authors independently screened the search results to identify eligible studies. Full-text articles of the retrieved studies were collected and independently assessed by two authors against the prespecified criteria (Figure 1). Any disagreements were discussed with a third-party and concluded by consensus.

Outcomes of interest

The primary outcome was survival to hospital discharge. The secondary outcomes were sustained ROSC, survival to hospital admission, and favorable neurological outcome at discharge, which was defined as a cerebral performance category score of 1-2 or a modified Rankin Score (commonly referred to as mRS) of 0-3.

Data extraction and assessment of the risk of study bias

Two authors individually extracted data from the selected articles using a standard data collection form. The data included basic characteristics (first author, publication year, study design, study location and setting, number and age of participants), initial presenting rhythm, treatment and interventions in the study groups, and the outcomes of interest. In cases of incomplete or missing data, or for clarification, we attempted to contact the corresponding author by email. Two authors independently assessed the risk of study bias using the Good Research for Comparative Effectiveness (referred to as GRACE) checklist for observational studies and the modified version of the Cochrane Collaboration tool for assessing the trial risk of bias for RCTs[13,14]. Discrepancies in the extracted data were resolved by discussion and overall consensus.

Data synthesis and statistical analysis

Data were imported into prepared record forms. In the meta-analysis, pooled odds ratios (ORs) were calculated by the Mantel-Haenszel method as summary measures for analysis of the dichotomous outcomes of interest. Heterogeneity among the included studies was estimated by the I^2 statistic (the percentage of total variability across studies due to heterogeneity). Values of < 25%, 25%-50%, and > 50% were considered as low, moderate, and high heterogeneity, respectively[15]. Data were pooled with a fixed-effect model, but if there was evidence of high heterogeneity (I^2 > 50%), a random-effects model was used instead. Publication bias arising from small-study effects was evaluated by visual examination of funnel plots and Egger's test. Review Manager version 5.3 (Nordic Cochrane Center, Cochrane Collaboration, 2014, Copenhagen, Denmark) was used to perform the quantitative statistical analysis[16]. All tests were two-tailed, and P values < 0.05 were considered statistically significant.

RESULTS

Study selection

The PRISMA flow diagram (Figure 1) shows how the 1760 retrieved studies were screened for inclusion in the review and meta-analysis. After removing duplicate studies, 1702 remained. Of those, 1670 were excluded following screening of the abstract to identify the inclusion and exclusion criteria. Full-text copies of the remaining 32 publications were screened before selecting six studies (Table 1) with a

Table 1 Characteristics of the included studies

Ref.	Age, yr	Study design, country/territory, enrollment period	Sample size (exposure/control)	Location	Shockable initial rhythm (exposure/control), %	Witnessed arrest (exposure/control), %	Bystander CPR (exposure/control), %	Intervention	Comparator	Outcomes of interest
Bolvardi *et al* [17], 2016	68.9 ± 16.0	RCT, Iran, 2015	50 (25/25)	OHCA	28 (20/36)	N/A	N/A	1 mg epinephrine plus 125 mg methylpredni-solone during the first cycle of resuscitation	1 mg epinephrine plus saline during the first cycle of resuscitation	Successful resuscitation; Survival to hospital discharge; Neurological outcomes at hospital discharge
Mentzelopoulos *et al*[9], 2009	67.4	RCT, Greece, Jul 2006 to Mar 2007	100 (48/52)	IHCA	14 (15/13)	81 (79/83)	N/A	1 IU vasopressin plus 1 mg epinephrine for the first 5 CPR cycles and 40 mg methylprednisolone. Shock after resuscitation was treated with stress-dose hydrocortisone (300 mg daily for 7 d with gradual tapering)	Placebo (saline) plus 1 mg epinephrine for the first 5 CPR cycles. Shock after resuscitation was treated with saline placebo	Sustained ROSC; Survival to hospital discharge
Mentzelopoulos *et al*[7], 2013	63.0	RCT, Greece, Sep 2008 to Oct 2010	268 (130/138)	IHCA	16.8 (16.7/16.9)	92.2 (91.3/93/1)	N/A	1 IU vasopressin plus 1 mg epinephrine for the first 5 CPR cycles and 40 mg methylprednisolone. Shock after resuscitation was treated with stress-dose hydrocortisone (300 mg daily for 7 d with gradual tapering)	Placebo (saline) plus 1 mg epinephrine for the first 5 CPR cycles. Shock after resuscitation was treated with saline placebo	ROSC ≥ 20 min; Survival to hospital discharge; Neurological outcomes at hospital discharge
Paris *et al*[10], 1984	N/A	RCT, United States, Mar 1982 to Jan 1983	83 (37/46)	OHCA	48.2 (41.3/56.8)	N/A	30.1 (36.9/21.6)	100 mg dexamethasone	The same volume of saline	Survival to hospital admission; Survival to hospital discharge
Tsai *et al*[11], 2007	72.5 ± 16.2	Prospective non-RCT, Taiwan, Oct 2004 to Jul 2005	97 (36/61)	Non-trauma, OHCA	10.3 (11/10)	75.3 (83/71)	N/A	100 mg hydrocortisone	Saline as placebo	Sustained ROSC; Survival to hospital discharge
Tsai *et al*[18], 2016	68.2	Retrospective, Taiwan, 2004-2011	145644 (2912/142732)	IHCA (at the ED)	20.6 (33.4/20.3)	N/A	N/A	Any forms of steroid use	No steroid use	Survival to hospital admission; Survival to hospital discharge; 1-yr survival

CPR: Cardiopulmonary resuscitation; ED: Emergency department; IHCA: In-hospital cardiac arrest; N/A: Not applicable; OHCA: Out-of-hospital cardiac arrest; RCT: Randomized-controlled trial; ROSC: Return of spontaneous circulation.

total of 146262 participants for inclusion in the systematic review and meta-analysis.

Characteristics of included studies

A total of six articles, published between 1984 and 2016, were included for data extraction and meta-analysis. Four were RCTs[7,9,10,17], one was prospective non-RCT[11], and the other was a retrospective study[18]. The studies were conducted in Asia (n = 3), Europe (n = 2), and North America (n = 1). Three studies included patients with OHCA[10,11,17] and three included patients with in-hospital cardiac arrest[7,9,18]. Two trials evaluated the clinical benefits of co-intervention with corticosteroid, vasopressin, or epinephrine protocols[7,9]. Four trials directly investigated the efficacy of steroids alone, including methylprednisolone[17], dexamethasone[10], hydrocortisone[11], and other steroids[18]. More than three-fourths of the cardiac arrests were witnessed. All studies reported the efficacy of corticosteroids on survival to hospital discharge. Table 1 summarizes the characteristics of the included studies. The risk of bias was high in two of the RCTs and low in two. Randomization and deviation from the intended interventions contributed to high risk of bias. All four RCTs had a low risk of bias for measurement of outcome. Both non-RCTs were determined to be of sufficient quality and having a low risk of bias according to the GRACE checklist. Table 2 summarizes the risk of bias assessment.

Primary outcome

Overall survival rate at hospital discharge: All six studies reported the association between steroid use and the survival rate at hospital discharge[7,9-11,17,18]. Four of the six were RCTs and two were non-RCTs. The overall effect size demonstrated a significant association between steroid use and survival rate at hospital discharge [OR: 3.51, 95% confidence interval (CI): 1.98-6.20, P < 0.001]. Subgroup analyses found that for the RCTs, effect size had a significant association between steroid administration and survival rate at hospital discharge (OR: 3.51, 95%CI: 1.63-7.55, P = 0.001). Conversely, steroids given during cardiac arrest in the non-RCT studies were not associated with increased survival rate at hospital discharge (OR: 2.32, 95%CI: 0.43-12.50, P = 0.33). There was no significant heterogeneity between the subgroups (I^2 = 0%, P = 0.66; Figure 2).

Secondary outcomes

Rate of sustained ROSC: Four studies examined the association between steroid use and the rate of sustained ROSC[7,9,11,17]. The pooled data was homogeneous (I^2 = 0%, P < 0.001). Patients who received a steroid during cardiac arrest had a better chance of sustained ROSC (OR: 2.69, 95%CI: 1.81-4.02, P < 0.001) than those who had not received a steroid. Subgroup analyses yielded similar results for RCTs and non-RCTs (Figure 3).

Overall survival rate at hospital admission: Two studies reported the association between steroid use and overall survival at hospital admission[10,18]. One was an RCT and the other was a non-RCT. Steroid administration during cardiac arrest did not show a survival benefit at hospital admission based on the pooled data (OR: 1.82, 95%CI: 0.34-9.61, P = 0.48; Figure 4).

Favorable neurological outcomes at hospital discharge: Two studies investigated the association between steroid use and the neurological outcome at hospital discharge and both were RCTs[7,17]. The overall effect size indicated that administration of steroid during cardiac arrest was significantly associated with an increased rate of favorable neurological outcomes at hospital discharge (OR: 3.02, 95%CI: 1.26-7.24, P = 0.01; Figure 5).

Publication bias: As shown in the funnel plot for the meta-analysis of the effect of steroid use and the primary outcome of survival rate at hospital discharge (Figure 6), there was no evidence of significant publication bias.

DISCUSSION

This meta-analysis compared the evidence on the use of steroids in adult cardiac arrest with placebo or no use of steroids. Review of the evidence found that steroid use was associated with an increased survival rate at hospital discharge, sustained ROSC, and favorable neurological outcomes at discharge. The overall study risk of bias ranged from low in two RCTs and both non-RCTs to high in two RCTs.

Table 2 Cochrane risk of bias assessment tool for randomized trials and the Good Research for Comparative Effectiveness checklist for nonrandomized trials

Randomized-controlled trials

Ref.	Randomization	Deviation from the intended interventions	Missing outcome data	Measurement of outcome	Selection of the reported result	Overall
Bolvardi *et al* [17], 2016	Low	High	Some concerns	Low	Some concerns	High
Mentzelopoulos *et al*[9], 2009	Low	Low	Low	Low	Low	Low
Mentzelopoulos *et al*[7], 2013	Low	Low	Low	Low	Low	Low
Paris *et al*[10], 1984	High	Low	Some concerns	Low	Some concerns	High

Non-randomized-controlled trials

Ref.	Adequate treatment	Adequate outcomes	Objective outcomes	Valid outcomes	Similar outcomes	Covariates recorded	New initiators	Concurrent comparators	Covariates accounted for	Immortal time bias	Sensitivity analysis
	D1	D2	D3	D4	D5	D6	M1	M2	M3	M4	M5
Tsai *et al*[11], 2007	+	+	+	+	+	+	+	+	+	+	+
Tsai *et al*[18], 2016	+	+	+	+	+	+	+	+	+	+	+

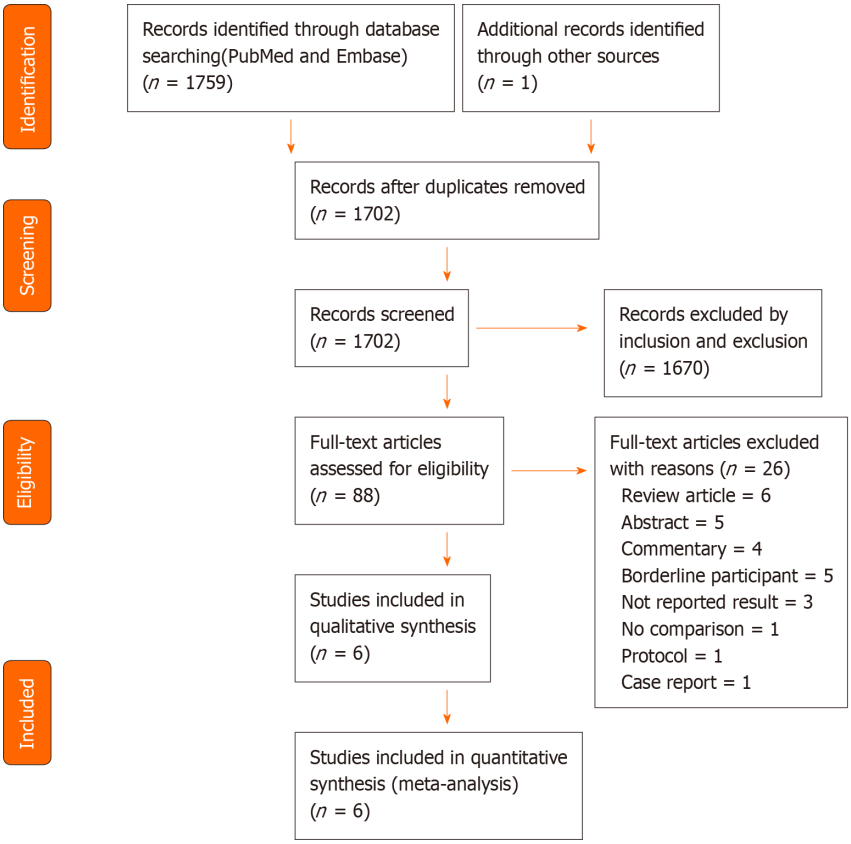

Figure 1 PRISMA flow chart of study selection.

The administration of corticosteroids during cardiac arrest has been proposed for decades; however, there is no strong evidence to support the efficacy of steroids to improve the outcomes of resuscitation[7,19]. Recent studies have described cardiac

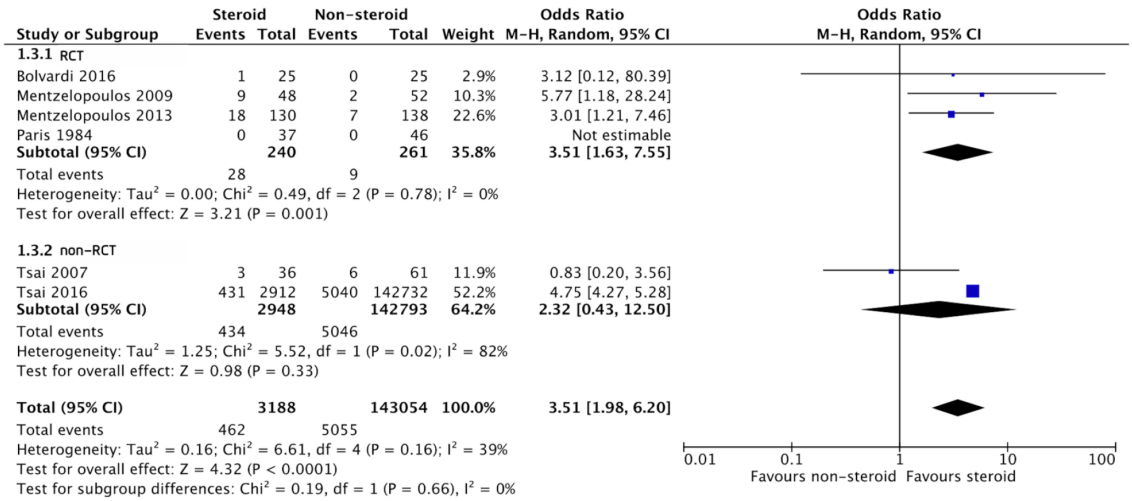

Figure 2 Forest plot comparing the odds ratios of survival at hospital discharge. RCT: Randomized-controlled trial; CI: Confidence interval.

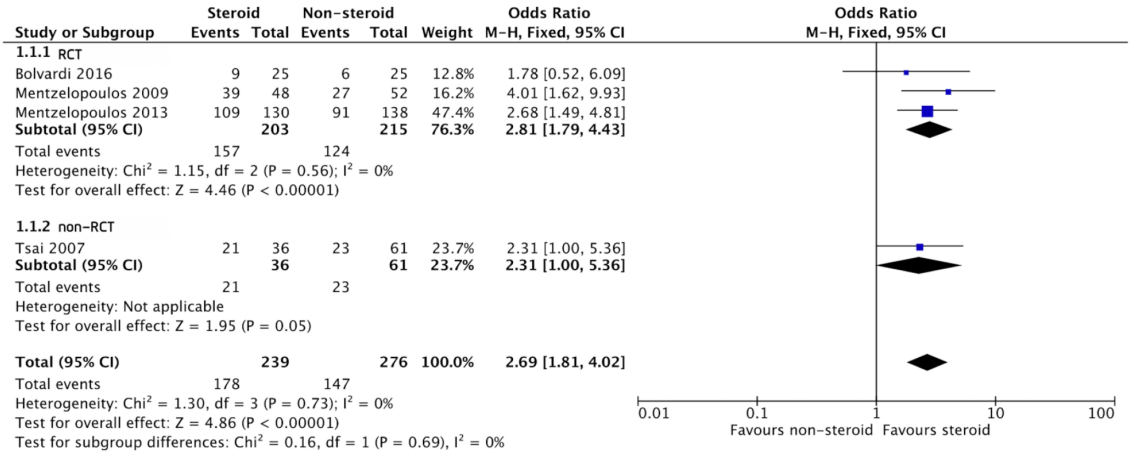

Figure 3 Forest plot comparing the odds ratios of the sustained return of spontaneous circulation. RCT: Randomized-controlled trial; CI: Confidence interval.

arrest-related adrenal insufficiency, finding that the condition was associated with increased mortality[19,20]. Ito *et al*[20] reported that cortisol levels were moderately low during and after cardiac arrest and CPR, which suggests impairment of adrenal function. Corticosteroids have anti-inflammatory and anti-apoptotic activity that can prevent organ toxicity, especially in patients with cardiac arrest[21]. The findings of this review are consistent with previous studies that documented the benefits of steroid administration in patients who survived cardiac arrest[8,22,23]. Patients who received steroids during cardiac arrest had better outcomes than those who did not receive steroids. The corticosteroid effects included short-term survival, represented by the rate of sustained ROSC, and survival at hospital discharge. Cardiac arrest results in a sepsis-like stage, with interruption of blood flow that leads to inadequate oxygen delivery, vasodilation, and cytokine activation[24,25]. Corticosteroid administration has been shown to improve cardiovascular function and to reduce a catecholamine surge, thereby decreasing inflammation and reversing the shock that occurs after cardiac arrest[7,11,19].

Two studies included in this review demonstrated a benefit of the combined administration of vasopressin, methylprednisolone, and epinephrine on improved survival at hospital discharge[7,9]. Cardiac arrest causes an overwhelming release of several stress hormones[7,25,26]. Vasopressin is a non-adrenergic vasopressor that is released from the anterior pituitary gland[27], and stimulation of plasma adrenocorticotropin (commonly known as ACTH) release by vasopressin might preserve hemodynamic function and promote ROSC[28,29].

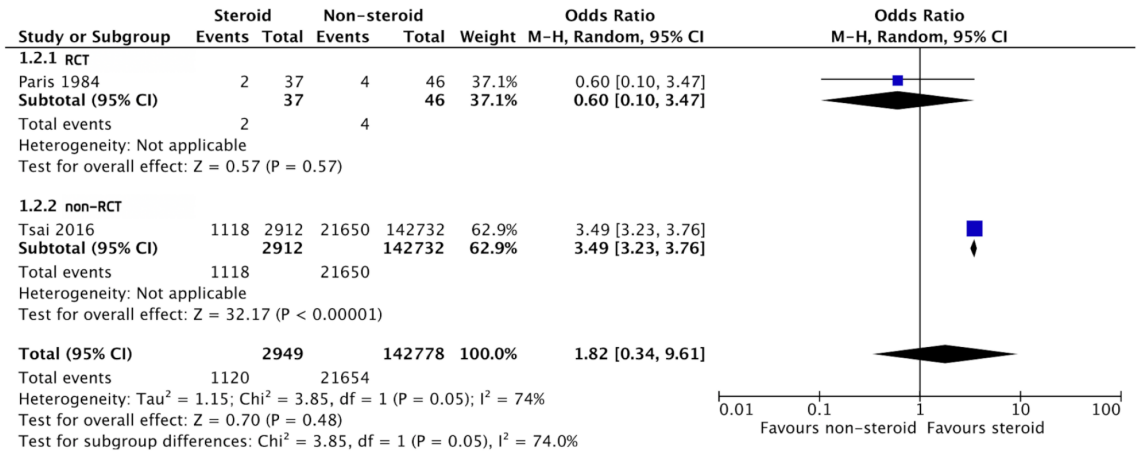

Figure 4 Forest plot comparing the odds ratios of survival at hospital admission. RCT: Randomized-controlled trial; CI: Confidence interval.

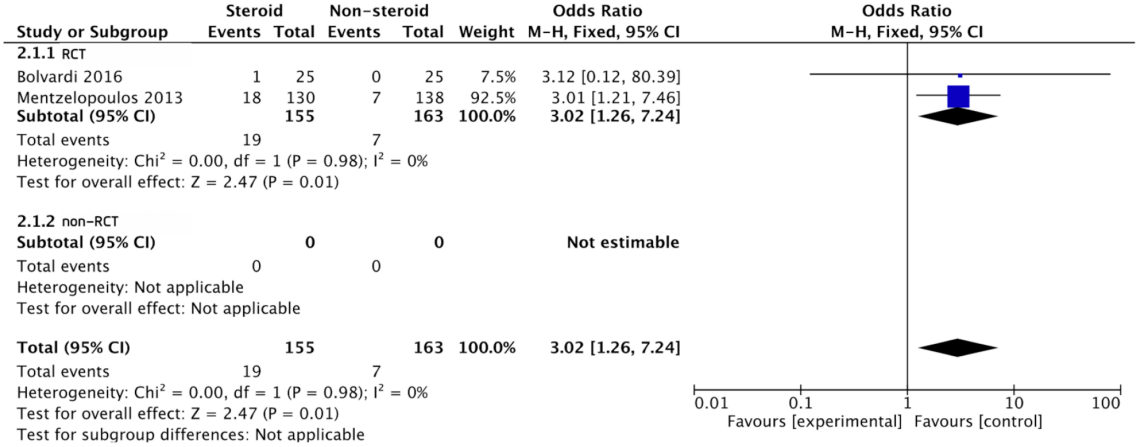

Figure 5 Forest plot comparing the odds ratios of favorable neurological outcome at hospital discharge. RCT: Randomized-controlled trial; CI: Confidence interval.

Limitations

This review has some limitations. First, the use of steroids defined in this review was different among studies, which resulted in inconclusive evidence and findings that might not be generalized to other populations. Second, our review did not mention the harmful effects of steroid administration, which might influence the clinical outcomes. Third, we included both RCTs and non-RCTs in the meta-analysis. Despite analysis of both groups separately, non-RCTs such as retrospective of observational studies carry a high risk of confounding by indication and selection bias and may have led to the heterogeneity observed in this study. Furthermore, considering all of the included studies, Tsai *et al*[18] had enrolled up to 95% of the participants in this review. However, the results of this study do not conflict from those of other studies. Finally, the included studies were conducted in different places and at different times. Standard guidelines regarding the management of patients with cardiac arrest usually update every 5 years, which will lead to variability in interventions and protocols across included studies.

CONCLUSION

Although the overall risk of bias of included studies ranged from low to high, steroid administration during cardiac arrest was associated with an increased rate of survival at hospital discharge, sustained ROSC, and favorable neurological outcome at hospital discharge. Steroid use may be optional for adults with cardiac arrest; however, further study concerning the use of steroid in the prepared protocol and selected circumstances are warranted.

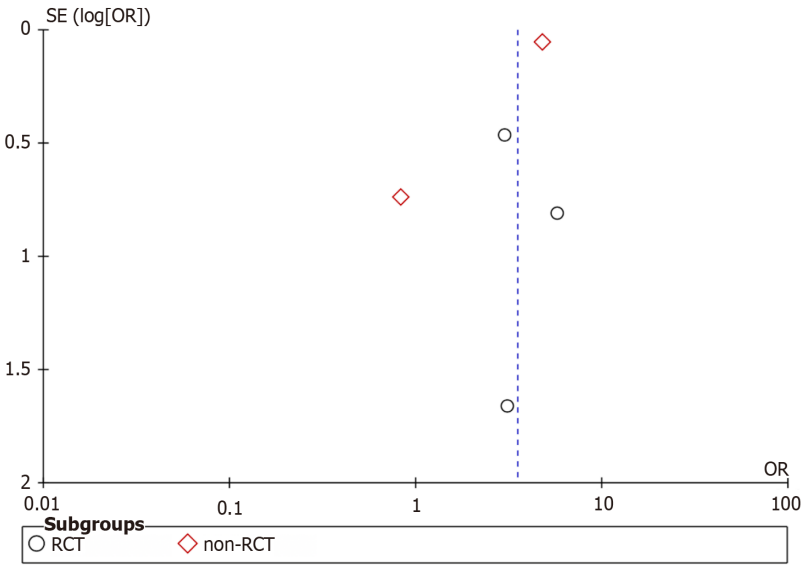

Figure 6 Funnel plot of steroid administration and survival at hospital discharge. OR: Odds ratio; RCT: Randomized-controlled trial.

ARTICLE HIGHLIGHTS

Research background

The clinical benefits of steroid administration during adult cardiac arrest remain controversial. According to the latest guidelines for managing adult cardiac arrest, steroid was not routinely recommended giving during resuscitation.

Research motivation

Previous studies have shown that patients who receive steroids after return of spontaneous circulation (ROSC) have improved outcomes. In contrast, few studies have investigated the benefits of steroid administration during resuscitation and the results are unclear.

Research objectives

The objectives of this review were to investigate the clinical benefits of steroids during adult cardiac arrest, including the survival rate at hospital discharge, sustained ROSC, the survival rate at hospital admission, and neurological outcome at hospital discharge.

Research methods

We conducted a systematic review and meta-analysis.

Research results

Steroid administration was associated with increased survival at hospital discharge. Steroid administration during cardiac arrest was associated with an increased rate of sustained ROSC and a favorable neurological outcome at hospital discharge.

Research conclusions

Although we could not draw firm conclusions, the use of steroids during cardiac arrest was associated with improved outcomes of resuscitation.

Research perspectives

Further study concerning the use of steroid in the prepared protocol and selected circumstances are warranted.

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CASE REPORT

Near-fatal Panton-Valentine leukocidin-positive *Staphylococcus aureus* pneumonia, shock and complicated extracorporeal membrane oxygenation cannulation: A case report

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Abstract

BACKGROUND

Panton-Valentine leukocidin (PVL) is an exotoxin secreted by *Staphylococcus aureus* (*S. aureus*), responsible for skin and soft tissue infections. As a cause of severe necrotising pneumonia, it is associated with a high mortality rate. A rare entity, the epidemiology of PVL *S. aureus* (PVL-*SA*) pneumonia as a complication of influenza coinfection, particularly in young adults, is incompletely understood.

CASE SUMMARY

An adolescent girl presented with haemoptysis and respiratory distress, deteriorated rapidly, with acute respiratory distress syndrome (ARDS) and profound shock requiring extensive, prolonged resuscitation, emergency critical care and venovenous extracorporeal membrane oxygenation (ECMO). Cardiac arrest and a rare complication of ECMO cannulation necessitated intra-procedure extracorporeal cardiopulmonary resuscitation, *i.e.*, venoarterial ECMO. Coordinated infectious disease, microbiology and Public Health England engagement identified causative agents as PVL-*SA* and influenza A/H3N2 from bronchial aspirates within hours. Despite further complications of critical illness, the patient made an excellent recovery with normal cognitive function. The coordinated approach of numerous multidisciplinary specialists, nursing staff, infection control, specialist cardiorespiratory support, hospital services, both adult and paediatric and Public Health are testimony to what can be achieved to save life against expectation, against the odds. The case serves as a reminder of the deadly nature of PVL-*SA* when associated with influenza and describes a rare complication of ECMO cannulation.

CONCLUSION

PVL-*SA* can cause severe ARDS and profound shock, with influenza infection. A timely coordinated multispecialty approach can be lifesaving.

Key Words: Panton-Valentine leukocidin-*Staphylococcus aureus*; Adolescent; Extracorporeal membrane oxygenation; Extracorporeal cardiopulmonary resuscitation; Case report

Core Tip: We present a case of profound vasoplegic shock and acute respiratory distress syndrome in a healthy adolescent after a mild prodromal illness. Acute cardiorespiratory failure persisted despite aggressive resuscitation and vasoactive support. Cardiac arrest and complicated extracorporeal membrane oxygenation (ECMO) cannulation necessitated emergency venoarterial-ECMO during cardiopulmonary resuscitation. Early respiratory samples confirmed H3N2 influenza and Panton-Valentine leukocidin-*Staphylococcus aureus* (PVL-*SA*) pneumonia: A rare and serious manifestation of the PVL-*SA*, usually associated with less severe skin and soft-tissue infections. The patient's ultimate survival and recovery depended on the extraordinary interplay and rapid utilisation of multidisciplinary teams which we highlight for the benefit of other services to ensure optimal outcomes, even against the odds.

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INTRODUCTION

Panton-Valentine leukocidin (PVL), an exotoxin produced by specific strains of *Staphylococcus aureus* (*S. aureus*), is primarily responsible for skin and soft tissue infections[1,2]. Complications can include necrotising pneumonia and associated acute respiratory distress syndrome (ARDS). PVL-*S. aureus* (PVL-*SA*) pneumonia is characterised by pyrexia and haemoptysis and is often preceded by an influenza-like illness [3]. It has a poor prognosis and high mortality, even in young patients.

United Kingdom guidance states that individuals under the age of 16 years should be admitted to Paediatric Intensive Care Units (PICU); however, a proportion are admitted to Adult Intensive Care Units (AICU) instead[4]. We report a case of near-fatal necrotising PVL-*SA* pneumonia in an adolescent patient co-infected with influenza treated by adult emergency services requiring the utilisation of the multidisciplinary team. The extremely rapid deterioration in this patient highlights the urgency of diagnosis, treatment and utilisation of specialist services, including extracorporeal membrane oxygenation (ECMO) service to optimise patient outcomes.

CASE PRESENTATION

Chief complaints

A 15-year-old girl, on a school trip to London from the Middle East, presented to the emergency room (ER) with 3 h of progressive shortness of breath and chest pain, after a one-day history of cough, difficulty breathing with new sudden haemoptysis.

History of present illness

One week before admission, some of her school friends had developed Influenza-like symptoms. The patient reported coryzal symptoms for one week before her trip but still felt well enough to travel. There was no history of cutaneous injury or pathology.

History of past illness

The patient was previously healthy with no past medical history. There was no history of immunodeficiency in her or her family.

Personal and family history

There was no history of immunodeficiency in her or her family. The patient had no known drug or food allergies.

Physical examination

On arrival in the ER, auscultation revealed crackles and reduced air entry in the lower right hemithorax. She coughed dark blood and became suddenly more distressed. She was tachypnoeic at 50 breaths/min and saturating at 92% on room air. Her heart rate was 120 beats/min, blood pressure 105/74 mmHg, and she was afebrile with cold extremities.

Laboratory examinations

Initial arterial blood gas analysis showed a pH of 7.42 (normal range: 7.35-7.45), $PaCO_2$ of 4.0 kPa (normal range: 4.7-6.0 kPa) and PaO_2 of 7.2 kPa (normal range: 10.5-13.5 kPa) despite supplementary oxygen. Blood lactate was 1.7 mmol/L (normal range: < 1.0 mmol/L), sodium bicarbonate level 19.5 mmol/L (normal range: 22-29 mmol/L) and base excess -5 mmol/L (normal range: -2-2 mmol/L). Of note, the patients' blood work up demonstrated a leukopaenia with neutrophil count 0.8 × 10^9/L (reference range 2.0-7.1 × 10^9/L) and c-reactive protein was 3.7 mg/L (reference range: < 10 mg/L). Blood film analysis was not performed. Full blood count and c-reactive protein results from initial laboratory investigation are presented in Table 1.

Imaging examinations

Plain erect radiographs of the chest taken during the initial period of the patient's admission to hospital before transfer to the severe acute respiratory failure (SARF) centre are shown in Figure 1. These radiographs, and subsequent cross-section computed tomography of the chest performed at the SARF, showed rapidly progressive consolidation and four-quadrant opacification consistent with the other features of ARDS[5].

Table 1 Full blood count and c-reactive protein from initial blood sampling taken on arrival to the Emergency Department

Test	Unit	Value
White blood cell count	$\times 10^9$/L	1.5
Haemoglobin	g/L	146
Haematocrit	L/L	0.45
Platelet count	$\times 10^9$/L	129
Neutrophil count	$\times 10^9$/L	0.8
Lymphocyte count	$\times 10^9$/L	0.6
Monocyte count	$\times 10^9$/L	0
Eosinophil count	$\times 10^9$/L	0
Basophil count	$\times 10^9$/L	0
C-reactive protein	mg/L	0.6

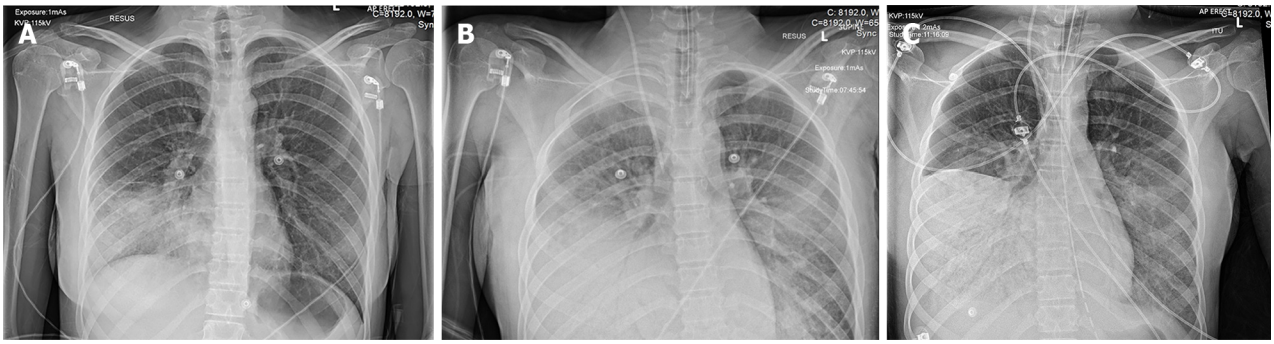

Figure 1 Chest radiograph. A: Plain AP erect chest radiograph taken shortly after arrival to the emergency room, showing dense consolidation of right middle and lower zones; B: Plain AP erect chest radiograph following tracheal intubation and central line insertion. Note progression of consolidation as seen in Figure 1A and changes in keeping with acute respiratory distress syndrome; C: Plain chest radiograph taken approximately 8 h after presentation. Note dense consolidation and air bronchograms seen in right lower lobe, progressing from previous chest radiographs.

Diagnostic and therapeutic bronchoscopy was performed, demonstrating copious yellow, protein-rich plasma-like secretions with over 300mL fluid suctioned from her bronchial tree. A white speckled appearance of the bronchial mucosa was apparent (Figure 2A). Bronchial washings were taken.

FINAL DIAGNOSIS

The patient was otherwise healthy with no previous surgery or trauma; therefore, an infective respiratory pathogen was suspected early in the patient's attendance. The presenting prodromal symptoms lead to consideration of a viral source, whilst the rapid deterioration with refractory septic shock raised the clinical suspicion of a coexistent bacterial pathogen. Other causes of vasoplegic shock were considered, including toxic shock syndrome but excluded based on history and clinical examination.

Given the travel history, suspicion of Middle East respiratory syndrome coronavirus (MERS-CoV) was high; therefore, investigations and therapy targeted this possibility, with personal protective equipment provided for staff. The concern regarding a potential emerging pathogen instigated quick microbiology/infectious disease (ID) advice and involvement of the Public Health England (PHE) laboratories.

Other commonly occurring community pathogens were considered, and the clinical narrative of contacts with family and fellow students with influenza-like symptoms placed this high on the differential list. The patient underwent rapid respiratory viral testing, which identified influenza A/H3N2. The same cultures grew *S. aureus* sensitive to methicillin (Figure 2B). The strain was confirmed as PVL-*SA* from PHE reference laboratory using whole-genome sequencing. All samples were negative for

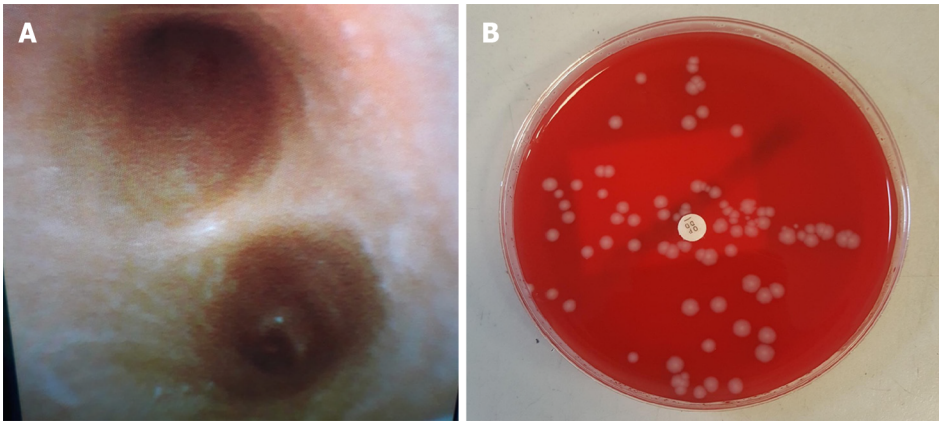

Figure 2 Emergency therapeutic and diagnostic bronchoscopy was performed in Adult Intensive Care Units. A: Bronchoscopic appearances of carina. Samples taken with bronchoalveolar lavage confirmed as Panton-Valentine leukocidin (PVL)-*Staphylococcus aureus* (*S. aureus*) and influenza A/H3N2; B: Blood agar plate showing colony forming units of *S. aureus* from bronchial alveolar lavage performed in Adult Intensive Care Units, subsequently identified as PVL producing *S. aureus* from Public Health England reference laboratory using whole genome sequencing.

MERS-CoV.

TREATMENT

Surviving sepsis protocols were implemented within 1 h following arrival to ER, and therapy escalated following deterioration[6]. This was initially intravenous (IV) ceftriaxone 2 g once daily, enteral azithromycin 500 mg once daily, and enteral oseltamivir 75 mg once daily. Antimicrobials were escalated to increase the bioavailability of gram-positive cover. IV linezolid 600 mg twice daily, IV clindamycin 900 mg four times a day, IV ceftriaxone 2 g once daily and IV clarithromycin 500 mg twice daily were all initiated approximately 6 h after presentation. This change followed advice from ID and microbiology teams to include toxin inhibition and improve lung penetration as per national guidelines. Emergency lifesaving therapy was required and initiated before any diagnostic test results were available, with escalation directed by the ID and microbiology team.

After a short period of non-invasive ventilation, rapid deterioration necessitated emergency intubation and mechanical ventilation, and the patient developed refractory shock whilst in the ER. Management of refractory shock required significant fluid resuscitation with high dose adrenaline (0.2 μg/kg/min) and noradrenaline (1.2 μg/kg/min) to maintain minimum survivable blood pressure. Bedside transthoracic echocardiography guided fluid resuscitation and demonstrated very hyperdynamic but notably underfilled ventricles. The patient remained cold peripherally with a peripheral capillary refill time of more than 5 s. Fluid resuscitation included serial 20% human albumin solution and crystalloids. Referral to the regional paediatric intensive care team was made, but retrieval was not feasible for several hours due to other clinical emergencies. The regional adult SARF referral centre was contacted for respiratory venovenous (VV)-ECMO support and retrieval.

After 6 h of resuscitation in ER, the patient was transferred to the AICU. The decision to admit was made based on the lack of PICU availability and the ongoing profound hypoxaemia, mixed metabolic and respiratory acidosis and noradrenaline/adrenaline dependent shock. Her clinical condition deteriorated with progressively worsening haemodynamic instability and hypoxaemia. She was persistently desaturating to 60%-75% with maximal volume-controlled ventilation on 100% oxygen, with an increased heart rate to 160 beats/min. She received approximately 6000 mL of crystalloid and albumin fluid resuscitation on admission to AICU. Shock dose IV corticosteroid (100 mg hydrocortisone) was administered, and she received 2 g/kg IV immunoglobulin (IVIg)[6]. The patient remained profoundly hypoxaemic with ongoing poor air entry to the right lung. Bronchoalveolar fluid aspiration was performed, with transient improvements in oxygen saturations, before the recurrence of alveolar flooding and samples sent for rapid laboratory analysis.

Despite these measures, the patient continued to deteriorate with worsening haemodynamic instability and hypoxaemia. She was taken to theatre to instigate VV-ECMO. Full ECMO cannulation protocols were followed, and vascular pre-assessment

was performed. Simultaneous cannulation of the right jugular and left and right femoral veins was complicated when the left femoral cannula became stuck, unable to be fully advanced or removed. Following vascular cut down by an assisting cardiothoracic surgeon to remove the cannula, the distal part of the cannula snapped, with proximal 10 cm remaining in the vessel as a foreign body. Haemorrhage was controlled manually then haemostasis was achieved by suture. The patient lost cardiac output. Cardiopulmonary resuscitation (CPR) was initiated, and immediate cannulation of the right femoral artery during extracorporeal CPR allowed venoarterial (VA)-ECMO to be established, resulting in the return of systemic output. During this time in theatre, aggressive fluid resuscitation continued, totalling 2000 mL crystalloid, six units of packed red cells, two pools cryoprecipitate, one bag of fresh frozen plasma and two pools of platelets, as guided by ultrasound assessment of central venous filling. From arrival in ER to her transfer to the ECMO centre, over approximately 16 h, the patient received an estimated 12.2 L of resuscitation fluids (230 mL/kg). The resuscitation process was adjusted from ER to ICU to maintain a life-sustaining blood pressure whilst reducing the very high levels of vasopressors and inotropes to minimise the risk of iatrogenic arrhythmias whilst maintaining acceptable cardiac output and oxygen delivery. Despite the measures described, adequate life-sustaining blood pressures were not adequately maintained, and high fluid volumes were required. At all times dynamic assessments of fluid responsiveness were used to guide resuscitation.

During her acute admission, there was involvement from the paediatric, anaesthetic, adult critical care, ECMO retrieval, cardiothoracic surgical, general surgical, ID, haematology and theatre teams. This, alongside the implementation of specialist shock pathways in a timely manner, was crucial to a subsequently positive outcome in a near-fatal case.

OUTCOME AND FOLLOW-UP

Following the establishment of VA-ECMO and transfer to the regional SARF centre, further contrast imaging demonstrated the retained cannula in the left common iliac artery (Figure 3). There was thread-like blood flow to the left leg. She developed ischaemia of the distal limbs worse on the left, with disseminated intravascular coagulation and multiple organ failure. Consequently, VA-ECMO was converted to VV-ECMO, removing the arterial cannula to improve the chances of perfusion and leg preservation. Collateral circulation developed with conservative management, and adequate lower limb perfusion occurred. After one month on VV-ECMO, a further three weeks on AICU and six weeks on PICU, the patient was successfully extubated with good neurological function. She made steady progress with respiratory and functional rehabilitation, although requiring a prolonged period of renal replacement therapy. Three months after her initial presentation, she was transferred to a non-tertiary United Kingdom hospital where she was recovering well with intensive physiotherapy assisted mobilisation. Mobility was improving, and a persistent left anterior lower leg skin wound eventually healed. The retained section of ECMO cannula remained in situ, causing no further clinical issue and is being followed up. At the time of this report, 18 months on, she is at home making good progress with ongoing community rehabilitation services. She is independently mobility following successful skin grafting to the left lower leg for non-healing wounds (Figure 4).

DISCUSSION

S. aureus secretes six cytolytic toxins, of which the best known is PVL. It is composed of two proteins and encoded by two genes lukS-PV and lukF-PV[7,8]. *S. aureus* produces pore-forming cytotoxins allowing bacteria to replicate inside host cells, preventing activation of the innate immune response. This can lead to cell lysis due to its ability to form pores in the cytoplasmic membrane. PVL is a strain of *S. aureus* that can cause severe skin and soft-tissues infections. Invasive infections can result in rare but rapidly fatal pneumonia in young and healthy individuals[9,10]. Initially presenting with fever, haemoptysis, and leukopaenia, PVL-*SA* pneumonia can quickly progress to ARDS with a high mortality rate[1,3].

Adolescents aged 12-19 years often have complex physical and psychological changes which require special consideration. Wood *et al*[11] reported that AICU staff suggest adolescents are to be transferred to PICU when they have more than one

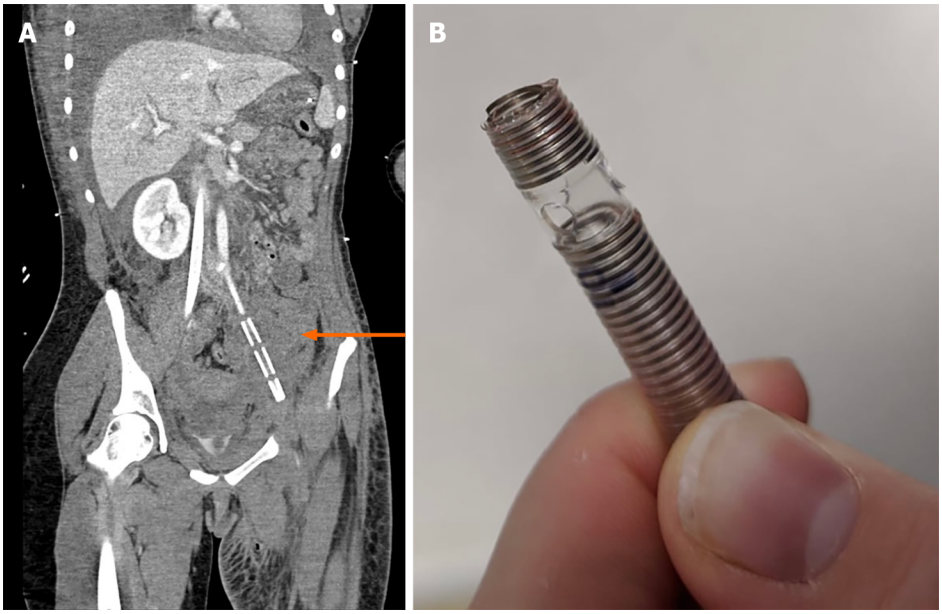

Figure 3 Computed tomography. A: Coronal computed tomography scan slice demonstrating retained extracorporeal membrane oxygenation (ECMO) cannula fragment (orange arrow); B: The torn end of the partially removed ECMO cannula.

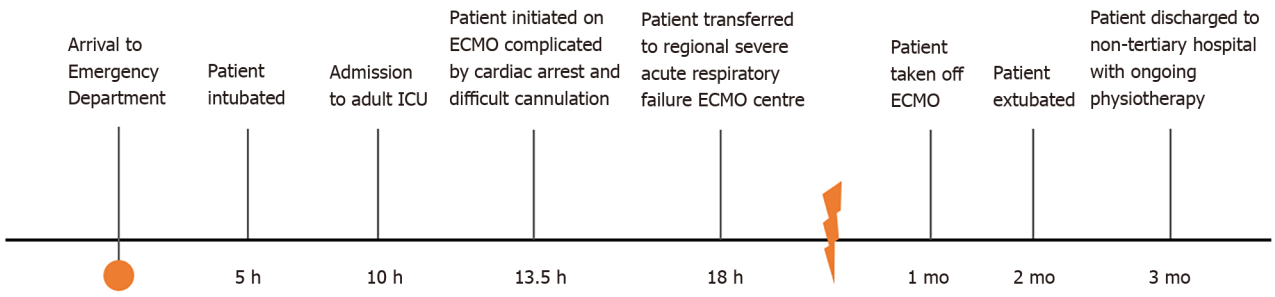

Figure 4 Timeline of key events with time since initial presentation. ICU: Intensive care units; ECMO: Extracorporeal membrane oxygenation.

system failure. Our patient weighed 53 kg and was considered physiologically adult. There was a clear discussion and establishment of collaborative care throughout her stay on AICU. This extended to her and her family with ongoing psychological support and a family liaison team throughout.

Vasoplegic shock (distributive) can be encountered in different clinical scenarios, including septic shock, toxic shock syndrome, post-cardiac bypass surgery, burns and trauma[12]. Fluid bolus therapy (FBT) is the mainstay of treatment in paediatric sepsis; however, clinical research in this area is challenging[13]. In 2018, Gelbart[14] reported that FBT had been used in paediatric sepsis management for several years without overarching evidence to support its appropriate use. Increasing attention is now turning to evidence that suggests harm can come from excessive fluid therapy. Under-resuscitation can lead to multiple organ dysfunction. However, over-resuscitation may result in pulmonary or peripheral oedema[15]. The United Kingdom resuscitation council guidelines for paediatric advanced life support[16] states that restricted fluid therapy with isotonic crystalloid may be more favourable than the more profuse use of fluids in some forms of septic shock. Vigorous fluids and albumin were administered to our patient at the known cost of potential pulmonary oedema to replace lost circulating volume and stabilise life-threatening cardiovascular collapse.

Increasingly, doctors are open to early discussions of extracorporeal life support (ECLS)[17]. During the H1N1 influenza A pandemic in 2009, due to the acute effects of severe respiratory failure, a third of patients admitted to AICU required ECLS and led to the creation of the United Kingdom national SARF ECMO service[17]. Noah *et al*[18] summarised four case reports with patients on ECMO for respiratory failure secondary to PVL-*SA*. Of these cases, two of the patients were 15 and 17-years-old, and both were successfully discharged to their local hospitals following eight and nineteen days on ECMO, respectively. Haider *et al*[19] reported a case of a 12-year-old boy who

developed PVL-*SA* pneumonia. The patient rapidly developed respiratory failure and died due to secondary cardiac arrest. The initiation of ECMO, despite complications, allowed time for other interventions to benefit our patient, particularly antimicrobial therapy. Without ECMO, judicious resuscitation and tertiary critical care, she would almost certainly have died. Further, the rapid intervention of an experienced cardiothoracic surgeon to prevent potential massive blood loss following ECMO complications highlights the importance of having the right people in the right place, at the right time.

Establishing the correct antimicrobial regimen is essential. The United Kingdom Health Protection Agency guideline[20] recommends using empirical broad-spectrum antimicrobials that suppress toxin production, such as clindamycin, linezolid and rifampicin. IV flucloxacillin is not recommended due to low necrotic tissue penetration, particularly as it may increase the PVL toxin production above the minimal inhibitory concentration. IVIg is recommended at a dose of 2 g/kg.

CONCLUSION

In summary, a healthy adolescent presented with worsening respiratory symptoms, rapidly progressing to profound fulminant shock and severe ARDS. This was secondary to Influenza A/H3N2 and PVL-*SA* pneumonia. In profound septic shock, consideration of both viral and bacterial infections should initiate rapid diagnostic tests where possible, in combination with appropriate and early anti-infective cover. Prompt intubation and ventilation, management of septic shock and ARDS with early fluid and vasopressor/inotropic resuscitation, IV antimicrobials, and IVIg plus extracorporeal support leading to high level tertiary critical care provided the framework for her remarkable survival, despite complicated ECMO cannulation and cardiac arrest. Early involvement of ID and microbiology specialists, along with PHE support, is required for optimal patient outcomes and staff protection when dealing with suspected high-risk infective pathogens**.** This case demonstrates the importance of collaboration between multidisciplinary teams and specialist centres with prompt ECMO referral in similar patients. It further highlights the importance of early ECMO initiation for suspected PVL-*SA*. It reveals the challenges of emergency management of critically unwell adolescents in centres without PICU availability. Patients like this require a multidisciplinary approach and the utilisation of various specialities to ensure positive outcomes. Finally, it is an example of what is achievable through coordinated and timely cooperation between acute care specialities, disciplines, medical services and agencies in emergency lifesaving situations.

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OPINION REVIEW

Point of care venous Doppler ultrasound: Exploring the missing piece of bedside hemodynamic assessment

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Abstract

Accurate assessment of the hemodynamic status is vital for appropriate management of patients with critical illness. As such, there has been a constant quest for reliable and non-invasive bedside tools to assess and monitor circulatory status in order to ensure end-organ perfusion. In the recent past, point of care ultrasonography (POCUS) has emerged as a valuable adjunct to physical examination in various specialties, which basically is a clinician-performed bedside ultrasound to answer focused questions. POCUS allows visualization of the internal anatomy and flow dynamics in real time, guiding apt interventions. While both arterial (forward flow) and venous (organ outflow or afterload) limbs of hemodynamic circuit are important for tissue perfusion, the venous side remains relatively under-explored. With recent data underscoring the deleterious consequences of iatrogenic volume overload, objective evaluation of venous congestion is gaining attention. Bedside Doppler ultrasound serves this purpose and aids in diagnosing and monitoring the congestion/venous blood flow pattern. In this article, we summarize the rationale for integrating this technology into routine care of patients with volume-related disorders, discuss the normal and abnormal waveforms, limitations, and future directions.

Key Words: Ultrasound; Point of care ultrasonography; Doppler; VExUS; Congestion; Hemodynamics; Heart failure; Nephrology; Critical care

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Core Tip: Point-of-care Doppler ultrasonography is emerging as a valuable bedside diagnostic tool for the assessment of venous congestion. Doppler interrogation of the abdominal veins such as the hepatic, portal, renal parenchymal veins in addition to inferior vena cava ultrasound provides useful insights into a patient's hemodynamics, when interpreted in conjunction with other sonographic parameters such as the cardiac pump function, lung ultrasound and conventional clinical assessment.

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INTRODUCTION

Objective assessment of hemodynamic status is fundamental to guide resuscitative efforts in a critically ill patient[1]. Among the myriad of methods used at the bedside, only a few have stood the test of time. Capillary refill time and passive leg raise with non-invasive cardiac output (CO) monitoring can be counted amongst these as both strategies have been shown to improve relevant patient outcomes in controlled trials[2, 3]. The success of these assessments seems to rely on avoiding unnecessary fluid loading thus mitigating fluid overload, which has been increasingly linked to adverse patient outcomes[4].

Inevitably, intensive care unit physicians will encounter over-resuscitated patients as well as those presenting with pre-existing volume overload[5]. While avoiding further fluid loading is important, efforts to actively decrease extracellular volume (de-resuscitation) have been shown to lead to potentially beneficial clinical outcomes[6]. De-resuscitation is especially relevant for patients presenting with or developing heart failure during the course of their critical illness as volume overload in this patient population results in increasing severity of venous congestion[7]. Increased left-sided filling pressures facilitate lung congestion and lead to worsening respiratory status[8]. Less appreciated however, are the consequences of systemic venous congestion secondary to increased right-sided filling pressures. Increased right atrial pressure (RAP) can be transmitted backwards across the venous tree and lead to congestive organ dysfunction[9]. This can manifest as elevated bilirubin from congestive hepatopathy[10], delirium from congestive encephalopathy[11], acute oliguric kidney injury from 'intra-capsular tamponade'[7], and gut edema resulting in increased endotoxemia[12,13].

The degree of congestive organ dysfunction is not only a function of absolute RAP, but also depends on the degree of transmission of such pressure to the peripheral organs. Increased RAP becomes initially attenuated along the venous vascular tree as a consequence of venous distensibility[14]. However, progressive increases in venous volume will eventually result in maximally stretched venous walls reaching the flat part of the venous compliance curve; At this point, pressure transmission will be greatly enhanced leading to peripheral organ congestion. Because of this, assessing congestion at the level of the organs can provide valuable information regarding the mechanisms of organ dysfunction[15]. Given venous congestion results in altered patterns of organ venous flow, Doppler point-of-care ultrasonography (POCUS) allows quantification of these alterations at the bedside[16].

INFERIOR VENA CAVA AS THE FIRST STEP IN THE ASSESSMENT OF CONGESTION

Sonographic assessment of the collapsibility/distensibility of inferior vena cava (IVC) to predict volume responsiveness has several caveats and, in our opinion, should not be used for such purpose[17]. However, a plethoric (> 20 mm) non collapsible IVC is

not normal and will only be seen in patients with pathological venous congestion[18]. Evaluation of the IVC using POCUS is a well-accepted surrogate of venous congestion as it mainly reflects RAP; However, many factors influence IVC size and collapsibility such as respiratory effort in spontaneously breathing patients[19] and the presence of intra-abdominal hypertension[20]. Another problem is inherent to the conventional long axis view of interrogation; Given the IVC is a three-dimensional structure with elliptical shape, evaluation of diameters in both long and short axes has been shown to be a better estimate of central venous pressure (CVP)[21].

Although a plethoric non-collapsible IVC establishes the presence of venous congestion, this information alone is not always adequate to guide management for two important reasons: Firstly, obstructive pathologies acutely leading to venous congestion need immediate resolution by specific interventions that have nothing to do with extracellular volume (cardiac tamponade, tension pneumothorax, massive pulmonary embolism). In these cases, focused cardiac ultrasound is necessary to establish diagnosis and management[22]. The second reason is that certain cardiac pathologies (chronic severe pulmonary hypertension, right ventricular failure, severe valvulopathies, restrictive cardiomyopathy or constrictive pericarditis) require elevated RAP in order to maintain CO; as such, excessive volume removal targeting a normal IVC diameter and collapsibility is not in the best interest of these patients[23]. However, progressive volume overload beyond what is needed to maintain CO will lead to an excessive increase in RAP, which can be transmitted to peripheral organs resulting in their dysfunction[7]. Thus, in this particular setting, evaluating pressure transmission using Doppler ultrasonography is a valuable non-invasive adjunct to overall clinical assessment.

NORMAL VENOUS DOPPLER FLOW PATTERNS

To assess the venous system with Doppler ultrasound, it is important to understand that flow pattern is the main variable being measured. Flow is generated by a pressure differential between two points, given a relatively constant vessel diameter, this pressure differential will determine flow velocity. Equilibration of pressures will cause flow to cease. When assessing flow with pulsed wave Doppler ultrasound, the direction is represented by positive or negative deflections from the baseline, while speed will be represented by the deflection amplitude. If the flow moves away from the transducer, the image will show a negative deflection (analogous to 'blue' on color Doppler). A positive deflection will be seen if flow is directed towards the transducer (analogous to 'red' on color Doppler)[24]. The normal venous flow patterns are determined by the changes in RAP throughout the cardiac cycle and modified by venous compliance and distance from the heart[25]. Therefore, the flow patterns will be different depending on the site being evaluated. Normal waveforms can be pulsatile with discernable flow corresponding to the phases of cardiac cycle as in the case of hepatic vein (HV), or continuous as with portal and intra-renal veins. Moreover, respirophasic changes in amplitude can be demonstrated reflecting the increased venous return during inspiration in spontaneously breathing patients.

HV flow pattern

In a normal CVP trace, atrial systolic contraction results in a rise in RAP represented as the A-wave. After the tricuspid valve closes (C-wave), the right atrium relaxes, and the ventricular systole pulls down the annulus towards apex resulting in a fall of RAP represented as the X-descent. The RA filling from the venous system during ventricular systole causes a progressive rise in RAP and forms the V wave. The Y-descent is then caused by tricuspid valve opening.

Since HV directly joins the IVC, their flow pattern is a mirror reflection of RAP variations throughout the cardiac cycle. Normal HV flow pattern consists of a positive/retrograde wave (A) that represents atrial systolic contraction analogous to A-wave of the CVP, and two negative/antegrade systolic (S) and diastolic (D) waves that represent the X and Y-descents of the CVP, respectively. Since X-descent is deeper than Y-descent, the HV S-wave usually has a larger amplitude than the D-wave (S > D) [26]. Figure 1 illustrates the normal time-correlated electrocardiographic (ECG) findings, CVP tracing and HV Doppler waveform.

Intra-renal and femoral venous flow patterns

In more distal vascular beds such as intra-renal and femoral veins, the tracing will not directly reflect RAP variations; this is explained by the high compliance of the venous

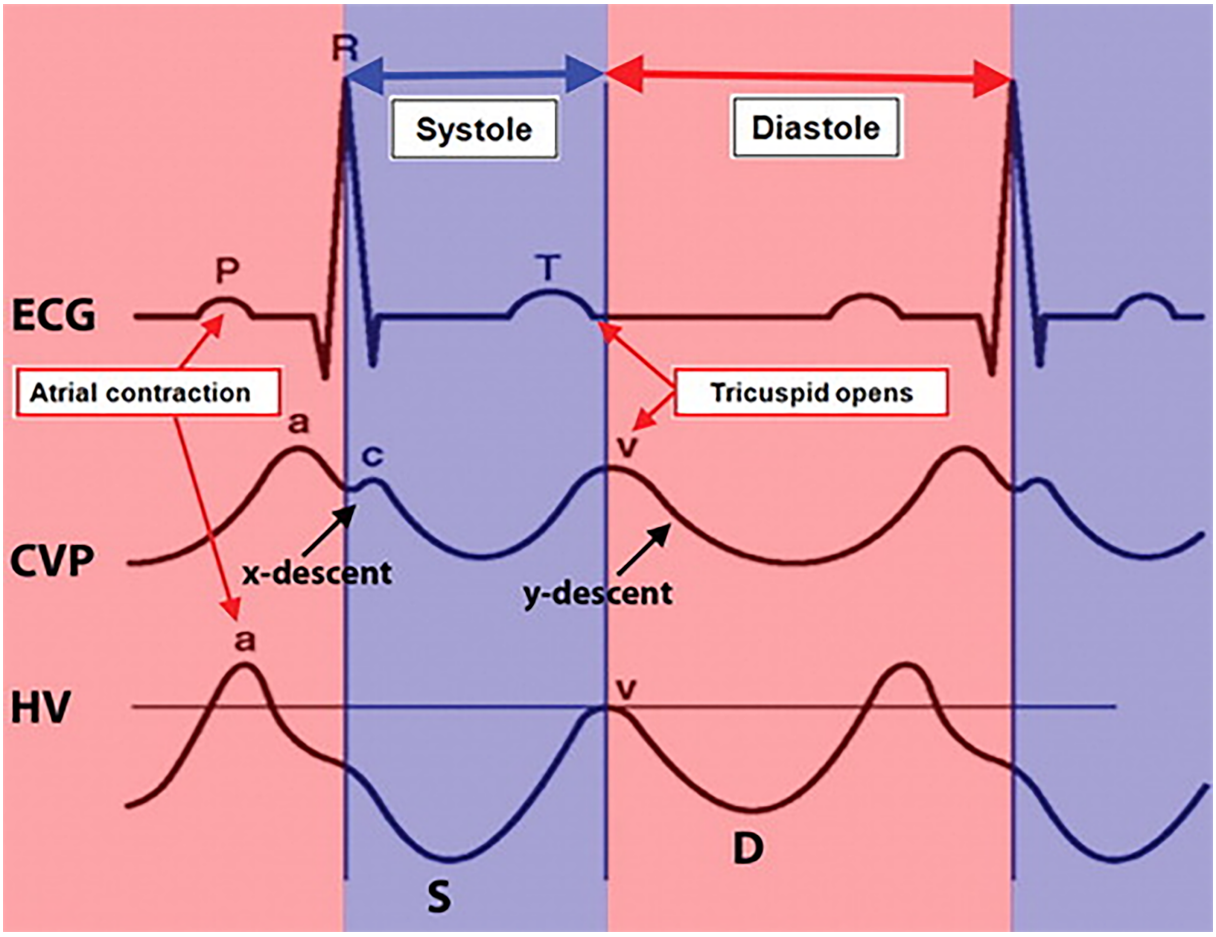

Figure 1 Normal time-correlated electrocardiographic findings, central venous pressure tracing, and hepatic venous waveform. The peak of the retrograde a wave corresponds with atrial contraction, which occurs at end diastole. The trough of the antegrade S wave correlates with peak negative pressure created by the downward motion of the atrioventricular septum during early to mid-systole. The peak of the upward-facing v wave correlates with opening of the tricuspid valve, which marks the transition from systole to diastole. The peak of this wave may cross above the baseline (retrograde flow) or may stay below the baseline (*i.e.*, remain antegrade). The trough of the antegrade D wave correlates with rapid early diastolic right ventricular filling. ECG: Electrocardiographic; CVP: Central venous pressure; HV: Hepatic venous. Citation: McNaughton DA, Abu-Yousef MM. Doppler US of the liver made simple. Radiographics 2011; 31: 161-188. Copyright © The Authors 2020. Published by Radiological Society of North America (RSNA®).

system and the attenuation of RAP variations with increasing distance from the heart. The flow pattern in normal distal veins will be predominantly continuous with no discernible waves, although low amplitude S and D-waves may be seen[27,28]. It is of note that the intra-renal Doppler is usually obtained at the level of interlobar vessels, which pass through the renal parenchyma and hence thought to better reflect organ perfusion compared to the main renal vein. Intra-renal venous trace is often accompanied by arterial trace above the baseline as the Doppler sample volume overlies both interlobar vein and artery, which are much smaller compared to other vessels such as HV.

Portal vein flow pattern

The portal vein (PV) is part of a distinct venous system that it is isolated from central veins by the hepatic sinusoids and from the arterial system by splanchnic capillaries. Therefore, the Doppler waveform of the normal PV will not reflect RAP variations unlike that of HV and appears as a characteristic positive (flow towards the transducer), continuous (or mildly pulsatile) flow[29].

ALTERED FLOW PATTERNS IN VENOUS CONGESTION

Hepatic vein Doppler alterations

When the RAP increases, the characteristic ascending and descending waves formed within the RA will change. As the RA filling pressure increases, the X-descent

decreases in amplitude while the Y-descent amplitude increases. This is due to loss of RA compliance and decreased right ventricular systolic pull of the tricuspid valve annulus. Right ventricular overload will eventually cause tricuspid annular dilation and tricuspid regurgitation, leading to obliteration of the X descent and fusion of C-V waves of the CVP waveform. All of this will be reflected in the HV flow; initially, the amplitude of the S-wave decreases compared to that of D-wave (S < D pattern)[30-32]. With worsening congestion, the S-wave can be obliterated or become reversed/retrograde if severe tricuspid regurgitation if present[33-35]. HV alterations have been shown to correlate with increased PV pulsatility, abnormal intra-renal venous flow and adverse kidney events including acute kidney injury (AKI) in recent studies[16,36-38].

Portal vein Doppler alterations

The main alteration in the PV waveform is progressive increase in pulsatility with elevated RAP. This can be quantified by the pulsatility fraction [(Vmax-Vmin/Vmax) × 100]; a pulsatility fraction ≥ 30% is considered mild elevation while ≥ 50% is considered severe. Further increases in RAP may lead to flow reversal (below the baseline) during systole[39-42]. The physiological explanation of pulsatility is the reduction of flow velocity during systole secondary to retrogradely transmitted waves from the right atrium during this phase of the cardiac cycle.

Most Clinical studies evaluating PV Doppler have been performed in the context of decompensated heart failure and cardiac surgery. PV pulsatility has been correlated with elevated RAP, clinical features of congestion[40], pulmonary wedge pressure, pulmonary artery resistance, right ventricular end diastolic pressure[39], left and right ventricle size[41], mean pulmonary artery pressure and peripheral vascular resistance [42]. Similar to HV, the recent focus has been to study the impact of PV pulsatility on clinical outcomes. In patients with decompensated heart failure, increased PV pulsatility was associated with worse clinical outcomes if present at discharge and predicted response to diuresis at admission[43,44]. In cardiac surgery patients, PV pulsatility was associated with congestive encephalopathy and delirium[11], AKI[45] and right ventricular dysfunction[46].

Intra-renal vein Doppler alterations

The intra-renal venous Doppler (IRVD) pattern is continuous, sometimes with a brief interruption during atrial systole. This pattern becomes biphasic as RAP increases and two distinct waves (S and D) can be observed. These waves are analogous to the normal hepatic waveform and represent increased pressure transmission from the heart to the interlobar renal veins[27]. With worsening congestion (intracapsular tamponade) the S-wave can either become reversed or disappear (obscured in the arterial trace). Though venous impedance index [(maximum flow velocity−minimum diastolic flow velocity)/maximum flow velocity] is frequently reported in studies to quantify renal venous pulsatility, pattern recognition described above is simpler. Moreover, when the waveform is discontinuous, the impedance index becomes 1 as the minimum velocity is zero and does not differentiate between biphasic and monophasic patterns. In this regard, renal venous stasis index (RVSI) proposed by Husain-Syed *et al*[47] better reflects the full continuum of renal congestion. It indicates the proportion of the cardiac cycle during which there is no venous outflow and is calculated as: Cardiac cycle time−venous flow time/cardiac cycle time. Therefore, monophasic pattern has a higher RVSI than biphasic pattern.

Multiple studies have shown that IRVD alterations are not merely a reflection of increased RAP, but also strong predictors of adverse clinical outcomes in patients with compensated[27] and decompensated heart failure[48], those undergoing cardiac surgery[45], patients with pulmonary hypertension and right heart failure[47].

In cardiac surgery patients, altered intra-renal Doppler pattern was shown to be a strong predictor of AKI. However, this was not replicated in less selected populations of critically ill patients[38,49]. Given the multitude of etiologies of AKI in addition to venous congestion (such as tubular injury) in such patients, this lack of association is not surprising. A visual summary of normal and altered venous flow patterns in the above-described veins is shown in Figures 2-4.

Femoral vein Doppler alterations

As opposed to intra-renal and PV, the common femoral vein is directly connected to the IVC facilitating the quick transmission of pressure waves as RAP increases. Flow in the normal femoral vein is relatively continuous with respiratory variability although a *low amplitude* positive/retrograde wave (A-wave) and anterograde S and D-waves maybe appreciated depending on the angle of insonation[28]. With elevations in RAP,

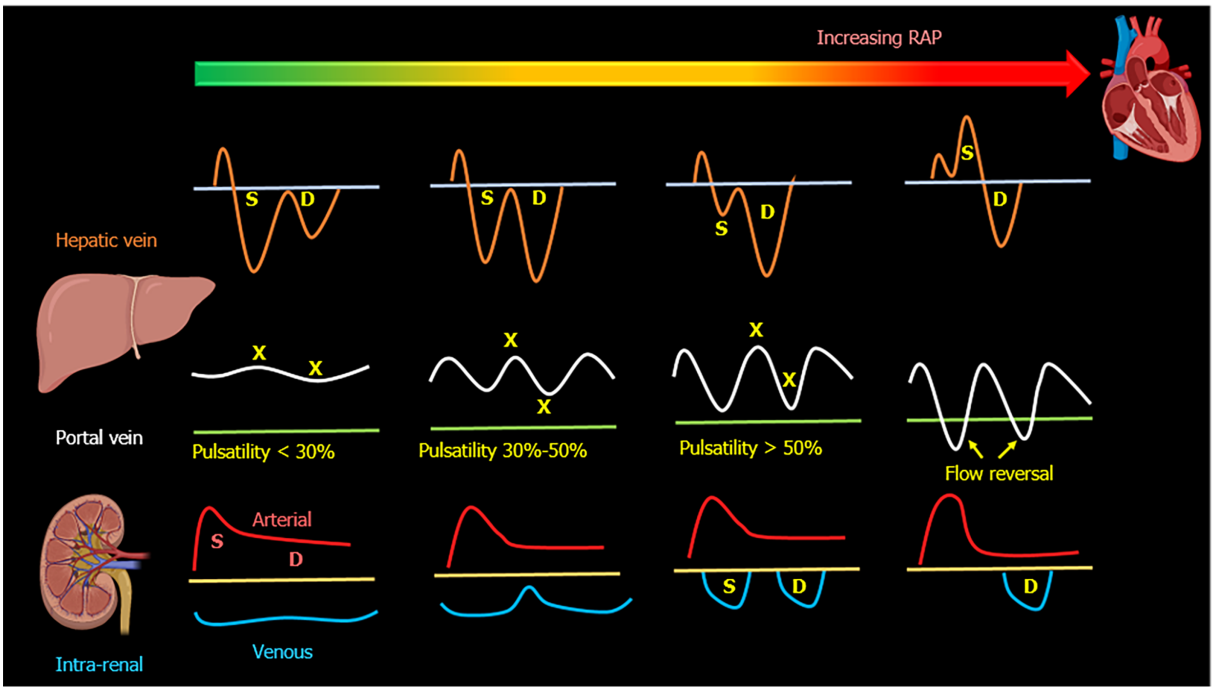

Figure 2 Transformation of the hepatic, portal, and intra-renal Doppler waveforms with increasing right atrial pressure. Asterisks on the portal waveform represent the highest and lowest points during a cardiac cycle used to calculate pulsatility fraction. RAP: Right atrial pressure.

the retrograde A-wave increases in amplitude or it will fuse with a reversed S-wave if severe tricuspid regurgitation is present. A retrograde wave velocity of ≥ 10 cm/s is considered abnormal and indicative of high RAP[50].

Few studies have integrated femoral vein Doppler flow into diagnostic algorithm; in a recent study including 47 patients with pulmonary thromboembolism, changes in the pulsatility pattern of the femoral vein were seen in all patients with right ventricular dysfunction[51]. Recently, it has been proposed as a quick way to diagnose right ventricular dysfunction in patients undergoing cardiac surgery[28]. Indeed, it is an attractive option in the emergency settings, where femoral vein is often sonographically assessed for central venous catheter placement. Table 1 summarizes the advantages and limitations of the Doppler evaluation of above-discussed vessels.

LIMITATIONS OF DOPPLER EVALUATION OF VENOUS CONGESTION

Doppler evaluation of venous congestion does not come caveat-free; first of all, the evaluation is operator dependent, meaning that the experience of the observer effects the image acquisition and interpretation. It is not unexpected because Doppler ultrasonography requires a higher skill level than for basic greyscale POCUS applications. Interobserver agreement has been reported mainly with experienced operators. For the HV, the kappa index was 0.95[52]; for the intra-renal venous Doppler and PV, the interobserver agreement was 87% and 95% respectively[45]; and for the femoral vein Doppler, the reproducibility of readings was 80%-98%[50]. Secondly, clinicians must be aware of the false negative and false positive findings that can interfere with interpretation. The HV Doppler should be accompanied by a simultaneous ECG as much as possible; otherwise, the observer can incorrectly identify A-wave as a retrograde S-wave and vice versa. Similarly, S and D waves can be confused for one another. Notably, pulsatile PV flow can be found in young healthy individuals with low body mass index, without elevations in RAP[53]. On the other hand, reduced PV pulsatility despite elevated RAP has been reported in patients with parenchymal liver disease[54-56]. Intra-renal venous Doppler is technically challenging to obtain and more time consuming; it can also be altered by obstructive urological pathologies[57]. Doppler interrogation of the femoral vein may be altered by application of excessive transducer pressure. Due to these limitations, isolated interpretation of individual waveforms may lead to incorrect conclusions. Therefore, assessing IVC and multiple venous sites including HV, PV, IRVD in an organized stepwise manner could enhance diagnostic performance. Corroborating this notion, a recent study employing a

Table 1 Advantages and limitations of the Doppler evaluation of various veins

	Advantages	Limitations
Hepatic vein	Easy to acquire images from the same window used to assess IVC.	Prone to erroneous interpretation without simultaneous EKG tracing.
		Influenced by arrhythmias (*e.g.*, S-wave can be smaller in atrial fibrillation), right ventricular systolic dysfunction.
		May never normalize in chronic pulmonary hypertension, structural tricuspid regurgitation irrespective of fluid status.
Portal vein	Easy to assess without EKG.	Not reliable in cirrhosis.
	Reliably changes with decongestive therapy - can monitor response to diuresis/ultrafiltration in real time.	Can be pulsatile in young, thin individuals without raised RAP.
	Tends to improve with decongestion, if not normalize even in chronic pulmonary hypertension.	
Renal parenchymal vein	Simultaneous arterial tracing functions as a built-in EKG.	Difficult to obtain optimal images.
		Not studied in chronic kidney disease/patients with structural renal abnormalities.
		Interstitial edema may hamper improvement with decongestive therapy in real time (improves but lags behind decongestion).
		May never normalize in chronic pulmonary hypertension, structural tricuspid regurgitation irrespective of fluid status.
Femoral vein	Technically easier to acquire images of the vein.	Susceptible to excessive transducer pressure.
		Dependent on correct Doppler angle if measuring absolute velocities (pattern evaluation is less angle dependent).

IVC: Inferior vena cava; RAP: Right atrial pressure; EKG: Electrocardiogram.

protocolized venous Doppler examination termed "VExUS" (venous excess ultrasound score) has shown greater specificity for organ injury than any individual assessments [16].

INTERNAL JUGULAR VEIN AND SUPERIOR VENA CAVA ULTRASOUND

Similar to IVC, internal jugular vein (IJV) ultrasound can also be used to estimate RAP non-invasively. In one study, < 17% increase in right IJV cross sectional area with Valsalva maneuver predicted an elevated RAP (≥ 12 mmHg) with 90% sensitivity and 74% specificity[58]. In patients who cannot follow instructions, assessment of IJV diameter at the end of inspiration and expiration can provide a rough idea of CVP. For example, in a study of 34 spontaneously breathing patients, mean IJV diameter was 7 mm in those with CVP < 10 cm H_2O [95% confidence interval (CI): 5.7-8.3] *vs* 12.5 mm (95%CI, 11.2-13.8) in those with CVP of ≥ 10 cm H_2O[59]. In intubated patients, it is of limited utility to predict CVP but an IJV distensibility of > 18% prior to volume challenge has shown to predict response to fluids[60]. While IJV ultrasound appears easy to perform, the amount of information it can provide is limited and cannot be used in lieu of VExUS. Moreover, it is subject to erroneous interpretations due to inadvertent application of excess transducer pressure, limited access to the neck because of the presence of central venous catheters, tracheostomy collars, braces *etc.* On the other hand, superior vena cava ultrasound has been studied in the context of predicting fluid responsiveness and shown to perform better than IVC[61]. However, transesophageal echocardiography is required to reliably access the vessel, which is not routinely performed in all clinical settings.

INTEGRATION OF BEDSIDE DOPPLER ULTRASOUND INTO GLOBAL HEMODYNAMIC ASSESSMENT

Venous Doppler ultrasound should not be used to 'determine' fluid status or assess fluid responsiveness. This novel bedside tool should be viewed as another piece of

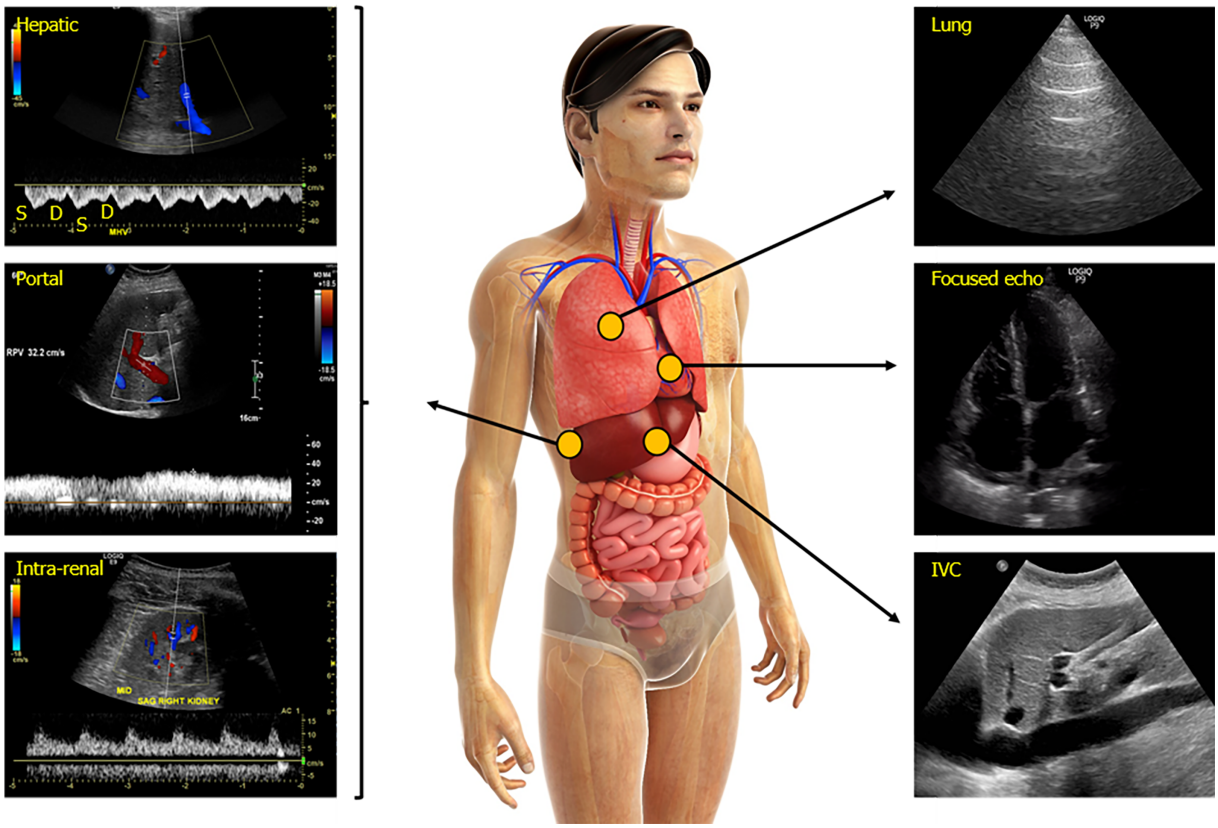

Figure 3 Figure illustrating the integration of venous Doppler with other vital pieces of sonographic assessment including focused cardiac and lung ultrasound. Normal waveforms shown. IVC: Inferior vena cava. Human body image licensed from Shutterstock®.

information in the global hemodynamic assessment of the critically ill patient in addition to other sonographic and clinical parameters. Since the information it yields might be particularly relevant for patients with oliguric AKI, the following discussion will center on the resuscitative efforts aimed at restoring renal perfusion (*renoresuscitation*). The first step in evaluating oliguric kidney injury is excluding obstructive pathology by kidney and urinary bladder ultrasound[62]. Also, looking for the cues to intrinsic kidney injury such as acute tubular necrosis or acute interstitial nephritis is of paramount importance as resuscitative efforts are unlikely to restore renal function in this situation[63]. Intrinsic AKI should be suspected when the clinical and laboratory data point to tubular dysfunction (exposure to nephrotoxins, prolonged hypotension, isosthenuria, high fractional excretion of sodium, abundant muddy brown casts on urine microscopy)[64]. A furosemide stress may help assessing renal tubular integrity as well as bears prognostic significance[63]. While acute glomerulonephritis is uncommon in patients with hospital-acquired AKI, finding of dysmorphic red blood cells on urine sediment examination should prompt nephrology consultation for investigation of glomerular causes of AKI.

On the other hand, evidence of preserved tubular function should lead to presumptive diagnosis of hemodynamic AKI caused by renal hypoperfusion. Evidence of global hypoperfusion (increased capillary refill time, skin mottling, altered mental status) increases the likelihood that resuscitative interventions could result in improved urine output. It is important to understand that renal perfusion pressure is proportional to the difference between mean arterial blood pressure (MABP) and renal venous pressure, and inversely proportional to renal arteriolar resistance[65]. Traditional resuscitative efforts have focused on increasing MABP (vasopressors) or increasing CO (fluids, inotropes). However, less attention has been paid to renal venous pressure even though this is an equally important determinant of renal perfusion. Measurement of intra-abdominal pressure should be performed if there is a suspicion of abdominal compartment syndrome, particularly in patients with trauma or tense ascites[66]. In addition, Doppler evaluation of venous congestion can point to renal congestion (intra-capsular tamponade) as the cause of renal hypoperfusion by demonstrating the effects of raised RAP on venous outflow[16,67]. This previously missing piece of the hemodynamic puzzle can add valuable information as oliguric

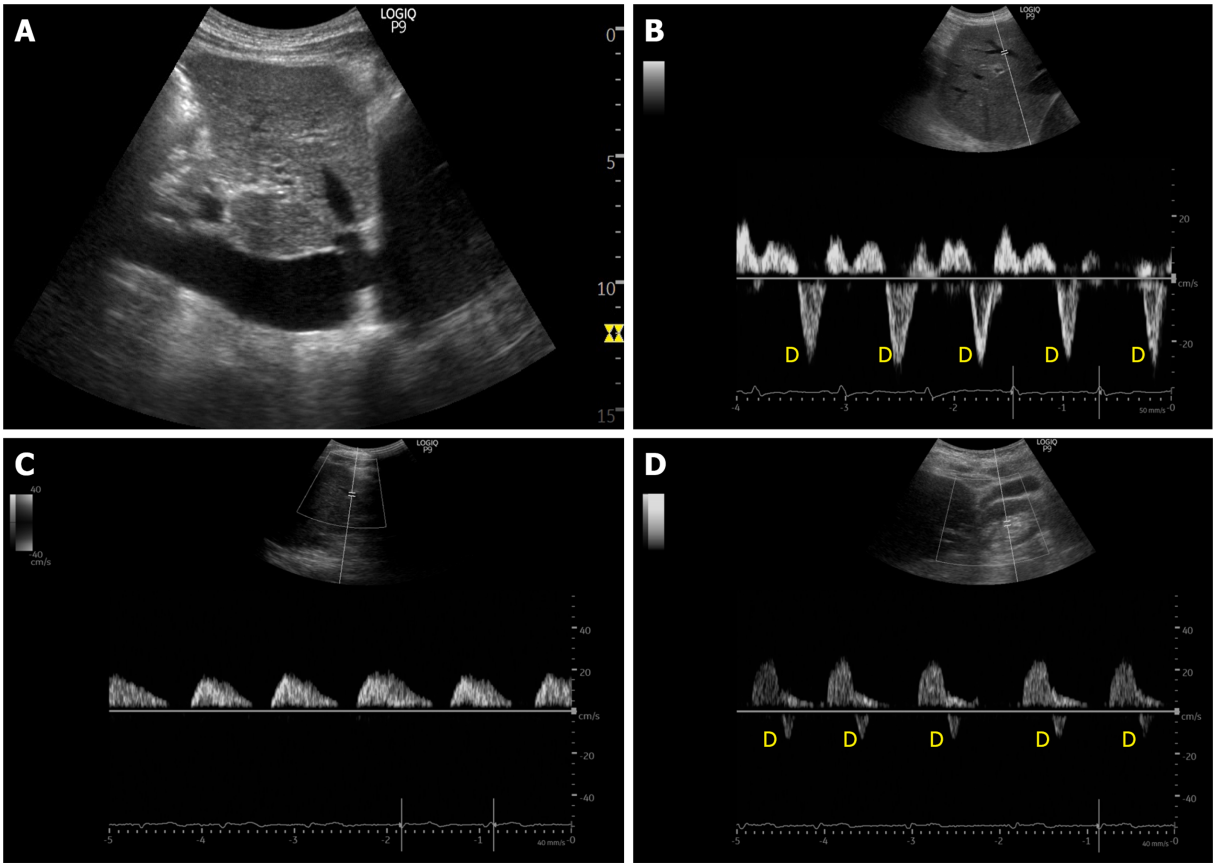

Figure 4 Example of ultrasound stigmata of severe venous congestion obtained from a patient with congestive heart failure exacerbation and tricuspid regurgitation. A: Dilated inferior vena cava; B: Hepatic vein Doppler demonstrating only D-wave below the baseline; C: Pulsatile portal vein with flow pauses in between the cardiac cycles; D: Ontra-renal vein demonstrating only D-wave below the baseline.

AKI in the presence of severe venous congestion will likely worsen with fluid administration but is likely to improve following decongestion[67-69]. Finally, it is also important to recognize that microvascular alterations underly many cases of sepsis associated AKI[70]. These alterations are an important determinant of glomerular hydrostatic pressure regardless of macrohemodynamics and as such, are not likely to improve with conventional resuscitative efforts.

Performing a comprehensive hemodynamic assessment using POCUS in addition to conventional evaluation is vital in the management of critically ill patients as multiple hemodynamic alterations might be present simultaneously (the so-called pump, pipes, leaks strategy)[70]. For example, a septic patient with pre-existing heart failure can display both vasodilation (low peripheral vascular resistance) and severe venous congestion. In this setting, vasopressors and diuretics can be used together to address these alterations. In summary, venous Doppler provides valuable information regarding a patient's hemodynamic status, when used in combination with multi-organ POCUS as well as clinical and laboratory data.

CONCLUSION

Multi-point Doppler evaluation of the venous system allows clinicians to assess the downstream effects of elevated RAP on peripheral organs. This tool should not be used as a marker of fluid status or volume responsiveness but rather as a means to determine if congestion is contributing to organ dysfunction and gauge the response to decongestive therapy. This information should be integrated into a comprehensive hemodynamic evaluation in order to choose the appropriate resuscitative strategy. Future studies should focus on investigating whether incorporating venous Doppler ultrasound in the diagnostic and treatment algorithms translates into better clinical outcomes. Furthermore, as most of the current data are from patients with heart failure, research should be undertaken in other subsets of patients susceptible to fluid overload such as those with liver cirrhosis and chronic kidney disease.

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MINIREVIEWS

Extracorporeal membrane oxygenation and inhaled sedation in coronavirus disease 2019-related acute respiratory distress syndrome

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Abstract

Coronavirus disease 2019 (COVID-19) related acute respiratory distress syndrome (ARDS) is a severe complication of infection with severe acute respiratory syndrome coronavirus 2, and the primary cause of death in the current pandemic. Critically ill patients often undergo extracorporeal membrane oxygenation (ECMO) therapy as the last resort over an extended period. ECMO therapy requires sedation of the patient, which is usually achieved by intravenous administration of sedatives. The shortage of intravenous sedative drugs due to the ongoing pandemic, and attempts to improve treatment outcome for COVID-19 patients, drove the application of inhaled sedation as a promising alternative for sedation during ECMO therapy. Administration of volatile anesthetics requires an appropriate delivery. Commercially available ones are the anesthetic gas reflection systems AnaConDa® and MIRUS™, and each should be combined with a gas scavenging system. In this review, we describe respiratory management in COVID-19 patients and the procedures for inhaled sedation during ECMO therapy of COVID-19 related ARDS. We focus particularly on the technical details of administration of volatile anesthetics. Furthermore, we describe the advantages

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of inhaled sedation and volatile anesthetics, and we discuss the limitations as well as the requirements for safe application in the clinical setting.

Key Words: Extracorporeal membrane oxygenation; COVID-19; Acute respiratory distress syndrome; Critical care; Volatile anesthetics; Inhaled sedation

Core Tip: This article summarizes the use of inhaled sedation for extracorporeal membrane oxygenation in patients suffering from coronavirus disease 2019 (COVID-19) related acute respiratory distress syndrome, including a description of respiratory management, the technical aspects, and requirements for delivery of volatile anesthetics. The article closes with important future considerations for inhaled sedation in critically ill COVID-19 patients undergoing extracorporeal membrane oxygenation therapy.

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INTRODUCTION

The ongoing pandemic is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that triggers a variety of symptoms in the human host. One major complication of infection with SARS-CoV-2 is the acute respiratory distress syndrome (ARDS). Coronavirus disease 2019 (COVID-19) related ARDS is a severe condition associated with high mortality and is the primary cause of death among COVID-19 patients. Treatment of this condition is mainly supportive and requires considerable resources, but effective coordination enables the health care system to cope with the influx of critically ill patients[1].

If respiratory failure occurs in COVID-19 patients despite all efforts, extracorporeal membrane oxygenation (ECMO) treatment over an extended period is the last remaining therapeutic option[2]. Since the outcome of this treatment is poor, better prevention and treatment are urgently needed.

ECMO therapy requires sedation of the patient, often *via* high doses of intravenous sedatives such as midazolam, ketamine, or propofol in combination with an opioid and neuromuscular blocking agent. The ongoing pandemic is exhausting supplies of these drugs, so alternative approaches have to be considered[3]. One practical alternative approach is inhaled sedation with volatile anesthetics, such as isoflurane, sevoflurane, or desflurane[4,5].

Beside the low costs, volatile anesthetics are associated with faster onset and offset of sedation and thus allow efficient control of administration. Application of these drugs does not rely on electronic infusion pumps, which have become scarce during the pandemic. In addition, volatile anesthetics cause fewer hallucinations and lower opioid needs than intravenous anesthetics. Moreover, a recent study suggests that inhaled sedation could be associated with a better outcome than intravenous sedation [6]. In particular, sevoflurane yielded superior outcomes than other anesthetics[7,8]. Nonetheless, the application of inhaled sedation faces limitations. Most critical care units lack proper delivery and gas scavenging systems for limiting pollution with volatile anesthetics[9]. Further, health care professionals require special training to administer appropriately the anesthetics and to recognize contraindications, such as malignant hyperthermia.

In this review, we summarize the requirements for inhaled sedation in COVID-19 patients under ECMO therapy, and we highlight the technical aspects of administration of volatile anesthetics.

RESPIRATORY MANAGEMENT IN COVID-19 PATIENTS

Continuous monitoring of oxygen saturation in the patient is necessary, since a drop in saturation indicates a severe progression of COVID-19. If oxygen levels fall, respiratory management is required, but spontaneous breathing should be maintained as long as possible and reasonable. A number of approaches to support spontaneous breathing is available and has been comprehensively summarized elsewhere[10]. A schematic overview of the strategy for respiratory management in COVID-19 patients is presented in Figure 1.

The use of nasal cannula is the first method of choice; however, the fraction of inspired oxygen (FiO_2) is limited to 0.3 to 0.4. If insufficient, high flow nasal cannula produces a high flow and continuous positive airway pressure, capable of achieving higher FiO_2. This can be further supported by shifting the patient in a prone position [11]. The last resort of noninvasive intervention for respiratory management is the use of bilevel positive airway pressure and pressure support ventilation. These measures are capable of providing high FiO_2 and can be combined with placing the patient in prone position for further support. It should be mentioned that these measures require high quality masks for respiration to prevent pressure injuries on the skin or the nose of the patient.

Severe hypoxia, which is associated with COVID-19 related ARDS, impairs consciousness, vigilance, or compliance. For instance, impaired compliance of the patient can hinder the use of facial masks, leading to a dramatic drop in oxygen saturation. Consequently, severe hypoxia requires invasive measures, *e.g.*, endotracheal intubation. The decision to initiate this invasive intervention has to be made with the patient, or the relatives if necessary, and requires an open discussion on respiratory management. After intubation, a bronchoscopy or a thoracic drainage system should be considered, and the patient should be placed in prone position to support breathing. The specific type of invasive intervention depends on ventilation pressure and lung compliance.

If the partial pressure of oxygen/FiO_2 ratio drops below 150 mmHg, the patient should be placed in prone position for more than 12 h[12]. Individual measures can be taken to manage severe hypoxia, such as application of inhaled nitric oxide, muscle relaxants, or recruitment maneuver. If respiratory function remains poor (*i.e.* lower than 20 mL/mbar, partial pressure of oxygen/FiO_2 ratio less than 80 mmHg, or pH less than 7.25) despite prone positioning, veno-venous ECMO is the last resort to save the life of the patient[13,14].

Deploying an ECMO system can only be considered if all other approaches are unsuccessful and if there are no contraindications[15]. ECMO therapy can cause adverse events and suboptimal responses, in particular in COVID-19 patients who are predisposed to bleeding and thrombotic complications[16]. Such events could suggest withdrawal of ECMO therapy. Furthermore, a recent study reported an in-hospital mortality of 37.4% for patients with severe COVID-19 related ARDS 90 d after the initiation of ECMO therapy[17]. This highlights the importance of an open discussion with the patient and relatives at an early stage in order to clarify treatment goals, expectations, and possible outcomes as well as to obtain consent from the patient regarding continuation or discontinuation of therapy[18].

During ECMO therapy, patients with ARDS in prone position should be kept in at least light sedation, corresponding to a Richmond Agitation-Sedation Scale of ≥ 2[12]. Sedation is associated with side effects such as delirium, respiratory depression, and immunosuppression. Further, deep sedation is a risk factor for COVID-19 patients and is associated with poorer outcome. Thus, sedation must be monitored carefully. Processed electroencephalogram monitoring is a very useful approach to assess anesthesia and to recognize burst suppression. In case of inhaled sedation, measurement of the end-tidal gas concentration or the corresponding minimum alveolar concentration is a recommended approach. If Richmond Agitation-Sedation Scale increases during ECMO therapy, intravenous sedation is necessary to stabilize the depth of sedation.

ADMINISTRATION OF VOLATILE ANESTHETICS DURING ARDS THERAPY

The prerequisite for using the Anaesthetic Conserving Device (ACD) AnaConDa® (Sedana Medical AB, Danderyd, Sweden) or the MIRUS™ system (TIM, Koblenz, Germany) depends on several clinical parameters (see Figure 1). If lung compliance is

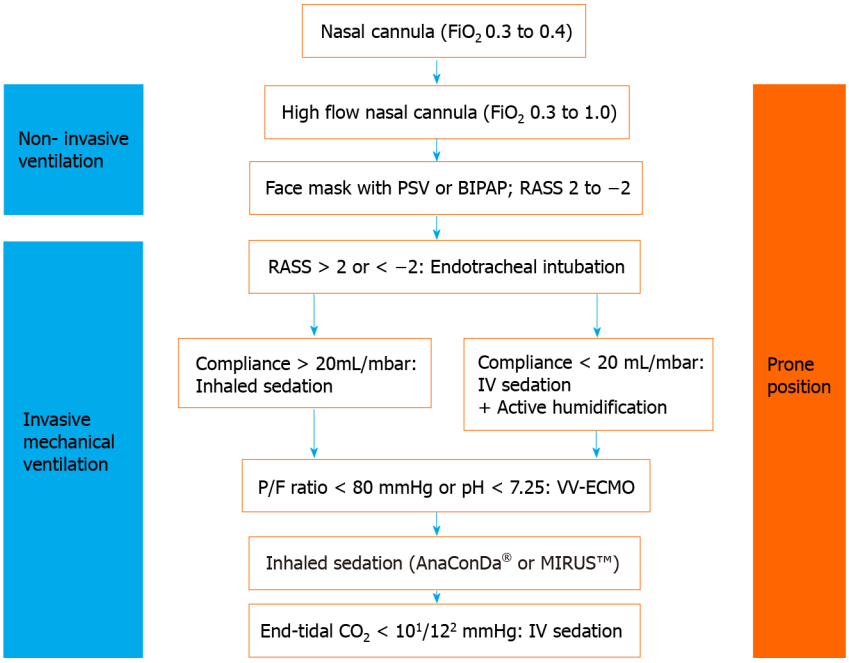

Figure 1 Overview of respiratory management of coronavirus disease 2019 related acute respiratory distress syndrome and inhaled sedation. [1]AnaConDa®; [2]MIRUS™. RASS: Richmond Agitation-Sedation Scale; PSV: Pressure support ventilation; BIPAP: Bilevel positive airway pressure; FiO_2: Fraction of inspired oxygen; PaO_2: Partial pressure of oxygen; P/F-ratio: PaO_2/FiO_2; VV-ECMO: Veno-venous ECMO.

acceptable, and CO_2 can be reduced sufficiently, both types of systems are able to maintain spontaneous breathing[19-21]. However, if lung compliance is poor, reduction of dead space and active humidification is necessary, which can be facilitated by inhaled sedation *via* a circle breathing system[22,23].

The AnaConDa® system is capable of achieving adequate sedation with isoflurane or sevoflurane. In addition to isoflurane and sevoflurane, the MIRUS system can also apply desflurane.

ADMINISTRATION OF VOLATILE ANESTHETICS DURING ECMO THERAPY

The pathophysiological basis for COVID-19 related ARDS is the altered blood-air barrier. The diffusion distance for adequate gas exchange in the lung alveoli is impaired by inflammation, edema, and accumulated mucus. These impairments severely limit O_2 uptake and CO_2 release. However, volatile anesthetics are still able to establish an effective concentration in the blood stream under ARDS conditions, provided the necessary concentration gradient is maintained[24,25]. Volatile anesthetics show superior diffusion properties than O_2 and CO_2, which can be attributed to the lipophilic nature of the anesthetic gas. Only if both the tubus and the bronchial system are completely clogged, intravenous sedation is necessary.

The ECMO system itself can be used for administration of volatile anesthetics[26,27]. This requires installation of a vaporizer into the oxygen tube and connection of a pipe for exhaust gas removal to the outlet and the negative pressure device. The inhaled and exhaled portion of the anesthetic gas must be carefully monitored in order to determine the depth of sedation and to detect possible leakage. Since leakage can easily lead to pollution of the intensive care unit (ICU), a proper scavenging system is crucial. Nonetheless, it must be noted that these scavengers can create high back pressure that increases the risk for gas embolism. Another important technical aspect to take into consideration is the type of membrane oxygenator. Transmembrane passage of the anesthetic gas is facilitated only *via* hollowfiber membrane oxygenators, which are made of polypropylene. If the oxygenators are made of poly(4methyl-1pentene), they do not permit transmembrane passage. In this case, volatile anesthetics have to be administered *via* an anesthetic gas reflection system.

One major anesthetic gas reflection system is the AnaConDa® system, which is commercially available as a larger version, *i.e.* ACD-100, and a smaller version, *i.e.*

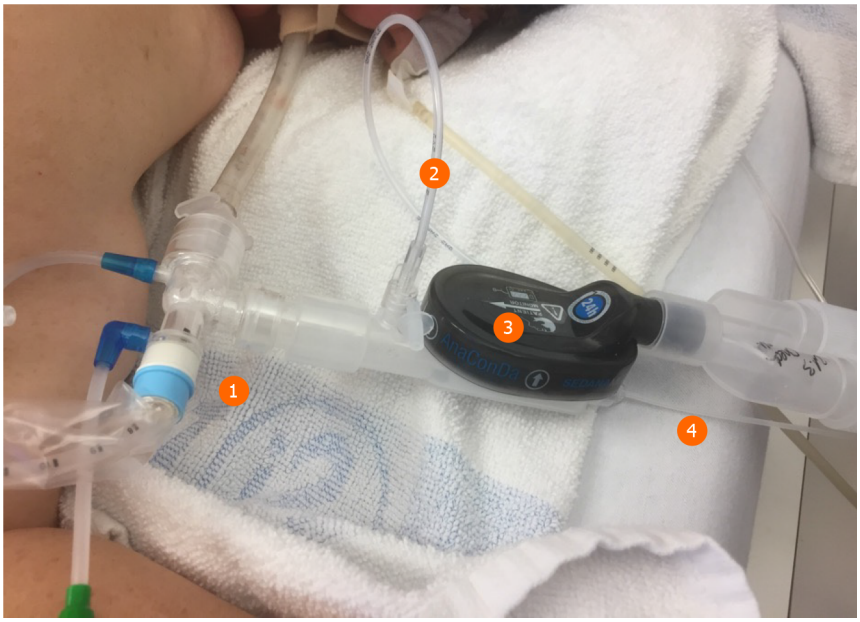

Figure 2 AnaConDa-S® system set up in prone position. [1]Closed loop suction system; [2]Port to monitor the volatile anesthetic and CO_2; [3]AnaConDa®-S with anesthesia gas reflector, bacterial and viral filter, and heat and moisture exchanger; [4]Evaporator with liquid line from syringe pump and liquid isoflurane or sevoflurane.

Figure 3 MIRUS™ setup in prone position and veno-venous-extracorporeal membrane oxygenation therapy. [1]Closed suction system; [2]Bacterial and viral filter and heat and moisture exchanger; [3]MIRUS™ reflector.

ACD-50 (which is also known as AnaConDa®-S) (Figure 2). The other major gas reflection system is the MIRUS™ system (Figures 3 and 4). Recent studies showed that the AnaConDa® systems can be used successfully for sedation of ARDS patients during ECMO therapy[20,28,29]. Similarly, a study using the MIRUS™ system demonstrated successful application of inhaled sedation for ECMO therapy in patients with COVID-19 related ARDS[30].

The CO_2 signal has no effect on the performance; nonetheless, a CO_2 pressure of at least 10 mmHg is an indication for an open and managed airway and is associated with a higher survival rate[31,32]. Consequently, the authors call for a minimum of 10 mmHg as standard for the AnaConDa® system. If this minimum cannot be maintained by adjusting the ventilation, the level of sedation must be monitored carefully and, if necessary, complemented by intravenous sedation of the patient.

Figure 4 Display of the MIRUS™ sevoflurane controller. The display shows the setting under normal operation.

By contrast, the MIRUS™ system requires an end-tidal CO_2 pressure of at least 15 mmHg. If the end-tidal CO_2 pressure drops below 12 mmHg, the MIRUS™ system stops administering the anesthetic, indicated by a red alert. This could result in the inadvertent awakening of the patient, which would then require intravenous sedation to restore anesthesia.

The most recent MIRUS™ systems (starting from version 2.0 onward) indicate a tidal volume of less than 200 mL by a yellow alert (Figure 5). During ECMO therapy, the minimum respiratory minute volume falls frequently below the minimum tidal volume of the MIRUS™ system. The yellow alert can be acknowledged in order to continue administration; however, this procedure is associated with the risk of overdosing with the anesthetic. In case of isoflurane, the MIRUS™ system displays a higher gas concentration under ECMO therapy. Hence, a concentration of more than 2% can be displayed, although it does not correspond to the actual end-tidal values. Because higher effective concentrations are required for the same MAC with sevoflurane and desflurane, this effect is not as pronounced with these gases. Nevertheless, the operator should choose the lowest wash-in speed (*i.e.* the setting "tortoise") for all of three anesthetics isoflurane, sevoflurane, and desflurane (Figure 5).

An important consideration for the application of anesthetic gas reflection systems is the volume of a breath that does not participate in gas exchange, *i.e.* the dead space. The volumetric dead space of the MIRUS™ system is 100 mL[19], whereas the volumetric dead space for the AnaConDa® system ACD-100 is 100 mL and 50 mL for the ACD-50[23]. However, the ECMO system eliminates CO_2 effectively. Thus, volumetric and reflective dead space of the anesthetic gas reflection systems are irrelevant for ECMO therapy.

Another alternative device for administration of volatile anesthetics is the circle breathing system. Usage of this system has been reported during the ongoing SARS-CoV-2 pandemic. However, to the best of our knowledge, the deployment of a circle breathing system in conjunction of ECMO therapy in the ICU has not been described in literature.

CONSUMPTION OF VOLATILE ANESTHETICS IN COVID-19 RELATED ARDS THERAPY USING ECMO

The SARS-CoV-2 pandemic is estimated to be one of the most expensive natural disasters in recorded history[33]. Besides economic repercussions due to the containment measures, adequate treatment of patients causes a substantial financial strain for the global health care systems. ECMO, in particular, is a very expensive procedure, and thus the reduction of associated costs is highly desirable. Treatment of COVID-19 related ARDS requires larger amounts of sedatives than treatment of non-COVID-19 patients. Consequently, treatment of COVID-19 patients, who undergo

Figure 5 Display of the MIRUS™ controller. Yellow alarm refers to a low tidal volume. In this case, the wash-in speed "tortoise" should be selected.

invasive mechanical ventilation without ECMO therapy, demands a large consumption of anesthetics. However, administration of volatile anesthetics with the AnaConDa® systems ACD-100 or ACD-50 during ECMO therapy is very cost-effective, as the low respiratory minute volume yields a usage of only 1 mL/h to 3 mL/h. The consumption of volatile anesthetics by the MIRUS™ system is in a comparable range and is estimated to be 3 mL/h to 5 mL/h (unpublished data).

Besides consumption, a certain amount of anesthetic gas is lost in the delivery system, *i.e.* at the exhalation outlet of the ventilator or at the oxygenator of the ECMO device. The exhalation outlet has the advantage that the gas flow can conduct viral particles and hence reduces the risk of infection for the health care personnel[34,35]. The oxygenator was used initially for intraoperative delivery of the anesthetic gas but modern reflection systems require containment of volatile anesthetics. For instance, the oxygenator of the Cardiohelp System (Getinge Group, Gothenburg, Sweden) does not leak anesthetic gas, according to the manufacturer and independent researchers[26]. While the loss of anesthetic gas *via* the oxygenator is theoretically still possible, instruments in the ICUs usually lack such device.

HYGIENE MEASURES FOR COVID-19 RELATED ARDS

Respiratory management has also to take into account the SARS-CoV-2 infection. Hence, tracheotomy is often avoided if the patient shows a high viral load. Nevertheless, tracheostomy is suggested to improve the outcome of COVID-19 patients, in particular, if the intervention is performed between day 13 and day 17 post intubation[36].

The handling of medical devices and instruments requires strict hygiene measures. Firstly, a closed suction system is mandatory (Figures 2 and 3). Secondly, the tube has to be clamped off prior to disconnect it from heat and moisture exchanger filters.

Here, the MIRUS™ system has an advantage since the heat and moisture exchanger filters are integrated in the device, so that the controller and measuring units remain in a clean and safe distance. By contrast, the AnaConDa® systems measure the concentration of the anesthetics in close proximity to the patient and hence are exposed to a high risk of contamination. However, the water trap at the gas monitor is sealed, which prevents intrusion of viral pathogens.

In order to connect either the MIRUS™ or the AnaConDa® system to the vacuum connection on the ICUs, a suitable gas flow conduction system is required. The CleanAir™ system (TIM, Koblenz, Germany) is recommended for gas flow conduction, because it is independent of the reflector (Figure 6). It operates well under vacuum, is sealed off the environment, and thus eliminates the risk of disseminating viral particles in the air[35].

OCCUPATIONAL ANESTHETIC GAS EXPOSURE WHILE USING ECMO THERAPY

The use of volatile anesthetics is beneficial for the treatment of patients with SARS-CoV-2 infection, but the exposure of health care professionals to waste anesthetic gas is a concern. Poor air-conditioning in ICUs and inconsistent international limits for anesthetic gas concentrations amplify the problem. The United States National Institute of Occupational Safety and Health defined an exposure limit of 2 ppm for isoflurane, sevoflurane, and desflurane, but other countries use higher exposure limits [35,38]. Most studies on air pollution report gas concentrations of less than 2 ppm while using MIRUS™ or AnaConDa® systems in mechanically ventilated patients; nonetheless, these studies use an air-conditioning system with at least six air exchanges per hour and a scavenging system (*e.g.*, vacuum-based open reservoir gas scavenging systems or adsorbers with activated charcoal)[35,38,39].

To the best of our knowledge, there are no studies focusing on occupational gas exposure by inhalational sedation in patients undergoing ECMO therapy. Nevertheless, Meiser and colleagues observed that gas consumption during isoflurane sedation *via* AnaConDa® was exceptionally low, and they concluded that the sweep gas of the oxygenator did not contain the volatile anesthetic[20]. Our group measured the air pollution using photoacoustic gas monitoring in a similar setting (single room, isoflurane *via* AnaConDa®, vacuum-based scavenging system, air-conditioning with 11 air exchanges per hour) and detected concentrations of approximately 0.5 ppm to 2 ppm (unpublished data). Obviously, a proper application of all systems must be ensured as well as "good workplace practice", including leak testing of the respirator and training of health care professionals. The conformity between the applied systems and respirators is of particular importance, as problems may occur even without active suction.

OUTCOME OF ECMO THERAPY

ECMO therapy is associated with high mortality and hence is deemed as the last resort after all other possible interventions failed. In case of COVID-19 related ARDS, the mortality 90 d post ECMO initiation is very high[17]. Besides the high mortality, ECMO therapy is also associated with a number of long-term effects, which are known from ICU survivors.

Postintensive care syndrome describes the impairments in physical function as well as cognitive and mental health that ICU survivors experience. The aftermaths of influenza A H1N1 or SARS showed that this syndrome can persist for years and hamper recovery[40]. In addition, a substantial portion of ICU survivors suffers from post-traumatic stress disorder. The data on ECMO survivors is sparse, but a limited number of studies demonstrated that these patients show impaired recovery, chronic pain, and mental illness, including post-traumatic stress disorder for up to 3 years after hospitalization[41-44]. Only very few studies suggest that ECMO treatment had no effect on ARDS patients after initiation of therapy[45]. Consequently, the authors of this article emphasize that indication for ECMO therapy must considered very carefully.

The application of inhaled sedation for ECMO treatment has a number of advantages. For instance, the supply of volatile anesthetics is currently not limited, in contrast to intravenous anesthetics. Volatile anesthetics are also less hallucinogenic, and patients require less opiates during inhaled sedation than during intravenous sedation. If applied properly, volatile anesthetics allow easier control of the depth of sedation of the patient, even if gas exchange is severely limited by COVID-19 related ARDS. Furthermore, the volumetric and reflective dead space of the delivery systems as well as CO_2 retention are negligible for ECMO therapy. So far, few studies reported the successful application of isoflurane and sevoflurane for ECMO therapy[6-8]. The application of volatile anesthetics depends on adequate delivery and gas scavenging systems, which are not established in all ICUs[9]; however, the lack of electronic infusion pumps for intravenous sedatives due to the SARS-CoV-2 pandemic could be an incentive to equip ICUs with such hardware.

Currently, the application of volatile anesthetics for inhaled sedation during ECMO treatment is still not widely established. Consequently, the health care personnel lacks the adequate training for application of this procedure as well as for recognizing contraindications of which malignant hyperthermia is the most notable one.

Figure 6 Example of a vacuum-based gas scavenging system (CleanAir™ system). [1]Expiration port of the ventilator; [2]Open reservoir scavenging system; [3]Vacuum line.

CONCLUSION

In COVID-19 related ARDS, inhaled sedation demonstrated many advantages, including spontaneous breathing and deep sedation in prone position. Inhaled sedation also allows safe monitoring of sedation depth *via* measurement of the anesthetic gas. In addition, veno-venous ECMO avoids problems concerning dead space and CO_2 increase, as sometimes seen during inhaled sedation *via* AnaConDa® or MIRUS™. Further, inhaled sedation allows administration of isoflurane, which shows favorable properties, especially in light of the shortage of intravenous sedatives. This procedure, however, requires preparation and training. Hence, medical professionals should use the time of moderate occupancy rates in the ICUs accordingly.

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MINIREVIEWS

Role of bronchoscopy in critically ill patients managed in intermediate care units - indications and complications: A narrative review

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Abstract

Flexible bronchoscopy (FB) has become a standard of care for the triad of inspection, sampling, and treatment in critical care patients. It is an invaluable tool for diagnostic and therapeutic purposes in critically ill patients in intensive care unit (ICU). Less is known about its role outside the ICU, particularly in the intermediate care unit (IMCU), a specialized environment, where an intermediate grade of intensive care and monitoring between standard care unit and ICU is provided. In the IMCU, the leading indications for a diagnostic work-up are: To visualize airway system/obstructions, perform investigations to detect respiratory infections, and identify potential sources of hemoptysis. The main procedures for therapeutic purposes are secretion aspiration, mucus plug removal to solve atelectasis (total or lobar), and blood aspiration during hemoptysis. The decision to perform FB might depend on the balance between potential benefits and risks due to frailty of critically ill patients. Serious adverse events related to FB are relatively uncommon, but they may be due to lack of expertise or appropriate precautions. Finally, nowadays, during dramatic recent coronavirus disease 2019 (COVID-19) pandemic, the exact role of FB in COVID-19 patients admitted to IMCU has yet to be clearly defined. Hence, we provide a concise review on the role of FB in an IMCU setting, focusing on its indications, technical aspects and complications.

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Core Tip: Less is known about the role of flexible bronchoscopy (FB) outside the intensive care unit, in particular in the intermediate care unit setting (IMCU). Here, we provide a concise review on the role of FB in IMCU settings, focusing on its indications, technical aspects and complications with a particular attention of its recent use in coronavirus disease 2019 patients. We reviewed the main diagnostic indications, such as viewing airway system/obstructions, detecting respiratory infections, and main therapeutic indications, such as secretion removal (toilet bronchoscopy) and manage hemoptysis.

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INTRODUCTION

Flexible bronchoscopy (FB) is a priceless tool for diagnostic and therapeutic purposes in critically ill patients in intensive care unit (ICU)[1,2]. Less is known about its role outside ICU, particularly in intermediate care unit setting (IMCU). In this setting too, FB is used both for diagnostic and therapeutic purposes. The leading indications in diagnostic work-up are: to visualize airway system/obstructions, to perform examinations to detect respiratory infections by means of bronchoalveolar lavage (BAL) and tissue sampling in specific circumstances, and to identify potential sources of hemoptysis. The main procedures for therapeutic purposes are aspiration of bronchial secretions, more frequently needed in patients with artificial airways, mucus plug removal to solve atelectasis (total or lobar) and blood aspiration during hemoptysis[3,4]. Although FB is generally safe, complications may occur, particularly in critically ill patients, and thus, the risk-benefit profile of each procedure should be carefully evaluated.

Herein, we review the role of FB in critical patients, mainly focusing on the management of subgroups admitted to IMCU.

INDICATIONS

The common indications for FB in the ICU are the visualization of the trachea and main bronchi, restoring airway patency (especially in patients with artificial devices), managing hemoptysis and diagnostic sampling. In this setting, Olopade *et al*[5] found that FB was required in patients with acute respiratory failure, mainly as removing abundant secretions (50%), collecting samples (35%), assessment of the airways patency (7%), and hemoptysis (2%). However, in an IMCU setting, Korkmaz Ekren *et al*[6] described a cohort of 28 critical patients treated with non-invasive ventilation (NIV) in which the most frequent FB indications were: diagnostic approach for opportunistic infections (64.3%) or malignancy (14.3%) and therapeutic approach for airway obstruction (14.3%) or alveolar hemorrhage (14.3%).

INFECTIONS

In the ICU, FB with BAL in community-acquired pneumonia is used when antibiotic therapy fails or to investigate potential alternative diagnoses[3]. In critically ill non-intubated patients, Cracco *et al*[7] reported a diagnostic yield of BAL of 59%. A clinical

context, where FB appears particularly useful is immunocompromised patients, such as transplant recipients, those with hematologic malignancies, active cancer and receiving immunosuppressive therapy. The identification of infectious agent leads to ongoing treatments being modified in a relatively high percentage of patients, especially when pulmonary infiltrates are present[8-10]. The overall diagnostic yield of BAL in immunosuppressed patients ranges from 31% to 74%[11,12], and predictors of higher sensitivity are early intervention (within the first 4 d from the onset of symptoms) and the presence of radiologic findings consistent with an alveolar pattern, as compared to interstitial or nodular pattern[10]. According to recent guidelines, in cases of suspected pulmonary invasive aspergillosis, BAL galactomannan measurement is strongly recommended[13,14]. Moreover, BAL and transbronchial lung biopsy (TBLB) might be used for cytological analysis in case of suspected *Pneumocystis jirovecii* pneumonia (formerly known as pneumocystis carinii), acute eosinophilic pneumonia (BAL eosinophils > 25%) or tuberculosis[15]. BAL is particularly considered gold standard for diagnosis of *Pneumocystis jirovecii*, showing a sensitivity of 90%-98% in absence of previous antibiotic use for treatment or prophylaxis[3].

Finally, in cystic fibrosis, FB may allow for a more accurate diagnosis of lower respiratory tract infections, guiding the choice of antimicrobials in non-sputum producers[16]. However, according to the latest Cochrane systematic review on this topic[17], there is no clear evidence to support its routine use compared to standard practice, in which treatment choice is based on the results of oropharyngeal culture and clinical symptoms.

HEMOPTYSIS/HEMORRHAGE

Hemoptysis is a challenging symptom associated with potentially life-threatening medical conditions[18]. FB plays a relevant role in this context, helping to diagnose the etiology, localize the site, and identify the source of the bleeding, essential for successful clinical management. Moreover, it allows for removal of clots, stopping active bleeding in certain cases (by means of bronchial blocker placement), and guiding angiographic embolization.

Mondoni *et al*[19] showed that the bleeding source detection rate of FB was higher in cases of moderate-severe hemoptysis rather than in mild ones, and when performed within 48 h from the last episode.

In massive hemoptysis, flexible FB can be unable to remove enough blood. In life-threatening hemoptysis, airways patency should be immediately preserved; in this context, rigid bronchoscopy (RB) or tracheal intubation under general anesthesia are better options in comparison with FB. Moreover, during RB, a Fogarty catheter or other bronchial blockers may be placed in order to stop active bleeding[18,20]. Alternatively, in cases of massive hemoptysis, FB can be useful for the selective main bronchial intubation to assure safe ventilation of non-bleeding site.

AIRWAY INSPECTION AND MANAGEMENT OF OBSTRUCTIONS

As previously stated, the role of FB in IMCU is essential to visualize airway system /obstructions and restore patency in different circumstances, such as atelectasis, lobar collapse due to mucoid plugs or inhalation injuries. Patients with artificial devices, such as tracheostomy cannula, frequently develop airway obstruc-tions due to mucus plugs, secretions or clots. Bronchoscopic management of these cases includes removal of endobronchial material by means of suction or forceps. The overall success rate for the correction of acute atelectasis caused by airway obstruction due to mucus plugs is more than 70% in various reports[21,22].

Moreover, FB can be performed to evaluate tracheomalacia or tracheal stenosis after tracheostomy[23,24]. In selected, more complicated cases, RB may be required.

Aspiration of gastric contents can be an indication for FB with lavage in critical care patients, especially when the aspirate is predominantly particulate[25]. In this setting, a prompt FB can reduce inflammatory reaction, thus preventing atelectasis and reducing both the risk of infection and the development of acute respiratory distress syndrome[26].

FB can be useful for the visualization of the airways in case of thoracic trauma and suspected bronchial injury[27]. Bronchial fracture may occur in 3% of penetrating chest trauma and, in this context, FB might help to locate and estimate the degree of air leak [28].

Lastly, FB can be used for percutaneous dilatational tracheostomy, which is a rare but possible bedside procedure in critical care.

TYPES OF BRONCHOSCOPIC PROCEDURES AND SEDATION

There are two main types of bronchoscopes: RB and FB. The latter is more commonly employed in an IMCU setting but, in certain life-threatening conditions, RB is the preferred tool, as it allows for better airway control. These aforementioned conditions include massive hemoptysis, removal of large foreign bodies or resistant mucus plugs, dilatation, or stent procedures in the tracheobronchial tree. Over the last years, disposable systems, not containing fiber-optic cables but a distal camera connected to a re-usable screen, have been increasingly adopted in clinical practice, partly replacing traditional FB scopes (Figure 1). These combine quality of image with low manufacturing costs and allow for the reduction of scope downtime by eliminating the need for disinfection between procedures and potentially decreasing the risk of cross-contamination and infectious outbreaks[2].

Patients admitted to an IMCU are usually at higher risk of complications because hypoxemia, hemodynamically instability, and at higher risk of bleeding because of thrombocytopenia or anticoagulant/antithrombotic treatment. Therefore, the risk-benefit profile of each procedure should be carefully evaluated, as well as the choice of the proper type of sedation, which is crucial for a successful outcome. According to recent international guidelines[3,29], all bronchoscopies should be performed under topical anesthesia by means of nasal nebulized lidocaine (100 mg) in association with conscious or deep sedation. Intravenous sedation should be offered to patients undergoing bronchoscopy to decrease anxiety and discomfort, improve pain control and produce anterograde amnesia. The depth of sedation should be tailored individually and according to the complexity of procedure; advanced diagnostic and therapeutic bronchoscopies require deep sedation and an anesthesiologist's assistance is highly recommended. The most common medications used for sedation and pain control are benzodiazepines (midazolam, up to 5 mg), opioids (fentanyl, up to 0.5-20 μg/kg) and propofol[30]. The combination of midazolam and opioids causes a synergistic effect on patients' pain tolerance, as well as on pain control and suppression of cough, thus improving tolerance to FB in difficult situations, including patients requiring NIV. NIV provides adequate gas exchange, reducing the workload of breathing during FB, and can be used both in severely hypoxemic and hypercapnic patients by means of different interfaces (Figure 2)[31].

Here, a brief description of the most common bronchoscopic procedures performed in IMCUs is provided.

SAMPLING PROCEDURES

BAL is a safe and minimally invasive bronchoscopic sampling method, indicated for several lung diseases (*e.g.*, immune-mediated, inflammatory, and infectious diseases). It can provide specimens for cytological and microbiological exams. Due to its excellent safety profile, BAL can be performed in critically ill patients, while carefully monitoring vital parameters. A complete airway inspection should precede BAL execution, which, in turn, should precede any biopsies[15,31,32]. The bronchoscope should advance as far as possible to the complete occlusion of the bronchial lumen of a third or fourth bronchial subsegment, in a wedged position. 60-180 mL of room temperature sterile saline is used, divided into 3 fractions, and introduced through the suction channel of the bronchoscope. It is then withdrawn by suction, aiming to retrieve as much fluid as possible, without causing airway collapse. The BAL fluid is subsequently stained and cultured for pathogens.

BRONCHIAL WASHING

Bronchial washing (BW) consists of the instillation and subsequent aspiration of small amounts of saline solution (usually 20-50 mL) mixed with bronchial secretions, into a specific bronchial trap. It may be useful to assess the microbiology of central airway secretions. A major limitation of this technique is the high risk of contamination with non-pathological organisms from upper airways that are not indicative of a real

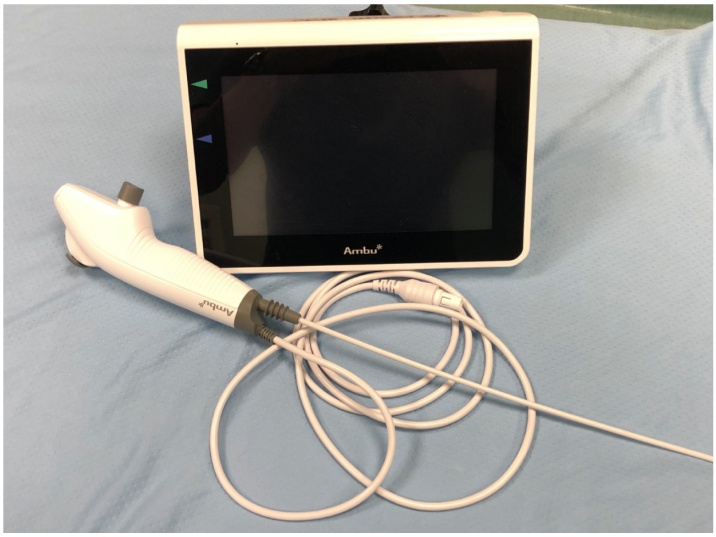

Figure 1 Disposable bronchoscopy.

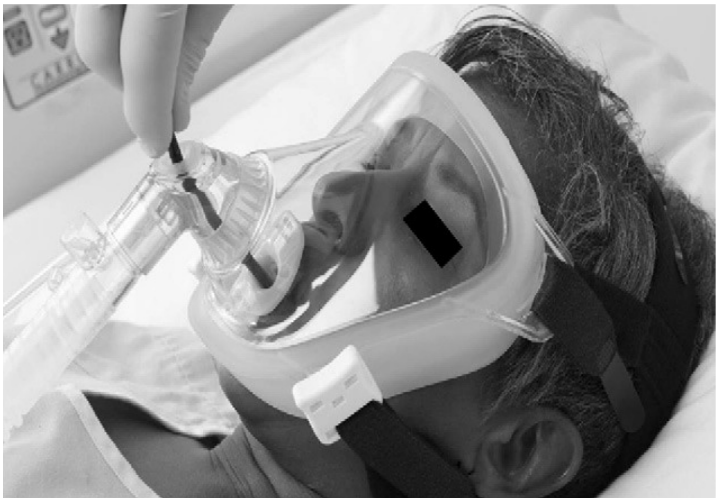

Figure 2 Face mask for non-invasive mechanical ventilation with diaphragm for the entry of the bronchoscope; oral insertion through the mouthpiece.

bronchial infection[33-36].

TISSUE SAMPLING TECHNIQUES

Patients admitted to IMCUs might occasionally present pulmonary consolidations and/or nodules. Tissue acquisition can be indicated in selected cases, and forceps and needles are the most common sampling tools adopted by bronchoscopists.

Endobronchial biopsy is recommended for the diagnosis of visible endobronchial lesions; forceps should be opened outside the distal end of the operating channel and pushed against the lesion. The tip of the forceps is then closed and extracted from the operating channel of the bronchoscope, and the specimen is then placed in formalin solution. Forceps biopsy showed a sensitivity of 72%-100% in the detection of TB granulomas (endobronchial TB)[35] and may be useful in ruling out malignancies or sarcoidosis, particularly in the latter, when associated with TBLB. TBLB is commonly used in diagnostic work-up of malignancy, diffuse lung disease and infection, when the lesion cannot be directly accessed with a bronchoscope. It is wedged into the bronchus pertaining to the anatomical site of the lesion, and the closed forceps are pushed into the peripheral area of the lung, opened at 5-6 mm from the lesion and then closed to collect a sample. TBLB is usually performed under fluoroscopy guidance, even though innovative navigation systems have been recently adopted in

clinical practice (*i.e.* electromagnetic navigation bronchoscopy, radial probe ultrasounds, virtual bronchoscopy).

Needle aspiration sampling techniques are also largely employed, especially for the diagnosis of peripheral lesions as well as in the case of hilar/mediastinal lymph nodes or masses[37,38]. A thin retractable needle (21-gauge for cytology sampling and 19-gauge for histology) is inserted into the working channel of the bronchoscope, and pushed into lesions through the tracheobronchial wall, blindly (conventional – cTBNA) or under endoscopic ultrasound guidance (EBUS-TBNA)[38].

AIRWAY OBSTRUCTION MANAGEMENT

Central airway obstruction (CAO) may occur in an IMCU setting. CAO is defined as the occlusion of 50% or more of tracheal or mainstem bronchial lumen and may occur either in a patient with malignant (lung cancer or metastases from extra thoracic malignancies) or benign conditions (inflammation, necrotizing tracheobronchial infection, mucus plug blockage, simple or complex post-tracheostomy or intubation stenosis).

Interventional pulmonology plays a major role in this context. Several ablative techniques are currently available and include 'immediate' or 'delayed' procedures based on the time expected to restore airway patency. In case of critical lesions, it is mandatory to promptly restore ventilation through 'immediate' techniques, whereas 'delayed' approaches, with a prolonged effect, should be reserved for a non-emergency setting, according to clinical and prognostic factors. Recent data has confirmed that almost every technique, when carried out by experienced hands and according to specific indications, is highly effective in restoring airway patency, with a valuable risk-benefit profile. In any case, deep sedation and endotracheal intubation through RB are required for a safer and effective management.

'Immediate' interventions include mechanical debulking, laser, electrocautery, and argon plasma coagulation. The most common 'delayed' techniques, requiring a staged procedure, are brachytherapy and photodynamic therapy[39]. Cryotherapy may be included in both categories as, according to the technology employed, it can result in either an immediate or delayed effect, called cryorecanalization and freeze–thaw cryotherapy respectively. All these techniques can be combined as part of a multi-modal approach, aimed both at improving therapeutic success rates and reducing the risk of complications.

Once airway patency has been restored, a stent placement can be considered in selected patients with high recurrence risk. Over the last years, more and more stents have become available, including tailored stents and metallic Y-shaped stents. However, complications after stent placement are not uncommon and may include clogging of the stent with secretions, ingrowth of granulation or tumor tissue at the ends of the stent, migration, or fracture of the mesh structure of the stent. As a result, proper artificial airway management includes securing the tracheal tube, monitoring tube position, maintaining patency, and appropriate regulation of cuff pressure.

BRONCHOSCOPY IN TIMES OF CORONAVIRUS DISEASE

Data on the risk-benefit profile of FB in patients with coronavirus disease 2019 (COVID-19) are still limited and controversial[30,40,41]. In patients with suspected COVID-19, FB seems to slightly increase the sensitivity of a molecular diagnosis compared to that of nasopharyngeal swabs (NPS)[41]. However, in cases with inconsistent thoracic imaging and negative NSP, BAL[42,43] presents a further limited role in the diagnosis of COVID-19. Moreover, FB generates aerosols and may increase the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission among healthcare workers[29,40].

In a non-ICU setting, a multicenter retrospective Italian study[43] reported the results of 108 FB, of which 75% were performed during oxygen supplementation, 12% while patients were breathing room air and 3% during NIV. In 72%, FB was performed to diagnose SARS-CoV-2 infection in patients with clinical and radiological suspicion of COVID-19 pneumonia and negative NPS, with a reported 57.7% (45 out of 78 patients) definite diagnosis of COVID-19 pneumonia. In 28% of cases, FB was performed on patients with a confirmed diagnosis of COVID-19 affected by the following clinical conditions: suspected concomitant lower respiratory tract infections, obstructive atelectasis, suspected tracheal intubation-related complications,

tracheostomy complications and severe hemoptysis. Moreover, the authors reported that healthcare workers did not acquire any infections after endoscopic procedures, performed according to World Health Organization guidelines on airborne precautions for aerosol-generating procedures[44].

In another Italian cohort[45] of 131 hospitalized patients with moderate disease (mostly in internal medicine wards), indications for FB were: 65% suspected SARS-CoV-2 infection, 13% alternative diagnosis (*i.e.* hemoptysis or lung consolidations), 20% suspected superinfections, and 2% lung atelectasis. A confirmed diagnosis of SARS-CoV-2 was reported in 37% of patients with double-negative NPS. Concordance of BAL and NPS was overall high (98.9%, $P > 0.0001$), as confirmed by Geri *et al*[46] as well (97.5% overall agreement with a moderate Cohen's $k = 0.487$). In particular, patients with moderate disease who underwent FB for a suspected SARS-CoV-2 infection presented a higher number of computed tomography (CT) alterations than patients with other indications. Moreover, since most of patients with moderate disease underwent FB several days after the development of symptoms, consequently BAL diagnostic yield resulted gradually decreased from symptom onset.

So far, scientific pulmonology societies[29,41] have issued a general recommendation against the use of FB in non-intubated SARS-CoV-2 suspected patients. However, it was postulated that the benefits of FB with BAL would outweigh side effects for patients and risks for the healthcare team in the case of: (1) at least one negative NPS; (2) instability from a respiratory point of view; and (3) atypical CT scan suggestive of an alternative diagnosis[47].

FB may also be helpful in intubated patients during the course of COVID-19 pneumonia to detect superinfections and to restore airway patency from obstructions secondary to thick distal secretions, particularly common after prolonged mechanical ventilation, and/or clots, due to anticoagulation drugs[48].

COMPLICATIONS

Overall, data from literature on FB safety in an ICMU setting reported a reassuring profile, with a complication and mortality rate of 1.1% and 0.02%, respectively[49]. Predictors of complications include "intrinsic", non-modifiable, patient conditions (age, presence of respiratory failure, severity of comorbidities, concomitant medications and coagulation abnormalities) and procedure-related factors (type of procedure, duration, sedation and operator's experience)[7,49]. In this context, a standardized protocol for FB execution in IMCU patients is highly recommended in order to guide the decision-making process on indications and timing, to estimate individualized risks and to arrange in advance proper interventions.

HYPOXEMIA

Transient hypoxemia is the most common adverse event, being the result of a combination of alveolar collapse and depletion of intra-alveolar oxygen due to frequent suctioning and massive washing of the alveoli during BAL. Conversely, hypercapnia is usually the expression of hypoventilation caused by airway obstruction. Since most patients admitted to IMCUs with acute respiratory failure are on oxygen supplementation or NIV, escalation in ventilatory support is one of the most common concern in the decision-making process, but in experienced hands and with adequate precautions, FB still has an acceptable safety profile in this context[50].

BLEEDING

Although patients admitted to IMCUs usually present a baseline high risk of hemorrhage due to concomitant comorbidities and medications (antiplatelets, anticoagulants, chemotherapy), the post-bronchoscopy bleeding rate is relatively low: 0.12% for FB with BAL and 3%-5% for TBLB or EBUS-TBNA[1]. To reduce the likelihood of this potential complication, it is crucial to optimize platelet count, prothrombin time and thromboplastin time values before FB and to effectively manage any drug that might influence coagulation parameters (warfarin, direct anti-coagulants, antiplatelets agents).

PNEUMOTHORAX

Pneumothorax rarely occurs during FB (0.1%) or TBLB (0.4%)[49]. Even though pneumothorax mostly happens within a few minutes after procedure, in a substantial minority of cases (approximately 40%) it can be delayed, requiring a careful monitoring of clinical parameters, particularly in patients under NIV.

In this context, in addition to a chest X-ray, a bedside lung ultrasound may be helpful for detecting pneumothorax with an extremely high diagnostic accuracy[51].

OTHERS

Hypoxemia occurring during FB may cause an increase in cardiac workload, with elevations of heart rate (approximately 40% above baseline), blood pressure (a rise of 30% above baseline) and cardiac index (approximately 17%-32% above baseline). Despite this, major arrhythmias, as well as myocardial infarction, are rare events during FB.

Iatrogenic trauma to airways and bronchospasm have also been occasionally reported whereas the onset of fever is relatively common, particularly after BAL (13%) or bronchial washing[52].

CONCLUSION

Future research directions and conclusions

In the past decades, interventional pulmonology has experienced a remarkable growth in available technology and equipment, as well as clinical and translational research efforts focused on patient-centered outcomes. Recent studies highlight the feasibility of using metagenomic sequencing on BAL for the microbiologic diagnosis of adults with severe community-acquired pneumonia[53,54]. Moreover, biomarkers and cytokines in BAL fluid may have diagnostic benefits for certain diseases in critically ill patients in the present and near future. Moreover, in COVID-19 pandemic, FB may be crucial to assess and understand the inflammatory status at broncho-alveolar level during different stages of infection[55-57].

The role of FB in ICMU setting has not yet fully established, but data from literature suggest that it is an essential tool in a not negligible proportion of pulmonary conditions.

However, standardized protocols on procedure execution as well as decision-making algorithms are currently lacking, leading to hugely different approaches in clinical practice, mainly depending on local sources and expertise availability.

As this field continues to push its boundaries, it is imperative to establish evidence and best practice guidelines.

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MINIREVIEWS

Timing of tracheostomy in mechanically ventilated COVID-19 patients

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Abstract

According to the World Health Organization as of September 16, 2021, there have been over 226 million documented cases of coronavirus disease 2019 (COVID-19), which has resulted in more than 4.6 million deaths and approximately 14% develop a more severe disease that requires respiratory assistance such as intubation. Early tracheostomy is recommended for patients that are expected to be on prolonged mechanical ventilation; however, supporting data has not yet been provided for early tracheostomies in COVID-19 patients. The aim of this study was to explore established guidelines for performing tracheostomies in patients diagnosed with COVID-19. Factors considered were patient outcomes such as mortality, ventilator-associated pneumonia, intensive care unit length of stay, complications associated with procedures, and risks to healthcare providers that performed tracheostomies. Various observational studies, meta-analyses, and systematic reviews were collected through a PubMed Database search. Additional sources were found through Google. The search was refined to publications in English and between the years of 2003 and 2021. The keywords used were "Coronavirus" and/or "guidelines" and/or "tracheostomy" and/or "intensive care". Twenty-three studies were retained. Due to the complex presentation of the respiratory virus COVID-19, previously established guidelines for tracheostomies had to be reevaluated to determine if these guidelines were still applicable to these critically ill ventilated patients. More specifically, medical guidelines state benefits to early tracheostomies in critically ill ventilated non-COVID-19 patients. However, after having conducted this review, the assumptions about the benefits of early tracheostomies in critically ill ventilated patients may not be appropriate for COVID-19 patients.

Key Words: Tracheostomy; Timing; COVID-19; SARS-CoV-2; Coronavirus

Country/Territory of origin: United States

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Core Tip: With the sudden onset coronavirus disease 2019 (COVID-19), guidelines for patient care were rapidly evolving to protect both providers and patients. However, it has yet to be determined if performing tracheostomies earlier or later was more beneficial for outcomes in patients infected with COVID-19. This review assesses studies that discuss the timing of tracheostomies in COVID-19 patients to establish appropriate guidelines for best patient outcomes.

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INTRODUCTION

After the first case of severe acute respiratory syndrome coronavirus 2 [coronavirus disease 2019 (COVID-19)] was documented in China in December 2019, the novel respiratory illness quickly turned into a pandemic and brought about a crisis to the current healthcare system. COVID-19 has played a large role in the number of diagnoses and hospitalizations not just in the United States, but worldwide. According to the World Health Organization (WHO) as of September 16, 2021, there have been over 226 million documented cases of COVID-19, which has resulted in more than 4.6 million deaths[1]. Likewise, hospital and intensive care unit (ICU) admissions have seen a drastic uptick as well. According to WHO, approximately 14% of patients develop a more severe disease, many of whom may require respiratory assistance[2, 3]. Initially, supplemental oxygen is given to patients with non-invasive means such as a nasal cannula, high flow oxygen, continuous positive airway pressure machines, or bilevel positive airway pressure machines. These patients may require a more invasive form of ventilation such as endotracheal intubation with mechanical ventilation. A tracheostomy is a common surgical procedure that is done when patients require prolonged mechanical ventilation[4].

The use of tracheostomies dates as far back to 3600 B.C. The open tracheostomy used to be the procedure of choice, however, over the last few decades, the percutaneous tracheostomy has become more popular since the procedure can be done at the bedside under the guidance of a bronchoscopy[5,6]. Tracheostomies provide several benefits to patients such as increasing patient comfort and have also proven to decrease the incidence of pneumonia and overall length of ICU stay[7]. Despite the many benefits, there is variability in the practice patterns in terms of timing of performing tracheostomies[8]. As for current guidelines in the United States, The American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) recommends that tracheostomies should not be performed prior to 14 days of endotracheal intubation[9]. If the patient is expected to be on prolonged mechanical ventilation (more than 3 wk), an early tracheostomy (ET) within the first seven days of intubation can be performed[8]. With proper maintenance, endotracheal intubation can be maintained for about one to two weeks without causing major injury to the larynx before needing to be converted to a tracheostomy[4,10]. With the current COVID-19 pandemic, many of the ventilated patients require prolonged mechanical ventilation and the mortality of these patients is very high as well[11]. Knowing the virulence and lethality of this disease, and taking into consideration that the tracheostomy can aerosolize the disease into the environment very quickly, performing this procedure can pose a potential hazard to providers. Taking this into account, extra precautions have been implemented for the safety of providers that will be performing this procedure such as full personal protective equipment, operating theatres or negative pressure rooms, and paralysis of the patient to prevent the possibility of coughing[12,13]. COVID-19 being a novel disease had very few known treatment options in the beginning. However, the management of the disease has mostly been protocolized but one thing that is still debatable is when and how to safely perform a tracheostomy in a ventilated patient.

This review aims to examine the timing of tracheostomy procedures performed in COVID-19 patients and their impact on outcomes.

CLINICAL PRESENTATIONS

A total of 23 studies were identified and selected for the review, Figure 1.

Guidelines

For COVID-19 patients, the AAO-HNS recommends that tracheostomies should not be performed in the first 2-3 wk of endotracheal intubation in hospitalized patients. They add that patients should be stable and preferably have a negative COVID-19 test[9,14]. Similar recommendations have been expressed by The British Association of Otorhinolaryngology, that a tracheostomy should not be performed within the first 14 d of intubation and COVID-19 status should be checked prior to performing the procedure [15]. The Infectious Disease Control Committee at Hospital Italiano de Buenos Aires followed guidelines that were also similar to those of the United States. Guidelines for tracheostomies in India vary slightly from other countries[13]. Because of a shortage of available tests, confirming COVID-19 status was not necessarily required before performing tracheostomy. Guidelines also suggest a more conservative approach where if there are any contradictions to intervention or unclear prognosis then tracheostomy should be delayed beyond the 14-d period.

Timing of tracheostomy and outcomes

Systematic reviews, meta-analyses and case report: Bier-Laning *et al*[16] conducted a study to review 59 institutions treating COVID-19 patients globally. The authors identified variability in the timing of performing tracheostomies in COVID-19 patients. However, while 91% of institutions recommended waiting a minimum of 14 days before performing the tracheostomy, only 78% of centers waited 14 d in order to pass the infectious period and retested patients before performing the procedure.

Another review stated that patients diagnosed with COVID-19 who required mechanical ventilation very rapidly deteriorate. The authors mentioned two studies: one from the United States and one from China- both of which showed very high mortality in ventilated patients. Therefore, suggesting that performing a tracheostomy early may not be very helpful[12].

Mandal *et al*[17] performed a review of papers that took into consideration COVID-19 patients that required tracheostomies. This study examined guidelines for timing, staff safety, procedure, technique, and post-operative care. The authors gathered recommended guidelines for tracheostomies from the United States, Canada, and India and assessed the measures concluding that guidelines were very similar. The authors concluded that a tracheostomy can be performed at or after the 2-wk waiting period as long as the patient's prognosis is good and the ventilator setting is at 50% oxygen. However, while the waiting period is strongly recommended, it is not necessary and can be bypassed for a tracheostomy to be performed sooner if the patient is still infectious given that the endotracheal tube is not proving to be sufficient.

A study published by Hiramatsu *et al*[18] included a case study of a patient that received a tracheostomy on the 28th day of having COVID-19 symptoms. The patient was elderly with many underlying conditions. After the tracheostomy, the patient's condition improved and was then eligible for transfer to another hospital. This study reflects back to the severe acute respiratory syndrome (SARS) pandemic of 2002. Tracheostomy studies conducted during this time reported that the timing from tracheal intubation to tracheostomy averaged 14 d to 25 d. In COVID-19 patients with acute respiratory failure, it is suggested that ETs (before 10 d) should be avoided.

A case report by Holmen *et al*[19] presented a case of a COVID-19 patient that required an extensive ICU stay due to prolonged endotracheal intubation. The patient tested negative for COVID-19 on the 37th day and a tracheostomy was later performed. Using this case, the authors raised questions about the guidelines regarding the infectivity period in COVID-19 patients[20].

An additional case report was assessed for this study. Two cases were presented, each in which the patients on mechanical ventilation underwent percutaneous tracheostomy within the two weeks of observing infectivity. Despite patients testing positive for COVID-19, the procedure can be performed safely with minimal infectivity and danger to the patients[21].

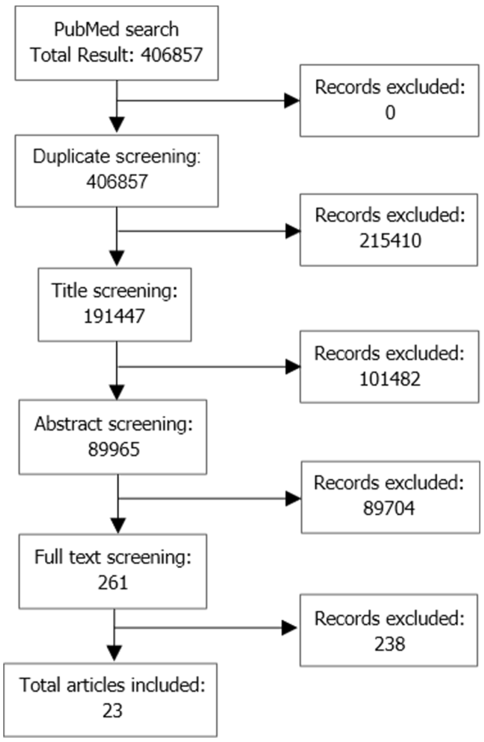

Figure 1 PRISMA Diagram for Literature Screening using the keywords "Coronavirus" and/or "guidelines" and/or "tracheostomy" and/or "intensive care". Observational studies, systematic reviews and meta-analyses were included in the selection process. This review was performed in accordance with PRISMA guidelines.

Observational Studies: A study conducted in China analyzed data from 80 patients who underwent elective tracheostomies. An ET was defined as the tracheostomy that was performed before 14 d and a late tracheostomy was defined as the procedure that was performed after 14 d. From this cohort, the median duration from endotracheal intubation to tracheostomy was 17.5 d. At the 60-d follow-up, 31 (38.8%) patients had been successfully weaned from the ventilator, 17 (21.2%) patients had been discharged from the ICU and a total of 43 (53.8%) patients had died. Late tracheostomy was associated with a lower death rate compared to ET, the hazard ratio of late tracheostomy was 0.34 (95% confidence interval: 0.17–0.70). Tracheostoma bleeding was a complication that occurred in 4 (13.3%) of ET patients and 10 (20.0%) of late tracheostomy patients. Subcutaneous emphysema occurred in one patient in each group. There was one incidence of both tracheostoma infection and mediastinal emphysema in the late tracheostomy group[22].

In a study from Italy, 50 patients were admitted in the ICU and were put on mechanical ventilation. The study cohort consisted of 23 patients who underwent a tracheostomy. ET was defined as if the procedure was performed before 10 d and late tracheostomy was defined as the tracheostomy was performed after 10 d. The average time between the initial intubation and tracheostomy was 13 d. The mean time that the patients were mechanically ventilated was 29 d and the mean length of stay in the ICU was 27 d. Nine tracheostomies were performed early, and 14 tracheostomies were performed late. After a median follow-up of 50 d, 9 (39.0 %) patients died, 5 (22.0%) were still receiving invasive mechanical ventilation (IMV) in the ICU, 3 (13.0%) were discharged from the ICU to be moved to the sub-intensive unit, and 6 (26.0%) were decannulated and discharged. Among the patients that were alive, the mean time from tracheostomy and decannulation was 26.8 d. Among deceased mean time from tracheostomy and death was 13.7 d. In this study, an ET was associated with a higher risk of mortality[23].

A study conducted in the United States of ten hospitals in the Chicagoland metropolitan area collected data from 486 hospitalized patients. Of the 138 patients that required IMV, only 19 (13.8%) intubated patients required tracheostomies. From the 138 IMV patients, 78 (56.5%) were eventually extubated and 21 had died making the mortality rate 15.2%. The timing of tracheostomy was not mentioned therefore information about the relationship of timing of tracheostomy to successful weaning or overall mortality was not provided. Thirty-nine patients remained intubated at the last

follow-up. The mean length of stay for hospitalized patients was 19 d. Of the 78 patients that were extubated, 30 (38.5%) were extubated within 1-7 d, 42 (53.8%) were extubated within 7-14 d, and 6 (7.7%) were extubated after 14 d. In this study, most deaths occurred within the 14-d incubation period[10].

Schuler *et al*[23] conducted a study consisting of 18 patients. Tracheostomies were performed between 2 d and 16 d after intubation. The authors state that while delaying tracheostomies minimizes risk to healthcare providers, complications such as myopathy, ventilator-associated respiratory muscle atrophy, neuropathy, and inability to wean, as well as other concerns such as over-occupation of ICU beds, lengthier sedation, and inability to communicate. In this study, ETs also reduced the number of patients requiring prone positioning which often leads to accidental decannulation of the ventilation tube. The authors state that taking into consideration the clinical state of the patient, performing an earlier tracheostomy may be beneficial.

An additional study observed 29 patients with COVID-19 that were admitted to the ICU and underwent a tracheostomy. Outcomes were mortality, ICU stay, and time on mechanical ventilation. Although the average time to tracheostomy was 15.2 d, which is considered a delayed procedure. The authors found that for each day of delay in performing the procedure, the number of days on mechanical ventilation increased by 0.6 d. Delayed tracheostomies did not impact ICU stay or mortality[24].

A study conducted in the United States at the University of Pennsylvania, tracheostomies were performed in 53 COVID-19 patients with acute respiratory failure. In these patients, the average (range) time from intubation to tracheostomy was 19.7 (8-42) d. At the time of follow-up, 30 (56.6%) patients had been removed from ventilator support, 16 (30.2%) had been discharged, 7 (13.2%) had been decannulated, and 6 (11.3%) had died. There was a weak positive correlation of ET to weaning the patients from the ventilator[25].

Botti *et al*[26] conducted a retrospective study on 44 COVID-19 ICU patients in Italy that underwent tracheostomies. This retrospective cohort study was focused on patients over 18 years of age with severe COVID-19 pneumonia that required mechanical ventilation. Average time from intubation to tracheostomy was 7 d. Of the 44 patients, 25 (56.8%) had reported complications at follow-up such as subcutaneous emphysema, infection, or mild hemorrhage. A total of 15 (34.1%) patients had died at follow-up but there was no correlation between the timing of tracheostomy and mortality (P = 0.82). ETs were performed at this center in order to increase ICU capacity but not necessarily because of the success of performing the procedure earlier.

A study conducted in Japan included 16 patients that received tracheal intubation but nearly a third (31.0%) required tracheostomies. The average time from intubation to tracheostomy was 20 d (14-27 d) which followed the study guidelines for performing a tracheostomy after 2-3 wk of intubation. There were no reported infections amongst providers[27].

Editorials and letters to the editor: In a letter to the editor, Ferri *et al*[28] analyzed a sample of 8 patients that underwent tracheostomies. Tracheostomies were performed on patients that were intubated for at least 14 days. Of these 8 patients, 2 (25%) patients died after the procedure and the median time from tracheostomy to death was 3 days. This mortality rate was lower than that of COVID-19 patients admitted to the ICU at the time. In this study cohort, an intubation period of less than 20 d was associated with an increased risk of death.

An editorial by Mesolella[29] discusses if the timing of tracheostomies is a factor that influences the clinical outcome of patients. In this editorial, the author states that even while early procedures have shown better outcomes such as mortality, pneumonia, and time of mechanical ventilation, there are many complications to performing a tracheostomy that outweighs the benefits. The author suggests that by the end of the waiting period of 21 d, the viral load would have decreased, minimizing the risk to health care providers and giving providers a more accurate prognosis for the patient.

A letter to the editor by Kwak *et al*[30] reviewed articles as well as data from NYU Langone Health for the accuracy and efficacy of proposed guidelines for performing tracheostomies on COVID-19 patients. At this center, researchers found that the mean time from endotracheal intubation to tracheostomy was 12.2 d and the onset of symptoms to tracheostomy was 22.8 d. The authors suggest that by day 12 from intubation or day 22 from the onset of symptoms, the viral load should be greatly decreased therefore not causing any more risk than a routine tracheostomy. ETs also showed decreased time on mechanical ventilation by an average of 6.7 d and overall length of hospital stay by an average of 6.9 d. Finally, the authors stated that despite performing ETs, none of the surgeons performing the procedures were infected with

Table 1 A description of studies collected for the review

Ref.	Title	Country	Following Guidelines for COVID-19 in the United States?	Timing of Tracheostomy	Type of Tracheostomy	Where was the Tracheostomy Done	Patient Outcome
Parker *et al* [9]	AAO Position Statement: Tracheotomy Recommendations During the COVID-19 Pandemic	United States	Yes	Can be considered after 2-3 weeks from intubation with negative COVID test	Unknown	ICU or operating room	Inconclusive
Hur *et al* [10]	Factors Associated with Intubation and Prolonged Intubation in Hospitalized Patients with Covid-19	United States	Yes	Assessed after ICU admission and intubation	Open	Operating Room	Unknown
Meng *et al* [11]	Early *vs* Late Tracheostomy in Critically Ill Patients: A Systematic Review and Meta-analysis	China	No	Various Timings	Open and Percutaneous	ICU or CCU	Early trach does not significantly alter the mortality, incidence of VAP duration of MV or length of ICU stay
Shiba *et al* [12]	Tracheostomy Considerations During the COVID-19 Pandemic	Global	Yes	Avoided if the patient is still infectious	Open and Percutaneous	Operating Room and ICU bedside	If the patient cannot be intubated, a laryngeal mask airway may be preferred over an emergent trach
Smith *et al* [13]	Tracheostomy in the intensive care unit: Guidelines during COVID-19worldwide pandemic	Argentina	No	After 21 days, negative COVID-19 test	Percutaneous	ICU	No benefits to early trach, but benefits to trach may be the possibility of decreasing sedation and delirium, increasing patient comfort, and reducing the incidence of laryngotracheal stenosis, ICU stay, and pneumonia
Heyd *et al* [14]	Tracheostomy Protocols During COVID-19 Pandemic	Global	Yes	>21 days depending on vent settings; patient shouldn't be infectious	Open	ICU or operating room	Inconclusive
Takhar, *et al*[15]	Recommendation of a Practical Guideline for Safe Tracheostomy During the COVID-19 Pandemic	Global	Yes	At least 14 days	Open and Percutaneous	Operating Room and ICU bedside	Tracheostomy should be avoided if the prognosis is not deemed favorable since the mortality is ~50%
Bier-Laning *et al*[16]	Tracheostomy During the COVID-19Pandemic: Comparison of International Perioperative Care Protocols and Practices in 26 Countries	Global	Yes	2-3 weeks from intubation preferably with negative COVID-19 test and falling inflammatory markers	Open and Percutaneous	Negative pressure room in ICU or Operating Room	Should reduce risk of virus exposure to providers and increase patient stability
Mandal *et al*[17]	A Systematic Review on Tracheostomy in COVID-19 Patients: Current Guidelines and Safety Measures	Global	Yes	At least 14 days; Patient should no longer be infectious	Open and Percutaneous	Operating Room and ICU bedside	Inconclusive
Hiramatsu *et al*[18]	Anesthetic and Surgical Management of Tracheostomy in a Patient With COVID-19	Japan	Yes	Day 28 of hospitalization	Open	Negative-pressure room in ICU	Patient improved by day 35 and transferred to another hospital
Holmenet al[19]	Delayed Tracheostomy in a Patient With Prolonged Invasive	United States	Yes	Day 41 of intubation	Unknown	Unknown	Patient status improved and was discharged to rehab facility on day 58

	Mechanical Ventilation due to COVID-19						of hospitalization
Marzban-Rad *et al* [20]	Early percutaneous dilational tracheostomy in COVID-19 patients: A case report	Iran	No	<10 days	Percutaneous	ICU	Early tracheostomy can be safely performed and improve patients' condition when necessary
Tang *et al* [21]	Tracheostomy in 80 COVID-9 Patients: A Multicenter, Retrospective, Observational Study	China	Yes	Before 14 days or after 14 days	Open and Percutaneous	ICU or Operating room	Trachs within 14 days were associated with an increased mortality rate
Volo *et al* [22]	Elective Tracheostomy During COVID-19 Outbreak: To Whom, When, How? Early Experience from Venice, Italy	Italy	No	Median timing was 13 days- 10 days was the cut off for early to late	Open and Percutaneous	ICU	Early tracheostomy was associated with a greater risk of mortality. This conclusion was combined with SOFA scores greater than 6 and D-dimer greater than 4
Schuler *et al*[23]	Surgical tracheostomy in a cohort of COVID-19 patients	Germany	No	Between 2-16 days	Open	ICU	No infection to staff, decreased sedatives, decrease the risk of myopathy, neuropathy, shortened ICU stay
Mata-Castro *et al* [24]	Tracheostomy in patients with SARS-CoV-2 reduces time on mechanical ventilation but not intensive care unit stay	Spain	No	15.2 days	Unknown	Operating theatre in ICU	Delay in trach increased days of mechanical ventilation
Chao *et al* [25]	Outcomes After Tracheostomy in COVID-19 Patients	United States	Yes	8-30 days, average 17.5 days	Open and percutaneous	Negative pressure room in ICU	Patients who underwent earlier trachs achieved ventilator liberation sooner than late trach, patients with ARDS on vents should be delayed
Botti *et al* [26]	The Role of Tracheotomy and Timing of Weaning and Decannulation in Patients Affected by Severe COVID-19	Italy	No	2-17 days, average 7 days	Open or percutaneous	Negative pressure room in ICU	Tracheostomies proved to be an easier approach for patients with blockages
Nishio *et al* [27]	Surgical strategy and optimal timing of tracheostomy in patients with COVID-19: Early experiences in Japan	Japan	Yes	14-27 days, average 20 days	Open	ICU	No differences in blood loss or infection from pre to post-procedure
Ferri *et al* [28]	Indications and Times for Tracheostomy in Patients With SARS CoV2-related	Italy	No	Intubated 14 days or more	Open	ICU	The mortality rate amongst trached patients was 25% compared to 26%
Mesolella *et al*[29]	Is Timing of Tracheotomy a Factor Influencing the Clinical Course in COVID-19 Patients?	Italy	Yes	After 18 days	Unknown	ICU	Decreased pneumonia, MV rates, ability to oral feed, avoid injury to the larynx
Kwak *et al* [30]	Tracheostomy in COVID-19 Patients: Why Delay or Avoid?	United States	No	12.8 Days	Unknown	Unknown	Decreased LOS, decreased MV, no infection to providers
McGrath *et al*[31]	Tracheostomy for COVID-19: business as usual?	Untied Kingdom	No	Case-specific	Open, percutaneous or hybrid	ICU or operating theatre	Safe for providers and patients, prevents prolonged ventilation, physiological status of patient is more important than the viral load

Observational studies, systematic reviews and meta-analyses were included in the selection process. This review was performed in accordance with

PRISMA guidelines. COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ICU: Intensive care unit.

COVID-19.

McGrath *et al*[31] discussed the changes that had been implemented for tracheostomies with the onset of COVID-19. The authors gathered that 30-d survival improved significantly with tracheostomy in general, and ICU length of stay was reported to be shorter with ETs. The authors concluded that the recommendation to postpone tracheostomies to minimize infectivity is second to the physiological status of the individual patient.

CONCLUSION

Due to the complicated presentation of COVID-19, the best practice for patient care and disease management has yet to be established. Case by case management, risk-benefit analysis, and justified medical judgement seems to provide the optimum course of action when presented with the role of providing care to these unique cases. Also, based on how critically ill COVID-19 patients are managed, guidelines will need to be established on appropriate landmarks for patients.

Various studies mention the complications associated with delaying tracheostomies [17,21,29]. Complications can be related to early or late procedure, severity of disease, comorbidities, type of tracheostomy performed, where the procedure was performed, and individual patient demographics. Many sources discussed the risk to providers performing tracheostomies on patients. The waiting period of a minimum of 14 d was mostly implemented to wait for the infectious period to pass in order to protect healthcare providers. However, in the studies that allowed ETs, there was no presentation of COVID-19 infection in providers from performing the procedure[30].

Studies on the timing of tracheostomies are still very scarce considering the novelty of the virus. However, using the limited data that is available and reflecting on studies from the 1918 H1N1 pandemic and the 2002 SARS pandemic, researchers and providers can attempt to predict how tracheostomies will define outcomes for COVID-19 patients. Other limitations of this study included varying qualities of studies gathered. Due to the novelty of the virus, researchers were limited in the number of participants that were able to be included in the study prior to publication. All eligible studies were included in this review regardless of quality due to a lack of available content. Further studies by authors aim to address these limitations.

Considering that tracheostomies are an aerosol-generating procedure, waiting to perform this procedure after the infectious period of 2-3 wk, may prevent or reduce the transmission of disease creating a safer environment for healthcare providers[18]. It was also mentioned that tracheostomies in general may not be beneficial in COVID-19 patients who are suffering from rapidly progressing disease[12]. The majority of studies showed a waiting period of 2 wk from the timing of intubation to performing a tracheostomy, Table 1.

In summary, the timing of tracheostomy in COVID-19 patients varied from institution to institution. However, the majority of data support delaying tracheostomies for after the first two weeks of intubation. Furthermore, the patient's overall health condition, physiological parameters, hemodynamics status and disease burden must be considered prior to proceeding with a tracheostomy.

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ORIGINAL ARTICLE

Retrospective Study

Sequential organ failure assessment score is superior to other prognostic indices in acute pancreatitis

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Abstract

BACKGROUND

Acute pancreatitis (AP) is a common surgical condition, with severe AP (SAP) potentially lethal. Many prognostic indices, including; acute physiology and chronic health evaluation II score (APACHE II), bedside index of severity in acute pancreatitis (BISAP), Glasgow score, harmless acute pancreatitis score (HAPS), Ranson's score, and sequential organ failure assessment (SOFA) evaluate AP severity and predict mortality.

AIM

To evaluate these indices' utility in predicting severity, intensive care unit (ICU) admission, and mortality.

METHODS

A retrospective analysis of 653 patients with AP from July 2009 to September 2016 was performed. The demographic, clinical profile, and patient outcomes were collected. SAP was defined as *per* the revised Atlanta classification. Values for APACHE II score, BISAP, HAPS, and SOFA within 24 h of admission were retrospectively obtained based on laboratory results and patient evaluation recorded on a secure hospital-based online electronic platform. Data with < 10%

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missing data was imputed *via* mean substitution. Other patient information such as demographics, disease etiology, and patient outcomes were also derived from electronic medical records.

RESULTS

The mean age was 58.7 ± 17.5 years, with 58.7% males. Gallstones (n = 404, 61.9%), alcohol (n = 38, 5.8%), and hypertriglyceridemia (n = 19, 2.9%) were more common aetiologies. 81 (12.4%) patients developed SAP, 20 (3.1%) required ICU admission, and 12 (1.8%) deaths were attributed to SAP. Ranson's score and APACHE-II demonstrated the highest sensitivity in predicting SAP (92.6%, 80.2% respectively), ICU admission (100%), and mortality (100%). While SOFA and BISAP demonstrated lowest sensitivity in predicting SAP (13.6%, 24.7% respectively), ICU admission (40.0%, 25.0% respectively) and mortality (50.0%, 25.5% respectively). However, SOFA demonstrated the highest specificity in predicting SAP (99.7%), ICU admission (99.2%), and mortality (98.9%). SOFA demonstrated the highest positive predictive value, positive likelihood ratio, diagnostic odds ratio, and overall accuracy in predicting SAP, ICU admission, and mortality. SOFA and Ranson's score demonstrated the highest area under receiver-operator curves at 48 h in predicting SAP (0.966, 0.857 respectively), ICU admission (0.943, 0.946 respectively), and mortality (0.968, 0.917 respectively).

CONCLUSION

The SOFA and 48-h Ranson's scores accurately predict severity, ICU admission, and mortality in AP, with more favorable statistics for the SOFA score.

Key Words: Pancreatitis; Severity scoring; Intensive care unit; Mortality; Sequential Organ Failure Assessment score; Ranson's score

Core Tip: Acute pancreatitis is a common surgical emergency requiring quick evaluation of its severity to guide further management principles. Both the sequential organ failure assessment (SOFA) and 48-h Ranson scores accurately predict severity, intensive care unit admission, and mortality in acute pancreatitis (AP), with more favorable statistics for the SOFA score. Simple bedside scores such as bedside index of severity in AP and harmless AP score are practical and straightforward tests to screen out mild disease at the onset, allowing physicians to preferentially allocate resources for severe AP patients.

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INTRODUCTION

Acute pancreatitis (AP) is a common surgical condition with an incidence of 50-80 *per* 100000 population[1-3]. Severe AP (SAP) occurs in 12%-20% of patients and has significant morbidity and mortality burden[4-6]. Early mortality (within the first two weeks) is attributed to cytokine storm and multisystem organ failure (OF). Delayed mortality (after two weeks) is attributed to infectious complications[7]. A primary concern for clinicians is the gross heterogeneity in clinical presentation and identifying patients predicted to manifest SAP and subsequent mortality risk. Therefore, an accurate scoring system on admission becomes critical to guide patient disposition and aggressiveness of treatment, resulting in better patient care and resource allocation. Though prevalent scoring systems have moderate to high accuracy, multiple laboratory variables are sometimes too cumbersome for routine clinical use[8,9]. The bedside index of severity in acute pancreatitis (BISAP)[10] and harmless acute pancre-

atitis score (HAPS)[11] are simple systems that can be computed using easily attained clinical parameters. The sequential organ failure assessment (SOFA) score developed initially by Vincent *et al*[12] was validated for use in AP[13]. The SOFA score is graded from 0 to 4 including markers PaO2/FiO2 ratio, Glasgow coma scale, mean arterial pressure or administration of vasopressors, bilirubin levels and platelet levels. While there have been studies that have compared the efficacy of these newer scores in predicting disease severity against classic scores such as the Ranson's score and Glasgow score, such as the retrospective studies by Khanna *et al*[14] and Tan *et al*[15], these remain few and far between. Fewer still have reported their utility in predicting critical clinical outcomes such as intensive care unit (ICU) admission and AP mortality, as evidenced by the retrospective study by Shafiq *et al*[16] and Li *et al*[17]. This paper aims to evaluate the utility of six widely reported prognostic indices [acute physiology and chronic health evaluation II (APACHE-II), BISAP, Glasgow score, HAPS, Ranson's score, SOFA)] in the prediction of three key determinants of disease outcomes: Severity of AP, the need for ICU admission, and mortality from AP.

MATERIALS AND METHODS

This is a retrospective cohort study of all patients admitted for AP under the Department of General Surgery at Tan Tock Seng Hospital, Singapore, between July 2009 and September 2016. Patients admitted under other departments were excluded from this study. As *per* departmental practice, all patients were scored using both the Ranson's and Glasgow scores within the first 48 h of admission. Values for APACHE II score, BISAP, HAPS, and SOFA within 24 h of admission were retrospectively obtained based on laboratory results and patient evaluation recorded on a secure hospital-based online electronic platform. SOFA scores were only calculated on admission. Patients with grossly insufficient data to compute any of the six scorings were excluded from the study. On the occasion where laboratory values, particularly ventilator settings and blood gas data, were unavailable for patients not admitted to the ICU, no points were given for the missing values. Data with < 10% missing data was imputed *via* mean substitution. Other patient information such as demographics, disease etiology, and patient outcomes were also derived from electronic medical records. This study was approved by the institutional review board, reference number DSRB 2016/00825.

Definitions

Diagnosis and complications of AP: Definitions relating to AP diagnosis and complications were adopted from the Revised Atlanta classification[18]. Patients with any two out of the following three clinical parameters satisfied the diagnostic criteria for AP: (1) Characteristic abdominal pain, maximal pain over the epigastric area often with radiation to the back; (2) Biochemical features of AP, characterized as a measured serum lipase or amylase of > 3 times the upper limit of normal as defined by the local laboratory; and (3) Presence of characteristic radiological findings consistent with AP on contrast-enhanced computer tomography, magnetic resonance imaging or ultrasonography.

Complications of AP were categorized into local and systemic complications. Local complications (LC) include acute peripancreatic fluid collections, pancreatic pseudocysts, acute necrotic collections, walled-off necrosis, gastric outlet dysfunction, splenic and portal vein thrombosis, and colonic necrosis. Systemic complications were defined as exacerbation of pre-existing comorbidity by AP and distinct from persistent OF. OF, specifically renal, cardiovascular, or respiratory failure, was defined as *per* the modified Marshal scoring system (score of 2 or more for any of the above systems)[19].

Study outcomes

Severity stratification of AP: According to Revised Atlanta guidelines[18], AP can be graded as mild, moderately severe, or severe. The mild AP was defined in the absence of LC or OF. Mild AP is typically self-resolving within a week. Moderately severe disease was defined as AP in the presence of either LC or transient OF resolving within 48 h. SAP was defined as AP in the presence of persistent OF lasting more than 48 h.

ICU admission

Any patient admitted to the ICU for a minimum of 24 h was considered to have received care in ICU.

Mortality

Mortality was defined as the patient's death within the same hospital admission from any cause attributable to AP.

Prognostic scoring

Ranson's score was the first developed to risk-stratify AP[8] and consists of 11 parameters, five scored at admission, and six scored at 48 h after admission. Glasgow score, otherwise known as the Glasgow-Imrie or Imrie score, was first described by Blamey *et al*[20] and consists of eight variables scored with values at 48 h after admission. The APACHE-II score was initially developed to predict survival in the ICU setting but was eventually proposed as a suitable assessment tool in AP[21-23]. APACHE-II consists of 15 laboratory variables measured at the time of admission. The BISAP score consists of five variables retrospectively derived from a large population-based study for the early prediction of mortality in AP[10], and values are scored upon admission. The HAPS was first described by Lankisch *et al*[11]. It was designed to rule out patients with AP requiring ICU treatment and scored within 30 min of admission. The SOFA score developed by Vincent *et al*[12] and validated for use in AP by Adam *et al*[13] in 2013 consists of five variables scored within 24 h of admission.

Statistical analysis

Statistical analysis was conducted using SPSS Statistics Version 23 (Armonk NY: IBM Corp). Categorical variables are presented as absolute numbers and proportions. Continuous variables are presented as mean ± standard deviation (SD). Variance within categorical variables was assessed using the Chi-square test or Fisher's exact test where appropriate. Variance within continuous variables was measured using the student's t-test. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratios (LR+ and LR-), diagnostic odds ratio (DOR), and overall accuracy were calculated for each prognostic index with regards to disease severity, ICU admission, and mortality. Receiver operating characteristic (ROC) curves and areas under the curve (AUC) were calculated for each score. Pairwise comparisons between AUCs of each index's ROC were conducted using the nonparametric method described by DeLong *et al*[24] in 1988.

RESULTS

Patient characteristics

From July 2009 to September 2016, 675 patients were managed for AP. Four patients failed to satisfy the diagnostic criteria for AP, and two patients had missing global data. Of the remaining 669 patients, a total of 16 patients was excluded due to insufficient data to compute APACHE-II score (n = 16), HAPS score (n = 3), Ranson's score (n = 4), and Glasgow score (n = 3). Altogether, 22 (3.3%) were excluded, and 653 patients were included.

The mean age ± SD of patients was 58.7 ± 17.5 years (range 20-98 years). There was a male predominance (n = 383, 58.7%). Hypertension (n = 339, 51.9%), hyperlipidemia (n = 235, 36%) and type 2 diabetes mellitus (T2DM) (n = 204, 31.2%) were common co-morbid conditions. 125 (19.1%) and 159 (24.4%) patients had a history of smoking and alcohol consumption, respectively. Gallstones was the most common aetiology (n = 404, 61.9%), followed by alcohol (n = 38, 5.8%) and hypertriglyceridemia (n = 19, 2.9%). 81 (12.4%) patients developed SAP, 20 (3.1%) patients required ICU admission, and 12 (1.8%) deaths were attributed to AP, all of whom had SAP.

Severity-stratified patient demographic and clinical profile is shown in Table 1. Patients with SAP were significantly older (64.2 *vs* 57.9, P = 0.002) and had higher prevalence of hypertension (69.1% *vs* 49.5%, P = 0.005), T2DM (44.4% *vs* 29.4%, P = 0.025) and ischaemic heart disease (22.2% *vs* 11.0%, P = 0.012). Asthma (4.9% *vs* 5.8%, P = 0.038) and smoking history (8.6% *vs* 20.5%, P = 0.042) were less prevalent among SAP patients. Most common interventions were cholecystectomy (n = 186, 28.5%), endoscopic retrograde pancreatography (n = 89, 13.6%) and endoscopic ultrasound (n = 12, 1.8%).

Score comparison

Comparative characteristics of all six scores regarding the severity stratification, ICU admission, and mortality are shown in Table 2. AUC of the six scores in predicting

Table 1 Demographic and clinical profile of patients with acute pancreatitis *n* (%)

Characteristic	Overall study population (*n* = 653)	Mild to moderately severe AP (*n* = 572)	Severe AP (*n* = 81)	*P* value
Mean age at admission (Range)	58.7 ± 17.5 (20-98)	57.9 ± 17.0 (20-95)	64.2 ± 20.0 (20-98)	0.002[a]
Gender				
Male	383 (58.7)	334 (58.4)	49 (60.5)	0.285
Ethnicity				0.099
Chinese	458 (70.1)	391 (68.4)	67 (82.7)	
Malay	43 (6.6)	36 (6.3)	7 (8.6)	
Indian	108 (16.5)	102 (17.8)	6 (7.4)	
Others	44 (6.7)	43 (7.5)	1 (1.2)	
Comorbidities				
Hypertension	339 (51.9)	283 (49.5)	56 (69.1)	0.005[a]
T2DM	204 (31.2)	168 (29.4)	36 (44.4)	0.025[a]
Hyperlipidemia	235 (36)	198 (34.6)	37 (45.7)	0.373
Ischaemic heart disease	81 (12.4)	63 (11.0)	18 (22.2)	0.012[a]
Cerebrovascular disease	51 (7.8)	43 (7.5)	8 (9.9)	0.768
Renal impairment	42 (6.4)	33 (5.8)	9 (11.1)	0.195
COPD	13 (2.0)	9 (1.6)	4 (4.9)	0.217
Asthma	37 (5.7)	33 (5.8)	4 (4.9)	0.038[a]
Others	120 (18.4)	107 (18.7)	13 (16.0)	0.919
Medications				
Immunosuppressed	2 (0.3)	2 (0.3)	0	0.467
Steroids	9 (1.4)	6 (1.0)	3 (3.7)	0.214
Anticoagulants	32 (4.9)	24 (4.2)	8 (9.9)	0.065
History of smoking	125 (19.1)	118 (20.5)	7 (8.6)	0.042[a]
History of alcohol consumption	159 (24.4)	145 (25.4)	14 (17.3)	0.454
Previous pancreatic disease	76 (11.6)	67 (11.7)	9 (11.1)	0.112
Chronic pancreatitis	30 (4.6)	29 (5.1)	1 (1.2)	0.098
Previous Cholecystectomy	44 (6.7)	38 (6.6)	6 (7.4)	0.809
Etiology				
Gallstones	404 (61.9)	350 (61.2)	54 (66.7)	0.390
Alcohol	38 (5.8)	34 (5.9)	4 (4.9)	0.437
Idiopathic	61 (9.3)	52 (9.1)	9 (11.1)	0.634
Hypertriglyceridemia	19 (2.9)	14 (2.4)	5 (6.2)	0.161
Autoimmune	4 (0.6)	4 (0.7)	0	0.491
Hypercalcemia	3 (0.5)	2 (0.3)	1 (1.2)	0.235
Drug induced	6 (0.9)	3 (0.5)	3 (3.7)	0.065
Others	47(7.2)	44 (7.7)	3 (3.7)	0.343

[a]$P < 0.05$. T2DM: Type 2 diabetes mellitus; COPD: Chronic obstructive pulmonary disease; AP: Acute pancreatitis; Idiopathic: Acute pancreatitis with no etiology despite extensive work up; Others: Etiologies of acute pancreatitis include trauma, pancreas cystic neoplasms, malignancy, iatrogenic causes such as endoscopic retrograde cholangiopancreatography.

SAP, ICU admission, and mortality are shown in Figures 1-3, respectively.

Table 2 Evaluation of prognostic indices for severe acute pancreatitis (*n* = 81), intensive care unit admission (*n* = 20), and mortality in acute pancreatitis (*n* = 12)

Score	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR-	Diagnostic odds ratio	Accuracy
SAP								
HAPS ≥ 1	79.0	49.7	18.2	94.4	1.569	0.423	3.712	53.3
BISAP ≥ 3	24.7	95.3	42.6	89.9	5.231	0.790	6.618	86.5
APACHE II ≥ 8	80.2	63.3	23.6	95.8	2.186	0.312	7.003	65.4
Ranson's ≥ 3	92.6	51.9	21.4	98.0	1.926	0.143	13.5	57.0
Glasgow ≥ 3	76.5	68.5	25.6	95.4	2.432	0.342	7.106	69.5
SOFA ≥ 7	13.6	99.7	84.6	89.1	38.84	0.867	44.786	89.0
ICU admission								
HAPS ≥ 1	90.0	47.2	5.1	99.3	1.706	0.212	8.057	29.9
BISAP ≥ 3	25.0	93.4	10.6	97.5	3.768	0.803	4.690	91.3
APACHE II ≥ 8	100.0	59.6	6.6	100.0	2.473	0	Nil	60.5
Ranson ≥ 3	100.0	47.9	5.7	100.0	1.918	0	Nil	49.5
Glasgow ≥ 3	75.0	64.5	7.0	99.3	2.110	0.388	5.440	65.1
SOFA ≥ 7	40.0	99.2	61.5	98.1	50.64	0.605	83.733	97.4
Mortality in AP								
HAPS ≥ 1	83.3	46.6	2.8	99.3	1.562	0.357	4.371	29.9
BISAP ≥ 3	25	93.1	6.4	98.5	3.642	0.805	4.523	91.9
APACHE II ≥ 8	100	58.7	3.6	100	2.419	0	Nil	59.1
Ranson's ≥ 3	100	47.3	3.4	100	1.896	0	Nil	48.2
Glasgow ≥ 3	75	63.8	4.1	99.5	2.072	0.392	5.289	64.2
SOFA ≥ 7	50.0	98.9	46.2	99.1	45.786	0.506	90.571	98.0

HAPS: Harmless acute pancreatitis score; BISAP: Bedside index of severity in acute pancreatitis; APACHE II: Acute physiology and chronic health evaluation–II; PPV: Positive predictive value; NPV: Negative predictive value; SAP: Severe acute pancreatitis; ICU: Intensive care unit; AP: Acute pancreatitis. HAPS, BISAP, and APACHE II were calculated at admission, Ranson's and Glasgow's were calculated at 48 h post-admission.

Prediction of SAP

In predicting SAP, there was a significant variation between scores: Sensitivity (13.6%-92.6%) and specificity (49.7%-99.7%). Ranson's score demonstrated the highest sensitivity (92.6%) but one of the lowest specificities (51.9%), only higher specificity than HAPS (49.7%). SOFA score demonstrated the lowest sensitivity (13.6%) but the highest specificity (99.7%). Positive predictive value (PPV) of all scores fell short of 50% aside from SOFA (84.6%). All scores demonstrated consistently high and comparable negative predictive values (NPV) in the prediction of severity. Ranson's score had the highest NPV (98.0%). Of all scores, SOFA demonstrated the most significant positive likelihood ratio (LR+) (38.84), DOR (44.786), and overall accuracy (89.0%).

Figure 1 shows the area under receiver-operator curves (AUROC) of all scores for predicting SAP. SOFA (0.966) and 48-h Ranson's score (0.857) demonstrated the highest AUROC. HAPS demonstrated the lowest AUROC (0.687). Nonparametric comparison of AUROC between SOFA and 48-h Ranson's score revealed SOFA had significantly greater AUROC (difference 0.109, $P < 0.0001$). SOFA score had a significantly higher AUROC than all other scores (all other scores $P < 0.0001$). 48-h Ranson's score had significantly higher AUROC as compared to APACHE-II ($P = 0.0163$), BISAP ($P < 0.0001$), Glasgow score ($P = 0.0007$), and HAPS ($P < 0.0001$).

ICU admission

In predicting ICU admission, sensitivity (25.0%-100%) and specificity (47.2%-99.2%)

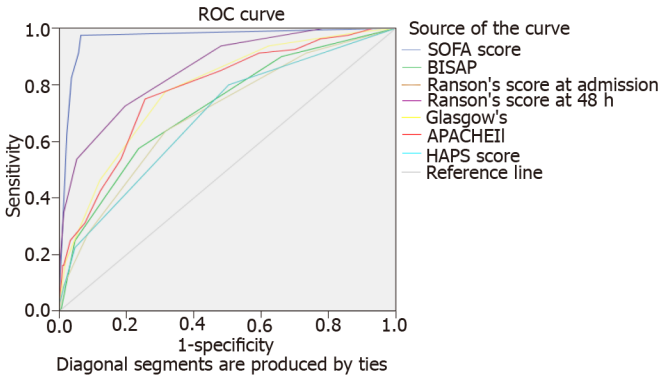

Figure 1 Area under receiver-operator curve for prognosticating severity in acute pancreatitis. ROC: Receiver operating characteristic; SOFA: Sequential Organ Failure Assessment; HAPS: Harmless acute pancreatitis score; BISAP: Bedside index of severity in acute pancreatitis; APACHE II: Acute physiology and chronic health evaluation–II.

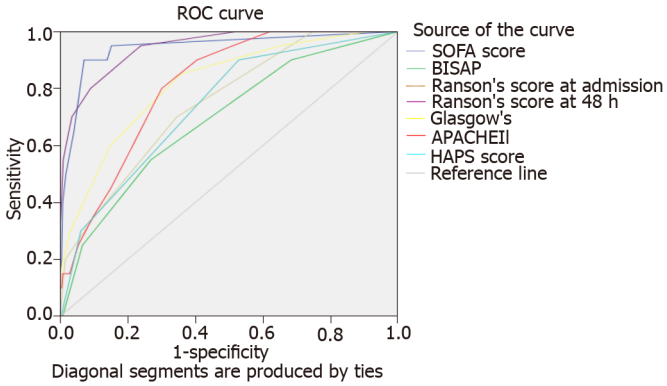

Figure 2 Area under receiver-operator curve for prognosticating intensive care unit admission in acute pancreatitis. ROC: Receiver operating characteristic; SOFA: Sequential Organ Failure Assessment; HAPS: Harmless acute pancreatitis score; BISAP: Bedside index of severity in acute pancreatitis; APACHE II: Acute physiology and chronic health evaluation–II.

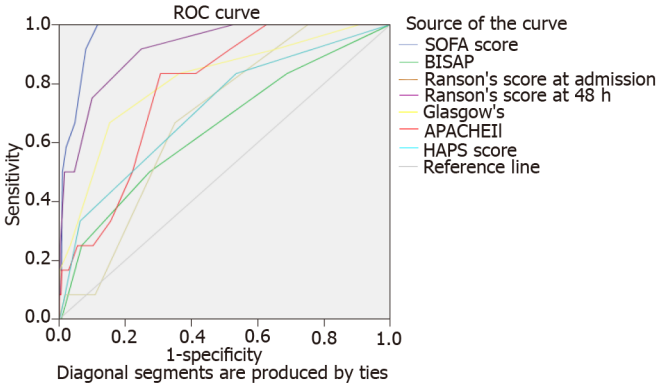

Figure 3 Area under receiver-operator curve for prognosticating mortality in acute pancreatitis. ROC: Receiver operating characteristic; SOFA: Sequential Organ Failure Assessment; HAPS: Harmless acute pancreatitis score; BISAP: Bedside index of severity in acute pancreatitis; APACHE II: Acute physiology and chronic health evaluation–II.

varied greatly among the various scores. APACHE-II and Ranson's scores displayed 100.0% sensitivity for predicting ICU admission. While BISAP demonstrated the lowest sensitivity (25.0%), it displayed high specificity (93.4%). SOFA demonstrated the highest specificity (99.2%). PPV of all scores was low (5.1%-10.6%) except SOFA (61.5%). All scores demonstrated high and comparable NPV in predicting ICU admission (97.5-100.0%). Of all scores, SOFA demonstrated the greatest LR+ (50.64), DOR (83.73), and overall accuracy (97.4%).

Figure 2 shows the AUROC of all scores for predicting ICU admission. SOFA (0.943) and 48-h Ranson's score (0.946) demonstrated the highest scores. Nonparametric comparison of AUROC of SOFA and 48-h Ranson's score revealed no significant difference (difference 0.003, $P = 0.933$). SOFA score had significantly higher AUROC than scores of HAPS ($P = 0.0009$), BISAP ($P < 0.0001$), Glasgow ($P = 0.0069$), and APACHE-II ($P = 0.001$). 48-h Ranson's score has significantly higher AUROC compared to other scores such as HAPS ($P = 0.0001$), BISAP ($P < 0.0001$), Glasgow ($P = 0.0066$), and APACHE-II ($P = 0.0005$).

Mortality in AP

In predicting mortality, variance in sensitivity (25.0%-100%) and specificity (47.2%-98.9%) were once again noted. APACHE-II and Ranson's both displayed 100.0% sensitivity for predicting mortality. In contrast, BISAP demonstrated the lowest sensitivity (25.0%). SOFA score demonstrated the highest specificity (98.9%). PPV of all scores was low (2.8%-46.2%). All scores demonstrated high and comparable NPV in predicting mortality (98.5%-100.0%). Of all scores, the SOFA score displayed the highest LR+ (45.786), DOR (90.571), and overall accuracy (98.0%) in predicting mortality.

Figure 3 shows the AUROC of all scores for predicting mortality. SOFA (0.968) and 48-h Ranson's score (0.917) demonstrated the highest scores. Nonparametric comparison of AUROC of SOFA and 48-h Ranson's score revealed no significant difference (difference 0.051, $P = 0.0.150$). SOFA score had significantly higher AUROC than scores of HAPS ($P = 0.0007$), BISAP ($P = 0.001$), Glasgow ($P = 0.0243$), and APACHE-II ($P = 0.0003$). 48-h Ranson's score has significantly higher AUROC compared to other scores such as HAPS ($P = 0.00690$), BISAP ($P = 0.0037$), and APACHE-II ($P = 0.0203$) but did not yield a significant difference when compared to Glasgow score ($P = 0.139$).

DISCUSSION

AP remains an important surgical condition, were determining its severity remains integral in guiding its management. We evaluated six standard prognostic scoring systems in predicting severity, ICU admission, and mortality. To our knowledge, this is the first study to compare the six prognostic scoring systems (APACHE-II, BISAP, Glasgow Score, HAPS, Ranson's score, SOFA) in a single sitting. In our study, the SOFA score and 48-h Ranson's score demonstrated a high correlation to predict the severity of AP, ICU admission, and mortality. The SOFA score had better statistical parameters and thus marginally outperformed 48-h Ranson's score.

Patient characteristics

AP patients demonstrated a comorbidity profile similar to those in other studies[10,13] with a predominance of cardiovascular and metabolic conditions. Male predominance in AP is similarly reported in other studies[25,26]. Predominant etiologies of AP identified were gallstones (61.9%) and alcohol (5.8%), consistent with the reported trend in the American College of Gastroenterology Guidelines (40%-70% for gallstones, 25%-35% for alcohol)[27]. The lower prevalence of alcoholic pancreatitis in our population may reflect lower consumption rates in the Asian population[25,28].

Prediction of SAP

For the more established scoring systems of APACHE-II, Glasgow score, Ranson's score, and BISAP, the high NPV corroborates current literature when predicting severity[26,29,30]. Simoes *et al*[25] present in their retrospective study of 126 patients the Ranson's score to have the highest NPV (95.7%), followed by APACHE-II (91.4% at 48 h) and then Glasgow score (87.7%)[25]. Our study follows a similar trend of Ranson's score having the highest NPV (98.0%). In a study by Cho *et al*[31] involving 161 patients, a high BISAP NPV (92.7%) was noted, which was consistent with our study's NPV as well (89.9%)[31]. Similarly, Gao *et al*[32] found that the 48-h Ranson's score has a reasonably high AUROC (0.830), comparable to APACHE-II and BISAP [32]. Our study presents data to supplement the current literature on their NPV for determining SAP for the newer scoring systems of HAPS and SOFA score. To our knowledge, the NPV for HAPS in determining severity has only been validated by Ma *et al*[33] in 2020. In a prospective study involving 703 patients, Ma *et al*[33] reported high NPV for HAPS (97.7%), comparable to our results[33]. For the SOFA scoring system, a study by Zhou *et al*[34] involving 406 patients revealed that the NPV of

SOFA (95.1%) was high, a finding consistent with our study (89.1%)[34]. Notably, even simple bedside scoring indices requiring five or fewer variables (HAPS, BISAP) have high NPVs. Zhou *et al*[34] even found the BISAP score to have the highest NPV (98.1%). Hence, these simple bedside scores' utility lies in their ability to screen out mild disease at the onset, allowing physicians to divert their focus to patients with SAP.

The incidence of SAP within our cohort (12.4%) is similar to that experienced internationally, with previously reported SAP rates ranging from 12%-20% of AP cases [4-6]. Risk factors we noted include older age, hypertension, T2DM, and ischemic heart disease. Zhou *et al*[34] also found similar trends with high incidence of T2DM (P = 0.004), but not cardiovascular disease (P = 0.123) and age (P = 0.162)[34]. This could be explained by variation in diagnostic criteria as well as the definition of comorbidities. Thus far, no large studies have determined an association between asthma and the severity of AP. In another retrospective study by Kim *et al*[35] involving 905 patients, risk factors for AP included smoking (P = 0.04, OR 7.22 for AP induced by gallstones, P = 0.05, OR 2.59 for AP induced by alcohol consumption)[35]. In our study, smoking and asthma have shown a protective effect on SAP. This could be due to variation in smoking history documentation, and these findings require prospective validation by others. Also, we pooled the data of moderately severe AP patients along with mild AP patients, and this could impact the results. Alcohol history and hyperlipidemia were not statistically significant risk factors for developing SAP. This could be due to the low prevalence of alcohol consumption and the small sample. While hyperlipidemia is a known etiology of AP, there has not been a difference detected in AP severity. In a prospective study by Balachandra *et al*[36] involving 43 patients, raised triglyceride levels did not correlate with higher APACHE-II scores (r^2 = 0.0015)[36]. However, at very high levels, a correlation may be possible. A univariate analysis done by Deng *et al*[37] involving 45 patients with SAP and hypertriglyceridemia (≥ 500 mg/dL) revealed that patients with hypertriglyceridemia tend to have more severe AP with higher APACHE-II scores and overall mortality[37]. Hence, more studies with higher power are necessary to determine hypertriglyceridemia's relationship with SAP.

The AUROC for prognosticating severity in AP was most remarkable for the SOFA score and 48-h Ranson's score. This is in contrast with Zhou *et al*[34] study, which reported AUROC for determining severity as BISAP (0.841), Ranson's (0.806), and SOFA score (0.806). Zhou *et al*[34] did not note any significant difference between pairwise comparisons of BISAP, SOFA, and 48-h Ranson's score (BISAP *vs* SOFA, Z = 0.956, P = 0 .339; BISAP *vs* Ranson's score, Z = 1.072, P = 0.284; SOFA *vs* Ranson's score, Z = 0.000, P = 1.000). It is also worthy to note that a combination of red-cell distribution width was proposed as a combination of severity scoring with BISAP, which gave the highest AUROC in Zhou *et al*[34]'s study (0.872). However, it must be noted that the AUROC value was still inferior to the AUROC of SOFA score in our study (0.966). Contrasted to our study, it was noted that there were statistically significant differences in DeLong pairwise comparisons between SOFA and all five other scoring systems and between 48-h Ranson's score and HAPS or BISAP scores. Another study by Hagjer *et al*[38] involving 60 patients noted the AUROC for determining the severity of AP for higher for BISAP score (0.875) than APACHE-II score (0.872)[38]. 48-h Ranson's score had a slightly lower AUROC value (0.810). However, the study's low power suggests the need for more higher-powered studies to validate this claim.

ICU admission

The incidence in our study of ICU admissions (3.1%) also aligns to gross estimates in the literature, 3.7% in European cohorts[27,39,40]. However, variations between ICU admission criteria in various institutions should be taken into consideration. In our study, AUROC for 48-h Ranson's score and SOFA score were the greatest for determining ICU admissions, while the BISAP score yielded a lower AUROC. This is directly compared to the study by Harshit Kumar *et al*[41], who described a similar trend where Ranson's score (0.910) and APACHE-II (0.885) yielded good AUROC values, while the BISAP score yielded a better score than our study (0.877)[41]. However, Harshit Kumar *et al*[41]'s study had a small sample size and thus was not adequately powered. This is the first study to evaluate the utility of scoring indices for determining the likelihood of ICU admission for AP. Most of the literature extrapolate the need for ICU admission from the severity of the AP, akin to how Majdoub *et al*[26] inferred the need for ICU admission *via* APACHE-II, BISAP, Glasgow, and Ranson's scoring systems by evaluating the AUROC predicting mortality and morbidity but did not directly measure the number of patients admitted to ICU[26]. In terms of NPV, both APACHE-II and 48-h Ranson's scores yielded a 100% NPV rate for ICU

admission.

Mortality in AP

The prediction of mortality using the six prognostic indices has been individually fairly well-reviewed in the literature. In a retrospective study by Zhang *et al*[42] involving 155 patients, the AUROC value for mortality in AP was best represented by the Ranson's score (0.904), followed by the APACHE-II score (0.812) and the BISAP score (0.791)[42]. This directly contrasts the scores in our case where mortality was best represented by the AUROC values of the SOFA score (0.968) and 48-h Ranson's score (0.917), followed by the APACHE-II score (0.779). The BISAP score yielded the lowest AUROC value (P = 0.647) in our study. While the general ranking of the scoring systems is similar, it must be essential to note that Zhang *et al*[42] noted alcohol as the primary etiology in AP (56.7%) and not gallstones (26.4%) explain the differences in AUROC values. Similarly, Khanna *et al*[14] noted in their retrospective study involving 72 patients, APACHE-II yielded the highest AUROC score for predicting mortality in AP (0.86, CI: 0.77-0.95) followed by Ranson's score (0.84), Glasgow score (0.83) and BISAP score (0.83)[14]. Other studies corroborate the finding that BISAP scoring does not predict mortality and Ranson's score as well[32], stating a lower sensitivity compared to Ranson's score within 48 h of admission and lower specificity than 48-h Ranson's score[43]. However, the literature has provided differing opinions on the best scoring system to predict mortality. Another retrospective study by Biberci Keskin *et al*[44] involving 690 patients reported AUROC values to predict in-hospital mortality to be highest when BISAP was used (0.92) when compared to HAPS (0.85) and Ranson's score on admission (0.82)[44]. While the low AUROC value for Ranson's score can be explained by the lack of 48-h Ranson's score data, it is interesting to note the discrepancy in AURCO values for BISAP and HAPS scores compared to our data. Contrastingly, Mikó *et al*[45] noted in their meta-analysis on predicting mortality that the AUROC of APACHE-II (0.91) is superior to that of Ranson's score (0.87), which is equivocal to that of BISAP score (0.87)[45]. Gao *et al*[32] reveal that Ranson's score yielded the highest AUROC (0.92) among APACHE-II and BISAP[32]. Alternatively, Biberci Keskin *et al*[44] suggests using the Japanese Severity Score (JSS), which yielded the highest AUROC value for in-hospital mortality in their study (0.94). The discrepancy in scoring AUROC values could be due to the definition of in-hospital mortality used, where a 30-d cap was placed by Biberci Keskin *et al*[44] compared to our definition of death within the same hospital admission without a time limit. Thus, the evaluation of BISAP score for short-term mortality can be explored. Furthermore, the prognostic accuracy of JSS is heterogenous in the literature describing the JSS as both more accurate[44] and less accurate than 48-h Ranson's score[43] in separate instances. In the same study by Hagjer *et al*[38] as mentioned above, the AUROC values for predicting mortality in AP is highest in both APACHE-II score (0.893) and BISAP (0.892) followed by 48-h Ranson's score (0.803)[38], contrasting both our study and the study by Zhou *et al*[34]. However, given the small sample size of 60, more higher-powered studies can be considered before making a judgement as to why there is such a discrepancy.

Overall, despite the differences in AUROC values, the consensus in the literature support 48-h Ranson's and APACHE-II scores as good predictors for mortality in AP. The SOFA score has yet to be studied aside from the initial study by Adam *et al*[13], where a mean SOFA score yielded an equivocally high AUROC score (AUROC = 0.904)[13]. Adam *et al*[13] also compared SOFA scores after ICU admission *vs* Ranson's and APACHE II for prognosis of mortality. Authors reported that SOFA score trends after ICU admission were a good indicator for mortality prediction[13]. The study examined 39 patients with SAP in the ICU, with an overall mortality of 71%. SOFA scores correlated significantly with mortality, while APACHE II had no statistically significant association with mortality. Within the study, all patients with SOFA score ≥ 11 at any time during ICU stay had higher mortality (80% sensitivity, 79% specificity, AU 0.837). This is comparable to our study in patients with SOFA score ≥ 7 (50% sensitivity, 98.9% specificity, AUC 0.968 in the prognosis of mortality secondary to AP. Another related study by Tee *et al*[46] demonstrated the SOFA score on day seven to be reliable in predicting late mortality in AP[46]. Interestingly, SOFA score on admission (AUC = 0.67) and 48 h after admission (AUC = 0.765) had smaller AUROC compared with the APACHE II score (AUC = 0.821) in the prediction of mortality. However, the SOFA score on day seven was the best in predicting mortality (AUC = 0.858). The utility of SOFA in predicting disease outcomes is congruent with the underlying pathophysiology of SAP, with OF being recognized as the bridge to poor outcomes, as reported by Buter *et al*[47]. As the pancreas is a highly vascularized organ where both foregut and midgut vessels meet[48], bradykinin-mediated vasodilation

and increase in vascular permeability cause further pancreatic ischemia, systemic hypotension, and subsequent OF[49]. Hence, the trending of SOFA scores throughout admission is a valuable tool to alert physicians to both the early critical phase due to systemic inflammatory response syndrome and the late critical phase, two weeks later, due to increased infection risks[50].

Limitations

Our study has several limitations. Firstly, this is a retrospective single-center study, and thus results cannot be generalized across the diverse demographic population in different geographic locations. Clinical variables such as the onset of abdominal pain rely on recall bias of patients and accuracy of clinical records, and these limitations can only be addressed by prospective study design. Though we had missing data, it was low (3.3%) and, in our opinion, is acceptable. Our study analyses prognostic indices at admission and not trends. It is known that response to resuscitation and daily trends are essential determinants to predict severity and mortality. Further studies can be done comparing the utility of trending such scores throughout inpatient stay. We do not routinely perform C-reactive protein, and thus, we could not include it in our analysis.

CONCLUSION

Overall, this study's six prognostic indices demonstrated high NPV in predicting severity, ICU admission, and mortality in AP. SOFA score and 48-h Ranson's score are superior to other prognostic scorings (Glasgow score, APACHE II, BISAP, HAPS) in severity stratification, prediction of ICU admission, and mortality.

ARTICLE HIGHLIGHTS

Research background

Acute pancreatitis (AP) is a common surgical disease, and severe AP (SAP) can be fatal. Many prognostic indicators, including; acute physiology and chronic health evaluation II (APACHE II), bedside index of severity in acute pancreatitis (BISAP), Glasgow score, harmless acute pancreatitis score (HAPS), Ranson score, and sequential organ failure assessment (SOFA) assesses the severity of AP and predicts mortality.

Research motivation

An accurate scoring system on admission of AP is critical to guide patient disposition and aggressiveness of treatment, resulting in both better patient care as well as better distribution of resources for each institution. Few studies have compared the efficacy of these newer scores in predicting disease severity against classic scores such as Ranson's score and Glasgow score, and fewer still have reported their utility in predicting key clinical outcomes such as intensive care unit (ICU) admission and mortality in AP.

Research objectives

A major concern for clinicians is the gross heterogeneity in clinical presentation and identifying patients predicted to manifest SAP. We evaluated these indices' utility in predicting severity, ICU admission, and mortality.

Research methods

This is a retrospective cohort study. All patients were scored using Ranson and Glasgow scores within the first 48 h after admission. The APACHE II score, BISAP, HAPS, and SOFA values within 24 h of admission are retrospectively obtained based on laboratory results and patient evaluations recorded on a secure online electronic platform of the hospital. Data with missing data < 10% are extrapolated by means of replacement. Other patient information, such as demographics, disease causes, and patient results are also derived from electronic medical records.

Research results

The mean age was 58.7 ± 17.5 years, with 58.7% males. Gallstones (n = 404, 61.9%), alcohol (n = 38, 5.8%), and hypertriglyceridemia (n = 19, 2.9%) were more common

aetiologies. 81 (12.4%) patients developed SAP, 20 (3.1%) required ICU admission, and 12 (1.8%) deaths were attributed to SAP. Ranson's score and APACHE-II demonstrated the highest sensitivity in predicting SAP (92.6%, 80.2% respectively), ICU admission (100%), and mortality (100%). While SOFA and BISAP demonstrated lowest sensitivity in predicting SAP (13.6%, 24.7% respectively), ICU admission (40.0%, 25.0% respectively) and mortality (50.0%, 25.5% respectively). However, SOFA demonstrated the highest specificity in predicting SAP (99.7%), ICU admission (99.2%), and mortality (98.9%). SOFA demonstrated the highest positive predictive value, positive likelihood ratio, diagnostic odds ratio, and overall accuracy in predicting SAP, ICU admission, and mortality. SOFA and Ranson's score demonstrated the highest area under receiver-operator curves at 48 h in predicting SAP (0.966, 0.857 respectively), ICU admission (0.943, 0.946 respectively), and mortality (0.968, 0.917 respectively).

Research conclusions

Overall, the six prognostic indices in this study demonstrated high negative predictive values in prediction of severity, ICU admission and mortality in AP. SOFA score and Ranson score at 48 h are superior to other prognostic scorings (Glasgow score, APACHE II, BISAP, HAPS) in severity stratification, prediction of ICU admission and mortality in AP.

Research perspectives

As we provide a retrospective single-center study, future renditions of this study could include multi-center analysis spanning across different countries to reduce bias. Further studies can also compare the utility of trending such scores throughout inpatient stay rather than retrospectively from patients' results on admission.

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ORIGINAL ARTICLE

Observational Study

Intensive care unit hospitalizations and outcomes in patients with severe COVID-19 during summer and fall surges in Georgia

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Institutional review board statement: Data from this study used de-identified data from the National Inpatient Sample Database. A publicly available all-payer inpatient care database in the United States. Institutional Review Board Approval Form or

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Abstract

BACKGROUND

There is limited data on the difference in the clinical characteristics and outcomes of patients with severe coronavirus disease 2019 (COVID-19) infection in the summer compared to the fall surge.

AIM

To compare the sociodemographic, clinical characteristics, and outcomes among mechanically ventilated patients with severe COVID-19 infection admitted to the intensive care unit (ICU) during the summer and fall surges in the year 2020.

METHODS

We included patients admitted to the ICU and treated with invasive mechanical ventilation for COVID-19 associated respiratory failure between April 1 and December 31, 2020. Patients were categorized into summer surge for ICU admissions between June 15, 2020, and August 15, 2020, and fall surge between

Document is not required.

Informed consent statement: Data from this study used de-identified data from the National Inpatient Sample Database. A publicly available all-payer inpatient care database in the United States. Informed patient consent is not required.

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October 15, 2020, and December 31, 2020. We compared patients' characteristics and outcomes using descriptive and inferential statistics.

RESULTS

A total of 220 patients were admitted to the Grady Memorial Hospital ICU and mechanically ventilated for COVID-19 associated hypoxemic respiratory failure during the period considered (125 during the summer surge and 95 during the fall surge). More women were admitted in the fall compared to summer (41.1% *vs* 36.8%, difference, 4.3%; 95%CI: 1.2, 7.5). Patients admitted in the fall had fewer comorbidities (chronic obstructive pulmonary disease, stroke, diabetes mellitus, obstructive sleep apnea and body mass index ≥ 35 kg/m^2). Overall, patients in the fall had a lower ICU mortality rate (27.4% *vs* 38.4%, difference, -11.0; 95%CI: -6.4, -18.2), shorter length of stay on the mechanical ventilator (7 d *vs* 11 d, difference, 4 d; 95%CI: 2.1, 6.6) and shorter ICU length of stay (9 d *vs* 14 d, difference, 5 d; 95%CI: 2.7, 9.4).

CONCLUSION

Patients admitted with severe COVID-19 infection requiring mechanical ventilation had better outcomes in the fall than summer. This difference observed is likely attributable to a better understanding of the condition and advances in treatment strategies.

Key Words: COVID-19; COVID-19 surge; Georgia; Intensive care unit; Mechanical ventilation

Core Tip: In this observational study, we compared the sociodemographic, clinical characteristics, and outcomes among mechanically ventilated patients with coronavirus disease 2019 (COVID-19) infection admitted to the intensive care unit (ICU) during the summer and fall surges in the year 2020. Compared to patients admitted with severe COVID-19 in the summer, those in the fall had better outcomes including decreased mortality and low length of stay in the ICU. This is likely due to the improved understanding of COVID-19 and the advances in treatment strategies.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first reported in the United States on January 20, 2020. The World Health Organization declared the novel viral infection a pandemic on March 11, 2020[1]. Within 1 year of the pandemic, more than 31 million cases and 500000 deaths have been recorded in the United States[2].

In the United States the pandemic has been characterized by waves of case surges attributed to holiday gatherings, relaxation of social distancing guidelines and removal of COVID-19 restriction during reopening after lockdown in different states[3,4]. Surges in COVID-19 cases are associated with increased hospitalizations including the intensive care units (ICU) placing significant strains on hospital resources[3]. The state of Georgia experienced resurgence of cases during the summer and fall seasons of 2020 with increased rates of hospitalizations[5].

We describe the differences in the sociodemographic, clinical characteristics, and outcomes in mechanically ventilated patients with severe COVID-19 infection admitted to the ICU of Grady Memorial Hospital (GMH) in Atlanta, Georgia across the surges in the summer and fall of year 2020.

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MATERIALS AND METHODS

We identified patients with positive reverse transcriptase–polymerase chain reaction nasopharyngeal swab test results for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) admitted to the GMH ICU (Morehouse school of medicine and Emory university ICU service) for hypoxemic respiratory failure and treated with invasive mechanical ventilation between April 1 and December 31, 2020. GMH is a level 1 trauma hospital in Atlanta, Georgia with more than 900 beds and one of the largest hospitals in Georgia. GMH played a significant role in the Georgia COVID-19 response by providing care to many COVID-19 patients in Georgia[6].

We extracted information on the age, sex, race/ethnicity, comorbidities, medication use, length of stay (LOS) on the mechanical ventilator, LOS in the ICU and ICU mortality outcomes from the electronic health record system. We obtained data from the Georgia State Department of Health to evaluate the trend of new COVID-19 cases between April 1 and December 31, 2020. Patients were categorized into summer surge for ICU admissions between June 15, 2020 and August 15, 2020 and fall surge between October 15, 2020 and December 31, 2020 based on the resurgence of COVID-19 cases in Georgia during the summer and fall periods. The study was approved by the Morehouse School of Medicine's Institutional Review Board (IRB). The IRB issued a waiver of HIPAA authorization to access electronic medical records.

We report summary statistics as means or medians and proportions for sociodemographic, clinical, and outcome variables of severe COVID-19 patients hospitalized in the ICU. We computed bivariable comparisons across summer and fall surges and reported the proportional differences with corresponding 95%CIs. All analyses were performed with version 3.5.2 of the R programming language (R Project for Statistical Computing; R Foundation). *P* values were 2-sided, with statistical significance set at $P < 0.05$.

RESULTS

A total of 220 patients were admitted to the GMH ICU and mechanically ventilated for COVID-19 associated hypoxemic respiratory failure during the period considered (125 during the summer surge and 95 during the fall surge). Table 1 describes the differences between the socio-demographic, clinical characteristics, and the outcomes of these patients across the two surge periods. Proportion of females was higher during the fall surge compared to the summer surge (41.1% *vs* 36.8%, difference, 4.3%; 95%CI: 1.2, 7.5). More patients had private insurance during the fall surge (36.8%*vs* 30.4%, difference, 6.4%; 95%CI: 1.5, 13.3) while fewer patients were uninsured during the summer (18.9% *vs* 28%, difference, -9.1%: 95%CI: -6.4, -12.5).

Patients admitted to the ICU during the fall surge had significantly higher burden of chronic kidney disease 4 and above, human immunodeficiency virus/acquired immune deficiency syndrome, hypertension, class 1 obesity (body mass index, BMI ≥ 30 kg/m^2 to < 35 kg/m^2) and tobacco use disorder, while fewer patients had chronic obstructive pulmonary disease (COPD), cerebrovascular accidents, diabetes mellitus (DM), obstructive sleep apnea and class 2 or greater obesity (BMI ≥ 35 kg/m^2). A significantly higher proportion of patients during the fall had no comorbidities at baseline compared to those in the summer (16.8% *vs* 9.6%, difference 7.2%; 95%CI: 2.8, 13.9). A greater proportion of patients in the fall surge were treated with remdesivir and dexamethasone.

The ICU mortality rate (27.4% *vs* 38.4%, difference, -11.0; 95%CI: -6.4, -18.2) was lower in the fall compared to summer. Similarly, patients in the fall had a shorter LOS on the mechanical ventilator (7 d *vs* 11 d, difference, 4 d; 95%CI: 2.1, 6.6) and shorter LOS in the ICU (9 d *vs* 14 d, difference, 5 d; 95%CI: 2.7, 9.4).

Figures 1 and 2 present trends of new COVID-19 cases and ICU hospitalizations in Georgia and GMH between April 1 – December 31, 2020. There was an increase in COVID-19 cases and ICU hospitalizations at GMH correlating with the summer and fall surges in Georgia. Dates corresponding to specific US national holidays are highlighted in Figure 1. Notably, the memorial holiday (May 25, 2020) preceded the surge of cases in the summer while the Labor Day (September 7, 2020) and Thanksgiving (November 26, 2020) holidays preceded the Fall surge.

Table 1 Sociodemographic, comorbidity, clinical, and outcome differences between surge 1 and surge 2 of Intensive care unit hospitalizations for coronavirus disease-19 Respiratory Failure at Grady Memorial Hospital, Atlanta, Georgia

Variables	Surge 1 (Summer 2020)	Surge 2 (Fall 2020)	Difference (95%CI)	*P* value
Total – *n* (%)	125	95		
Age, median (IQR)	61.5 (51-69)	61 (51.5-71)	0.5	0.34
< 55 yr	41 (32.8)	30 (31.6)	-1.2 (-3.8, 6.5)	0.39
55–64 yr	38 (30.4)	25 (26.3)	-4.1 (-6.2, -2.3)	0.04
65–74 yr	27 (21.6)	27 (28.4)	6.8 (4.5, 10.3)	0.04
> 75 yr	19 (15.2)	13 (13.7)	-1.5 (-5.5, 2.5)	0.19
Race				
Non-Hispanic Black	86 (68.8)	61 (64.2)	-4.6 (-10.7, 1.1)	0.1
Non-Hispanic White	22 (17.6)	17 (17.9)	0.3 (-1.7, 2.5)	0.18
Hispanic	10 (8)	8 (8.4)	0.4 (-1.6, 2.4)	0.26
Others[1]	7 (5.6)	8 (8.4)	2.8 (0.9, 4.9)	0.09
Gender				
Female	46 (36.8)	39 (41.1)	4.3 (1.2, 7.5)	< 0.01
Male	79 (63.2)	56 (58.9)	-4.3 (-2.4, -6.2)	< 0.01
Health insurance				
Medicaid only	7 (5.6)	5 (5.3)	-0.3 (-2.3, 1.5)	0.41
Medicare only	20 (16)	15 (15.8)	-0.2 (-1.8, 1.3)	0.12
Medicaid/Medicare	25 (20)	22 (23.2)	3.2 (1.0, 5.8)	0.05
Private insurance/Self pay	38 (30.4)	35 (36.8)	6.4 (1.5, 13.3)	0.02
Uninsured	35 (28)	18 (18.9)	-9.1 (- 6.4, -12.5)	0.04
Comorbid diseases				
Asthma	13 (10.4)	9 (9.5)	-0.9 (-4.8, 2.8)	0.22
Coronary artery disease	20 (16)	12 (12.6)	-3.4 (-8.5, 1.7)	0.11
Cancer (solid organ tumors)	12 (9.6)	6 (6.3)	-3.3 (- 8.2, 1.9)	0.18
Congestive heart failure	29 (23.2)	20 (21.1)	-2.1 (- 6.6, 2.1)	0.4
Chronic kidney disease 3 and above	17 (13.6)	16 (16.8)	3.2 (1.6, 5.1)	0.02
Chronic liver disease	10 (8)	9 (9.5)	1.5 (0.8, 2.47)	0.13
Chronic obstructive pulmonary disease	22 (17.6)	12 (12.6)	-5.0 (-10.1, -5.6)	0.04
Cerebrovascular accident	21 (16.8)	11 (11.6)	-5.2 (-10.3, -5.8)	0.02
Diabetes mellitus	62 (49.6)	41 (43.2)	-6.4 (-3.1, -9.8)	< 0.01
HIV/AIDS	4 (3.2)	8 (8.4)	5.2 (2.7, 8.2)	< 0.01
Hypertension	85 (68)	67 (70.5)	2.5 (1.3, 4.9)	< 0.01
Obstructive sleep apnea	14 (11.2)	6 (6.3)	-4.9 (-1.9, 8.8)	< 0.01
Body mass index				
< 30 kg/m^2	37 (29.6)	29 (30.5)	0.9 (0.4, 1.4)	0.078
≥ 30 kg/m^2 to < 35 kg/m^2	48 (38.4)	40 (42.1)	3.7 (1.6, 5.9)	< 0.01
≥ 35 kg/m^2	40 (32)	26 (27.4)	-4.6 (-1.3, 8.7)	< 0.01
Tobacco use (current smoker)	51 (40.8)	45 (47.4)	6.6 (3.2, 11.8)	< 0.01
No of comorbidities				
None	12 (9.6)	16 (16.8)	7.2 (2.8, 13.9)	< 0.01

1	8 (6.4)	5 (5.3)	-1.1 (-3.4, 1.1)	0.46
> 1	105 (84)	78 (82.1)	-1.9 (-5.1, 1.3)	0.37
Treatment received in the ICU				
Hydroxychloroquine	6 (4.8)	0 (0)	-4.8 (- 2.5, -7.6)	0.03
Azithromycin	25 (20)	14 (14.7)	-5.3 (- 3.1, -7.9)	0.04
Hydroxychloroquine + Azithromycin	36 (28.8)	0 (0)	-28.8 (-19.4, 41.1)	< 0.01
Remdesivir	44 (35.2)	42 (44.2)	9.0 (3.4, 10.2)	< 0.01
Dexamethasone	0	22 (23.2)	23.2 (18.3, 29.1)	< 0.01
Length of stay, median (IQR) (range), d				

[1]American Indian or Alaska Native, Asian, and Native Hawaiian or other Pacific Islander. Differences calculated as surge 2 – surge 1. Negative values represent decrease in surge 2. Null value = 0. HIV: Human immunodeficiency virus; AIDS: Acquired immunodeficiency syndrome; COVID-19: Coronavirus disease 2019; ICU: Intensive care unit; IQR: Interquartile range.

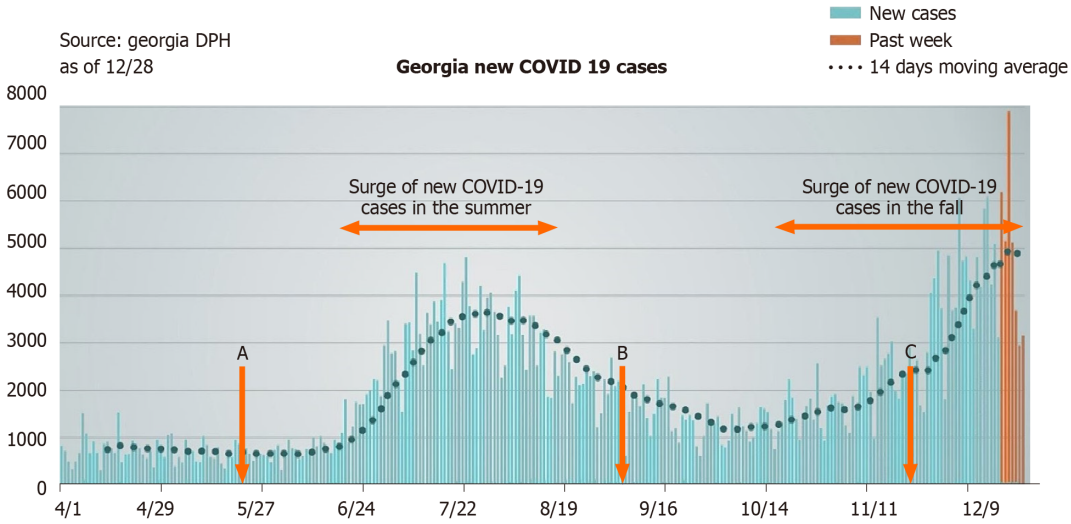

Figure 1 New coronavirus disease 2019 cases in Georgia State (April 1 – December 15, 2020). A: Memorial Day Holiday May 25, 2020; B: Labor Day Holiday September 7, 2020; C: Thanksgiving Holiday November 26, 2020.Cited: Georgia State Department of Health COVID-19 Daily Status Report. https://dph.georgia.gov/covid-19-daily-status-report. Accessed 12/28/2020. Figure reproduced with permission.

DISCUSSION

We observed increased ICU hospitalizations for COVID-19 associated respiratory failure requiring invasive mechanical ventilation corresponding to the surges of cases during the summer and fall of 2020 in Georgia. ICU hospitalizations during the reporting period were consistently guided by severity of symptoms, comorbidities, clinical and diagnostic findings, respiratory status, and indications for mechanical ventilation. Therefore, the higher ICU census noted during the surges likely reflects increased rates of COVID-19 prevalence in the community.

ICU mortality was 11% lower among patients in the fall cohort than those in the summer. Also, the length of time a patient spent on the mechanical ventilator and in the ICU were shorter during the fall when compared to the summer. These observed differences could be explained by a number of factors. First, patients in the fall cohort had a higher proportion of patients with no comorbidities at baseline and fewer patients relative to the summer cohort, with specific chronic medical problems such as DM, COPD and class 2 obesity or greater, which have been associated with severe COVID-19 course and poorer outcomes. Second, more patients in the fall surge received Food and Drug Administration (FDA)-approved and Centers for Disease Control and Prevention (CDC) recommended treatments, including dexamethasone and remdesivir, which have been shown to improve outcomes among COVID-19 patients. The Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial demonstrated a lower 28 d mortality among COVID-19 patients treated with

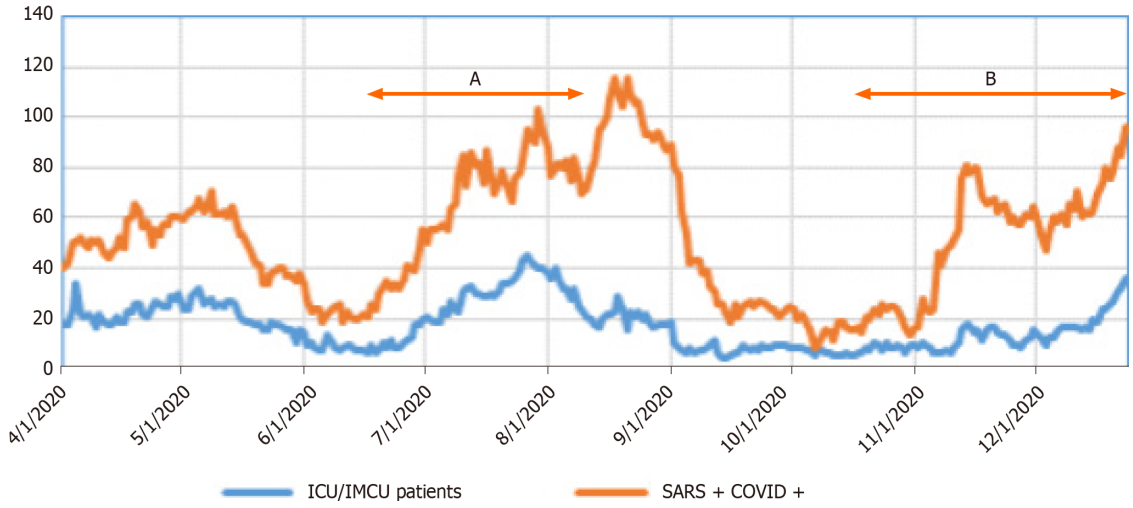

Figure 2 Daily hospital census of coronavirus disease-19 infected patients at Grady Memorial Hospital (April 1- December 15, 2020). A: Hospitalizations during the surge of new cases in the summer; B: Hospitalizations during the surge of new cases in the fall. ICU: Intensive care unit; MICU: Medical intensive care unit.

dexamethasone compared to placebo[7]. There is also evidence that remdesivir, when compared to placebo is associated with a shorter duration of mechanical ventilation or extracorporeal membrane oxygenation (ECMO) for COVID-19 respiratory failure[8]. Third, the improved outcomes likely mirror a combination of better understanding of COVID-19 pathophysiology, availability of novel therapies and better medical management.

It is not surprising that the summer and fall surges were preceded by major holidays as there have been numerous similar reports globally. Attending events that involve large gatherings typically seen during holidays increases the chances of COVID-19 infection[3]. For instance, the Lunar New Year holiday coincided with the start of the pandemic when millions of people left the city of Wuhan in China to visit relatives in other parts of the country and the world[9]. In the United Kingdom, the early COVID-19 epidemic followed a one-week school holiday break from February 17 to February 21, 2020 when thousands of people came back infected with SARS-CoV-2 virus from tourist activities in northern Italy and Spain[10]. Also, Canada reported its highest numbers of COVID-19 infection cases in the two weeks following the Thanksgiving holiday on October 12, 2020[2].

Our study has some limitations. First, this was a single center study with unique institutional practices and findings that may not be generalizable. Second, there are socio-behavioral and political circumstances that may have contributed to the surge of COVID-19 cases during the fall and summer seasons of 2020 that we could not measure in this study.

CONCLUSION

In this single-center study, we found significant differences in the sociodemographic, clinical characteristics, and outcomes among mechanically ventilated COVID-19 patients in the ICU during the 2020 summer surge compared to the fall surge. ICU mortality, LOS on mechanical ventilator, and LOS in the ICU were all significantly lower in the fall than summer. This finding is likely a result of our improved understanding of COVID-19 and advancement in management strategies.

ARTICLE HIGHLIGHTS

Research background

There is limited data on the difference in the clinical characteristics and outcomes of patients with severe coronavirus disease 2019 (COVID-19) infection in the summer compared to the fall surge.

Research motivation

Surges in COVID-19 cases are associated with increased hospitalizations including the intensive care units (ICU) placing significant strains on hospital resources. Knowledge about the differences in the clinical characteristics and outcomes between each surge will provide useful information on how to decrease related morbidity and mortality.

Research objectives

To compare the sociodemographic, clinical characteristics, and outcomes among mechanically ventilated patients with severe COVID-19 infection admitted to the (ICU) during the summer and fall surges in the year 2020.

Research methods

The authors included mechanically ventilated COVID-19 patients managed at Grady Memorial Hospital (GMH) from April 1 and December 31, 2020. Patients were categorized into two groups, those admitted in the summer (June 15, 2020 - August 15, 2020) and fall (October 15, 2020 - December 31, 2020). We compared patients' characteristics and outcomes using descriptive and inferential statistics.

Research results

A total of 220 patients were admitted to the GMH ICU and mechanically ventilated for COVID-19 (125 during the summer surge and 95 during the fall surge). Patients admitted in the fall had fewer comorbidities, lower mortality rate, shorter length of stay on the mechanical ventilator and shorter ICU length of stay.

Research conclusions

Patients admitted with severe COVID-19 infection requiring mechanical ventilation had better outcomes in the fall than in summer.

Research perspectives

Further studies are needed to replicate these findings.

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SYSTEMATIC REVIEWS

Management of genitourinary trauma – current evaluation from the Sub-Saharan region: A systematic review

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Abstract

BACKGROUND

Trauma is a major cause of morbidity globally and the sixth leading cause of death, accounting for 10% of all mortalities. The genitourinary trauma is estimated for approximately 10% of all patients presenting with trauma, and the kidney is the most injured genitourinary organ globally. However, there is a paucity of data on genitourinary injury from the Sub-Saharan, and there may be variations from common genitourinary organs injured in developed nations.

AIM

To provide insight on the epidemiology and management of genitourinary trauma in Sub-Saharan Africa with recommendations based on international guidelines.

METHODS

A thorough literature search of genitourinary trauma was conducted using PubMed, Google Scholar and African Journal Online.

RESULTS

A total of 30 studies from the Sub-Saharan region were eligible for the study and reviewed for epidemiology, biodata, types of injury, mechanisms of injury, treatment and follow-up. After evaluating 21904 patients presenting with urological emergencies, approximately 6.6% of cases were due to genitourinary trauma. The commonest injury was urethral 42.9% (22.2-62.2%) followed by injury to the external genitalia (penis, scrotum, testes) 25.1% (8.8-67.7%).

CONCLUSION

Genitourinary injury in Sub-Saharan Africa is underreported, and the presence of more trauma registries, trained urologists and trauma facilities could improve the overall standard of care as well as providing data for research and development in the field.

Specialty type: Urology and nephrology

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Key Words: Genitourinary trauma; Urethral injury; Sub-Saharan; Ureteric; Kidney

Core Tip: The genitourinary trauma accounts for about 10% of all patients presenting with trauma, and the kidney is the most injured genitourinary organ globally. In Sub-Saharan Africa, after evaluating 21904 patients presenting with urological emergencies, approximately 6.6% of cases were due to genitourinary trauma. The commonest injury was urethral injury followed by injury to the external genitalia (penis, scrotum, testes).

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INTRODUCTION

Trauma is a major cause of morbidity globally and the sixth leading cause of death, approximately 10% of all mortalities[1]. Trauma is most common in the ages between 15-45 years with a male predominance[2,3]. A global trauma morbidity and mortality study by James *et al*[4] reported that in 1990, there were about 4260493 injury deaths, which subsequently increased to 4484722 deaths in 2017. The increasing trauma burden is now of global concern making it a component of the Sustainable Development Goal to promote the well-being of all ages affected.

The genitourinary tract has continually been injured in about 10% of patients presenting with trauma[5]. Renal trauma is the most frequent injury occurring in about 5% of all traumatic injury and 10% of abdominal injuries[1]. A registry of 43000 trauma victims in France by Paparel *et al*[6] showed that the rate of genitourinary injury was 0.5%, with the kidney (43%) and testes (24%) most affected. Motor vehicle accidents account for more than 70% of blunt renal injuries.

Ureteral trauma is rare and occurs in less than 1% of all urological trauma[5]. A review of the National Trauma Data Bank in the United States revealed that ureteral injury is more common amongst the younger population usually due to penetrating trauma than blunt trauma[7]. About 88% of the penetrating trauma was due to gunshot wounds, while most blunt injuries were associated with motor vehicle accidents (50%)[5]. Nearly 91% of patients with ureteral injuries have associated injuries usually in the colon, appendix and small bowel[7,8]. The rate of iatrogenic injuries following gynecological procedures range from 0.2-7.3 per 1000 surgeries[9] with 80% involving the pelvic ureters.

The majority of bladder ruptures are extraperitoneal (70%) and associated with blunt trauma in 51%-86% of cases[5]. The rate of intraperitoneal bladder rupture is much lower at 17%-39%. Patients with bladder rupture are frequently diagnosed with pelvic fracture ranging from 35%-90%, which denotes a strong association between these injuries[10]. Penetrating bladder injuries are less common (14%-49%) and caused by gunshot wounds in about 88% of injuries[11].

Urethral injuries are rare and represent 4% of genitourinary trauma. Urethral injury is about 5 times more likely to occur in males than females[12]. Blunt trauma especially straddle type injury is more frequently associated with the anterior urethra, mainly the bulbar portion. Perhaps urethral catheterization could be the commonest cause of anterior urethral injury, but data is lacking to establish the exact incidence. Posterior urethral injuries associated with pelvic injury are the most common non-iatrogenic urethral injury in developed and industrialized countries[13].

Traumatic injury to the external genitalia is found in about 27%-68% of all patients with genitourinary trauma[5]. Blunt trauma accounts for 85% of scrotal and testicular injuries, and nearly 40%-60% of penetrating genitourinary injuries involves the penis, scrotum and testes. The rate of penile trauma ranges from 10%-16% of genitourinary injuries with penile fracture being even more underreported[14].

The epidemiology of genitourinary trauma is not well established in most parts of Sub-Saharan Africa due to the lack of trauma registries. Most reports are extrapolated from hospital-based data and does not reflect the true incidence. The rate of traumatic injuries to the genitourinary tract is expected to rise in Africa with the increase in motor vehicle accidents and gunshot wounds from civil or domestic conflicts.

This review has provided insight on the epidemiology and management of genitourinary trauma in Sub-Saharan Africa. Moreover, the standard management guidelines of genitourinary trauma have been summarized to identify the gaps in the standard of care.

MATERIALS AND METHODS

Search strategy

A thorough literature search of genitourinary trauma was conducted from 2000 to 2020 using the various search engines and databases (PubMed, Google Scholar, African Journal Online AJOL). The key search terms were "genitourinary trauma" and "traumatisme génito-urinaire." Each keyword was appended with the following indexes: guideline, Sub-Saharan Africa, Africa, Senegal, Mali, Cote d'Ivoire, Ghana, Nigeria, Kenya, Liberia, Tanzania and Burkina Faso.

Inclusion and exclusion

Duplicated articles on genitourinary trauma during the search were also excluded from the study. Other publications on genitourinary trauma from Europe, United States and Asia were excluded from the analysis and used for discussion in the background and main text. The American Urological Association guideline on urological trauma and the European Association of Urologists guideline on genitourinary trauma were summarized to provide clarity on the current standard of care in the discussion section. A total of 123 articles were retrieved after selection of relevant articles on genitourinary trauma. Both the French and English language text were considered for inclusion and only publications from the Sub-Saharan region were included for both quantitative and qualitative analysis.

Eligibility and data extraction

The title, abstract and full text of the retrieved literature were screened for eligibility. About 30 publications on genitourinary trauma from the Sub-Saharan region met the desired objective for synthesis. Published articles on genitourinary trauma, urological emergencies as well as urological complication from obstetric and gynecological surgeries were assessed for epidemiology, biodata, types of injury, mechanisms of injury, treatment and follow-up. A PRISMA flow chart is used to summarize the selection criteria as shown in Figure 1.

RESULTS

Epidemiology of genitourinary injuries in the Sub-Saharan region

A pool analysis of eight retrospective studies (Figure 2) from Senegal[15-17], Burkina Faso[18], Benin[19,20], Guinea[21], Nigeria[22-24] and Ivory Coast[25,26] evaluating 21904 patients presenting with urological emergencies revealed that approximately 6.6% of cases were due to genitourinary trauma. Further analysis of genitourinary trauma in the Sub-Saharan region showed that the rate of urethral injury[16,19,21,27,28] was the highest 42.9% (22.2%-62.2%) followed by injury to the external genitalia (penis, scrotum, testes) [15,16,19-21,24-28] at a rate of 25.1% (8.8%-67.7%). The results showed the incidence rate bladder injury[16,19-22,24-28] to be 18.2% (3.8%-38.5%), ureteric injury[19,20,27] 16.6% (15.7%-18%) and kidney injury[16,19,20-22,24-28] 8.6% (1.9%-14.1%).

Penile trauma, penile fracture and post circumcision injury

A pool analysis of six publications (Table 1) from the Sub-Saharan[29-34] region involving 98 patients with penile trauma showed that about 75.2% of penile trauma presented fracture of the tunica albuginea with or without concomitant urethral injury. The mean age was 36.5 years with range of 0.003-73 years. Other penile injuries included rupture of the penile dorsal vein[29], penile contusion[30], genital mutilation, post-circumcision injury and penile gunshot injury[32]. Patients presenting with

Table 1 Penile trauma, causes of injury, treatment and complications

Ref.	Country/Territory	No. of patients	Age range in yr	Mean age in yr	Penile injury	Causes of penile injury	Treatment	Complications
Sow *et al* [29]	Senegal	23	19-47	32.4	Fracture of tunica albuginea-82.6%; Fracture of tunica albuginea + partial urethral injury; Rupture of the penile dorsal vein	Sexual intercourse, masturbation, firearm, self-circumcision attempt	Evacuation of hematoma and repair of the albuginea	ED, coital penile pain, penile chordee
Paré *et al* [30]	Burkina	6	30-43	38.3	Fracture of tunica albuginea - 83.3%; Penile Contusion	Sexual intercourse	Evacuation of hematoma and repair of the albuginea	No ED
Odzébé *et al*[31]	Congo Brazzaville	09	25-73	46.3	Fracture of tunica albuginea	Sexual intercourse; Masturbation	Evacuation of hematoma and repair of the albuginea	ED; Penile chordee
Oranusi *et al*[32]	Nigeria	23	0.003-43	28.9	Penile fracture (34.8%) - (Sexual intercourse); Genital mutilation 26% (self-inflicted/assault); Post circumcision 13% (untrained nurses), Penile gunshot injury		Repair of albuginea, refashioning of residual penile stump, repair of albuginea	Not specified
Omisanjo *et al*[33]	Nigeria	15	23-56	35.2	Penile fracture 100% + concomitant urethral injury 26.7%	Sexual intercourse 66.7%; Rolling over erect penis 20% Masturbation 13%	Evacuation of hematoma and repair of the albuginea	ED 6.7%; Penile chordee 13.3%
Barry *et al* [34]	Guinea	22	22-51	37.8	Penile fracture 100%	Sexual intercourse 59.1%; Masturbation 31.8%; Rolling over erect penis 9.1%	Evacuation of hematoma and repair of the albuginea	No ED

ED: Erectile dysfunction.

genital mutilation were either self-inflicted or due to assault. In 2012, Orakwe *et al*[35] also reported three cases of genital mutilation caused by ritualistic attacks in Nigeria.

The commonest cause of penile fracture was sexual intercourse[29-34]. Other causes of penile fracture were masturbation[29,31-34] and rolling over an erect penis[33,34].

The management approach to the penile fracture was evacuation of the hematoma and repair of the tunica albuginea[29-34]. Few studies from Senegal, Congo and Nigeria reported a complications such as erectile dysfunction and abnormal penile curvature after albuginea repair for penile fracture[29-31,33,34].

A retrospective study of 23 patients by Oranusi *et al*[32] showed that post circumcision injury was seen in 13% of patients with penile trauma most of which was performed by untrained nurses. Another study by Appiah *et al*[36] in Ghana reviewing 72 patients with circumcision related injuries showed that urethrocutaneous fistula was the commonest injury (77.8%) followed by glans amputation (6.9%). The majority of these cases were operated during the neonatal period (94.7%), mostly by nurse practitioners (77.8%).

Urological complications of obstetrics and gynecology surgeries

A total of seven studies[37-43] were reviewed for urological complications of obstetric and gynecological operations involving 233 patients (Table 2). The mean age was 39.6 years with a range of 16-74 years. The ureters were the commonest urological organ injured (17.2%-87%)[37-43] followed by bladder injury (3.8%-28.6%)[37,39,41-43]. The ureters were frequently injured by either ligation, laceration or transection. The laterality of ureteric injury revealed left ureteric injury 34.1%, right ureteric injury 18.5% and bilateral ureteric injury 20.6%. Most of these injuries occurred following total abdominal hysterectomy 17.9% to 92.9% and to a lesser extent myomectomy, cesarean section and ovariectomy[37-43]. The distal ureters were the most commonly injured segment, as such a ureteroneocystostomy was performed more frequently (36.0%-81.3%). Other interventions included laceration repair, psoas hitch, Boari's flap, nephroureterectomy in patient with right colonic tumor and nephrectomy for non-functioning kidney.

Table 2 Urological complications of obstetrics and gynecology surgeries

Series	Country/territory	Patient population	Age range in yr	Mean age in yr	Urological injury	Causes of injury	Intervention
Papoola *et al* [37]	Nigeria	11	28-65	43.8	Ureteric injury (45.5%); Bladder injury (18.2%)	TAH-60%; Ovariectomy	UNC: 36%; Uretero-ureterostomy; Bladder repair; Catheter drainage
Kingsley *et al* [38]	Nigeria	20	N/A	34.5 ± 3.8	L. ureteric injury (50%); R. ureteric injury (21.4%); Bilateral (28.6%)	TAH-55%; Myomectomy, CS, excision of right colonic tumor	UNC: 67.8%; Psoas hitch, Boari's flap, TUU, R. Nephroureterectomy
Ekeke *et al*[39]	Nigeria	25/8270	24-62	38.4	L. ureteric injury (37.5%); R. ureteric injury (33.3%); Bilateral (29.2%); Bladder injury (28%)	TAH-48%, Subtotal H-16%, CS:12%, ovariectomy, VVF repair.	Ureteric laceration repair-40%, UNC: 44%, Boari's flap, bladder repair
Mensah *et al* [40]	Ghana	14	18-74	N/A	Bilateral ureteral injury	TAH-92.9%; VVF repair-7.1%	Dialysis-36%; UNC, deligation, psoas hitch, TUU
Sebukoto *et al* [41]	Tanzania	105/11219	N/A	N/A	Ureteral injury 17.2%; R. ureter 6.7%; L. ureter 4.8%; Bilateral 5.7%; Bladder injury 3.8%	C-Section 34.3%; TAH- 17.1%	
Chianakwana *et al*[42]	Nigeria	32	N/A	N/A	Ureteric injury 87%; Bladder injury 9.4%; Urethral Injury 2.1%	TAH, Myomectomy	UNC 81.3%; Bladder repair; Tube ureterostomy
Obarisiagbon *et al*[43]	Nigeria	16	16-50	41.5	Left ureter 44%;Right ureter 12.5%; Bilateral 18.8%; Bladder injury 25%	TAH 75%; C-section 31%	UNC 68.8%; Bladder repair; Conservative; Nephrectomy

L: Left; R: Right; N/A: Not available; CS: Cesarean section; TAH: Total abdominal hysterectomy; TUU: Transureteroureterostomy; UNC: Ureteroneocystostomy; VVF: Vesicovaginal fistula; H: Hysterectomy.

DISCUSSION

Overview

To date, some urological or surgical institutions have formulated guideline statements for the management of urogenital trauma including the American Urological Association, European Association of Urologists, World Society of Emergency Surgery and the American Association for the Surgery of Trauma[1-3]. The contemporary management of genitourinary trauma in Sub-Saharan Africa is extrapolated from these guidelines. It is therefore essential that insight into the diagnostic and management algorithm of genitourinary trauma is available to all urologists in the region.

Patients with genitourinary injuries should be approached systematically like all other trauma patients. The hemodynamic status, the mechanism of injury and associated injuries must be fully assessed to guide decision making[3]. The presence of hematuria, flank pain and lower ribs fracture should raise the index of renal trauma. Male patients with pelvic fracture associated with blood at the urethral meatus and high riding prostate may denote an associated urethral injury.

The exact incidence of urological injury in the Sub-Saharan region remains vague due to the lack of reporting and availability of trauma registry. Nevertheless, trauma represent a significant proportion of disease burden in the region. A pool analysis of 21904 patients presenting with urological emergencies from Senegal[15-17], Burkina Faso[18], Benin[19,20], Guinea[21], Nigeria[22-24] and Ivory Coast[25,26] revealed that approximately 6.6% of cases were due to genitourinary trauma. This finding is however lower than the global estimate of genitourinary injury at 10%. A 5-year audit of 527 deaths at a teaching hospital in Nigeria showed that trauma was the commonest cause of mortality (41.8%), and urological causes accounted for 6% of mortality[44].

Renal trauma

Adult and pediatric trauma patients presenting with gross or microscopic hematuria and decreasing systolic blood pressure require an enhanced intravenous contrast computed tomography (CT) scan with immediate and delayed images[1-3]. Imaging

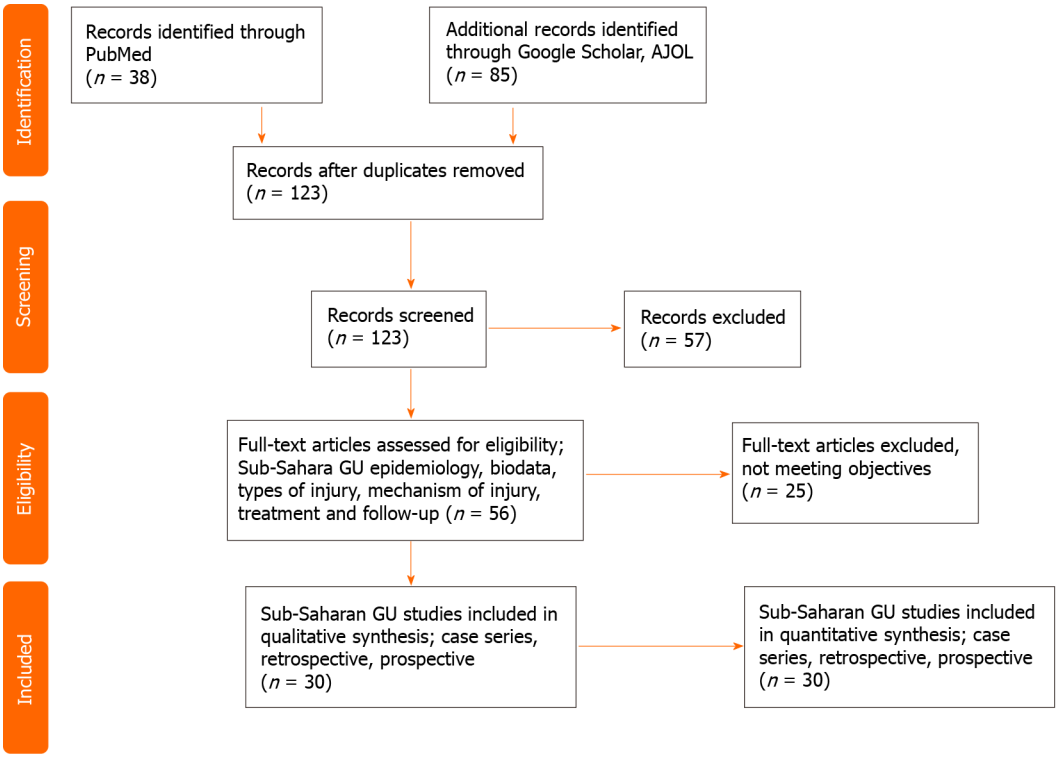

Figure 1 PRISMA chart shows eligibility of studies on genitourinary trauma in Sub-Saharan Africa. GU: Genitourinary; AJOL: African Journal Online.

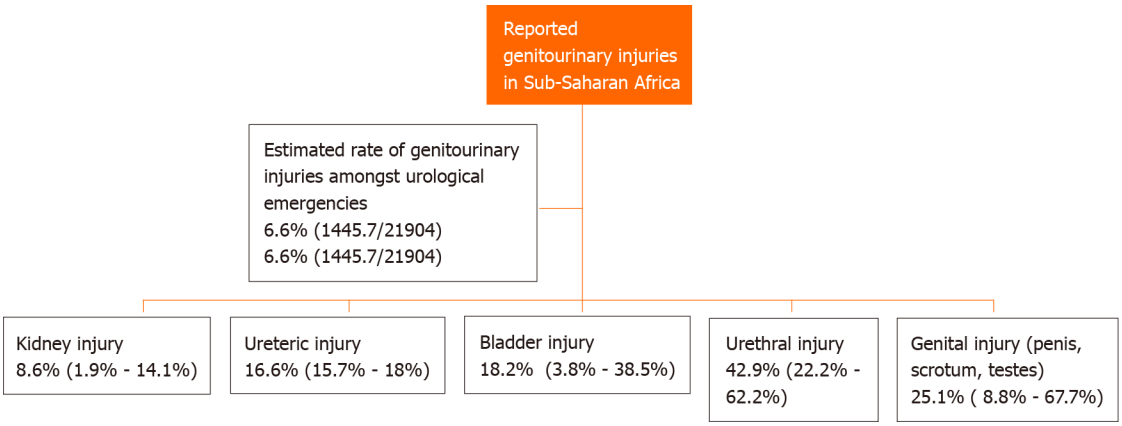

Figure 2 Flowchart of genitourinary injuries in the Sub-Saharan region.

will also be required for patients with significant blunt force to the flank, rib fracture, rapid deceleration and penetrating injury to the abdomen, flank or lower chest.

In stable patients with grade I-III renal injury (Table 3), expectant management is indicated. These include intensive care admission, bed rest, serial hematocrit and blood transfusion. These interventions lower the rate of nephrectomies and preserves renal function.

Patients who are hemodynamically unstable despite ongoing resuscitation suggest ongoing bleeding and will require immediate intervention. These patients can either benefit from surgery or angioembolization. The goal of surgery is to arrest further bleeding and repair the kidney if feasible. An on-table intravenous pyelogram is required to assess the function of the contralateral kidney as the possibility of nephrectomy is likely in most cases[1-3].

In centers with interventional radiologists, minimally invasive treatment like angioembolization of bleeding segment vessels is possible in selected patients.

A follow-up CT scan should be performed in patients with deep renal lacerations (American Association for the Surgery of Trauma Grade IV-V) (Table 3) undergoing

Table 3 Renal injury scale – American Association for Surgery of Trauma[3]

Grade	Type	Description
Grade (I)	Contusion	Gross or microscopic hematuria
	Hematoma	Non-expanding subcapsular hematoma, parenchyma spared
Grade (II)	Hematoma	Confined non-expanding perirenal hematoma
	Laceration	< 1 cm parenchymal tear without urine extravasation
Grade (III)	Laceration	> 1 cm parenchymal tear without urine leakage
Grade (IV)	Laceration	Parenchymal tear across the renal cortex, medulla and collecting system
	Vascular	Injury to major branch of renal artery or vein with contained hemorrhage
Grade (V)	Laceration	Kidney is completely shattered
	Vascular	Devascularized kidney from renal hilum avulsion

Citation: Coccolini F, Moore EE, Kluger Y, Biffl W, Leppaniemi A, Matsumura Y, Kim F, Peitzman AB, Fraga GP, Sartelli M, Ansaloni L, Augustin G, Kirkpatrick A, Abu-Zidan F, Wani I, Weber D, Pikoulis E, Larrea M, Arvieux C, Manchev V, Reva V, Coimbra R, Khokha V, Mefire AC, Ordonez C, Chiarugi M, Machado F, Sakakushev B, Matsumoto J, Maier R, di Carlo I, Catena F; WSES-AAST Expert Panel. Kidney and uro-trauma: WSES-AAST guidelines. World J Emerg Surg 2019; 14: 54. Copyright© The Authors 2019. Published by BMC. The authors have obtained the permission for table using from the BMC Publishing Group (Supplementary material).

observation who present with fever, worsening flank pain, falling hematocrit and abdominal distension. The risk of urinoma and hemorrhage is high in grade IV-V injury; as such, the rate of intervention is likely after 48 h[1]. Urinary drainage can be done using ureteral stent along with a percutaneous urinoma drain or percutaneous nephrostomy.

The rate of renal trauma in the Sub-Saharan Africa was approximately 8.6% with a range of 1.9%-14.1% from the review. A prospective study from Ofoha *et al*[28] in Nigeria evaluating 104 patients with genitourinary trauma showed that renal trauma accounted for 13.5% of urogenital trauma, and grade V renal injury was the commonest renal injury. About 80% of these cases required operative management with the rate of nephrectomy at 50%. A retrospective review of 86 patients with traumatic urological injury in Nigeria by Salako *et al*[22] found that the blunt trauma (57.1%) and motor vehicle accident (28.6%) were the commonest mechanisms of renal injury. Most of the patients in the study presented with total hematuria (78.6%) with associated injuries including intestinal perforation, spinal injury and limb fracture.

Ureteral trauma

In polytraumatized patients especially with visceral injuries, vascular injuries and complex pelvis or vertebral fractures, ureteral injury should be suspected[2]. The absence of hematuria does not rule out injury to the ureters. Therefore, stable patients not requiring exploratory laparotomy should undergo an intravenous contrast enhanced abdomino-pelvic CT scan with 10-min delayed images to assess for ureteral injury[1-3]. Contrast extravasation, absence of contrast distal to the suspected zone of injury and ipsilateral hydronephrosis are suggestive of ureteral injury.

Patients who proceed to laparotomy without preoperative imaging should have their ureters mobilized and inspected. Intra-ureteral dye using methylene blue can aid detection of the injured segment. Ureteral laceration discovered during laparotomy should be repaired in stable patients. Contused ureters should be managed with ureteral stenting or resection and primary repair in selected patients, particularly gunshot wounds[1,2]. Percutaneous nephrostomy and distal ligation of the injured ureter is a viable alternative following inability to stent especially for damage control in polytraumatized patients. Definitive repair is delayed until the patient is hemodynamically stable.

Females with ureterovaginal fistula from gynecological surgery or pelvic trauma can be initially managed with ureteral stent with a reported success rate of 64%[1,2]. Nevertheless, a ureteral reimplantation is necessary in the presence of stent failure. Ureteral reimplantation can be performed along with a Boari's flap, psoas hitch or a transureteroureterostomy with good outcome.

Ureteral injuries occurring proximal to the iliac vessels are best repaired using a tension free spatulated end to end ureteral anastomosis over a ureteral stent. If primary repair is not feasible, a ureteroneocystostomy is another option. A simple ureteroneocystostomy is a viable procedure for ureteral injury distal to the iliac vessels [1-3]. To allow tension free repair, other maneuvers to mobilize the bladder should be performed when necessary. When the ureter is injured during an endoscopic procedure, a ureteral stent should be placed with or without a periureteral drain followed by delay repair in some cases. If urine drainage is unsuccessful, an open or laparoscopic ureteral repair is indicated.

After analysis of the seven studies in the review, findings showed the ureters are commonly injured following gynecological procedures especially abdominal hysterectomy at a rate of 17.9% to 92.9%[37-43]. Retrospective analyses by Kingsley *et al*[38] and Ekeke *et al*[39] evaluating ureteral injuries after gynecological surgeries in Nigeria revealed that leakage of fluid per vagina or surgical site was the commonest presentation. Other recorded presentations were the presence of abdominal pain, abdominal distension and prolonged ileus. A series involving 14 patients with bilateral ureteral obstruction at a teaching hospital in Ghana by Mensah *et al*[40] showed that 81% of the patients presented with hydronephrosis with 36% requiring hemodialysis for severe hyperkalemia. All the injuries involved the distal third of the ureter. The surgeon's assessment of intraoperative conditions that might have contributed directly to the bilateral ureteric injury were excessive bleeding, distorted anatomy and adhesions. A retrospective review by Chianakwana *et al*[42] reporting ureteral injury following gynecological procedures mentioned that most of these operations were performed by senior registrars (43.8%) and general practitioners (43.8%) in peripheral hospitals.

Bladder trauma

Gross hematuria is a common sign of bladder injury. Patients presenting with gross hematuria and pelvic fracture is an absolute indication for bladder imaging using retrograde cystography to evaluate the presence of bladder injury[1-3]. Suprapubic pain, inability to void or low urine output are other indicators of a potential bladder rupture. Plain film cystography has similar sensitivity to CT cystography for assessing bladder rupture.

In the setting of blunt or penetrating trauma, intraperitoneal rupture must be repaired because it is unlikely to heal with catheter drainage alone[1-3]. Bacterial translocation leading to sepsis and peritonitis is the end result if intraperitoneal bladder rupture is left untreated. A follow-up cystography is required to assess for healing in complex repair.

Uncomplicated extraperitoneal rupture are drained using a urethral catheter for 2-3 wk to allow bladder healing. A follow-up cystography is essential to assess for bladder healing. Complicated extraperitoneal bladder injury with bony spicules, concurrent rectal/vaginal injury or bladder neck injury are best managed with primary repair during the repair of other injuries[1,2].

A quantitative analysis of 13 studies evaluating genitourinary trauma[16,19-22,24-28] in the Sub-Saharan region showed the incidence rate of bladder injury to be 18.2% (3.8%-38.5%). Another report from the Sub-Saharan region revealed blunt trauma from motor vehicle accidents was the most frequent mechanism of injury causing more intraperitoneal bladder rupture (26.1%) than extraperitoneal bladder rupture (21.7%) [22]. The presence of hematuria, abdominal distension, cystography and/or cystoscopy were used to diagnose bladder injury in the study[22].

A prospective study by Ofoha *et al*[28] in evaluating 104 patients with genitourinary trauma in Nigeria showed that 24% of patient had bladder injury. Intraperitoneal bladder rupture was more common at 64% compared to extraperitoneal rupture at 24%. The fact that gunshot and motor vehicle accident were the commonest mechanism of injury in this study explains the predominance of intraperitoneal rupture.

Urethral trauma

Trauma patients presenting with blood at the urethral meatus should be offered prompt retrograde urethrogram to assess for partial or complete urethral disruption[1-3]. Blind catherization should be avoided in this setting or limited to single attempt by an experienced practitioner. In the presence of pelvic fracture urethral injury, a suprapubic catheter should be placed to establish proper drainage[1-3]. A good communication should be maintained between the urologist and orthopedics desiring open reduction and internal fixation to reduce the risk of plate infection from adjacent suprapubic tube. In patients who are hemodynamically stable, an endoscopic realignment can be attempted. However, prolonged attempts at realignment in the

emergency setting only aggravate the risk of developing urethral stricture. Pelvic fracture urethral injury is associate with a high rate of urethral stricture, erectile dysfunction and urinary incontinence[1,2]. Therefore, these patients have to be followed over a year as most will require urethroplasty or endoscopic treatment with direct vision urethrotomy. Stable patients presenting with uncomplicated penetrating injury of the anterior urethra can undergo spatulated primary urethral repair. In the setting of extensive tissue destruction, a delayed repair should be offered. Patients with blunt trauma to the bulbar urethral from straddle injury should receive suprapubic catheter for urinary diversion. The rate of subsequent urethral stricture is high after straddle injury. Therefore, close monitoring using cystoscopy, uroflowmetry and retrograde urethrogram is essential for management[1-3].

The analyzed data from this review[16,19,21,27,28] showed that urethral trauma was the most frequent injury of the genitourinary system in the Sub-Saharan region at a rate of 42.9% (22.2%-62.2%). A report from a teaching hospital in Cotonou Benin assessing 32 patients with genitourinary trauma by Ouattara *et al*[20] showed that urethral rupture accounted for 50% of external genital injury. As such, acute urinary retention (42.1%) and urethrorrhagia (13.2%) were common presentations. Data from a teaching hospital in Nigeria assessing 104 patients with genitourinary trauma reported a high rate of urethral injury with 92% of patients receiving suprapubic urinary diversion and deferred urethroplasty[28].

Genital trauma

Penile fracture should be suspected when a patient presents with a history of penile snapping, swelling and ecchymosis during a sexual intercourse/manipulation followed by immediate detumescence[1-3]. Penile fracture can be diagnosed by history and physical exam alone. However, in equivocal cases, ultrasound can be done to evaluate penile fracture, which is cheaper and readily available. Magnetic resonance imaging should be reserved for cases with ambiguous sonographic findings[1,2]. Patients with penile fracture, blood at the urethral meatus and inability to void should be assessed for concomitant urethral injury using either urethroscopy or retrograde urethrogram. All cases of penile fracture should be repaired at presentation. The injured corpus cavernous should be properly exposed, and the tunica is repaired using absorbable sutures[1]. Early repair is associated with better outcome.

Patients presenting with scrotal swelling, scrotal ecchymosis and inability to identify the testicular contour on physical exam following a blunt or penetrating trauma should undergo scrotal exploration. Moderate debridement of devitalized tissues and tunica closure or orchidectomy for non-salvageable testes are options based on intraoperative findings[1,2]. Reconstructive techniques for extensive genital wounds include advancement flaps, pedicle flaps or skin graft.

Individuals with traumatic penile amputation will require urgent penile replantation. The amputated segment can be wrapped in a saline soaked gauze in a bag and placed in a separate ice bag. The urologist should perform a macroscopic repair with re-anastomosis of the corporal bodies, spatulated urethral repair and penile skin repair [1,2]. A vascular surgeon should be consulted for a microvascular repair of the dorsal veins, dorsal arteries and nerves[1].

Genital injuries often leave patients with scarred or poorly functional genitalia. The social and emotional intimacy of these patients are too frequently deterred by these injuries. It is always prudent to involve psychological and reproductive counseling for affected individuals.

The rate of external genital injury (penis, scrotum, testes) in the Sub-Saharan region [15,16,19-21,24-28] was also found to be relatively high at a rate of 25.1% (8.8%-67.7%). Data from a pool analysis of penile trauma in Sub-Saharan Africa[29-34] showed that about 75.2% of penile trauma were penile fracture (fracture of the tunica albuginea) with or without concomitant urethral injury. Most of these injuries had optimal outcomes with early repair. The review has also shown that post-circumcision injury is currently rising especially when these procedures are being performed in the neonatal period by untrained nurses. Circumcision is a delicate procedure that is mistaken by most health practitioners as minor. The anatomy of the genitals in neonates is delicate and as such should be handled by trained health practitioners preferably urologists. The lack of specialists in most Sub-Saharan settings compels mid-level health workers to assume major operative roles.

CONCLUSION

The management of genitourinary injury is challenging. The choice of conservative or operative management for genitourinary trauma is crucial for optimal outcome especially in renal injury. Prompt repair of external genital injuries can produce satisfactory results. However, patients should be counseled about the possibility of sexual dysfunction. Genitourinary injury in Sub-Saharan Africa is underreported. The presence of more trauma registries, trained urologists and trauma facilities can improve the overall standard of care and provide data for research and development in the field.

ARTICLE HIGHLIGHTS

Research background

The research tends to highlight the burden of genitourinary injury in the Sub-Saharan region and the differences in the injury pattern from developed nations.

Research motivation

Due to paucity of information and publication on urological injuries in the Sub-Saharan nations, it was essential to review and synthesize the available data in the region.

Research objectives

The manuscript has provided insight into management challenges of genitourinary trauma in developing nations of Africa and summarized the available international guidelines to identify progress and gaps in the region.

Research methods

This research is a systematic review in accordance with the PRISMA guideline.

Research results

Amongst urological emergencies, genitourinary trauma accounted for 6.6% of cases. Urethral injury and injury to the external genitalia accounted for most of the trauma burden as compared to renal injury in developed nations.

Research conclusions

A trauma registry is necessary to promote research and improvement in trauma care. Prompt repair of injuries to the external genitalia has shown satisfactory results.

Research perspectives

The manuscript has highlighted the paucity of data on genitourinary trauma in Sub-Saharan Africa. The research intends to project the need for investment in trauma care and to establish trauma registries around the continent.

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META-ANALYSIS

Recovery after acute kidney injury requiring kidney replacement therapy in patients with left ventricular assist device: A meta-analysis

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Abstract

BACKGROUND

Acute kidney injury (AKI) is a common and severe complication after left ventricular assist device (LVAD) implantation with an incidence of 37%; 13% of which require kidney replacement therapy (KRT). Severe AKI requiring KRT (AKI-KRT) in LVAD patients is associated with high short and long-term mortality compared with AKI without KRT. While kidney function recovery is associated with better outcomes, its incidence is unclear among LVAD patients with severe AKI requiring KRT.

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AIM

To identify studies evaluating the recovery rates from severe AKI-KRT after LVAD placement, which is defined by regained kidney function resulting in the discontinuation of KRT. Random-effects and generic inverse variance method of DerSimonian-Laird were used to combine the effect estimates obtained from individual studies.

METHODS

A total of 268 patients from 14 cohort studies that reported severe AKI-KRT after LVAD were included. Follow-up time ranged anywhere from two weeks of LVAD implantation to 12 mo. Kidney recovery occurred in 78% of enrollees at the time of hospital discharge or within 30 d. Overall, the pooled estimated AKI recovery rate among patients with severe AKI-KRT was 50.5% (95%CI: 34.0%-67.0%) at 12 mo follow up. Majority (85%) of patients used continuous-flow LVAD. While the data on pulsatile-flow LVAD was limited, subgroup analysis of continuous-flow LVAD demonstrated that pooled estimated AKI recovery rate among patients with severe AKI-KRT was 52.1% (95%CI: 36.8%-67.0%). Meta-regression analysis did not show a significant association between study year and AKI recovery rate (P = 0.08). There was no publication bias as assessed by the funnel plot and Egger's regression asymmetry test in all analyses.

RESULTS

A total of 268 patients from 14 cohort studies that reported severe AKI-KRT after LVAD were included. Follow-up time ranged anywhere from two weeks of LVAD implantation to 12 mo. Kidney recovery occurred in 78% of enrollees at the time of hospital discharge or within 30 d. Overall, the pooled estimated AKI recovery rate among patients with severe AKI-KRT was 50.5% (95%CI: 34.0%-67.0%) at 12 mo follow up. Majority (85%) of patients used continuous-flow LVAD. While the data on pulsatile-flow LVAD was limited, subgroup analysis of continuous-flow LVAD demonstrated that pooled estimated AKI recovery rate among patients with severe AKI-KRT was 52.1% (95%CI: 36.8%-67.0%). Meta-regression analysis did not show a significant association between study year and AKI recovery rate (P = 0.08). There was no publication bias as assessed by the funnel plot and Egger's regression asymmetry test in all analyses.

CONCLUSION

Recovery from severe AKI-KRT after LVAD occurs approximately 50.5%, and it has not significantly changed over the years despite advances in medicine.

Key Words: Acute kidney injury; Kidney recovery; Kidney replacement therapy; Left ventricular assist devices

Core Tip: Left ventricular assist devices (LVAD) are mechanical support tools that augment cardiac output and improve kidney perfusion. Acute Kidney Injury (AKI) is a common complication after LVAD implantation. High short- and long-term mortality is associated with severe AKI requiring Kidney replacement therapy (KRT) in LVAD patients compared with those without KRT. While kidney function recovery is associated with better outcomes, the recovery rate is unclear among LVAD patients with severe AKI requiring KRT. To investigate this further, we conducted the current systematic review and meta-analysis evaluating kidney recovery rate after AKI-KRT among LVAD patients. We report that the pooled estimated AKI recovery rate among patients with severe AKI-KRT was 50.5% (95%CI: 34.0%-67.0%) at 12 mo follow up.

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INTRODUCTION

Heart transplantation remains the treatment of choice for patients with severe end-stage heart failure. Deteriorating kidney function is commonly noted among advanced heart failure patients secondary to cardiorenal physiology and is associated with unfavorable outcomes[1-4]. Left ventricular assist devices (LVAD) are mechanical support tools that augment cardiac output by unloading the left ventricle and improving kidney perfusion. LVAD is used as a bridge to transplantation for patients on the transplant list or destination therapy for individuals who are not ideal transplant candidates[5].

Even though kidney perfusion improves in most patients, acute kidney injury (AKI) is a common and severe complication following LVAD implantation with an incidence of 37%[6]. About one-third of them (13%) sustain severe AKI post LVAD placement needing kidney replacement therapy (KRT)[6]. As reported in previous studies, severe AKI-KRT in LVAD patients is associated with high short and long-term mortality compared to those without KRT[7]. Risk factors associated with increased risk of AKI post LVAD insertion include older age, use of intra-aortic balloon pump (IABP), lower mean total protein and albumin levels, post-implantation shock, elevated central venous pressure > 16 mmHg, longer cardiopulmonary bypass times, postoperative right ventricular failure and preexisting chronic kidney disease before implantation[8-10].

Kidney recovery is defined as independence from KRT in AKI-KRT patients within fourteen d of the initial injury [11]. In a study by Grinstein *et al*[12], early kidney improvement is defined as an increase in eGFR ≥ 15% within one week of LVAD implantation. In a recent prospective, multicenter assessment, serial evaluation, and subsequent sequelae (ASSESS-AKI) cohort study by Bhatraju *et al*[13] evaluating the incidence and progression of chronic kidney disease (CKD) and dialysis in patients who sustained AKI episodes as compared to patients without AKI, a 2- and 3-fold higher risk of major kidney adverse effects were reported among those with resolving and non-resolving AKI, respectively, as compared to patients without AKI. Additionally, patients with non-resolving AKI had higher De Novo and progressive CKD rates than no AKI and resolving AKI.

Early improvement in kidney function in patients with AKI after LVAD placement is associated with decreased length of stay and fewer complications [14]. Kidney recovery is associated with a favorable prognosis in estimating postoperative kidney function in adults and children undergoing LVAD placement [15]. While recovery of kidney function is associated with better outcomes, kidney recovery rates among LVAD patients with severe AKI-KRT are unknown. We, therefore, conducted the current metanalysis to report the incidence of kidney recovery among patients needing KRT post LVAD implantation at 30 d or at the time of discharge and up to 12 mo.

MATERIALS AND METHODS

Search strategy

This manuscript follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis)[16] statement and MOOSE (Meta-analysis of Observational Studies in Epidemiology)[17] guidelines. A systematic search was conducted through the Ovid MEDLINE, EMBASE, and Cochrane Library from database inception to January 2020 using the following search terms: ('left ventricular assist device' OR 'lvad' OR 'ventricular assist device') AND ('acute kidney failure' OR 'acute kidney injury' OR 'renal replacement therapy' OR dialysis). The detailed search strategy for each database is summarized in Supplementary material. No language restrictions were applied.

Inclusion criteria

The following inclusion criteria determined the eligibility of each article, including: (1) The nature of the study is observational or conference abstract; (2) Study population consisted of patients with LVAD; and (3) The rates of kidney recovery after AKI episode among patients after LVAD placement is considered one of the outcomes of

interest. Exclusion criteria consisted of pediatric patients, case series, and studies that did not mention outcomes of interest. Study eligibility was independently evaluated by two investigators (Kovvuru K and Kanduri SR). Any disagreements were resolved by mutual consensus. The quality of each study was appraised using the Newcastle–Ottawa quality scale[18], which assesses six components, including: (1) Representativeness of the subjects; (2) Ascertainment of the exposure; (3) Demonstration of the outcome of interest was not present at the start of the study; (4) Assessment of outcome; (5) Follow-up duration period was long enough for an outcome to occur; and (6) Adequate follow-up duration.

Review process and data extraction

The titles and abstracts of all identified studies were screened (Kovvuru K and Kanduri SR) before a full-text review. The full-text of the screened articles was reviewed to determine their eligibility. We created a standardized data collection form to extract the relevant information from the included studies, including the first author's name, year of publication, country of origin, study design, sample size, AKI definition, number of patients with AKI, rate of kidney recovery, duration of follow up. Kidney recovery was defined as independence from dialysis after an episode of severe AKI.

Measurements

The rates of kidney recovery among patients with severe AKI-KRT and kidney recovery rates among the subgroup of patients with continuous-flow devices entered the meta-analysis. The results were reported in percentage along with 95% confidence interval (CI). A Forest plot of each analysis was created. Results were presented in percentage for categorical data and in mean ± SD or median (interquartile range) for continuous data.

Evaluation of publication bias

Publication bias was evaluated by funnel plot (if the total number of studies was > 10 [18] and Egger's regression intercept. An intercept P value of less than 0.05 was considered significant for potential publication bias.

Statistical analysis

All statistical analyses were performed by the Comprehensive Meta-analysis version 3 software (Eaglewood, NJ, United States). Statistical heterogeneity of the included studies was assessed using Cochran's Q-test and I^2 statistics. An I^2 value of ≤ 25% represents insignificant heterogeneity, 25%-50% represents low heterogeneity, 50%-75% represents moderate heterogeneity, and > 75% represents high heterogeneity. For analyses with I^2 > 50%, the results were analyzed by the random-effects model to minimize the heterogeneity and external variance[20]. A P value of less than 0.05 represents statistical significance.

RESULTS

Study characteristics

A total of 14 studies[7,8,21-31], consisting of 268 subjects, were included in the current meta-analysis. Figure 1 provides a flowchart of the literature search and study selection for this analysis. Included studies were published from 2000 to 2019. The study designs included retrospective and prospective cohort studies. The total duration of follow-up was anywhere from 2 wk to 12 mo. Table 1 illustrates study characteristics and kidney recovery rates among patients included in this systematic review.

Asleh *et al*[30] reported among patients requiring KRT after LVAD placement, one-third had kidney recovery, one-third required outpatient hemodialysis, and one-third of the patients died before hospital discharge. In study by Borgi *et al*[7] patients with post LVAD AKI were more likely to suffer longer hospital stay (32.4 *vs* 18.7; P = 0.05), right ventricular (RV) failure (25% *vs* 5.6%; P = 0.01) and a higher mortality rate as compared to non-AKI groups at 30-day (17.9% *vs* 0%; P < 0.001), 180-day (28.6% *vs* 2.8%; P < 0.001), and 360- day (28.6% *vs* 6.9%; P = 0.012), respectively. In a study by Demirozu *et al*[21], patients with sustained clinical recovery after LVAD eventually had kidney recovery. Muslem *et al*[32] evaluated long-term mortality after LVAD placement and reported that severe AKI (*i.e.*, stages 2 and 3) was associated with

Table 1 Study characteristics and outcomes included in the systematic review

Study	Year	Country	Patients	AKI definition	No of patients with AKI	Rate of kidney recovery
Kaltenmaier *et al*[31]	2000	Germany	LVAD-implantation during 1988-1995; Pulsatile Berlin Heart System HeartMate 2000, Novacor.	KRT	55	3/55 = 6%; Kidney recovery at hospital discharge
Demirozu *et al* [21]	2011	United States	LVAD implantation during 2003-2009; Continuous HeartMate II	KRT	15	10/15 = 67%; Kidney recovery at 7 mo
Hasin *et al*[8]	2012	United States	LVAD from 2007 to 2010; Continuous HeartMate II	KRT	8	2/8 = 25%; Kidney recovery at 6 mo
Popov *et al*[22]	2012	United Kingdom	Patient with end-stage heart failure underwent LVAD implantation-2007-2011; Continuous Heart Ware	KRT	12	10/12 = 83%; Kidney recovery post-op/
Borgi *et al*[7]	2013	United States	End-stage heart failure LVAD during 2006-2011; Continuous HeartMate II; Heart Ware	AKI (KDIGO); KRT	28; 9	17/28 = 60%; Kidney recovery one month; 4/9 = 44.5%; Kidney recovery after KRT--one month
Sumida *et al*[23]	2014	Japan	LVAD implantation during 2011-2013; LVAD type not specified	AKI; KDIGO; KRT	11; 6	11/11 = 100%; Kidney recovery at Hospital discharge; 4/6 = 66.6%; Kidney recovery after KRT at hospital discharge
Deschika *et al* [24]	2016	Germany	LVAD recipients with pre-operative biventricular impairment who received an additionally RVAD	KRT	9	9/9 = 100%; Kidney recovery at hospital discharge
Shebab *et al*[25]	2016	Australia	Dilated cardiomyopathy and severe biventricular failure -underwent dual HVAD implantation as a bridge to transplant during 2011-2014; Continuous Heart Ware	KRT	4	3/4 = 75%; Kidney recovery at post-op
Nadziakiewicz *et al*[26]	2016	Portland	Patients with end-stage heart failure underwent LVAD implantation during 2007-2014; Continuous Heart ware, HeartMate II	KRT	7	5/7 = 72%; Kidney recovery after KRT- 2 weeks
Raichlin *et al*[27]	2016	United States	End-stage heart failure with preexisting kidney dysfunction underwent LVAD implantation - 2009-2014; Continuous HeartMate II	KRT	15	6/15 = 40%; Kidney recovery after KRT -one month
Muslem *et al*[32]	2018	Netherlands, United States	LVAD implantation during 2004-2015; Continuous Heart ware, HeartMate II	KRT	23	14/23 = 61%; Kidney recovery after KRT at one year
Schmack *et al* [28]	2018	Germany	End-stage heart failure patients underwent LVAD from 2010 to 2017; Continuous Heart Ware	KRT	32	5/32 = 16%; Kidney recovery one-month post-KRT
Shebab *et al*[29]	2018	Australia	LVAD implantation as a bridge to transplant from 2007 to 2016; Continuous Heart Ware	KRT	19	15/19 = 79%; Kidney recovery after KRT Post-op
Asleh *et al*[30]	2019	United States	LVAD implantation during 2007-2017; ContinuousHeartMate II; HeartMate III; Heart Ware	KRT	54	18/54 = 33%; Kidney recovery at hospital discharge

AKI: Acute kidney injury; KDIGO: Kidney Disease Improving Global Outcomes; N/A: Not available; KRT: Kidney replacement therapy; LVAD: Left ventricular assist device.

higher mortality (hazard ratio 2.2, [95%CI: 1.1 to 4.5], $P = 0.027$) at one year. Schmack *et al*[28] reported higher pre-operative blood urea nitrogen (BUN) and low albumin levels as strong predictors of the need for kidney replacement therapy post LVAD implantation.

Additionally, they reported a negative association between postoperative hemodialysis and short-term survival. Sumida *et al*[23] reported plasma NGAL levels perioperatively could help predict severe AKI-KRT, while lower NGAL levels were associated with kidney recovery in patients after LVAD implantation.

Rates of Kidney Recovery from severe Acute Kidney Injury after LVAD

78.5% of patients had kidney recovery occurred at the time of hospital discharge or within 30 d. Overall, the pooled estimated rates of AKI recovery among patients with severe AKI-KRT was 50.5% (95%CI: 34.0%-67.0%) (Figure 2) and did not significantly change over the years despite advances in medicine. Meta-regression analysis did not

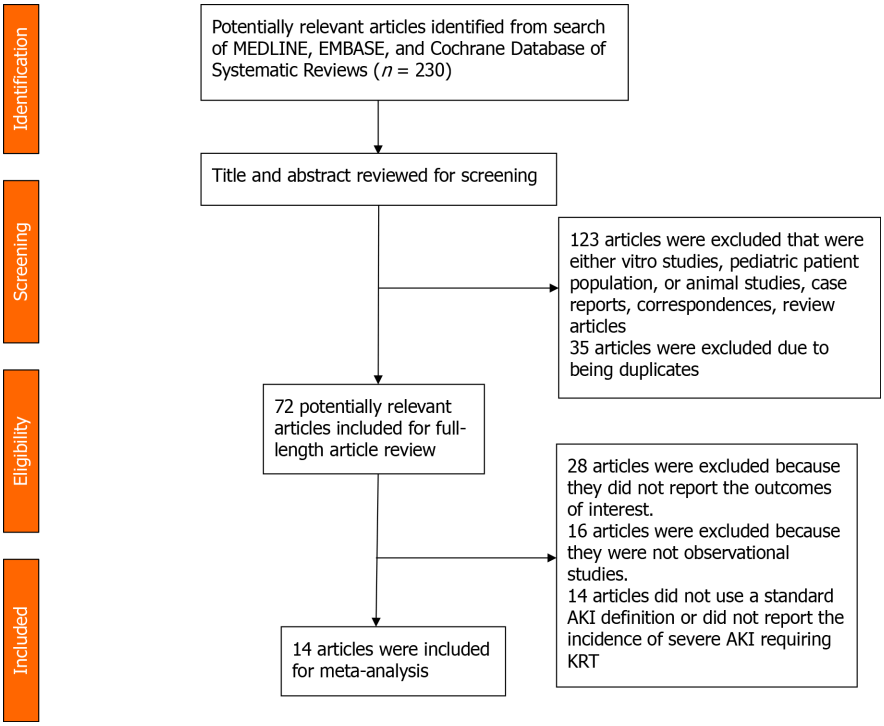

Figure 1 This picture provides a flowchart of the literature search and study selection for this analysis.

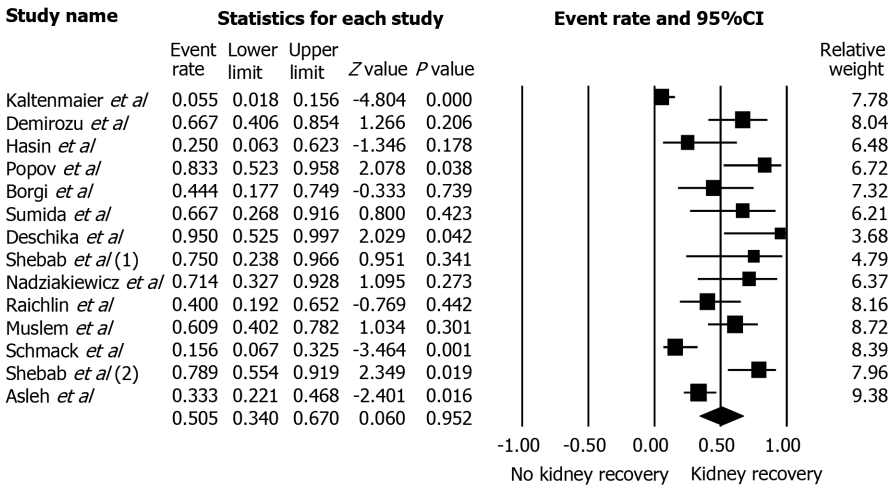

Figure 2 Kidney recovery of acute kidney injury kidney replacement therapy after left ventricular assist device placement.

demonstrate a significant association between study year and AKI recovery rate (P = 0.08).

Rates of kidney recovery from severe AKI among continuous flow LVAD

The data on pulsatile-flow LVAD were limited, as the majority (85%) of patients used continuous-flow LVAD. Subgroup analysis of continuous-flow LVAD demonstrated the pooled estimated rates of AKI recovery among patients with severe AKI-KRT was 52.1% (95%CI: 36.8%-67.0%) (Figure 3).

Evaluation for publication bias

Funnel plots (Figure 4) and Egger's regression asymmetry tests were performed to assess publication bias in analysis evaluating the rate of AKI recovery. No significant publication bias in the meta-analysis evaluating rates of AKI recovery among patients with AKI (P = 0.17) was evident.

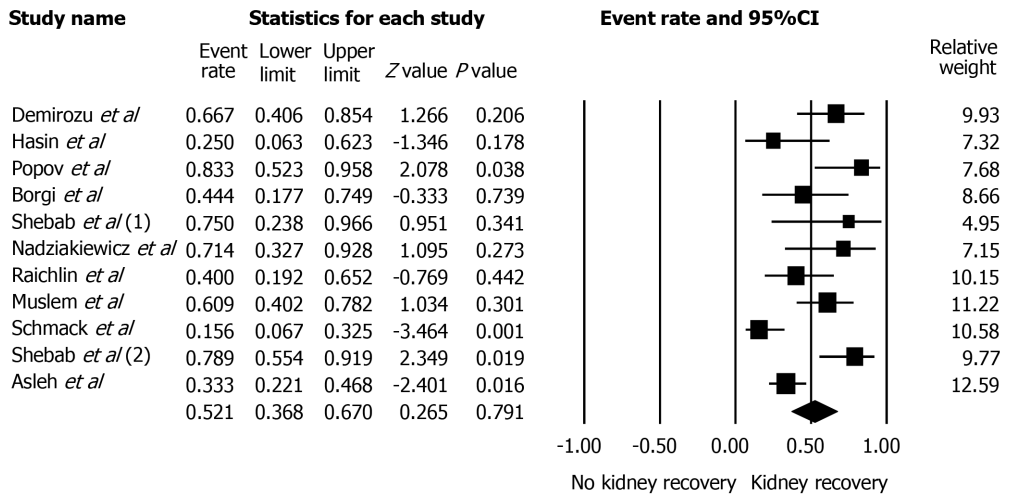

Figure 3 Subgroup analysis of kidney recovery of acute kidney injury kidney replacement therapy after continuous-flow left ventricular assist device.

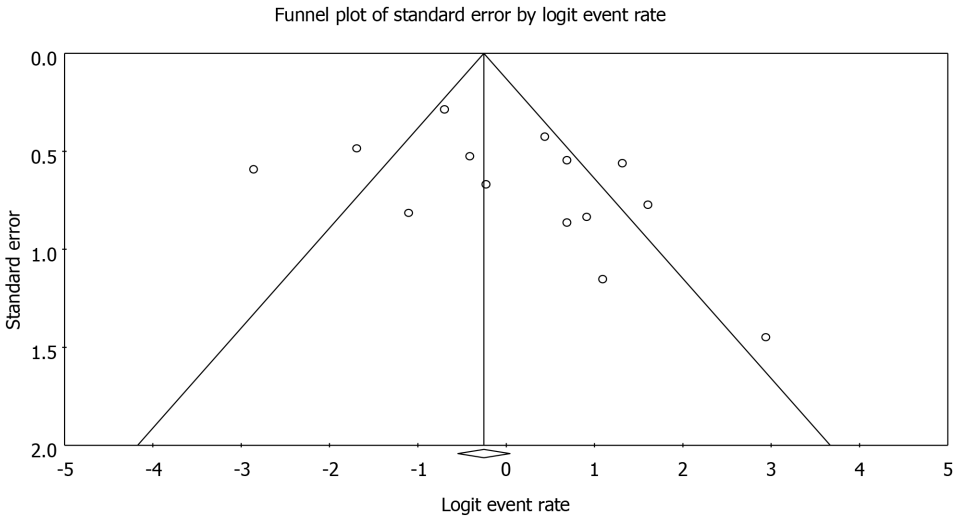

Figure 4 Funnel Plot of kidney recovery of acute kidney injury kidney replacement therapy after left ventricular assist device placement.

DISCUSSION

Our analysis included 14 cohort studies that defined severe AKI as needing KRT(AKI-KRT). Kidney recovery occurred in 78.5% of patients at the time of hospital discharge or within 30 d of LVAD implantation. The initial improvement in kidney function could be secondary to hemodynamic stabilization, cardiac output optimization, and reduction in kidney venous pressures. The subsequent rise in cardiac output facilitates kidney perfusions and glomerular filtration rates (GFR)[33].

In our analysis, kidney function recovery occurred in about half of individuals with AKI-KRT. Even though 70% had initial kidney recovery within 30 d of LVAD initiation, kidney recovery rates when followed for up to 12 mo were only 50%. This observation is consistent with previous studies demonstrating a sustained and gradual decline in GFR at long-term follow-up. As evidenced by Brisco *et al*[34], even though half of the patients had initial improvement in GFR after one month of LVAD implantation, a significant decline in GFR was noted at one year. Similar findings were also reported by Hasin *et al*[8] with initial improvement in GFR at one month followed by an eventual decline at 3 and 6 mo, respectively.

The potential mechanisms for the eventual decline in kidney functions are multifactorial. Chronic hemolysis is caused by shear stress leading to red blood cell breakdown and pigment nephropathy[35]. Subsequent development of right ventricular failure after LVAD placement could contribute to a decline in kidney functions. Additionally, GFR could be overestimated post LVAD implantation

secondary to reduced creatinine generation from sarcopenia and volume overload. Cystatin-based calculations of kidney clearances can be used to provide better insight into kidney functions [36].

Lack of pulsatility among continuous flow devices could lead to structural changes in the arterial system, perpetuating aortic wall stiffness. Animal studies demonstrated periarteritis and subsequent inflammation with continuous-flow devices, potentiating increased AKI risk[37]. However, the previous metanalysis reported almost similar AKI rates among patients with continuous and pulsatile flow devices[6]. Subgroup analysis on continuous-flow LVAD revealed pooled incidence of kidney recovery after AKI episode leading to KRT independence was 52%. Given limited data, we could not analyze kidney recovery among AKI-KRT with pulsatile flow LVAD. However, we hypothesize that recovery rates after AKI-KRT among patients with pulsatile flow LVAD could be similar to continuous flow devices given similar AKI rates.

Another interesting observation in our analysis is pooled incidence of kidney recovery from KRT is 50%, which is reassuring compared to kidney recovery rates of other cohorts like hematopoietic stem cell transplant (HSCT). The pooled estimated kidney recovery rates after severe AKI-KRT at 100 d among the HSCT cohort are as low as 10%[38]. This difference could be secondary to multiple factors as patients after HSCT are much sicker from underlying terminal cancer and exposed to high-dose chemotherapy or radiation. However, the HSCT cohort was followed for only 100 d, and unclear if long-term follow-up would generate encouraging results.

Few measures to enhance kidney recovery during the post-AKI/acute kidney disease (AKD) phase include medication reconciliation, avoidance of nephrotoxic drugs, avoiding supra therapeutic vancomycin levels, and contrast agents. Meticulous care should be taken to minimize hypotension during dialysis sessions[39]. Adequate catheter care education should be provided to patients and families at discharge and as an outpatient. Patients should be well informed of blood pressure goals, diuretics, bodyweight targets, and sick day protocol during the recovery period. The severity of kidney disease should be considered while managing AKI patients after LVAD, especially those requiring KRT[40]. An algorithmic approach should be protocolized in implementing diagnostic and therapeutic interventions to facilitate rapid and complete kidney function recovery.

Our study has few strengths. This is the first study analyzing kidney recovery rates after severe AKI-KRT among patients with LVAD implantation. We report that about half of the patients, when followed closely, have dialysis independence after LVAD. To mention few limitations, the cohort studies included in our analysis might not identify a causal relationship between patients with AKI-KRT and kidney recovery rates. However, they report associations between the two variables. The overall analysis showed significant statistical heterogeneity questioning the validity of included studies. However, we found similar rates of kidney recovery in the sub-group analysis. Additionally, we do not have the mean GFR of patients before LVAD insertion and after kidney recovery from KRT. Lastly, data on AKI recovery impact on outcomes among patients after LVAD insertion were not reported.

CONCLUSION

In conclusion, recovery from severe AKI-KRT after LVAD occurs in approximately 50.5%. Recovery of kidney functions is associated with improved kidney function, fewer complications, and better outcomes than patients with non-resolving AKI. Hence, adequate measures should be taken to facilitate diagnostic and therapeutic approaches aiming for early and complete kidney recovery.

ARTICLE HIGHLIGHTS

Research background

Acute kidney injury (AKI) is a common (37%) and severe complication after left ventricular assist device (LVAD) implantation, and 13% require kidney replacement therapy (KRT). Severe AKI requiring KRT in LVAD patients is associated with high short-term and long-term mortality compared with those without KRT.

Research motivation

While recovery of kidney function is associated with better outcomes, the recovery

rates of kidney function among LVAD patients with severe AKI-KRT are unclear.

Research objectives

To demonstrate the rates of kidney recovery among patients with AKI-KRT after LVAD implantation.

Research methods

Eligible articles were searched through Ovid MEDLINE, EMBASE, and the Cochrane Library. The inclusion criteria included adult patients with recovery from severe AKI-KRT after LVAD placement, which is defined by regained kidney function resulting in discontinuation of KRT.

Research results

A total of 268 patients from 14 cohort studies with severe AKI-KRT after LVAD were enrolled. Follow-up time ranges from 2 wk of LVAD implantation up to 12 mo. 78.5% of kidney recovery occurred at the time of hospital discharge or within 30 d. The majority (85%) of patients used continuous-flow LVAD. Overall, the pooled estimated AKI recovery rates among patients with severe AKI-KRT were 50.5% (95%CI: 34.0%-67.0%). While the data on pulsatile-flow LVAD was limited, subgroup analysis of continuous-flow LVAD demonstrated the pooled estimated AKI recovery rates among patients with severe AKI-KRT was 52.1% (95%CI: 36.8%-67.0%). Meta-regression analysis did not show a significant association between study year and AKI recovery rate (P = 0.08). There was no publication bias as assessed by the funnel plot and Egger's regression asymmetry test in all analyses.

Research conclusions

Recovery from severe AKI-KRT after LVAD occurs approximately 50.5%, and it has not significantly changed over the years despite advances in medicine.

Research perspectives

Our study results offer a perspective of rates of kidney recovery after AKI-KRT among patients with LVAD implantation. As recovery of kidney functions is associated with improved outcomes compared to those with no AKI recovery, we suggest a meticulous approach to monitoring patients post AKI and acute kidney disease in achieving early and complete kidney recovery.

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