ISSN 2220-3141 (online)

# World Journal of

# *Critical Care Medicine*

Quarterly Volume 14 Number 2 June 9, 2025

Published by Baishideng Publishing Group Inc

World Journal of Critical Care Medicine

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## INDEXING/ABSTRACTING

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## RESPONSIBLE EDITORS FOR THIS ISSUE



**NAME OF JOURNAL**
*World Journal of Critical Care Medicine*

**ISSN**
ISSN 2220-3141 (online)

**LAUNCH DATE**
February 4, 2012

**FREQUENCY**
Quarterly

**EDITORS-IN-CHIEF**
Julian E Losanoff

**EDITORIAL BOARD MEMBERS**
https://www.wjgnet.com/2220-3141/editorialboard.htm

**PUBLICATION DATE**
June 9, 2025



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*World J Crit Care Med* 2025 June 9; 14(2): 100623

DOI: 10.5492/wjccm.v14.i2.100623

ISSN 2220-3141 (online)

EDITORIAL

# Transformative impact of point-of-care testing in critical care

Pradeep K Dabla, Aashima Dabas

**Specialty type:** Critical care medicine

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade B, Grade C, Grade C, Grade C

**Novelty:** Grade B, Grade C, Grade B, Grade B

**Creativity or Innovation:** Grade B, Grade C, Grade B, Grade C

**Scientific Significance:** Grade B, Grade B, Grade B, Grade B

**P-Reviewer:** Lopes LCP; Tang YX

**Received:** August 21, 2024

**Revised:** January 6, 2025

**Accepted:** January 14, 2025

**Published online:** June 9, 2025

**Processing time:** 189 Days and 19.7 Hours

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## Abstract

The advent of point-of-care testing (POCT) has revolutionized the approach to patient management, especially for pediatric care. POCT provides rapid, on-the-spot biochemical and microbiological evaluations, bypassing delays typically associated with central laboratory testing, enabling swift clinical decision-making. Additionally, POCT has proven to be a valuable prognostic tool for monitoring electrolyte, lactate, creatinine levels, often a marker of severe illness and poor outcomes. POCT enables its faster identification, allowing for prompt interventions. This capability is essential in managing conditions like sepsis, where timely treatment can significantly impact survival rates. However, the implementation of POCT is not without its challenges. Variability in sample handling, particularly with heparinized syringes, can affect the accuracy of certain measurements, such as potassium levels. The absence of comprehensive follow-up data and cost-effectiveness analyses in some studies indicate the need for continued research to optimize the use of POCT. In conclusion, POCT is a transformative tool in critical care, offering prompt and reliable assessments that significantly enhance patient management. As technology advances, the integration of POCT into emergency departments and intensive critical care units holds great promise for improving the quality of healthcare and patient survival rates.

**Key Words:** Point-of-care testing; Emergency departments; Intensive care unit; Critical care; Pediatric care; Artificial intelligence

**Core Tip:** Point-of-care testing has transformed patient management in emergency and intensive care settings by delivering rapid, on-the-spot biochemical and microbiological evaluations. This allows swift clinical decisions which are pivotal for severe medical conditions such as sepsis. Research highlights a strong agreement between point-of-care testing and central lab results for key analytes such as electrolytes and lactate, which is crucial for accurate assessments and timely interventions. Despite the challenges such as sample handling variability, future advancements, including artificial intelligence, hold the potential for faster and more accurate diagnostics, improving overall healthcare quality.

**Citation:** Dabla PK, Dabas A. Transformative impact of point-of-care testing in critical care. *World J Crit Care Med* 2025; 14(2): 100623
**URL:** https://www.wjgnet.com/2220-3141/full/v14/i2/100623.htm
**DOI:** https://dx.doi.org/10.5492/wjccm.v14.i2.100623

## INTRODUCTION

Point-of-care testing (POCT) in critical care has revolutionized the healthcare landscape by providing rapid diagnostics directly at the bedside[1]. The POCT is a medical diagnostic procedure that is performed near or at the site of patient care leading to an immediate improvement in the ongoing treatment and patient outcome[2,3]. Therefore, by mitigating diagnostic delays and enabling prompt, precise interventions in life-threatening situations, POCT enhances efficiency in emergency and intensive care settings, ultimately leading to significant reduction in morbidity and mortality[1]. Initially met with skepticism over analytical performance, increasing evidence now indicates POCT platforms align well with traditional laboratory instruments for many analytes, reinforcing their reliability for direct clinical implementation[4,5].

## REAL WORLD SETTINGS: SPEEDING UP PEDIATRIC CARE

POCT diagnostics, using a minimally invasive devices and technology, become particularly imperative in acute care settings, such as pediatric emergency departments, intensive care units, and remote locations, where expeditious patient evaluation and prognostication are pivotal to optimizing clinical outcomes. For instance, some devices that require minimal sample volumes offer an advantage by reducing the blood loss typically associated with phlebotomy. Additionally, the simpler user interface of a POCT makes it more convenient for use for the general public in the community settings and in the absence of trained technical manpower. As POCT platforms advance to offer more testing options, their relevance in pediatric emergency medicine is becoming more widely acknowledged. For example, in pediatric patients with fever, it is crucial to quickly determine the source of infection (such as bacterial or viral) and identify those at high risk for serious bacterial infections[6]. C-reactive protein (CRP) is a useful biomarker for rapidly identifying inflammatory processes. In an earlier study, the use of POCT for CRP resulted in a substantial reduction in consultations and medical interventions in the emergency department, without significantly altering patient outcomes[7].

## ADVANTAGES IN CRITICAL CARE PEDIATRIC SETTINGS

Children with chronic illness may have additional challenges in attending healthcare appointments and undergoing diagnostic testing. Most of these children would require more than one diagnostics requirement while presenting ill. The caregiver or the child may refuse to give consent for sampling through venipuncture or procedures like endoscopy. The use of POCT in clinical decision making is likely to be very beneficial and safe in these settings[8]. Additionally, advancements in POCT technology have enabled real-time data integration of POCT devices in remote areas, primary health care and homes, allowing automated, real-time, electronic transmission of POCT results and related information with a referral center to guide management and further action in emergency settings. This integration of POCT devices enhances access to quality diagnostics in underserved regions, prevents adverse events and improves patient outcomes [9].

## IMPROVING EFFICIENCY AND RESOURCE MANAGEMENT

POCT enhances efficiency in healthcare by delivering rapid, on-site diagnostics, in both acute and remote patient care environments. This efficiency boosts patient throughput and minimizes the reliance on central laboratories, which helps cut costs associated with lab tests and specialized staff[10-14]. A study by Crocker *et al*[11] showed the use of implementation of point-of-care (POC) diagnostic platforms in ambulatory settings resulted in cost reduction and optimizations in clinical operations. Authors reported that subsequent to the deployment of POCT, there was a 21% reduction in the number of tests ordered per patient, accompanied by a marked decline of 89% in follow-up phone calls. Numerous reports have highlighted the clinical and economic advantages of implementing POCT systems, such as shorter

turnaround times, reduced length of stay, lower mortality rates, reducing wait times, reduced preanalytical and postanalytical testing errors and shortening hospital stays[12]. An earlier study by Winkelman *et al*[13], observed that the medical cost was less while using central laboratory testing turn around time of POC blood gas analysis (4.5 minutes) nearly equaled central laboratory testing (6 minutes). Nijman *et al*[12] found that the bedside CRP reduced the median length of stay in children requiring an laboratory diagnostic CRP test from 178 minutes to 148 minutes, a 30-minute (19%) decrease. In a study among 897 patients, Goldstein *et al*[10] compared the POC test panel (i-STAT system, complete blood count, electrocardiograms, low dose X-ray) to standard diagnostic methods for cost-effectiveness. Results showed that the standard control investigations cost dollars 9.93 higher than the POCT systems dollars 9.93, if the entire test panel were performed on a patient. While low dose X-ray-based tests saved time, they were more expensive. Higher staffing costs further favored POCT as a more economical option. Studies have reported POCT also streamlines operations by optimizing the use of medical equipment and space, further contributing to cost savings[11].

## EXPERIENCES WITH POCT

Traditional POCT devices are available for diagnosing and managing both acute and chronic conditions. These encompass a variety of diagnostic assays including, glucose meters, hemoglobin A1c, and ketone tests; urine creatinine, epidermal growth factor receptor, urinary protein: Creatinine ratio for renal function; troponin and brain natriuretic peptide for diagnosing myocardial infarction; hemoglobin and gastric/fecal occult blood tests for anemia and bleeding; prothrombin, and activated partial thromboplastin time for coagulation profile; urine drug tests, blood gas, electrolytes; CRP and electron spin resonance for inflammation; rapid tests for human immunodeficiency virus, respiratory syncytial virus, influenza, and, more recently, severe acute respiratory syndrome coronavirus 2. Recent advancements in POCT platforms have broadened the range of available assays to include important chemistry and immunoassay markers in various settings[15].

### *Antimicrobial stewardship*

The role of POCT in antimicrobial stewardship has also been found promising. The use of multiplex cards using polymerase chain reaction aids in identifying viruses/parasites to limit the injudicious use of antimicrobials in children presenting with acute undifferentiated febrile illness like influenza[16]. It may also aid in deciding the need for hospitalization that further reduces healthcare costs and risk of hospital acquired infections[17].

### *Electrolyte*

Handheld devices, such as the Nova StatStrip blood gas analyzer provide real-time electrolyte analysis, crucial for monitoring critically ill patients and adjusting treatment plans based on dynamic changes in electrolyte levels[18]. These can process less commonly measured electrolytes like calcium and magnesium in the same volume of blood. The disturbances in levels of these electrolytes aids in decision making and prognosis of sick children[19]. The measurement of these multiple analytes at a single point in time on the same sample also aids in interpretation of plausible biological association. The use of artificial intelligence has improved risk stratification and prognosis algorithms[20].

### *Microbial testing*

Rapid antigen tests, such as the Abbott BinaxNOW™ and the Quidel Sofia™ SARS Antigen fractional iron absorption, deliver quick results for detecting severe acute respiratory syndrome coronavirus 2, facilitating timely isolation and management of coronavirus disease 2019 patients. The identification and timely treatment of serious bacterial infection in children is challenging. The use of biomarkers that can be measured using POCT like CRP, neutrophil counts, lactate *etc.* can aid in better decision making[21].

### *Hematology testing*

Portable hematology analyzers, like the Hemochron Signature Elite, provide immediate results for coagulation profiles, aiding quick treatment decisions in trauma cases or for patients on anticoagulant therapy[22]. Devices such as the i-STAT system offer rapid blood gas and electrolyte testing, crucial for managing premature infants with complex hematological needs[23].

### *POCT ultrasound in emergency room settings*

It is used to quickly assess trauma patients for internal bleeding in the abdomen or chest, guiding immediate surgical or medical intervention. Ultrasound guidance for procedures like central line insertion or paracentesis enhances accuracy and reduces complications, ensuring safety[24,25].

**Severe acute respiratory distress syndrome corona virus-2 detection:** POCT could radically transform the healthcare system's capacity to quickly detect and manage coronavirus disease 2019, especially in remote areas where lab-based nucleic acid amplification testing is unfeasible. Unlike traditional lab polymerase chain reaction tests, which take about two days for results, the Abbott ID NOW™ coronavirus disease 2019 diagnostic assay delivers prompt results - positive results in 6 minutes and negative in 12 - using nucleic acid amplification technology for qualitative severe acute respiratory distress syndrome corona virus-2 detection from nasal and nasopharyngeal swabs[26].

## CHALLENGES: GOVERNANCE AND SAFETY AUDIT REQUIREMENTS

A survey across the United Kingdom and Ireland on use of POCT for managing paediatric patients showed most of the POCT were being performed by the nursing staff. The action on these reports was taken by the doctor or the consultant in the majority except for the gas analysis. The issue identified was that most POCT reports could not be entered into the electronic system and had to be recorded manually[27,28]. Though POCT is likely to be advantageous in primary care settings, there may be additional challenges in these settings related to accountability of conducting the test, work distribution in primary care settings, standardization of protocol on management of a child based on the POCT report, patient safety and funding[29].

Therefore, improving awareness and training on the use of POCT as a triaging tool becomes important. A few areas that need improvement with the use of POCT are mentioned below: (1) Simpler home-monitoring of children with chronic illness for emergencies like ketoacidosis (in children with diabetes), dyselectrolytemia (malabsorption, diabetes insipidus, tubulopathy). Therefore, all metabolic emergencies cannot be monitored or detected at home[30]; (2) Ensuring quality and validity of POCT - this requires a periodic calibration of POCT devices to ensure the device meets manufacturer specifications, enhancing test reliability and reducing the risk of false results. A few devices are claimed to have zero-maintenance and repair costs. However, calibration is not inbuilt as a regular protocol. The end-user may fail to recognize the error in reporting that may make results invalid till a replacement of the device can be arranged[31-33]; (3) Ensuring diagnostic accuracy and modifying treatment - the use of POCT is beneficial if it can address a diagnostic uncertainty that arises at the end of clinical examination, and can be resolved for instituting specific clinical management. For example, the use of POCT nasal swab polymerase chain reaction to detect influenza can avoid overuse of antibiotics. However, this may not be true for a few POCT where the sensitivity is high but specificity is low[34]; (4) Most of the experience on use of POCT is derived from use in adult settings that were tested later in pediatric settings. However, the applicability, clinical utility and cost-effectiveness will vary in children. For example, the most common cause of hyperglycemia with metabolic acidosis in a sick child could be systemic inflammatory response syndrome instead of acute complication of diabetes which is more common in adults. Therefore, the test algorithms for action based on POCT will be different from adults[35]; and (5) Additionally, in infants and children, pediatric reference interval studies for POCT systems are lacking, undermining the accuracy and standard of test result interpretation of test results. The interpretation of the normal range of the analytes needs to be as per the age of the child. For example, the normal serum bicarbonate level in a newborn is lower (16-24 meq/L) than a child (18-26 meq/L)[35]. Further investigations are imperative to delineate age-specific reference ranges and critical thresholds as novel POCT systems are progressively integrated into clinical practice.

### *Future directions*

Future directions for POCT include the development of more sophisticated and user-friendly devices, integration with digital health systems for seamless data management, and expanding testing capabilities to cover a broader range of conditions. Innovations such as advanced biosensors, lab-on-a-chip technologies, and artificial intelligence-driven analytics will further enhance accuracy and efficiency[19,36]. For lateral immunoassays, Yan *et al*[37] used magnetic nanoparticles conjugated with antibodies to detect analytes like human chorionic gonadotropin, cardiac troponin I, creatine phosphokinase and myoglobin, measuring magnetic signals with an immunoassay reader. They employed a novel data-processing method using a support vector machine classifier and custom waveform reconstruction to enhance sensitivity and accuracy for weak signals. Human chorionic gonadotropin was quantitatively detected with a detection limit of 0.014 mIU/mL, well below the typical < 5 mIU/mL cut-off of laboratory instruments. Microfluidic "lab-on-a-chip" technology boasts a high surface-area-to-volume ratio, facilitating fast analysis time and enabling POCT. It holds significant potential to perform intricate diagnostic assays, such as nucleic acid short tandem repeat fingerprinting, by integrating all requisite functional modules within a single chip[38]. These developments promise significant transformation in the clinical practice paradigm of emergency and critical care.

## CONCLUSION

In conclusion, with ongoing technological advancements, the integration of POCT into emergency departments and intensive care units holds immense potential for enhancing healthcare quality and increasing patient survival rates. Implementation of existing POCT systems in emergency and critical care brings the laboratory directly to the patient, streamlining the testing process and reducing the time to clinical intervention, thereby significantly enhancing patient management. Current evidence highlights several key benefits for patient care, including shorter length of stay, rapid diagnosis, better outcomes for acute conditions, and lower hospitalization costs. Studies have reported additional administrative and economic benefits with adequate education and training such as enhanced staff satisfaction and optimized workflow efficiency. However, before clinical deployment of POCT, careful attention to their analytical requirements is essential. Not all POCT systems are homogeneous, and discrepancies between POCT devices and central laboratory analyzers continue to be documented, often necessitating device-specific test interpretation. Nonetheless, despite these challenges, the development of innovations, like lab-on-a-chip platforms and AI-driven analytical frameworks, will greatly enhance the operational efficiency of POCT devices in critical care settings.

## FOOTNOTES

**Author contributions:** Dabla PK designed the overall concept and outline of the manuscript; Dabas A contributed to discussion and design of manuscript; Dabla PK and Dabas A contributed to writing and editing of the manuscript; and all authors thoroughly reviewed and endorsed the final manuscript.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.



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**S-Editor:** Bai Y
**L-Editor:** A
**P-Editor:** Guo X

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World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

*World J Crit Care Med* 2025 June 9; 14(2): 101587

DOI: 10.5492/wjccm.v14.i2.101587

ISSN 2220-3141 (online)

OPINION REVIEW

# Sepsis in liver failure patients: Diagnostic challenges and recent advancements

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**Specialty type:** Gastroenterology andhepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade B, Grade B, Grade C

**Novelty:** Grade B, Grade B, Grade C

**Creativity or Innovation:** Grade B, Grade B, Grade C

**Scientific Significance:** Grade B, Grade B, Grade B

**P-Reviewer:** Liang GD; Seshadri PR; Zhou JF

**Received:** September 19, 2024

**Revised:** January 19, 2025

**Accepted:** February 12, 2025

**Published online:** June 9, 2025

**Processing time:** 160 Days and 17.4 Hours

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## Abstract

Acute liver failure (ALF) and acute-on-chronic LF (ACLF) are prevalent hepatic emergencies characterized by an increased susceptibility to bacterial infections (BI), despite significant systemic inflammation. Literature indicates that 30%–80% of ALF patients and 55%–81% of ACLF patients develop BI, attributed to immunological dysregulation. Bacterial sepsis in these patients is associated with adverse clinical outcomes, including prolonged hospitalization and increased mortality. Early detection of bacterial sepsis is critical; however, distinguishing between sterile systemic inflammation and sepsis poses a significant challenge due to the overlapping clinical presentations of LF and sepsis. Conventional sepsis biomarkers, such as procalcitonin and C-reactive protein, have shown limited utility in LF patients due to inconsistent results. In contrast, novel biomarkers like presepsin and sTREM-1 have demonstrated promising discriminatory performance in this population, pending further validation. Moreover, emerging research highlights the potential of machine learning-based approaches to enhance sepsis detection and characterization. Although preliminary findings are encouraging, further studies are necessary to validate these results across diverse patient cohorts, including those with LF. This article provides a comprehensive review of the magnitude, impact, and diagnostic challenges associated with BI in LF patients, focusing on novel advancements in early sepsis detection and characterization.

**Key Words:** Liver failure; Sepsis; Bacterial infection; Acute liver failure; Acute-on-chronic liver failure

**Core Tip:** Patients with liver failure (LF) are prone to bacterial sepsis due to immune dysregulation. Up to 80% of such patients develop bacterial infection, which is associated with various complications and poor outcomes. Therefore, it is imperative to diagnose bacterial sepsis at the earliest. However, differentiating between patients with and without sepsis can be challenging, as LF itself can mimic sepsis by inducing systemic inflammation and organ failure. Several novel biomarkers for sepsis and machine learning techniques are being investigated, as conventional biomarkers have shown inconsistent results in LF patients. This article addresses the magnitude, impact, challenges, and recent developments in understanding bacterial sepsis in LF patients.

**Citation:** Kumar R, Kumar A, Kumar S. Sepsis in liver failure patients: Diagnostic challenges and recent advancements. *World J Crit Care Med* 2025; 14(2): 101587
**URL:** https://www.wjgnet.com/2220-3141/full/v14/i2/101587.htm
**DOI:** https://dx.doi.org/10.5492/wjccm.v14.i2.101587

## INTRODUCTION

Sepsis is a global health problem, and despite advancements in therapeutics, patients carry a substantial risk of in-hospital mortality[1]. A Global Burden of Disease Study reported an incidence of sepsis at 677.5 cases per 100000 age-standardized population, contributing to 19.8% (11 million) of global deaths[2].In 2019, sepsis resulted in 13.7 million deaths worldwide, with significant regional variations in mortality rates, ranging from 52.2 deaths per 100000 people in high-income regions to 230 deaths per 100000 people in sub-Saharan Africa[3]. The mortality rate from sepsis is significantly higher among intensive care unit (ICU) patients; a meta-analysis by Fleischmann *et al*[4] reported a pooled mortality rate of 41.9% in ICU-treated sepsis, vis-a-vis 26.7% in hospital-treated sepsis. Consequently, the World Health Organization declared sepsis a global health problem in 2017. The hallmark of sepsis is a dysregulated host response to infection, resulting in life-threatening organ failure[5]. Although BI are the most common cause of sepsis, infections from viruses, parasites, or fungi can also lead to the condition. The liver serves as a vital first line of defense against various pathogens[6]. Thus, patients with liver failure (LF) are at an increased risk of microbial infections and face a high risk of death from sepsis[7-9]. Early and accurate recognition of sepsis is essential for improving outcomes through more targeted medical treatment.

Acute LF (ALF) and acute-on-chronic LF (ACLF) are two common hepatic crises that can occur in patients with normal liver function and those with chronic liver diseases, respectively. These conditions are distinct but share several common features, including acute onset, jaundice, coagulopathy, hepatic encephalopathy, and a high short-term mortality rate[10,11]. Additionally, these conditions clinically resemble sepsis in diverse ways, including the development of systemic inflammatory response syndrome (SIRS) and organ failure[12-15]. Therefore, distinguishing between LF patients with and without sepsis can be challenging. ALF and ACLF patients paradoxically exhibit heightened susceptibility to BI despite significant systemic inflammation. This vulnerability appears to be related to immunological dysregulation, resulting in either a suppressed or exhausted adaptive immune system[9,16]. Once SIRS is triggered by an acute insult, the body develops a compensatory anti-inflammatory response, which may lead to immune paralysis and bacterial infections (BI) (Figure 1).

BI is one of the most common causes of ACLF and a frequent complication thereof too. Nearly one-third of ACLF patients present with BI, while half develop them during follow-up[6]. Notably, ACLF caused by BI exhibits greater mortality rates compared to other precipitating events[17-19]. In one study, the 30-day survival rate was only 33.8% in patients with BI as a trigger, compared to 71.6% among those without BI[18]. It is challenging but vital to distinguish between sepsis and sterile inflammation in LF patients. Without appropriate antibiotic therapy, mortality rates in sepsis patients generally rise by 3.3% to 7.6% every hour[20,21]. Thus, early identification of BI and timely antibiotic therapy are crucial for LF patients. This article addresses the magnitude, impact, challenges, and recent developments in understanding sepsis in LF patients, primarily due to BI.

## IMMUNE DYSFUNCTION IN LF PATIENTS

The liver plays a critical role in the proper functioning of the immune system, as it neutralizes pathogens and enhances immunological tolerance. When innate immune cells are activated by an acute hepatic insult, a cascade of cytokines and chemokine is triggered, resulting in a severe SIRS. Uncontrolled systemic inflammation may lead to a vicious cycle of immunological dysfunction at multiple cell levels[22]. A compensatory anti-inflammatory response syndrome (CARS) develops throughout, leading to functional monocyte deactivation, a critical event in the development of systemic immunological dysfunction[1]. Depending on the stage of LF, macrophages may exhibit both tissue-destructive and tissue-repair effects. Additionally, the proliferation of suppressor cells produced from monocytic myeloids, through the programmed cell death protein 1/programmed death-ligand 1 axis, and a decrease in the bacterial clearance of Kupffer cells further compromise antimicrobial responses in LF patients[23]. Overall, an inappropriate CARS, along with the dysfunction and exhaustion of both innate and adaptive immune systems in LF patients leads to functional immune paralysis[24].Therefore, a dysregulated immune response in LF not only contributes to the progression of liver disease

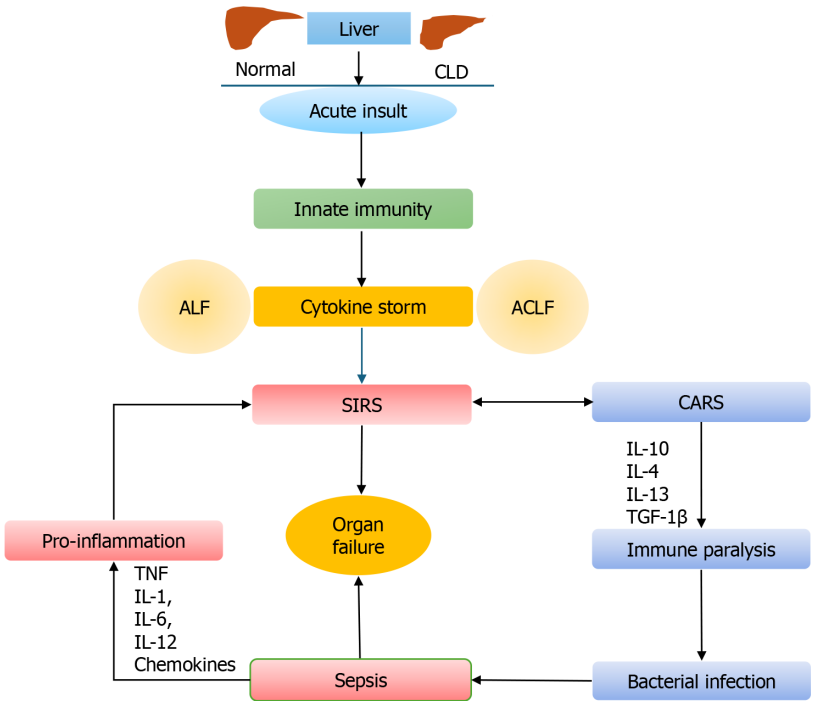


**Figure 1 Schematic diagram showing immune dysregulation in liver failure patients.** Acute insult results not only in systemic inflammation, but also compensatory anti-inflammatory response which leads to immune paralysis and heightened susceptibility to bacterial infection. ALF: Acute liver failure; ACLF: Acute-on-chronic liver failure; CLD: Chronic liver disease; CARS: Compensatory anti-inflammatory response syndrome; SIRS: Systemic inflammatory response syndrome; IL: Interleukin; TNF: Tumor necrosis factor; TGF: Transforming growth factor.

but also increases the risk of overwhelming sepsis, organ failure, and mortality[25,26].

Further, liver transplantation (LT) remains the definitive treatment for ALF and ACLF patients, offering a chance of long-term survival. However, post-transplant sepsis poses a significant challenge, particularly within the first month post-transplant[27]. The risk of infection correlates with the immunosuppressive regimen and graft function and is further exacerbated by the SIRS triggered by reperfusion injury and surgical stress. Moreover, immunosuppressant therapy after LT can lead to delayed presentation of infectious clinical symptoms, underscoring the importance of prompt diagnosis and rapid treatment for favorable outcomes.

## CHARACTERISTICS OF BI IN ALF AND ACLF

There is a high prevalence of BI in both ALF and ACLF patients (Table 1). In ALF patients, BI occur in 30%–80%[8,28-30]. In a prospective observational study from King's College Hospital, London, Rolando *et al*[29] found culture-positive BI in 80% of 50 ALF patients. The most common site of infection was the respiratory tract (47.1%), with gram-positive bacteria accounting for 69.8% of all infections, and Staphylococcus aureus being the most common isolate (35.8%). In a retrospective study by Karvellas *et al*[30] from Canada, BI were found in 35% of ALF patients (72/206). Gram-negative organisms were observed in 52% of isolates, while gram-positive organisms were found in 44%. In a large cohort of ALF patients ($n$ = 540) from India, BI were present at admission or developed within 48 hours in 22.2% of patients, while 34.3% developed them after 48 hours. Among infected patients, 54.9% were culture-positive, with 90% of isolates being gram-negative bacteria, the most common being Acinetobacter (32.7%). The respiratory tract was the most common site of isolation of organisms (45.8%), followed by bacteraemia in 28.2%[31].In a retrospective cohort study from the United States, Zider *et al*[28] found BI in 41% (62/150) of ALF patients, with the respiratory tract being the most common site (64.5%), followed by the urinary tract (54.8%).Notably, 40% of patients had more than one site of infection. In a recent study from India, multi-drug resistant (MDR) organisms accounted for 70% of BI, and 7% of infections were caused by pan-drug resistant organisms, underscoring the seriousness of this situation. The most prevalent presentations were pneumonia (50%), followed by urinary tract infections (UTIs) in 22%[8]. BI leading to sepsis can manifest at any point during ALF, with the median time of infection reported to vary from 3 to 10 days[29,30]. Immune dysfunction primarily causes early infections, while invasive procedures contribute to late episodes[30]. Early infections are mainly caused by bacteria from the endogenous normal flora, whereas later infections involve exogenous microorganisms.

ACLF patients have an extraordinarily high prevalence of BI, ranging from 55% to 81%[9]. In a large European cohort study consisting of 407 ACLF patients, 37% presented BI at the time of ACLF diagnosis, and 46% of the remaining patients developed BI during follow-up (4 weeks). The most common site of infection at presentation was spontaneous bacterial peritonitis (SBP) (26.9%), while UTIs were the most common during follow-up (23%)[18]. In a retrospective cohort study from China, 81.2% of 389 patients with ACLF had BI, respiratory tract infections (49.4%) and SBP (37.3%)

**Table 1 Prevalence of bacterial infections amongacute liver failure or acute-on-chronic liver failure patients in different countries**

| Ref. | Country | Patients | *n* | Overall infection | Remarks |
|---|---|---|---|---|---|
| Cai *et al*[32], 2017 | China | ACLF | 389 | 81.2% | Pneumonia 49.4%, SBP 37.3%, UTI 13.3%. Gram positive sepsis 59.8%, Gram negative 55.3% |
| Fernández *et al* [18], 2018 | Europe | ACLF | 407 | 66.1% | BI at diagnosis 37%, BI during follow-up 46%. BI was associated with higher inflammation and worse outcomes |
| Karvellas *et al*[30], 2009 | Canada | ALF | 206 | 35% | Gram positive organisms in 44% of isolates, gram negatives in 52%, and 4% was fungal |
| Kaur *et al*[8], 2024 | India | ALF | 143 | 64% | Overall infection was 77% including fungal infection in 17.3%, MDR 70% |
| Liu *et al*[33], 2021 | China | ACLF | 140 | 69.2% | SBP 36.1%, pneumonia 23.7%, and multi-site infection 22.7%. Gram-negative bacteria 68.4%, and Gram-positive 31.6% |
| Moreau *et al*[35], 2013 | Europe | ACLF | 303 | 32.6% | SBP 10.6%, Pneumonia 61%, UTI 6.1% |
| Mücke *et al*[19], 2018 | Europe | ACLF | 173 | 41% | SBP 32.4%, pneumonia 25.4% |
| Rolando *et al*[29], 1990 | England | ALF | 50 | 80% | Respiratory tract infection 47%,and gram-positive bacteria 69.8% |
| Shalimar *et al*[31], 2017 | India | ALF | 540 | 49% | BI at diagnosis 22.2%, BI during follow-up 34% |
| Shalimar *et al*[34], 2018 | India | ACLF | 572 | 66.7% | Gram negative sepsis 91.6%. Pneumonia 45%, SBP 21.1%, UTI (15.2%) |
| Zhai *et al*[43], 2020 | China | ACLF | 289 | 64% | Gram negative sepsis 58.3%, Pneumonia 55.7%, SBP 47.6% |
| Zhang *et al*[37], 2022 | China | ACLF | 539 | 58.8% | SBP 31.54%, UTI 26.53%, Pneumonia 12.9%. Gram-positive sepsis 23.76%, Gram-negative sepsis 62.87% |
| Zider *et al*[28], 2016 | United States | ALF | 150 | 41% | One site infection 60%, multi-site infection 40%. Pneumonia 64% and UTI 55% |

ALF: Acute liver failure; ACLF: Acute-on-chronic liver failure; BI: Bacterial infection; MDR: Multi-drug resistance; SBP: Spontaneous bacterial peritonitis; UTI: Urinary tract infection.

being the most prevalent forms. Gram-positive organisms (59.8%) were more frequently observed than gram-negative organisms (55.3%)[32].In another retrospective cohort study from China, BI occurred in 69.2% of 140 hepatitis B virus (HBV)-related ACLF patients, with SBP (36.1%) being the most common form of infection, followed by the lung infection (23.7%). Gram-negative BI were more common than gram-positive ones (68.4% *vs* 31.6%)[33]. In a large retrospective cohort study from India, 66.7% of 572 ACLF patients had BI, with gram-negative bacteria accounting for 91.6% of infections and pneumonia being the most common infection (45%)[34].

The risk of BI rises with the increasing severity of ACLF. Local epidemiological factors appear crucial in imparting the risk of BI in ACLF patients. Asian nations have reported a greater incidence of BI in ACLF than in Europe[19,32-38]. According to a multicenter international study, the incidence of BI-triggered ACLF was 59% in Asia, 75% in the Indian subcontinent, and 39% in Europe[28]. Thus, the most common forms of BI among ACLF patients appear to be SBP and pneumonia. Gram-negative bacteria are the predominant pathogens worldwide, while gram-positive bacteria have been reported to be more prevalent in Northern Europe (39%)[17]. Of particular concern is the increasing prevalence of MDR and extensively drug-resistant (XDR) organisms in ACLF patients. An international study of hospitalized patients with cirrhosis, including those with ACLF ($n$ = 1302), found that 34% of MDR bacteria were present in culture-positive infections, with frequency varying geographically, from < 20% in the United States to > 70% in India. XDR organisms were found in 33% of cases in India[39], while in Europe (CANONIC study), BI were MDR in 15.8% at diagnosis and 18.8% on follow-up[18].

## IMPACT OF BI ON OUTCOMES IN LF

A normal liver plays an essential regulatory role in sepsis and homeostasis. When the liver is already dysfunctional, sepsis can exacerbate hepatic injury, amplify systemic inflammation, and lead to multiple organ dysfunction. Bacterial sepsis is the leading cause of mortality in ALF patients, accounting for 10% to 52% of deaths. Infections caused by MDR organisms are associated with a higher incidence of advanced HE, multiorgan failure, longer hospitalization, and increasing mortality rates[8]. BI have been identified as independent predictors of persistent hyperammonemia in ALF, which in turn is associated with worsening HE and poor outcomes[40,41].

In ACLF, BI cause clinical deterioration, prolonged hospitalization, and increased mortality[9,42,43]. The mortality rates of ACLF patients at 28 days (35.5%–45.5%) and 90 days (50.7%–56.9%) are worse in patients with BI than those without[18,33,43-45]. BI are independent predictors of survival in patients with ACLF grade 1 and grade 2[9]. ACLF patients with multiple site infections have been found to have a higher incidence of septic shock, grade-3 ACLF, and 28-day mortality rates[9]. The failure of empirical antibiotic treatment in BI by MDR organisms further increases short-term mortality[18,19,46,47]. The site of infection also appears to affect mortality rates in ACLF; for instance, SBP is linked to increased risks of 90-day mortality compared to cutaneous, bone, or soft tissue infections[7].

## CHALLENGES IN DIAGNOSING SEPSIS IN LF PATIENTS

Both ALF and ACLF trigger marked systemic inflammation driven by tissue damage, which mimics a dysregulated host response to pathogens. Thus, differentiating sterile systemic inflammation from sepsis becomes challenging in such patients. Fever can be absent in up to 30% of patients with ALF and 56% of patients with ACLF[31,48]. Total leucocyte counts (TLC) and neutrophil-lymphocyte ratios can both be elevated in inflammatory states without infection, making them unreliable for discrimination. Blood culture is the gold standard for bloodstream infections; however, its long processing time (72 hours or more) and low sensitivity make it unreliable. Conventional culture methods are often not sensitive enough to identify many unusual infections. Moreover, distinguishing between colonization and infection can be challenging when cultures are positive.

C-reactive protein (CRP) is an acute-phase protein synthesized in the liver following inflammatory stimuli; hence, CRP lacks specificity for BIs. In a meta-analysis, Tan *et al*[49] found CRP having a pooled sensitivity of 80% for overall sepsis, but a pooled specificity of only 61%. Further, there is a lag time of 12 to 24 hours before CRP concentrations begin to rise, limiting its usefulness as an early biomarker. Due to reduced hepatic parenchyma, CRP levels are often low in ALF patients. Silvestre *et al*[50], in a case series of ALF patients, discovered CRP to be markedly decreased and even undetectable in some ALF patients, despite the presence of sepsis. Procalcitonin (PCT) upregulation has been suggested as a means to distinguish between BI and other inflammatory conditions[51]. In healthy subjects, PCT is produced in the medullary C-cells of the thyroid gland. However, BI cause a profound increase in the expression of the *CALC-I* gene, leading to the release of PCT from various cell types. Following infection, PCT levels increase faster than CRP, usually within 2 to 3 hours, peaking at 24 hours. PCT levels are highest in patients with gram-negative sepsis, while they are only slightly elevated in patients with fungal infection[52]. In a meta-analysis, PCT demonstrated an area under the receiver operating characteristics (AUROC) curve of 85%, making it a viable biomarker to distinguish sepsis from other non-inflammatory conditions[53]. However, non-infectious inflammation can also cause an increase in PCT. While PCT appears to be a good assay for BI detection in the general population, it has limited discriminatory value in critically ill patients[54]. PCT levels can be elevated in ALF patients due to massive hepatocyte necrosis and systemic inflammation. In a study on ALF patients, PCT was unable to distinguish between those with or without BI[55]. In ACLF subjects, PCT was higher in the sepsis group, but its discriminating value was only modest, with the AUROC curve of 69%[48]. Additionally, PCT shows poor diagnostic sensitivity and AUROC curve when predicting BI in patients with impaired renal function, as well as in immunocompromised and autoimmune patients[56]. Lin *et al*[57] proposed an infection score comprising serum PCT, CRP, and neutrophils%, to predict BI in ACLF patients; however, the discriminating potential of this score remained modest, with an AUROC curve of 74%. A meta-analysis found that interleukin (IL)-6 had good diagnostic value for differentiating BI in patients with cirrhosis, with pooled sensitivity and specificity of 85% and 91%, respectively[58]. Serum IL-6 has been identified as an independent predictor of mortality in patients with HBV-ACLF [59]. Nevertheless, IL-6 is a pro-inflammatory cytokine, and its predictive role for sepsis in LF—a condition marked by intense systemic inflammation—requires further study.

## NEWER BIOMARKERS AND FUTURE PERSPECTIVE

There is an urgent need for novel biomarkers to improve the diagnosis of BI in patients with LF. Before effective biomarkers can be developed and used in clinical settings, significant work is needed regarding methodology, standardization, and validation. Although numerous novel biomarkers for sepsis exist, based on proteomic, metabolomic, and genomic variables, only a few have been studied concerning liver disease (Table 2). Moreover, many of these biomarkers share the same drawbacks as traditional ones, and it is challenging to determine which is superior due to the lack of comparability caused by different methodologies and heterogeneous study populations.

Newer biomarkers such as soluble triggering receptor expressed on myeloid cell-1 (sTREM-1) and presepsin, a soluble CD14 subtype, have shown good sensitivity (83–85%) and moderate specificity (78%–79%) in differentiating sepsis from SIRS[60,61]. In a recent study, sTREM-1 and presepsin levels were significantly higher in ACLF patients with sepsis vis-a-vis those without. Further, sTREM-1 and presepsin outperformed TLC, PCT, and CRP in predicting sepsis. Additionally, diagnostic efficiency improved when sTREM-1 or presepsin was combined with the CLIF-SOFA score, achieving AUROC curves of 87% and 91%, respectively[48]. In another study, a presepsin level ≥ 2300 pg/mL was significantly associated with the early diagnosis of BI in ACLF patients[62]. Extra-hepatic BI can trigger hepatic macrophage activation. Recently, macrophage activation markers have been significantly associated with infection in ALF patients. Specifically, sCD206 was elevated in serum and upregulated on CD14+ monocytes[63]. Moreover, ACLF patients with BI and non-survivors exhibited higher levels of CD206[64]. Thus, sCD206 should be investigated as a potential biomarker of sepsis and mortality in LF patients. High-density lipoprotein cholesterol (HDL-C), which can bind to bacterial lipopolysaccharides,

**Table 2 Studies on biomarkers of sepsispatients within acute liver failure or acute-on-chronic liver failure**

| Ref. | Country | Patients | Biomarker(s) | Results and remarks |
|---|---|---|---|---|
| Silvestre *et al*[50], 2010 | Europe | ALF | CRP | CRP levels are markedly decreased in ALF, even in presence of sepsis |
| Igna *et al*[62], 2022 | Europe | ACLF | Presepsin, PCT and CRP | Presepsin, CRP, and PCT levels were higher in sepsis patients. Presepsin ≥ 2300 pg/mL had excellent (AUROC 0.95) for sepsis |
| Rule *et al*[55], 2015 | USA | ALF | PCT | PCT levels > 2.0 ng/mL could not differentiate ALF patients with or without BIs |
| Huang *et al*[68], 2017 | China | ACLF | Prostaglandin E2 | Serum Prostaglandin E2 Level 141pg/mL predicted infection with AUROC curve of 0.83 |
| Chen *et al*[48], 2021 | China | ACLF | sTREM-1, Presepsin, and PCT | sTREM-1 and presepsin were significantly higher in sepsis patients, with higher accuracy compared to CRP and PCT |
| Cavazza *et al*[63], 2024 | United States | ALF | sCD206 | sCD206, a soluble markers of macrophage activation, independently predictedinfection |
| Yadav *et al*[69], 2022 | India | ACLF | IL-1Ra, IL-18, TREM1, PD-L1, and TIM3 | Higher baseline and rising levels of IL-1Ra, IL-18, TREM1 soluble factors, and suppressive monocytes ($PDL1^{+ve}$, $TIM3^{+ve}$)predictedrisk of sepsis within 72 hours |
| Lin *et al*[57], 2020 | China | ACLF | PCT, neutrophils% and CRP | The AUROC of the infection score,comprisingPCT, neutrophils% and CRP, for discriminatingBI was 0.740 |
| Yuet al[80], 2024 | China | ACLF | BTLA | BTLA levels, a member of the CD28Igsuperfamily, significantly increased in the $CD4^+$ T cells andwere positively correlated with infection complications |

ALF: Acute liver failure; ACLF: Acute-on-chronic liver failure; AUROC: Area under receiver operating characteristic curve; BI: Bacterial infection; CRP: C-reactive protein; PCT: Procalcitonin; IL-1Ra: Interleukin-1 receptor antagonist; IL-18: Interleukin-18; TREM1: Triggering receptor expressed on myeloid cells 1; PD-L1: Programmed death ligand 1; TIM3: T-cell immunoglobulin and mucin domain-containing protein 3; BTLA: B- and T-lymphocyte attenuator.

has an inverse correlation with BI[65]. Low HDL-C levels have been associated with poor outcomes in patients with cirrhosis and ACLF[66,67]. Therefore, HDL-C could also serve as a potential biomarker of BI in LF patients. In a study from China, serum prostaglandin E2 (> 140 pg/mL) predicted infection with modest accuracy (AUROC curve of 0.83) in ACLF patients[68]. In another recent study from India, higher baseline and rising levels of soluble factors such as IL-1 receptor antagonist, IL-18, sTREM-1, and suppressive monocytes predicted the risk of early sepsis in ALF patients[69]. Bacterial DNA testing, which primarily detects 16S ribosomal ribonucleic acid genes, enables rapid and wide-ranging detection of bacteria. However, limitations include inconsistent results, low comparability due to the wide range of PCR techniques, and compromised interpretation because the tests detect DNA rather than live pathogens[70,71]. Some other novel markers of sepsis include mid-regional pro-adrenomedullin and microfluidic assays for the spontaneous motility of neutrophils[72,73]. However, their performance in patients with LF remains to be tested. A summary of the performance, advantages, and limitations of various traditional and novel biomarkers of sepsis is provided in Table 3.

Recent years have seen advancements in the early detection and characterization of sepsis through machine learning techniques. These techniques involve the assessment of multiple sepsis biomarkers, such as cytokines, metabolites, damage-associated molecular patterns, microRNAs, and soluble or membrane receptors. Wang *et al*[74] developed a random forest model using 20 Laboratory parameters, achieving an AUROC of 91% for predicting sepsis in ICU patients. Zhao *et al*[75] employed XGBoost and LightGBM algorithms, with the LightGBM model yielding an AUROC of 97.1% for early sepsis prediction. A comparative study evaluating six machine learning algorithms found that the random forest model exhibited superior performance, with an F-measure of 99.9% and an AUROC curve of 91.8%[76]. Further, a recent comprehensive network meta-analysis of 73 articles, involving 457932 septic patients and 256 models, demonstrated the superior predictive performance of machine learning models, with a pooled AUROC of 82.5%. The analysis highlighted the substantial influence of inherent characteristics and algorithms of different models on their effectiveness in predicting sepsis. Neural network and decision tree models demonstrated the highest AUROC metrics[77]. To distinguish between sterile inflammation and early sepsis, Cahill *et al*[78] proposed a machine-learning classifier based on circulating levels of 31 cytokines. This investigation yielded several new findings, including the identification of macrophage-derived chemokine (MDC/CCL22) as a potential marker of sepsis. Despite the potential of machine learning models, such as neural networks, decision trees, and random forests, in clinical settings, their effectiveness is hindered by study heterogeneity, variability in sepsis definitions, and the lack of standardized validation procedures. To address this gap, there is a pressing need for standardized reporting and validation frameworks to ensure the reliability and generalizability of machine learning tools in diverse clinical contexts, including those with ALF and ACLF[79]. It was recently shown that CD4+ T cells in ACLF patients have significantly higher levels of B- and T-lymphocyte attenuator (BTLA), a member of the CD28 Ig superfamily, which is positively associated with BI. Further, administering a neutralizing anti-BTLA antibody reduced BI and mortality in a mouse ACLF model. These findings may provide new targets for therapeutic interventions[80]. Another proof-of-concept study identified Synaptotagmin 13 and IL-1 family member 10 as potential

**Table 3 Summary of the performance, advantages, and limitations of various traditional and novel biomarkers of sepsis**

| Biomarkers | Overall performance for sepsis | Advantages | Limitations |
|---|---|---|---|
| CRP | Pooled sensitivity 80% and pooled specificity 61% for BI in general[49] | Wide availability. Low cost | Low specificity for BI. Falsely low levels in liver failure. Lag time: 12-24 hours. False positive in inflammation |
| PCT | Pooled sensitivity 77% and pooled specificity of 79% in general[53] | Easily available. Validated across multiple studies. Rapid elevation, 3–4 hours after BI | Modest to poor discriminatory role in liver failure patients. Varying cut-off levels. False positive in inflammation. Poor performance in renal failure and immunocompromised patients |
| IL-6 | Pooled sensitivity 85% and specificity 91% for BI in cirrhosis [58] | Estimation is accurate, fast, and simple | It is a non-specific pro-inflammatory cytokine. Needs further studies in liver failure patients |
| HDL-C | HDL-C has an inverse correlation with BI[65,66] | Simple test. Low-cost. Widely available | Inverse correlation also exists between HDL-C and liver disease per se. Needs further studies as a biomarker for sepsis |
| Presepsin | Overall diagnostic sensitivity 83% and specificity 78%[59] | Better performance in liver failure patients than CRP and PCT[48]. Specific association with gram negative sepsis-Detectable within 2 hours of BI | Limited availability. Expensive test. More effective as an adjunct biomarker than when used alone. Requires further validation studies |
| sTREM-1 | Pooled sensitivity 85% andspecificity 79% for differentiating sepsis from SIRS[61] | Early detection, < 2 hours after BI. Short half-life, making it useful for treatment response | Not routinely available. Varying cut-off levels. Requires further validation studies. Only modest performance when used alone |
| Bacterial DNA testing | Next-Generation Sequencing methodenables the identification of all bacteria in the blood and body fluid[70,71] | Quick and wide-ranging detection of bacteria | Not routinely available. Primer cross-reactivity with human DNA. Limited specificityand inconsistent results. DNA without a live pathogen compromises interpretation |
| sCD206 | Significant association with infection (AUROC 71%) and mortality in ALF (AUROC 81%) [63] | It is among few novel biomarker evaluated in ALF patients | Not routinely available for use. Levels also increases in fungal and viral infection.Requires further validation studies |

CRP: C-reactive protein; BI: Bacterial infection; PCT: Procalcitonin; IL: Interleukin; HDL: High density lipoprotein; sTREM-1: Soluble triggering receptor expressed on myeloid cell-1; SIRS: Systemic inflammatory response syndrome; AUROC: Area under receiver operating characteristics; ALF: Acute liver failure.

biomarkers of sepsis using advanced technologies, such as matrix-assisted laser desorption/ionisation and multiplex antibody arrays[81]. It is necessary to assess the usefulness of these potential biomarkers of sepsis in patients with ALF and ACLF.

## CONCLUSION

Immune dysregulation not only contributes to the pathogenesis of ALF and ACLF but also increases the risk of infection. BI represent a frequent complication in patients with LF that negatively impact survival. Therefore, early detection and effective treatment of BI are fundamental to improving the survival of such patients. Many efforts are underway to distinguish sepsis from SIRS in patients with acute hepatic injury. Unfortunately, conventional biomarkers have produced inconsistent and disappointing results. Extensive research is being conducted to aid in the identification of sepsis biomarkers. While many novel circulating biomarkers have been discovered recently, only a few have been studied in the context of LF. Thus, the validation of current sepsis biomarkers in liver disease patients, and the search for new, accurate, and cost-effective ones, must remain a priority in human research. Emerging research has highlighted the potential of machine learning-based approaches for enhancing the early detection and characterization of sepsis. Although preliminary results are promising, further prospective research is warranted to validate these findings across diverse patient populations, including individuals with LF, and to establish the clinical utility and generalizability of these approaches.

## FOOTNOTES

**Author contributions:** Kumar R and Kumar A designed the concept, collected the data and wrote the manuscript research study; and Kumar S collected the data and wrote the manuscript. All authors have read and approved the final manuscript.

**Conflict-of-interest statement:** None of authors have any conflict of interest to declare pertaining to this submission.

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**S-Editor:** Liu H
**L-Editor:** A
**P-Editor:** Guo X

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World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

*World J Crit Care Med* 2025 June 9; 14(2): 98791

DOI: 10.5492/wjccm.v14.i2.98791

ISSN 2220-3141 (online)

*MINIREVIEWS*

# Why should lymphocytes immune profile matter in sepsis?

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**Specialty type:** Critical care medicine

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade B, Grade B

**Novelty:** Grade B, Grade B

**Creativity or Innovation:** Grade B, Grade B

**Scientific Significance:** Grade B, Grade B

**P-Reviewer:** Hassan FE

**Received:** July 5, 2024

**Revised:** December 11, 2024

**Accepted:** December 19, 2024

**Published online:** June 9, 2025

**Processing time:** 233 Days and 19.1 Hours

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## Abstract

The global incidence of critical illness has been steadily increasing, resulting in higher mortality rates thereby presenting substantial challenges for clinical management. Among these conditions, sepsis stands out as the leading cause of critical illness, underscoring the urgent need for continued research to enhance patient care and deepen our understanding of its complex pathophysiology. Lymphocytes play a pivotal role in both innate and adaptive immune responses, acting as key regulators of the balance between pro-inflammatory and anti-inflam-matory processes to preserve immune homeostasis. In the context of sepsis, an impaired immunity has been associated with disrupted lymphocytic metabolic activity, persistent pro-inflammatory state, and subsequent immunosuppression. These disruptions not only impair pathogen clearance but also predispose pati-ents to secondary infections and hinder recovery, highlighting the importance of targeting lymphocyte dysfunction in sepsis management. Moreover, studies have identified absolute lymphocyte counts and derived parameters as promising clinical biomarkers for prognostic assessment and therapeutic decision-making. In particular, neutrophil-to-lymphocyte ratio, and lymphopenia have gained recognition in the literature as a critical prognostic markers and therapeutic target in the management of sepsis. This review aims to elucidate the multifaceted role of lymphocytes in pathophysiology, with a focus on recent advancements in their use as biomarkers and key findings in this evolving field.

**Key Words:** Lymphocytes; Neutrophil-to-lymphocyte ratio; Sepsis; Septic shock; Chronic critical illness; Persistent inflammation, immunosuppression, and catabolism syndrome

**Core Tip:** Lymphocytes are essential effectors in the immune response to sepsis, contributing to both the initial defense against infection and the regulation of inflammation during the progression to chronic organ failure. One hallmark of sepsis is a profound disruption in lymphocyte homeostasis, that may lead to the development of an immunosuppressive state. Lymphocytes counts and derived variables show significant potential as prognostic markers in sepsis, offering insight into mortality risk and the likelihood of persistent organ dysfunction.

**Citation:** Nedel W, Henrique LR, Portela LV. Why should lymphocytes immune profile matter in sepsis? *World J Crit Care Med* 2025; 14(2): 98791
**URL:** https://www.wjgnet.com/2220-3141/full/v14/i2/98791.htm
**DOI:** https://dx.doi.org/10.5492/wjccm.v14.i2.98791

## INTRODUCTION

The immune system is premised on defending organisms from invaders and promoting healing of injuries. Its responses are broadly categorized into two mechanisms: Innate and adaptive immunity[1,2]. The innate response corresponds to the initial reaction, in which cells originating from the myeloid progenitor differentiate to halt the spread of harmful agents. Polymorphonuclear cells and macrophages play a central role in this phase, eliminating pathogens through phagocytosis[3]. Specialized innate immune cells, such as dendritic cells, further enhance the immune response by transforming into antigen-presenting cells after phagocytizing the antigen. These cells bridge innate and adaptive immunity by presenting antigens to lymphocytes, thereby initiating the adaptive immune response[1,3]. This enables lymphocytes to perform immune recognition, thereby distinguishing between inert endogenous components and harmful external agents and memorizing antigen patterns[1,2].

This review addresses the role of lymphocytes counts and derived parameters in the immune response, with a particular focus on their involvement in sepsis. Additionally, it discusses lymphocytes as clinical biomarkers and their emerging potential as therapeutic targets in sepsis management. Lymphocytes constitute approximately 40% of the white blood cell population and include B cells, T cells, and natural killer cells and their subtypes (Figure 1). B cells and T cells are critical components of the adaptive immune response system, mediating responses to bacterial and viral pathogens, through antibody production and cell-mediated immunity, respectively[4]. In the context of sepsis, lymphocytes play a pivotal role in orchestrating the host immune response during both the acute and chronic phases of the syndrome[1]. Importantly, the lymphocytic response to sepsis may present distinct phenotypic profiles that are often associated with different clinical outcomes[4]. These profiles are influenced by the stage of the immune response - whether early or late - and are characterized by differences in lymphocyte proliferation, the expression of immunity-related proteins, and the secretion of signaling molecules. These cellular phenotypic transitions depend on metabolic plasticity to meet the substantial energy demands associated with immune activation, proliferation, and effector functions[2].

## HOW LYMPHOCYTES RESPOND DURING SEPSIS

Sepsis is a global health priority[5] and is associated with a high mortality rate, even in middle-income countries[6] and high-income countries[7]. Despite different definitions over the last few decades, sepsis is best defined as a syndrome shaped by pathogens and host factors in a dysregulated systemic host response[8]. It is regulated by inflammatory effectors such as tumor necrosis factor alpha, interleukin (IL)-6, and IL-1, which modulate cellular responses and influence patients' clinical outcomes[9]. Therefore, sepsis can potentially interfere with the host immune system and result in drastic changes[10]. During the first 24 hours - 48 hours following sepsis onset, the immune response is dominated by a pro-inflammatory burst, characterized by robust activation of cytokine pathways. Beyond this acute phase, the immune system undergoes a shift toward an anti-inflammatory state, often described as compensatory or maladaptive[11,12]. This transition can compromise immune surveillance and contribute to immune dysfunction.

One hallmark of sepsis is a profound disruption in lymphocyte homeostasis, characterized by a significant reduction in lymphocyte counts, termed sepsis-induced lymphopenia. This may lead to the development of an immunosuppressive state, predisposing individual patients to secondary infections induced by low pathogenicity invaders thereby exacerbating patient morbidity and delaying recovery[9]. This depletion affects $CD4^+$ T cells and $CD8^+$ T cells, B cells, and natural killer cells, resulting in impaired lymphocyte functionality and contributing to immune paralysis. The duration of immunoparalysis needs to be hampered since it contributes to increased morbidity associated with sepsis[11,13]. Therefore, lymphocytes phenotype in sepsis may transit through states of acute response, persistent pro-inflammatory signaling to immunosuppression. Both quantitative and qualitative disturbances in lymphocytes have been observed across these states[14]. Indeed, a reduced lymphocyte count combined with metabolic dysregulation can further disrupt the crosstalk between the adaptive and innate immune systems, undermining the coordinated response required to resolve injury effectively[15,16].

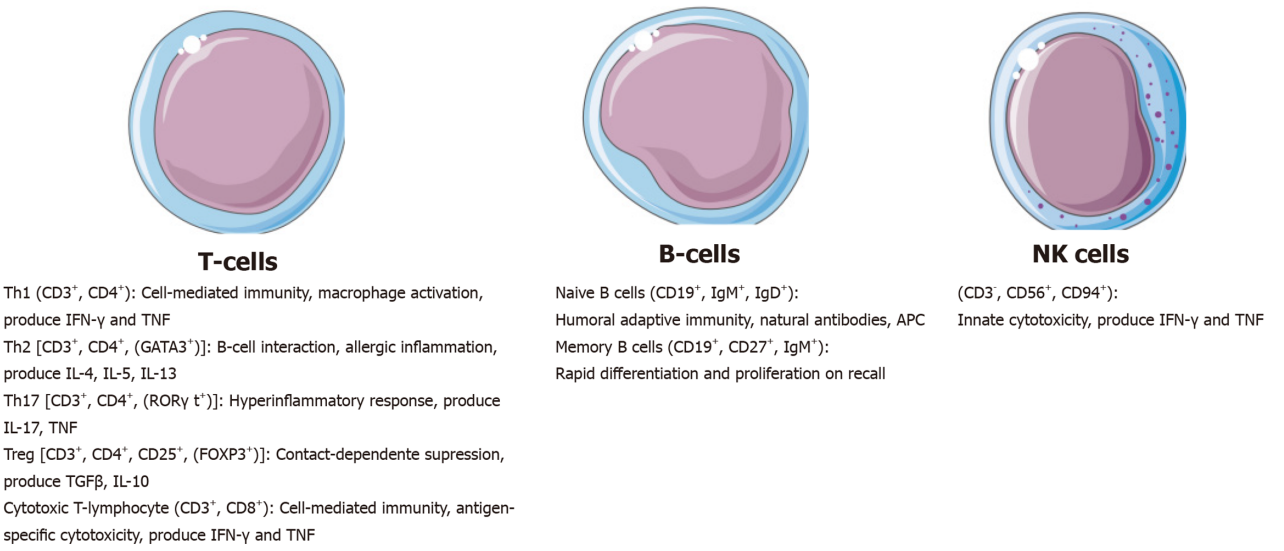


**Figure 1 Schematic view of the main subtypes of lymphocytes involved in sepsis.** Th: T-helper; IFN: Interferon; TNF: Tumor necrosis factor; IL: Interleukin; Treg: Regulatory T-cell; TGF: Transforming growth factor; APC: Antigen presenting cells; Ig: Immunoglobulin; NK: Natural killer.

## ARE LYMPHOCYTES ASSOCIATED WITH THE PROGNOSIS OF SEPSIS?

The use of inflammatory biomarkers for prognostic and therapeutic assessments in sepsis has gained significant attention. Biomarkers such as C-reactive protein, procalcitonin, IL-1β, and IL-6 are widely studied but not always accessible in clinical practice, particularly in middle- and low-income countries. This underscores the requirement of inexpensive, easy-to-perform, and reproducible biomarkers to aid clinical decision-making in sepsis management[17,18]. Lymphocyte-derived variables have emerged as promising biomarkers in recent years, providing insights into both acute injury and the progression of chronic sepsis. These variables can be derived from routine peripheral blood samples, and include total lymphocyte counts and ratios of lymphocytes to other immune cells (*e.g.*, neutrophils and monocytes) or immune-related molecules (*e.g.*, albumin and high-density lipoprotein). For instance, lymphopenia - defined as an absolute circulating lymphocyte count < 1000 cells/mm$^3$ -has been associated with worse prognosis in sepsis, with derived ratios like the neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR) providing additional read-out of patients with worse prognosis[4,19].

Several studies in different countries and subgroups of intensive care unit (ICU) patients have demonstrated strong associations between lymphopenia, its derived markers, and unfavorable clinical outcomes (Table 1)[20-32]. In a large Taiwanese database, it was found that an early lymphopenia was linked to increased one-year mortality in critically ill surgical patients, with this association remaining robust after advanced statistical adjustments such as propensity score matching[33]. Similarly, elevated NLR levels have been correlated with higher mortality in ICU patients[34], and the persistence of lymphopenia has been tied to worse outcomes, including increased risk of nosocomial infections, acute kidney injury, and 28-day mortality[35,36]. Both the monocyte-lymphocyte ratio and NLR showed accurate performance as biomarkers[35]. The prognostic value of lymphocyte counts and ratios extends beyond traditional ICU settings. For instance, in the context of corona virus infectious disease-2019, elevated NLR has been predictive of disease severity, prolonged ICU stays, and mortality[37,38]. Other ratios, such as the platelet-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio, have shown promise as moderate predictors of septic shock progression during prolonged ICU stays[39-41].

Sepsis-induced lymphopenia involves apoptotic mechanisms mediated by death receptor activation and mitochondrial pathways in lymphocytes[39-41]. This reduction is particularly significant in CD8$^+$ T cells, with survivors of septic shock showing recovery of these cell counts after five days post-ICU admission[42]. Decreases in T-cell subpopulations (CD3$^+$, CD4$^+$, and CD8$^+$) and B cells have been associated with an increased risk of nosocomial infections and diminished immunoglobulin M production[43,44]. However, the functional implications of lymphocyte subclasses remain underexplored, necessitating further investigation to refine their prognostic value and therapeutic target potential.

The impact of lymphopenia varies across the sepsis timeline (Figure 2). At sepsis onset, lymphopenia may not always correlate with 28-day mortality, but resolution of lymphopenia by day 4 has been linked to improved outcomes, even after adjusting for confounders[45]. Conversely, persistent lymphopenia from ICU admission to day 3 significantly increases the risk of secondary infections and 28-day mortality[46]. These findings suggest that lymphocyte trajectories during critical illness, particularly persistent lymphopenia, may serve as an accurate biomarker for short-term mortality, chronic critical illness development, and sepsis progression to septic shock[26,47]. When compared with the non-lymphopenic group, patients with sepsis and lymphopenia more frequently required ICU admission, had a longer hospital length of stay, and presented with a higher rate of in-hospital, and 30-day mortality[35,46,48]. Despite these promising findings, the clinical applicability of lymphocyte-derived biomarkers remains limited by inconsistencies in cutoff definitions for persistent lymphopenia, which range from 760 cells/μL to 1000 cells/μL across studies[35].

**Table 1 Observational studies exploring lymphocyte-derivates variables and clinical outcomes in sepsis**

| Ref. | Population | Variable measured | Outcome |
|---|---|---|---|
| Biyikli *et al*[20] | Adult patients older than 65 years with sepsis or septic shock in emergency admission | Platelet-lymphocyte ratio | Platelet-lymphocyte ratio was not associated with 30-day mortality (207.6 in non-survivors *vs* 168.3 in survivors) |
| Djordjevic *et al*[21] | Critically ill injured patients admitted to surgical ICU | PLR, MLR, NLR | There was no difference in the biomarkers regarding hospital mortality in septic trauma patients (8.5 in non-survivors *vs* 9.6 in survivors) |
| Gharebaghi *et al*[22] | Critically-ill patients with sepsis due to gram-negative pathogens | Neutrophil-lymphocyte ratio | Patients who deceased had increased values of NLR in day 2 (14.9 *vs* 9.3) and in day 3 of ICU admission (17.2 *vs* 9.1), but not at day 1 (13 *vs* 9.8) |
| Goda *et al*[23] | Neurosurgical critically ill patients with cathteter-associated urinary tract infections or central line-associated bloodstream infections | Neutrophil-lymphocyte ratio | An increased NLR was an independent predictor of in-hospital mortality in central-line associated bloodstream infections (7.29 in non-survivors *vs* 4.46 in survivors) |
| Guo *et al*[24] | Critically ill patients with sepsis, from MIMIC-IV database | Neutrophil + monocyte/lymphocyte ratio | An increased NMLR is associated with increased 30-day mortality (12.24 non-survivors *vs* 8.71 in survivors) |
| Hsu *et al*[25] | Critically ill cirrhotic patients with septic shock | LMR and NLR | Non-survivors had increased NLR (13 *vs* 10.3) and decreased LMR (1.1 *vs* 2.3) when compared with survivors |
| Li *et al*[26] | Critically ill septic shock patients | NLR | NLR at day 3 and delta NLR (day 3 - day 1), but not NLR at day 1 were associated with 28-day mortality, in univariate and multivariate analysis |
| Liang *et al*[27] | Critically ill patients with bloodstream infections | NLR | Delta NLR (NLR 48 hours - NLR at 0 hour) were higher in patients with shock |
| Liu *et al*[28] | Critically ill patients with sepsis, from MIMIC-IV database | LHR | Low values of LHR were associated with 90-day mortality |
| Lorente *et al*[29] | Critically ill patients with sepsis | NLR | Increase in NLR at day 1, day 4 and day 8 were associated with 30-day mortality, when controlled for SOFA score and lactate at this time intervals |
| Sari *et al*[30] | Critically ill patients with sepsis | NLR | NLR at day 1 of sepsis is not associated with ICU mortality. At day 3, NLR greater than 15 is strongly associated with mortality |
| Wu and Qin[31] | Critically ill patients with sepsis | NLR, PLR, MLR | There was no difference between variables measured at baseline in survivors and non-survivors at 28-days post ICU admission |
| Xiao *et al*[32] | Adult septic patients from MIMIC-IV database | N/LP | High and middle terciles of N/LP at baseline were associated with an increase in the incidence of septic AKI (HR 1.3 and 1.2, respectively), as compared with the lower tercile |

ICU: Intensive care unit; PLR: Platelet-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; AKI: Acute kidney injury; HR: Hazard rate; LHR: Lymphocyte-to-high-density lipoprotein ratio; LMR: Lymphocyte-to-monocyte ratio; MIMIC: Medical information mart for intensive care; N/LP: Neutrophil to lymphocytes and platelets ratio; SOFA: Sequential organ failure assessment; NMLR: Neutrophil + monocyte/lymphocyte ratio.

Additionally, while lymphopenia is associated with 90-day mortality and rehospitalization, its predictive accuracy for these outcomes is modest[49]. Larger, multicenter studies are needed to validate these findings and explore the implications of lymphopenia on clinically meaningful outcomes beyond mortality, including functional recovery and quality of life in different patient subgroups.

## ARE LYMPHOCYTES ASSOCIATED WITH CRITICAL CHRONIC ILLNESS?

Sepsis remains a leading cause of mortality, with most deaths occurring within 72 hours of diagnosis, underscoring the importance of early recognition and intervention to improve survival rates[11]. However, some patients progress to a state of persistent critical illness, characterized by worsening or unresolved multiple organ failure and a heightened risk of unfavorable outcomes. Even after surviving the acute phase of sepsis, patients often endure prolonged ICU stays and remain vulnerable to secondary infections. This condition, now termed persistent inflammation, immunosuppression, and catabolism syndrome (PIICS), is associated with substantial clinical, economic, and social burdens[50]. PIICS manifests as long-term dysfunction across multiple systems, including neurocognitive, muscular, respiratory, renal, and

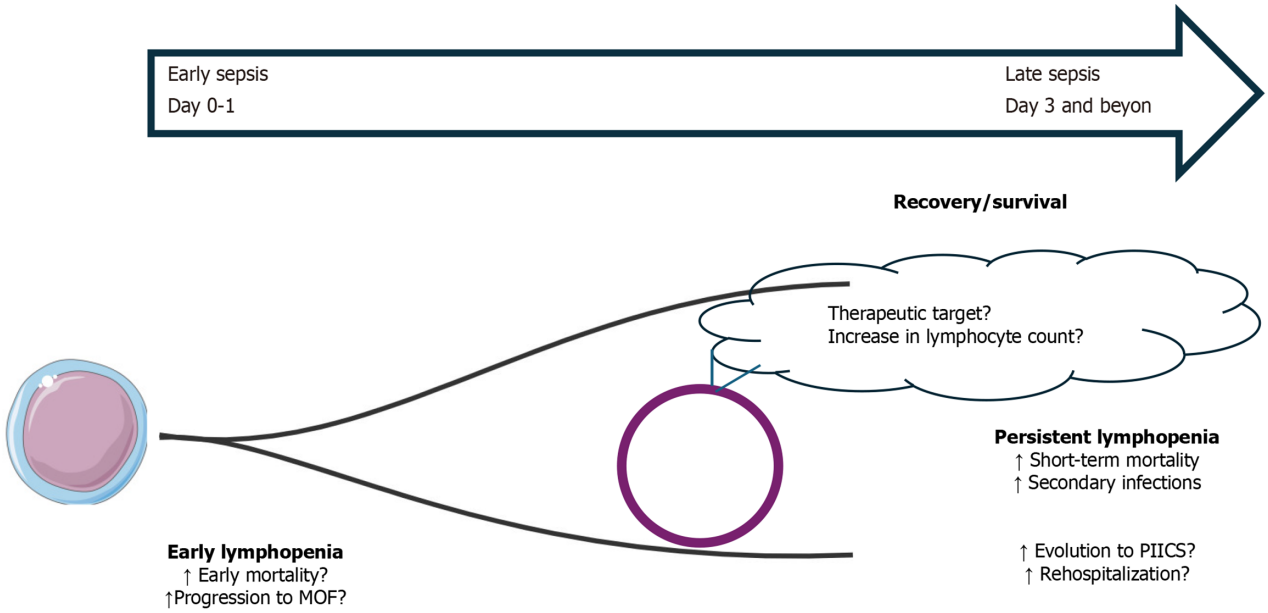


**Figure 2 Evolution of lymphocyte count in sepsis.** MOF: Multiorganic failure; PIICS: Persistent inflammation, immunosuppression and catabolism syndrome.

cardiovascular functions, often leading to lasting functional impairment. A defining feature of immunosuppression in PIICS is lymphopenia, specifically a lymphocyte count below 800 cells/μL. During sepsis, a compensatory anti-inflammatory response mediated by cytokines such as IL-10 and transforming growth factor beta counterbalances the initial pro-inflammatory cascade driven by IL-6 and IL-1[51]. While this response may mitigate tissue damage, it can also induce T-cell exhaustion and expand regulatory T-cell (Treg) populations, a subset of immunomodulatory $CD4^+$ T cells that suppress immune responses to control inflammation[52,53]. Tregs play a dual role in perpetuating persistent inflammation and immunosuppression, impairing the host's ability to resolve infections or respond to new threats[53,54].

Interestingly, the dysregulated expression of IL-6, IL-1, and IL-10 in sepsis has been shown to interfere with lymphocyte metabolism[55]. Persistent inflammation further disrupts mitochondrial function diminishing bioenergetic capacity and exacerbating immunoparalysis[56]. The mitochondrial bioenergetic dysfunction impairs adenosine triphosphate support in the presence of a hypercatabolic state, thereby undermining the appropriate immune function [56]. This imbalance sustains a vicious cycle of unresolved inflammation, hypercatabolism, and progressive lymphocyte-mediated immunosuppression or immune exhaustion. Sepsis-induced immunoparalysis involves multiple mechanisms within the adaptive immune response, including lymphocyte apoptosis, diminished antigen presentation, impaired antigen-driven proliferation, increased suppressive Treg populations, and T-cell exhaustion[11]. While studies recognized that both lymphopenia and reduced T-cell functionality have been strongly associated with adverse outcomes[10] the precise relationship between these variables requires further investigation (Figure 3). Nowadays, lymphopenia is a hallmark of chronic critical illness[57], especially when it occurs alongside PIICS[58]. This persistent immunosuppressive state contributes to prolonged disease courses and underscores the need for targeted interventions to restore lymphocyte function and mitigate long-term complications in sepsis survivors.

## ARE LYMPHOCYTES POTENTIAL THERAPEUTIC TARGETS?

Recent findings have highlighted immunostimulatory therapies as novel strategies to restore host defense in sepsis and prevent opportunistic infections[59]. Among these, IL-7 stands out as a promising candidate for addressing sepsis-induced T-lymphocyte immune dysfunction. IL-7 has demonstrated the ability to enhance T-cell survival and functionality, exhibiting anti-apoptotic properties, promoting robust proliferation of $CD4^+$ T cells and $CD8^+$ T cells, and improving cytokine production. However, its effects are primarily limited to naïve and memory T lymphocytes rather than effector-activated T cells[59].

To date, two clinical trials have specifically assessed recombinant human IL-7 in septic patients with lymphopenia. In a phase II randomized controlled trial, Francois *et al*[60] observed a 3-fold to 4-fold sustained increase in lymphocyte counts, including a rise in circulating $CD4^+$ T cells and $CD8^+$ T cells, without inducing cytokine storms, exacerbating inflammation, or causing organ dysfunction. A more recent trial also reported significant increases in absolute lymphocyte counts (including both $CD4^+$ and $CD8^+$ subsets) with IL-7 administration compared to placebo[14]. Both studies confirmed the safety profile of IL-7, though intravenous administration was associated with transient fever and respiratory distress, adverse effects not observed with intramuscular administration[14]. It is worth noting that these trials were not designed to evaluate key clinical outcomes such as mortality, length of hospital stay, or days free from organ support. Consequently, the long-term benefits of IL-7, including its impact on reinfections, rehospitalizations, and

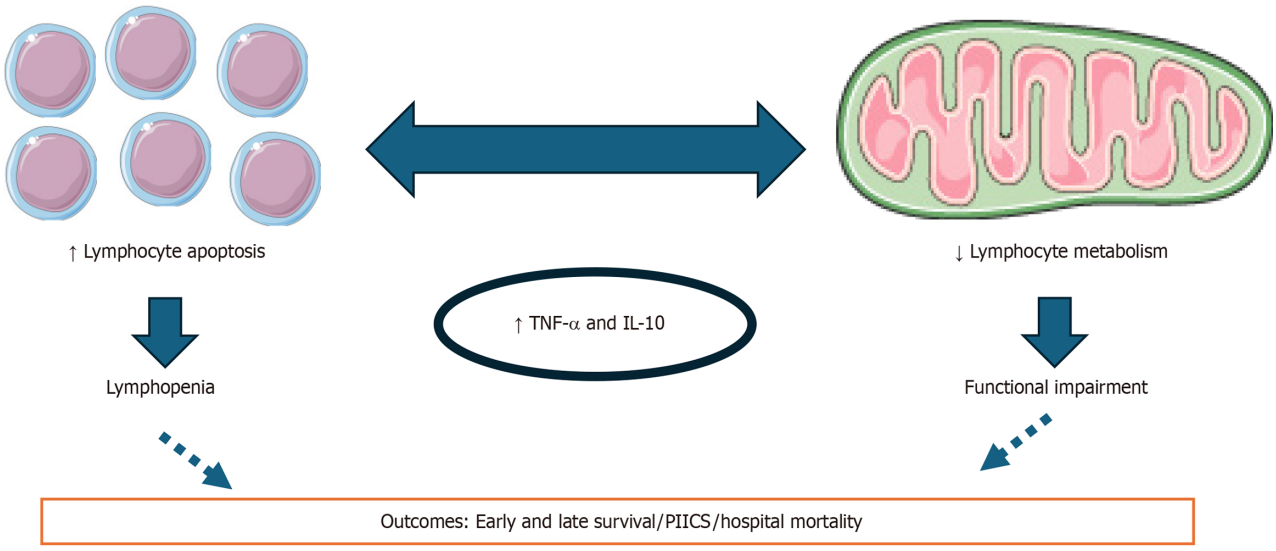


**Figure 3 Interplay between inflammatory response, quantitative and qualitative impairment in lymphocytic response in sepsis.** TNF: Tumoral necrosis factor; IL: Interleukin; PIICS: Persistent inflammation, immunosuppression and catabolism syndrome.

non-infectious complications, remain uncertain. Further research is needed to determine the specific patient populations most likely to benefit, such as those with lymphopenic sepsis at admission *vs* patients with persistent lymphopenia during their clinical course.

## CONCLUSION

Lymphocytes play a central role in the host's response to sepsis, both in the initial immune activation and in the progression to chronic organ failure. Lymphocyte counts and their derived variables hold significant promise as prognostic biomarkers in septic patients. However, large-scale, multicenter studies are essential to validate their clinical utility and to explore the therapeutic potential of lymphocyte-targeting interventions such as IL-7. These efforts will be critical in refining strategies to improve the management and outcomes of patients with sepsis.

## FOOTNOTES

**Author contributions:** Nedel W, Henrique LR, and Portela LV reviewed the literature and wrote the manuscript; and all authors thoroughly reviewed and endorsed the final manuscript.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.



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**S-Editor:** Bai Y
**L-Editor:** A
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World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

*World J Crit Care Med* 2025 June 9; 14(2): 98939

DOI: 10.5492/wjccm.v14.i2.98939

ISSN 2220-3141 (online)

MINIREVIEWS

# Psychological first aid in the intensive care unit

Traci N Adams, Carol S North

**Specialty type:** Critical care medicine

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade C, Grade C, Grade C

**Novelty:** Grade B, Grade C, Grade C

**Creativity or Innovation:** Grade C, Grade C, Grade C

**Scientific Significance:** Grade C, Grade C, Grade C

**P-Reviewer:** Adnyana IMDM; Huang DB

**Received:** July 9, 2024

**Revised:** November 27, 2024

**Accepted:** December 16, 2024

**Published online:** June 9, 2025

**Processing time:** 232 Days and 18.2 Hours

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## Abstract

The intensive care unit (ICU) is a stressful environment for patients and their families as well as healthcare workers (HCWs). Distress, which is a negative emotional or physical response to a stressor is common in the ICU. Psychological first aid (PFA) is a form of mental health assistance provided in the immediate aftermath of disasters or other critical incidents to address acute distress and re-establish effective coping and functioning. The aim of this narrative review is to inform the development and utilization of PFA by HCWs in the ICU to reduce the burden of distress among patients, caregivers, and HCWs. This is the first such review to apply PFA to the ICU setting.

**Key Words:** Intensive care unit; Stress; Distress; Psychological first aid; Mental health



**Core Tip:** Psychological first aid is a form of mental health assistance provided in the immediate aftermath of disasters or other critical incidents to address acute distress and re-establish effective coping and functioning. It can be applied in the intensive care unit setting to patients, families, and healthcare workers.

**Citation:** Adams TN, North CS. Psychological first aid in the intensive care unit. *World J Crit Care Med* 2025; 14(2): 98939

**URL:** https://www.wjgnet.com/2220-3141/full/v14/i2/98939.htm

**DOI:** https://dx.doi.org/10.5492/wjccm.v14.i2.98939

## INTRODUCTION

The intensive care unit (ICU) is a stressful environment for patients and their families as well as healthcare workers (HCWs)[1]. Stressors such as codes, procedures, family meetings, and deaths abound in the ICU; therefore, distress, which is a negative emotional or physical response to a stressor, such as emotions of sadness or frustration or physical symptoms including diminished hunger or chest pain, is common among ICU providers, conscious patients in the ICU, and families[1]. Distress can be debilitating and may warrant interventions such as active listening, group discussion, and other supportive measures. Because training on measures to alleviate distress is not a required part of critical care training, many HCWs know little about how to assist patients and families or their own colleagues in coping with distress in the ICU.

Stressors that occur on a large scale and affect many individuals are known as disasters. Because disasters are just one type of stressor, we can apply the best practices learned from disaster mental health (MH) to the stressors associated with healthcare work[2]. One such practice is psychological first aid (PFA). PFA is a form of MH assistance provided in the immediate aftermath of disasters or other critical incidents to address acute distress and re-establish effective coping and functioning[2,3]. It was developed through expert consensus and is flexible for use in various settings, populations, and cultures[3]. PFA can be provided by both MH and other critical incident responders[3,4].

Several PFA programs, including RAPID-PFA at Johns Hopkins[5], have been instituted to train HCWs and emergency personnel on MH aspects of emergency response. However, most PFA programs, including RAPID-PFA, train workers to respond to major traumatic incidents but not to daily stressors occurring in the ICU such as codes or difficult family meetings, which are very stressful but inherently different from mass casualty events based on size and severity[3-7]. It is therefore essential to adapt PFA to the ICU setting. Studies have shown that when HCWs are offered PFA training during a pandemic, lack of staff time and inability to meet in person substantially limit the uptake and effectiveness of PFA[7,8]. Teaching PFA to HCWs at high risk for distress, such as ICU workers, in times of normative operations may better prepare them to support their patients, families, and one another through daily stressors occurring in the ICU as well as equip them for disasters such as pandemics or mass casualty events[9].

The aim of this narrative review is to inform the development and utilization of PFA by HCWs in the ICU to reduce the burden of distress among patients, caregivers, and HCWs. This is the first such review to apply PFA to the ICU setting. There are several available versions of PFA, but they generally contain all the same basic elements[3-5]. The paragraphs below will summarize the elements of PFA.

## ELEMENTS OF PFA

### *Being there*

The first element of PFA is simply being there, or the "ministry of presence". Effective providers of PFA aspire to be present, unobtrusive, helpful, and compassionate, with sensitivity to interpersonal cues about touch, distance, and privacy. In disasters such as terrorist attacks, natural disasters, or mass casualty events, being there involves attending to immediate physical needs, providing comfort, and addressing concerns. In the ICU, HCWs can be present by spending quality time with patients and families negotiating difficult circumstances and with their own colleagues who may be facing significant stressors. They might sit with a grieving family even after the family meeting concludes or pause rounds to help a colleague who has just endured a difficult procedure or code. Because HCWs are physically present for extended periods in the ICU to witness stressful moments in medical care directly, they can reach more individuals than can point-in-time services such as formal counseling offered by external providers outside the critical care team.

### *Safety and stabilization*

In natural disasters or terrorist attacks, provision of safety and stabilization entails removing people from avoidable exposure to physical harm. Physical harm may occur in the ICU setting when members of the healthcare team or others are physically or verbally attacked by patients or their family members. In such situations, notifying security and physically redirecting HCWs and others from harm may be necessary for initiation of PFA. More often, before a conflict escalates to physical violence or self-harm, individuals may lose the ability to function appropriately or even show warning signs of potentially disruptive behavior. For them, safety and stabilization may be established simply by giving the person a few minutes of privacy to process the situation and calm down, by enlisting the calming assistance of friends and family, or even by separating disruptive individuals from others to facilitate de-escalation. For anyone contemplating impending harm to self or others, HCWs are advised to seek security and/or medical assistance immediately and not leave the person unsupervised.

### *Skilled listening*

Skilled listening is a central part of PFA. In administering PFA to other HCWs in the ICU or to patients and their families, HCWs attentively listen to their stories with concerned interest. They can invite individuals' thoughts, gently probing for details while avoiding the revisiting of unnecessary painful details of the stressful or traumatic experience as indicated by the person's apparent reluctance to discuss them.

Medically relevant information is obtained through genuinely interested listening to the distressed person's reports of stressful exposures, injuries, medical history, medications, and psychiatric history. This information is best elicited without forcing discussion of difficult feelings, which may be counter-therapeutic in the immediate aftermath of a critical incident when strong emotions may be overwhelming. For example, if a resident is distressed after a procedural

complication, sitting with the resident and asking "How are you doing" and then pausing to listen without interruption is far more helpful than probing for the details of the procedure.

The best way to develop skilled listening is to practice under the observation of a trained professional who is adept at this practice. Appendix A contains several scenarios that HCWs can use for role playing to learn the practice of skilled listening.

### Education and reassurance

Helping people understand what is going on with the situation and within themselves is a vital function of PFA. The type of education and reassurance provided in PFA depends on the characteristics of the individual and the stressor. Individuals with no psychiatric disorder may be comforted by normalizing and validating their emotional responses. They can be reassured that disturbing feelings they may have that are foreign to their experience do not necessarily indicate psychopathology and that most people do not develop psychiatric illness after exposure to intense stressors, including major disasters[2,6,10,11]. In the ICU, HCWs may apply the principles of education and reassurance to grieving families or other HCWs experiencing significant work-related stressors.

If a psychiatric disorder is suspected, the PFA provider may need to help the person-overcome stigma to facilitate acceptance of psychiatric evaluation. It may help to discuss the biological basis of emotions, how medications work to help resolve emotional difficulties, and that treatment is effective. Of note, it is important for critical incident responders to know that according to current diagnostic criteria in psychiatry[12], naturally occurring medical illness, even if life-threatening or occurring in a pandemic, is not defined as a traumatic event, and thus post-traumatic stress disorder (PTSD) is not an expected outcome. This does not imply that stressors not constituting traumatic events by this definition are not important or can be discounted, because many stressors may be more severe and have more negative MH outcomes than events formally qualifying as stressors. In other words, it should be emphasized that trauma and PTSD are not required for psychiatric evaluation and care to be warranted. Psychiatric disorders that most commonly begin after stressful events include depressive and anxiety disorders. Psychoeducation can reduce the number of sick days taken by individuals with psychopathology and can improve willingness to accept psychiatric evaluation[7,8].

Risk communication is an important skill set within the education and reassurance component of PFA because it informs and guides people to make the wisest decisions and choose the safest behaviors[2,10]. Clear and consistent risk communication delivered by trusted members of the leadership team is particularly important in the ICU during times of crisis such as pandemics, because it helps keep HCWs informed and safe and increases confidence in the leadership's guidance and support of workers at the institutional level[2,10].

### Coping and stress management

PFA may begin to address coping and stress management by giving individuals initial permission to cry, feel bad, be nonproductive, and focus on themselves for a limited time. Application of crisis coping skills can help individuals regain control of some aspect of the situation and start to restore routines, which can help them start to address their situation and begin to feel better. Coping skills include effective utilization of social supports as well as personal techniques such as positive self-talk, exploration of perspectives and meaning in the experience, self-care, and appropriate use of humor. Some people are prone to digress to extremes (*e.g.*, excessive eating, foregoing rest and sleep) in crisis situations, and PFA for them may include reminders to seek balance in self-care activities and avoid excesses.

In times of ordinary ICU operations, stress management may include purposeful self-care practices such as finding down time and seeking support from family and friends away from work[2]. Especially during times of crisis in the ICU such as a pandemic, HCWs may need to advocate for their institutions to broaden the pool of front-line workers and ensure sufficient time away from work for recovery[2].

### Problem solving

As problems arise following a disaster or other major stressor, overwhelmed or distressed individuals may be assisted with problem solving by someone who is not compromised by such extreme experience and has a clear head to lend sound reasoning skills. In the ICU, overwhelmed HCWs and especially trainees can be aided with practical problem solving through techniques of making lists, prioritizing, weighing advantages and disadvantages of possible choices, breaking problems into manageable units, and maintaining sight of the larger perspective and progress. Assistance with problem solving may also be applicable to patients and families who are facing difficult decisions. People may be able to grow and gain strength from overwhelming experience if they have guidance and encouragement to explore new behaviors and develop previously untried problem-solving skills.

### Connect with support

Sources of support that can help people in times of crisis include not only family and friends but also formal support services. Psychosocial service professionals such as social workers and HCWs have skills and resources that can hasten the road to recovery. Research has shown that people who lack social supports may have heightened risk for psychological adjustment problems following trauma or major stressors.

Asking patients to consider involving trusted friends or family in difficult discussions may help them navigate difficult news and medical decisions. Similarly, allowing an ICU team to gather together informally outside of work to spend time together and discuss their experiences can hasten their return to usual operations following an intense stressor.

### Acute symptom management

After critical incidents, the most bothersome early incident-related symptoms are likely to involve hyperarousal[6,11].

Physical hyperarousal symptoms may include insomnia or jitteriness and restlessness. Emotional hyperarousal symptoms may include irritability, nervousness, anxiety, worry, fear, panic, and inability to concentrate. Tools to facilitate distraction from immediate distress can be helpful for symptom management, including, for example, engaging in absorbing and enjoyable activities such as games, puzzles, reading, movies, music, and dancing[10]. Relaxation techniques such as deep breathing, muscle relaxation, and pre-hypnotic induction through listening to relaxing scenarios can help ameliorate hyperarousal symptoms. Examples of relaxation exercises are provided in appendix B. Individuals with overwhelming symptoms may warrant short-term pharmacotherapy by a psychiatrically trained physician to reduce tension[10]. In the ICU, both distressed HCWs as well as patients and their family members can be led through exercises to help calm their symptoms. Additionally, HCWs can be given time away from work to engage in pleasurable and engaging activities that they enjoy to distract them from their symptoms.

### *Know when more help is needed*

Specialized assistance may be needed for individuals with persistence or escalation of intolerable symptoms despite interventions, pre-existing psychiatric illness requiring ongoing treatment, or requests for additional help. For these individuals, timely evaluation and/or stabilization by a psychiatrically trained clinician may be warranted[2,10]. Urgent help may need to be enlisted for acutely worrisome behavior such as indications of impending harm to self or others or for disorientation or altered level of consciousness, and for individuals who are too overwhelmed to be able to provide essential care for themselves and/or dependents[2,10].

During times of crisis such as pandemics or mass casualty events, institutions can mobilize psychiatric professionals and institute psychiatric screening measures to systematically identify high-risk individuals[2]. ICU clinicians providing PFA should familiarize themselves with MH resources that are available inside and outside of their institutions so that they will be able to help connect colleagues with psychiatric assistance. National crisis hotlines are also available to everyone (call or text 988 for the National Suicide Prevention Lifeline). Institutional leadership can facilitate this PFA component by clearly communicating available MH resources directly to employees[2].

### *Caring for the caregivers*

Critical care workers or family members of disaster victims can themselves experience psychological distress or even become full-fledged MH casualties in difficult circumstances or critical incidents[6,10,11]. Factors contributing to caregiver distress include extended and severe exposure to intense stressful circumstances, exposure to injury and infection, worry about loved ones involved in the incident, loss of personal property, difficult working conditions, long work hours and cumulative fatigue, separation from usual supports and familiar comforts, and ethical dilemmas[6,10].

All elements of PFA can address general distress of clinicians in the ICU, but this last step focuses on their needs specifically related to critical incidents. For this component, caregivers can follow the same basic advice they give to those they are assisting, including rest, nutrition, hygiene, exercise, relaxation, and healthy balance.

Caring for colleagues may particularly involve offering positive support and encouraging words, helping out with their work, monitoring their fatigue levels, and facilitating restorative time together. Restorative time can include breaking bread together at meals, gathering to share experiences, and conducting follow-up meetings to review operations and work out any kinks for next the time.

Healthcare organizations can assist critical care personnel with distress by providing equitable workload distribution; observation of workers for distress and fatigue; risk communication and active listening; compassionate gestures; encouragement and recognition of service; and organized peer support, crisis counseling, and formal group therapy or individual treatment[2]. It is best for institutions is to prepare in advance by establishing these types of functions for HCWs that are ready to go when the need arises[10].

## CONCLUSION

Stressors abound in the ICU, and distress is common among ICU clinicians as well as patients and their families[1]. PFA can be implemented for these groups to address acute distress and re-establish effective coping and functioning. Healthcare organizations can be tasked with partnering with ICU clinicians to facilitate application of the elements of PFA through institutional supports[2].

This article has detailed the use of representative PFA practices for HCWs, patients, and caregivers under the ordinary stresses of the ICU as well as during extraordinary circumstances such as individual critical incidents and collective disasters, especially pandemics such as coronavirus disease 2019. The narrative review format of this article may limit reproducibility, and there is no available evidence to assess the effectiveness of the exercises provided.

Further, while this article provides practical guidance for the general application of PFA in these settings and circumstances, development of formal specific procedures for the ICU is needed. Then, research is needed to measure outcomes such as burnout scores and prevalence of psychiatric illness, assess effectiveness, and inform further improvement of the use of PFA in this setting and in resource-limited settings. Formal development of PFA practices has the potential to greatly reduce distress and improve the effectiveness of HCWs in various ICU settings and circumstances.

## FOOTNOTES

**Author contributions:** Adams TN and North CS contributed to conceptualizing, writing, and editing the manuscript; all of the authors read and approved the final version of the manuscript to be published.

**Conflict-of-interest statement:** The authors do not have any conflicts of interest to report.



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**S-Editor:** Luo ML
**L-Editor:** A
**P-Editor:** Zhang XD

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World Journal of Critical Care Medicine

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*World J Crit Care Med* 2025 June 9; 14(2): 99654

DOI: 10.5492/wjccm.v14.i2.99654

ISSN 2220-3141 (online)

*MINIREVIEWS*

# Role of interventional pulmonology in intensive care units: A scoping review

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**Specialty type:** Critical care medicine

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade B, Grade D

**Novelty:** Grade B, Grade B

**Creativity or Innovation:** Grade B, Grade C

**Scientific Significance:** Grade B, Grade C

**P-Reviewer:** Huang DB; Liang GD

**Received:** July 27, 2024

**Revised:** October 31, 2024

**Accepted:** December 23, 2024

**Published online:** June 9, 2025

**Processing time:** 215 Days and 5.3 Hours

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## Abstract

Interventional pulmonology (IP) represents a rapidly growing and developing subspecialty within pulmonary medicine. To the intensivist, given the elaborate undertakings with respect to airway, lung and pleural disease management-IP has shown an increasing presence and remain a major ally in the care of these patients. Thus, an understanding of the different roles that IP could offer to the intensivist is of prime importance in the multi-disciplinary care of the complex patients within the intensive care units, particularly in relation to lung, airway and pleural diseases. This review article will explore the different intersections of IP in critical care and discuss the applications of this discipline within the highly complex critical care environment.

**Key Words:** Hemoptysis; Central airway obstruction; Rigid bronchoscopy; Critical care; Tracheostomy

**Core Tip:** The role of interventional pulmonology (IP) in critical care is described within this review article which will highlight the role of IP in the management of critically ill patients, particularly in patients with respiratory failure due to several reasons including hemoptysis, central airway obstruction and its different etiologies including malignancies, foreign body aspirations, blood clots and mucus. Moreover, the role of IP in management of pleural diseases, use of different tools such as endobronchial ultrasound in diagnosis of pulmonary vascular issues in the critically ill patient will be described. Finally, the role of IP in performing bedside procedures such as tracheostomy and percutaneous ultrasound gastrostomies with consequent economic benefits and decrease in lengths of stay will be outlined.

**Citation:** Halawa ARR, Farooq S, Amjad MA, Jani PP, Cherian SV. Role of interventional pulmonology in intensive care units: A scoping review. *World J Crit Care Med* 2025; 14(2): 99654
**URL:** https://www.wjgnet.com/2220-3141/full/v14/i2/99654.htm
**DOI:** https://dx.doi.org/10.5492/wjccm.v14.i2.99654

## INTRODUCTION

Interventional pulmonology (IP) procedures are indispensable in managing patients hospitalized in the intensive care unit (ICU). The applications of IP include but are not limited to patients with central airway obstruction (CAO), hemoptysis, and respiratory failure resulting from numerous causes such as foreign bodies, blood clots and mucoid impaction of airways. Various equipments in the interventional pulmonologist's arsenal, including rigid bronchoscopy (Figure 1A), argon plasma coagulation (APC) and cryotherapy (Figure 1B) are of crucial importance while addressing these challenging cases. Moreover, pleural diseases are common in the critical care units and a structured approach to manage these conditions is of particular importance. The increasing utility of endobronchial ultrasonography in the ICU and its influence on clinical decision-making is gaining recognition. The decision to pursue tracheostomy is pertinent in patients who are faced with prolonged dependence on mechanical ventilation. Additionally, establishing nutritional access in the same setting through a gastrostomy tube is frequently required. Both procedures are being performed by interventional pulmonologists at the bedside. The purpose of this review article is to provide an outline of the different pathways and roles IP plays in the care of patients in critical care units.

## HEMOPTYSIS

The expectoration of blood from the lower respiratory tract is referred to as hemoptysis. While unlikely to be associated with exsanguination and hemorrhagic shock, it may lead to respiratory failure due to ventilation/perfusion mismatch, or subsequent airway blockage. Hemoptysis, when leading to such respiratory complications is referred to as life-threatening hemoptysis. There is no precise quantitative parameter to define life-threatening hemoptysis, one criteria based on blood volume that has been suggested is approximately 150 mL in a 24-hour period or a bleeding rate that is greater than or equal to 100 mL/hour, which in layman terms would equate to half a cup of blood[1].

Blood supply to the lungs is composed of two sources, the pulmonary arteries and the bronchial arteries. The pulmonary artery circulation is a low-pressure system supplying the lung parenchyma, in contrast to the bronchial artery circulation which is a relatively high-pressure system supplying the bronchial tree, and 2% of the total vascular supply to the lung. In most cases of non-life-threatening hemoptysis, the origin is usually from the pulmonary artery circulation, compared to life-threatening hemoptysis, in which the source is more likely from a bronchial artery[2]. The most common causes of non-life-threatening hemoptysis in developed countries are acute bronchitis, bronchiectasis, pneumonia, lung cancer, and bronchial neoplasms[3]. Other noteworthy etiologies are autoimmune disorders such as anti-glomerular basement membrane, systemic lupus erythematosus, vasculitis, pulmonary embolism (PE), tuberculosis, and medications such as VEGF inhibitors[4]. Rare etiologies include pulmonary arteriovenous malformations, which may be seen in the setting of hereditary hemorrhagic telangiectasia, pulmonary artery aneurysms, and aorto-bronchial or broncho-pulmonary arterial fistulas. Furthermore, coagulopathy due to medications, renal failure, or liver disease can predispose to hemoptysis in patients with underlying lung pathology[4]. Despite a thorough workup, up to 30% of patients with hemoptysis may not have a cause identified, however, repeating work up when symptoms recur may yield a diagnosis [5].

### *Diagnosis*

Management of patients with hemoptysis is centered around assessment of hemodynamic stability and respiratory compromise. In hemodynamically stable patients, a thorough history and physical should be obtained, in addition to imaging of the chest. Determination of the frequency and severity of bleeding is of utmost importance. It is crucial to ascertain if there is true airway bleeding or a potential mimicker such as hematemesis. Clues on physical exam that may point towards pseudo-hemoptysis include stigmata of liver disease, visualization of hematemesis, blood-tinged nasal crusting, and nasopharyngeal or mucosal ulceration. Laboratory studies such as hemoglobin, platelet count, liver function tests and coagulation profile should be collected. Even though hemoglobin may be normal in the acute setting, airway bleeding leads to mortality secondary to asphyxiation rather than blood loss, therefore clinicians should be vigilant in


**Figure 1 Instrument.** A: Rigid bronchoscopy and its accessories–notice the different types of forceps with its larger sizes which are helpful in foreign body removal; B: ERBE combined argon plasma coagulation and cryotherapy machine.

cases of hemoptysis. As mentioned above, as little as 150 cc of blood would be enough to occlude the airways.

### *Management*

In cases of hemodynamic instability or respiratory failure, endotracheal intubation should be contemplated to ensure airway security. It is essential to intubate using a large-bore endotracheal tube (size 8 mm or larger) whenever feasible. This is performed in preparation for bronchoscopic procedures; however, intubation should not be delayed if a size 8 endotracheal tube is unavailable. Other conservative yet life-saving measures in patients with known lung pathology include patient positioning. Placing the patient in lateral decubitus position with the bleeding lung down is vital to prevent aspiration of blood into the unaffected lung. With bronchoscopic guidance, selective mainstem intubation of the unaffected lung can be utilized to isolate the bleeding lung or a double lumen endotracheal tube can be inserted. Although double lumen endotracheal tubes have been advised, their role in the acute setting is questionable, primarily due to the difficulty of insertion and poor suction capabilities given the small size of the lumen[6].

Following intubation, bronchoscopy should be promptly conducted to identify the cause of hemorrhage and suction aspirated blood, therefore enhancing ventilation-perfusion (V/Q) matching. An endobronchial blocker balloon can be concurrently positioned to isolate the hemorrhaging section and regularly deflated to evaluate hemostasis and the potential recurrence of bleeding. It is essential to document the balloon's depth and regularly observe ventilator waveforms to evaluate potential balloon movement or displacement.

The decision to pursue computed tomography angiography (CTA) before or after bronchoscopy depends on the clinical context and patient stability. Computed tomography (CT) is highly sensitive in localizing the source of bleed, which can be as high as 77%[7,8]. Additionally, the diagnostic yield increases when combined with bronchoscopy. CTA allows for visualization of pulmonary parenchyma and vasculature which can assist in localizing the bleeding vessel.

Both rigid and flexible bronchoscopy can be performed to manage hemoptysis, however rigid bronchoscopy is often not readily available at the bedside. Rigid bronchoscopy can be utilized for better access and passage of large instruments into the trachea and bronchi, suctioning, and lavage. While not readily available, the role of rigid bronchoscopy in patients presenting with life threatening hemoptysis from central airway tumors is lifesaving. Central airway tumors may present with hemoptysis in 20% of cases (Figure 2), and life-threatening hemoptysis is seen in only 3% of cases[9]. Several measures can be undertaken to achieve hemostasis (Table 1). Ice-saline lavage has been routinely used to control bleeding and is believed to cause hemostasis by inducing local vasoconstriction and decreased blood flow to the lavaged segment [3]. Other hemostatic agents that can be instilled are vasopressin analogues such as desmopressin, diluted epinephrine, fibrinogen-thrombin solution and tranexamic acid[10]. Additionally, the use of bronchoscopic tools such as electrocautery, or APC can be utilized to alleviate bleeding malignant or benign lesions. Additionally, other measures such as endobronchial tamponade with a fogarty balloon has been described. Although the above measures can achieve temporary hemostasis, patients with massive hemoptysis should be evaluated for bronchial artery embolization and surgical and interventional radiology consultation should be obtained.

## ENDOBRONCHIAL ULTRASONOGRAPHY IN THE ICU

Endobronchial ultrasound (EBUS) has emerged as a valuable tool in the diagnosis and management of various pulmo-

**Table 1 Tools in hemoptysis**

| Feature | Flexible bronchoscopy | Rigid bronchoscopy |
|---|---|---|
| Invasiveness | Less invasive; performed *via* nose or mouth | More invasive; requires general anesthesia and operating room |
| Airway control | Limited | Excellent |
| Reach | Greater; can access smaller, more peripheral airways | Limited; may not reach distal airways as effectively |
| Working channel | Narrower | Wider |
| Suctioning capacity | Limited | Greater |
| Instrument size | Limited | Larger instruments can be used |
| Visualization | May be limited in larger airways | Better visualization due to larger instruments |
| Tamponade | Possible, but less effective | Easier to achieve direct compression |
| Versatility | Allows for biopsies, lavages, and some therapeutic interventions | Primarily used for airway control and managing massive hemoptysis |
| Sedation | Often done under conscious sedation | Requires general anesthesia |
| Recovery time | Faster | Longer due to general anesthesia |
| Complications | Lower risk | Higher risk, although rare |
| Patient tolerance | Generally, more comfortable | Less comfortable due to larger scope |

This table provides a general comparison. The best choice of bronchoscopy depends on the specific clinical situation and the expertise of the bronchoscopist.

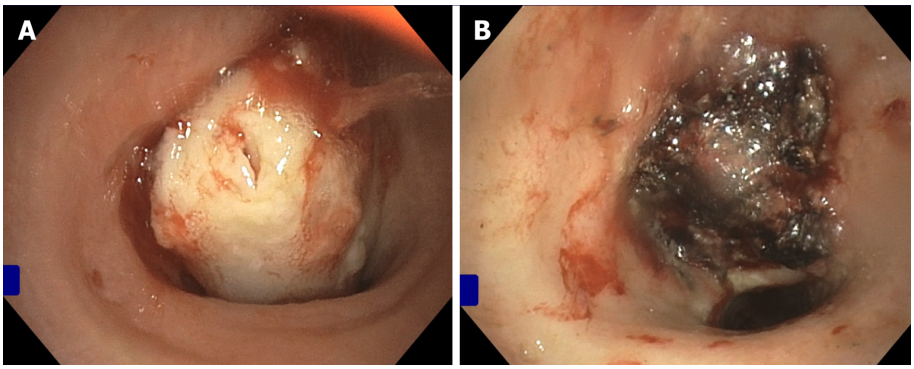


**Figure 2 Clinical manifestation.** A: 64 years old man who presented with hemoptysis secondary to adenocarcinoma of the lung with tracheal involvement. Note the tumor occupying the trachea with bleed; B: Rigid bronchoscopy was performed following which a combination of mechanical debulking, argon plasma coagulation and cryo-debulking was performed with resolution of hypoxemic respiratory failure and hemoptysis.

nary conditions. It can be used in the assessment of intrathoracic and airway pathology, as well as diagnosis and staging of pulmonary malignancy. The utilized probes are the radial probe and the convex probe. Radial probe EBUS is employed to identify peripheral lung lesions alongside navigational or robotic bronchoscopy to enhance biopsy yield and reduce complication rates[11,12]. Convex probe EBUS on the other hand is more commonly used, especially in sampling mediastinal, hilar, paratracheal, and parabronchial tissue for staging of pulmonary malignancy. Although EBUS was initially utilized in the outpatient setting, its application has expanded to encompass critically ill patients admitted in the ICU.

EBUS involves the insertion of a flexible bronchoscope equipped with an ultrasound transducer. The ultrasound transducer is fitted with a balloon that is connected to a guide sheath, which can be inflated with saline, to serve as an ultrasound wave transmitter and improve visualization. Needle aspiration of mediastinal or pulmonary structures is done under direct ultrasound visualization using a particular needle, sizes of which range between 19G to 22G[13].

In comparison to the outpatient setting, the indications of EBUS in the critically ill are similar. Patients with mediastinal lymphadenopathy who are critically ill may undergo EBUS to evaluate whether an infectious, inflammatory, or neoplastic process is ongoing. In the setting of infectious processes, EBUS guided transbronchial needle aspiration (TBNA) may aid in accurate diagnosis and facilitating timely initiation of appropriate antibiotics and treatment. If there is a concern for malignancy, EBUS can help establish the diagnosis while simultaneously perform tumor staging. The same applies to sampling lung lesions that are proximal and accessible by EBUS.

### *EBUS and mediastinal lymph node sampling in the ICU*

The data on use of EBUS in critically ill patients is scarce and only limited to single center experiences. The largest of these studies was published by Decavèle *et al*[14], which included 9 critically ill patients, 4 of which were mechanically ventilated. Rapid onsite evaluation of the cytological specimens lead to a change in management of 4 of 6 patients. Koh *et al*[15] published a case series of 6 patients, all of which were mechanically ventilated. A diagnosis was made in 5 out of the 6 patients, all of which were diagnosed with malignancy, and no major complications were documented. Okachi *et al* [16] describes a case of pulmonary Cryptococcus in a patient with negative serologies diagnosed by EBUS-TBNA, and prompt initiation of antifungal therapy. Additionally, endoscopic ultrasonography (EUS) is employed to get samples from lymph node stations 5, 6, 8, and 9, which are inaccessible *via* EBUS. This can be accomplished with a convex probe EBUS scope or an EUS scope. The transesophageal approach may be preferred in patients with tenuous respiratory status who may not tolerate obstruction of their endotracheal tube[17,18]. However, performing EUS requires additional expertise, and is not routinely performed by all interventional pulmonologists.

### *EBUS and mediastinal vasculature*

Mediastinal and hilar vasculature can be visualized with the use of convex probe EBUS, and there is data to suggest that central pulmonary emboli can be diagnosed with EBUS. A pilot study published in 2009 with 32 patients who were diagnosed with PE with CTA, collectively having 101 PE, EBUS was able to detect 96%, and all patients were diagnosed with at least 1 PE. None of the patients developed complications, and the mean procedure time was less than 5 minutes. Of note, the endoscopists were able to access and analyze the CTA prior to the procedure, and none of the patients were on mechanical ventilation[19]. Not all patients may be candidates to undergo pulmonary CTA, or lung perfusion scintigraphy, due to critical illness or contrast allergies, and EBUS may be utilized to diagnose PE at bedside. However more robust data is needed to evaluate the use of EBUS for diagnosing PE, especially in the critical care setting[20].

There are several challenges to the use of EBUS in the ICU. EBUS probes may not be readily available, and EBUS-TBNA requires a multidisciplinary team including respiratory therapists, technologists, cytotechnologists, and an assistant who is familiar with handling the EBUS equipment. Furthermore, performing EBUS in a mechanically ventilated patient may considerably reduce the cross-sectional area of the endotracheal tube, leading to diminished tidal volume, ventilation, alveolar recruitment, and an elevated risk of cardiac compromise. However, this can be mitigated by minimizing suctioning, and avoiding prolonged procedure time, and increasing fractional inspired oxygen ($FiO_2$)[21].

Although data is limited to single centers regarding using EBUS in the ICU, the utility of EBUS is promising, especially in the diagnosis of benign and malignant lesions, in addition to inflammatory and infectious processes. However, its utility should be reserved to specific patients to limit complications and promote effective use of resources.

## FOREIGN BODY ASPIRATION

Foreign body aspiration (FBA) is an uncommon but significant cause of hospitalizations, respiratory compromise and ICU admission. Its prevalence is higher in children, and current data suggests that the incidence of non-fatal choking in children under the age of 14 occurs at a rate of 20.4 per 100000. 55.2% of these episodes occur in children < 4 years of age. Data from the National Safety Council demonstrated that approximately 80 percent of patients with FBA were younger than the age of 15. Mortality peaks in children < 1 year of age and adults > 75 years of age[22]. The prevalence of FBA in adults is unknown, and data is limited to single center case series.

Aspirated material can be subdivided into organic and inorganic material. Inorganic FBA includes dental debris, appliances, or prostheses during dental procedures, nails or pins (Figures 2 and 3). Furthermore, iatrogenic aspiration from bronchoscopic tools such as brushes or needles can occur. Organic material (food particles) can be aspirated due to incomplete chewing or poor swallowing. It is important to know the nature of the aspirated foreign body (FB), since organic and inorganic material may require different bronchoscopic tools for removal (Figure 4). Organic foreign bodies constitute bones (*i.e.*, from fish), meat, fruit, and seeds (Figure 5). Extraction of organic foreign bodies tends to be more challenging, since they tend to cause more local inflammation and granulation tissue formation. Additionally, they can expand from airway moisture and worsen obstruction. In contrast, inorganic foreign bodies may cause inflammation, though to a lesser extent, but may cause direct airway injury if sharp or abrasive. Pills, such as iron tablets and potassium chloride pills, when aspirated, can result in significant airway edema and ulceration, as reported in some case reports[23, 24].

### *Diagnosis*

Clinical presentation varies and depends on the degree of obstruction, location of the FB, and chronicity. The most common symptom is cough, and patients may also present with hemoptysis, foul-smelling sputum, or chest pain[25]. Dyspnea is uncommon and asphyxiation is rare[26]. Patients may have a chronic cough due to distal obstruction and recurrent post-obstructive pneumonia. Other signs suggesting chronicity include unilateral wheeze, and complications from retained foreign bodies such as bronchial stenosis, bronchiectasis, abscess, pneumothorax and pneumomediastinum [25]. Some patients may not recall a history of choking or aspirating[25,26].

If the patient is stable and there is no concern for respiratory compromise, imaging should be obtained. However, if there is suspected asphyxiation, imaging should not delay intervention. A postero-anterior and lateral X-ray of the chest is an appropriate initial test. Of note, most foreign bodies are radiolucent and may not be easily visualized on plain film. However, inorganic foreign bodies, especially metallic objects, are radiopaque and can be visualized[27]. Other signs that may suggest aspiration on imaging are focal hyper-lucency, which may suggest air trapping. Additionally, airspace

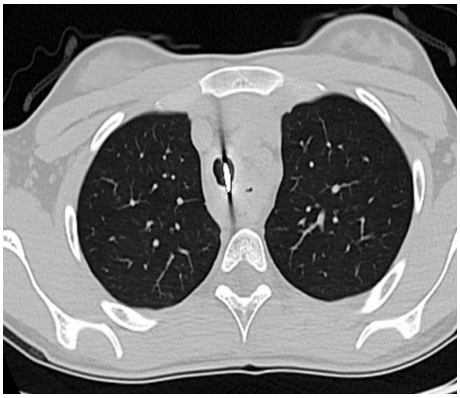

**Figure 3 Computed tomography scans of chest in axial view showing aspirated coin in mid trachea.**

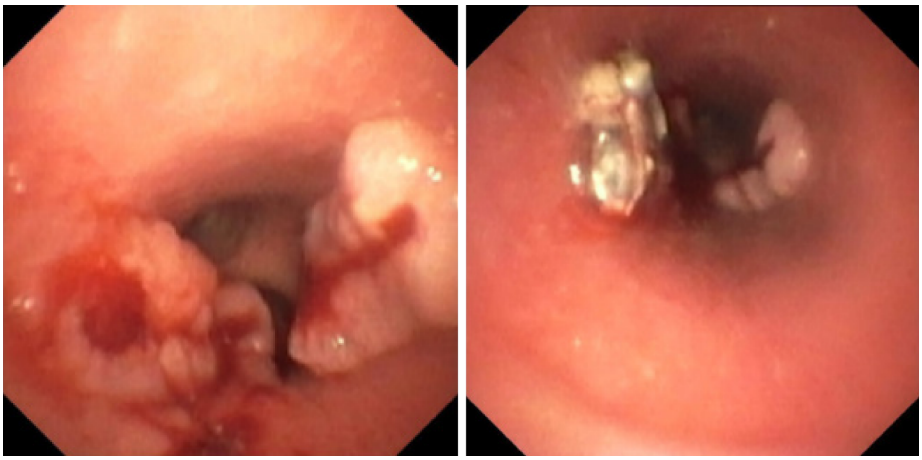

**Figure 4 Rigid bronchoscopy was performed which showed granulation tissue around the coin which was then removed with rigid forceps.**

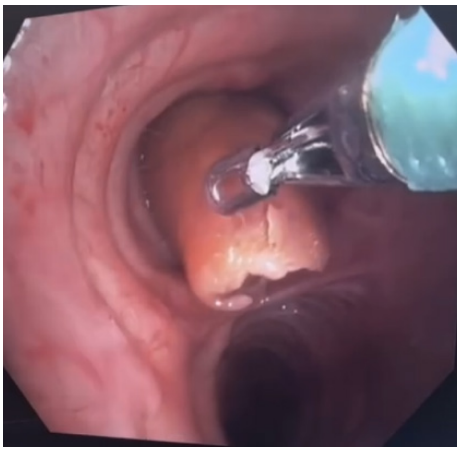

**Figure 5 Bronchoscopy showing aspirated hot dog in the right main stem bronchus which was removed with forceps.**

disease such as consolidation, atelectasis, or mediastinal shift may point towards the presence of foreign bodies. CT could be considered especially if there is a high index of suspicion and chest radiographs are negative. If acutely aspirated, foreign bodies may be more easily visualized in the airway. Although not routinely performed, three-dimensional imaging on a multi-detector multi-slice CT (*i.e.*, virtual bronchoscopy) can be utilized to enhance the detection of aspirated foreign bodies[28].

### Management

In cases of life-threatening asphyxiation, initial measures should focus on securing the airway with an endotracheal tube, and if ventilation is unsuccessful, emergent tracheotomy or cricothyrotomy should be considered. Following securement of the airway, laryngoscopic evaluation of the oropharynx is necessary, especially if the FB is in the supraglottic/glottic regions, since one-third of life-threatening asphyxiation occurs due to a supraglottic FB. If supraglottic and visualized, it can be retrieved with Magill forceps[29].

In some cases of life-threatening FBA, and in cases of non-life-threatening FBA, flexible bronchoscopy is the diagnostic and therapeutic procedure of choice. In a retrospective study of 103 patients with FBA, data suggested that rigid bronchoscopy may be more effective in patients with a history of previous failed attempt of retrieving the FB, and in patients with a delayed diagnosis, and especially if the patient has no significant comorbidities[30]. Depending on the FB, proper planning and selection of instruments is prudent. Commonly used instruments are forceps, grasping claws, snares, fish net baskets, magnet-tipped probes, and cryoprobes. Forceps are commonly used for FB extraction and are preferable for less friable foreign bodies such as bones, plastic and metallic objects. The use of forceps in organic material is not recommended, since it can increase the risk of fragmentation and distal displacement of the FB into the airway.

Baskets and snares are used for friable foreign bodies and organic foreign bodies. There are several different types of baskets including fishnet basket, zero-tip retrieval basket, grasping basket and mini-grasping basket. As the basket is contained within its sheath, the sheath is advanced through the working channel, into the airway, between the FB and the airway wall, and beyond the FB. Once the sheath is distal to the FB, the basket is deployed behind the FB, and the basket is pulled back in a rotational axis to snare the FB. The whole apparatus, including the basket, sheath, and bronchoscope are then withdrawn. Fishnet baskets have a similar mechanism.

Cryoprobe is commonly utilized by interventional pulmonologists to biopsy and debulk endobronchial tumors, and in obtaining biopsies of lung parenchyma. Organic FB with moisture can freeze and adhere to the cryoprobe. The cryoprobe is inserted through the working channel, and advanced into the airway until it's in contact with the foreign object. The probe is activated, and the cryogen is released, freezing the FB which adheres to the probe, and can be withdrawn. Also, saline can be instilled onto foreign bodies to enhance freezing and adherence, and this can be applied to inorganic FBs [31].

If large foreign bodies are present within the central airway, or if the patient is at high risk of respiratory compromise, rigid bronchoscopy should be considered, especially if prior attempts with flexible bronchoscopy have failed. Rigid bronchoscopy allows greater access to the central airways and allows gas exchange while simultaneously advancing multiple instruments into the airways including grasping forceps, suction catheters, and even the flexible bronchoscope. Optical forceps could also be used to allow for direct visualization, rigid telescope and rigid forceps can be used for FB retrieval (Table 2).

Following the removal of any FB, the bronchial tree should be reexamined for residual fragments and other foreign bodies. It is important to note that some foreign bodies are too large to be withdrawn through the endotracheal tube, and at times, the bronchoscope, FB, and endotracheal tube must be withdrawn altogether, and the patient may need to be re-intubated.

## CAO

CAO is a potentially life-threatening condition which constitutes obstruction of airflow in the trachea and/or mainstem bronchus. This may occur secondary to primary lung malignancy, metastatic disease, or benign disease. Although the incidence of CAO is not well-defined in the literature, more recent data suggests that airway obstruction can be seen in up to 13% of patients with lung cancer, and a further 5% of patients developing CAO upon follow up[32]. Additionally, the incidence of benign conditions that result in CAO such as tracheomalacia (TM) and tracheal strictures is unknown. Multiple classification systems have been implemented in CAO, such as malignant and nonmalignant, intrinsic or extrinsic (*i.e.*, intraluminal or extra-luminal), and dynamic or fixed (such as tracheobronchomalacia or tracheal stenosis, respectively)[33].

Primary lung cancer is the most common cause of CAO. Squamous cell carcinoma more commonly affects the airways; however, adenocarcinoma has also been reported to cause CAO. This occurs due to extension of parenchymal tumor into the airway lumen, or from extrinsic compression of the airway. Primary airway tumors such as carcinoid, adenoid cystic carcinoma, are less common. Other malignant causes are thyroid cancer and esophageal cancer. Benign etiologies are tracheal strictures which may occur secondary to endotracheal tubes or tracheostomy tubes, FBA, and tracheobronchomalacia[33].

### Diagnosis

Several radiological clues may point towards CAO, but if life-threatening obstruction is suspected, securing the airway with intubation followed by direct inspection should not be delayed. Clues on the chest radiograph may include tracheal deviation or mediastinal shift from mass effect, tracheobronchial filling defect, or signs of obstruction such as pneumonia, atelectasis, or lobar collapse. A CT scan may show similar findings and may also reveal intraluminal defects in the airways with better characterization of mediastinal and hilar structures. Although pulmonary function test is recommended and may demonstrate characteristic patterns on flow volume loops, it may not be feasible to perform in critically ill patients (Figure 6).

**Table 2 Tools used in aspirated foreign bodies**

| Tool | Type of FB | Technique | Advantages | Disadvantages |
|---|---|---|---|---|
| Forceps | Inorganic | Advanced through the working channel of the bronchoscope, external grip-handle can be used to open and close the forceps | Common, available, and easy to use. Able to grip thin, small, or flat shaped objects | Risk of fragmentation and distal displacement with organic FB |
| Snares | Organic and inorganic | Looping or lassoing technique, passed through the bronchoscope to encircle the FB under direct visualization | Useful for larger or irregularly shaped objects such as dental prosthesis, allows for secure capture | Not as readily available. Difficult to use on small or slippery FB |
| Baskets | Organic and inorganic | Expands to ensnare and retrieve the FB. After its deployed out of the sheath and past the foreign body, the basket is pulled back in a rotation axis to snare the foreign body | Good for retrieving multiple small objects, or irregularly shaped FB | Limited to soft or pliable FB, less effective for large or rigid FB. Friable objects may also fragment and fall out of the basket, in which case a fishnet basket may be more useful |
| Cryoprobe | Organic, or FB with high moisture/water content | Freezes the FB to the probe, allowing for extraction. The probe along with the bronchoscope is then retrieved through the endotracheal tube | Excellent for organic material, non-fragmenting. Useful for extraction of granulation tissue formed around the FB. Tracheal and bronchial cartilaginous tissue are resistant to cryotherapy | Requires precision, risk of damaging nearby tissue. Care must be taken so that the adjoining mucosa does not form part of the crystal |

FB: Foreign body.

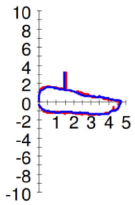


**Figure 6 Spirometry showing flattened inspiratory and expiratory loops consistent with fixed upper airway obstruction in a patient with subglottic stenosis.**

### *Management*

In patients with non-life-threatening CAO, heliox, which is less dense than inhaled nitrogen and oxygen, may be considered to promote more laminar flow of air through the large airways and at branch points. Heliox can be administered through non-rebreather or non-invasive ventilation. In patients with life-threatening CAO, initial management should be centered on securing the airway with endotracheal intubation and mechanical ventilation. For those where intubation is not feasible or unsuccessful, rigid bronchoscopic intubation should be considered, in addition to emergency cricothyrotomy or tracheostomy if the lesions are at or above the vocal cords. Fiberoptic intubation should also be considered to directly visualize the obstruction and avoid trauma. Intubation with a minimum size 8 mm endotracheal tube is recommended. In severe cases, consideration for veno-venous extracorporeal membrane oxygenation (ECMO) (or venoarterial-ECMO in patients with cardiac dysfunction) can be considered in select patients as a temporizing measure until the CAO can be treated[34]. Management will be further discussed based on whether the CAO is secondary to malignant or non-malignant etiologies.

### *Non-malignant CAO*

There are several causes of non-malignant CAO, the most common being tracheal strictures, which can be a complication of endotracheal or tracheostomy tubes. Non-malignant etiologies can also include FBA, and hyperdynamic collapse from tracheobronchomalacia. Granulation tissue formation from stents, surgical anastomosis (*i.e.*, lung transplant recipients), autoimmune disease such as granulomatosis with polyangitis (Figure 7) or relapsing polychondritis can also lead to CAO. Management of non-malignant CAO is treated differently depending on the underlying disorder.

In the setting of subglottic/tracheal stenosis, restoring airway patency can be achieved with either rigid or flexible bronchoscopy. After accessing the airway, radial cuts are made into scar tissue with an electrocautery needle knife, followed by balloon dilatation (Figure 7B). Balloon dilatation alone may be ineffective in some cases, and combining dilation with electrocautery cuts helps avoid use of excessive pressure and iatrogenic mucosal tears with balloon dilation. In patients with more complex stenosis, a circular resection can also be performed followed by dilatation. Following dilation, stents can be deployed to maintain airway patency for benign strictures[35].

TM is characterized by weakness in the wall of the airway, which results in significant airway narrowing during expiration. Several classification systems have been proposed, such as the appearance of the trachea (*i.e.*, crescent, lateral,

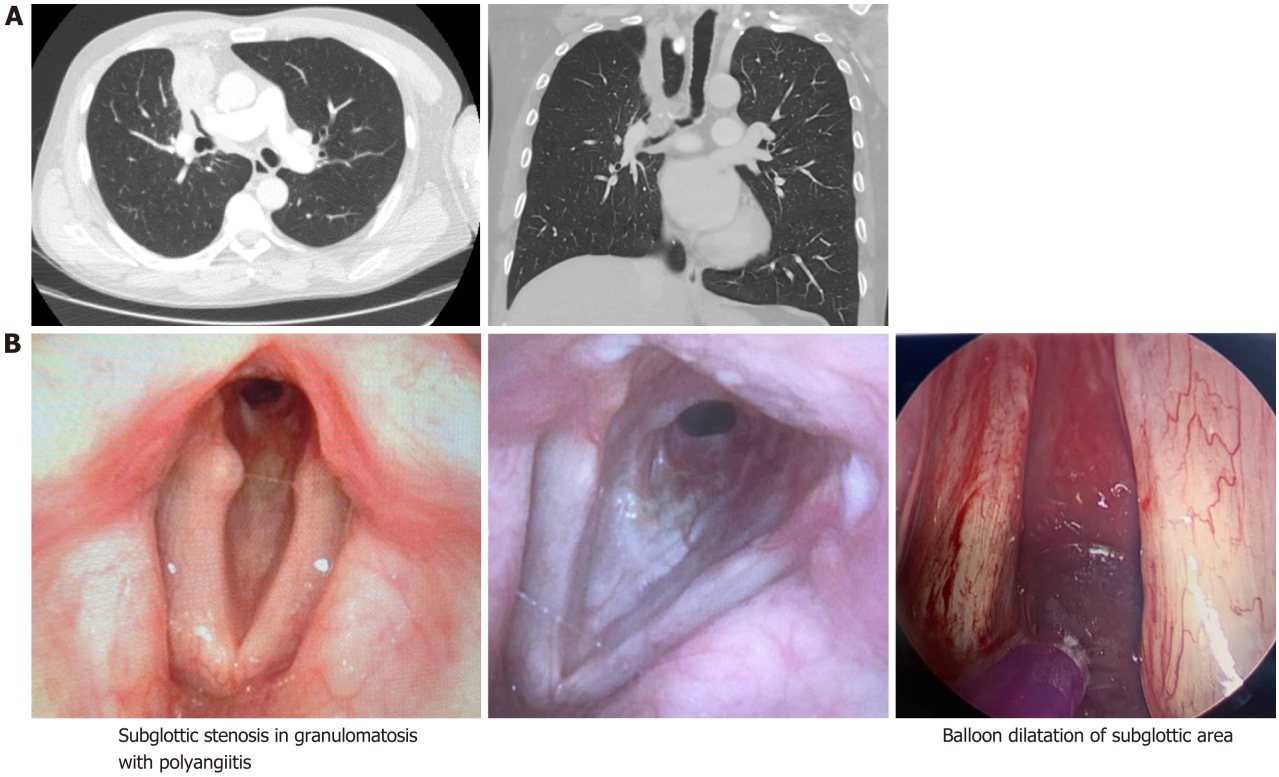


**Figure 7 Computed tomography scans and bronchoscopy.** A: Computed tomography scans showing right upper lobe atelectasis in a 53-year-old patient with granulomatosis with polyangitis; B: Bronchoscopy showing subglottic stenosis in the same patient following which balloon dilatation was performed to relieve the stenosis.

or circumferential TM), distribution of narrowing (tracheal, bronchial, segmental or diffuse), or etiology (*i.e.*, congenital or acquired)[36].

Published data supports the use of stent placement (Figure 8) in benign CAO, in addition to TM[37]. The choice of stent depends on the clinical scenario. Uncovered self-expanding metallic stents can be used in the short term, are more easily placed, deployed with flexible bronchoscopy, and preserve mucociliary function. However, they have a black box warning for treatment of benign airway disease and are not recommended for long-term use. Additionally, they are not useful for patients with diffuse disease. Silicone stents are firm, durable, and may be easier to reposition. They are preferred for long term use in patients with dynamic airway collapse who are not surgical candidates. However, they do have a higher rate of migration, infection, and impair mucociliary clearance. Furthermore, deployment and removal require rigid bronchoscopy.

APC refers to noncontact electrocoagulation and has been utilized as a more common alternative to contact electrocautery. When a 5000V spark is created at the tip of a probe, a tungsten electrode ionizes argon gas, releasing argon plasma. The argon plasma finds the nearest tissue and results in coagulative necrosis[38]. It has been used in open surgery for treatment of superficial hemorrhage, in addition to gastro-intestinal endoscopy to achieve hemostasis in gastrointestinal bleeds. There are case reports that describe the use of APC to treat airway obstruction resulting from granulation tissue at the site of surgical anastomosis, including airway stents and endoprosthesis, however, it does not result in tumor vaporization and is not ideal for the debulking large masses[38,39].

### *Malignant CAO*

Multiple modalities can be utilized to manage malignant CAO. Management is centered on restoring airway patency by tumor debulking, airway dilation, and preserving patency with stenting in the setting of intraluminal or extraluminal obstruction (Figure 9).

Rigid bronchoscopy is commonly utilized where the airway can be dilated with the barrel of the rigid bronchoscope, and serial dilation can be performed in less urgent cases with either balloons or semi-rigid dilators, which is the preferred method due to less mucosal trauma and consequent granulation tissue formation. Of note, rigid bronchoscopy may be the modality of choice in central tumors where coring out may be the only option, especially if patients are hypoxemic.

Electrocautery has been reported in the management of malignant CAO. In pedunculated masses causing CAO, electrocautery with a snare device can be used to cauterize the stalk and remove the mass. Laser therapy is the mainstay of tumor debulking. A variety of lasers have been utilized in the past, such as the $CO_2$ laser, argon laser, and the Nd:YAG laser. Due to its effective tissue penetration, and minimal absorption by hemoglobin, the Nd:YAG laser is most commonly used[40]. Its use in benign and malignant CAO, and its effectiveness in restoring airway diameter, in addition to symptomatic improvement in patients has been well-documented[40]. APC does not result in tumor vaporization and is not recommended for debulking endobronchial masses[38,39]. It is important to note that all thermal modalities such as

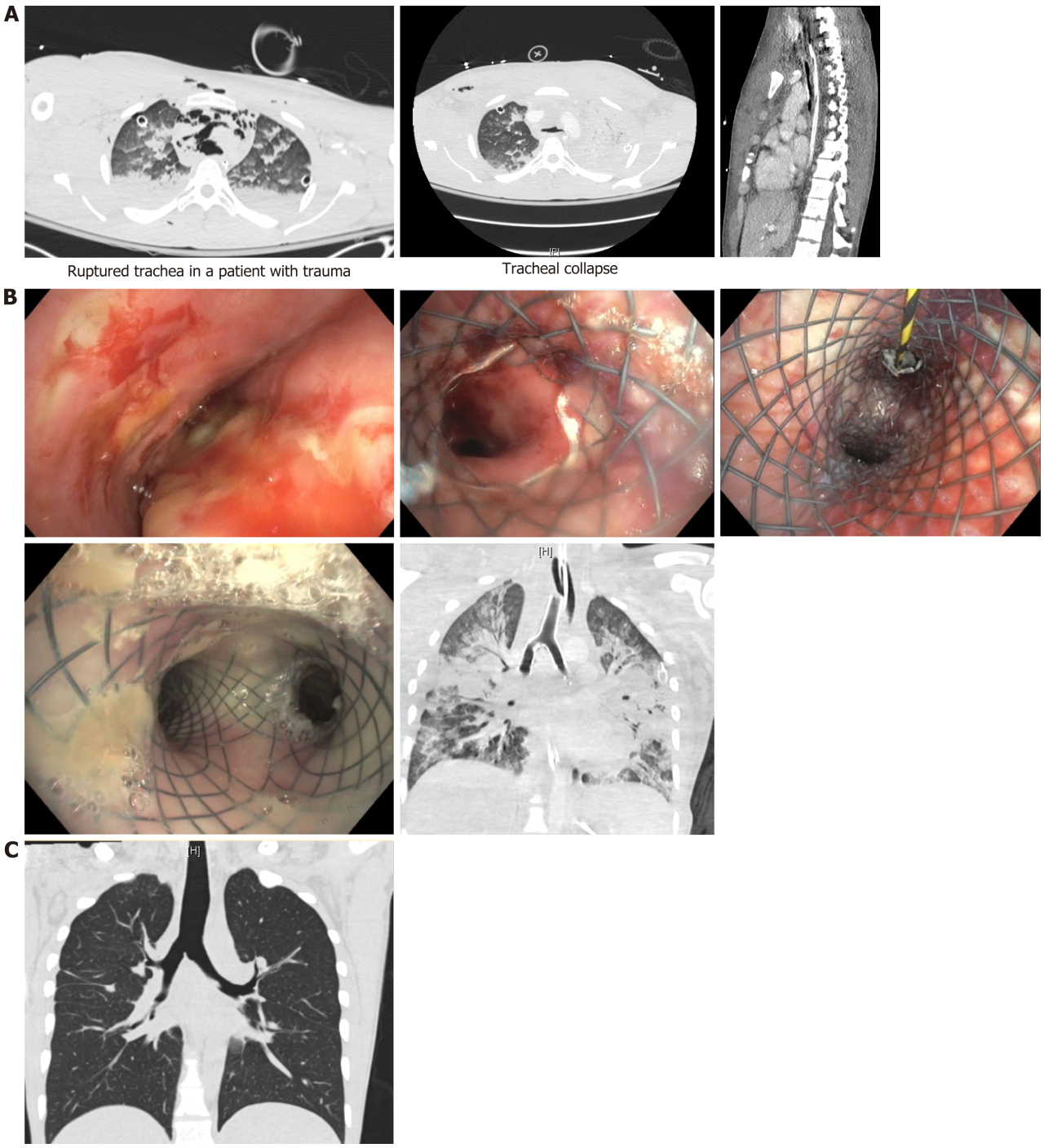


**Figure 8 Tracheal surgery.** A: Computed tomography scans in an 18-year-old patient showing tracheal rupture following motor vehicle accident; B: With extracorporeal membrane oxygenation support, rigid bronchoscopy was performed followed by placement of Y stent; C: Tracheal tear healed following which Y stent was removed.

laser, electrocautery, or APC require a reduction in $FiO_2$, and not all patients may tolerate such a reduction, limiting their role in such settings. Cryotherapy, on the other hand, may be utilized in this setting (Table 3).

Cryotherapy can be effective in treating malignant CAO. One study showed its utility in resolving hemoptysis in malignant disease in up to 93% of patients, in addition to complete endobronchial tumor removal in 82% of patients[41]. Airway stenting has been used to treat malignant CAO, and stents consist of two types, metallic stents, and silicone stents. Metal stents can be covered or uncovered. For malignant airway obstruction, covered metallic stents are used to prevent tumor ingrowth. Uncovered metallic stents are rarely used and are difficult to extract. As mentioned, silicone stents may require rigid bronchoscopy for placement, have a higher risk of migration, but are more easily removed (Table 4).

Depending on underlying lung reserve and patient effort, the physiologic effects of CAO occur when at least 50% of airway is occluded[42]. Therapeutic bronchoscopy can be considered successful when at least 50% of airway patency is restored. In ICU patients, the evidence supports the use of modalities mentioned above in patients with CAO and acute hypoxic respiratory failure requiring mechanical ventilation, and favorable outcomes including early extubation and

**Table 3 Tools in central airway obstruction**

| Tool | Technique | Indication | Advantages | Disadvantages |
|---|---|---|---|---|
| Electro-cautery | Electrical current applied *via* a probe to burn or coagulate tissue, electrocautery knives can also be used for tissue resection prior to dilation | Removal of tumors, hemostasis, tissue resection in subglottic stenosis | Precise control, minimal bleeding, and immediate effect. Useful in removal of pedunculated masses (electro-cautery snare) | Risk of thermal injury to surrounding tissue, requires low fractional inspired oxygen |
| Balloon dilation | Balloon catheter inserted and inflated to dilate stenosed airways | Tracheal/bronchial stenosis | Minimally invasive. Can be utilized prior to stent placed to achieve long-term airway patency | Risk of tearing or perforation of the airway |
| Laser therapy | Used to cut or vaporize obstructive tissue in the airway (Nd:YAG laser most commonly used) | Obstruction from tumors or benign growths | High precision, effective in debulking obstructive lesions | Risk of thermal injury. Risk of damaging surrounding tissue. Costly, not widely accessible |
| Cryo-probe | Freezing tissue with liquid nitrogen or other cryogenic substance, allowing tissue adhesion and destruction | Treatment and debulking of benign or malignant tumors. Foreign body removal | Minimizes bleeding. Effective for organic tissue | Multiple treatments may be required to debulk large tumors |
| Argon plasma coagulation | Non-contact thermal coagulation using ionized argon gas | Useful in control of bleeding, useful in granulation tissue formed at the site of surgical anastomosis | Effective for superficial bleeding lesions, less risk of perforation | Does not result in tumor vaporization, and not ideal for debulking large masses |

**Table 4 Airway stents**

| | Metallic endobronchial stent | | Silicone endobronchial |
|---|---|---|---|
| | Covered | Uncovered | |
| Indications | Malignant tracheobronchial obstruction. Prevention of tumor ingrowth. Tracheoesophageal fistulas | Limited uses due to significant potential complications. Anastomotic dehiscence following lung transplantation. Can be used for benign conditions, but only short term, however not first line | Benign airway stenosis. Post-lung transplant airway complications. Malignant airway obstruction (palliative) |
| Advantages | Prevents tumor ingrowth. Reduces risk of fistula formation. Can be placed with flexible bronchoscopy | Lower risk of migration than covered stents. Can be placed with flexible bronchoscopy. Preserve muco-ciliary function | Easily removable. Less granulation tissue formation compared to metallic stents. Can be used in benign disease. Can be customized during the procedure (*i.e.*, cut to adjust length). Varying shapes, such as cylindrical, or Y-shaped |
| Disadvantages | Higher migration risk. May obstruct smaller airways or bronchi | Tumor or granulation tissue can grow through the stent, leading to restenosis. Black box warning in benign disease, due to tissue hyperplasia, embodiment in tissue, and consequent occlusion. Difficult to remove | Higher migration risk compared to metallic stents. Requires rigid bronchoscopy for placement |

discharge[37,43-46]. The AQuIRE registry highlights the benefit and utility of therapeutic bronchoscopy in malignant CAO, and reports clinically significant improvement in health-related quality of life in up to 42% of patients, and improvement in dyspnea[44].

## MANAGEMENT OF PLEURAL DISORDERS IN THE ICU

### *Pleural effusions*

Pleural effusions are common among critically ill patients and may affect up to 50% of patients in the ICU[47]. Depending on the volume of pleural fluid and other factors, patients may complain of dyspnea, chest pain, and cough. The clinical impact of these effusions is not often clear, and the treating clinician must decide if the potential benefits of draining the pleural effusion outweigh the procedural risks[48].

There are numerous causes of pleural effusions which can be divided into either transudative or exudative based on lights criteria or the three-test rule[49,50]. Pleural effusions can be caused by several conditions including heart failure, infections, liver failure, critical illness, mechanical ventilation, pneumonia, malignancy, bleeding/hemothorax, hypoalbuminemia, and volume overload. The patient's history and physical exam findings along with radiological and laboratory data can all guide clinicians towards the most likely etiology.

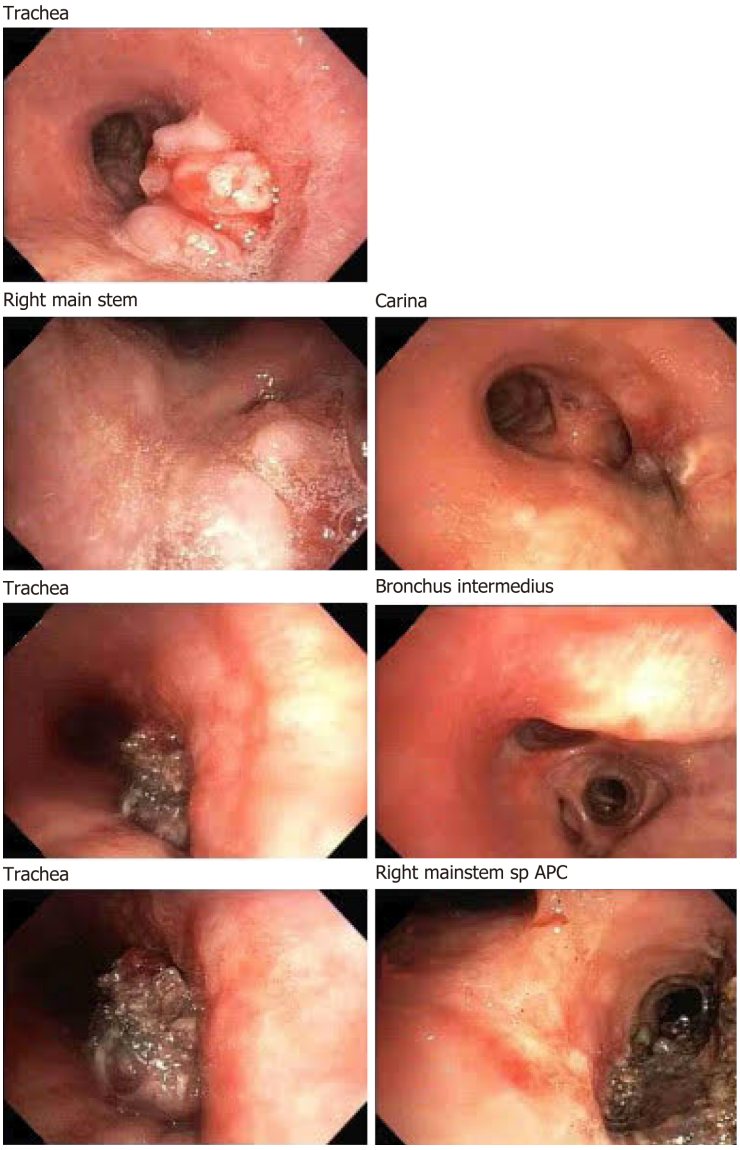


**Figure 9 Bronchoscopy showing tumor involvement with squamous cell carcinoma of the lung, which was debulked with electrocautery snaring, and hemostasis was achieved with APC.** Note that tracheal tumor is now debulked and right airway is better visualized (right row). APC: Argon plasma coagulation.

Despite the ubiquity of pleural effusions in critically ill patients, there is a lack of prospective trials regarding the safety and efficacy of draining them in the ICU. It is unclear if drainage influences hospital or ICU length of stay or duration of mechanical ventilation[48]. Some studies have demonstrated improvement in oxygenation especially following larger volume thoracentesis (> 500 mL) and low rate of procedural complications[48]. Drainage of pleural effusions is often done for diagnosis and to improve respiratory mechanics, especially in patients who are difficult to wean from the ventilator [51].

### *Complicated parapneumonic effusion and empyema*

Around 20%-40% of patients with pneumonia may develop a parapneumonic pleural effusion and around 5%-10% may progress to empyema[52]. Patients who are at higher risk for pneumonia are also at higher risk for empyema with risk factors including malnutrition, alcohol and drug use, and poor dentition[52]. Bacteria such as streptococcus pneumonia, staphylococcus and oral anaerobes are among the most common culprits of parapneumonic effusions and empyemas[53].

Empyemas associated with pneumonia typically develop in three stages; the first involves an exudative, free flowing fluid that develops due to increased interstitial edema, stage two involves bacterial translocation into the pleural space causing fibrin deposition and loculations, the third and final stage involves organization of the pleural space that may cause a trapped lung and be a nidus for further infections[54]. Other causes constitute trauma, thoracic surgery, esophageal rupture, descending cervical infections may allow bacteria to directly invade the pleural space and cause empyema[53].

### *Diagnosis*

Diagnosis of pleural effusion is often based on physical exam and radiological investigations. Chest X-rays are commonly done in the ICU but may miss small or moderate effusions in approximately half of the patients[54]. Erect chest X-rays are often not feasible in this patient population. CT scans may diagnose incidental effusions and point-of-care ultrasonography is an excellent modality of choice for diagnosis and in guiding clinicians towards possible etiologies of the effusion (Figure 10A)[55].

In patients with suspected infected pleural space, initial diagnosis is typically made by performing a thoracentesis. On ultrasound, a loculated effusion along with thickened parietal pleura, homogenous echogenicity and separation of visceral and parietal pleural are some signs that may suggest empyema[56].

The appearance of frank blood during thoracentesis may indicate the presence of a hemothorax especially in patients who have had recent surgery, trauma, or procedures such as thoracentesis. On ultrasound, findings such as increased echogenicity of pleural fluid and the hematocrit sign, which is the appearance of layering and increasing echogenicity with depth points towards the possibility of a hemothorax[55].

### *Management*

For newly diagnosed pleural effusions, thoracentesis is often performed to visualize and analyze the pleural fluid which helps narrow possible etiologies. However, not every pleural effusion requires thoracentesis. For example, if the underlying etiology is secondary to known disease such as decompensated heart failure, thoracentesis can be held until diuresis has been attempted and has failed to resolve the effusion.

Complicated parapneumonic effusions (CPPE) and empyemas require appropriate antibiotics and drainage of the pleural space. Evacuation of the pleural space is important to allow lung expansion and prevent long-term consequences such as trapped lung. Tube thoracostomy should be performed in CPPE to allow complete and continuous drainage but that may not be possible if there are extensive loculations. Professional society guidelines do not recommend routine use of combination tissue plasminogen activator (TPA) and DNase in patients with complicated pleural effusions or early empyemas[57,58]. British Thoracic Society (BTS) guidelines recommend that it may be used when initial chest tube drainage stops, and a residual pleural collection remains[57].

### *Procedural considerations*

Image guidance with ultrasonography is recommended for thoracentesis or chest tube placement, and the procedure should be done with aseptic technique. It improves success rates, decreases potential complications and is recommended by professional societies[57,58]. This is especially important for patients on mechanical support where inadvertent lung parenchymal puncture may result in a clinically significant pneumothorax. Small bore tubes (< 14 French) have gained favor in recent years for drainage of CPPE or empyema based on evidence that they are similar in efficacy to large bore chest tubes[58]. Once the chest tube is placed, routine flushing is recommended to prevent occlusion and if there is suspicion of inadequate drainage, with evidence of persistent effusion on imaging, TPA-DNase is recommended[59].

## PNEUMOTHORAX AND PERSISTENT AIR LEAK MANAGEMENT IN THE ICU

Pneumothorax refers to the presence of air within the chest cavity. It occurs secondary to trauma or may be spontaneous. The latter is further divided into either primary (not associated with any known lung disease) or secondary spontaneous pneumothorax (SSP) (associated with underlying lung disease such as emphysema). Primary spontaneous pneumothorax (PSP) is much more common in younger males compared to females whereas SSP is more likely to occur in older individuals due to increased prevalence of underlying lung disease[60].

Persistent air leak (PAL) is defined as continued air flow from the endobronchial tree into the pleural cavity, exceeding 5-7 days. The exact incidence of PAL is unknown, and the optimal management strategy is unclear. Often, critically ill patients cannot safely undergo complex surgeries therefore minimally invasive therapies to manage PAL have become more prevalent in recent years.

### *Diagnosis*

Patients can present with non-specific symptoms such as dyspnea and chest pain. Diagnosis is made with imaging of the chest. Stable patients can undergo either chest X-ray or CT scans depending on the clinical scenario. For unstable patients, initial bedside ultrasonography is a sensitive test that can alert clinicians towards the possibility of pneumothorax. A hydropneumothorax implies the presence of both air and fluid in the pleural space and may appear as an air-fluid level on chest imaging.

### *Management*

PSP and SSP are managed differently. BTS guidelines recommend a conservative strategy for asymptomatic PSP regardless of size. However, if conservative therapy is not an option, needle aspiration or chest tube insertion can be considered for PSP. For SSP, chemical pleurodesis can be done even after the first episode due to the high rate of recurrence seen in this demographic.

If patients with pneumothorax develop a PAL, professional society guidelines recommend surgical evaluation however chemical or blood patch pleurodesis may be considered in cases where surgery is not an option[57]. The use of endobronchial valves (EBV) to stop PALs (Figure 10B and C) is a more recent development in this field. EBVs are one-

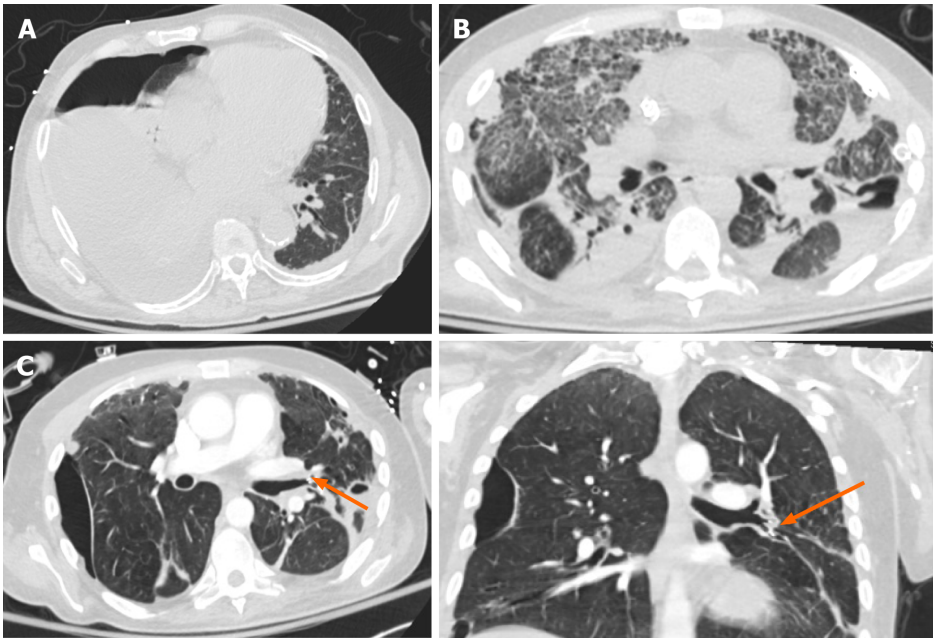


**Figure 10 Computed tomography chest in axial view.** A: Computed tomography (CT) chest in axial view showing presence of hydropneumothorax needing the placement of a 14F chest tube; B: CT chest in axial view of a 45-year-old patient showing pneumothorax with chest tube in left side (arrow); C: With a persistent air leak, endobronchial valves were placed in the lingula as seen on axial and coronal views (arrow).

way valves which allow airflow out of the bronchus while limiting the inflow of air, which helps resolve PAL. Once the EBVs are in place and effective, cessation of air leak is expected, and the chest tube can be removed. This allows the pleura to heal, and the EBVs can be removed after approximately 6 weeks.

There is a lack of guidelines on the use of EBV for PAL, however several case series have described great success with their use[61]. BTS guidelines recommend thoracic surgery involvement after 48 hours of air leak and recommend surgery as first line. If surgery is not an option, autologous blood patch pleurodesis or EBV can be considered[57]. However autologous blood patch pleurodesis may be associated with empyema, with one study reporting it as a complication in up to 9% of cases[62].

### *Procedural considerations*

Needle aspiration may be attempted in patients with PSP to decrease hospitalizations and is as effective as large bore chest tubes. If needle aspiration fails, small bore chest tubes should be inserted. Although needle aspiration may be attempted in patients with small SSP, it is more likely to fail. If a chest tube is inserted, it may be attached to a Heimlich valve or chest drain, but routine suction is not needed. Suction may be used for patients with PAL or inadequate lung expansion after insertion of chest tube[57].

For PAL, chemical or blood patch pleurodesis may be attempted when surgery is not an option. In the United States, a humanitarian device exemption from the Federal Drug Administration (FDA) exists for the use of EBV in the management of PAL. Currently only the Spiration valve is approved for this indication whereas the Zephyr valve is still under the process of approval for use in PAL.

## TRACHEOSTOMY

Tracheostomy is a commonly performed procedure in patients who require prolonged mechanical ventilation due to respiratory insufficiency. Tracheostomy can be performed surgically or percutaneously, and percutaneous tracheostomy (PT) has become more prevalent and performed at bedside by interventional pulmonologists and intensivists in the ICU.

### *Procedural considerations*

Common indications for PT are inability to wean patients off the ventilator, or chronic respiratory failure due to neurological or neuromuscular disease. Other indications include trauma, angioedema, malignancy, or patients with obstructive sleep apnea refractory to conventional therapies. With reference to surgical tracheostomy, there are several relative contraindications which include obesity, coagulopathy, inability to extend the neck (*i.e.*, trauma or C-spine surgery), and high ventilator support. In contrast, there is data to suggest that the percutaneous approach can be performed safely in these high-risk patients[63]. Additionally, there is data to suggest that there is no significant difference in mortality, bleeding, false passage, or subglottic stenosis between surgical and PT[64,65]. Furthermore, PT has been shown to have a lower rate of wound infection and stomatitis[65].

### *Procedural technique*

PT is performed by insertion of a tracheal cannula using a modified Seldinger approach through the anterior tracheal wall between the 2nd and 3rd tracheal rings. After the trachea is accessed with a needle, a guidewire is inserted, and dilation is performed until the stoma is large enough for the tracheostomy tube to be introduced. This can be done with simultaneous intraluminal visualization by using a bronchoscope , or with ultrasound guidance[66,67].

Tracheostomy results in patient comfort, improved work of breathing due to less airway resistance, decreased need for sedation, and decreased ICU length of stay, and should always be considered in patients with prolonged dependance on mechanical ventilation.

## PERCUTANEOUS GASTROSTOMY TUBE PLACEMENT

Critically ill patients who need prolonged life-sustaining support are in a state of severe catabolism, and establishing enteral access to start nutrition is paramount[68]. Percutaneous endoscopic gastrostomy (PEG) tubes are a safe and effective method to provide enteral nutrition to patients who require prolonged enteral access.

### *Procedural considerations*

Indications for PEG tube placement includes patients that require long-term nutritional support and have a functional gastrointestinal tract, without sufficient oral intake. The most common indication is dysphagia secondary to neurological diseases such as stroke, amyotrophic lateral sclerosis and Guillain-Barré syndrome or dementia. Other indications include upper gastrointestinal obstruction due to malignancy or trauma. Contraindications include coagulopathy, sepsis, severe ascites, peritonitis, peritoneal carcinomatosis, and gastric outlet obstruction[69].

### *Procedural technique*

There are several techniques for gastrostomy tube insertion, and these can be categorized into endoscopic guided (peroral) techniques, and direct percutaneous techniques. The peroral technique utilizes endoscopy to guide gastrostomy tube insertion, in addition to transillumination and insufflation of the stomach to align the gastric wall to the abdominal wall[70]. Of note, it may be difficult in patients with upper gastrointestinal pathology which limits the passage of the endoscope. Percutaneously, gastrostomy tubes can be placed with ultrasound guidance [percutaneous ultrasound gastrostomy (PUG)]. With the use of an existing orogastric or nasogastric tube, the stomach is insufflated, and a specialized orogastric tube with a magnet is advanced to the stomach, the gastric wall can be aligned with the abdominal wall using an external handheld magnet, and the gastrostomy tube is inserted using Seldinger technique[71].

There is no data to compare patient outcomes with each technique. It is important to note that percutaneous ultrasound gastrostomy requires less equipment and is less costly. Additionally, the point of care ultrasound magnet-aligned gastrostomy system that was developed is only FDA approved for patients with a body mass index between 30-35 and abdominal wall thickness less than 4.5 cm. Furthermore, data is lacking to evaluate the safety and efficacy of this technique in comparison to the standard PEG technique[71,72].

Gastrostomy tubes are becoming more frequently placed by interventional pulmonologists following tracheostomy. This is done to minimize risks associated with sedation, and both procedures can be coordinated by the same proceduralist. One prospective study evaluated the use of PEG tube placement with endoscopic guidance performed by interventional pulmonologists and reported a 97.6% success rate[73]. Another retrospective study demonstrated a success rate of 97% when performed by interventional pulmonologists[74].

In summary, PUG tube placement is being increasingly performed by interventional pulmonologists, this can limit costs, and minimize risks associated with sedation if performed following tracheostomy. This translates to lower duration of stay in the ICUs with associated lower hospitalization costs.

## CONCLUSION

IP with its rapid advancements is fast becoming an important subspecialty in the management of critically ill patients, particularly in patients with hypoxemic/hypercapnic respiratory failure due to several reasons. While this manuscript outlines several of the roles an interventional pulmonologist can offer in the critical care environment, the list is not all encompassing and with the different technological advancements that are fast upcoming within IP, the advantages and benefits of IP within critical care is likely to increase. Moreover, future studies comparing the bedside techniques performed by IP *vs* interventional radiology or surgery should be performed to assess cost-effectiveness within the ICU.

## FOOTNOTES

**Author contributions:** Halawa ARR, Farooq S, Amjad MA, and Cherian SV were responsible for conception and design; Jani PP and Cherian SV were responsible for administrative support and provision of study materials or patients; Halawa ARR, Farooq S, and Amjad MA were responsible for collection and assembly of data and data analysis and interpretation; Halawa ARR, Farooq S, Amjad MA, Jani PP, and Cherian SV were responsible for manuscript writing; all of the authors read and approved the final version of the manuscript to be published.

**Conflict-of-interest statement:** There are no conflicts of interest.



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**S-Editor:** Luo ML
**L-Editor:** A
**P-Editor:** Zhang YL

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World Journal of Critical Care Medicine

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*World J Crit Care Med* 2025 June 9; 14(2): 101708

DOI: 10.5492/wjccm.v14.i2.101708

ISSN 2220-3141 (online)

*MINIREVIEWS*

# Venous excess ultrasound: A mini-review and practical guide for its application in critically ill patients

Wei Ven Chin, Melissa Mei Ing Ngai, Kay Choong See

**Specialty type:** Critical Care Medicine

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade B, Grade B, Grade C, Grade C

**Novelty:** Grade B, Grade B, Grade C, Grade C

**Creativity or Innovation:** Grade B, Grade B, Grade B, Grade C

**Scientific Significance:** Grade B, Grade B, Grade B, Grade C

**P-Reviewer:** Juneja D; Zou ZY; Huang DB

**Received:** September 24, 2024

**Revised:** January 21, 2025

**Accepted:** February 17, 2025

**Published online:** June 9, 2025

**Processing time:** 156 Days and 5.1 Hours

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## Abstract

Advancements in healthcare technology have improved mortality rates and extended lifespans, resulting in a population with multiple comorbidities that complicate patient care. Traditional assessments often fall short, underscoring the need for integrated care strategies. Among these, fluid management is particularly challenging due to the difficulty in directly assessing volume status especially in critically ill patients who frequently have peripheral oedema. Effective fluid management is essential for optimal tissue oxygen delivery, which is crucial for cellular metabolism. Oxygen transport is dependent on arterial oxygen levels, haemoglobin concentration, and cardiac output, with the latter influenced by preload, afterload, and cardiac contractility. A delicate balance of these factors ensures that the cardiovascular system can respond adequately to varying physiological demands, thereby safeguarding tissue oxygenation and overall organ function during states of stress or illness. The Venous Excess Ultrasound (VExUS) Grading System is instrumental in evaluating fluid intolerance, providing detailed insights into venous congestion and fluid status. It was originally developed to assess the risk of acute kidney injury in postoperative cardiac patients, but its versatility has enabled broader applications in nephrology and critical care settings. This mini review explores VExUS's application and its impact on fluid management and patient outcomes in critically ill patients.

**Key Words:** Diuretic; Point-of-care ultrasound; Ultrasound; Venous congestion; Venous excess ultrasound

**Core Tip:** Precise fluid management in critically ill patients is a considerable challenge, as peripheral oedema is common and often complicates accurate assessment of their volume status. The Venous Excess Ultrasound (VExUS) Grading System has emerged as a valuable tool for assessing fluid intolerance and venous congestion across various clinical settings. This mini review emphasizes the application of VExUS to enhance fluid management strategies and its potential to improve patient outcomes. By integrating VExUS into clinical workflows, healthcare providers can better address fluid-related complications and optimize care for patients with complex needs.

**Citation:** Chin WV, Ngai MMI, See KC. Venous excess ultrasound: A mini-review and practical guide for its application in critically ill patients. *World J Crit Care Med* 2025; 14(2): 101708
**URL:** https://www.wjgnet.com/2220-3141/full/v14/i2/101708.htm
**DOI:** https://dx.doi.org/10.5492/wjccm.v14.i2.101708

## INTRODUCTION

Fluid administration, a fundamental aspect of critical care, is a simple yet sophisticated intervention that hinges on clinical judgement. To execute it correctly, clinical acumen is required, which, when done well, is often the defining characteristic of a remarkable clinician[1]. Underhydration and overhydration are common in clinical practice, and most importantly, both contribute to higher mortality rates[2,3]. With an ageing population in many countries globally, today's patient pool tends to present with multiple co-morbidities[4,5]. This adds to the complexity of clinical cases, posing additional challenges in achieving the delicate balance of fluid management. Technology advancements help overcome these challenges by integrating advanced diagnostic gadgets into the clinician's traditional clinical skills. One such tool is point-of-care ultrasound (POCUS). POCUS enhances the clinician's real-time assessment capabilities by providing valuable insights for diagnostic, monitoring, and therapeutic options[6]. Furthermore, it is simple to perform and readily available at the bedside.

In 2020, Beaubien-Souligny *et al*[7] conducted a study on grading system prototypes, namely Venous Excess Ultrasound (VExUS) A, VExUS B, VExUS C, VExUS D, and VExUS E, to predict the likelihood of acute kidney injury (AKI) in post-operative cardiac surgery patients. The study found that the VExUS C prototype had a high specificity of 96% in identifying severe venous congestion that may lead to AKI. The prototype involves measuring the size of the inferior vena cava (IVC) and analyzing the pulse-wave Doppler ultrasound on the hepatic vein, portal vein, and renal vein. The study concluded that post-operative cardiac surgery patients admitted to the intensive care unit (ICU) with at least two severe alterations in venous flow and an IVC diameter of 2 cm or more are at risk of AKI. Clinical medicine has since adopted the VExUS grading system. Subsequently, the clinical utility of VExUS extended to areas such as cardiology, nephrology, emergency medicine, and intensive care medicine.

This minireview provides a step-by-step practical guide for using the VExUS grading system in clinical practice. Before looking into the VExUS clinical usage, we will begin by elucidating the fundamental principles of ultrasonography, which will aid readers in comprehending the technical and interpretive aspects of the VExUS clinical application.

## TECHNICAL ASPECTS OF VEXUS

In ultrasonic probes, the piezoelectric crystals are responsible for the generation of sound waves that form ultrasonic images. Typically, diagnostic ultrasonography uses 1–30 MHz sound waves[8]. We recommend low-frequency probes, particularly those within the frequency range of 1 to 5 MHz, for VExUS evaluation. This is because most of the structures being assessed, such as the hepatic vein, portal vein, and renal vein, are located deep within the abdomen. Among the low-frequency probes, there are two options: The curvilinear probe and the phased array probe. The curvilinear probe has a frequency range of 2 to 5 MHz, while the phased array probe has a frequency range of 1 to 5 MHz. We prefer the curvilinear probe as it has bigger footprint, allowing better lateral resolution compared to phased array probes[8]. Furthermore, when performing VExUS evaluation with a phased array probe, it may be necessary to adjust the color Doppler scale to a low flow velocity of 20–30 cm/s or switch to an abdominal preset[9].

In the VExUS grading system, pulsed wave (PW) Doppler analysis is one of the most important elements throughout the assessment. The Doppler study analyses the Doppler shift, which is the change in frequency of the reflected echo, to determine the relative motion, thus revealing the velocity and flow direction[10-12]. There are three Doppler modalities: Color Doppler, power Doppler, and spectral Doppler[13]. In the color Doppler mode, red typically denotes flow towards the transducer, and blue denotes flow away from the transducer. However, this remains true if only the color Doppler bars are not inverted, in which the red bar is positioned above the baseline and the blue bar is positioned beneath the baseline. Power Doppler will not denote the flow direction, but it is more sensitive when detecting low-velocity flow[14]. Therefore, in situations where color Doppler fails to capture any waves in low flow velocity vessels, switching to power Doppler could be beneficial. The types of spectral Doppler are continuous-wave and PW. PW Doppler mode evaluates the speed of blood flow at the sampling volume or PW gate area and shows blood flow velocity over time as a graph[12,15]. A positive deflection (above the baseline) on the trace indicates blood moving towards the transducer, while a negative deflection (below the baseline) indicates blood moving away from the transducer. In general, it is not advisable

to use PW for flow velocities above 200 cm/s. This is because duplex ultrasound imaging, which combines brightness (B) mode and PW Doppler, cannot accurately measure velocities beyond this threshold (Nyquist limit) due to aliasing. Aliasing may lead to an underestimation of the velocity, as the Doppler signal falsely creates an appearance of the flow reversing or oscillating in the opposite direction[8,12,16]. In addition to the aliasing concern, the insonation angle has a significant impact on PW Doppler. Generally, an insonation angle between zero and 60 degrees should be maintained to avoid underestimating velocities[8,12]. Figure 1 provides an example of how the insonation angle affects the flow velocity measurement of the portal vein. In this example, there is underestimation of the actual velocity of the portal vein blood flow from about 30 cm/s to roughly 20 cm/s when the insonation angle is near 90 degrees.

Fortunately, VExUS focusses on identifying waveform pattern recognition rather than measuring precise velocities, which eliminates the complexities of Doppler shift formula calculation. Since precise velocities are not being measured, insonation angles are also of little concern. Moreover, the flow velocity for the hepatic vein is usually less than 40 cm/s [17], the portal vein is 20–40 cm/s[18], and the renal vein is less than 40 cm/s[19]. As a result, concerns about aliasing are not significant. These advantages make VExUS assessments easier to perform and user-friendly for even novice POCUS users. Table 1 summarizes key ultrasonography formulae relevant to the technical performance of VExUS. While these formulae underpin VExUS, they do not need to be calculated by clinicians in routine practice.

## ACQUIRING IMAGES FOR VEXUS

In performing VExUS grading, the initial step involves identifying the IVC, which can be located using either a curvilinear or phased array probe. Figure 2 depicts the instructions for locating the IVC using a curvilinear probe, while Figure 3 illustrates the instructions for locating the IVC using a phased array probe. By locating the inferior cavoatrial junction and observing the hepatic vein's drainage into it, one can confirm the identification of the IVC and distinguish it from other vessels based on these anatomical landmarks. In contrast to the IVC, the aorta tends to be pulsatile, with a thicker and brighter hyperechoic wall. The optimal location for the IVC's size measurement is 3-5 cm away from the inferior cavoatrial junction or 2 cm away from the junction where the hepatic vein drains[20-23]. Figure 4 displays the IVC images obtained *via* the subcostal approach. To guarantee the precision of the IVC measurement, it is recommended to do the antero-posterior internal diameter measurement for both the longitudinal and transverse axis. At times, body habitus can make it difficult to obtain clear images *via* subcostal view, and clinicians may need to identify the IVC using a right-lateral intercostal approach, also known as transhepatic view. However, it is important to recognise that the IVC measurements obtained from the subcostal view and right lateral approach may not be directly comparable due to limited studies supporting their interchangeability. The right lateral approach often serves as a valuable rescue view for challenging body habitus, but the results obtained need to be interpreted cautiously. Integrating artificial intelligence guidance software into current ultrasound technology could potentially address this issue and improve the accuracy of IVC evaluation[24-28]. According to the VExUS grading system, an IVC < 2 cm indicates grade zero with no venous congestion; if the IVC is greater than or equal to 2 cm, proceed with the Doppler study analysis of the hepatic, portal, and renal veins.

As shown in Figure 5, you can identify the hepatic vein using either the subcostal approach or the right lateral intercostal approach, with the pointer directed towards the patient's cephalad and right. Hepatic veins consist of right, middle, and left hepatic veins; any one of them can be analyzed for VExUS. The portal vein can be identified *via* the subcostal approach, lateral intercostal approach, or intercostal approach at the mid-clavicular line, as depicted in Figure 6. It is easily identifiable due to its hyperechoic vessel wall and typically exhibits hepatopetal flow (blood flow that is directed toward the liver) in a normal situation, as indicated by the red color when using a color Doppler.

Lastly, the most technically challenging vessels are renal veins. Acquiring images of the renal interlobar or arcuate veins can be challenging due to their deep location within the abdomen. Once the color Doppler is activated and the renal vein is not visible, you can improve detection by reducing the pulse repetition frequency. If visibility remains insufficient, increasing the color gain may enhance the signal but be cautious of excessive noise due to the high gain setting. If these adjustments still fail to produce a satisfactory image, consider scanning the left renal veins. The failure rate for detecting a renal vein, especially in challenging candidates with obese body habitus, can be as high as 25%[29].

In the hepatic vein Doppler study, concomitant electrocardiogram (ECG) recordings are recommended. Nevertheless, this is not universally practised, since many regions with limited resources might lack the necessary ECG tracer technology in most of their portable POCUS devices. Methodologically, it is still possible to accurately perform the hepatic vein Doppler study, although the analysis of the waveform may become somewhat less accurate in the absence of the guidance of an ECG trace. Figure 7 depicts the hepatic Doppler waveform pattern in a normal condition. There are typically three distinct phases, each of which corresponds to the cardiac cycle[30]. The right atrial contraction causes a minor elevation in pressure and minimal backflow into the hepatic vein, resulting in the small amplitude of the atrial contraction waveform, known as the 'a' wave. As the retrograde flow flows from the right atrium towards the hepatic vein, the 'a' wave appears above the baseline. During ventricle systole, tricuspid annulus elongation produces suction power, facilitating the venous return to the right atrium. This creates the largest anterograde flow from the hepatic vein into the right atrium, resulting in the appearance of an S wave below the baseline. Finally, during the ventricle diastole, blood flows from the right atrium into the right ventricle, giving rise to another anterograde flow of hepatic vein into the right atrium, known as the D wave. This wave is typically smaller in amplitude than the S wave. Between the S wave and the D wave transition, there is a V wave, which corresponds to atrial overfilling just prior to tricuspid valve opening[31]. In the cases of venous congestion or elevated right atrial pressure, the amplitudes of the 'a' and V waves will become more prominent, while the amplitudes of the S wave will decrease. In extreme cases, reversed flow may even occur. The

**Table 1 The essential ultrasonography formulae relevant to venous excess ultrasound**

| Formula | Relevance |
|---|---|
| λ = c/f. λ is the wavelength, c stands for the sound velocity in the tissue, and f is the frequency[8,11,12] | The equation illustrates the inverse relationship between frequency and wavelength. The lower frequency corresponds to longer wavelengths, which allow them to penetrate deeper into the tissues as longer wavelengths reduce scattering and absorption. However, longer wavelengths lead to reduced spatial resolution, thereby diminishing the ability to distinguish between two objects. Thus, lower-frequency probes have better penetration but lower resolution images, while higher-frequency probes have the opposite characteristics |
| Doppler shift = (2 × f) × (V/c) × cos θ. f is ultrasound frequency, V stands for blood flow velocity, c for speed of sound in the tissue, and θ for insonation angle | The Doppler shift is directly proportional to blood flow velocity, and aliasing tends to happen when the Doppler shift surpasses the Nyquist limit[12,13]. Besides, this formula illustrates the importance of the insonation angle in the PW study. Adjusting PW's insonation angle to zero, or at least less than 60 degrees, is ideal as it maximizes the Doppler shift at zero degrees (cos 0 = 1), whereas at 90 degrees (cos 90 = 0), there is essentially no Doppler shift |
| Nyquist limit = PRF/2. PRF stands for pulse repetition frequency | PRF is the rate at which the ultrasound system emits pulses of sound waves and receives their echoes. It is also known as the sampling rate, measured in hertz (Hz), and typically ranges from 1000 to 5000 Hz in clinical settings |
| PRF = 1/pulse duration. PRF stands for pulse repetition frequency. Pulse duration is the period between pulses | According to the inverse proportional relationship, the lower the PRF, the longer the pulse duration. Prolonging the pulse duration allowed for deeper transmission and improved sensitivity to low-velocity flow. But the trade-off features of lower PRF will include lowering the Nyquist limit and increasing the chances of aliasing, where the Doppler signal falsely creates an appearance of the flow reversing or oscillating in the opposite direction[12,13] |

PRF: Pulse repetition frequency.

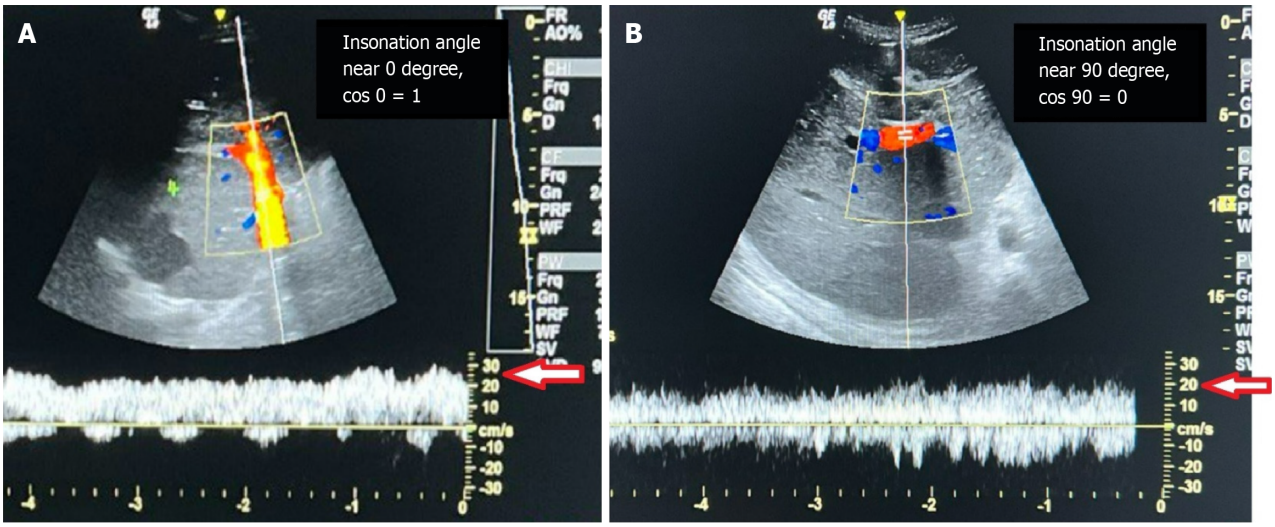



**Figure 1 The influence of the insonation angle of the pulse wave spectral Doppler on the flow velocity measurement of the portal vein.** A: The left-hand side image showed an insonation angle of near 0 degrees; B: The right-hand side image showed an insonation angle of near 90 degrees for the portal vein of the same patient in the same setting. We underestimated the actual velocity of the portal vein blood flow from about 30 cm/s to roughly 20 cm/s when the insonation angle is near 90 degrees.

interpretation of the hepatic vein Doppler waveform entails comparing the relative amplitudes of the systolic (S) and diastolic (D) waves; therefore, identifying the phases of the cardiac cycle is relatively important for the waveform interpretation. Thus, it is always advisable to connect the 3-lead ECG module to the dedicated port of the ultrasound machine to have a simultaneous ECG trace alongside the Doppler waveform. On the ECG, the P wave corresponds to atrial depolarization, the QRS complex corresponds to ventricular depolarization, and the T wave corresponds to ventricular repolarization. Therefore, when concurrent ECG tracing is present, we can identify the systole phase from the peak of the R wave to the midpoint of the T wave, and the diastole phase from the midpoint of the T wave to the peak of the R wave.

The portal vein, formed by the confluence of the splenic and superior mesenteric veins, accounts for 75% of the blood flow to the liver. It serves as the primary vessel of the portal venous system, located posterior to the hepatic artery and common bile duct and extending towards the hepatic hilum, where it bifurcates into the right and left branches[33]. In the context of VExUS, it is advisable to assess the main portal vein rather than using the other branches, as there may be cases of discordant waveforms[34]. Given the considerable distance between the portal vein and the right atrium, in normal conditions the blood flow in the portal vein typically exhibits a monophasic, low velocity Doppler signal with slight respiratory variation, mostly at a velocity ranging from 20 to 40 cm/s[18,35]. The pulatility fraction, or pulsatility index, is evaluated by the formula of [(maximal velocity minus minimum velocity)/maximal velocity][36,37]. A pulsatility fraction

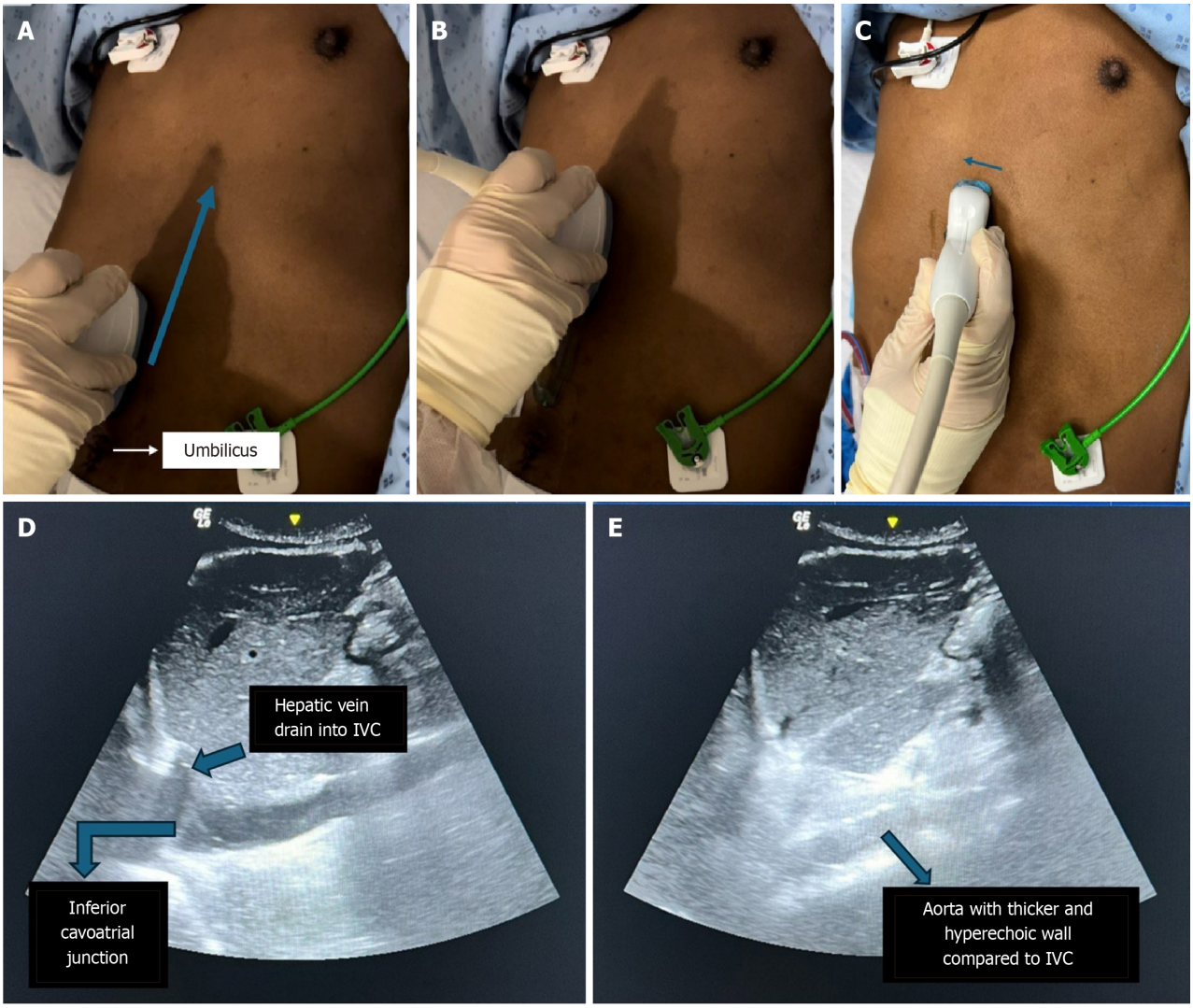



**Figure 2 Measures for locating the inferior vena cava using a curvilinear probe.** A: Firstly, place the curvilinear probe near the umbilicus, then slide it cephalad, with the indicator pointing towards the patient's head; B: Once probe reaching subxiphoid area, you should be able to visualize the liver; C: Tilt the probe slightly towards the patient's right, and the inferior vena cava (IVC) will be seen; D: Locate the anatomical landmarks of the inferior cavoatrial junction and the hepatic vein draining into the IVC to confirm the identification of the IVC; E: To check that the IVC is identified correctly, tilt the probe slightly to the patient's left, and an aorta with a thicker and more hyperechoic wall will be seen.

or pulsatility index of less than 30% is considered normal, 30%–50% is considered mildly abnormal, and more than 50% is considered severely abnormal. Figure 8 shows some examples of the portal vein Doppler waveform.

The renal vein is the most difficult vessel to image, but its proximity to the renal artery makes it easy to interpret its waveform pattern. The renal artery waveform provides a reference point for identifying systolic and diastolic cardiac cycles. Figure 9 shows some examples of the renal vein Doppler waveform. In normal circumstances, the renal vein should appear as a continuous monophasic Doppler flow throughout the cardiac cycle, but as it becomes more congested, it will appear to have biphasic flow with systole and diastole. In severe venous congestion, there might be a complete pause of renal vein flow during the systole phase. This is because the kidney is an encapsulated organ, and venous congestion with its back pressure effect can significantly impede systolic renal venous flow[38].

## INTERPRETING VEXUS

In VExUS, there are 4 grades: Grade 0 indicates that the IVC measures less than 2 cm, signifying no congestion in any organ, while Grade 1, with an IVC of 2 cm or more and any combination of normal or mildly abnormal waveforms, reflects only mild congestion. Grade 2 is characterized by an IVC of 2 cm or more along with one severely abnormal waveform, indicating severe congestion in a single organ, whereas Grade 3 denotes severe congestion affecting at least two organ systems, represented by an IVC of 2 cm or more and two or more severely abnormal waveforms[7,32,34]. Figure 10 provides a graphic representation of the interpretation of the VExUS grading system. This grading system aids clinicians in identifying venous congestion, which can significantly impact organ function and cellular perfusion in patients.

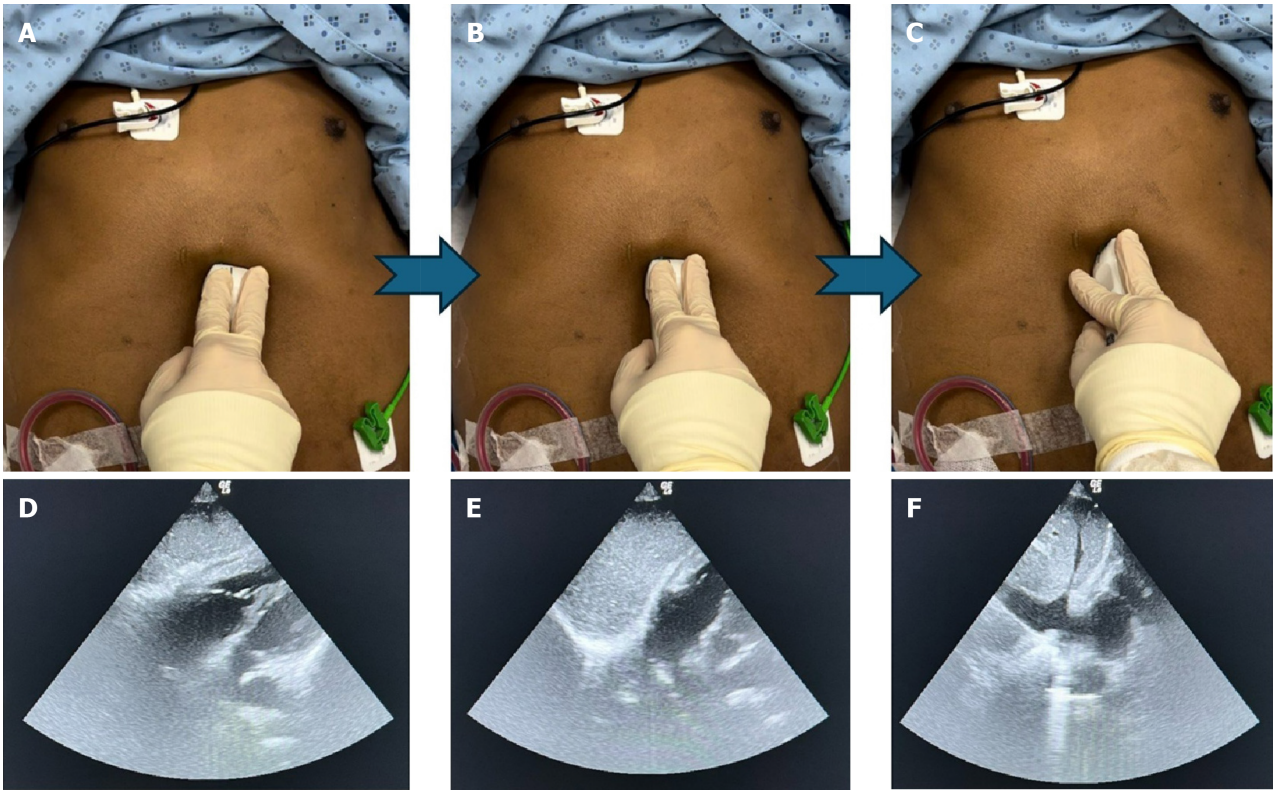
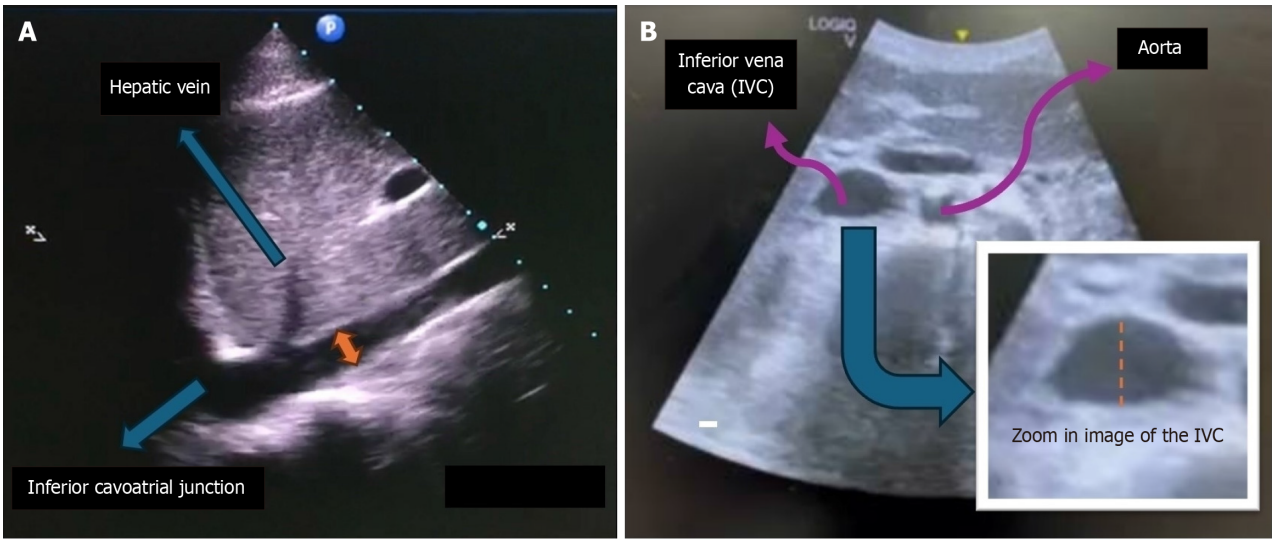



**Figure 3 Measures for locating the inferior vena cava using a phased array probe.** A and D: Firstly, get an ideal subcostal four chambers echo view; B and E: Rock the probe towards the patient's right, bringing the right atrium (RA) to the center of the screen; C and F: Once the RA is in the center, rotate the probe in an anticlockwise direction to open up the inferior vena cava.




The optimal location to measure the IVC's internal diameter along its longitudinal axis is 3-5 cm from the inferior cavoatrial junction or 2 cm from where the hepatic veins meet, as the orange arrow shows

When measuring the IVC's internal diameter along its transverse axis *via* a subcostal approach, try to obtain the most rounded IVC to avoid foreshortening of the vessel and minimise error

**Figure 4 Inferior vena cava images obtained *via* the subcostal approach.** To guarantee the precision of the Inferior vena cava measurement, it was recommended to do the antero-posterior internal diameter measurement for both the longitudinal and transverse axis. A: Longitudinal axis; B: Transverse axis.

The delivery of oxygen is dependent on arterial oxygen levels, haemoglobin concentration, and cardiac output, with the latter influenced by preload, afterload, and cardiac contractility. A delicate balance of these factors ensures that the cardiovascular system can respond adequately to varying physiological demands, thereby safeguarding tissue oxygenation and overall organ function during states of stress or illness. In normal physiology, preload or venous return is dependent on mean systemic filling pressure (Pmsf) and right atrial pressure. The venous system contains stressed and

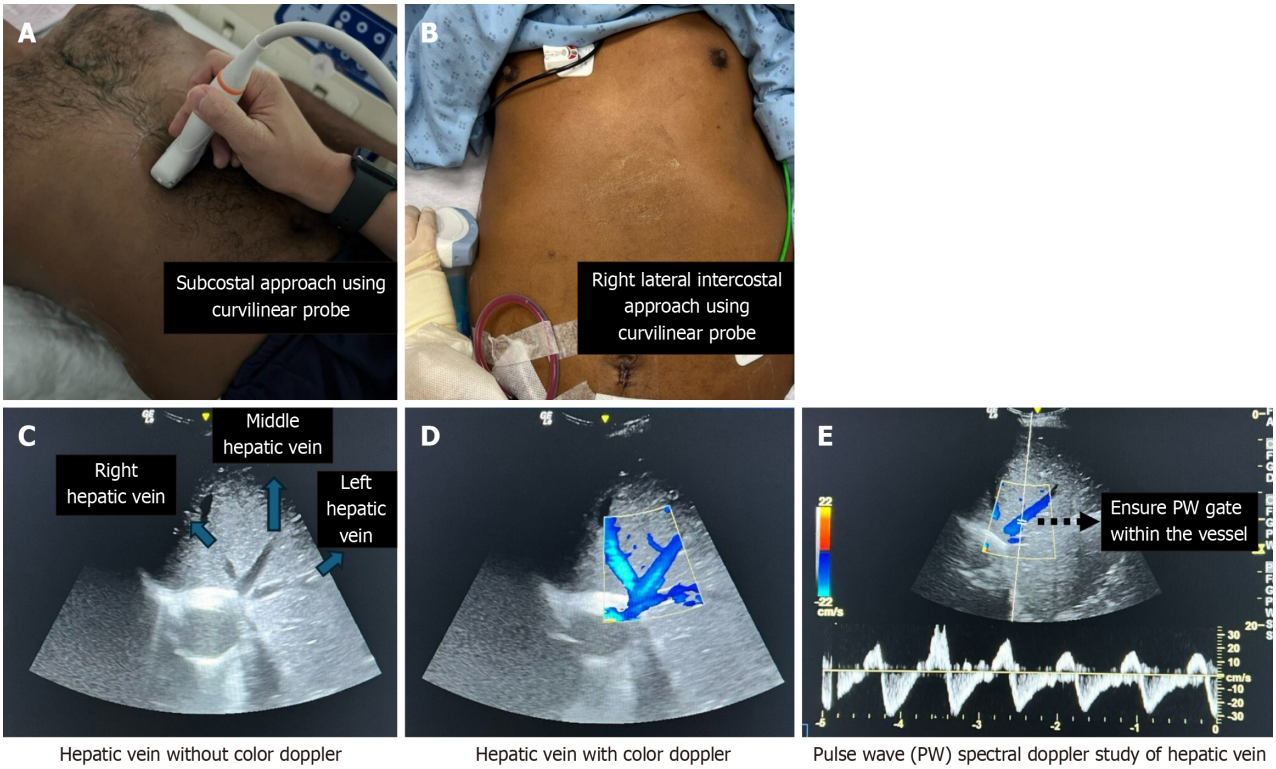



**Figure 5 Measures for locating the hepatic vein using a curvilinear probe and performing a pulse wave spectral Doppler study on the hepatic vein.** Locating the hepatic vein using either the subcostal approach or the right lateral intercostal approach, with the pointer directed cephalad and towards the patient's right. A: Subcostal approach; B: Right lateral intercostal approach; C: Hepatic veins consist of right, middle, and left hepatic veins; any one of them can be analyzed for Venous Excess Ultrasound; D: Activating the color Doppler revealed the hepatic vein in blue; E: Once identified, place the pulse wave sample volume, also known as the PW gate, within the hepatic vein.

unstressed volumes, with the latter being blood that does not exert pressure against vessel walls[39]. The stressed volume, venous capacitance, and venous compliance all influence the Pmsf, which typically ranges from 7 to 10 mmHg when there is no flow in the systemic vascular system[40]. Clinical conditions can shift these volumes; for example, sepsis-induced vasodilatation increases venous compliance and unstressed volume, which reduces Pmsf[41]. Conversely, in a fluid overload situation, there is an increase in total blood volume and stressed volume, thus increasing the Pmsf. As a result, an increase in Pmsf can lower organ perfusion pressure, calculated as mean arterial pressure minus Pmsf, thereby restricting blood flow and affecting organ perfusion[42]. While fluid responsiveness warrants careful consideration, administering fluid boluses to individuals with fluid intolerance is not advisable[43-45].

One of the mainstays of fluid management in venous congestion is the use of loop diuretics, *e.g.*, frusemide. Ultrafiltration through hemodialysis, which includes intermittent hemodialysis and continuous kidney replacement therapy, is an effective alternative to diuretics for removing excess fluid from the body. The administration of diuretic and hemodialysis necessitates meticulous clinical discernment, as an incorrect dosage may result in serious consequences such as hypovolemic shock or inadequate fluid removal. However, traditional assessments often fall short, particularly when directly assessing fluid composition within the body, necessitating the use of integrated care techniques[46,47]. The VExUS grading system provides us with detailed information on fluid intolerance. A higher grade is indicative of fluid intolerance. Thus, the VExUS grading system serves as a "green light" sign for diuresis or fluid removal when the VExUS grade is 1-3 and a "red light" sign to halt diuresis or fluid removal when the VExUS grade is 0.

## CLINICAL APPLICATIONS OF VEXUS

Due to its clinical importance, researchers conducted numerous studies to explore the clinical applications of VExUS, and Table 2 is the summary of studies relevant to VExUS. Additionally, Table 3 presents hypothetical clinical scenarios where the application of VExUS in clinical medicine is possible.

## PREDICTION OF AKI

Both Beaubien-Souligny *et al*[7] and Viana-Rojas *et al*[48] studies demonstrated that systemic venous congestion measured by VExUS can predict the development of AKI. The difference lies in the fact that Beaubien-Souligny *et al*[7] focused on

**Table 2 Summary of the studies relevant to utility of venous excess ultrasound in various clinical settings**

| Ref. | Study objectives | Clinical outcomes |
|---|---|---|
| Andrei *et al*[53], 2023 | Prospective observational study to describe prevalence of venous congestion based on VExUS grading in general ICU patients, and its association with AKI injury and 28-day mortality | Low prevalence of severe venous congestion (16% and 6% of VExUS grades 2 and 3 respectively), which did not change over the study period. No significant association between admission VExUS scores and AKI ($P$ = 0.136) or 28-day mortality ($P$ = 0.594) |
| Beaubien-Souligny *et al*[7], 2020 | To develop a prototypical VExUS grading system and to validate the model in predicting post cardiac surgery related AKI | Severe congestion (Grade 3) defined by the VExUS C grading system was the most strongly associated with AKI (HR = 3.69, 95%CI: 1.65–8.24, $P$ = 0.001) |
| Bhardwaj *et al*[52], 2020 | Prospective cohort study on the correlation between serial VExUS score and AKI in patients with cardiorenal syndrome | Resolution of AKI showed significant correlation with improvement in VExUS grade ($P$ = 0.003). There was significant association between changes in VExUS grade and fluid balance ($P$ = 0.006) |
| Landi *et al* [54], 2024 | Prospective, observational study to determine if venous congestion (using VExUS grading) predicts heart failure related hospitalization and mortality in patients admitted to the emergency department, with acute decompensated heart failure | In patients with a VExUS grade of 3, the probability of both readmission and mortality was significantly greater compared to those with lower grades |
| Longino *et al*[49], 2024 | Prospective cohort study to assess the diagnostic accuracy of VExUS grade for elevated intracardiac pressure | AUC values for VExUS as predictor of right atrial pressure > 10 mmHg was 0.9 (95%CI: 0.83-0.97), and significantly greater than inferior vena cava diameter or inferior vena cava collapsibility index |
| Rihl *et al* [51], 2023 | To determine whether VExUS score can be used to guide decongestion in ICU patients with severe AKI, and whether the modification of the score is associated with an increase in the number of RRT-free days in 28 days | Patients with higher VExUS grades (> 1) used more diuretics. Patients who reduced the VExUS grade in 48 hours had more RRT-free days at Day 28 (28.0; 8.0-28.0) than patients who did not reduce VExUS grade (15.0; 3.0-27.5), $P$ = 0.012 |
| Rola *et al* [32], 2021 | Case series on the use of VExUS in identifying pathophysiology and guiding clinical management | Case 1 Continuous drainage of ascites was performed until 12 L was removed. Intravenous frusemide was restarted at a higher dose until a net balance of negative 1000 mL per 8-hour shift was achieved. Case 2 A planned surgical cholecystectomy was cancelled as ultrasound results showed venous congestion instead of cholecystitis. Patient was discharged home with frusemide and an outpatient cardiology review. Case 3 A patient with preexisting pulmonary hypertension received high-dose intravenous frusemide until a net balance of negative 1200 mL per 24 hour was achieved, followed by dose titration to achieve a negative balance of 3200 mL per 24 hours. Dobutamine was further decreased to 3 mcg/kg/min. Case 4 A patient with severe venous congestion and hyperkalemia was treated with intravenous frusemide 200 mg and thereafter hemodialysis was started as there was no diuretic response. A repeat VExUS scan showed improvement in venous congestion, and the patient produced 800 mL of urine. Further diuresis with intravenous frusemide infusion 200 mg/day and spironolactone 50 mg twice a day was given, and a negative fluid balance of 15.5 L was achieved. Case 5 Patient underwent ultrafiltration, and 5 L of fluid was removed within 24 hours. Over the next 48 hours, lactate normalized, and vasopressor requirements improved. VExUS showed refractory shock was related to volume overload and RV dysfunction |
| Viana-Rojas *et al* [48], 2023 | Prospective, single-center study to evaluate the association between venous congestion assessed with VExUS and the incidence of AKI in patients with acute coronary syndrome | As the degree of VExUS increased, a higher proportion of patients developed AKI: VExUS = 0 (10.8%), VExUS = 1 (23.8%), VExUS = 2 (75.0%), and VExUS = 3 (100%; $P$ < 0.001). A significant association between VExUS ≥ 1 and AKI was found (odds ratio: 6.75, 95%CI: 2.21–23.7, $P$ = 0.001) |
| Wong *et al* [50], 2024 | Single-center, observational study to evaluate the utility of VExUS to access volume status, in relation to patient's weight and fluid removal during dialysis | Patients with normal VExUS grades and elevated VExUS grades had no difference in starting weight, dry weight, or fluid removal. Patients with VExUS grades > 1 had more fluid removed than those with VExUS grade 0. All patients with VExUS grades > 1 had impaired right ventricular systolic function |

VExUS: Venous excess ultrasound; AKI: Acute kidney injury; ICU: Intensive care unit; HR: Hazard ratio.

**Table 3 Hypothetical clinical scenarios where the application of venous excess ultrasound in clinical medicine is possible**

| Clinical scenario | Clinical application of VExUS |
|---|---|
| Cardiomyopathy cases such as ischemic cardiomyopathy, septic cardiomyopathy, dengue cardiomyopathy *etc.* | By detecting the presence of venous congestion *via* the VExUS grading system, it helps the clinician to decide when to cease fluid therapy. Conversely, when no venous congestion is detected using VExUS, clinicians may be guided to cease diuretic therapy |
| End stage renal failure | By detecting the presence of venous congestion *via* the VExUS grading system, it helps the clinician to optimize the adequacy of fluid removal *via* dialysis |
| Cases required large amount of fluid resuscitation such as diabetic ketoacidosis, hyperosmolar hyperglycemic state *etc.* | By detecting the presence of venous congestion *via* the VExUS grading system, it helps the clinician to detect the threshold to cease the fluid resuscitation |
| Acute pulmonary oedema secondary to cardiomyopathy, hypoalbuminemia, hypertensive emergency, acute renal failure, acute liver failure *etc.* | By detecting the absence of venous congestion *via* the VExUS grading system, it helps the clinician to detect the threshold to cease the diuretic therapy |

VExUS: Venous excess ultrasound.

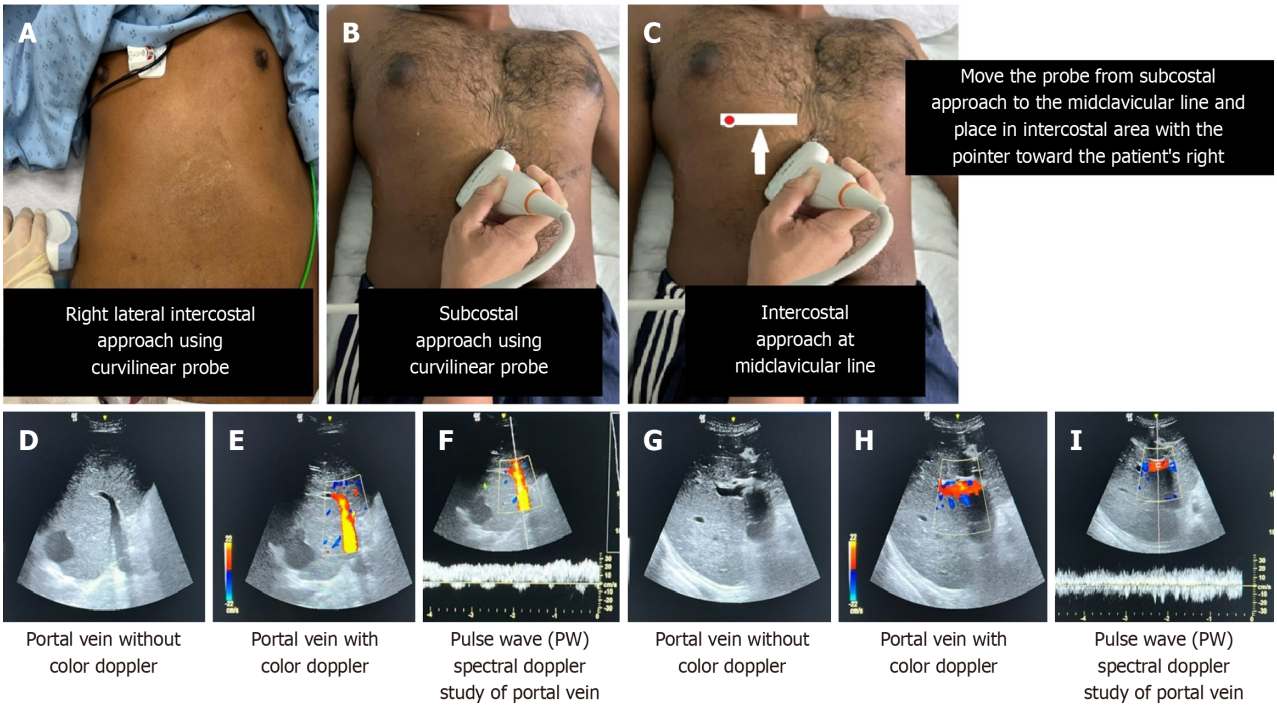



**Figure 6 Measures for locating the portal vein using a curvilinear probe and performing a pulse wave spectral Doppler study on the portal vein.** On the left-hand side of the image, we locate the portal vein using the right lateral intercostal or subcostal approach. A: Right lateral intercostal approach; B: Subcostal approach. On the right-hand side of the image, we locate the portal vein using the intercostal approach at the midclavicular line; C: Intercostal approach at the midclavicular line. The portal vein images on each side exhibit slight differences, as do the insonation angles of the portal vein and the pulse wave gate; D-F: Right lateral intercostal or subcostal approach will give an insonation angle of near 0 degree; G-I: Intercostal approaches at the midclavicular line will give an insonation angle of near 90 degrees, which could underestimate the flow velocity measurement.

the post-cardiac surgery population, while Viana-Rojas *et al*[48] studied patients with acute coronary syndrome. The other study by Longino *et al*[49] found that VExUS grade was strongly linked to right atrial pressure, mean pulmonary arterial pressure, pulmonary capillary wedge pressure, and AKI in hospitalized patients.

## GUIDING FLUID REMOVAL

The ACUVEX study[50], a single-center observational study with 33 study samples, found that fluid removal improves venous congestion among those with elevated VExUS scores. Despite the improvements, it's noteworthy that neither the left ventricle's systolic function parameter (left ventricular outflow tract velocity time integral) nor the right ventricle's systolic function parameter (tricuspid annular plane systolic excursion) showed any improvement. This implies that the improvement in the VExUS score could precede the systolic parameters of the right and left ventricles, or that the improvements in the score may not have a direct correlation with the ventricles' cardiac performance. Besides, this study

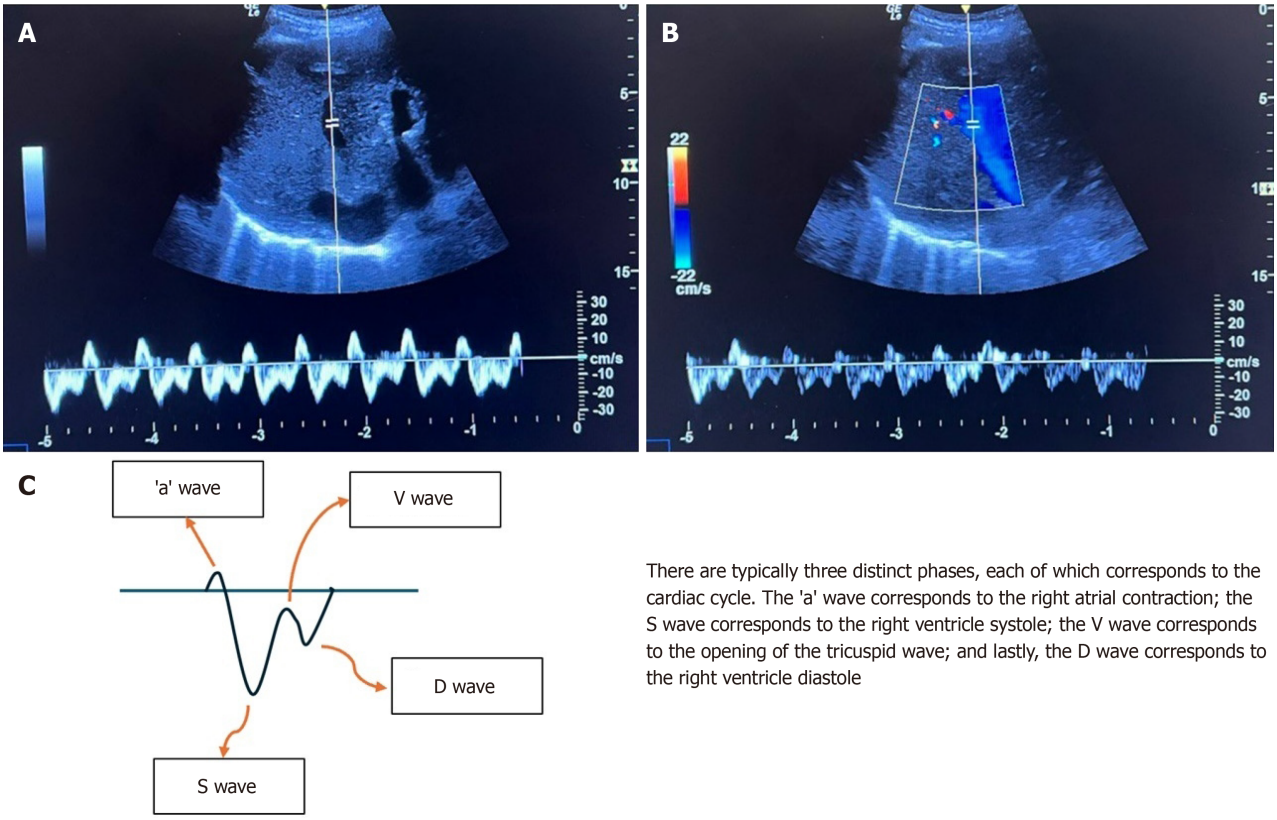



**Figure 7 The morphology of the hepatic vein pulse-wave Doppler waveform in a normal condition.** A: Hepatic vein without color doppler; B: Hepatic with color doppler; C: Hepatic vein pulse-wave doppler waveform in a normal condition.

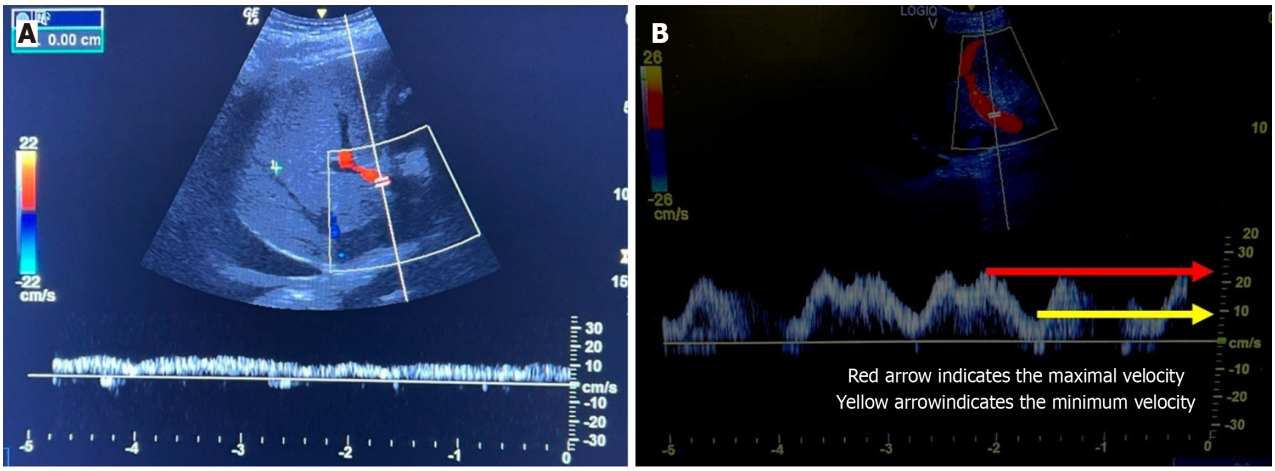
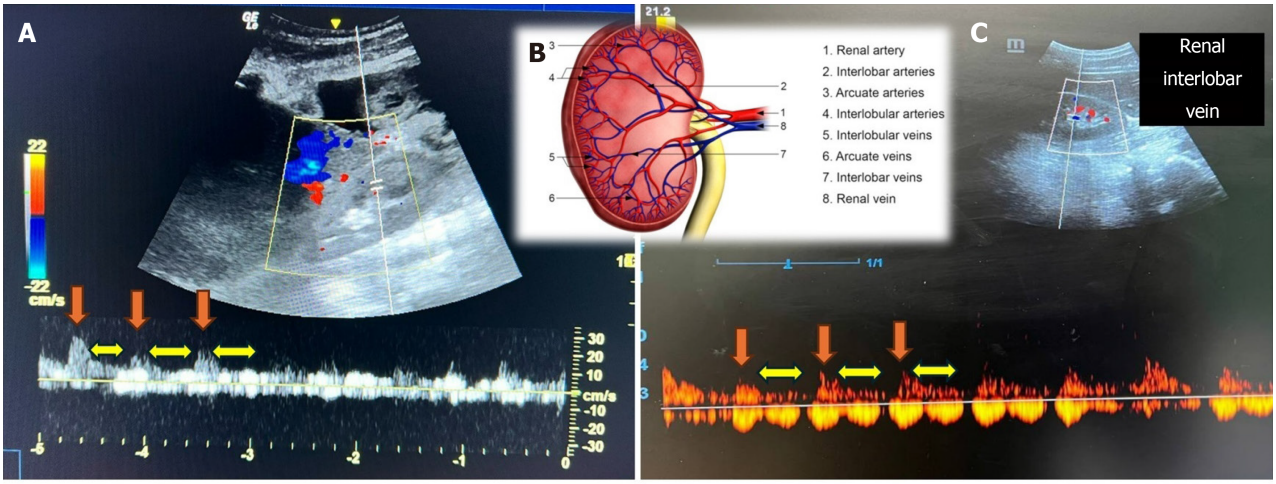



**Figure 8 Examples of the portal vein Doppler waveform.** A: In normal condition, the portal vein Doppler waveform exhibit a monophasic flow; B: In a congested portal vein, the portal vein doppler waveform exhibit a pulsatility index > 50%.

reveals individuals with elevated VExUS scores also exhibited both right and left ventricle dysfunction. This observation prompted the authors to hypothesize that the VExUS score could potentially indicate cardiac function, not just volume status. However, given the limited sample size, further research is necessary to explore all these hypotheses. As well as the ACUVEX study, Rola *et al*[32] shared a case series of a patient with pulmonary hypertension and another obstetric case where VExUS-guided hemodialysis fluid removal led to a better clinical outcome.

In addition, the AKIVEX study[51] showed patients with a reduced VExUS score within 48 hours had more kidney replacement therapy-free days at day 28 compared to those without a reduced score. AKIVEX[51], a quasi-experimental study, involved a larger sample size analysis of 90 patients admitted to the ICU who developed severe AKI. This study found higher diuretic usage among patients with a higher VExUS score. Similarly, Bhardwaj *et al*[52] demonstrated a significant correlation between AKI injury resolution and improvement in the VEXUS grade, as well as a significant association between changes in the VEXUS grade and fluid balance. Both AKIVEX[51] and Bhardwaj *et al*[52] highlighted that traditional parameters such as central venous pressure, fluid balance, peripheral oedema, and weight gain were not




In this pulse-wave (PW) doppler study, the renal artery doppler waveform appears above the baseline, and the renal vein doppler waveform appears below it. This picture is an example of a normal renal vein doppler waveform, which is monophasic throughout the cardiac cycle, with the orange arrow indicating systole and the yellow arrow indicating diastole

In this pulse-wave (PW) doppler study, the renal artery doppler waveform appears above the baseline, and the renal vein doppler waveform appears below it. This picture is an example of an abnormal renal vein doppler waveform in which there is a discontinuous biphasic flow with distinct systole and diastole phases, with the orange arrow indicating systole and the yellow arrow indicating diastole

**Figure 9 Examples of the renal vein Doppler waveform.** Renal interlobar or arcuate veins are the optimal Doppler sampling sites while performing Venous Excess Ultrasound grading assessments for renal veins. A: Normal renal vein doppler waveform which is monophasic throughout the cardiac cycle; B: Congested renal vein will exhibit a discontinuous biphasic flow with distinct systole and diastole phases; C: Renal interlobar vein.

different between the group with ultrasonographic evidence of venous congestion and the group without congestion.

## GENERAL MONITORING AND PROGNOSIS

The prospective multicentric study by Andrei *et al*[53], which looked at 145 patients in the general ICU, found that the prevalence of systemic venous congestion assessed by the VExUS is low. Besides, VExUS scores did not significantly change during the first days of the ICU stay, and systemic venous congestion (VExUS ≥ 2) was not associated with AKI or 28-day mortality. This study distinguishes itself from earlier studies that focused on cardiac or nephrology patients by examining a more diverse cohort of non-cardiac patients, including those with septic shock, trauma, and stroke, who typically do not showcase significant cardiac disease or hypervolemia. The findings suggest that various non-cardiac factors contribute to AKI risk in the general ICU population, indicating that moderate congestion alone may not be the primary factor driving AKI. Furthermore, these findings were consistent with the AKIVEX[51] study, which was conducted among ICU patients with severe AKI and found that there is a higher prevalence of sepsis among those with VExUS ≤ 1, indicating that the AKI in this group is likely due to sepsis rather than congestive nephropathy.

Apart from studies performed in the cardiac, nephrology and intensive care unit settings, Landi *et al*[54] did a study in the emergency setting among patients with acute decompensated heart failure. Landi *et al*[54] found severe venous congestion, defined as a VExUS score of 3 at the initial assessment predicted inpatient mortality, heart failure-related death, and early readmission. This study highlighted that the VExUS score was found to be technically feasible in almost all patients, despite tachypnoea and incomplete cooperation, proving feasibility and adequate interpretation even in an emergency department setting.

## LIMITATIONS OF VEXUS

The VExUS grading system, while valuable in assessing venous congestion, has its own limitations, especially in the image acquisition and interpretation challenges. The VExUS grading system involves different structures, each susceptible to certain caveats. Several factors can affect the size of the IVC, making its interpretation challenging at times. These include respiratory effort, positive ventilation, cardiac pathology such as right heart failure or tricuspid regurgitation, intra-abdominal pressure, and not to forget about local mechanical factors such as the presence of an IVC filter, IVC thrombosis, or the presence of an ECMO catheter. Tricuspid regurgitation, pulmonary hypertension, and right heart failure may all lead to persistent IVC dilation. Therefore, these conditions may consistently elevate the VExUS score, making normalization unattainable. Additionally, the use of high positive end expiratory pressure and low tidal volume ventilation during the treatment of acute respiratory distress syndrome may also lead to a larger IVC. In any healthy individual, portal vein pulsatile flow is observable during deep inspiration. Furthermore, because the pulsatility of portal veins inversely correlates with body mass, individuals with low body weight can also observe portal vein pulsatile flow despite absence of venous congestion. Individuals with stiff liver parenchyma, such as those suffering from cirrhosis or

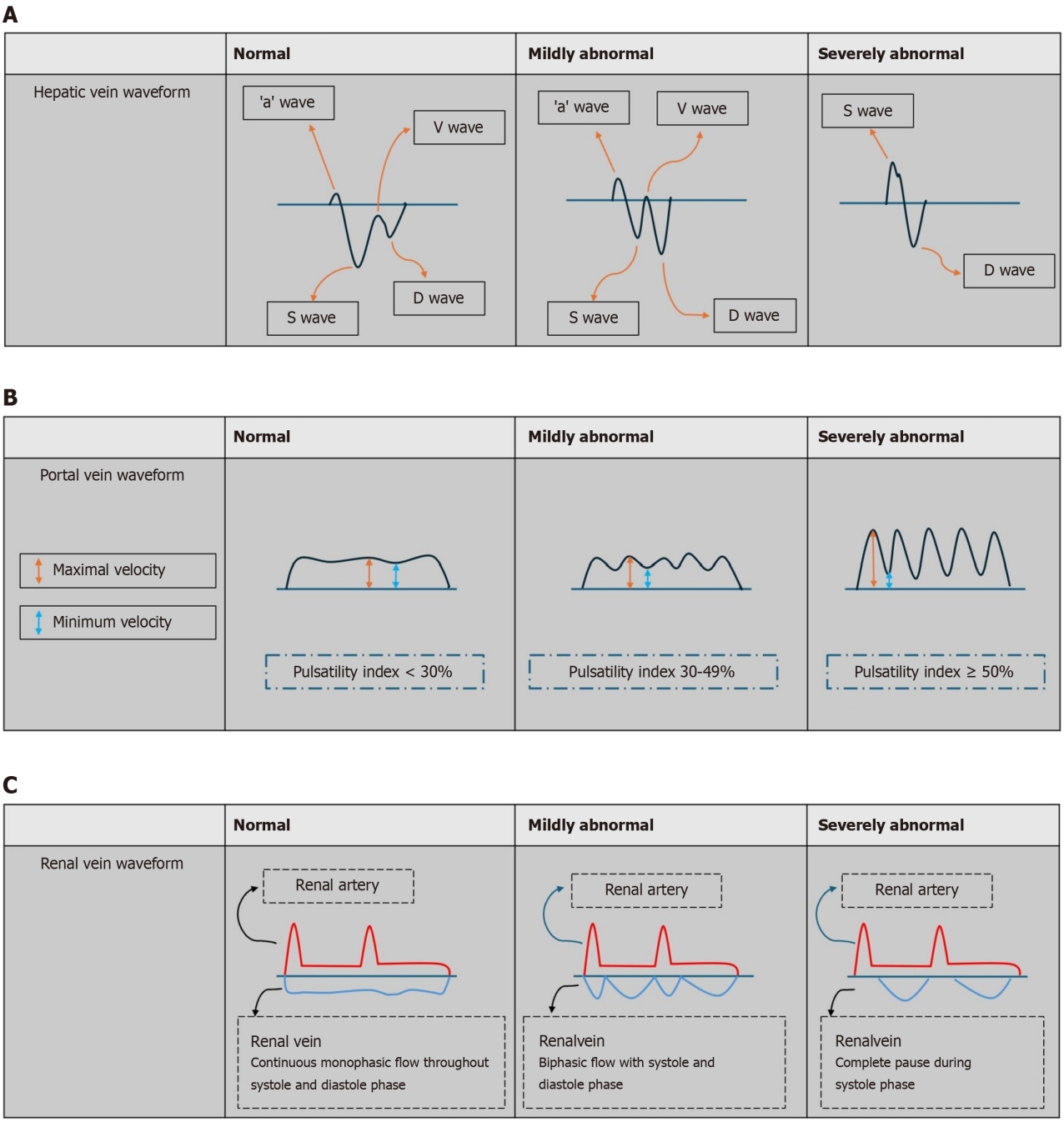



**Figure 10 Graphic representation of the interpretation of the venous excess ultrasound grading system.** Grade 0: Inferior vena cava (IVC) < 2 cm signifying no congestion. A: Grade 1: IVC ≥ 2 cm and any combination of normal or mildly abnormal waveforms, reflects only mild congestion; B: Grade 2: IVC ≥ 2 cm with one severely abnormal waveform, indicating severe congestion in a single organ; C: Grade 3: IVC ≥ 2 cm with ≥ two severely abnormal waveforms, denotes severe congestion affecting at least two organ system.

non-alcoholic fatty liver disease, may exhibit altered hepatic vein waveforms characterized by diminished phasic oscillations, as well as a non-pulsatile portal vein, which can occur even in the presence of significant venous congestion. These changes are indicative of increased resistance to blood flow due to fibrosis or steatosis in the liver[17,32]. As mentioned earlier, renal vein image acquisition can be challenging, and interpretation of the hepatic vein waveform without ECG tracing guidance can be misleading.

## CONCLUSION

In summary, VExUS serves as a valuable tool for identifying venous congestion. It should be integrated with traditional diagnostic assessments, which include a comprehensive clinical history, physical examination that includes lungs auscultation, pedal oedema, skin turgor, jugular venous pressure, and the interpretation of cardiothoracic ratio in chest X-rays. This integration can enhance the accuracy of the overall diagnostic assessment. The VExUS score can also serve as a

monitoring parameter after therapeutic measurements. Despite involving multiple assessment components, such as the use of a color Doppler and spectral Doppler, the overall performance is feasible and manageable with a thorough understanding of the technical aspects and proper guidance from individuals who are familiar and experienced with VExUS usage.

## FOOTNOTES

**Author contributions:** Chin WV wrote the manuscript; Ngai MMI participated in drafting sections and reviewing written content; See KC provided supervision and revised the manuscript.

**Conflict-of-interest statement:** Wei Ven Chin has no conflict of interest to disclose, Melissa Ngai has no conflict of interest to disclose, Kay Choong See has received honoraria from GE Healthcare and Medtronic, and has no other conflicts of interest to disclose.



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**S-Editor:** Liu H
**L-Editor:** A
**P-Editor:** Zhao YQ

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*World J Crit Care Med* 2025 June 9; 14(2): 101777

DOI: 10.5492/wjccm.v14.i2.101777

ISSN 2220-3141 (online)

*MINIREVIEWS*

# Post-reperfusion syndrome in liver transplant recipients: What is new in prevention and management?

Austin James Puchany, Ibtesam Hilmi

**Specialty type:** Critical care medicine

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade A, Grade B, Grade B, Grade B

**Novelty:** Grade A, Grade B, Grade B, Grade B

**Creativity or Innovation:** Grade A, Grade B, Grade C, Grade C

**Scientific Significance:** Grade A, Grade B, Grade B, Grade B

**P-Reviewer:** Semash K; Wang L; Wang Y

**Received:** September 26, 2024

**Revised:** November 22, 2024

**Accepted:** December 19, 2024

**Published online:** June 9, 2025

**Processing time:** 154 Days and 7.5 Hours

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## Abstract

Post-reperfusion syndrome (PRS) in liver transplant recipients remains one of the most dreaded complications in liver transplant surgery. PRS can impact the short-term and long-term patient and graft outcomes. The definition of PRS has evolved over the years, from changes in arterial blood pressures and heart and/or decreases in the systemic vascular resistance and cardiac output to including the fibrinolysis and grading the severity of PRS. However, all that did not reflect on the management of PRS or its impact on the outcomes. In recent years, new scientific techniques and new technology have been in the pipeline to better understand, manage and maybe prevent PRS. These new methods and techniques are still in the infancy, and they have to be proven not in prevention and management of PRS but their effects in the patient and graft outcomes. In this article, we will review the long history of PRS, its definition, etiology, management and most importantly the new advances in science and technology to prevent and properly manage PRS.

**Key Words:** Liver transplant; Post-reperfusion syndrome; Machine perfusion; Hypothermic machine perfusion; Normothermic machine perfusion; Caval blood flush vent; Ischemic pre-conditioning

**Core Tip:** In this article, we review the newest updates in the definition, pathophysiology and risk factors for post-reperfusion syndrome (PRS). We discuss the latest recommendations for management of PRS. We analyze and the novel advances in liver donor preservation and their potential impact on prevention of PRS.

**Citation:** Puchany AJ, Hilmi I. Post-reperfusion syndrome in liver transplant recipients: What is new in prevention and management? *World J Crit Care Med* 2025; 14(2): 101777
**URL:** https://www.wjgnet.com/2220-3141/full/v14/i2/101777.htm
**DOI:** https://dx.doi.org/10.5492/wjccm.v14.i2.101777

## INTRODUCTION

Liver transplantation represents a life-saving intervention for patients with end-stage liver disease. The surgical process involves complex steps, including the critical moment of reperfusion, where blood flow is restored to the graft liver. One of which is unclamping of the portal vein which can lead to hemodynamic instability. This spectrum of hemodynamic changes and its complications can lead to post-reperfusion syndrome (PRS). PRS is a well-recognized complication that can significantly impact the immediate and long-term outcomes of liver transplant recipients. PRS can promote more intraoperative transfusion as well as prolong intensive care unit (ICU) and overall hospital length of stay, therefore it has impact on morbidity and mortality for the recipient[1,2]. This syndrome is characterized by a spectrum of physiological disturbances and clinical symptoms that can jeopardize graft function and patient recovery.

PRS in liver transplantation is classically defined as a decrease in mean arterial pressure (MAP) by 30% from baseline for 1 minute and occurring withing 5 minutes of graft reperfusion. Other associated hemodynamic factors include decreased systemic vascular resistance (SVR) and heart rate (HR) as well as increased central venous pressure (CVP) and pulmonary capillary wedge pressure[3]. PRS can further be classified on degree of severity based on magnitude and length of hemodynamic changes[4]. For example, mild PRS is when there is < 30% decrease in MAP or HR < 5 minutes that is responsive to a fluid bolus, 1 g of IV calcium or epinephrine less than 100 ug without the need for continuous vasopressors intraoperatively. Significant PRS occurs with > 30% decline in MAP or HR, arrythmias promoting hemodynamic instability or asystole and the need for a continuous infusion of vasopressors intraoperatively. Additionally significant PRS includes prolonged (> 30 minutes) or recurrent (reappearing within 30 minutes after resolution) fibrinolysis requiring treatment with antifibrinolytics[5]. One study tested both definitions (Aggarwal *et al*[3] and Hilmi *et al*[5]) and found that both were able to reasonably predict 3-month mortality following orthotopic liver transplant (OLT)[6].

## ETIOLOGY AND PATHOPHYSIOLOGY

PRS is believed to result from a cascade of physiological events triggered by the restoration of blood flow to the ischemic liver graft. Following release of the portal vein clamp the right heart is exposed to, cold, acidic blood with vasoactive inflammatory reactants that results in increases in CVP, pulmonary vascular resistance, and pulmonary artery pressures with decreased systemic pressure. The elevated pulmonary pressures can cause right ventricular failure which can lead to decreased left ventricular filling pressures precipitating the hemodynamic changes associated with PRS[7-9].

The release of ischemic byproducts following unclamping of the portal vein and inferior vena cava (IVC) clamps can precipitate the metabolic derangements associated with PRS, these include lactic acidosis, hyperkalemia, and hypocalcemia. These electrolyte derangements can evoke arrythmias and ST and T-wave changes. Additionally, there is often an increase in partial pressure of carbon dioxide, a metabolic byproduct of cellular respiration and metabolism in the new organ which can affect blood flow and ventilation dynamics[10]. Other byproducts of ischemia such as heparinoids, cytokines and chemokines can evoke a systemic inflammatory response (SIRS) and lead to coagulopathy. As well as the endogenous heparin release from the donor liver can contribute to coagulopathy. Fibrinolysis can occur *via* decreased activity of plasminogen activator inhibitor and from tissue-plasminogen activator released from the donor liver and ischemic tissues below the clamp[11].

Ischemia during the preservation stage of the transplantation process can also result in ischemic reperfusion injury of the new liver graft which is thought to contribute to PRS. During storage, Ischemia produces lytic enzymes like xanthine oxidase and NADPH oxidase that can produce reactive oxygen species (ROS) that can damage the new liver and surrounding tissues. These ROS are sensed by Kupffer cells in the liver which release cytokines like tumor necrosis factor alpha (TNF-α) and other inflammatory substances that can produce a SIRS response[12,13]. One study found that the levels of TNF-α secreted from the liver correlated to vasopressor requirements following reperfusion.

Microcirculatory changes occur due to an imbalance of endothelin-1 and nitric oxide (NO) in the sinusoids which lead to accumulation of neutrophils and platelets in blood vessels leading to ischemia. This promotes hepatocellular necrosis and activation of local inflammatory reactants (Kupffer cells) leading to further oxidative injury[14]. Intestinal bacteria can play a role in PRS through bacterial translocation from disruption of the intestinal barrier from surgical manipulation and portal venous congestion. Endotoxemia can occur within 30 minutes of liver ischemia due to lack of protection from removed Kupffer cells in anhepatic phase. Also, gut translocation can activate the complement cascade with formation of

the membrane attack complex potentially leading to post-reperfusion hypotension, but this exact mechanism remains unclear[15].

Following reperfusion, exposure of the recipient's blood to basement membrane of the damaged transplanted sinusoidal cell endothelium can evoke activation of the kallikrein-kinin system leads to breakdown of kininogen increases bradykinin levels, a vasoactive substance that can contribute to PRS[16].

Patients with advanced cirrhosis have higher levels of NO due to endotoxin-induced stimulation of the inducible NO synthase, NO produces cyclic guanosine monophosphate (cGMP) which decreases SVR and causes hypotension as well as ROS that cause further oxidative injury. Studies have shown that higher baseline levels of cGMP have been associated with higher catecholamine vasopressor requirement and longer ICU stay[17].

Some risk factors for developing PRS include donor age, recipient age, Model for End-Stage Liver Disease Score, organ size difference, degree of microvascular steatosis, patient specific factors such as elevated creatinine, low calcium and hemoglobin levels, left ventricular diastolic dysfunction and prolonged cold ischemic time[18] (Table 1).

## PREVENTION

PRS can have a significant impact on patient morbidity, mortality and outcomes. As previously stated, it can prolong hospital and ICU stay as well as increase the likelihood of graft failure, therefore its prevention is essential. A number of approaches have been reported to prevent PRS attempting to reduce its hemodynamic and other systemic effects as well as decrease the incidence and severity. Prior to reperfusion, metabolic and electrolyte abnormalities should be corrected, and volume status should be assessed and optimized, as the cardiac and hemodynamic effects of PRS can occur abruptly.

### *Metabolic and electrolyte correction*

Reperfusion can induce a large potassium release leading to hyperkalemia. Hyperkalemia has been associated with higher post-op mortality following OLT[19]. Higher baseline potassium, plus intraoperative red blood cell (RBC) transfusions are independent risk factors for developing post reperfusion hyperkalemia[20]. Administration of insulin doses (1-2 units) with each unit of RBCs as opposed to one large bolus immediately prior to reperfusion have been shown to lower pre-reperfusion serum potassium levels. Additionally, a bolus of calcium (chloride or gluconate) directly before graft reperfusion can treat the hypocalcemia generally associated with transfusion and reperfusion, as well as stabilize the myocardium from an abrupt increase in serum potassium following reperfusion. The use of sodium bicarbonate surrounding reperfusion is controversial. Some propose that it can counter hyperkalemia and attempt to optimize serum pH to increase the effectiveness of vasopressors if need following reperfusion[21]. However, there is emerging evidence that a moderate to severe acidotic state may have protective effects on the brain, myocardium, liver and kidneys, therefore aggressive correction of acidosis with sodium bicarbonate has been shown to worsen the ischemic reperfusion induced oxidative stress injured cells[22-26].

### *Agents for hemodynamic augmentation*

Reperfusion can release vasoactive substances from the transplanted liver that can evoke bradycardia, decrease cardiac contractility and decrease SVR. Vasopressor Pretreatment has been implemented to combat hypotension following reperfusion, given that hypotension has been associated with greater incidence of graft malfunction, post-operative renal failure and mortality. Atropine can be given to prevent bradycardia but does not help raise MAP. A 10-20 microgram bolus of epinephrine is more effective at attenuating PRS given the ability to increase both HR and MAP[4,27]. Preemptive phenylephrine and epinephrine administration have been shown to reduce the incidence of PRS but did not have an effect on hospital length or stay or mortality. Other vasopressors like norepinephrine, ephedrine, dopamine and vasopressin have been used. Norepinephrine may be favorable over phenylephrine given it can increase cardiac contractility in addition to SVR *vs* just SVR alone with phenylephrine. Ephedrine started 5 minutes prior to reperfusion at a rate of 2.5-5 mg/minute (with targeted MAP goal of 85-100 mmHg), was shown to reduce the incidence of PRS and need for rescue vasopressors following reperfusion[28]. Patients with severe liver disease tend to be catecholamine and vasopressin depleted therefore exogenous vasopressin administration has been effective for treatment of PRS refractory to other catecholamine inducing vasopressors[29]. It can be effective in patients with severe acidosis to which epinephrine and norepinephrine are less effective[30].

### *Methylene blue and hydroxocobalamin*

Methylene blue (MB) is an inhibitor of NO synthase which decreases production of NO a potent vasodilator released in following ischemic reperfusion. MB inhibits NO and the production of cGMP as well as increases vascular smooth muscle and myocardium sensitivity to catecholamines thus increasing SVR, MAP and cardiac contractility. Prophylactic administration of MB prior to reperfusion allowed for significant increases in MAP and cardiac index without significant changes in SVR following reperfusion, when compared with placebo. Additionally, patients given MB had lower lactate levels following reperfusion suggesting a benefit to graft function[31]. MB can also be used to treat hypotension refractory catecholamines and vasopressin at a dose of 100 mg or 2 mg/kg[32].

Hydroxocobalamin is a strong NO scavenger and can be used for refractory vasoplegia in OTL. Additionally, it takes up hydrogen sulfide, a substance released in patients with liver failure that causes vasodilation. Hydroxocobalamin can be effective when MB is contraindicated (such as in G6DP deficiency due to risk of hemolysis or in patients taking MAO-Is due to risk of serotonin syndrome)[33].

**Table 1 Potential cellular and physiologic causes of post-reperfusion syndrome**

| Category | Physiologic change | Hemodynamic change |
|---|---|---|
| Release of vasoactive substances | Inflammatory cytokines (nitrous oxide, endothelin-1, bradykinin, reactive oxygen species) | Increased CVP; increased PVR; increased PAP; decreased SVR; decreased ABP; decreased CI; decreased HR; ST changes; T-wave changes |
| Electrolyte disturbances | Hypothermia; acidosis; hyperkalemia; hypocalcemia; hyperphosphatemia | |
| Embolic phenomena | Thromboembolic; air emboli | |

ABP: Arterial blood pressure; CI: Cardiac index; CVP: Central venous pressure; HR: Heart rate; PAP: Pulmonary artery pressure; PVR: Pulmonary vascular resistance; SVR: Systemic vascular resistance.

## MANAGEMENT

### *Protease inhibitors*

Protease Inhibitors like aprotinin were designed for inhibition of fibrinolysis and were studied in OLT to assess the need for blood transfusion perioperatively but were shown to decrease the hemodynamic effects associated with PRS. Aprotinin works by inhibiting plasmin generation and thus fibrinolysis, but at higher doses it can inhibit serine proteases like those necessary for the kallikrein-kinin system thus blunting the production of bradykinin a strong vasodilator released during ischemic-reperfusion. The improved vascular tone and not necessarily reduced bleeding is thought to be the main benefit from protease inhibitor use in PRS[34,35]. These results were seen with a bolus of aprotinin following induction of anesthesia, followed by a continuous infusion. Aprotinin has been shown to combat the SIRS associated with reperfusion and PRS. Of note there is an increased risk for intracardiac thrombus formation with use of antifibrinolytics in OLT[36]. Numerous studies have been done with aprotinin in numerous settings and the drug is no longer used due to safety concerns. Other antifibrinolytic agents such as epsilon-aminocaproic acid (EACA) and Tranexamic Acid (TXA) have been studied for use in OLT and have shown lower incidence of PRS and reduced blood product requirements with TXA proving superior to EACA[37].

### *Magnesium sulfate*

Supplementation with magnesium sulfate has shown to be protective in PRS for various reasons. It provides cellular protection during ischemia by blocking excess calcium influx thus stabilizing the electrical transmembrane potential. Magnesium administration prior to reperfusion has been shown to reduce serum lactate levels suggesting possible protection against ischemic reperfusion-injury[38]. Magnesium blocks immunologic response reducing production of interferon-y and increasing production of interlukin-4 and interlukin-10 creating a better balance of cytokines and improved hemodynamics after reperfusion[39]. Overcorrection of magnesium should be avoided because hypermagnesemia can cause hypotension.

### *Ischemic preconditioning*

Ischemic preconditioning (IPC) is a method of applying brief periods of ischemia and reperfusion to tissue prior to a longer ischemic event. It was first used on heart muscles but has been trialed on other tissues including liver[40]. It was thought that this strategy can decrease ischemic reperfusion injury and thus decrease incidence and severity of PRS. Multiple studies including a Cochrane review have tested IPC in OLT, but these have only demonstrated a reduction in ischemic reperfusion injury but not improvements in long term outcomes. There was no statistically significant difference in ICU stay, hospital length of stay, primary graft function, need for transplantation or mortality between the two groups [41].

## NEW ADVANCES

### *Machine perfusion*

The type of liver graft (*i.e.,* those taken after cardiac death) can play a role in graft success. Those taken after cardiac death are underutilized because they are associated with increased risk of primary graft failure. They are more susceptible to ischemia reperfusion injuries and biliary system complications[42,43]. Static cold storage (SCS) has been the gold standard for graft preservation but allows for anerobic metabolism to persist leading to depletion of ADP and accumulation of ROS. SCS has four primary limitations: The storage duration is restricted, it may cause additional harm during organ storage, it does not reverse ongoing organ damage and organ viability cannot be assessed during storage. This can be critical in "high risk" donors[44].

Machine perfusion (MP) is a new method of preservation being implemented and studied to help ameliorate the downfalls of SCS. It allows for more useable organs especially from "high risk" donors. It can decrease cold ischemic time and thus reduce potential damage in organs more susceptible to ischemia[45]. There are two primary forms of MP, normothermic MP (NMP) and hypothermic MP (HMP).

### NMP

NMP maintains graft normothermia while delivering ample oxygen and nutrients during graft harvesting, preservation and implementation. NMP allows for assessment of objective graft parameters and the ability to detect and remove organs that are not transplantable. NMP can be used to estimate graft survival by analyzing hemodynamic parameters, liver and bile duct function and liver injury indices[46,47]. A phase III multicenter randomised controlled trial (RCT) found that NMP subjects had lower incidence of graft injury, organ loss and longer mean preservation time[48]. Mergental *et al*[49] found that high risk donor livers that under went SCS then NMP had good immediate post-operative function after 7 months follow-up. This showed that a viability assessment with NMP allows for livers previously deemed unusable to be successfully transplanted in lower risk patients[49]. No studies have been conducted that measured the effects of NMP with direct reduction in PRS and but there is thought that a more adequately preserved graft could reduce the incidence of PRS and thus these studies should be pursued.

### Normothermic regional perfusion

Normothermic regional perfusion (NRP) is a method of providing in situ perfusion to a portion of the donor's body following circulatory arrest[50,51]. It can only be used in donation after cardiac death (DCD) liver allografts compared with hypothermic oxygenated perfusion (HOPE) and NMP which can be used in both donation after brain death (DBD) and DCD donors. Five to twenty minutes following circulatory arrest, extracorporeal membrane oxygenation (ECMO) is initiated *via* cannulation of the aorta or femoral artery and venous return from the IVC or femoral vein[52]. There are two types of NRP, abdominal-NRP (A-NRP) and thoracoabdominal-NRP (TA-NRP). A-NRP provides *in situ* perfusion to abdominal organs through the IVC and intrarenal aorta. TA-NRP provides *in situ* perfusion of abdominal and thoracic organs *via* cannulation of the aortic arch and right atrium. Through TA-NRMP there is restoration of cardiac function with aortic clamping to prevent brain perfusion[53]. There are ethical concerns with restarting cardiac function, so this method has been controversial in is being reviewed in some institutions[54]. There has not been a RCT on NRP documented in the literature however there is retrospective studies showing better results than SCS. Results show that NRP can improve outcomes in DCD organ transplant through prevention of early allograft dysfunction (EAD), decreasing biliary complications, improving graft survival and decreasing retransplantation risk[52,55].

When assessing long term outcomes of NMP and NRP, more data is needed however some early studies some promise. Gaurav *et al*[56] performed a single center retrospective analysis looking at donors preserved with NRP, NMP and SCS. They found that the NRP group had higher 6-month survival (NRP: 94%, NMP: 90%, and SCS: 87%) and 3 year survival (NRP: 90%, NMP & SCS: 76%). Additionally, two observational cohort studies by Hessheimer *et al*[50,57] compared NRP and SCS preserved livers and found that the NRP group had lower incidence of overall biliary complications, ischemic-type biliary lesions, and graft loss and patient death. Finally, a retrospective analysis by Watson *et al*[58] comparing NRP *vs* standard DCD prepared donors, the NRP group had less incidence of Ischemic cholangiopathy which can lead to improved long-term outcomes.

### HMP

HMP uses cold temperature to slow cellular metabolism while flushing out metabolites. One form HOPE delivers the perfusate through the portal vein. Dual HOPE involves delivering perfusate through the portal vein and hepatic artery [59]. Multiple studies have shown that liver grafts obtained from DCD have comparable postoperative outcomes to those from DBD. Additionally, HOPE has been compared to SCS in DCD allografts with the HOPE treated grafts showing lower incidence of PRS, early allograft injury, and graft failure as well as improved long term graft survival and decreased late onset morbidity[60,61].

HOPE was shown to have less complications and enhanced graft survival. Because of these positive effects it may allow for increased use of less optimal organs which will help with the increased demand for organs. A study by Horné *et al*[62] compared 100 liver transplants with 50 preconditioned with HOPE and 50 treated with SCS and found that 12% of HOPE treated organs experienced PRS compared to 42% that underwent SCS. HOPE treated livers also had lower vasopressor requirements and potassium levels and the overall incidence of EAD decreased by 44%. This suggests that HOPE offers greater hemodynamic stability and less EAD and PRS compared to the traditional SCS method[62].

There remains limited data on the long term outcomes of HOPE, however there are a few studies that show improvements in long term out comes. A RCT by Czigany *et al*[61] found that HOPE reduced late onset morbidity and enhanced log-term graft survival. Another RCT by Ravaioli *et al*[63] found that HOPE treated grafts had lower graft dysfunction rates and longer graft survival compared to SCS. Additionally, van Rijn *et al*[64] found that HOPE was associated with fewer non-anastomotic biliary strictures compared to SCS treated donors.

### Caval blood flush vent

Many studies have assessed flushing and venting grafts with different types of fluid (LR, albumin, blood) and *via* different routes (arterial, portal and caval) but most of these studies found inconsistent results on metabolic changes (potassium) and on outcomes[65-70]. It was thought that adding caval venting following a LR/albumin portal vein flush could prevent metabolic changes (acidic, hypothermic, hyperkalemic blood) from the initial reperfusion bolus from entering the systemic circulation allowing for better hemodynamic stability and thus decreasing the incidence of PRS. Stoll *et al*[71] performed a prospective observational study that analyzed 20 Liver transplants, with 16 receiving a caval blood flush vent (along with a standard chilled LR/albumin portal vein flush) and 4 who did not receive the caval flush. They found that those who underwent caval flush had better preservation of MAP and HR but CVP and lab values (blood gas, electrolytes and hemoglobin) were similar between the two groups. They concluded that caval venting (along with traditional portal vein chilled LR/albumin flush) could have favorable hemodynamic protection but the literature is

**Table 2 Comparison of Techniques for preventing post-reperfusion syndrome including advantages and limitations**

| Technique | Advantages | Limitations |
|---|---|---|
| Static cold storage | Cheaper, current gold standard, many studies showing efficacy | Storage duration is restricted, potential for harm during storage, does not reverse ongoing damage, organ viability can't be assessed during storage |
| Hypothermic machine perfusion | Can use on high risk donors, can use in DBD and dcd allografts, lower incidence of graft injury, organ loss, allows for longer mean preservation time, enhance organ availability reduce waitlist mortality | Limited data on long term benefits, need to cool to sub-physiologic temperature |
| Normothermic machine perfusion | Can use at physiologic temperatures, can use on high-risk donors, can use in DBD and DCD allografts, lower incidence of graft injury, organ loss, allows for longer mean preservation time, enhance organ availability reduce waitlist mortality | Limited data on long term benefits |
| Normothermic regional perfusion | Very affective for DCD donors | Only used in DCD liver allograft management, ethical considerations with TA-NRP |
| Caval blood flush vent | Hemodynamic protection<br>cheapest, decreased requirement for vasopressors and inotropes | Limited studies on short and long term benefits |
| ECMO | Eliminate the need for extensive immunosuppressive treatments, expand the donor organ pool, cheaper than MP | Patients usually very ill with multi-organ failure and systemic infections, bilirubin levels hard to measure in short term, limited data on long term benefits, ethical concerns |

DBD: Donation after brain death; DCD: Donation after circulatory death; ECMO: Extracorporeal membrane oxygenation; MP: Machine perfusion; TA-NRP thoracoabdominal normothermic regional perfusion.

sparse, and more studies are needed[71]. Further research is needed to evaluate the effects of caval venting on graft function, morbidity, and mortality, and we encourage including real-time transesophageal echocardiography to better explain the proposed mechanism of hemodynamic changes.

### *Application of extracorporeal therapies*

The demand for organ donation is continuously outgrowing the supply of viable organs. This is true in liver transplantation. Numerous strategies have been developed to help address this issue. One strategy is using ECMO at the time of death to increase organ viability, however there is limited studies and guidelines on the use of this strategy. One study by Rajsic *et al*[72] analyzed the existing evidence and found 20 publications that reported on 147 patients (who were diagnosed of death by standard neurological criteria) whose organs were procured while on ECMO support. The organs of these donors were used in 359 recipients with 85/359 being liver transplantations, with an 89% graft survival rate. Overall, the organs treated with ECMO support had 92% graft survival rate and 98% recipient survival rate. A retrospective trail by Hsieh *et al*[73] reviewed ECMO with DBD and ECMO with DCD *vs* just a DBD group alone. They found that the DCD with ECMO group had longer cold ischemic time, warm ischemic time, and split liver transplantation than the DBD group alone, with statistical significance. The DBD with EMCO and DCD with ECMO groups had less vasopressor requirements than the DBD group and the DBD with ECMO had a higher survival rate than DBD alone, however these results were statistically insignificant. This highlights a potential strategy for improved graft procurement and graft survival. Further studies are needed to investigate the role of ECMO in graft preservation and viability and the role of ECMO treated grafts in reducing PRS.

In patients with acute liver failure where organ recovery might occur, extracorporeal liver perfusion (ECLP) *via* a genetically modified pig donor may offer an approach to preserve organ viability. It may decrease the need for immunosuppressive therapies and liver transplant at all. Some preclinical studies showed that ECLP with pig livers can possibly preserve injured human livers for approximately 1 week. Although the numbers were small, they showed a survival benefit and may highlight safe technique for bridging patients to liver transplantation[74-78] (Table 2).

## CONCLUSION

PRS remains a significant challenge in liver transplantation, with complex underlying mechanisms and substantial clinical implications. The underlying direct mechanisms of PRS remain unknown, however the metabolic and hemodynamic changes associated with it are largely apparent and should be optimized throughout surgery to help lessen the effects and prevent PRS. A comprehensive understanding of PRS, coupled with vigilant monitoring and targeted management strategies, is essential for optimizing outcomes in liver transplant recipients. Most of the studies regarding PRS are performed on recipient from deceased donors however, in our clinical experience PRS has been shown to be milder in recipients from live-liver donors, which is believed to be due to short ischemia time and improved graft quality. There is limited data comparing graft and patient outcomes between these two donor groups and future studies are necessary. Additionally, Further studies into the efficacy of MP, IPC, caval venting and ECMO and their effects on PRS, graft function and morbidity/mortality are essential to implementation of this technology and ultimately improving

patient outcomes.

## FOOTNOTES

**Author contributions:** Puchany AJ performed literature review, writing – original draft; Hilmi I performed conceptualization, review, and editing.

**Conflict-of-interest statement:** Both authors have nothing to disclose.



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**S-Editor:** Lin C
**L-Editor:** A
**P-Editor:** Guo X

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World Journal of Critical Care Medicine

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*World J Crit Care Med* 2025 June 9; 14(2): 102521

DOI: 10.5492/wjccm.v14.i2.102521

ISSN 2220-3141 (online)

*MINIREVIEWS*

# Redefining haemostasis: Role of rotational thromboelastometry in critical care settings

Sahil Kataria, Deven Juneja, Omender Singh

**Specialty type:** Critical care medicine

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade B, Grade B, Grade C

**Novelty:** Grade B, Grade B, Grade C

**Creativity or Innovation:** Grade B, Grade C, Grade C

**Scientific Significance:** Grade B, Grade B, Grade B

**P-Reviewer:** Silva SML; Yan J; Yang GY

**Received:** October 21, 2024

**Revised:** January 20, 2025

**Accepted:** February 8, 2025

**Published online:** June 9, 2025

**Processing time:** 129 Days and 19.9 Hours

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## Abstract

Management of patients with acute hemorrhage requires addressing the source of bleeding, replenishing blood volume, and addressing any coagulopathy that may be present. Assessing coagulopathy and predicting blood requirements in real-time in patients experiencing ongoing bleeding can pose substantial challenges. In these patients, transfusion concepts based on ratios do not effectively address coagulopathy or reduce mortality. Moreover, ratio-based concepts do not stop bleeding; instead, they just give physicians more time to identify the bleeding source and plan management strategies. In clinical practice, standard laboratory coagulation tests (SLCT) are frequently used to assess various aspects of blood clotting. However, these tests may not always offer a comprehensive understanding of clinically significant coagulopathy and the severity of blood loss. Furthermore, the SLCT have a considerable turnaround time, which may not be ideal for making prompt clinical decisions. In recent years, there has been a growing interest in point-of-care viscoelastic assays like rotational thromboelastometry, which provide real-time, dynamic information about clot formation and dissolution.

**Key Words:** Bleeding; Critical care; Haemorrhage; Intensive care unit; Rotational thromboelastometry; Viscoelastic tests

**Core Tip:** Point of care viscoelastic tests like rotational thromboelastometry (ROTEM) can provide real-time, dynamic information about clot formation and dissolution and prove to be a valuable tool for assessing coagulation in numerous critical care settings. Unlike traditional coagulation tests, ROTEM can provide whole-blood evaluations which may aid the physicians to quickly identify coagulation issues and administer targeted treatments. With emerging technology and increasing clinical experience, new applications may emerge, and ROTEM may become an integral part of modern haemostatic management.

**Citation:** Kataria S, Juneja D, Singh O. Redefining haemostasis: Role of rotational thromboelastometry in critical care settings. *World J Crit Care Med* 2025; 14(2): 102521
**URL:** https://www.wjgnet.com/2220-3141/full/v14/i2/102521.htm
**DOI:** https://dx.doi.org/10.5492/wjccm.v14.i2.102521

## INTRODUCTION

Acute haemorrhage is a critical medical condition that demands rapid and effective management to prevent life-threatening complications. The primary goals in treating patients with significant bleeding include identifying and controlling the source of hemorrhage, restoring blood volume, and addressing any underlying coagulopathy. However, evaluating and managing coagulopathy during active bleeding presents considerable challenges. Traditional approaches to bleeding control, such as ratio-based transfusion strategies, often fall short of effectively managing coagulopathy or reducing mortality[1,2]. While these strategies may offer temporary support, they do not directly stop the bleeding. Instead, they buy time for clinicians to locate the bleeding source and initiate definitive treatment. Additionally, standard laboratory coagulation tests (SLCT), including prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet count, are limited in their ability to provide a timely and comprehensive assessment of bleeding risk and coagulopathy severity, as they often require 30 to 90 minutes for results and are not designed to guide transfusion decisions in acute settings[3,4].

In this context, point-of-care viscoelastic assays, such as rotational thromboelastometry (ROTEM), have become valuable tools for evaluating real-time coagulation status. Unlike traditional tests that assess individual components of the clotting cascade, ROTEM provides a dynamic, whole-blood assessment of the clotting process, capturing the interactions between clotting factors, platelets, and fibrinogen. This real-time analysis of clot formation, stabilization, and lysis enables clinicians to rapidly identify specific coagulation abnormalities, such as hyperfibrinolysis or thrombocytopenia, and tailor treatments accordingly[5]. For instance, administering fresh frozen plasma (FFP) to a patient experiencing bleeding due to thrombocytopenia or hyperfibrinolysis may be of limited benefit and could expose the patient to unnecessary risks, such as infections or alloimmunization[6,7].

The use of ROTEM in clinical practice offers several advantages over SLCT, providing immediate and actionable insights that can significantly improve the management of patients experiencing acute bleeding. This article delves into the principles of ROTEM, its clinical applications across various medical scenarios, and practical approaches to interpreting its results. By integrating ROTEM into acute hemorrhage management protocols, healthcare professionals can enhance their ability to make informed decisions quickly, ultimately improving patient outcomes in critical bleeding situations.

## OVERVIEW OF THROMBOELASTOMETRY: ROTEM

Viscoelastic testing facilitates the assessment and graphical depiction of the dynamic viscoelastic characteristics of whole blood during the coagulation process. Thromboelastography (TEG), initially introduced by Professor Hartert[8] in 1948, is a comprehensive technique for assessing the complete blood coagulation process, represented graphically from the onset of clot formation to fibrinolysis. The ROTEM system represents an advancement over TEG, developed in Munich between 1995 and 1997. In contrast to conventional laboratory coagulation tests conducted on centrifuged plasma fractions, viscoelastic assays that utilize whole blood, offer the benefit of a more comprehensive assessment of the interactions between cellular and plasma components (Table 1).

### *Principle for ROTEM*

A blood clot can be characterized as a Maxwell body, demonstrating both viscous and elastic characteristics. Viscoelastic assays assess the clot's "shear modulus", reflecting its propensity to deform when subjected to opposing forces. Each material possesses a distinct shear modulus; however, in the case of blood, this property undergoes alterations throughout the clotting process.

In conventional TEG, a cuvette containing whole blood is utilized, and a pin connected to a torsion wire is submerged within the sample. The cup undergoes a rotational movement of 4.45° over a duration of 5 seconds, incorporating a 1-second pause at both the beginning and the conclusion of the motion. The pin exhibits unrestricted movement when the blood is in a liquid state. The formation of blood clots and fibrin strands between the cup and the pin restricts the pin's

**Table 1 Advantages of viscoelastic testing over traditional laboratory conventional coagulation testing**

| | Viscoelastic assays | Standard laboratory conventional coagulation test |
|---|---|---|
| Specimen type | Whole blood sample | Platelet-poor plasma |
| Result turnaround | Rapid results in minutes | Extended turnaround time |
| Testing site | Assessable and analysable at point of care | Conducted in a central laboratory |
| Clotting system assessment | Offers a comprehensive view of *ex-vivo* clotting | Indicates adequacy of thrombin generation, without insights beyond that |
| Validation for acute bleeding | Efficacy proven in multiple randomized controlled trials for improving patient safety and outcomes | Not validated for predicting bleeding risk or guiding transfusion |

movement. This restriction is subsequently transformed into an electrical signal, a TEG tracing[9].

ROTEM functions with distinct operational principles. The pin traverses an arc measuring 4.75°, with the cup remaining stationary. As coagulation initiates and fibrin strands develop, the rotation of the pin becomes progressively limited (Figure 1). The observed decrease in movement is captured through optical detection, subsequently transformed into an electrical signal, processed using specialized software, and ultimately depicted in a graphical format. ROTEM enhances TEG by providing four channels for concurrent sample or diagnostic analyses, in contrast to the two channels available with TEG. Furthermore, ROTEM exhibits reduced sensitivity to mechanical stress and vibration compared to TEG[10].

While TEG and ROTEM function based on similar principles, the results obtained from each are not interchangeable. This variation is attributed to the mechanical differences inherent in the instruments and the unique mechanisms of action associated with their respective reagents[11]. ROTEM employs more potent activators than traditional TEG, which utilizes kaolin. ROTEM utilizes ellagic acid (INTEM) and tissue factor (EXTEM) as activators, demonstrating greater efficacy in initiating the coagulation process than kaolin. As a result, ROTEM tracing may exhibit reduced sensitivity to the impacts of low molecular weight heparins and various other anticoagulants. TEG functional fibrinogen values have the potential to overestimate fibrinogen levels in comparison to fibrinogen thromboelastometry (FIBTEM) maximum clot firmness (MCF), attributable to the varying capacities of the reagents to inhibit platelet function[12]. As a digitized point-of-care system, ROTEM presents numerous benefits for routine clinical application, including standardized measurement methodologies, pathway sub-analysis capabilities, and the provision of rapid, replicable digital signatures.

### *Comprehending ROTEM parameters*

Historically, the curve has been plotted on both sides and measured in millimetres. The comprehensive tracing offers valuable information regarding the *ex-vivo* clot formation status of an individual's whole blood. The elastic time points are categorized into the coagulation and clot lysis phases[10]. These can be further examined through clot initiation, kinetics, and clot strength (Figure 2 and Table 2).

### *ROTEM apparatus and associated reagents*

The ROTEM device comprises several essential components, including the measurement system, disposable test kits, and software designed for data analysis. Ensuring an appropriate setup and calibration is essential for achieving precise results. A blood sample may be analyzed in its native state without adding any reagents, or it may undergo recalcification if collected in a citrate tube. The presence of citrate may affect the outcomes; however, it remains the preferred method in situations where immediate processing is unfeasible[13]. The storage of citrate tubes ensures the stability of samples for a minimum duration of 2 hours. Repeated sampling from the same tube should be avoided, as this practice may lead to the activation of platelets and coagulation factors[14]. Different activators or inhibitors can be introduced to the sample to illustrate various facets of haemostasis, accelerate the initiation of coagulation, or target specific elements such as fibrinogen or platelets (Table 3)[12,15]. The ROTEM system employs three distinct categories of reagents[15]: (1) The ROTEM delta system uses polybrene to neutralize up to 5 IU/mL of heparin, ensuring accuracy in high-heparin settings like a cardiopulmonary bypass; (2) The ROTEM sigma system automates tests with cartridge-based assays, categorizing results as EXTEM C, FIBTEM C, and APTEM C; and (3) ROTEM delta and platelet single-use reagents lack heparin inhibitors, which are unsuitable for unfractionated heparin (UFH) patients. Clotting issues are assessable *via* INTEM (S) and HEPTEM (S).

### *Analysis of ROTEM*

ROTEM reference ranges have been determined for various populations, including healthy individuals, across different age groups, such as neonates, infants, children, adolescents, adults, and pregnant women during the first to third trimester and peri-partum periods[16-18]. Understanding the influence of age, gender, and pregnancy on ROTEM parameters is essential for making precise clinical decisions. Elderly patients frequently demonstrate a reduction in clotting time (CT) alongside an increase in amplitude MCF. Throughout pregnancy, the alterations in haemostasis can be effectively demonstrated using TEG and ROTEM, which indicate a "prothrombotic phenotype" marked by reduced CT and an increase in MCF, primarily due to heightened fibrinogen concentrations.

**Table 2 Rotational thromboelastometry parameters and their clinical significance**

| ROTEM parameters | Clinical significance |
|---|---|
| Clot initiation: Clotting time | The time from the beginning of the test until a significant increase in resistance is observed, marking the onset of initial fibrin formation |
| Clot kinetics: Clot formation time | The duration from CT to reaching a clot firmness of 20 mm, reflecting fibrin polymerization and clot stabilization with the involvement of activated platelets and fibrin-stabilizing factor XIII |
| Clot kinetics: Alpha angle | The slope during the early phase of clot development, represented by the angle between the tangent line from the baseline to a 20 mm amplitude, indicates the rate of fibrin accumulation and cross-linking |
| Clot strength: Maximum clot firmness | The highest resistance recorded, due to enhanced clot stabilization by polymerized fibrin, activated platelets, and factor XIII, represents the maximum strength of the clot |
| Clot strength: Maximum lysis | The percentage decrease in MCF at specific intervals of 30 and 60 minutes, indicating clot stability and breakdown |

CT: Clotting time; MCF: Maximum clot firmness; ROTEM: Rotational thromboelastometry.

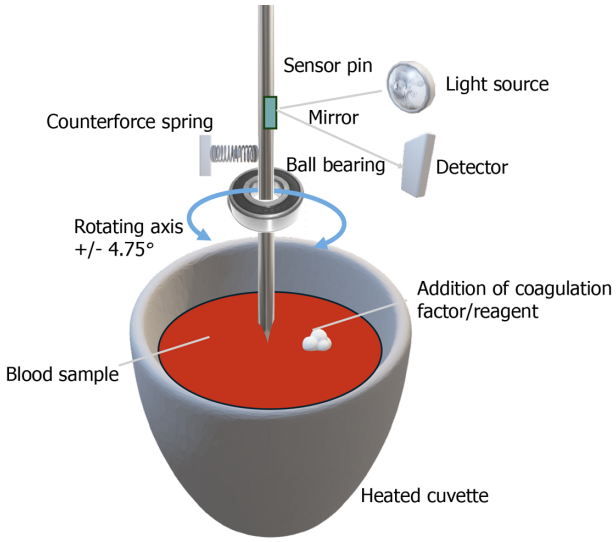



**Figure 1 Fundamental concept of rotational thromboelastometry.**

The ROTEM analysis is evaluated along the temporal axis from left to right (Figure 2). As functional assays, ROTEM demonstrates sensitivity to quantitative and qualitative changes in factors and substrates. Colloids have been shown to disrupt the initiation of coagulation and the polymerization of fibrinogen, resulting in a prolonged CT and a reduction in MCF, even following minor haemodilution[19,20]. ROTEM results offer valuable information regarding the underlying causes of a patient's bleeding; however, they cannot predict subsequent bleeding events. Therefore, the initial step must involve assessing the presence or absence of clinically significant bleeding and determining the potential requirement for blood transfusion. This evaluation should consider the plausibility of the findings, the patient's medical history, existing comorbidities, and the anticipated surgical source of the bleeding. If both point-of-care viscoelastic testing (ROTEM delta or ROTEM sigma) and platelet function assessment (ROTEM platelet) yield normal results, it is essential to evaluate and address the possibility of surgical bleeding. Therefore, it is advisable to refrain from acting on pathologic laboratory results (numbers) when there is no evidence of bleeding, given the low positive predictive values of specific tests such as SLCTs (14%-24%), viscoelastic assessments (15%-24%), and platelet function evaluations (27%-50%)[21,22]. This approach is crucial to prevent potential overtreatment, which could lead to thromboembolic complications and escalate healthcare expenditures.

Typically, an extension of the CT is attributed to a defect in the initiation of coagulation, whereas a diminished MCF results from a deficiency in substrates such as fibrinogen, platelets, or factor XIII. Conversely, a shortened CT or elevated MCF results from an enhanced initiation of coagulation or increased substrate levels, respectively. Clot formation time (CFT) reflects the kinetics of clot formation and is fundamentally dependent on substrates, primarily fibrinogen and platelets.

ROTEM results must be interpreted in a defined sequence, commencing with $A5_{FIB}$/$A10_{FIB}$ (amplitude of clot firmness 5 and 10 minutes after clotting time in FIBTEM, respectively), prior to CT EXTEM ($CT_{EX}$), rather than relying on their availability. In severe haemorrhage, fibrinogen levels may decrease to critical thresholds (< 1 g/L), potentially leading to an extended $CT_{EX}$. This phenomenon is not observed in cases of bleeding attributable to anticoagulants or haemophilia. Consequently, the accurate interpretation of $CT_{EX}$ values is contingent upon the adequacy of the FIBTEM clot amplitude

**Table 3 Rotational thromboelastometry delta/sigma and rotational thromboelastometry platelet assays**

| Assay | Activators and additives | Clinical significance |
|---|---|---|
| ROTEM delta/sigma | | |
| EXTEM | Calcium chloride + recombinant tissue factor + polybrene | Allow fast assessment of clot formation |
| | | Explores the extrinsic coagulation pathway; VKAs; DOACs |
| | | Increased values indicate need of PCC or FFP |
| | | Not affected by aprotinin |
| | | Sensitive to heparin |
| FIBTEM | Calcium chloride + recombinant tissue factor + polybrene + platelet inhibitor (cytochalasin D) | Depicts fibrin polymerization |
| | | Assesses the contribution of fibrinogen to clot strength independent of platelets |
| | | May also indicate XIII deficiency |
| | | Used to calculate dose of fibrinogen concentrate or cryoprecipitate |
| APTEM | Calcium chloride + recombinant tissue factor + polybrene + aprotinin/tranexamic acid | Inhibition of premature lysis by addition of aprotinin/tranexamic acid |
| | | In combination with EXTEM: (1) Rapid confirmation of fibrinolysis; (2) Verifying the effect of antifibrinolytic effect; and (3) Differential diagnosis of clot retraction and XIII deficiency |
| INTEM | Calcium chloride + ellagic acid | Assessment of clot formation and fibrin polymerization |
| | | Explores the intrinsic coagulation pathway |
| | | Increased values indicate need of FFP |
| HEPTEM | Calcium chloride + ellagic acid + heparinase | Testing in patients with very high heparin plasma concentrations |
| | | In combination with INTEM |
| | | To see UFH and protamine effects |
| NATEM | Calcium chloride | Expression of tissue factor on circulating cells, such as monocytes or cancerous cells |
| ECATEM | Calcium chloride + ecarin | Is sensitive for direct thrombin inhibitors (*e.g.*, hirudin, argatroban, bivalirudin, dabigatran) |
| | | Not sensitive to heparin |
| ROTEM platelet assays: These tests are used in patients treated with antiplatelet drugs or other medications that may affect platelet function, as well as in patients with suspected platelet dysfunction due to extracorporeal circulation, trauma, sepsis, or other reasons | | |
| ARATEM | Arachidonic acid | The platelets are activated with arachidonic acid to assess platelet function, particularly in patients treated with cyclooxygenase inhibitors such as acetylsalicylic acid |
| | | Effects of CPB, trauma and sepsis on platelet function |
| ADPTEM | Adenosine di-phosphate | Platelets are activated using ADP to assess platelet function in patients treated with ADP receptor antagonists such as clopidogrel |
| | | Effects of CPB, trauma and sepsis on platelet function |
| TRAPTEM | Thrombin receptor activating peptide-6 | Platelets are activated using thrombin receptor activating peptide to evaluate platelet function in patients treated with PAR-1 receptor antagonists like vorapaxar or GP IIb/IIIa receptor antagonists such as abciximab |
| | | Effects of CPB, trauma and sepsis on platelet function |

ROTEM: Rotational thromboelastometry; DOACs: Direct oral anticoagulants; VKAs: Vitamin K antagonist; PCC: Prothrombin complex concentrate; FFP: Fresh frozen plasma; UFH: Unfractionated heparin; CPB: Cardiopulmonary bypass; ADP: Adenosine di-phosphate; PAR-1: Protease-activated receptor-1.

measured at 5 and 10 minutes ($A5_{FIB}$/$A10_{FIB}$, respectively)[15]. Furthermore, elevated thrombin generation correlates with an increased risk of thromboembolic complications compared to substituting substrates, especially fibrinogen. The administration of FFP in response to prolonged $CT_{EX}$ values may pose increased risks. Therefore, prioritizing the management of clot firmness, as evidenced by a decreased $A5_{FIB}$/$A10_{FIB}$ and A5 in the EXTEM assay ($A5_{EX}$), is essential over the management of thrombin generation [FFP or prothrombin complex concentrate (PCC) administration], which is indicated by prolonged $CT_{EX}$ and CT in the INTEM assay[15,23].

In cases where there is a suspicion of a "heparin effect", a dual testing approach is employed utilizing ROTEM, specifically the INTEM and HEPTEM assays. A prolonged CT in INTEM compared to HEPTEM suggests a heparin effect. If no distinction is observed, it can be inferred that a heparin effect is absent. Consideration of the specific reagents employed in ROTEM testing is crucial, as some reagents may exhibit a greater susceptibility to interference from heparin than others. Given their sensitivity to heparin, it is essential to remove or mitigate the effects of heparin before performing

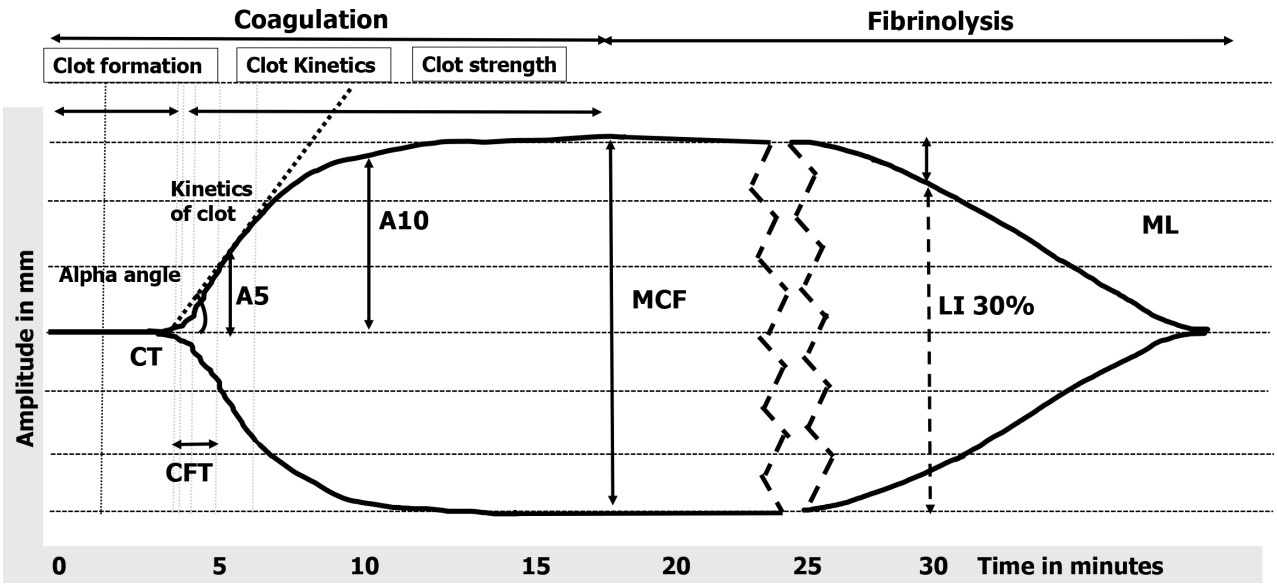



**Figure 2 Rotational thromboelastometry tracing.** CT: Clotting time; CFT: Clot formation time; MCF: Maximum clot firmness; LI 30%: The proportion of clot stability retained 30 minutes after clotting time, relative to the maximum clot firmness value; ML: Maximum lysis.

tests with single-use reagents such as EXTEM and FIBTEM.

Clot analysis represents a standard physiological mechanism; however, when it transpires at heightened levels, it can considerably compromise clot stability and the overall haemostatic function, a condition referred to as hyperfibrinolysis. In ROTEM analysis, hyperfibrinolysis is characterized by $ML_{EX}$ (maximum lysis in EXTEM) values of ≥ 7.5% at 30 minutes or ≥ 15% at 60 minutes[15,23]. FIBTEM serves as the most sensitive and specific assay for the identification of hyperfibrinolysis, indicated by $ML_{FIB}$ (maximum lysis in EXTEM) values equal to or exceeding 10%. In contrast, APTEM is employed to validate the presence of hyperfibrinolysis and to assess the efficacy of antifibrinolytic treatment. It is essential to recognize that ROTEM is limited to the detection of systemic hyperfibrinolysis and does not have the capability to identify local hyperfibrinolysis.

## CLINICAL APPLICATIONS OF ROTEM

ROTEM is utilized in various clinical scenarios, especially in environments where swift and thorough evaluation of coagulation is essential.

### *Trauma-induced coagulopathy*

Uncontrolled hemorrhage is a leading cause of death in trauma, often linked to trauma-induced coagulopathy (TIC), a multifactorial failure of the coagulation system. TIC has a mortality rate of nearly 50%, requiring increased blood transfusions and causing higher morbidity[24]. This condition is driven by factors such as protein C activation, endothelial disruption, fibrinogen depletion, and platelet dysfunction[25,26].

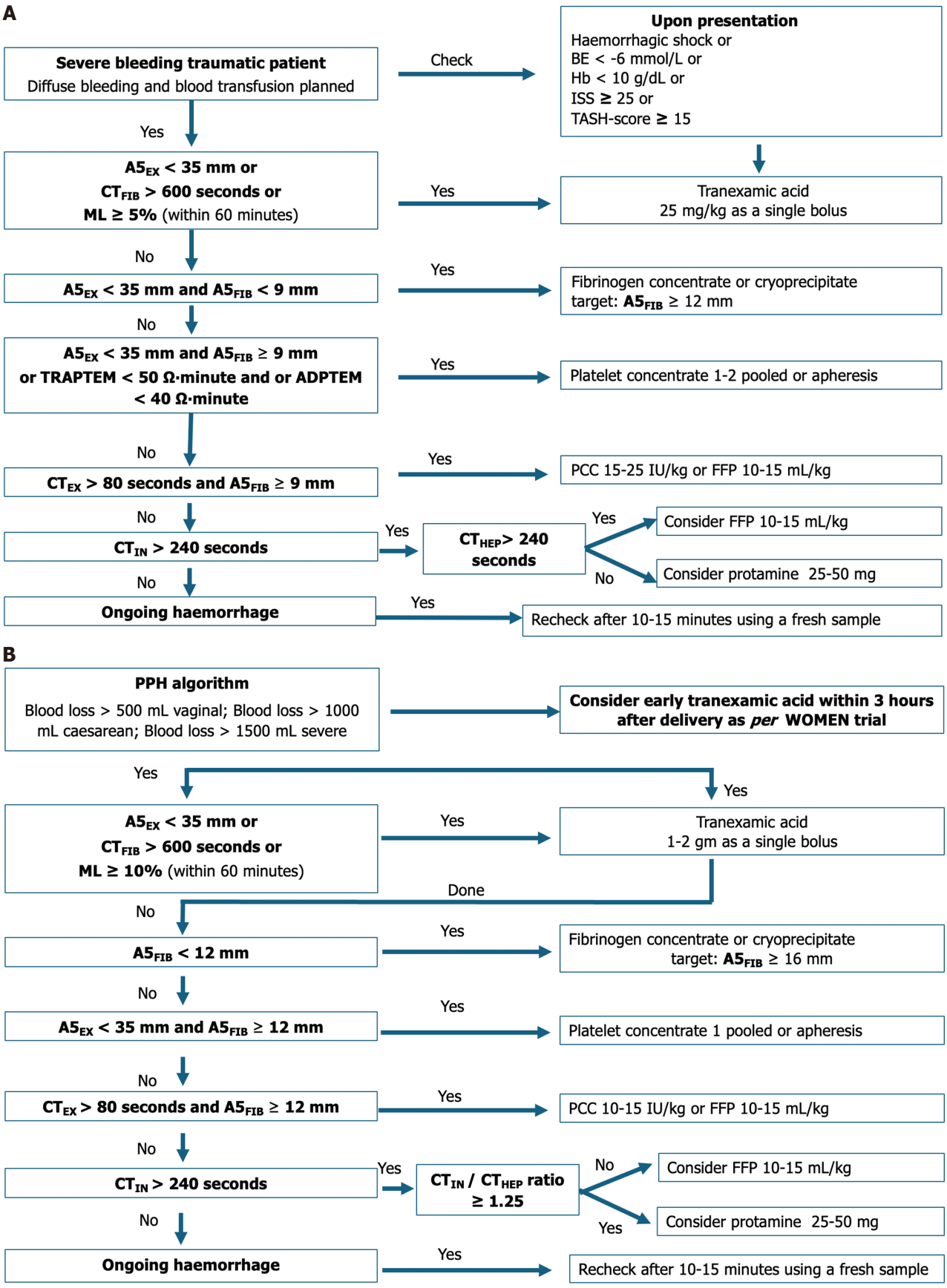
Standard coagulation tests have limitations in directing transfusion strategies and detecting hyperfibrinolysis in trauma patients. Studies show that ROTEM is more effective than SLCT in assessing and managing TIC[27,28]. The ITACTIC trial, involving 396 trauma patients, compared viscoelastic haemostatic assays like ROTEM with SLCT[29]. While no significant difference in mortality or transfusion requirements was observed at 24 hours, viscoelastic assays showed better guidance for transfusions in cases of traumatic brain injury with international normalized ratio (INR) > 1.2.

ROTEM can quickly identify TIC, with $A5_{EX}$ < 35 mm and $A5_{FIB}$ < 9 mm, indicating hypofibrinogenemia and $CT_{EX}$ > 80 seconds, suggesting impaired thrombin generation[15]. Hyperfibrinolysis, present in severe trauma cases, can be detected using ROTEM parameters ($A5_{EX}$ < 35 mm or $CT_{FIB}$ (clotting time in FIBTEM) > 600 s or EXTEM or FIBTEM maximum lysis (ML) ≥ 5% within 60 minutes)[30], with early tranexamic acid (TA) treatment reducing mortality, as demonstrated in the CRASH-2 trial[31].

In trauma patients, ROTEM offers essential insights for managing haemorrhage, as supported by a variety of clinical guidelines[32,33]. ROTEM provides real-time insights into the clotting process, enabling clinicians to customize interventions more precisely. This capability is crucial for effective haemorrhage management and optimizing blood product utilization (Figure 3A)[15].

### *Post partum haemorrhage*

ROTEM is utilized in obstetric care to address bleeding complications, especially postpartum haemorrhage (PPH), recognized as the primary cause of significant maternal morbidity and mortality globally. Timely diagnosis and prompt intervention are critical for achieving positive outcomes. Management strategies for PPH encompass laboratory-driven,


A
Severe bleeding traumatic patient
Diffuse bleeding and blood transfusion planned
Check
Upon presentation
Haemorrhagic shock or
BE < -6 mmol/L or
Hb < 10 g/dL or
ISS ≥ 25 or
TASH-score ≥ 15
Yes
A5EX < 35 mm or
CTFIB > 600 seconds or
ML ≥ 5% (within 60 minutes)
Yes
Tranexamic acid
25 mg/kg as a single bolus
No
A5EX < 35 mm and A5FIB < 9 mm
Yes
Fibrinogen concentrate or cryoprecipitate
target: A5FIB ≥ 12 mm
No
A5EX < 35 mm and A5FIB ≥ 9 mm
or TRAPTEM < 50 Ω·minute and or ADPTEM
< 40 Ω·minute
Yes
Platelet concentrate 1-2 pooled or apheresis
No
CTEX > 80 seconds and A5FIB ≥ 9 mm
Yes
PCC 15-25 IU/kg or FFP 10-15 mL/kg
No
CTIN > 240 seconds
Yes
CTHEP> 240
seconds
Yes
Consider FFP 10-15 mL/kg
No
Consider protamine 25-50 mg
No
Ongoing haemorrhage
Yes
Recheck after 10-15 minutes using a fresh sample
B
PPH algorithm
Blood loss > 500 mL vaginal; Blood loss > 1000
mL caesarean; Blood loss > 1500 mL severe
Consider early tranexamic acid within 3 hours
after delivery as per WOMEN trial
Yes
Yes
A5EX < 35 mm or
CTFIB > 600 seconds or
ML ≥ 10% (within 60 minutes)
Yes
Tranexamic acid
1-2 gm as a single bolus
Done
No
A5FIB < 12 mm
Yes
Fibrinogen concentrate or cryoprecipitate
target: A5FIB ≥ 16 mm
No
A5EX < 35 mm and A5FIB ≥ 12 mm
Yes
Platelet concentrate 1 pooled or apheresis
No
CTEX > 80 seconds and A5FIB ≥ 12 mm
Yes
PCC 10-15 IU/kg or FFP 10-15 mL/kg
No
CTIN > 240 seconds
Yes
CTIN / CTHEP ratio
≥ 1.25
No
Consider FFP 10-15 mL/kg
Yes
Consider protamine 25-50 mg
No
Ongoing haemorrhage
Yes
Recheck after 10-15 minutes using a fresh sample

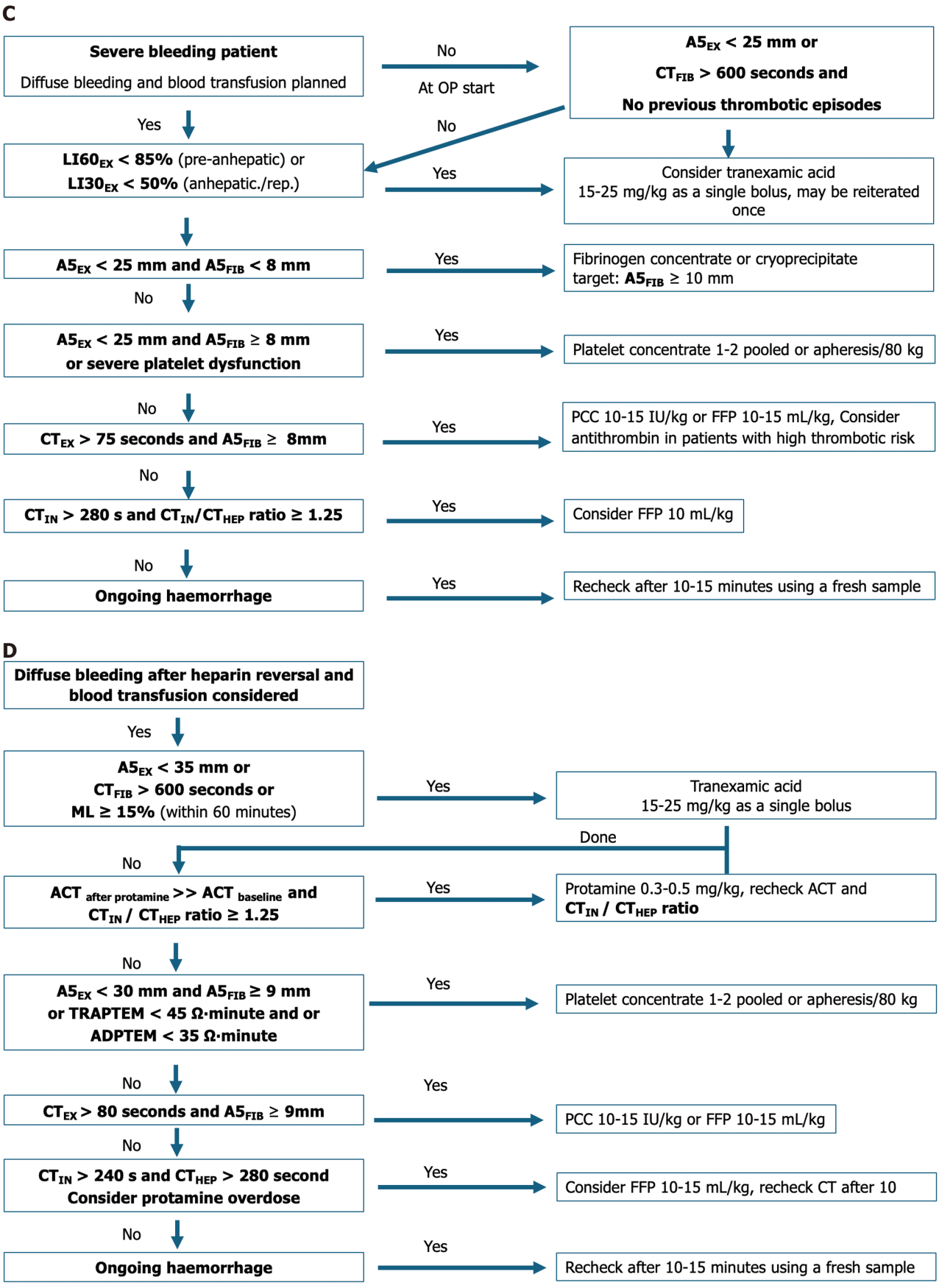



**Figure 3 Rotational thromboelastometry-guided management with acute bleeding and an indication for blood transfusion.** A: In trauma; B: In post-partum haemorrhage; C: In liver transplantation; D: In cardiac surgery. ACT: Activated clotting time; $A5_{EX}$: Amplitude of clot firmness 5 minutes after clotting time in EXTEM; $A5_{FIB}$: Amplitude of clot firmness 5 minutes after clotting time in fibrinogen thromboelastometry; BE: Base excess; $CT_{FIB}$: Clotting time in fibrinogen thromboelastometry; $CT_{IN}$: Clotting time in INTEM; $CT_{HEP}$: Clotting time in HEPTEM; FFP: Fresh frozen plasma; Hb: Hemoglobin; ISS: Injury severity score; $LI30_{EX}$:

Lysis index at 30 minutes in EXTEM; $LI60_{EX}$: Lysis index at 60 minutes in EXTEM; ML: Maximum lysis; TASH: Trauma associated severe hemorrhage; PCC: Prothrombin complex concentrate; PPH: Post-partum hemorrhage.

formula-driven, and goal-directed approaches that utilize viscoelastic coagulation monitoring techniques such as ROTEM. Several recent algorithms for managing PPH have integrated ROTEM-guided strategies to optimize treatment.

In 2014, Mallaiah *et al*[34] conducted a study at the Liverpool Women's Hospital comparing traditional transfusion protocols with a fibrinogen-centered approach. Guided by ROTEM, they administered fibrinogen concentrate based on specific thresholds, resulting in reduced blood product use and fewer complications associated with transfusions. Girard and colleagues from Austria, Germany, and Switzerland proposed a four-step PPH management algorithm in the same year[35]. It involves: Recognizing PPH and increasing uterine tone within 30 minutes; Interdisciplinary management with coagulation monitoring (ROTEM/TEG) and administration of TA and fibrinogen; Maintaining hemodynamic stability; and using invasive measures if bleeding persists. Similarly, the Share Network Group introduced a five-step approach tailored to specific coagulopathies during PPH, addressing hyperfibrinolysis, fibrinogen deficiency, thrombocytopenia, other clotting factor deficits, and factor XIII deficiency[36]. ROTEM was used to guide fibrinogen supplementation, with a trigger set at FIBTEM MCF < 18 mm. In Cardiff, Collis *et al*[37] introduced a protocol activated for bleeding over 1000 mL, using ROTEM to guide fibrinogen administration when FIBTEM is below 7 mm, ensuring timely and targeted management (Figure 3B).

### *Sepsis*

In sepsis, early procoagulant states may progress to disseminated intravascular coagulation (DIC), consuming platelets and clotting factors and shifting from hypercoagulability to hypocoagulability, increasing bleeding risk[38]. ROTEM helps detect coagulopathy early in critically ill patients, differentiating between normal, hypercoagulable, and hypocoagulable states, which are linked to mortality[39]. ROTEM also identifies patients without DIC who remain hypercoagulable, guiding the initiation of prophylactic anticoagulation. Sequential ROTEM measurements provide a dynamic picture of sepsis-induced coagulopathy as it evolves from hypercoagulability to DIC. ROTEM correlates with the Japanese Association for Acute Medicine DIC score and outperforms SLCTs in predicting DIC[40].

Research indicates that specific thromboelastometry parameters, including the lysis index, demonstrate superior accuracy in the diagnosis severe sepsis when compared to conventional biomarkers such as procalcitonin, interleukin-6, or C-reactive protein[41,42]. Furthermore, abnormal thromboelastometry values have been associated with improved predictive capability for 30-day survival rates in sepsis compared to conventional scoring systems such as the sequential organ failure assessment or simplified acute physiology score II[43].

Thus, integrating serial ROTEM with conventional tests could improve the diagnosis and management of DIC, enhancing outcomes for sepsis patients. Further studies are required to standardize ROTEM use for detecting coagulation changes in sepsis.

### *Acute liver disease*

In acute liver injury and acute liver failure (ALF), elevated INR often gives a false impression of increased bleeding risk, leading to cautious use of anticoagulation[44]. ROTEM, which assesses whole-blood coagulation, may offer better predictions for bleeding in ALF than traditional tests like INR. A study of 200 ALF patients found ROTEM abnormalities correlated with disease severity, and platelet count proved a stronger bleeding risk indicator than INR, suggesting platelet transfusions may be more effective than plasma[45]. The data suggests a significant prevalence of haemostatic disruption in severe cases; however, further investigation is required to confirm the efficacy of ROTEM in directing treatment strategies and mitigating bleeding risk in ALF.

### *Chronic liver disease*

Cirrhosis disrupts haemostasis and creates a delicate balance, further affected by conditions like sepsis or acute kidney injury[9]. SLCTs are poor predictors of bleeding risk and transfusion needs in cirrhotic patients[46]. Thrombocytopenia is common, with a platelet count of $50 \times 10^9$/L to $55 \times 10^9$/L often used as a threshold for procedures, though the benefit of prophylactic transfusions is unclear[47,48]. Similarly, fibrinogen levels, rather than INR, guide bleeding risk, with a target of 120 mg/dL during active bleeding[47,48]. Viscoelastic tests like ROTEM and TEG better predict bleeding by assessing clot strength and hyperfibrinolysis, which is common in cirrhosis.

ROTEM helps distinguish coagulation deficiencies from heparin-like effects caused by glycosaminoglycans and detects hyperfibrinolysis[49]. The HEPTEM test can confirm heparin-like activity, offering insights beyond standard tests. Current guidelines recommend using viscoelastic tests selectively, particularly in high-risk cirrhotic cases, to assess INR and platelet abnormalities[50]. The findings from the RECIPE trial will shed light on the effectiveness of a ROTEM-based algorithm for guiding prophylactic blood component administration in cirrhotic patients, potentially enhancing clinical outcomes and minimizing unnecessary transfusions[51].

### *Liver transplantation*

Significant haemorrhage during liver transplantation is challenging due to cirrhosis, blood loss, and clotting factor changes. Despite abnormal clotting profiles like thrombocytopenia and elevated INR, bleeding risk isn't always higher due to a rebalanced haemostatic state[52]. ROTEM is highly effective in managing haemorrhage during liver transplants, offering superior guidance over SLCTs. It can reduce red blood cell transfusions by 62%, FFP by 95%, and platelet use by

66%, leading to fewer massive transfusions and more targeted use of fibrinogen concentrate and PCC[53,54].

Key ROTEM indicators like A5 help detect low platelet and fibrinogen levels. EXTEM CT over 80 seconds suggests PCC may be needed, while prolonged INTEM CT points to FFP transfusion. If EXTEM MCF is below 35 mm and FIBTEM MCF is above 6 mm, platelet transfusion is recommended, and fibrinogen concentrate is used when both EXTEM and FIBTEM MCF are low. ROTEM also detects fibrinolysis (ML > 15% of MCF), and if present, TA can be used to control bleeding, particularly during or after the anhepatic phase (Figure 3C)[55].

### Cardiac surgery

Cardiopulmonary bypass frequently leads to a propensity for bleeding, attributable to various factors, including the effects of heparin, inadequate protamine dosing, hypothermia, haemodilution, heightened fibrinolysis, depletion of coagulation factors, diminished platelet counts and function. In the context of cardiac surgery, a crucial timeframe of 30 to 45 minutes is established for implementing haemostatic interventions following the reversal of heparin with protamine prior to the transfer of the patient to the intensive care unit. Implementing rapid point-of-care testing and facilitating prompt treatment decisions are critical during this time frame. The European Association for Cardio-Thoracic Surgery advocates using TEG/ROTEM in cardiac surgery to minimize the requirement for blood transfusions and enhance the management of blood product administration[56].

In complex cardiac surgeries, using heparin-neutralizing reagents in ROTEM delta and sigma enables effective ROTEM analysis despite elevated heparin levels after bypass. This capability supports the prompt ordering of blood products such as cryoprecipitate and platelet concentrates (Figure 3D)[57,58]. It is essential to identify any residual heparin or protamine overdose prior to implementing additional haemostatic interventions. It is essential to recognize that an extended activated CT (ACT) does not necessarily signify the presence of residual heparin. Furthermore, employing a 1:1 heparin-to-protamine reversal ratio may result in protamine overdose, subsequently leading to increased ACT[59,60].

### Myocardial infarction

Myocardial infarction (MI) is a critical emergency that requires swift intervention to restore blood flow using medications, surgical techniques, or non-surgical methods. Managing MI involves not only reestablishing blood supply but also carefully monitoring coagulation to reduce bleeding and thrombotic complications[61]. Viscoelastic assays like ROTEM and TEG have become valuable tools for assessing coagulation in MI patients and guiding treatment decisions.

Despite standard antiplatelet therapy, such as aspirin and clopidogrel, some MI patients remain in a hypercoagulable state, increasing their risk of recurrent ischemic events. In a study by Zhao *et al*[62], MI patients undergoing percutaneous coronary intervention showed enhanced clot strength and faster clot formation, even while on antiplatelet therapy. Approximately 50% of these patients remained hypercoagulable. Additionally, those with low responsiveness to antiplatelet therapy experienced significantly more ischemic events within three months. These findings emphasize the utility of TEG in identifying patients who may need adjustments in their treatment.

Similarly, other studies have shown that patients with high platelet reactivity before cardiac stenting face a higher risk of adverse events. Viscoelastic testing can be used to tailor antiplatelet therapy by switching to stronger agents like ticagrelor or prasugrel to improve outcomes[63,64]. ROTEM also plays a role in assessing bleeding risks, helping clinicians decide whether to adjust antithrombotic therapy.

Overall, integrating ROTEM and TEG in managing MI allows for more personalized treatment, enhancing safety by balancing the risks of bleeding and thrombosis. Although more research is needed to standardize protocols, current evidence supports using viscoelastic testing to improve outcomes in MI patients.

### Cardiac arrest

Following resuscitation from cardiac arrest, individuals frequently encounter post-cardiac arrest syndrome (PCAS), which arises from various factors, including reperfusion failure, ischemia-reperfusion injury, and cerebral damage[65,66]. PCAS has the potential to initiate a systemic inflammatory response and activate coagulation, which may result in organ dysfunction[66]. TEG and ROTEM have been utilized to evaluate coagulation abnormalities after spontaneous circulation (ROSC) return, with findings indicating their possible role as prognostic instruments.

A study involving 75 patients with out-of-hospital cardiac arrest demonstrated that increased clot firmness, measured by A30 of EXTEM, correlated with a successful ROSC. Specifically, an A30 value of ≥ 48.0 mm, with a lactate level of < 12.0 mmol/L, exhibited a high specificity of 94.7% for predicting ROSC[67]. ROTEM has indicated that hyperfibrinolysis may elevate the risk of bleeding following cardiac arrest, thereby suggesting the potential utility of antifibrinolytics such as TA in therapeutic interventions. In light of the current discourse surrounding the efficacy of targeted temperature management, the utilization of viscoelastic assays may assist in pinpointing patients who are most likely to benefit from this therapeutic approach.

### Stroke

ROTEM provides valuable real-time insights into coagulation processes in both ischemic and haemorrhagic strokes, guiding treatment decisions. In acute ischemic stroke, it assesses hypercoagulability and monitors fibrinolysis during thrombolytic therapy[68]. Studies show hypercoagulable states in stroke patients, with reduced R and K times, even before receiving recombinant tissue plasminogen activator (rtPA). However, responses to rtPA vary, suggesting that standard dosing may not suit all patients[69]. ROTEM can also help identify individuals at higher risk of haemorrhagic transformation after thrombolysis, characterized by a rapid clotting response, potentially reflecting compensatory mechanisms to mitigate bleeding risks[70]. Similarly, in haemorrhagic stroke, ROTEM detects early hypercoagulability, potentially reflecting a compensatory mechanism to manage bleeding. Faster clot formation is linked to hematoma

expansion, providing insights into which patients may benefit from earlier surgical intervention[71]. ROTEM is also effective in evaluating anticoagulation status, particularly with direct oral anticoagulants (DOACs), offering guidance on whether to withhold rtPA or initiate reversal therapy.

Integrating ROTEM into stroke management allows for more personalized treatment, improving safety during thrombolysis and optimizing surgical decisions. Further research is needed to establish standardized parameters for using ROTEM in clinical practice.

### *Chronic kidney disease*

Patients with chronic kidney disease (CKD) experience both hyper- and hypo-coagulability, as identified through advanced haemostasis assessments[72]. ROTEM analysis in CKD patients indicated a prothrombotic state characterized by reduced CFT, increased MCF, and hypofibrinolysis[73]. This prothrombotic tendency is thought to stem from chronic inflammation, reduced clearance of pro-inflammatory substances like advanced glycation end-products, oxidative stress, and dialysis-related complications such as vascular access infections. These factors can activate the endothelium and platelets, increasing liver production of coagulation factors and further promoting a prothrombotic state.

Platelet dysfunction in CKD, a key factor in primary haemostasis, likely contributes to the increased bleeding risk. Multiple electrode aggregometry (MEA) testing has revealed platelet aggregation defects in end stage renal disease patients, with epidermal growth factor receptor significantly affecting ROTEM and platelet aggregation results[74]. MEA provides a rapid assessment of platelet function before procedures like renal biopsies or vascular line insertions and may help predict bleeding risk. It can also guide the safe use of antiplatelet medications like aspirin and clopidogrel, commonly used in uremic CKD patients. However, some studies suggest that MEA only evaluates platelet aggregation and that increased levels of von Willebrand factor in CKD may compensate for this defect[75,76].

While ROTEM may not be effective in predicting bleeding risk in CKD patients, its potential to assess arterial and venous thromboembolic events warrants further investigation. MEA could complement standard coagulation tests by providing more detailed insights into platelet function and bleeding risk in CKD patients, but further prospective studies are needed to confirm its clinical utility.

### *Monitoring anticoagulants*

Anticoagulants are essential for preventing venous thromboembolism in high-risk patients and treating conditions like nonvalvular atrial fibrillation and acute MI[77,78]. They are also widely used to prevent clotting during dialysis and other clinical procedures. ROTEM is highly effective in monitoring various anticoagulants, including UFH, low-molecular-weight heparin (LMWH), and DOACs (Table 4)[5]. It offers real-time insights into clotting dynamics and can help tailor anticoagulant management, especially during bleeding emergencies or invasive procedures.

**UFH:** While aPTT, ACT, and anti-FXa assays are commonly used to monitor UFH, aPTT often does not correlate well with UFH levels[79,80]. ROTEM is more sensitive in detecting small amounts of UFH, with CT and CFT prolonged at concentrations as low as 0.1 IU/mL[81]. The HEPTEM assay helps neutralize heparin's effect, improving diagnostic accuracy for detecting heparin rebound compared to ACT or aPTT[15].

**LMWHs:** Routine monitoring of LMWH is generally not required, but in high-risk cases ROTEM can be useful as aPTT is not useful for monitoring LMWH[82]. LMWH primarily affects clot initiation rather than propagation or strength, with MCF influenced more by fibrinogen levels, platelet count, and platelet function. Studies show that LMWH causes dose-dependent prolongation of CT and CFT and a reduction in MCF[83]. Studies show mixed results on how LMWHs affect clot strength. While enoxaparin and tinzaparin did not impact ROTEM's MCF or CFT in some research, other studies found that high, but not therapeutic, doses of dalteparin reduced MCF[84].

There is no standardized ROTEM protocol for monitoring LMWH therapy. However, using minimal tissue factor-triggered ROTEM provides more accurate insights into LMWH effects. Newer tests, like PiCT-ROTEM, offer the potential for better dose adjustments and monitoring in critically ill patients. Further research is needed to establish clear guidelines for ROTEM use in LMWH therapy[82].

**DOACs:** DOACs, such as dabigatran and rivaroxaban, typically don't require routine monitoring, but in emergencies or when the patient's drug history is unknown, ROTEM can assess anticoagulation effects. While SLCTs are unreliable for DOACs, ROTEM detects prolonged CT in INTEM and EXTEM assays. Modified ROTEM triggers, like low tissue factor or ecarin, enhance accuracy[82]. Schäfer *et al*'s team developed an advanced algorithm combining standard and modified thromboelastometry tests to detect and differentiate between various anticoagulants, including direct factor Xa inhibitors, direct thrombin inhibitors, and vitamin K antagonists[85]. Machine learning and decision-tree analysis improved detection accuracy from 94% to 98%, though further validation in a multicentre study is needed.

**Anticoagulation reversal with ROTEM:** ROTEM is valuable in guiding anticoagulant reversal, particularly for agents like dabigatran. It offers real-time monitoring and supports the use of reversal agents like idarucizumab (for dabigatran) or PCC for other anticoagulants[82,86].

## LIMITATIONS

ROTEM is important for evaluating coagulation status across diverse clinical environments. Nevertheless, it presents multiple constraints:

**Table 4 Monitoring anticoagulant effects using rotational thromboelastometry**

| Anticoagulant type | ROTEM parameters | Details |
|---|---|---|
| Parenteral anticoagulants | | |
| UFH | INTEM-CT | Prolonged CT correlates to aPTT levels |
| | HEPTEM-CT | Normalized if prolonged CT was due to UFH/LMWH |
| | INTEM/HEPTEM CT-ratio | Correlation with anti-FXa activity > 0.1 IU/mL |
| LMWH | INTEM-CT | Low sensitivity, but prolonged only if anti-FXa activity is > 0.4 IU/mL |
| | NATEM/NAHEPTEM CT-ratio | Correlates with anti-FXa activity > 0.1 IU/mL |
| | TFTEM | Correlates anti-FXa activity |
| | PiCT | Correlates anti-FXa activity |
| Fondaparinux | INTEM-CT | Only prolonged in case of supratherapeutic plasma concentrations |
| Direct thrombin inhibitors | EXTEM-CT | Correlation with plasma concentrations of argatroban and bivalirudin |
| | ECATEM-CT | Prolongation specific for direct thrombin inhibitors |
| Oral anticoagulants | | |
| VKAs | EXTEM-CT | Correlates with PT-INR |
| | INTEM and HEPTEM-CT | INTEM and HEPTEM CT values typically remain normal |
| Dabigatran (correlates with plasma concentration) | ECATEM-CT | Prolonged, specific for direct thrombin inhibitors |
| | TFTEM/ECATEM CT-ratio < 2 | Detects dabigatran effects |
| | EXTEM and FIBTEM-CT | Prolongation of CT in EXTEM and FIBTEM due to dabigatran |
| | INTEM and HEPTEM-CT | Prolonged clotting times |
| Rivaroxaban, edoxaban (correlates with plasma concentration) | TFTEM and EXTEM-CT | Prolongation of CT with rivaroxaban and edoxaban |
| | TFTEM/ECATEM CT-ratio > 2 | Detects rivaroxaban and edoxaban |
| | INTEM and HEPTEM-CT | Less sensitive to rivaroxaban/edoxaban |
| | ECATEM-CT | Normal, specific for DTIs |
| Apixaban (correlates with plasma concentration) | EXTEM and INTEM-CT | Less sensitive to low concentrations of apixaban |
| | TFTEM/ECATEM CT-ratio > 2 | Detects apixaban effects |
| | TFTEM CT | Sensitive to low concentrations of apixaban |
| | ECATEM-CT | Normal, specific for DTIs |

CT: Clotting time; ROTEM: Rotational thromboelastometry; NATEM: Nonactivated thromboelastometry; TFTEM: Low tissue factor thromboelastometry; PiCT: Prothrombinase-induced clotting time; LMWH: Low-molecular-weight heparin; UFH: Unfractionated heparin; VKAs: Antivitamin K antagonists; ECATEM: Ecarin-activated assay; aPTT: Activated partial thromboplastin time; anti-FXa: Anti-factor X activated; INR: International normalized ratio; PT: Prothrombin time; DTI: Direct thrombin inhibitor.

It is essential to recognize that the cup and pin mechanism employed in ROTEM does not faithfully mimic *in vivo* vascular mechanics, and neither of these techniques can identify primary haemostasis defects. The reagents employed in these assays induce a notable elevation in thrombin synthesis, activating platelets through the protease-activated receptors 1 and 4. This process may have the capacity to overshadow and obscure any inhibition of platelet activity. Consequently, ROTEM exhibits limited sensitivity regarding the impact of platelet inhibitors such as aspirin and clopidogrel and in identifying von Willebrand disease[10,15].

ROTEM is typically performed at a standard temperature of 37 °C, simulating normal physiological conditions. However, this approach may not accurately reflect the coagulation dynamics in patients experiencing acidosis or hypothermia common clinical scenarios in trauma, sepsis, or during surgeries. These conditions significantly alter coagulation processes, with hypothermia causing a proportional prolongation of CT as temperature decreases. Similarly, acidosis, while having a minimal independent effect on coagulation, can exacerbate hypocoagulability when combined with hypothermia, as reflected in ROTEM parameters, emphasizing the compounded impact of these conditions rather than acidosis alone[87,88].

The role of red blood cells in the clot formation process must be considered while evaulating whole blood samples. A variety of studies have investigated the influence of haematocrit on viscoelastic parameters. Haematocrit levels demonstrate an inverse correlation with ROTEM MCF in individuals diagnosed with iron deficiency anaemia. Nonetheless, this may present an advantage rather than a limitation, particularly in utilizing FIBTEM as an alternative to plasma fibrinogen concentration. In diluted conditions, frequently observed in patients experiencing bleeding, the influence of haematocrit seems minimal[89].

ROTEM's visual processes are intricate and require specialized training for precise interpretation. The intricacies involved may result in user variability, especially in individuals needing sufficient training. Furthermore, the absence of level 1 evidence derived from high-quality randomized controlled trials hinders these methods' clinical application and acceptance.

Furthermore, the presence of alcohol in the bloodstream may influence the precision of results, which could result in an erroneous assessment of coagulation status. The uncertainty surrounding the impaired clot formation observed raises questions about whether it is an artefact or a true physiological response. Additional investigation is warranted to elucidate these findings. Consequently, it is imperative to exercise caution when interpreting results in patients presenting with elevated blood alcohol levels[90].

While ROTEM offers advanced and dynamic insights into coagulation processes, its high initial and operational costs present a significant challenge, particularly for smaller healthcare facilities or those in resource-limited environments. The financial investment required to acquire the device, procure reagents, and train specialized personnel can be substantial. Moreover, ongoing expenses for maintenance and consumables can strain budgets, especially in institutions with a lower patient volume or infrequent use of ROTEM, making it harder to justify its cost relative to its benefits. Additionally, lack of standardization may diminish the perceived utility of ROTEM and impact its cost-effectiveness. Consequently, conventional coagulation tests such as PT/INR and aPTT remain more cost-effective and readily accessible, making them the preferred option in many healthcare settings despite their inability to provide comprehensive and dynamic assessments of coagulation profiles[15].

## CONCLUSION

ROTEM is a pivotal tool for evaluating coagulation across various clinical scenarios, offering real-time and detailed insights into clot dynamics, including formation, strength, and stability. Unlike conventional coagulation tests which provide limited and static snapshots, ROTEM delivers dynamic whole-blood analyses that capture the intricate interplay of cellular and plasma components in haemostasis. This enables healthcare professionals to accurately identify coagulation abnormalities and implement targeted interventions with precision. ROTEM's personalized nature further enhances its utility. Generating patient-specific coagulation profiles allows clinicians to tailor therapies, reducing unnecessary blood product usage and associated risks such as transfusion reactions, fluid overload, and immunosuppression. This not only improves patient outcomes but also optimizes healthcare resource utilization. As medical technologies advance, the potential applications of ROTEM are set to expand significantly. Innovations such as machine learning and decision-support systems promise to enhance its accuracy and predictive capabilities. In contrast, developing new reagents tailored to specific clinical needs, such as dual-pathway activators and DOAC-specific assays will refine its precision and broaden its scope. These advancements are poised to elevate ROTEM's utility in managing complex haemostatic disorders, enabling more precise, individualized care and improving patient outcomes. Ongoing research and multicentre trials are expected to establish standardized protocols, ensuring their reliability and effectiveness across diverse patient populations and clinical settings.

## FOOTNOTES

**Author contributions:** Kataria S and Juneja D performed the majority of the writing, and researched the project; Kataria S prepared the figures and tables and performed data accusation; Singh O provided inputs in writing; All three authors reviewed the manuscript.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.



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**S-Editor:** Fan M
**L-Editor:** A
**P-Editor:** Guo X

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World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

*World J Crit Care Med* 2025 June 9; 14(2): 100844

DOI: 10.5492/wjccm.v14.i2.100844

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

# Cannabis use disorder and severe sepsis outcomes in cancer patients: Insights from a national inpatient sample

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**Specialty type:** Critical care medicine

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade A, Grade B, Grade C

**Novelty:** Grade A, Grade B, Grade C

**Creativity or Innovation:** Grade A, Grade B, Grade C

**Scientific Significance:** Grade A, Grade B, Grade B

**P-Reviewer:** Yanik F; Zhu LM

**Received:** August 28, 2024

**Revised:** January 8, 2025

**Accepted:** February 8, 2025

**Published online:** June 9, 2025

**Processing time:** 183 Days and 6.2 Hours

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## Abstract

### *BACKGROUND*

The burden of cannabis use disorder (CUD) in the context of its prevalence and subsequent cardiopulmonary outcomes among cancer patients with severe sepsis is unclear.

### *AIM*

To address this knowledge gap, especially due to rising patterns of cannabis use and its emerging pharmacological role in cancer.

***METHODS***
By applying relevant International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification codes to the National Inpatient Sample database between 2016-2020, we identified CUD(+) and CUD(-) arms among adult cancer admissions with severe sepsis. Comparing the two cohorts, we examined baseline demographic characteristics, epidemiological trends, major adverse cardiac and cerebrovascular events, respiratory failure, hospital cost, and length of stay. We used the Pearson $\chi^2$ d test for categorical variables and the Mann-Whitney *U* test for continuous, non-normally distributed variables. Multivariable regression analysis was used to control for potential confounders. A *P* value ≤ 0.05 was considered for statistical significance.

***RESULTS***
We identified a total of 743520 cancer patients admitted with severe sepsis, of which 4945 had CUD. Demographically, the CUD(+) cohort was more likely to be younger (median age = 58 *vs* 69, $P < 0.001$), male (67.9% *vs* 57.2%, $P < 0.001$), black (23.7% *vs* 14.4%, $P < 0.001$), Medicaid enrollees (35.2% *vs* 10.7%, $P < 0.001$), in whom higher rates of substance use and depression were observed. CUD(+) patients also exhibited a higher prevalence of chronic pulmonary disease but lower rates of cardiovascular comorbidities. There was no significant difference in major adverse cardiac and cerebrovascular events between CUD(+) and CUD(-) cohorts on multivariable regression analysis. However, the CUD(+) cohort had lower all-cause mortality (adjusted odds ratio = 0.83, 95% confidence interval: 0.7-0.97, $P < 0.001$) and respiratory failure (adjusted odds ratio = 0.8, 95% confidence interval: 0.69-0.92, $P = 0.002$). Both groups had similar median length of stay, though CUD(+) patients were more likely to have higher hospital cost compared to CUD(-) patients (median = 94574 dollars *vs* 86615 dollars, $P < 0.001$).

***CONCLUSION***
CUD(+) cancer patients with severe sepsis, who tended to be younger, black, males with higher rates of substance use and depression had paradoxically significantly lower odds of all-cause in-hospital mortality and respiratory failure. Future research should aim to better elucidate the underlying mechanisms for these observations.

**Key Words:** Cannabis/marijuana; Sepsis; Cardiovascular outcomes; Major adverse cardiac and cerebrovascular events; Pulmonological complications; Cancer



**Core Tip:** Cannabis use disorder (CUD) in cancer patients with severe sepsis is associated with lower in-hospital mortality and respiratory failure despite higher rates of substance use and depression. CUD(+) patients, who are more likely to be younger, male, and black, also face increased hospital costs. These findings highlight the complex interplay between CUD and sepsis outcomes in cancer, suggesting the need for further research into the mechanisms behind these observations.

**Citation:** Sager AR, Desai R, Mylavarapu M, Shastri D, Devaprasad N, Thiagarajan SN, Chandramohan D, Agrawal A, Gada U, Jain A. Cannabis use disorder and severe sepsis outcomes in cancer patients: Insights from a national inpatient sample. *World J Crit Care Med* 2025; 14(2): 100844
**URL:** https://www.wjgnet.com/2220-3141/full/v14/i2/100844.htm
**DOI:** https://dx.doi.org/10.5492/wjccm.v14.i2.100844

## INTRODUCTION

Cannabis use disorder (CUD) is defined by a set of diagnostic criteria, including patterns of gradually increasing intake, craving, unsuccessful attempts to limit use, disruptions in social and professional obligations, use in settings that pose physical harm, and the development of tolerance and withdrawal symptoms[1]. A meta-analysis of 21 studies identified that cannabis users have a one in five risk of developing CUD, and weekly or more frequent use increased the risk of cannabis dependence to one in three[2]. A study of Veterans Health Administration patients between 2005 and 2019 showed an increased prevalence of CUD over 14 years, from 1.38% to 2.25% in states where cannabis is not legal, 1.38% to 2.54% in states with medical cannabis laws only, and 1.40% to 2.56% in states with medical cannabis and recreational cannabis laws. However, the impact that legalization by state laws played on this up-trending pattern of use is relatively small and inconsistent across age groups, with the authors citing other possible factors like a concurrent rise in psychiatric and pain disorders, increased cannabis potency, decreasing public risk perception, and a lucrative cannabis industry as possibly playing a bigger role[3].

Among cancer patients as well, age seems to play a role in cannabis use and perceptions about availability and risk. One study identified significantly higher use rates among those with past or recent cancer diagnosis in the middle age population compared to those without cancer, whereas this effect was not observed in younger or older age groups. Cousins *et al*[4] reported that 8.9% of total cancer patients and 9.9% of cancer patients who had been diagnosed in the past

year had reported cannabis use. In general, increasing perceived risk and difficulty in access seemed to be a function of increasing age[4]. There are several approved cannabis-based medications on the market targeting a wide variety of cancer-related issues like chemotherapy-induced nausea and vomiting, fatigue, anorexia, and chronic pain[5]. A study among 2970 patients with advanced cancer between 2015 and 2017 showed 95.9% of patients reported improvement in palliative symptoms with cannabis use at six-month follow-up[6]. In 2019, the American Cancer Society estimated 1.7 million new cancer diagnoses and more than 600000 deaths[7]. Hence, advancing novel therapeutic modalities to address this morbidity and mortality burden is imperative.

In recent years, the anticancer effects of cannabis have been explored more. Some researchers have noted its potential for modulating tumor growth in several *in vitro* and *in vivo* models, though this effect seems to be dependent on the type of cancer and drug dosage[8]. For example, a 2021 meta-analysis of 34 studies revealed a negative association between non-testicular cancer and cannabis use, though this study was notable for a high degree of heterogeneity ($I^2$ = 79.2%), obscuring the interpretation of its results[9]. Sepsis arises secondary to a dysregulation in the host response to infection, causing end-organ compromise that is life-threatening[10-12]. The incidence of sepsis or severe sepsis in cancer is variable in the literature. One large database study that included 29795 severe sepsis admissions with cancer found an overall incidence of 16.4 cases per 1000[13]. Another study found that across 19 million hospitalizations for sepsis between 2008 and 2017, one in five had concurrent cancer, with 80% of those being solid cancers[14]. Common sources are pulmonary, genitourinary, and abdominal, with gram-negative organisms like E. coli being most commonly encountered[15,16]. The rate of sepsis-related readmission appears higher in the cancer cohort *vs* the non-cancer cohort (6.2% *vs* 5.4%, $P < 0.001$) [17]. A 2013-2014 study of the United States National Readmissions Database found higher rates of in-hospital mortality among cancer-related sepsis admissions *vs* non-cancer-related sepsis (27.9% *vs* 19.5%, $P < 0.001$). Sepsis survivors also appear to have higher rates of all-cause mortality and major adverse cardiovascular events at long-term follow-up[18]. In contrast, a retrospective analysis of 20975 admissions between 2003 and 2014 demonstrated an improving trend in sepsis-associated mortality in cancer patients compared to those without cancer [adjusted (odds ratio) = 0.53, 95% confidence interval (CI): 0.45-0.63][19]. There is insufficient data on the impact of CUD on severe sepsis and subsequent cardiopulmonary outcomes in cancer patients, which we have studied and intend to provide a basis for further research on this topic.

## MATERIALS AND METHODS

### Source

The National Inpatient Sample (NIS) is part of the Agency for Healthcare Research and Qualities Healthcare Cost and Utilization Project. We utilized the 2016-2020 dataset for our study. It is the largest public, all-payer dataset, and weighted survey analysis of the NIS datasets produces results that are representative estimates of the national outcomes[20]. As this database is de-identified to protect patient confidentiality, Institutional Review Board approval is not needed.

### Study population

The study utilized the International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification diagnostic codes F12.1x and F12.2x (excluding F12.21 for dependence in remission) to identify cases of CUD, and R65.2x to identify cases of severe sepsis. The Revised Clinical Classifications Software was used to identify our two cohorts among all adult cancer patients admitted with severe sepsis between 2016 and 2020; specifically, the group with CUD(+) and the group without CUD(-)[21,22]. Both primary and secondary discharge diagnoses of severe sepsis and CUD were considered in distributing our cohorts (Figure 1).

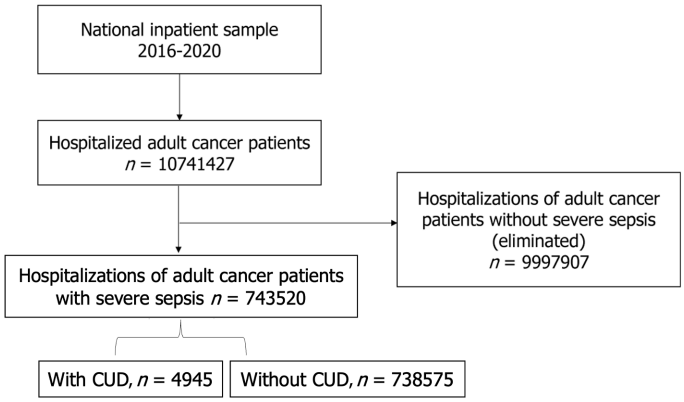


**Figure 1 Flowchart of patient selection of study population.** This flowchart depicts the selection process for hospitalized adult cancer patients with severe sepsis from the National Inpatient Sample database between 2016 and 2020. Total of the 10741427 hospitalized adult cancer patients, those without severe sepsis were excluded, resulting in a cohort of 743520 patients. This cohort was further divided into two groups: Those with cannabis use disorder (*n* = 4945) and those

without cannabis use disorder (*n* = 738575). CUD: Cannabis use disorder.

### Outcomes

Between the two cohorts, we compared patient demographics, hospital-specific features, and comorbidities among cancer patients admitted with severe sepsis. Primary outcomes were the prevalence and trends in CUD, major adverse cardiac and cerebrovascular events, and respiratory failure. Secondary outcomes were the hospital length of stay, cost, and impact on the utilization of healthcare resources.

### Statistical analysis

IBM SPSS statistics (Version 25.0) with weighted data and complex sample modules with strata and cluster designs were used for our statistical analysis [IBM Corp. (2020). IBM SPSS statistics for Windows (Version 25.0) Armonk, NY: IBM Corp]. Categorical variables were expressed as percentages and continuous variables were expressed as medians with ranges between the 25$^{th}$ and 75$^{th}$ percentile. We used Pearson-chi squared test for categorical variables and Mann-Whitney *U* test for continuous non-normally distributed variables. Statistical significance was set at a *P* value of less than 0.05. Multivariable regression analysis was used to analyze primary outcomes after adjusting for age, sex, race, median household income, payer type, hospital bed size, hospital location and teaching status, hospital region and patient comorbidities. Results of this regression analysis were expressed as adjusted OR with 95%CI and *P* values.

## RESULTS

### Epidemiology and patient characteristics

We identified a total of 743520 adult (≥ 18 years) cancer patients who were hospitalized with a primary discharge diagnosis of severe sepsis between 2016-2020. Out of these total hospitalizations, 4945 patients had a secondary diagnosis of CUD while 738575 patients served as control. The prevalence of severe sepsis with CUD was found to be 4.6%. Figure 2A depicts the trends in cannabis use among hospitalized cancer patients with severe sepsis. We compared the baseline demographics, hospital-specific characteristics, and comorbidities between the two cohorts (Table 1). Severe sepsis hospitalizations with CUD(+) cohort consisted of predominantly younger population (median age 58 years *vs* 69 years), males (67.9% *vs* 32.1%), blacks (23.7 *vs* 14.4%), low median income population (0-25$^{th}$ quartile 36.7% *vs* 27.2%), and Medicaid enrollees (35.2% *vs* 10.7%). Among hospitals in the west, there were more hospitalizations for severe sepsis among cancer patients with CUD than without (34.1% *vs* 24.2%) (Table 1, Figure 2B). We included patients with both hematological malignancies (leukemia and lymphoma) as well as non-hematological malignancies in our study. There was no statistically significant difference in the distribution of these malignancies in both cohorts (Supplementary Table 1).

### Associated comorbidities

Comorbidities including chronic pulmonary disease (34.8% *vs* 26.1%), depression (16.2 *vs* 9.8%), alcohol abuse (13.1% *vs* 2.9%), and tobacco use (28.8% *vs* 25.2%) were significantly more in the CUD(+) cohort than CUD(-) cohort. Diabetes mellitus with complications (18.8% *vs* 12.9%), hyperlipidemia (31.1% *vs* 20.3%), and obesity (12% *vs* 10.4%) were significantly higher in the CUD(-) cohort. Other comorbidities were not significantly different in both cohorts (Table 1 and Figure 2B).

### Cardiopulmonary outcomes

There was no significant difference in major adverse cardiac and cerebrovascular events in both cohorts (adjusted OR = 0.86, 95%CI: 0.74-1.01, *P* = 0.059). There was no significant difference in the odds of acute myocardial infarction, cardiac arrest, and acute ischemic stroke. However, the odds of respiratory failure were lower in the CUD(+) cohort (adjusted OR = 0.8, 95%CI: 0.69-0.92, *P* = 0.002) (Table 2).

### Inpatient mortality

All-cause mortality during hospitalization was found to be less in severe sepsis patients in the CUD(+) cohort compared to the CUD(-) cohort (2.9% *vs* 4.7%, *P* < 0.001). A multivariate regression analysis was performed to assess the inpatient all-cause mortality, which showed lower odds of mortality (adjusted OR = 0.83, 95%CI: 0.7-0.9, *P* = 0.002) in severe sepsis patients with CUD compared to the CUD(-) cohort (Tables 2 and 3, Figure 3).

### Trends in cannabis use among hospitalized cancer patients with severe sepsis - 2016-2020

There was a significant linear upward trend in the incidence of acute MI in severe sepsis patients with CUD compared to the non-CUD cohort from 2016-2020 (*P* trend < 0.001). However, there was no significant linear trend in death during hospitalizations and respiratory failure in the CUD cohort from 2016 to 2020 (Figure 4).

### Secondary outcomes

Though the median length of hospitalization stay was similar in both cohorts (7 days), there was a statistical difference in the length of stay with a *P* value of 0.034, suggesting a difference in the distribution of the length of stay between the two

**Table 1 Baseline demographics, hospital-specific admitting characteristics and co-morbidities among cancer patients admitted for severe sepsis with *vs* without cannabis use disorder**

| Baseline characteristics of cancer patients hospitalized with severe sepsis (*n* = 743520) | CUD(-) (*n* = 738575) | CUD(+) (*n* = 4945) | *P* value |
|---|---|---|---|
| Demographics | | | |
| Age at admission, years (median with 25$^{th}$-75$^{th}$ percentile values) | 69 (61-77) | 58 (49-64) | < 0.001 |
| Sex | - | - | < 0.001 |
| Males | 57.2 | 67.9 | - |
| Females | 42.8 | 32.1 | - |
| Race | - | - | < 0.001 |
| White | 70.8 | 64.8 | - |
| Black | 14.4 | 23.7 | - |
| Hispanic | 10 | 9.5 | - |
| Asian or Pacific Islander | 4.3 | 1.1 | - |
| Native American | 0.6 | 0.9 | - |
| Median household income[1] | - | - | < 0.001 |
| 0$^{th}$-25$^{th}$ | 27.2 | 36.7 | - |
| 26$^{th}$-50$^{th}$ | 25 | 26.9 | - |
| 51$^{th}$-75$^{th}$ | 24.6 | 21.5 | - |
| 76$^{th}$-100$^{th}$ | 23.2 | 14.9 | - |
| Payer type | - | - | < 0.001 |
| Medicare | 66.1 | 38.2 | - |
| Medicaid | 10.7 | 35.2 | - |
| Private | 21.4 | 22.4 | - |
| Self-pay | 1.8 | 4.1 | - |
| No charge | 0.1 | 0.1 | - |
| Hospital-specific admitting characteristics | - | - | - |
| Hospital location and teaching status[2] | - | - | < 0.001 |
| Rural | 6 | 5.6 | - |
| Urban non-teaching | 19.5 | 15.8 | - |
| Urban teaching | 74.5 | 78.7 | - |
| Hospital region | - | - | < 0.001 |
| Northeast | 17.9 | 10.8 | - |
| Midwest | 21 | 20.3 | - |
| South | 36.8 | 34.8 | - |
| West | 24.2 | 34.1 | - |
| Comorbidities | | | |
| Acquired immunodeficiency syndrome | 0.9 | 4.7 | < 0.001 |
| Diabetes without chronic complications | 11 | 7.3 | < 0.001 |
| Diabetes with chronic complications | 18.8 | 12.9 | < 0.001 |
| Hypertension, complicated | 29.6 | 19.3 | < 0.001 |
| Hypertension, uncomplicated | 29.4 | 31 | 0.012 |
| Hyperlipidemia | 31.1 | 20.3 | < 0.001 |

| | | | |
|---|---|---|---|
| Chronic pulmonary disease | 26.1 | 34.8 | < 0.001 |
| Obesity | 12 | 10.4 | 0.001 |
| Peripheral vascular disease | 7.6 | 8.2 | 0.11 |
| Hypothyroidism | 13.2 | 7.3 | < 0.001 |
| Valvular disease | 1.1 | 0.3 | < 0.001 |
| Tobacco use | 25.2 | 28.8 | < 0.001 |
| Alcohol abuse | 2.9 | 13.1 | < 0.001 |
| Cocaine use | 0.2 | 6.9 | < 0.001 |
| Depression | 9.8 | 16.2 | < 0.001 |
| Prior myocardial infarction | 4.5 | 4.7 | 0.521 |
| Prior transient ischemic attack or stroke | 4.4 | 3.7 | 0.022 |
| Prior cancer | 15.3 | 14.3 | 0.038 |
| Prior chemotherapy | 9.6 | 12.2 | < 0.001 |
| Prior radiotherapy | 6.6 | 8.9 | < 0.001 |
| Autoimmune conditions | 3 | 2.2 | 0.003 |

[1]Quartile classification of estimated median household income based on patients' ZIP code, https://hcup-us.ahrq.gov/db/vars/zipinc_qrtl/nrdnote.jsp
[2]A teaching hospital is one that has at least one Accreditation Council for Graduate Medical Education-approved residency program. Urban/rural classification is designated by Core Based Statistical Area, https://hcup-us.ahrq.gov/db/vars/hosp_bedsize/nrdnote.jsp
Values are in percentages unless specified. Accompanying *P* value for significance. CUD: Cannabis use disorder.

**Table 2 Primary and secondary in-hospital outcomes among cancer patients admitted for severe sepsis with *vs* without cannabis use disorder**

| Outcomes | CUD(-) (*n* = 738575) | CUD(+) (*n* = 4945) | *P* value |
|---|---|---|---|
| MACCE | 36 | 28.4 | < 0.001 |
| All-cause in-hospital mortality | 30.5 | 23.4 | < 0.001 |
| Acute myocardial infarction | 7.2 | 5.5 | < 0.001 |
| Cardiac arrest, ventricular fibrillationand ventricular flutter | 0.6 | 0.8 | 0.038 |
| Acute ischemic stroke | 2 | 1.7 | 0.207 |
| Respiratory failure | 50.9 | 48.6 | 0.002 |
| Disposition of patient[1] | - | - | < 0.001 |
| Routine | 18.8 | 31.5 | - |
| Transfer to short term facility | 3.4 | 3 | - |
| Other transfers (SNF, ICF *etc.*) | 25.8 | 17.8 | - |
| Home healthcare | 21 | 21.8 | - |
| Length of stay (median, days) | 7 | 7 | 0.034 |
| Total cost of hospitalization (median, USD) | 86615 | 94574 | < 0.001 |

[1]Disposition is at time of discharge and subject to state-specific differences in classification, https://hcup-us.ahrq.gov/db/vars/disp/nisnote.jsp
Values are in percentages unless stated. Accompanying 95% confidence intervals and *P* values for significance. CUD: Cannabis use disorder; MACCE: Major adverse cardiac and cerebrovascular events; SNF: Skilled nursing facility, ICF: Intermediate care facility; USD: United States dollar.

cohorts. The cost of hospitalization was found to be significantly higher in the CUD cohort compared to the non-CUD cohort (median cost 94574 dollars *vs* 86615 dollars, $P < 0.001$) (Tables 2 and 3).

**Table 3 Multivariable regression analysis of primary outcomes comparing cancer patients admitted for severe sepsis with *vs* without cannabis use disorder**

| Events | Adjusted OR | 95%CI | *P* value |
|---|---|---|---|
| MACCE | 0.86 | 0.74-1.01 | 0.059 |
| All-cause in-hospital mortality | 0.83 | 0.7-0.97 | 0.022 |
| Acute myocardial infarction | 1.03 | 0.77-1.37 | 0.84 |
| Cardiac arrest, ventricular fibrillationand ventricular flutter | 1.14 | 0.51-2.52 | 0.754 |
| Acute ischemic stroke | 0.89 | 0.53-1.5 | 0.671 |
| Respiratory failure | 0.8 | 0.69-0.92 | 0.002 |

Values are as adjusted odds ratios. Accompanying 95% confidence intervals and *P* values for significance. Factors adjusted for are age, sex, race, median household income, payer type, elective status, hospital bed size, hospital location and teaching status, hospital region, acquired immunodeficiency syndrome, autoimmune conditions, depression, diabetes with and without chronic complications, hypertension (complicated and uncomplicated), hyperlipidemia, chronic pulmonary disease, obesity, peripheral vascular disease, hypothyroidism, valvular disease, drug abuse, alcohol abuse, smoker status, cocaine abuse, prior myocardial infarction, prior transient ischemic attack or stroke, and prior cancer history. OR; Odds ratio; CI: Confidence interval; MACCE: Major adverse cardiac and cerebrovascular events.

## DISCUSSION

In our study of cancer patients admitted with severe sepsis, the CUD(+) cohort was more likely to be younger, male, black, and Medicaid enrollees. They had lower rates of cardiovascular comorbidities but higher rates of chronic pulmonary disease, substance use, and depression. They had lower odds of all-cause mortality and respiratory failure, but higher median cost of hospital stay compared to the CUD(-) cohort. In line with our findings, several authors have also previously examined the higher rates of cannabis use and dependence among young adults and blacks[4,23-25]. Furthermore, we report higher rates of CUD in hospitals based in the western United States. This is reflective of data from the Substance Abuse and Mental Health Services Administration's 2021 National Survey on Drug Use and Health, where the Western states of Washington, Oregon, Nevada, and California reported the highest rates of marijuana use[26].

Our study revealed higher rates of comorbid alcohol use (13.1% *vs* 2.9%) and mood disorders (16.2% *vs* 9.8%) amongst the CUD(+) arm. Though concurrent alcohol and CUD are understudied, some authors have noted a significant two-way association between major depressive disorder and concurrent alcohol and cannabis use[27]. One primary care-based electronic health record study reported significantly higher odds for other substance use and most mental health conditions, including social anxiety, bipolar disorder, and depression, among those with CUD or cannabis use[28]. We, too, find that patients with CUD were more likely to have higher rates of concomitant depression. Animal studies have explored the neuromodulatory effects of cannabis on gamma-aminobutyric acid and glutamate neurotransmission, though this is still of unclear clinical significance[29,30].

A nationally representative 2018 survey of medical oncologists reported that nearly half (46%) recommend medical marijuana to their patients[31]. From a patient perspective, active users most often cited cannabis use for physical and neuropsychiatric symptoms, including pain, poor sleep or appetite, nausea, low mood and stress[32]. Interestingly, one study of cancer patients undergoing treatment noted that those using cannabis also tended to report more severe symptoms, though whether this is linked to cannabis use is unclear due to the cross-sectional design[25]. A multivariable analysis of different cancers found a statistically significant association between patients with gastrointestinal cancers and cannabis use[33]. A minority of patients discuss cannabis use with their healthcare providers or have medical authorization for its usage, with rates of around 25% and 30% respectively[33,34].

A cross-sectional study of 905 participants in Australia found comparable rates of CUD (32%) among those who used cannabis medically *vs* those who reported illicit use, with withdrawal and tolerance symptoms being the most common manifestations[35]. Another study found that around 80% of medical users also report recreational use and are more prone to daily usage, highlighting the overlap between medical and recreational cannabis use[36]. The significance of these study findings are underscored by data that suggest important gaps in medical literacy among regular cannabis users on its health effects, with a tendency to underestimate risks and overestimate benefits[37]. In fact, evidence-based studies regarding the potential risks and benefits of medical cannabis have been heterogeneous and inconsistent[38-40]. In part, this is due to its federal status as a Class I narcotic, limiting research funding[41].

Cannabinoids (CBs), the most well-researched chemical compound of cannabis, exert their action in the human body *via* the endocannabinoid system and are classified pharmacologically into the intoxicating tetrahydrocannabinol, non-intoxicating cannabidiol (CBD) and several other minor, less well-studied CBs[42]. Experiments investigating the cardiovascular effects of CBD in various pathological states have exhibited a wide range of effects. For example, reductions in stress related hypertension, not causing hypotension in animal hypertension models as well as vascular and cardiac protection in models of diabetes, sepsis and MI[43]. There is also a fair amount of basic science data supporting the ability of CBs to attenuate inflammatory pathways and oxidative stress by downregulating pro-inflammatory cytokines in sepsis[44-47]. Though much of this research has focused on CBD and tetrahydrocannabinol, more recent

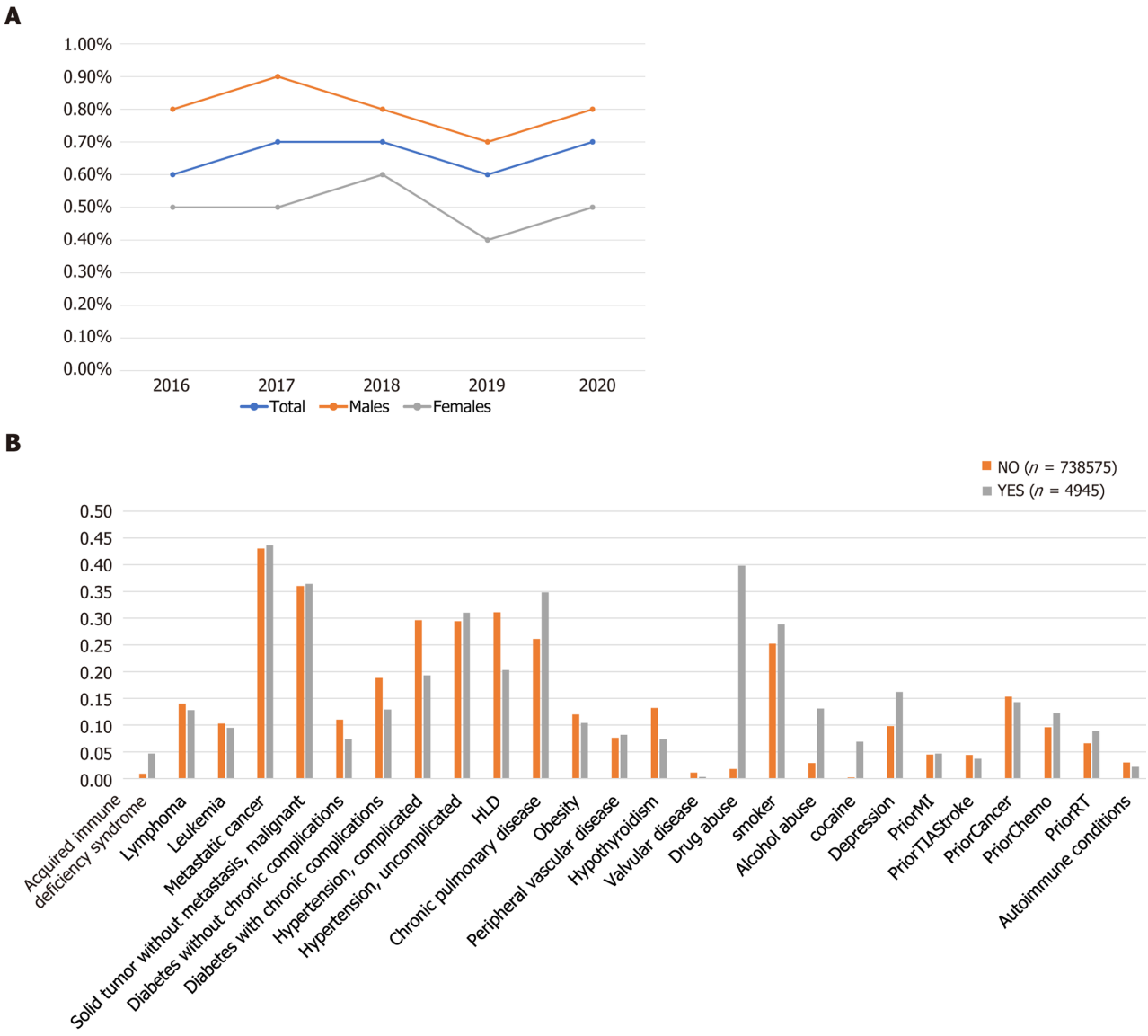


**Figure 2 Epidemiology and patient characteristics.** A: Trends in cannabis use among hospitalized cancer patients with severe sepsis. This line graph displays the proportion of patients receiving vasopressors during their hospitalization over a five-year period. Trends are shown for the total patient population, as well as for males and females separately; B: Comparison of comorbidities between cannabis use disorder (CUD) (+) and CUD(-) cohorts, expressed as percentages. This figure displays the percentage of patients with various comorbidities in the two cohorts: Those with and without CUD. HLD: Hypomyelinating leukodystrophy.

studies have also demonstrated similar anti-inflammatory properties during the lipopolysaccharide-induced, macrophage-mediated, cytokine storm of sepsis among minor cannabinoid groups like tetrahydrocannabivarin, cannabichromene, and cannabinol[48]. Some authors have also cited its anticancer potential through a diverse range of mechanisms like inducing apoptosis, inhibiting cancer signaling, cell proliferation, and angiogenesis *via* CB receptors expressed on tumor cells[45,49,50]. In contrast, a mendelian randomization study reported an increased risk for squamous cell lung carcinoma in individuals with genetic predisposition towards cannabis use[51]. An important consideration here also is the pharmacological interaction between CBs and conventional cancer therapies. Some studies have noted its ability to act synergistically alongside certain chemotherapy agents like paclitaxel, for example, through its effect on transport channels, increasing intracellular drug concentrations[52,53]. A 2021, phase 1b randomized, placebo controlled trial of 21 patients with recurrent glioblastoma being treated with temozolomide demonstrated improved one year survival rates in the intervention arm, which was concurrently administered the cannabis formulation, nabiximols (83% *vs* 44%, $P = 0.042$), though this study was not adequately powered to compare outcomes[54]. However, others have highlighted the contradictory effect of CBs in reducing the efficacy of certain agents, like immunotherapy and metal based drugs, through the modulation of T cell function and production of detoxifying proteins, respectively[53,55,56].

The link between inflammation, sepsis, and its subsequent adverse consequences like shock, metabolic acidosis and end-organ dysfunction is through the systemic inflammatory response syndrome, during which there is a hypermetabolic accumulation of hydrogen peroxide[47,57]. Hence, reducing maladaptive inflammation could be an important component of future therapeutic options aiming to improve outcomes in sepsis[43,58,59]. For example, a mouse sepsis experiment demonstrated decreased systemic inflammation, as well as cardiac and renal protective effects in mice injected with CBD compared to controls[60]. There have been other observational data with concurrent findings of paradoxically improved

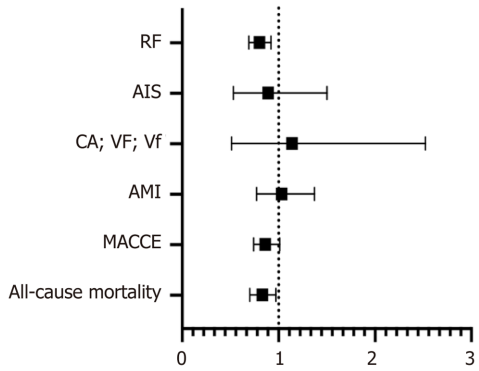


**Figure 3 Forest plot demonstrating primary outcomes.** This forest plot displays the adjusted odds ratios and 95% confidence intervals for various in-hospital outcomes among patients with cannabis use disorder compared to those without cannabis use disorder. RF: Respiratory failure; AIS: Acute ischemic stroke; CA: Cardiac arrest; VF: Ventricular fibrillation; Vf: Ventricular flutter; AMI: Acute myocardial infarction; MACCE: Major adverse cardiac and cerebrovascular event.

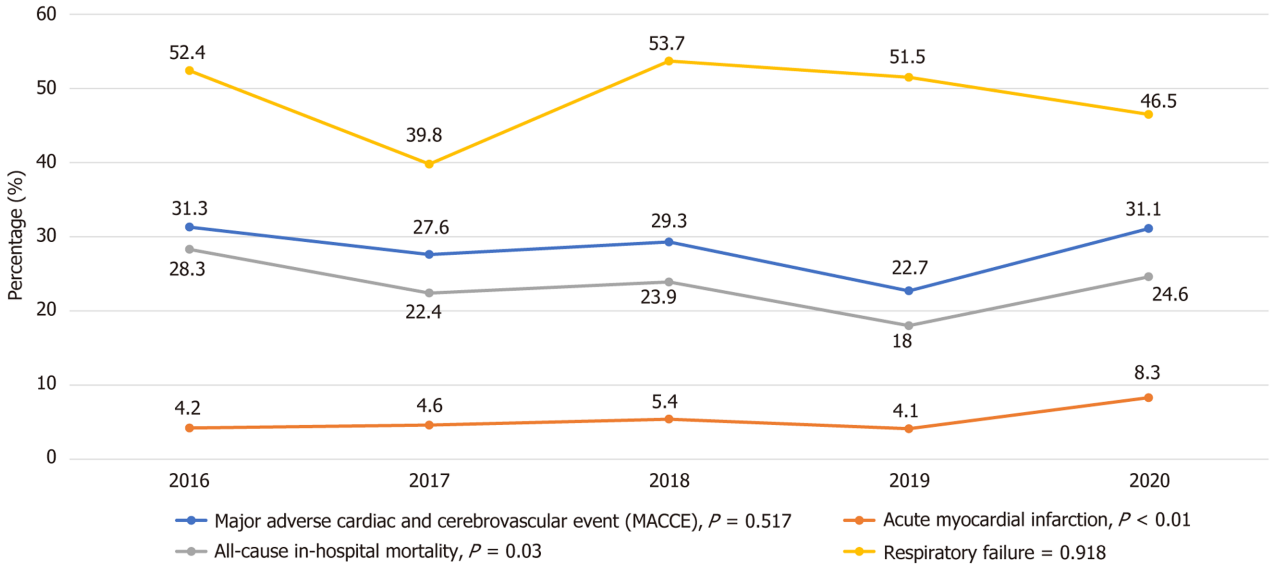


**Figure 4 Trends in primary outcomes among cancer patients with cannabis use disorder admitted with severe sepsis.** This line graph illustrates the percentage of patients experiencing specific in-hospital outcomes over five years. MACCE: Major adverse cardiac and cerebrovascular event.

outcomes among cannabis users. One NIS study between 2005 and 2014 found that among 6073862 COPD admissions, those with cannabis use (0.4%) had statistically significantly lower odds of in-hospital mortality and pneumonia compared to those without cannabis use (99.6%). The cannabis use cohort also had lower odds of sepsis and respiratory failure, but this did not reach statistical significance[61]. In another cross-sectional analysis of the NIS database between 2007-2011, multivariable logistic regression showed lower in-hospital mortality among cancer patients with active marijuana use *vs* non-users (OR = 0.44, 95%CI: 0.35-0.55)[62]. In a retrospective cohort study of 510007 vascular surgery patients, those with CUD had a lower incidence of sepsis in the perioperative period (OR = 0.64, 95%CI: 0.47-0.85), though this association was not statistically significant on sensitivity analysis[63]. In contrast, there have also been studies showing cannabis use to be associated with higher risk for some adverse outcomes. For example, a mendelian randomization study of patients with genetic liability for cannabis use identified a greater risk for small vessel strokes and atrial fibrillation on multivariate analysis[64]. Another population-level cohort study comparing individuals reporting cannabis use within one year to propensity-matched controls found that the cannabis use group had significantly higher rates of emergency room visits and hospital admissions, though there was no difference in all-cause mortality (OR = 0.99, 95%CI: 0.49-2.02)[65].

The major strength of our study is that it utilizes the largest inpatient dataset, which encompasses hospitalizations across 47 states participating in Healthcare Cost and Utilization Project, approximating around 97% of the United States population, or around 7 million unweighted and 35 million weighted admissions nationwide. This allows for an analysis of trends and outcomes across various sociodemographic factors and co-morbidities. As a result, clinicians can better understand nationwide patterns, associations and disease burden. However, our study also has some limitations. The major limitation is that, as a population level administrative dataset, the NIS collects data from admission related International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification codes and not individual patients. Additionally, through the retrospective cohort design, there is a possibility of unmeasured confounding factors, selection,

and sampling bias. Hence, no causality can be inferred regarding outcomes of CUD in sepsis among cancer patients. Furthermore, data regarding prior *vs* current cancer, chemotherapy regimen, age related variations in cancer profile, laboratory and microbiological data and the source of sepsis could not be assessed, which may have influenced the findings in our study by introducing uncontrolled confounders. Despite these limitations, we provide contemporary results from the largest database for outcomes of severe sepsis in cancer patients with CUD.

Prospective cohort studies with standardized data collection on cancer staging, treatment history, and microbiological data can help better account for these variables and improve the robustness of the study findings. Additionally, further research is needed to continue to elucidate the underlying immunological mechanisms of how cannabis use may influence the prognosis of critically ill patients. Furthermore, our study emphasizes the need for heightened awareness of CUD among cancer patients and its potential effects on sepsis outcomes. Healthcare providers need education on this relationship to deliver informed care. Importantly, policies should promote access to treatment for CUD treatment and support integrated care models for this vulnerable population.

## CONCLUSION

Our study is unique in investigating the implications of CUD on severe sepsis outcomes in the cancer population. We found among cancer patients with severe sepsis, those with CUD tended to be younger, black, male, Medicaid enrollees and had higher rates of substance use disorder, depression, chronic pulmonary disease and healthcare utilization cost. However, they had lower rates of cardiovascular co-morbidities and paradoxically lower odds of all-cause mortality and respiratory failure on multivariable regression analysis. A possible link in unraveling this paradox is the potential for CBs to modulate the systemic inflammatory response syndrome of sepsis.

With the increasing prevalence of cannabis use, we aim to inform clinicians about the importance of understanding how CUD affects sepsis in cancer patients. Focusing on the presence of CUD among these patients can enhance care and management. Furthermore, future studies with prospective designs would allow for better control of confounders and more robust conclusions. Additionally, research should also aim to clarify the underlying pathophysiological mechanisms of CUD in sepsis and investigate potential therapeutic options. In the interim, we express concern over findings in the present literature which suggest significantly overlapping recreational and medicinal usage of cannabis and low disclosure rates of such use in the physician-patient relationship, consequently limiting informed decision making and predisposing cancer patients towards CUD without clear medical benefit.

## FOOTNOTES

**Author contributions:** Sager AR, Desai R, and Jain A performed data curation, visualization, and interpretation; Sager AR and Desai R they contributed equally to this article, they are the co-first authors of this manuscript; Desai R has made significant contributions in terms of conceptualization, methodology, editorial work and executive analysis; Sager AR, Mylavarapu M, Shastri D, Devaprasad N, Thiagarajan SN, and Agrawal A wrote the manuscript; Desai R, Jain A, Mylavarapu M, Chandramohan D, and Gada U reviewed and edited the manuscript; and all authors have read and approved the final manuscript.

**Institutional review board statement:** We used a publicly available anonymous national database with de-identified patient information and therefore did not require Institutional Review Board approval.

**Informed consent statement:** We used a publicly available anonymous national database without any way to trace the identity of the patients, and therefore, informed consent was not obtained.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Data sharing statement:** We used a publicly available anonymous national database, *i.e.*, the National Inpatient Sample (datasets from 2016 to 2020).

**STROBE statement:** The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.



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**S-Editor:** Bai Y
**L-Editor:** A
**P-Editor:** Zhang YL

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World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

*World J Crit Care Med* 2025 June 9; 14(2): 101957

DOI: 10.5492/wjccm.v14.i2.101957

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

# Characteristics and outcomes of trauma patients with unplanned intensive care unit admissions: Bounce backs and upgrades comparison

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**Specialty type:** Critical care medicine

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade A, Grade A

**Novelty:** Grade A, Grade A

**Creativity or Innovation:** Grade A, Grade B

**Scientific Significance:** Grade A, Grade B

**P-Reviewer:** Ahmed F; Konstantinou PK

**Received:** October 3, 2024

**Revised:** November 21, 2024

**Accepted:** December 9, 2024

**Published online:** June 9, 2025

**Processing time:** 146 Days and 18.1 Hours

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## Abstract

***BACKGROUND***

The need for an emergency upgrade of a hospitalized trauma patient from the floor to the trauma intensive care unit (ICU) is an unanticipated event with possible life-threatening consequences. Unplanned ICU admissions are associated with increased morbidity and mortality and are an indicator of trauma service quality. Two different types of unplanned ICU admissions include upgrades (patients admitted to the floor then moved to the ICU) and bounce backs (patients admitted to the ICU, discharged to the floor, and then readmitted to the ICU). Previous studies have shown that geriatric trauma patients are at higher risk for unfavorable outcomes.

***AIM***

To analyze the characteristics, management and outcomes of trauma patients who had an unplanned ICU admission during their hospitalization.

***METHODS***
This institutional review board approved, retrospective cohort study examined 203 adult trauma patients with unplanned ICU admission at an urban level 1 trauma center over a six-year period (2017-2023). This included 134 upgrades and 69 bounce backs. Analyzed variables included: (1) Age; (2) Sex; (3) Comorbidities; (4) Mechanism of injury (MOI); (5) Injury severity score (ISS); (6) Glasgow Coma Scale (GCS); (7) Type of injury; (8) Transfusions; (9) Consultations; (10) Timing and reason for unplanned admission; (11) Intubations; (12) Surgical interventions; (13) ICU and hospital lengths of stay; and (14) Mortality.

***RESULTS***
Unplanned ICU admissions comprised 4.2% of total ICU admissions. Main MOI was falls. Mean age was 70.7 years, ISS was 12.8 and GCS was 13.9. Main injuries were traumatic brain injury (37.4%) and thoracic injury (21.7%), and main reason for unplanned ICU admission was respiratory complication (39.4%). The 47.3% underwent a surgical procedure and 46.8% were intubated. Average timing for unplanned ICU admission was 2.9 days. Bounce backs occurred half as often as upgrades, however had higher rates of transfusions (63.8% *vs* 40.3%, $P = 0.002$), consultations (4.8 *vs* 3.0, $P < 0.001$), intubations (63.8% *vs* 38.1%%, $P = 0.001$), longer ICU lengths of stay (13.2 days *vs* 6.4 days, $P < 0.001$) and hospital lengths of stay (26.7 days *vs* 13.0 days, $P < 0.001$). Mortality was 25.6% among unplanned ICU admissions, 31.9% among geriatric unplanned ICU admissions and 11.9% among all trauma ICU patients.

***CONCLUSION***
Unplanned ICU admissions constituted 4.2% of total ICU admissions. Respiratory complications were the main cause of unplanned ICU admissions. Bounce backs occurred half as often as upgrades, but were associated with worse outcomes.

**Key Words:** Unplanned intensive care unit admissions; Trauma intensive care unit; Bounce backs; Upgrades; Level 1 trauma center; Geriatric trauma patients; Quality of care indicator



**Core Tip:** Unplanned intensive care unit (ICU) admissions constituted 4.2% of all trauma ICU admissions. Although upgrades happened more often, bounce backs were associated with worse outcomes, particularly in geriatric patients. Traumatic brain injuries and thoracic injuries together accounted for more than half of the injuries in trauma patients who required an unplanned ICU admission and this tendency was more pronounced in bounce backs and in geriatric patients. Three quarters of unplanned ICU admissions occurred within the first 72 hours of hospitalization. The main reasons for unplanned ICU admissions were respiratory complications. Patients with unplanned ICU admissions had twice the mortality of general trauma ICU patients.

**Citation:** Fokin AA, Wycech Knight J, Gallagher PK, Xie JF, Brinton KC, Tharp ME, Puente I. Characteristics and outcomes of trauma patients with unplanned intensive care unit admissions: Bounce backs and upgrades comparison. *World J Crit Care Med* 2025; 14(2): 101957
**URL:** https://www.wjgnet.com/2220-3141/full/v14/i2/101957.htm
**DOI:** https://dx.doi.org/10.5492/wjccm.v14.i2.101957

## INTRODUCTION

Studies on unplanned intensive care unit (ICU) admissions have been published before and addressed primarily medical and surgical ICU, while studies related to unplanned ICU admissions in trauma patients remain scarce[1-5]. Unplanned admissions to the ICU foreshadow serious clinical implications, including increased lengths of stay, increased hospital costs and higher mortality[4,6-8]. When it comes to the definitions, unplanned ICU admissions are typically divided into two different groups: (1) Upgrades; and (2) Bounce backs. Patients transferred to the ICU after initial admission to the floor are termed upgrades[9]. Meanwhile, patients readmitted to an ICU during the same hospitalization following transfer to a lower level of care (step down unit or floor) are termed either bounce backs, ICU re-admissions, returns, return transfers or rebounds[2,10,11]. Unplanned ICU admissions are considered a quality metric indicator by the American College of Surgeons Trauma Quality Improvement Program[4]. Traditionally, there is more focus on bounce backs, as they have been considered a potentially preventable event and therefore a target for improvements[6,7,10,12,13]. Moreover, the rates and definitions of unplanned ICU admissions in trauma patients vary widely and continue to be a point of discussion[1,2,4,5,8].

The goal of this study was to analyze the characteristics, management and outcomes of trauma patients who had an unplanned ICU admission during their hospitalization. Particular focus was on the comparison of upgrades and bounce

backs and of geriatric and non-geriatric patients.

## MATERIALS AND METHODS

This institutional review board approved, retrospective cohort study was granted a waiver of informed consent and included 4791 adult trauma patients who were admitted to the trauma ICU of an urban level 1 Trauma Center between January 2017 and May 2023. Our 14-bed trauma ICU unit has a nurse to patient ratio of 1:2 or 1:1 for higher acuity, critically injured patients. Unplanned ICU admissions were observed in 203 trauma patients. Patients who were under 18 years old, died on admission, or who did not require a trauma ICU admission were excluded from the study. Analyzed variables included: (1) Age; (2) Sex; (3) Comorbidities; (4) Mechanism of injury (MOI); (5) Injury type; (6) Injury severity score (ISS); (7) Glasgow Coma Scale (GCS); (8) Blood transfusions; (9) Number of consultations; (10) Rate of surgical interventions; (11) Reasons for unplanned ICU admissions; (12) Timing of unplanned ICU admission; (13) Respiratory complications; (14) Mechanical ventilation requirements; (15) ICU length of stay; (16) Hospital length of stay; and (17) Mortality.

Patients with unplanned ICU admissions were either upgraded (134 patients) or readmitted (69 patients) to the ICU during their hospitalization. These two definitively different groups of patients were compared. To ensure comparability in the severity of trauma between the groups, propensity score matching by ISS was done, which resulted in 61 pairs (61 upgrades and 61 bounce backs) for comparison. Taking into account the known serious consequences of geriatric trauma, a further analysis of the geriatric population was performed where 141 geriatric patients with unplanned ICU admissions were compared to 62 non-geriatric patients with unplanned ICU admissions. We also analyzed 72 severely injured patients with ISS ≥ 16. Multivariate analysis of the predictors of respiratory complications was performed due to the high prevalence of respiratory complications among the study population. The flow chart of the study is presented in Figure 1.

### *Definitions*

Unplanned ICU admissions were characterized as either upgrades or bounce backs. Upgrades were defined as the initial admission of a trauma patient to the floor and an unplanned upgrade to the ICU during the same hospital stay. Bounce backs were defined as an initial admission of a trauma patient to the ICU, followed by a downgrade to the floor with subsequent re-admission to the ICU. These definitions are presented in Figure 2 and are based on the current National Trauma Data Standard Dictionary[9].

Severely injured patients were defined as having ISS ≥ 16[14,15]. Mortality was defined as an in-hospital mortality or a hospice discharge[16,17]. Geriatric patients were defined as ≥ 65 years old[18,19]. Indicative variables were identified *via* international classification of diseases-10 codes and extracted from patient's electronic medical records.

### *Statistical analysis*

Statistical analysis was performed using IBM Statistical Package for the Social Sciences Statistics software version 23.0 (IBM, Armonk, New York). Propensity score matching was done without replacement, with a 0.2 caliper, and a randomized order of patients while drawing matches, which resulted in a one-to-one, paired selection. Propensity score matching was used to ensure that the injury severity and number of patients was comparable in the groups of upgrades and bounce backs to determine differences in outcomes. The analyses included group characteristics and bivariate correlation comparisons. Categorical variables were analyzed with $\chi^2$ tests. Variable means were analyzed using independent samples $t$ tests and Mann Whitney-$U$ test based on adequate sample sizes and normal distribution. Statistical significance was assumed when the calculated $P$ value was below 0.05. Analysis also included the use of multivariable logistic regression to determine the predictors of respiratory complications. Multivariable logistic regression is one of the best statistical tools to test which patient injury characteristics can be independent predictors for later complications or outcomes.

## RESULTS

Unplanned ICU admissions constituted 4.2% of all trauma ICU admissions (203/4791). Characteristics of 203 patients with unplanned ICU admissions are presented in Table 1. The mean age was 70.7 years, two thirds were male, the main MOI was falls, mean ISS was 12.8, mean GCS was 13.9, 35.5% had ISS ≥ 16, the mean time between the floor admission and unplanned ICU admission was 2.9 days and mortality was 25.6%. Distribution of the main injuries among patients with unplanned ICU admissions is depicted in Figure 3. The main injury was traumatic brain injury (TBI) followed by chest trauma. The reasons for unplanned ICU admissions are presented in Figure 4, with respiratory insufficiency being the most common.

Of all unplanned ICU admissions, 66% were upgrades and 34% were bounce backs. The comparison between upgrades and bounce backs is presented in Table 2. In general, bounce backs were more severely injured and required more treatment efforts. To account for differences in the trauma severity between the upgrades and bounce backs, patients were propensity score matched by ISS. The comparison between propensity score matched patients is presented in Table 3. After propensity score matching, bounce backs required more transfusions, consultations, intubations and stayed in the ICU and hospital longer.

**Table 1 General characteristics of patients with unplanned intensive care unit admissions, *n* (%)**

| Variable | ICU (*n* = 203) |
|---|---|
| Age (years), mean (SD) | 70.7 (19.9) |
| Geriatric | 141 (69.5) |
| Sex (male/female) | 138 (68.0)/65 (32.0) |
| Comorbidities | 186 (91.6) |
| Mechanism of injury | - |
| Fall | 139 (68.5) |
| Motor vehicle | 59 (29.1) |
| Other (assault, accident, and burn) | 5 (2.5) |
| Glasgow Coma Scale, mean (SD) (range) | 13.9 (2.7) (3-15) |
| ISS, mean (SD) (range) | 12.8 (7.8) (1-38) |
| ISS ≥ 16 | 72 (35.5) |
| Upgrade/bounce back | 134 (66.0)/69 (34.0) |
| Main injury | - |
| Head-traumatic brain injury | 76 (37.4) |
| Thorax | 44 (21.7) |
| Spine | 26 (12.8) |
| Hip/pelvis | 22 (10.8) |
| Abdominal | 11 (5.4) |
| Extremities | 7 (3.4) |
| Facial | 8 (3.9) |
| Cardiac | 6 (3.0) |
| Pulmonary contusion | 14 (6.9) |
| Pneumothorax | 18 (8.9) |
| Hemothorax | 26 (12.8) |
| Pneumohemothorax | 11 (5.4) |
| Any blood transfusion | 98 (48.3) |
| Any surgical procedure | 96 (47.3) |
| Number of consultations, mean (SD) | 3.6 (1.9) |
| Mechanical ventilation requirement | 95 (46.8) |
| Endotracheal intubation | 94 (46.3) |
| Tracheostomy | 14 (6.9) |
| ICU length of stay (days), mean (SD) | 8.7 (12.5) |
| Hospital length of stay (days), mean (SD) | 17.6 (23.8) |
| Mortality | 52 (25.6) |
| Time: Floor-ICU admission (days), mean (SD) | 2.9 (5.4) |

ICU: Intensive care unit; ISS: Injury severity score.

The timing of unplanned ICU admission of propensity score matched upgrades and bounce backs is presented in Figure 5. Majority of upgrades happened within the first 72 hours of admissions to the floor.

The comparison of geriatric and non-geriatric patients with unplanned ICU admissions is presented in Table 4. Even being similarly injured, geriatric patients had a higher mortality. The distribution of the timing of the unplanned ICU admission in geriatric and non-geriatric patients is presented in Figure 6, and followed a similar trend.

**Table 2 Characteristics comparison of upgrades and bounce backs, *n* (%)**

| Variable | Upgrades (*n* = 134) | Bounce backs (*n* = 69) | *P* value |
|---|---|---|---|
| Age (years) (mean) | 72.4 | 67.5 | 0.1 |
| Geriatric | 99 (73.9) | 42 (60.9) | 0.1 |
| Sex (male/female) | 86 (64.2)/48 (35.8) | 52 (75.4)/17 (24.6) | 0.1 |
| Comorbidities | 126 (94.0) | 60 (87.0) | 0.1 |
| Mechanism of injury | - | - | 0.2 |
| Fall | 96 (71.6) | 43 (62.3) | - |
| Motor vehicle | 34 (25.4) | 25 (36.2) | - |
| Other (assault, accident, and burn) | 4 (3.0) | 1 (1.4) | - |
| Glasgow Coma Scale (mean) | 14.6 | 12.4 | < 0.001[a] |
| ISS (mean) | 11.2 | 15.8 | < 0.001[a] |
| ISS ≥ 16 | 37 (27.6) | 35 (50.7) | 0.001[a] |
| Main injury | - | - | 0.003[a] |
| Head-traumatic brain injury | 42 (31.3) | 34 (49.3) | - |
| Thorax | 25 (18.7) | 19 (27.5) | - |
| Spine | 23 (17.2) | 3 (4.3) | - |
| Hip/pelvis | 17 (12.7) | 5 (7.2) | - |
| Abdominal | 5 (3.7) | 6 (8.7) | - |
| Extremities | 7 (5.2) | 0 (0.0) | - |
| Facial | 8 (6.0) | 0 (0.0) | - |
| Cardiac | 5 (3.7) | 1 (1.4) | - |
| Pulmonary contusion | 5 (3.7) | 9 (13.0) | 0.01[a] |
| Pneumothorax | 7 (5.2) | 11 (15.9) | 0.01[a] |
| Hemothorax | 12 (9.0) | 14 (20.3) | 0.02[a] |
| Pneumohemothorax | 4 (3.0) | 7 (10.1) | 0.03[a] |
| Any blood transfusion | 54 (40.3) | 44 (63.8) | 0.002[a] |
| Any surgical procedure | 60 (44.8) | 36 (52.2) | 0.3 |
| Number of consultations (mean) | 3.0 | 4.8 | < 0.001[a] |
| Mechanical ventilation requirement | 51 (38.1) | 44 (63.8) | 0.001[a] |
| Endotracheal intubation | 50 (37.3) | 44 (63.8) | < 0.001[a] |
| Tracheostomy | 6 (4.5) | 8 (11.6) | 0.1 |
| ICU length of stay (days) (mean) | 6.4 | 13.2 | < 0.001[a] |
| Hospital Length of Stay (days) (mean) | 13.0 | 26.7 | < 0.001[a] |
| Mortality | 28 (20.9) | 24 (34.8) | 0.03[a] |
| Time: Floor-ICU admission (days) (mean) | 2.0 | 4.5 | < 0.001[a] |

[a]Denotes a statistically significant difference ($P < 0.05$).
ICU: Intensive care unit; ISS: Injury severity score.

Of 203 patients with unplanned ICU admissions, 80 (39.4%) patients were admitted for respiratory complications, which included 45 upgrades and 35 bounce backs. General patient characteristics, injury characteristics and interventions in 80 patients with unplanned ICU admissions for respiratory complications are presented in Table 5. In total, 81 respiratory events occurred among the 80 patients, which are all presented in Figure 7. Multivariable analysis showed that the only independent significant predictor for respiratory insufficiency leading to an unplanned ICU admission was the presence of rib fractures ($P = 0.04$, odds ratio = 2.8, 95%CI: 1.4–5.6). This finding is clinically important as thoracic injuries

**Table 3 Characteristics comparison of upgrades and bounce backs propensity score matched by injury severity score, *n* (%)**

| Variable | Upgrades (*n* = 61) | Bounce backs (*n* = 61) | *P* value |
|---|---|---|---|
| Age (years) (mean) | 74.8 | 68.7 | 0.04[a] |
| Geriatric | 47 (77.0) | 39 (63.9) | 0.1 |
| Sex (male/female) | 41 (67.2)/20 (32.8) | 45 (73.8)/16 (26.2) | 0.4 |
| Comorbidities | 57 (93.4) | 55 (90.2) | 0.5 |
| Mechanism of injury | - | - | 0.9 |
| Fall | 41 (67.2) | 40 (65.6) | - |
| Motor vehicle | 19 (31.1) | 20 (32.8) | - |
| Other (assault, accident, and burn) | 1 (1.6) | 1 (1.6) | - |
| Glasgow Coma Scale (mean) | 14.7 | 12.8 | < 0.001[a] |
| ISS (mean) | 13.9 | 13.8 | 0.5 |
| ISS ≥ 16 | 27 (44.3) | 27 (44.3) | 1.0 |
| Main injury | - | - | 0.2 |
| Head-traumatic brain injury | 23 (37.7) | 29 (47.5) | - |
| Thorax | 12 (19.7) | 19 (31.1) | - |
| Spine | 7 (11.5) | 3 (4.9) | - |
| Hip/pelvis | 9 (14.8) | 4 (6.6) | - |
| Abdominal | 3 (4.9) | 4 (6.6) | - |
| Extremities | 2 (3.3) | 0 (0.0) | - |
| Facial | 3 (4.9) | 0 (0.0) | - |
| Cardiac | 1 (1.6) | 1 (1.6) | - |
| Pulmonary contusion | 3 (4.9) | 7 (11.5) | 0.2 |
| Pneumothorax | 2 (3.3) | 9 (14.8) | 0.03[a] |
| Hemothorax | 6 (9.8) | 14 (23.0) | 0.1 |
| Pneumohemothorax | 2 (3.3) | 7 (11.5) | 0.1 |
| Any blood transfusion | 26 (42.6) | 38 (62.3) | 0.03[a] |
| Any surgical procedure | 28 (45.9) | 30 (49.2) | 0.7 |
| Number of consultations (mean) | 3.1 | 4.6 | < 0.001[a] |
| Mechanical ventilation requirement | 25 (41.0) | 38 (62.3) | 0.02[a] |
| Endotracheal intubation | 25 (41.0) | 38 (62.3) | 0.02[a] |
| Tracheostomy | 5 (8.2) | 6 (9.8) | 0.8 |
| ICU length of stay (days) (mean) | 6.1 | 11.3 | < 0.001[a] |
| Hospital length of stay (days) (mean) | 12.5 | 21.7 | < 0.001[a] |
| Mortality | 16 (26.2) | 22 (36.1) | 0.2 |
| Time: Floor-ICU admission (days) (mean) | 2.0 | 4.4 | 0.003[a] |

[a]Denotes a statistically significant difference ($P < 0.05$).
ICU: Intensive care unit; ISS: Injury severity score.

were the second most frequent co-injuries in our study population and potentially contributed to the respiratory complications in these patients. Among patients with unplanned ICU admissions for respiratory complications, 13.8% had respiratory comorbidities. Patients with unplanned ICU admissions for respiratory complications had more than twice the mortality of the general trauma ICU population.

**Table 4 Characteristics comparison of geriatric and non-geriatric patients with unplanned intensive care unit admissions, *n* (%)**

| Variable | Geriatric (*n* = 141) | Non-geriatric (*n* = 62) | *P* value |
|---|---|---|---|
| Age (years) (mean) | 81.8 | 45.5 | < 0.001[a] |
| Sex (male/female) | 89 (63.1)/52 (36.9) | 49 (79.0)/13 (21.0) | 0.03[a] |
| Comorbidities | 139 (98.6) | 47 (75.8) | < 0.001[a] |
| Mechanism of injury | - | - | < 0.001[a] |
| Fall | 114 (80.9) | 25 (40.3) | - |
| Motor vehicle | 25 (17.7) | 34 (54.8) | - |
| Other (assault, accident, and burn) | 2 (1.4) | 3 (4.8) | - |
| Glasgow Coma Scale | 14.4 | 12.6 | 0.1 |
| ISS (mean) | 12.4 | 13.6 | 0.4 |
| ISS ≥ 16 | 46 (32.6) | 26 (41.9) | 0.2 |
| Upgrade/bounce back | 99 (70.2)/42 (29.8) | 35 (56.5)/27 (44.5) | 0.1 |
| Main injury-admission | - | - | 0.005[a] |
| Head-traumatic brain injury | 56 (39.7) | 20 (32.3) | - |
| Thorax | 31 (22.0) | 13 (21.0) | - |
| Spine | 22 (15.6) | 4 (6.5) | - |
| Hip/pelvis | 14 (9.9) | 8 (12.9) | - |
| Abdominal | 2 (1.4) | 9 (14.5) | - |
| Extremities | 4 (2.8) | 3 (4.8) | - |
| Facial | 4 (2.8) | 4 (6.5) | - |
| Cardiac | 6 (4.3) | 0 (0.0) | - |
| Pulmonary contusion | 7 (5.0) | 7 (11.3) | 0.1 |
| Pneumothorax | 11 (7.8) | 7 (11.3) | 0.4 |
| Hemothorax | 22 (15.6) | 4 (6.5) | 0.1 |
| Pneumohemothorax | 8 (5.7) | 3 (4.8) | 0.8 |
| Any blood transfusion | 67 (47.5) | 31 (50.0) | 0.7 |
| Any surgical procedure | 52 (36.9) | 44 (71.0) | < 0.001[a] |
| Number of consultations (mean) | 3.5 | 3.9 | 0.4 |
| Mechanical ventilation requirement | 52 (36.9) | 43 (69.4) | < 0.001[a] |
| Endotracheal intubation | 51 (36.2) | 43 (69.4) | < 0.001[a] |
| Tracheostomy | 7 (5.0) | 7 (11.3) | 0.1 |
| ICU length of stay (days) (mean) | 6.8 | 13.1 | 0.02[a] |
| Hospital length of stay (days) (mean) | 13.1 | 27.9 | < 0.001[a] |
| Mortality | 45 (31.9) | 7 (11.3) | 0.002[a] |
| Time: Floor-ICU admission (days) (mean) | 2.1 | 4.7 | 0.2 |

[a]Denotes a statistically significant difference ($P < 0.05$).
ICU: Intensive care unit; ISS: Injury severity score.

## DISCUSSION

In our study, unplanned ICU admissions constituted 4.2% of all trauma ICU admissions with a mortality of 25.6%. Rubano *et al*[5] reported a 3.9% rate of unplanned ICU admissions from all trauma center admissions and a 28.2% rate of unplanned ICU admissions from all trauma ICU admissions, with a mortality of 18.4%.

**Table 5 Characteristics of patients with unplanned intensive care unit admissions due to respiratory complications, *n* (%)**

| Variable | Respiratory complications (*n* = 80) |
|---|---|
| Age (yaers) (mean) | 69.0 |
| Geriatric | 52 (65.0) |
| Sex (male/female) | 53 (66.3)/27 (32.7) |
| Comorbidities | 72 (90.0) |
| Mechanism of injury | - |
| Fall | 50 (62.5) |
| Motor vehicle | 28 (35.0) |
| Glasgow Coma Scale (mean) | 14.3 |
| ISS (mean) | 11.9 |
| ISS ≥ 16 | 22 (27.5) |
| Upgrade/bounce back | 30 (37.5)/50 (62.5) |
| Main injury | - |
| Head-traumatic brain injury | 16 (20.0) |
| Thorax | 26 (32.5) |
| Spine | 14 (17.5) |
| Hip/pelvis | 9 (11.3) |
| Abdominal | 5 (6.3) |
| Extremities | 3 (3.8) |
| Facial | 5 (6.3) |
| Pulmonary contusion | 7 (8.8) |
| Pneumothorax | 10 (12.5) |
| Hemothorax | 15 (18.8) |
| Pneumohemothorax | 6 (7.5) |
| Any blood transfusion | 39 (48.8) |
| Any surgical procedure | 43 (53.8) |
| Number of consultations (mean) | 3.9 |
| Mechanical ventilation requirement | 54 (67.5) |
| Endotracheal intubation | 53 (66.3) |
| Tracheostomy | 13 (16.3) |
| ICU length of stay (days) (mean) | 12.8 |
| Hospital length of stay (days) (mean) | 21.1 |
| Mortality | 24 (30.0) |
| Time: Floor-ICU admission (days) (mean) | 4.0 |

ICU: Intensive care unit; ISS: Injury severity score.

Within our patients, upgrades constituted 66% and bounce backs 34% of unplanned ICU admissions. On the contrary, Jensen *et al*[8] reported the opposite numbers for unplanned ICU admissions with 69% being bounce backs and 31% being upgrades.

Bounce backs have been addressed more often in the literature and the rates of bounce backs were reported to be from 3.6% to 5.6% in all adult trauma admissions[6,10,13,20] or from 19.8% to 69% in all unplanned ICU admissions[5,8]. The mortality rates in bounce backs have ranged from 10.8% to 22.3%[6,7,10,12]. In our study, bounce backs accounted for 1.4% of all trauma ICU admissions, or 34% of unplanned ICU admissions with a mortality of 34.8%, which is on the higher end of the reported mortality, which may be due to a higher proportion of geriatric patients.

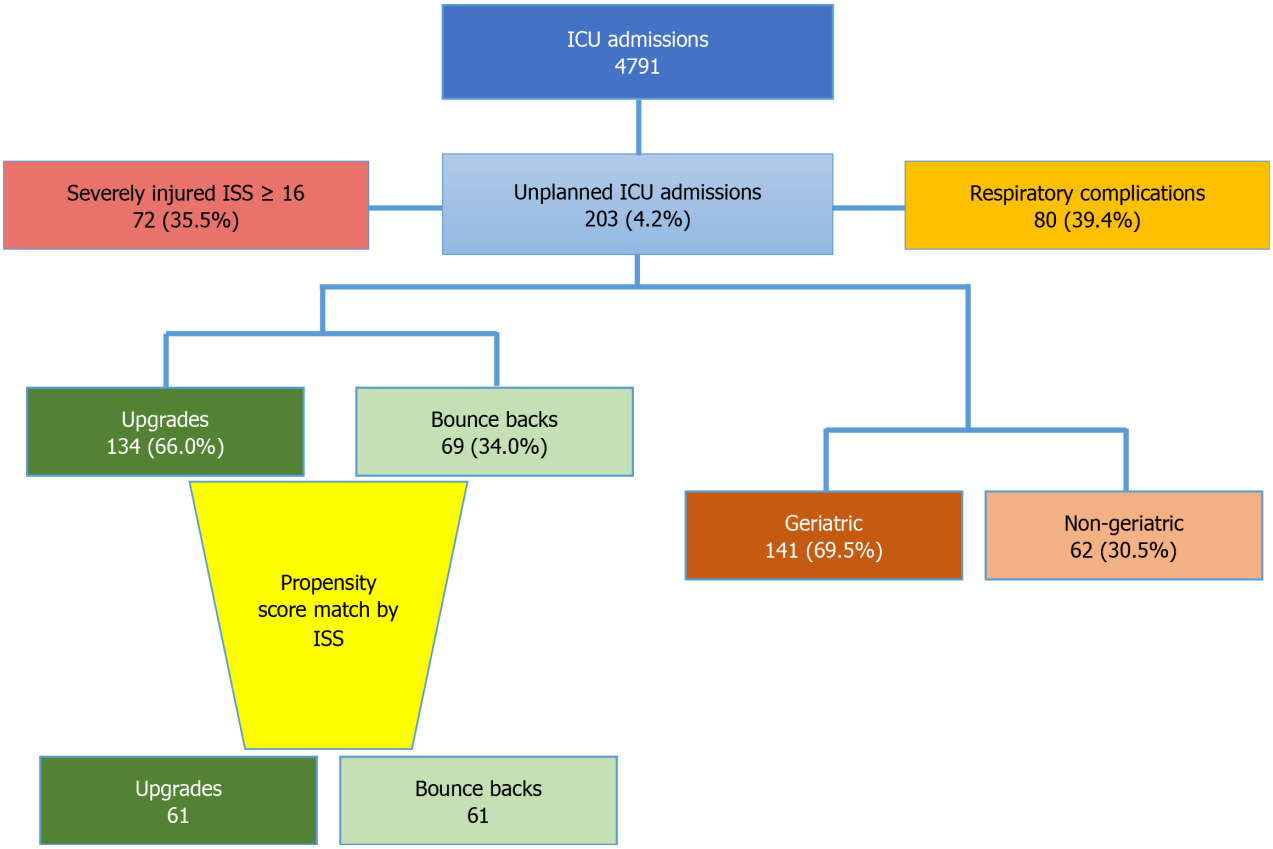



**Figure 1 Study flow chart.** ICU: Intensive care unit; ISS: Injury severity score.

The rates of upgrades were reported to be around 4.4% in all trauma ICU admissions[4], or from 31% to 80.2 % in unplanned ICU admissions in trauma patients[5,8]. Mortality in upgrades was reported between 5.4% and 20%[4,8]. In our study, the rates were in line with previously reported data, as upgrades accounted for 2.8% of all trauma ICU admissions, or 66% of unplanned ICU admissions with a mortality of 20.9%. In our patients, mortality was statistically significantly higher in bounce backs compared to upgrades. After propensity score matching by ISS, mortality was higher in bounce backs, however, it did not reach the statistical significance.

The frequency of bounce backs can be reduced by recognizing specific risk factors, such as particular comorbidities and/or injuries, in certain categories of patients and by using an aggressive prophylactic treatment to target these risk factors after the patient is transferred to the floor. A reduction in upgrades can be achieved by following best practice guidelines and having institutional algorithms for ICU admission of particular diagnosis-related groups (*e.g.* direct ICU admission for a geriatric patient with ≥ 3 rib fractures). The comparison of propensity score matched patients revealed that despite comparable injury severity and type of injury, upgrades were elevated from the trauma floor to the ICU earlier than bounce backs, suggesting an initial undertriage and a potentially preventable event.

The wide range of reported numbers of upgrades and bounce backs in different studies can be attributed to different patient mix, variability in the inclusion and exclusion criteria, and to the use of different definitions[1,2]. Some authors limit inclusions to patients admitted to the ICU for 24 hours or more[2,21,22], exclude patients with the initial ICU stay of < 4 hours[23], while others exclude returns within 6 hours[24]. The frequency of unplanned ICU admissions may also be affected by the trauma ICU bed occupancy rates or depend on the demand.

In particular, the timing of the unplanned ICU admissions varies between different studies. It can include the entire time of hospitalization, be limited to just the first 48 hours of floor hospitalization, or include the first 72 hours[1,2,6,13,23]. Currently, there is no standardized, comprehensive, and across-the-board accepted definition of unplanned ICU admissions. It seems logical to include a certain time limit in the definition, as later admissions may be more related to the development of lingering complications than to premature discharge from the ICU or any deficiency in treatment on the floor[25]. Many studies address readmissions within the first 48 hours of initial ICU discharge, as this time frame has stronger relationship with the ICU interventions, such as mechanical ventilation[26,27]. We agree with the opinion of Fakhry *et al*[13] that since most of the patients (71.6%) are admitted to the ICU within the first 72 hours, this may be an appropriate cut off for trauma patients. In our study, more than 3/4 (78.3%) of patients were admitted to the ICU within the first 72 hours of hospital admission and almost 2/3 within 48 hours. These first few days on the trauma floor are crucial for the prevention of unfavorable developments and should be designated for aggressive preventive treatment.

### *Geriatric vs non-geriatric comparison*

Due to an aging population with a more active lifestyle, geriatric trauma is on the rise and is a subject of renewed interest [28-30]. However, publications regarding unplanned ICU admissions in geriatric trauma patients are scarce[11,31]. In our

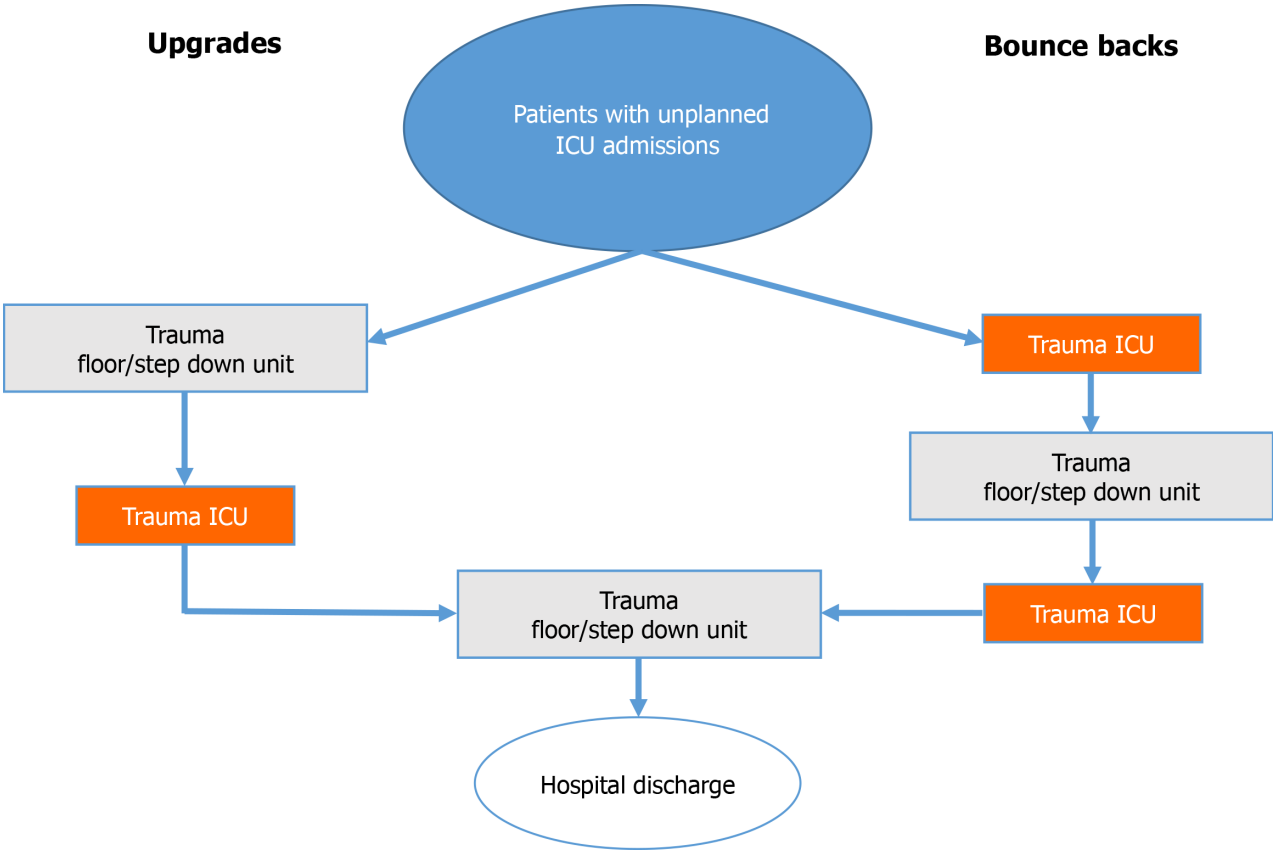



**Figure 2 Upgrades and bounce backs definitions.** ICU: Intensive care unit.

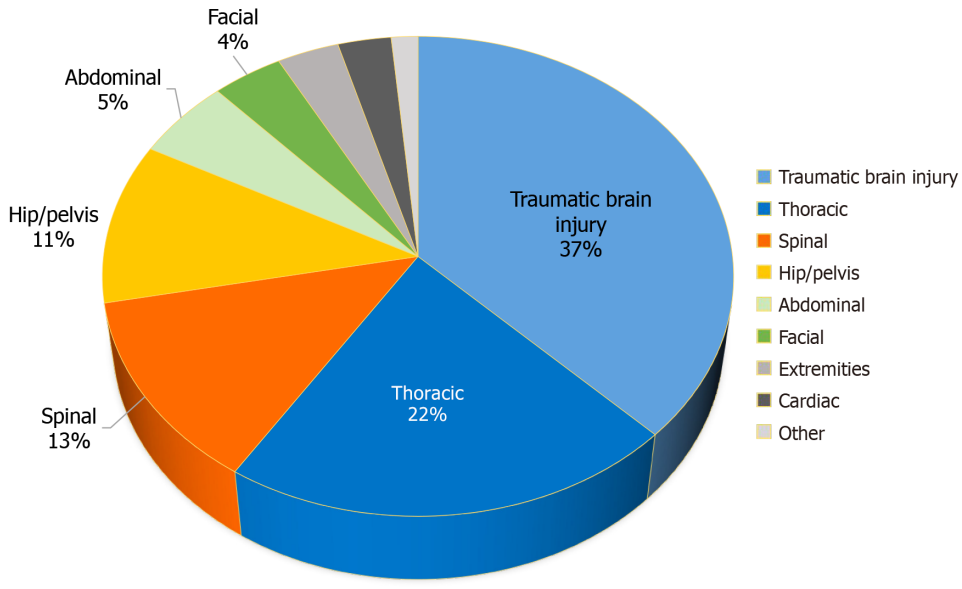



**Figure 3 Distribution of main injuries among patients with unplanned intensive care unit admissions.**

study of unplanned ICU admissions, geriatric patients had more comorbidities and more falls as MOI than non-geriatric patients, however the ISS was comparable. In both subgroups, upgrades were more common than bounce backs, however upgrades were even more prevalent in geriatric patients compared to non-geriatric patients, suggesting higher initial undertriage in the elderly population. In addition, the time for elevating patients to the ICU was 2 days shorter in geriatric compared to non-geriatric patients. Mortality among our geriatric patients was almost three times higher than in non-geriatric patients and reached 31.9%. In both age groups mortality was higher in bounce backs compared to upgrades and both bounce backs and upgrades mortality was three times higher in geriatric compared to non-geriatric patients. Our data are in agreement with Laytin and Sims[11] who in the analysis of bounce backs also reported a three

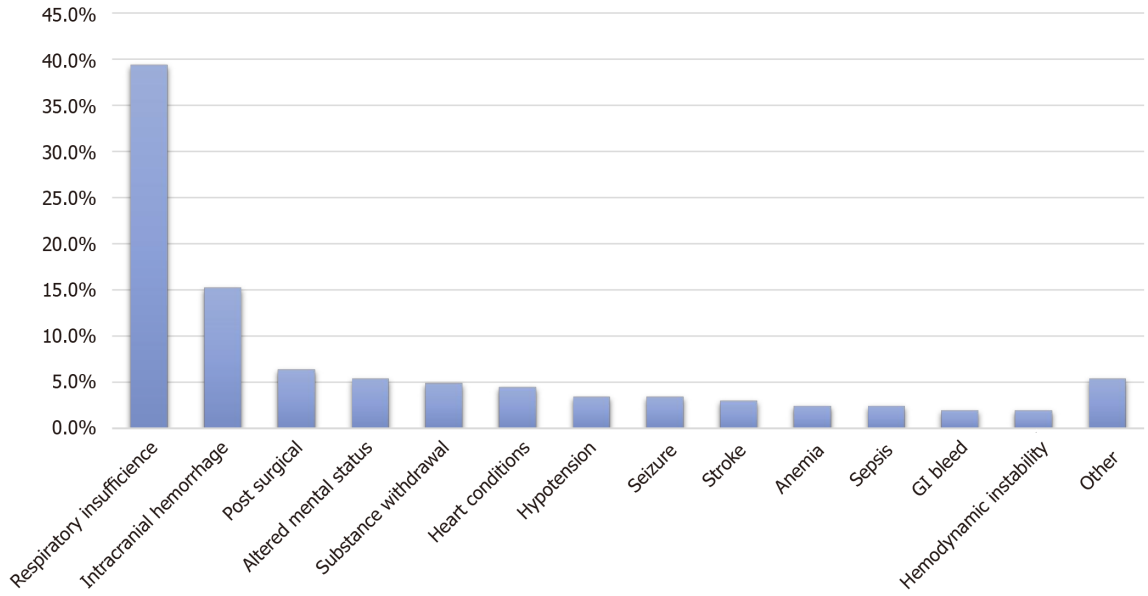



**Figure 4 Reasons for unplanned intensive care unit admissions.** GI: Gastrointestinal.

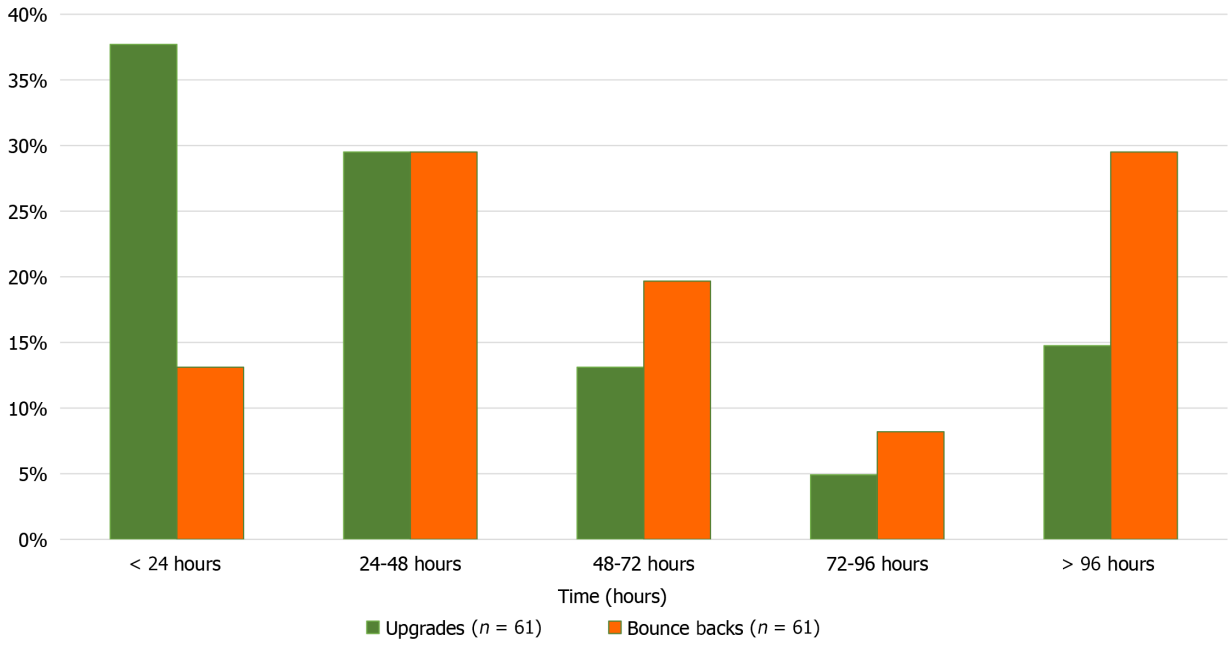
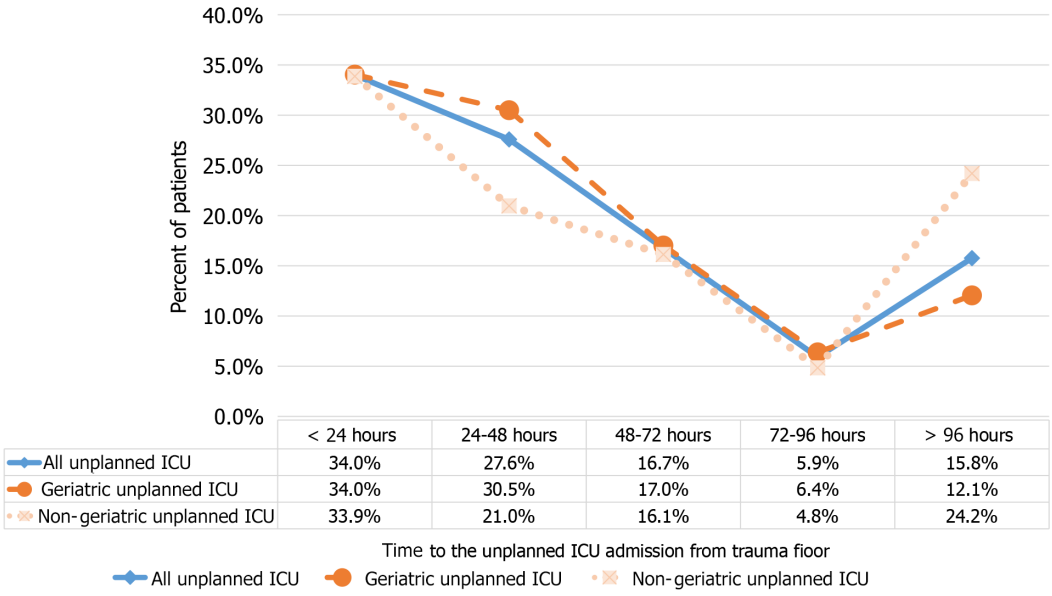



**Figure 5 Distribution of timing from the floor to the intensive care unit admission in propensity score matched upgrades and bounce backs.**

times higher mortality in geriatric trauma patients compared to adult readmissions. In another analysis of geriatric patients by Mulvey *et al*[31], bounce backs were twice as common, but bounce backs and upgrades had comparable mortality, around 10%.

### *Respiratory complications*

Several investigators observed a high prevalence of respiratory complications among patients with unplanned ICU admissions[6,10,32]. Respiratory complications were the main cause of unplanned ICU admissions in 40% of our trauma patients. Our results are similar to Yin *et al*[32] and Jensen *et al*[8] who reported that in about 40% of patients the primary reason for the return to the ICU within 48 hours or for an unplanned ICU admission was respiratory distress. Furthermore, Ranney *et al*[4] reported that significant injuries to the thorax and respiratory deterioration were the most common etiologies of trauma ICU upgrades. Multivariable analysis in our study showed that the presence of rib fractures was the only independent predictor for respiratory insufficiency leading to an unplanned ICU admission. With thoracic injuries being the second most frequent co-injuries in our study population, it is of clinical importance to view patients




| | < 24 hours | 24-48 hours | 48-72 hours | 72-96 hours | > 96 hours |
|---|---|---|---|---|---|
| All unplanned ICU | 34.0% | 27.6% | 16.7% | 5.9% | 15.8% |
| Geriatric unplanned ICU | 34.0% | 30.5% | 17.0% | 6.4% | 12.1% |
| Non-geriatric unplanned ICU | 33.9% | 21.0% | 16.1% | 4.8% | 24.2% |

**Figure 6 Distribution of timing from the floor to the intensive care unit admission in all, geriatric and non-geriatric patients.** ICU: Intensive care unit.

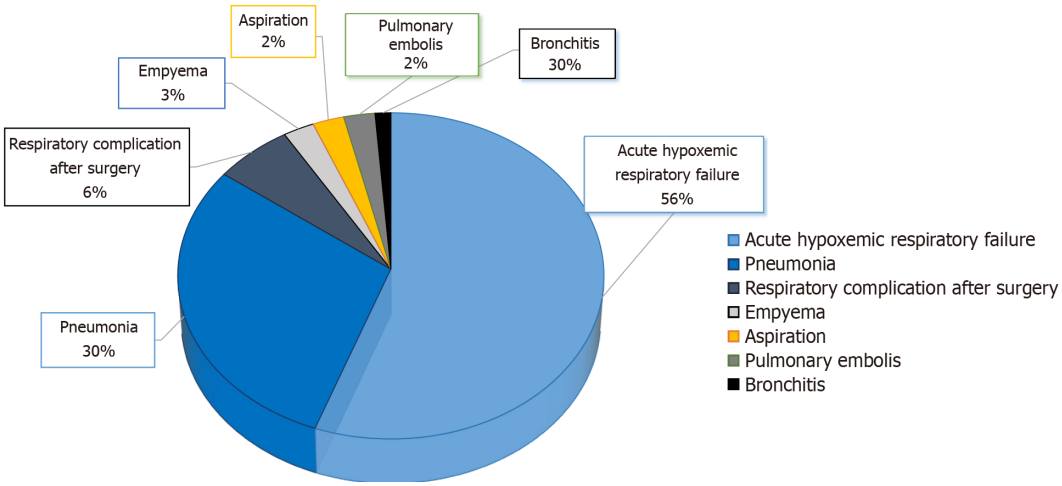



**Figure 7 Respiratory causes of unplanned intensive care unit admissions in trauma patients.**

with rib fractures as at risk to develop respiratory complications, which may result in unplanned ICU admissions. The other tested variables, such as chronic obstructive pulmonary disease (COPD), pulmonary contusion and hemo/pneumothorax were not significant predictors. However, in a number of studies, COPD was found to be significantly associated with unplanned trauma ICU readmissions or trauma ICU upgrades[4,6,7].

Respiratory deterioration was the main reason for ICU return, accounting for 60% of upgrades and 62% of bounce backs[4,12]. Other studies also reported high rates of respiratory complications in bounce back patients of 43% and 48.6% [10,13]. Bradburn *et al*[6] identified unplanned intubation as one of the strongest predictors of ICU bounce backs. Our data is in line, as most of the respiratory complications were in bounce back patients where head and chest injuries were the most common. Other authors also recognized that patients with TBI comprised almost half of the initial readmissions [10]. In our propensity score matched comparison, bounce backs had significantly higher mechanical ventilation requirements, with more endotracheal intubations compared to upgrades. High mortality rates in patients with respiratory complications necessitate proactive search for early signs of respiratory insufficiency.

Among our patients with respiratory complications, the mean time before unplanned ICU admission was 4 days, which indicates that there is available time that should be used for aggressive prophylactic of this complication, such as a mandatory respiratory therapy, early mobilization and dysphagia screening.

### *Severely injured patients*

The ISS of 16 or more is the most commonly used definition of severely injured patients and level 1 and level 2 trauma centers are designated for the treatment of these patients[14,15,33]. Johns[23] found that ISS > 17 was among the risk

factors for trauma ICU readmissions. Of all unplanned ICU admissions at our trauma center, patients with ISS ≥ 16 accounted for just above 1/3 and this number was significantly higher among bounce backs compared to upgrades, however there was no statistically significant difference between geriatric and non-geriatric patients. These findings also indicate that the severity of injury per se cannot completely explain all unplanned ICU admissions and that other factors or a combination of factors must be taken into account, such as age, frailty, comorbidities or injury type.

### *ICU quality of care indicator*

Some authors have considered ICU readmission or bounce back rates as a potential indicator of the quality of care for critically ill patients[27,34,35]. In a comparison review Duke *et al*[35] referred to the suggested < 5% of ICU readmission rates as a recommended benchmark. ICU readmission rate within 48 hours of ICU discharge is a clinical performance measure to gauge ICU safety and the quality of care[36,37]. Al-Jaghbeer *et al*[38] suggested that ICU readmission rates may not be a good measure of hospital performance, yet may be viewed as "sentinel events" that can be a marker of system-level inefficiencies. Others mentioned that the readmission rate is a crude indicator and is a complementary measure of ICU quality of care, but should only be applied if the patient case-mix is taken into account[39,40].

Discussions between the "quicker and sicker "discharge from the ICU *vs* the poor quality of treatment received in the ward as the cause of ICU readmission continue[38,41]. It was reported that the premature discharge is likely not the cause of bounce backs and that keeping patients in the ICU longer reduces the occurrence of bounce backs due to more aggressive care, however due to the overall low incidence of bounce backs prolonged ICU stay may be inefficient and cost prohibitive[12]. Delayed ICU discharge of patients with one or more risk variables, or better matching to the receiving unit are also recommended[13]. Van Sluisveld *et al*[26] did not find an association between the discharge practices and the rates of ICU readmissions. Kramer *et al*[40] suggested that readmission is more of a proxy for the patient characteristics, particularly the severity of the illness, than a quality measure for ICU. Additionally, the ability of clinicians to predict unplanned readmissions was found to be limited, regardless of the level of experience[3].

Different scores, including the Acute Physiology and Chronic Health Evaluation, the Stability and Workload Index for Transfer, the Sequential Organ Failure Assessment score, the Therapeutic Intervention Scoring System, the Nursing Activity Score and the Clinical Risk of Acute ICU Status during Hospitalization Score have been applied to predict the risk of readmissions, with different rates of accuracy[22,34,42,43].

### *Practical recommendations*

To lessen the amount of unplanned ICU admissions in trauma patients: (1) To reduce upgrades: Improve initial triage, especially among geriatric patients and follow ICU admission guidelines and algorithms; and (2) To reduce bounce backs: After floor admission recognize specific risk factors, focus on the early detection and prophylactic treatment of potential complications.

Patients with TBI or thoracic trauma may require special attention and require adherence to the institutional policies.

Geriatric patients with early onset of respiratory difficulties or those with TBI with notable intracranial bleeding should be considered for a direct admission to the ICU upon hospital arrival.

The first 2-3 days after admission are crucial for the prevention of unplanned ICU admissions and must be dedicated for aggressive targeting of anticipated complications and preventive treatment.

### *Limitations*

The retrospective nature of this study brings up restrictions in prerecorded data and assessments available for extraction from patient's charts. Although the analysis encompassed data from a considerable amount of time, data from only one level 1 trauma center was included. The participating urban level 1 trauma center is located in a primarily geriatric catchment area.

## CONCLUSION

Unplanned ICU admissions constituted 4.2% of all trauma ICU admissions. Although upgrades happened more often, bounce backs required more intensive interventions and prolonged hospital care and were associated with worse outcomes, particularly among geriatric patients. Traumatic brain injuries and thoracic injuries together accounted for more than half of the injuries in patients who required an unplanned ICU admission and this tendency was more pronounced in bounce backs and in geriatric patients. Three quarters of unplanned ICU admissions occurred within the first 72 hours of hospitalization. The main reason for unplanned ICU admissions was respiratory complication. Patients with unplanned ICU admissions had twice the mortality of general trauma ICU patients. The first three days after admission are crucial for the prevention of unplanned ICU admissions and must be dedicated to preventive treatment for any anticipated complications.

## FOOTNOTES

**Author contributions:** Fokin AA, Wycech Knight J, and Puente I conceptualized and designed the research study; Fokin AA and Puente I overlooked the study; Wycech Knight J, Gallagher PK, Xie JF, Brinton KC, and Tharp ME performed the research; Fokin AA, Wycech Knight J, Gallagher PK, Xie JF, Brinton KC, and Tharp ME analyzed the data; Fokin AA, Wycech Knight J, Gallagher PK, Xie JF, Brinton

KC, Tharp ME, and Puente I contributed to writing the original draft and the revision; all of the authors read and approved the final version of the manuscript to be published.

**Institutional review board statement:** This study was approved by the MetroWest Institutional Review Board, Framingham, MA under the protocol No. 2023-060.

**Informed consent statement:** This retrospective study was granted a waiver of informed consent by the MetroWest Institutional Review Board.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest. The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

**Data sharing statement:** Deidentified data and study materials are available upon reasonable request from the corresponding author at alexander.fokin@tenethealth.com.

**STROBE statement:** The authors have read the STROBE statement–checklist of items, and the manuscript was prepared and revised according to the STROBE statement–checklist of items.



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**S-Editor:** Luo ML
**L-Editor:** A
**P-Editor:** Guo X

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World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

*World J Crit Care Med* 2025 June 9; 14(2): 98004

DOI: 10.5492/wjccm.v14.i2.98004

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Retrospective Study

# Incidence and outcome of rhabdomyolysis after type A aortic dissection surgery: A retrospective analysis

Praveen C Sivadasan, Cornelia S Carr, Abdul Rasheed A Pattath, Samy Hanoura, Suraj Sudarsanan, Hany O Ragab, Hatem Sarhan, Arunabha Karmakar, Rajvir Singh, Amr S Omar

**Specialty type:** Critical care medicine

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**
**Scientific Quality:** Grade C
**Novelty:** Grade C
**Creativity or Innovation:** Grade C
**Scientific Significance:** Grade C

**P-Reviewer:** Yu J

**Received:** June 14, 2024
**Revised:** October 27, 2024
**Accepted:** December 10, 2024
**Published online:** June 9, 2025
**Processing time:** 257 Days and 11.3 Hours

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## Abstract

*BACKGROUND*

Rhabdomyolysis (RML) as an etiological factor causing acute kidney injury (AKI) is sparsely reported in the literature.

*AIM*

To study the incidence of RML after surgical repair of an ascending aortic dissection (AAD) and to correlate with the outcome, especially regarding renal function. To pinpoint the perioperative risk factors associated with the development of RML and adverse renal outcomes after aortic dissection repair.

***METHODS***
Retrospective single-center cohort study conducted in a tertiary cardiac center. We included all patients who underwent AAD repair from 2011-2017. Post-operative RML workup is part of the institutional protocol; studied patients were divided into two groups: Group 1 with RML (creatine kinase above cut-off levels 2500 U/L) and Group 2 without RML. The potential determinants of RML and impact on patient outcome, especially post-operative renal function, were studied. Other outcome parameters studied were markers of cardiac injury, length of ventilation, length of stay in the intensive care unit), and length of hospitalization.

***RESULTS***
Out of 33 patients studied, 21 patients (64%) developed RML (Group RML), and 12 did not (Group non-RML). Demographic and intraoperative factors, notably body mass index, duration of surgery, and cardiopulmonary bypass, had no significant impact on the incidence of RML. Preoperative visceral/peripheral malperfusion, though not statistically significant, was higher in the RML group. A significantly higher incidence of renal complications, including de novo postoperative dialysis, was noticed in the RML group. Other morbidity parameters were also higher in the RML group. There was a significantly higher incidence of AKI in the RML group (90%) than in the non-RML group (25%). All four patients who required de novo dialysis belonged to the RML group. The peak troponin levels were significantly higher in the RML group.

***CONCLUSION***
In this study, we noticed a high incidence of RML after aortic dissection surgery, coupled with an adverse renal outcome and the need for post-operative dialysis. Prompt recognition and management of RML might improve the renal outcome. Further large-scale prospective trials are warranted to investigate the predisposing factors and influence of RML on major morbidity and mortality outcomes.

**Key Words:** Rhabdomyolysis; Ascending aortic dissection surgery; Acute kidney injury; Postoperative renal outcome; Open heart surgery; Type A aortic dissection



**Core Tip:** Renal complications contribute significantly to postoperative morbidity and mortality. Rhabdomyolysis (RML) is one of the etiological factors leading to tubular damage and acute kidney injury (AKI) perioperatively. There is no robust data on RML after ascending aortic dissection (AAD) surgery. Our single-center retrospective study, among AAD patients, evaluated the incidence of RML and its impact on renal outcome-We found a relatively high incidence (64%) of RML coupled with a higher rate of AKI and the need for renal replacement therapy. Further prospective studies are warranted to identify the risk factors of RML and its impact on outcomes.

**Citation:** Sivadasan PC, Carr CS, Pattath ARA, Hanoura S, Sudarsanan S, Ragab HO, Sarhan H, Karmakar A, Singh R, Omar AS. Incidence and outcome of rhabdomyolysis after type A aortic dissection surgery: A retrospective analysis. *World J Crit Care Med* 2025; 14(2): 98004
**URL:** https://www.wjgnet.com/2220-3141/full/v14/i2/98004.htm
**DOI:** https://dx.doi.org/10.5492/wjccm.v14.i2.98004

## INTRODUCTION

Despite ongoing research, the etiology of acute kidney injury (AKI) remains incompletely understood, especially after aortic dissection surgeries. Omar *et al*[1] recently reported the association between rhabdomyolysis (RML) and AKI during cardiac surgery. However, there is no robust data regarding the same in aortic dissection surgeries specifically.

RML is a syndrome characterized by the breakdown of skeletal muscles and the release of toxic intracellular contents into the systemic circulation, causing damage to the renal tubules. Multiple factors are involved in the etiology of RML, predominantly direct trauma to muscles, as seen in crush injuries, burns, or prolonged muscle compression. It can also be associated with congenital disorders of metabolism, certain drugs (anesthetic agents, neuroleptic agents, and statins), infections, and sustained muscle contraction (seizures and prolonged exercise)[2]. Ischemia, followed by reperfusion of the muscle tissue, is a significant contributor to RML[3], which is relevant in the context of this study. The illness might vary in severity from asymptomatic elevations in markers of muscle injury [namely creatinine kinase (CK) and myoglobin] to severe cases associated with extreme enzyme elevation and renal shutdown culminating in dialysis[4]. Postoperative RML is being increasingly recognized as a cause of renal failure. RML is a well-known complication after bariatric, urologic, and orthopedic surgery[5]. One retrospective review that analyzed myoglobin as a marker of myocardial injury post-cardiac surgery, reported myoglobin to be superior to CK for the prediction of the need for renal replacement therapy (RRT) and mortality[6]. Relevant to this context is the difference in the kinetics of clearance of CK

compared to myoglobin: The serum CK begins to rise within 2 to 12 hours following the onset of muscle injury and reaches its maximum within 24 to 72 hours, whereas myoglobin has a much shorter half-life and tends to get cleared as early as 6-8 hours[1-3] The literature linking RML to cardiac surgery was largely confined to isolated case reports[7] until Omar *et al*[1] published their study[1]. The aforementioned study held in our center found an unusually high incidence of RML among the patients undergoing type A aortic dissection repair and laid the foundation for this broader retrospective analysis, specifically looking for a link between RML and aortic surgery.

AKI complicates recovery from cardiac surgery in up to 30% of patients and places them at a 5-fold increased risk of death during hospitalization. The etiology is often multifactorial, and preventive strategies are limited. AKI that requires RRT occurs in 2–5% of patients following cardiac surgery and is associated with a 50% mortality[8].

Aortic surgery is specifically associated with a higher incidence of renal complications than other types of cardiac surgery (with a reported incidence of AKI ranging from 18% to 55%)[9]. A significant number of patients with ascending aortic dissection (AAD) have chronic renal impairment on presentation[10]. The etiology of AKI post-AAD includes renal malperfusion, systemic inflammatory response syndrome, ischemia-reperfusion injury, hypertension, obesity, contrast-induced nephropathy, prolonged operation time, massive blood transfusion, and perioperative hypotension[11]. Renal failure and dialysis after aortic dissection surgery are independent predictors of mortality as per the International Registry of Acute Aortic Dissection. Perioperative predictors for postoperative AKI and RRT, according to various studies, were - estimated preoperative glomerular filtration rate, coronary ischemic time, renal artery involvement in dissection, total arch replacement, preoperative oliguria, longer cardiopulmonary bypass and hypothermic circulatory arrest times, high body mass index (BMI), elevated C reactive protein, perioperative sepsis, and postoperative bleeding requiring a surgical revision[12-16]. Currently, there are no published studies linking RML with aortic dissection except for case reports[17-21]. Myoglobin has reportedly been linked to renal morbidity and mortality after thoracic and thoracoabdominal aortic surgeries[18].

## MATERIALS AND METHODS

In this retrospective study, we reviewed the charts of all patients who underwent surgical repair of type A aortic dissection from 2011 to 2017 in a tertiary care cardiac surgical center in Qatar. We obtained prior approval from the Institutional Review Board (reference number MRC-01-18-073), and a waiver of informed consent for data collection was secured.

### *Data collection*

The patient data were collected anonymously from the electronic medical records using the prescribed data collection sheet. We included all patients who underwent AAD surgery except those who didn't have a post-operative CK/myoglobin value. We also excluded patients with renal dysfunction before surgery.

### *Surgical technique*

In our center, the surgical and anesthetic techniques for AAD surgery follow a standard protocol. We use general anesthesia, endotracheal intubation, and positive pressure ventilation in all cases. The patient is monitored with a 5-lead electrocardiogram, pulse oximetry, nasopharyngeal and rectal temperatures, bilateral radial/brachial arterial lines, cerebral oximetry (using near-infrared spectroscopy-INVOS™; Medtronic Inc, Minneapolis, MN, United States), and transesophageal echocardiography.

After systemic heparinization, arterial access for cardiopulmonary bypass is achieved through femoral, axillary, or ascending aortic cannulation (or a combination). A standard two-stage cannula is placed into the right atrium. Following initiation of cardiopulmonary bypass, the patients are cooled to 18-24 degrees centigrade. Depending on the anatomy of the dissection, the operations performed are a valved conduit with reimplantation of the coronary ostia or an interposition graft with or without complete/partial arch replacement. When circulatory arrest or arch replacement takes place, selective antegrade cerebral perfusion *via* the right axillary artery is used at a flow rate of 6-10 mLs/Kg/min (guided by the right upper limb invasive arterial pressure line and bilateral cerebral oximetry).

Following the surgical repair, complete de-airing, full rewarming, return of cardiac function, and acceptable metabolic parameters, cardiopulmonary bypass is weaned. Residual heparinization is reversed with protamine, and hemostasis is achieved. The administration of procoagulants and blood products is guided by rotational thromboelastometry to promote hemostasis. Inotrope/vasopressor usage is guided by echocardiography-derived cardiac output measurements, as well as arterial pressure readings. The patient is ventilated until the drainage is acceptable and other weaning criteria are satisfied.

### *Laboratory*

It is our department protocol to estimate serum CK and myoglobin levels for all cardiac surgery patients, including aortic dissections, on the first day after surgery and to follow up on these values if they are significantly elevated.

Based on the highest value of CK recorded, our study divided patients into two groups – Group 1- with RML (CK above cut-off levels of 2500 U/L) and Group 2 without RML. The determinants of RML and the impact of the same on the outcome - predominantly renal function were evaluated. Collected data included preoperative and intraoperative variables potentially affecting the renal outcome and incidence of RML: Age, BMI, preoperative creatinine, statin use, the delay from onset of symptoms to surgical intervention, renal artery involvement, peripheral and visceral malperfusion, duration of surgery, bypass time, cross-clamp time, circulatory arrest time, propofol dosage, *etc.* We also collected data

relating to patient outcomes in terms of mortality and morbidity indicators -focusing mainly on the renal outcome.

### Study objectives

The primary objective of this study was to elucidate the incidence of RML following type A aortic dissection surgery and to correlate its severity with the patient outcome -primarily in terms of renal function. Other outcome measures included mechanical ventilation duration, length of intensive care unit (ICU) stay, duration of hospital stay, and mortality. We also proposed to formulate a risk-scoring system based on preoperative and intraoperative variables to predict the development of RML after AAD surgery.

### Study definitions

We followed the same definition for RML used by Omar *et al*[1] in their study. In cardiac surgery, a higher cut-off value (2500 U/L) to diagnose RML is proposed to account for the release of CK from related myocardial injury[1]. Clinical indicators like dark urine, muscle pain, and fluctuation in serum potassium levels were not incorporated in the diagnostic criteria of RML, as these findings are relatively common in post-cardiac surgery settings as a sequela of cardiopulmonary bypass. The patients were divided into two groups based on this diagnostic cutoff: Group A with RML (highest CK value above 2500 U/L) and Group B without RML (highest CK below 2500 U/L). AKI was defined using the KDIGO criteria of AKI-KDIGO criteria which defined AKI as a 0.3 mg/dL (≥ 26.5 μmol/L) Serum Creatinine increase from baseline within 48 hours of surgery, a 1.5 times Serum Creatinine increase from baseline within 7 days of surgery[22]. The original KDIGO criteria also uses urine output below 0.5 mL/kg/hour for 6 hours to define AKI. Urine output criteria were not used to define AKI, following the footsteps of a similar study[9]. Malperfusion was defined as symptoms, physical examination findings, or deranged laboratory results suggesting abnormal perfusion to visceral organs/ extremities[23].

### Statistical analysis

Descriptive statistics were performed as mean and standard deviations for continuous variables and frequency and percentages for categorical variables. $\chi^2$ tests were performed to see the association between the RML *vs* non-RML group and other independent categorical variables. Meanwhile, student *t*-tests (unpaired) were performed to see significant mean differences between the RML *vs* non-RML group with continuous variables. Levene's test for equality of variances was taken into consideration for *P* value. Correlation was performed between CK peak and change in creatinine μmol/liter. Likewise, the correlation was performed for myoglobin values *vs* change in creatinine and CK peak *vs* myoglobin. A correlation *P* value of 0.05 (two-tailed) was considered for a statistically significant level[24]. SPSS 22.0 statistical software was used for the analysis. Clinical and laboratory data were entered into a database (Microsoft Excel 97, Redmond, WA, United States), and statistical analyses were performed (Version 22, IBM Corp., Armonk, NY, United States).

## RESULTS

### Perioperative variables

Forty-four patients underwent aortic dissection surgery in our center during the period 2011-2017. Out of these, seven patients died on the table, and two didn't have post-op CK levels and hence were excluded from the study. Additionally, two patients with preexisting chronic kidney disease were also excluded. Of the remaining 33 patients, 21 patients (63.64%) developed RML based on our diagnostic cut-off value of CK (Group RML), and 12 did not (Group non-RML). The study design is summarized in Figure 1.

Other preoperative and intraoperative factors, like critical preoperative clinical status, congestive heart failure, cannulation method, type of surgical procedure, *etc*., did not have a significant impact on the incidence of RML postoperatively (Table 1). The RML group of patients had a higher BMI, though not statistically significant (*P* value 0.07). Of note, patients with a delayed presentation for surgery tend to develop RML less frequently than those presenting early (*P* value 0.03).

Analyzing the variables, it is apparent that almost all the patients who had a preoperative malperfusion belonged to the RML group (six patients) as against one patient in the non-RML group, the difference was not statistically significant ( *P* value 0.39). Amongst the six malperfusion cases in the RML group, three had peripheral malperfusion, two had visceral, and one had combined visceral and peripheral malperfusion. One case in the non-RML group had peripheral malperfusion. The observed higher incidence of renal artery involvement by dissection in CT angiogram in the RML group also failed to reach statistical significance.

### Outcome measures

There were 2 ICU mortalities in the RML group, while there were none in the non-RML group, with the small number precluding statistical analysis for significance. AKI, as defined by KDIGO criteria, occurred in 22 patients out of 33 study patients (67% of patients). There was a significantly higher incidence of AKI in the RML group (90%) than in the non-RML group (25%), *P* = 0.002. The cumulative occurrence of de novo postoperative dialysis was 12% in the study population and was observed only in the RML group (19% within the group). Apart from significantly higher troponin levels in the RML group (*P* = 0.003), the other morbidity parameters like length of ventilation, inotrope duration, ICU, and hospital length of stay didn't have a statistically significant difference between the groups (Table 2).

Figure 2A depicts the correlation between the change in creatinine in mmol/L (the difference between the peak creatinine and preoperative baseline) and the highest CK levels (U/L). Even though a significant correlation exists

**Table 1 Preoperative and intraoperative characteristics**

| Parameter | Group non-RML, *n* = 12 | Group RML, *n* = 21 | *P* value |
|---|---|---|---|
| Age | 46.75 ± 14.23 | 44.38 ± 11.87 | 0.56 |
| Sex: Female | 2 (16.7) | 1 (4.8) | 0.25 |
| Body mass index | 26.14 ± 3.33 | 32.08 ± 14.92 | 0.07 |
| Delay from the onset of symptoms to hospital admission | 52.81 ± 104.53 | 26.85 ± 33.67 | 0.03 |
| Preoperative Hb in gm/dL | 12.95 ± 1.86 | 13.41 ± 1.80 | 0.97 |
| Preoperative liver function (alanine aminotransferase) unit/liter | 47.33 ± 36.97 | 52.47 ± 39.77 | 0.76 |
| Preoperative ejection fraction | 48.80 ± 9.48 | 49.62 ± 7.07 | 0.81 |
| Preoperative cardiac arrest | 0 (0) | 1 (4.8) | 0.44 |
| Preop renal artery involvement by dissection | 3 (25) | 9 (43) | 0.30 |
| Preop peripheral/visceral malperfusion | 1 (8.3) | 6 (28.5) | 0.39 |
| Preoperative mechanical ventilation | 0 (0) | 1 (4.8) | 0.44 |
| Euroscore-logistic | 20.22 ± 14.83 | 16.27 ± 13.30 | 0.52 |
| Additive euroscore | 11.5 ± 3.46 | 11.05 ± 2.67 | 0.75 |
| Anesthesia time in minutes | 423.83 ± 73.34 | 495.57 ± 128.35 | 0.07 |
| Duration of surgery in minutes | 365.83 ± 70.13 | 433.6 ± 113.00 | 0.15 |
| Cardiopulmonary bypass time in minutes | 200.67 ± 66.11 | 213.43 ± 63.08 | 0.73 |
| Femoral Artery cannulation | 8 (73) | 13 (62) | 0.823 |

Data are *n* (%) or mean ± SD. RML: Rhabdomyolysis.

**Table 2 Outcome variables**

| Parameter | Group non-RML | Group RML | *P* value |
|---|---|---|---|
| Peak creatinine in mmol/L | 113.25 ± 44.79 | 250.01 ± 165.50 | < 0.01 |
| Change in creatinine in mmol/L | 18.75 ± 30.04 | 124.33 ± 129.48 | < 0.01 |
| Peak troponin in ng/mL | 1243.23 ± 794.63 | 6257. 48 ± 9157.77 | < 0.01 |
| New acute kidney injury | 3 (25) | 19 (90) | < 0.01 |
| Mortality | 0 (0) | 2 (9.5) | 0.27 |
| Length of intensive care unit stay in hours | 92.83 ± 84.62 | 120.57 ± 124.73 | 0.45 |
| Length of hospital stay in days | 11.67 ± 6.38 | 16.52 ± 21.96 | 0.35 |
| Duration of mechanical ventilation | 21.42 ± 25.52 | 36.68 ± 40.81 | 0.12 |
| Inotrope duration | 22.33 ± 24.86 | 37.04 ± 47.68 | 0.25 |
| New post-operative dialysis | 0 (0) | 4 (19.04) | 0.04 |

Data are *n* (%) or mean ± SD. RML: Rhabdomyolysis.

between the two ($P = 0.0001$), the correlation was not strong enough, as elicited by a Pearson coefficient of 0.38.

Figure 2B demonstrates the correlation between the change in creatinine in mmol/L (the difference between the peak creatinine and preoperative baseline) and postoperative myoglobin levels (ng/mL). A degree of correlation was noted (like the one observed with CK values) with a correlation coefficient of 0.28 ($P = 0.0001$).

Figure 2C Demonstrates a near linear correlation between CK (U/L) and myoglobin levels (ng/mL) as expected - correlation coefficient 0.61 ($P = 0.0001$). Similarly, there was some weak correlation between the peak troponin levels and change in creatinine, as outlined in Figure 3.

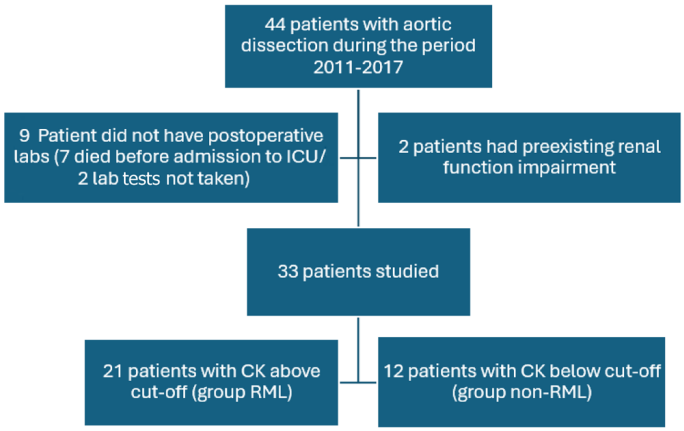


**Figure 1 Study design.** CK: Creatinine kinase; ICU: Intensive care unit; RML: Rhabdomyolysis.

## DISCUSSION

The key findings of this study were: (1) Unusually high prevalence of RML amongst patients with AAD compared to other cardiac surgical patients; (2) Strong association of RML with AKI; (3) Patients with high BMI were more likely to develop RML (even though the association wasn't statistically significant); (4) Higher occurrence of malperfusion in the RML group (again not to the level of statistical significance); and (5) Delayed presentation for surgery was associated with a lesser risk of RML. To the best of our knowledge, no previous studies looked at these associations in Aortic Dissection Surgery.

### *Malperfusion and RML*

Our study substantiates the hypothesis that aortic dissection surgery is associated with an unusually high incidence of RML (63%) compared to general cardiac surgical cases reported by Omar *et al*[1] (8.41%). The possible explanation for this predisposition could be occult ischemia to the lower limb following femoral cannulation, ischemia to paraspinal muscles due to malperfusion, and prolonged positioning due to a comparatively longer duration of the surgery[1,17]. It is postulated that the lumbar arteries that supply the paraspinal muscles may become compromised due to hypoperfusion or occlusion from aortic cross-clamping, obstruction of the vessels within the false lumen of the dissection, or athero-embolic phenomena. The resultant ischemia causes edema and necrosis of the paraspinal muscles, subsequently increasing the pressure within the paraspinal compartment[17]. We did observe a higher incidence of malperfusion (peripheral/visceral) amongst the RML group, though the difference didn't reach statistical significance. Malperfusion is known to have a significant impact on patient outcomes in terms of mortality, and management strategies tailored to the presence and severity of malperfusion are still in the process of evolution[18]. GERAADA (German Registry for Acute Aortic Dissection Type A) risk scoring system incorporates visceral and peripheral malperfusion as one of the determinants of mortality[25]. However, studies analyzing the association between malperfusion and AKI/RML are sparse in the literature. Sandridge *et al*[26], in their review, outlined the management strategies of malperfusion.

Miller *et al*[18], in an observational trial of 109 patients requiring thoracic/thoracoabdominal aortic repair, reported a dialysis requirement of 38% in the postoperative period. This study's dialysis rate was high, probably because of the liberal inclusion criteria used. Myoglobin levels were strongly predictive of postoperative renal dysfunction, which also agreed with our observations. However, this study was done in patients undergoing thoraco-abdominal aortic aneurysm surgery without the use of cardiopulmonary bypass. Still, risk factors like femoral cannulation and prolonged positioning associated with muscle damage are common in both patient cohorts. The same group has also reported the relationship between loss of Somato-Sensory Evoked Potential signals in the cannulated leg and adverse renal outcome, indicating leg ischemia as a potential contributing factor for RML[27].

The proposed risk factors for RML, like the presence of diabetes or hypertension, didn't have a significant impact on the incidence of RML in our study. Femoral cannulation could theoretically be associated with a higher incidence of RML because of the potential for limb ischemia, but our study couldn't demonstrate a difference in outcome in terms of RML with femoral cannulation.

Patients who developed RML were more obese compared to the non-RML group, but this difference failed to achieve statistical significance. Zhao *et al*[9] reported a higher incidence of AKI (66.7%) among obese patients with type A aortic dissection. They found elevated preoperative serum Creatinine level and 72-hour drainage volume as independent predictors of AKI, but they didn't investigate the contribution of RML to the development of kidney injury. The association between BMI and the risk of RML has been well-documented in bariatric and trauma surgeries as well[28,29].

### *Renal outcome*

The incidence of AKI in our study population was 67%, which is slightly higher than that reported in the literature for AAD cases. It is noteworthy that the incidence of de novo postoperative dialysis (12%) in our study is comparable to the previous literature[12-14]. This difference in AKI incidence could be attributed to the variation in the definition of AKI used in various studies, surgical techniques, demographic characteristics, and institutional protocols for the initiation of

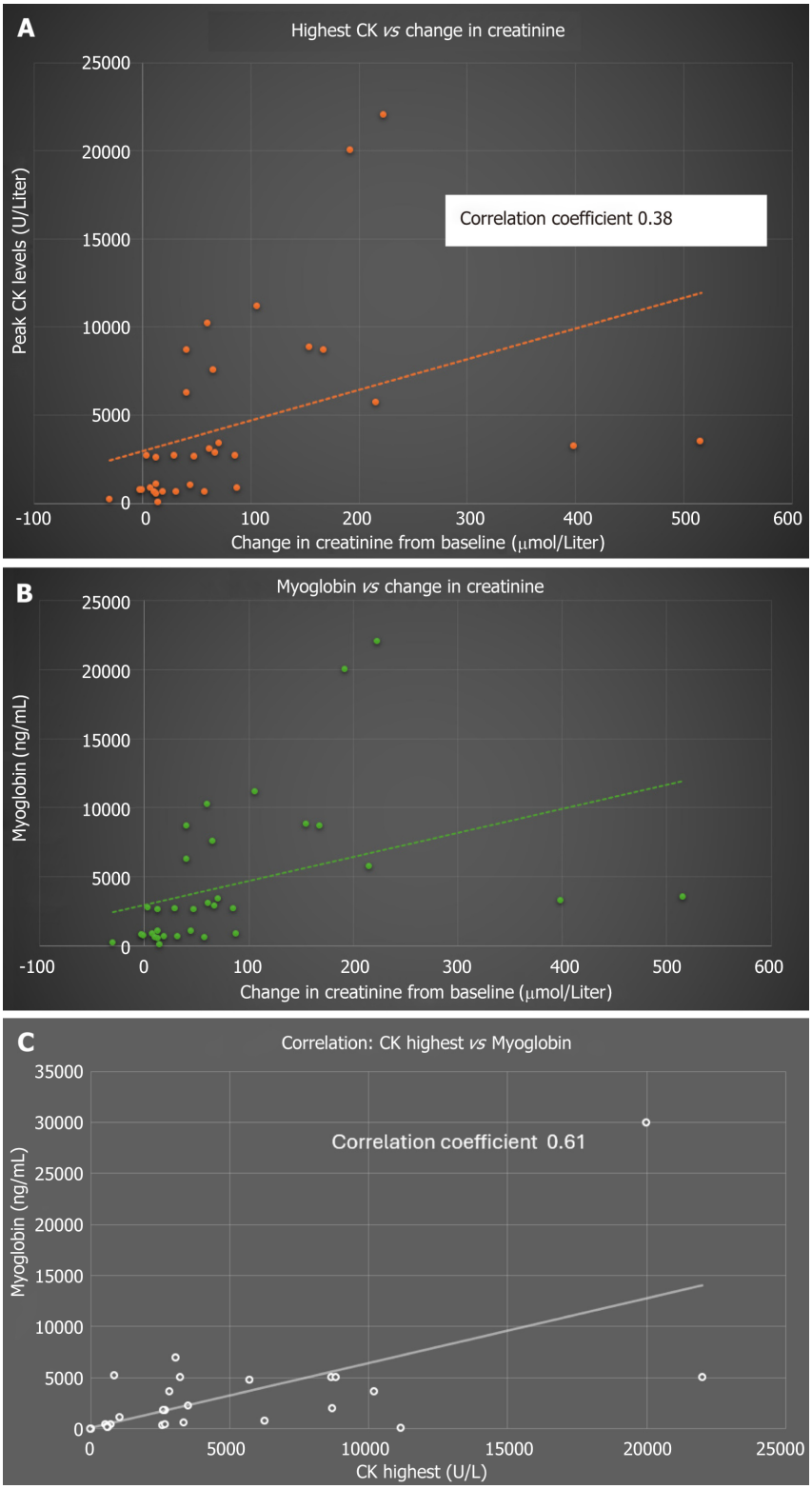


**Figure 2 Correlation data-renal function and rhabdomyolysis markers.** A: Correlation between change in creatinine and creatinine kinase (CK) levels. Correlation between change in creatinine in mmol/liter (peak creatinine-baseline creatinine) on the X axis and peak CK levels U/L on the Y axis; B: Correlation between change in creatinine and myoglobin levels. Correlation between change in creatinine mmol/liter (peak creatinine-baseline creatinine) on the X axis and peak myoglobin levels ng/mL on the Y axis; C: Correlation between peak CK (U/L) and myoglobin levels (ng/mL). Correlation between peak CK values on the X axis and peak myoglobin levels on the Y axis.

CVVHD. Ko *et al*[12], in their study, which included 375 patients, reported an incidence of 44.0% AKI, out of which 9% required temporary dialysis and a further 3% progressed to end-stage renal disease. They also observed that the mortality and major adverse cardiovascular and cerebrovascular events correlated significantly with the severity of AKI. Duration of Extracorporeal circulation, BMI, perioperative peak serum C-reactive protein concentration, renal malperfusion, and perioperative sepsis were found to be risk factors for AKI.

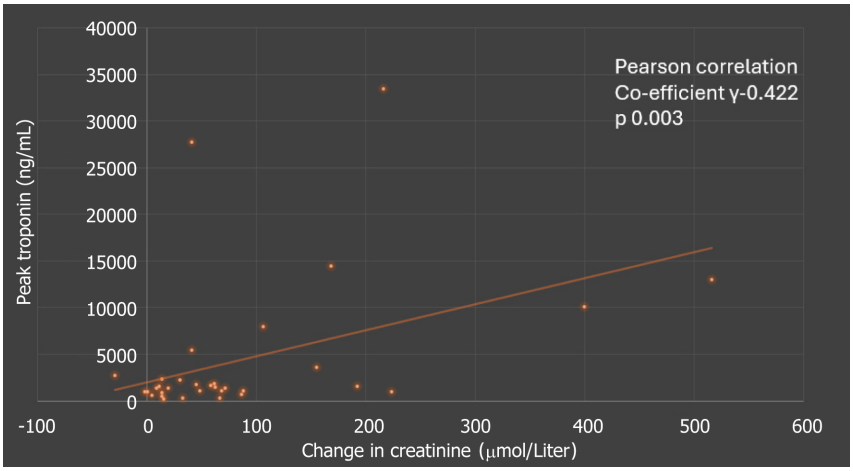


**Figure 3 Peak troponin *vs* change in creatinine-correlation between change in creatinine (peak creatinine-baseline creatinine) on the X axis and peak troponin levels on the Y axis.**

Imasaka *et al*[13], in their retrospective review, reported an incidence of 15.8% of RRT. The proposed risk factors for postoperative RRT were estimated glomerular filtration rate, coronary ischemic time, and total arch replacement. Sansone *et al*[14] observed a 37.8% incidence of AKI needing CVVHD after type A aortic dissection. Preoperative oliguria, longer Cardiopulmonary bypass /circulatory arrest times, and postoperative bleeding requiring a surgical revision were implicated as the predominant risk factors for the adverse outcome. Similarly, Ghincea *et al*[15] reported a 32% incidence of AKI following aortic arch surgery. In the multivariable analysis, significant predictors of AKI were history of hypertension and CPB duration. Kato *et al*[30] reported hypertension, type A aortic dissection, and low platelet levels as risk factors for AKI after aortic dissection surgery.

### *RML and high cardiac markers*

One interesting observation from the study was that, despite using a higher cut-off value for CK to define RML (to account for the myocardial injury associated with cardiac surgery), we observed a significantly higher value of troponin in the RML group. This was not associated with other signs of myocardial damage, as evidenced by an insignificant difference in inotropic requirements (Table 2). This difference could be explained by the fact that in RML, cardiac enzymes may be elevated, unrelated to the degree of muscle damage[31-33]. Yet another explanation could be the higher incidence of AKI in the RML group. AKI is known to be associated with delayed clearance of troponins, as reported by Omar *et al*[34]. Myoglobin, as an alternative marker for RML, has the advantage of being unaffected by the degree of myocardial injury. However, the faster clearance from the circulation makes myoglobin less reliable than CK in quantifying RML[3,5]. Hence, it was not used as the primary marker of RML in our study.

### *Relation between delay in presentation and severity of RML*

Yet another finding that evolved from the review was that RML was more frequent in those patients who underwent early surgical intervention. One possible explanation could be that some degree of stabilization of perfusion is established as the disease progresses towards chronicity. Yet another possibility is some form of ischemic preconditioning, which offers protection against ischemia in chronic dissection cases[35]. However, we were not able to find any literature justifying this argument.

### *Preventive strategies*

Interventions like aggressive fluid loading and forced diuresis titrated to a urine output of 200-300 mL/hour might help to mitigate the severity of renal failure in patients at risk of RML[5]. Due to the retrospective nature of the study, we were not able to assess the impact of these interventions on the renal outcome. However, considering the findings from our prior publication[1], we are focusing on the above line of management in patients at risk of RML, especially when there is unexplained hyperkalemia in the immediate postoperative period.

This study has several limitations- The sample size was small. The study was retrospective, which precluded further standardization of the design. We could not incorporate clinical indicators of RML in the diagnostic criteria due to the context of cardiac surgery. The study was not powered enough to do a multivariate analysis to investigate the risk factors for RML. We believe that a higher sample size would probably have enabled us to establish a significant association between malperfusion and RML.

## CONCLUSION

In this study, we found a high incidence of RML after aortic dissection surgery, which paralleled an adverse renal

outcome. Further large-scale prospective trials are warranted to investigate the predisposing factors (predominantly organ malperfusion) and influence of RML on major morbidity and mortality outcomes.

## ACKNOWLEDGEMENTS

The authors are immensely indebted to all members of the Hamad Medical Corporation for fulfilling the requirements for research. The authors thank all members of the Cardiothoracic Surgery department, Cardiac Anesthesia and CTICU division, Heart Hospital, Hamad Medical Corporation, Qatar, for the required data and patient pool. The authors also thank every member of the medical research department of Hamad Medical Corporation for their support throughout this project. Our sincere thanks to Dr. Abulaziz Alkhulaifi, Chairman of the Cardiothoracic Surgery Department, for his administrative support.

## FOOTNOTES

**Author contributions:** Omar AS, Sivadasan PC, Singh R designed and conceptualized the study and performed patient enrollment screening; Sivadasan PC, Sudarsanan S, Hanoura S, Ragab HO, Sarhan H, Karmakar A completed the data collection and charting; Sivadasan PC, Omar AS, Sudarsanan S, Hanoura S contributed to data management and interpretation, formulating discussion and conclusion; Carr CS, Pattath AA reviewed scientific content and English grammar of the manuscript, provided administrative support; Singh R did the statistical analysis.

**Supported by** Hamad Medical Corporation, No. MRC-01-18-073.

**Institutional review board statement:** The Corporate Institutional Review Board approved the study with reference number MRC-01-17-058.

**Informed consent statement:** Since it was a retrospective review, the ethics committee granted a waiver of informed consent. However, the patient data were deidentified and then stored anonymously using computer-generated codes.

**Conflict-of-interest statement:** All authors declared no conflict of interest in relation to this publication.

**Data sharing statement:** The manuscript-related data and materials are available in Hamad Medical Corporation Medical Research Center database. Subject to approval from the medical research center of Hamad Medical Corporation, data will be made available on request to the corresponding author.



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**S-Editor:** Liu H
**L-Editor:** Filipodia
**P-Editor:** Zhang YL

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World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

*World J Crit Care Med* 2025 June 9; 14(2): 99975

DOI: 10.5492/wjccm.v14.i2.99975

ISSN 2220-3141 (online)

SYSTEMATIC REVIEWS

# Management of critical care emergencies in children with autism spectrum disorder

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**Specialty type:** Critical care medicine

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**
**Scientific Quality:** Grade C
**Novelty:** Grade B
**Creativity or Innovation:** Grade B
**Scientific Significance:** Grade B

**P-Reviewer:** Ye S

**Received:** August 4, 2024
**Revised:** December 13, 2024
**Accepted:** December 30, 2024
**Published online:** June 9, 2025
**Processing time:** 206 Days and 23.9 Hours

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## Abstract

*BACKGROUND*

Managing critical care emergencies in children with autism spectrum disorder (ASD) presents unique challenges due to their distinct sensory sensitivities, communication difficulties, and behavioral issues. Effective strategies and protocols are essential for optimal care in these high-stress situations.

***AIM***
To systematically evaluate and synthesize current evidence on best practices for managing critical care emergencies in children with ASD. The review focuses on key areas, including sensory-friendly environments, communication strategies, behavioral management, and the role of multidisciplinary approaches.

***METHODS***
A comprehensive search was conducted across major medical databases, including PubMed, Embase, and Cochrane Library, for studies published between 2000 and 2023. Studies were selected based on their relevance to critical care management in children with ASD, encompassing randomized controlled trials, observational studies, qualitative research, and case studies. Data were extracted and analyzed to identify common themes, successful strategies, and areas for improvement.

***RESULTS***
The review identified 50 studies that met the inclusion criteria. Findings highlighted the importance of creating sensory-friendly environments, utilizing effective communication strategies, and implementing individualized behavioral management plans. These findings, derived from a comprehensive review of current evidence, provide valuable insights into the best practices for managing critical care emergencies in children with ASD. Sensory modifications, such as reduced lighting and noise, visual aids, and augmentative and alternative communication tools, enhanced patient comfort and cooperation. The involvement of multidisciplinary teams was crucial in delivering holistic care. Case studies provided practical insights and underscored the need for continuous refinement of protocols.

***CONCLUSION***
The review emphasizes the need for a tailored approach to managing critical care emergencies for children with ASD. Sensory-friendly adjustments, effective communication, and behavioral strategies supported by a multidisciplinary team are integral to improving outcomes. Despite progress, ongoing refinement of care practices and protocols is necessary. This ongoing process addresses remaining challenges and engages healthcare professionals in continuous improvement of care for children with ASD in critical settings.

**Key Words:** Autism spectrum disorder; Critical care emergencies; Sensory sensitivities; Behavioral management; Communication strategies; Multidisciplinary approach; Pediatric intensive care; Emergency protocols



**Core Tip:** This comprehensive systematic review highlights the importance of tailored approaches in managing critical care emergencies in children with autism spectrum disorder (ASD). The study examines various case studies by examining the need for sensory-friendly environments, effective communication strategies, and multidisciplinary care. Key strategies include minimizing sensory overload, using visual aids, involving caregivers, and implementing structured routines. The findings underscore the significance of individualized care plans and the potential for improved outcomes through targeted interventions and training programs for healthcare providers. This review advocates for continuous refinement of protocols to better meet the unique needs of children with ASD in emergency settings.

**Citation:** Al-Beltagi M, Saeed NK, Bediwy AS, Alhawamdeh R, Elbeltagi R. Management of critical care emergencies in children with autism spectrum disorder. *World J Crit Care Med* 2025; 14(2): 99975
**URL:** https://www.wjgnet.com/2220-3141/full/v14/i2/99975.htm
**DOI:** https://dx.doi.org/10.5492/wjccm.v14.i2.99975

## INTRODUCTION

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by persistent deficits in social communication and interaction, as well as restricted, repetitive patterns of behavior, interests, or activities. Symptoms of ASD typically emerge in early childhood and vary widely in severity, reflecting the spectrum nature of the disorder[1]. Recent estimates from the Centers for Disease Control and Prevention indicate that ASD affects approximately 1 in 54 children in the United States. The prevalence of ASD has increased over recent decades due to heightened awareness and refined diagnostic criteria[2]. The cause of ASD is multifactorial, involving both genetic and environmental components. Genetic predisposition is significant, with studies highlighting a higher concordance rate among monozygotic twins than dizygotic twins, though no single gene has been pinpointed as causative[3]. Additionally, environmental factors, such as advanced parental age, prenatal exposure to certain medications or infections, and birth complications, may also play a role[4].

Children with ASD face significant challenges in social communication. They often struggle to start and maintain conversations, understand social cues, and use gestures and facial expressions. They may prefer solitary activities and have difficulty forming and maintaining relationships[5]. Additionally, they exhibit restricted and repetitive behaviors, such as repetitive movements, strict adherence to routines, and intense interest in specific topics or objects. Sensory sensitivities are also common, with children showing hyper- or hypo-reactivity to sensory stimuli like sounds, lights, textures, or smells. This can lead to significant anxiety and behavioral issues[6].

Critical care emergencies are acute medical conditions immediately threatening a patient's life, requiring rapid and intensive medical intervention. These include severe respiratory or cardiovascular events, neurological crises, major trauma, sepsis, anaphylaxis, metabolic disturbances, significant hemorrhage, and acute poisoning or overdose[7]. Managing these emergencies necessitates prompt assessment, stabilization, and treatment by a multidisciplinary team, often within an intensive care unit (ICU), to prevent deterioration and improve survival outcomes. Children with ASD have a high prevalence of medical comorbidities such as epilepsy, gastrointestinal issues, and sleep disorders that can lead to acute medical crises that require immediate and intensive care[8]. Addressing critical care emergencies in children with ASD is paramount due to their unique challenges, which include significant communication barriers, sensory sensitivities, and behavioral issues. These factors complicate the management of medical emergencies, necessitating specialized approaches[9]. This article aims to outline key considerations and strategies for managing critical care emergencies in children with ASD, ensuring their unique needs are met effectively. This includes addressing communication barriers, sensory sensitivities, behavioral challenges, medical considerations, and the importance of a multidisciplinary approach to provide compassionate and comprehensive care during emergencies.

## MATERIALS AND METHODS

This comprehensive systematic review aimed to synthesize existing knowledge on managing critical care emergencies in children with ASD. The methodology adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and reproducibility. We conducted a structured search across multiple databases, including PubMed, Embase, Scopus, and the Cochrane Library, using a combination of relevant keywords and Medical Subject Headings terms. The search terms included "Autism Spectrum Disorder" "critical care" "emergency management" "ICU" "sensory sensitivities" "behavioral challenges" "communication strategies" and "multidisciplinary approach". Filters were applied to include only English-language articles published between January 2000 and July 2024.

We included peer-reviewed articles that specifically addressed critical care management for pediatric patients with ASD, focusing on sensory sensitivities, communication strategies, behavioral management, and multidisciplinary approaches. Eligible studies encompassed randomized controlled trials, observational studies, systematic reviews, meta-analyses, case studies, and guidelines. Studies were excluded if they focused on non-ASD populations or adult patients, addressed non-emergency or outpatient care settings, lacked sufficient methodological quality or peer review, or were opinion pieces, editorials, or conference abstracts.

The study selection process involved two independent reviewers who screened titles and abstracts to identify potentially relevant studies. Then, full-text articles were reviewed for eligibility based on the inclusion and exclusion criteria. Discrepancies were resolved through discussion or consultation with a third reviewer. Two reviewers independently extracted data using a standardized data collection form. The data included study design, sample size, interventions, outcomes, and main findings.

The PRISMA flowchart (Figure 1) illustrates the study selection process. Of the 255 records initially identified, 123 articles were assessed for eligibility. Detailed reasons for exclusion included duplicate setting ($n$ = 35), no full text available ($n$ = 47), non-ASD population ($n$ = 14), non-emergency or outpatient settings ($n$ = 13), and insufficient methodological quality ($n$ = 12). Ultimately, 50 studies were included in the final analysis. Synthesized findings from these articles were categorized into four key thematic areas: Sensory-friendly environments, communication strategies, behavioral management, and multidisciplinary approaches.

The quality of the included studies was evaluated using appropriate tools, including the Cochrane Risk of Bias Tool for randomized controlled trials, the Newcastle-Ottawa Scale for observational studies, and the Critical Appraisal Skills Program checklist for qualitative studies. Case studies were assessed for their clarity, relevance, and potential contributions to practical guidelines. Quantitative analyses were performed where possible, including pooled estimates and descriptive statistics to identify trends. Meta-analytic methods were applied to evaluate the efficacy of interventions across studies, focusing on key outcomes such as reducing sensory overload and improving patient cooperation. The review adhered to ethical guidelines, ensuring a transparent and reproducible process without the need for ethical approval.

## RESULTS

Our comprehensive systematic review identified and analyzed 123 studies that met the inclusion criteria. These included 50 research studies, 53 review articles, 12 systematic reviews and meta-analyses, 3 case studies, 3 editorials, and 2 guidelines and policies on managing critical care emergencies in children with ASD (Figure 1). The findings were organized into key thematic areas: Sensory-friendly environments (12 articles), communication strategies (12 articles), behavioral management (13 articles), and the role of multidisciplinary approaches (13 articles).

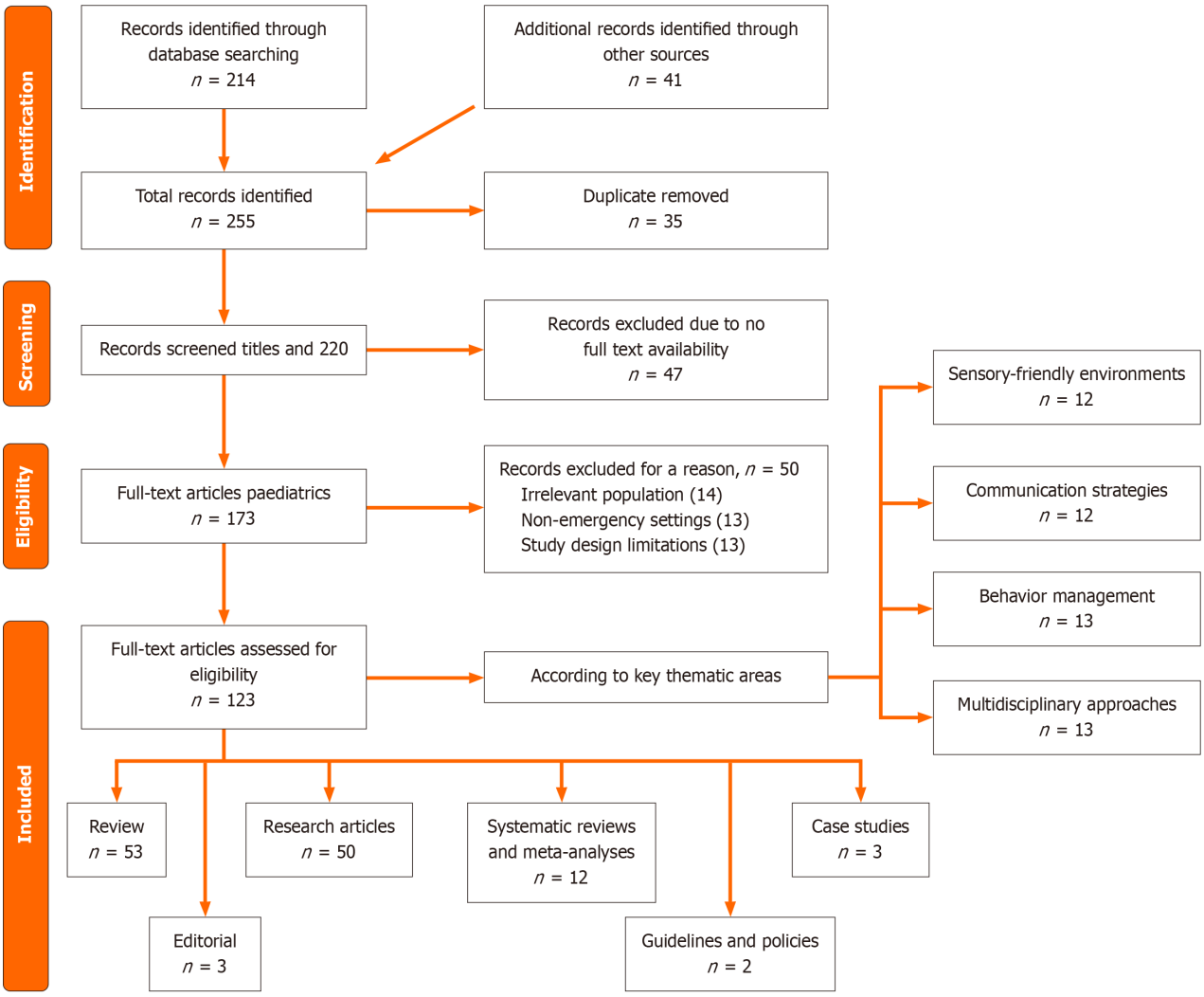


**Figure 1 The flow chart of the included studies.**

### *Sensory-friendly environments*

The review highlighted that creating a sensory-friendly environment in the critical care setting is crucial for managing children with ASD. Studies consistently reported that modifications such as dimming lights, reducing noise levels, and using noise-canceling headphones significantly decreased anxiety and distress in these children. Environmental adjustments, such as providing familiar comfort items and creating quiet, designated areas for retreat, were also effective in reducing sensory overload and improving patient comfort. Table 1 shows the studies on providing Sensory-Friendly Environments in the critical care setting.

### *Communication strategies*

Effective communication emerged as a critical factor in managing critical care for children with ASD. Simplified language, visual aids, and the use of augmentative and alternative communication (AAC) tools were frequently mentioned as essential for facilitating understanding and cooperation. The involvement of caregivers in the communication process was consistently emphasized, with studies showing that caregiver presence and input helped calm the child and provide valuable insights into their needs (Table 2).

### *Behavioral management*

The review found that behavioral management strategies, including de-escalation techniques and structured routines, were pivotal in handling emergencies involving children with ASD. Techniques such as calm verbal interactions, providing clear explanations of procedures, and using visual schedules were reported to help manage behavioral outbursts and reduce stress. Multiple studies underscored the importance of individualized behavioral plans tailored to the child's specific needs and preferences (Table 3).

### *Multidisciplinary approaches*

The role of multidisciplinary teams in managing critical care for children with ASD was a recurring theme. The review found that collaboration among pediatricians, intensivists, nurses, behavioral therapists, occupational therapists (OTs),

**Table 1 Selected studies on sensory-friendly environments**

| Ref. | Type of study | No. and age of patients | Focus | Key findings |
|---|---|---|---|---|
| Crasta *et al*[19], 2020 | Comparative observational study | 69 children, 6-10 years | Sensory processing | Highlighted differences in sensory attention profiles between ASD and neurotypical children |
| Gonçalves and Monteiro[20], 2023 | Review | | Auditory sensory alterations | Systematic review showing auditory hyperreactivity in ASD |
| Gentil-Gutiérrez *et al*[21], 2021 | Cross-sectional | 60 children, 3-10 days | Sensory environment and ASD | Emphasized the importance of a sensory-friendly design to reduce distress in ASD children |
| Riquelme *et al*[22], 2016 | Comparative cross-sectional study | 57 children, 4-15 years | Tactile sensitivity | Found abnormal tactile responses linked to increased anxiety in clinical settings |
| Trevarthen and Delafield-Butt[24], 2013 | Review | | Sensory movement in ASD | Advocated movement-based therapies for sensory integration |
| Pfeiffer *et al*[25], 2011 | Randomized controlled trial | 37 children, 6-12 years | Sensory integration therapy | Showed positive effects on sensory regulation in ASD |
| Nair *et al*[26], 2022 | Case study | 87 children, 6-16 years | Lighting and colors | Identified that soft lighting and neutral colors reduced overstimulation |
| Ikuta *et al*[27], 2016 | Case-control | 21 children, 4–16 years | Noise-canceling headphones | Demonstrated that these devices significantly improved coping in noisy environments |
| Thompson and Tielsch-Goddard[28], 2014 | Prospective, descriptive, quality improvement project | 43 children | ASD surgical care | Recommended pre-surgery sensory modifications |
| Lönn *et al*[29], 2023 | Explorative qualitative study | 26 children, 6-15 years | Weighted blankets | Found significant improvements in anxiety and sleep |
| Drahota *et al*[31], 2012 | Review | | Hospital sensory environments | Showed improved outcomes through sensory-focused interventions |
| Giarelli *et al*[37], 2014 | Descriptive observational study | Environmental stimuli | Sensory obstacles in emergency care | Identified barriers to providing sensory-friendly environments |

ASD: Autism spectrum disorder.

speech and language pathologists (SLPs), dietitians, and mental health professionals resulted in more effective and holistic care. Multidisciplinary approaches facilitated integrated care plans and ensured that all aspects of the child's needs were addressed comprehensively (Table 4).

We provided 5 case studies to provide practical insights into real-world applications of these strategies. They successfully managed sensory sensitivities, behavioral challenges, and communication barriers in critical care settings. However, case studies also revealed limitations and challenges, such as variability in the implementation of strategies and the need for further refinement of protocols. Overall, the review highlighted that while significant progress has been made in understanding and addressing the unique needs of children with ASD in critical care settings, there remains a need for ongoing refinement of practices and protocols. The evidence supports a holistic, individualized approach that incorporates sensory-friendly modifications, effective communication strategies, and the collaborative efforts of a multidisciplinary team to improve outcomes for children with ASD in critical care.

## DISCUSSION

### *Communication strategies in critical care for children with autism*

Effective communication is essential when managing critical care emergencies for children with ASD. Recognizing and addressing their unique needs through tailored communication strategies ensures their safety, comfort, and cooperation during medical interventions[10].

### *The importance of communication in emergencies*

In critical care settings, effective communication directly influences the quality of care and outcomes for children with ASD. These children often face significant challenges with traditional communication methods, making it difficult to express their needs, pain, or discomfort[11]. A lack of effective communication can exacerbate anxiety, lead to non-compliance, and intensify the medical emergency. By adopting appropriate communication strategies, healthcare providers can alleviate the child's stress, improve cooperation, and ensure that critical information is accurately exchanged[12]. This enhances immediate care and helps build trust and a sense of security between the child, their caregivers, and the medical team.

**Table 2 Selected studies on communication strategies**

| Ref. | Study type | No. and age of patients | Focus | Key findings |
|---|---|---|---|---|
| Araujo *et al*[10], 2022 | Qualitative multi-case study | 4 adolescents and 4 health care professionals | Communication strategies | Demonstrated that tailored strategies improved patient cooperation |
| Johnson *et al*[11], 2023 | Review | | Pain communication scoping review | Showed gaps in assessing pain communication in ASD children |
| Bell and Condren [12], 2016 | Review | | Empowering communication | Demonstrated improved outcomes with structured language |
| Randi *et al*[13], 2010 | Review | | Teaching reading to ASD children | Advocated clear, concise instructions to improve learning |
| Arthur-Kelly *et al* [14], 2009 | Review | | Visual supports | Highlighted benefits of visual aids for communication in ASD |
| Swanson *et al*[15], 2020 | Review | | Caregiver speech | Showed that caregiver involvement enhanced language comprehension |
| Amato and Fernandes[17], 2010 | Comparative observational study | 20 children, 2-10 years | Verbal and non-verbal communication | Explored interactive communication methods |
| Tsang *et al*[18], 2019 | Review | | Primary care management | Advocated early intervention with communication-focused strategies |
| Forbes and Yun[36], 2023 | Review | | Visual support in activities | Highlighted increased participation with visual aids |
| Knight and Sartini [45], 2015 | Review | | ASD comprehension strategies | Identified effective strategies for education settings |
| Palese *et al*[46], 2021 | Two-phase validation study | 141 children and adolescents, 6–16 years | Pain communication tools | Validated tools for pain assessment in non-verbal ASD children |

ASD: Autism spectrum disorder.

**Table 3 Selected studies on behavioral management**

| Ref. | Study type | No. and age of patients | Focus | Key findings |
|---|---|---|---|---|
| Newcomb and Hagopian[34], 2018 | Review | | Severe behaviors in ASD | Showed efficacy of behavioral plans in emergency settings |
| Wright *et al*[43], 2016 | Review | | Social Stories™ | Demonstrated reduced challenging behaviors |
| Hillgrove-Stuart *et al* [40], 2013 | Randomized controlled trial | 99 toddlers | Distraction techniques | Highlighted the effectiveness of toys for reducing stress |
| Schuetze *et al*[41], 2017 | Review | | Reinforcement learning | Explored reinforcement learning strategies for ASD |
| Giarelli *et al*[37], 2014 | Descriptive observational study | Environmental stimuli | Behavioral barriers in care | Identified challenges in managing ASD behaviors |
| Spears and McNeely [39], 2019 | Quality improvement study | Pediatric populations of all sizes and ages within the organization | Crisis prevention | Advocated comprehensive de-escalation training |
| Kronish *et al*[38], 2024 | Simulation-based educational study | 22 teenage patients | Agitated ASD patients | Recommended standardized de-escalation protocols |
| Abright[42], 2020 | Editorial | | Reducing aggression | Showed positive outcomes with behavior modification |
| Balasco *et al*[6], 2020 | Review | | Sensory-driven behaviors | Highlighted links between sensory abnormalities and behaviors |
| Elbeltagi *et al*[30], 2023 | Review | | Play therapy | Identified significant behavioral benefits |

ASD: Autism spectrum disorder.

**Table 4 Selected studies on multidisciplinary approaches**

| Ref. | Study type | No. and age | Focus | Key findings |
|---|---|---|---|---|
| Straus *et al*[9], 2019 | Review | | Environmental considerations | Showed improved outcomes with collaborative care |
| Thompson and Tielsch-Goddard[28], 2014 | Prospective, descriptive, quality improvement project | 43 children | Surgery management | Demonstrated benefits of team coordination |
| Al-Beltagi[8], 2021 | Review | | Medical comorbidities | Highlighted comorbidities' impact on multidisciplinary care |
| Kanter, 2011[7] | Review | | Public health emergencies | Advocated integrated strategies for critical scenarios |
| Newcomb and Hagopian [34], 2018 | Review | | Multidisciplinary interventions | Showed success in reducing problem behaviors |
| Crasta *et al*[19], 2020 | Comparative observational study | 69 children, 6-10 years | Sensory collaboration | Highlighted team efforts in sensory integration |
| Balasco *et al*[6], 2020 | Review | | Tactile interventions | Demonstrated importance of occupational therapy in ASD |
| Drahota *et al*[31], 2012 | Review | | Sensory-focused outcomes | Integrated outcomes from collaborative sensory strategies |
| Almandil *et al*[3], 2019 | Review | | Genetic factors | Highlighted the role of genetics in care strategies |
| Al-Beltagi *et al*[1], 2023 | Review | | Viral comorbidities | Advocated multidisciplinary management in ASD crises |

ASD: Autism spectrum disorder.

### *Simplified language and visual aids*

Children with ASD often respond well to simplified and straightforward language. Clear, concise instructions devoid of medical jargon help them understand what is happening and what is expected of them[13]. For example, instead of saying, "An intravenous line is necessary to administer fluids and medications" a more accessible approach would be, "We will place a small tube in your arm to help you feel better". Visual aids such as pictures, diagrams, and step-by-step visual schedules can complement verbal communication, making complex procedures easier to grasp. For instance, a picture sequence illustrating a blood draw can prepare the child for each step, reducing anxiety and making the process more manageable[14].

### *Involvement of caregivers*

Caregivers play a vital role in supporting children with ASD during emergencies. Familiar with the child's unique communication style, preferences, and potential triggers, caregivers can offer critical insights and assistance. Their involvement can help healthcare providers interpret the child's nonverbal cues, understand specific needs, and provide emotional reassurance[15]. Moreover, having a trusted caregiver present during interventions significantly reduces the child's anxiety and promotes cooperation. Encouraging caregivers to participate actively—by explaining procedures in a way the child understands, comforting them during interventions, or helping to calm distress—ensures consistency in support and enhances the child's overall experience in the high-stress environment of critical care[16].

### *Nonverbal cues and gestures*

Nonverbal communication plays a key role in interacting with children with ASD, who often rely heavily on body language and facial expressions to express their needs and emotions. Healthcare providers should remain observant of the child's nonverbal signals, such as body posture, facial expressions, or behavioral changes, to assess their level of comfort, pain, or anxiety[17]. For example, a child who cannot verbally articulate pain might exhibit signs such as grimacing, withdrawal, or unusual quietness. Recognizing and responding to these cues enables timely and appropriate care. Additionally, using simple gestures and demonstrations can enhance understanding. Pointing to a body part or mimicking an action provides a clear, visual representation of instructions, facilitating better communication and engagement[18].

### *Sensory sensitivities in children with autism in the critical care setting*

**Common sensory sensitivities in children with ASD:** Children with ASD often exhibit heightened sensory sensitivities, which can significantly influence their ability to cope in a critical care setting. These sensitivities may involve exaggerated or diminished responses to sensory stimuli, including noise, light, touch, texture, taste, and smell. Common sensory sensitivities in children with ASD include auditory, visual, tactile, olfactory, gustatory, proprioceptive, and vestibular sensitivities[19].

Auditory sensitivities, such as a heightened response to loud or sudden noises from alarms, medical equipment, or the bustling hospital environment, can trigger anxiety, agitation, or meltdowns[20]. Bright or flickering lights and the visual clutter of a busy hospital room may contribute to sensory overload as children with ASD struggle to process visual input effectively[21]. Tactile sensitivities, such as discomfort with hospital gowns, IV lines, or certain medical instruments, may lead to distress or aversion to physical contact and medical procedures[22]. Similarly, strong smells from cleaning agents, medications, or food, as well as unusual tastes, can cause nausea or discomfort, affecting a child's willingness to eat or participate in procedures[23]. Sensitivities to movement, such as being transferred on a stretcher or experiencing positional changes, can be unsettling, with children exhibiting either heightened or diminished awareness of body position and movement, impacting their comfort and response to care[24].

**Strategies to minimize sensory overload:** Minimizing sensory overload is essential for effectively managing critical care in children with ASD. Strategies include environmental adjustments, creating calm and quiet spaces, controlling sensory inputs, maintaining predictable routines, and utilizing sensory tools[25]. Environmental adjustments might involve reducing noise by turning off unnecessary alarms or using sound-dampening materials, as well as dimming or adjusting lights to create a softer visual atmosphere. Reducing visual clutter by organizing the room and minimizing distractions can also help[26].

Providing a quiet or dedicated retreat space where the child can decompress is another important strategy. This space should minimize sensory stimuli and offer a calm, safe environment to help the child regulate[27]. For auditory sensitivities, noise-canceling headphones or earplugs can be provided. Dimmable lamps or light filters may address visual sensitivities, while soft, familiar textures like blankets or stuffed animals can ease tactile discomfort. Establishing predictable routines and preparing the child for medical procedures through clear explanations can reduce stress and improve cooperation[28]. Gradual desensitization to medical equipment and procedures through short, non-invasive exposures can help the child acclimate to new sensory experiences. Sensory tools such as fidget toys, chewable items, or weighted blankets offer additional comfort and support self-regulation during medical interventions[29].

**Role of familiar comfort items:** Familiar comfort items, such as favorite toys, blankets, or other personal belongings, can play a significant role in reducing anxiety and providing reassurance for children with ASD in critical care settings[30]. These items help create a sense of security and stability in the unfamiliar hospital environment, allowing the child to feel connected to their home and routine[31]. Many comfort items also possess sensory qualities that can help regulate sensory input; for example, a soft blanket or stuffed animal may provide tactile comfort, mitigating sensitivity to other physical sensations.

In addition to offering emotional reassurance, familiar items can serve as a positive distraction during medical procedures, helping the child cope with stress and focus on something comforting and recognizable[32]. These items also reinforce a sense of routine and predictability, which is especially valuable for children with ASD. By implementing strategies to minimize sensory overload and incorporating familiar comfort items, healthcare providers can create a more supportive and accommodating environment. This approach not only reduces stress for the child but also enhances their ability to cope with medical interventions, contributing to better immediate experiences and long-term outcomes in critical care settings[33].

### *Behavioral challenges in children with autism in the critical care setting*

**Predictability and structure in emergency settings:** Children with ASD often rely on predictability and structure to feel secure. However, emergency settings' chaotic and unpredictable nature can pose significant challenges for them. Behavioral difficulties such as anxiety, meltdowns, aggression, and self-injurious behaviors are often exacerbated by sudden changes, unfamiliar faces, and unexpected procedures commonly encountered in emergency care[34].

To mitigate these challenges, healthcare providers should implement strategies that introduce predictability and structure into the emergency care process whenever feasible. Establishing consistent steps for each procedure is a key approach. This includes explaining what will happen, identifying who will be involved, and providing an estimated timeline[35]. Visual schedules can further enhance predictability by outlining the steps of the emergency care process using pictures or diagrams, helping the child anticipate what will happen next and reducing their anxiety. Additionally, clear, simple, and concrete explanations of procedures are essential. Avoiding medical jargon and breaking information into manageable parts can facilitate understanding[36].

Whenever possible, assigning consistent staff members to work with the child can build familiarity and trust. The presence of familiar faces can alleviate stress and behavioral issues[9]. Minimizing unnecessary noise and activity is also crucial to creating a calm and quiet environment. Reducing sensory stimuli helps the child feel more secure and less overwhelmed, promoting a smoother emergency care experience[37].

**De-escalation techniques:** De-escalation techniques are vital for managing behavioral challenges in children with ASD during critical care emergencies. These approaches help calm the child, prevent distress from escalating, and ensure safety for both the child and the healthcare providers[38].

Effective communication is fundamental. Speaking calmly, softly, and neutrally, while avoiding raising one's voice or showing frustration, is crucial since children with ASD are highly sensitive to emotional tones. Similarly, non-threatening body language, such as maintaining a relaxed posture and avoiding sudden movements, can help put the child at ease [39].

Distraction techniques can redirect the child's focus away from distressing stimuli. Engaging the child with a favorite toy, activity, or discussing a preferred topic can provide relief and cooperation[40]. Offering simple choices, such as "Would you like to hold your teddy bear or look at the picture book while we do this?", can give the child a sense of control and reduce anxiety. Positive reinforcement is another effective tool; praising and rewarding the child for staying

calm or following instructions, even for small achievements, can encourage desired behaviors[41]. Finally, allowing time-outs or breaks in a quiet space when the child becomes overwhelmed provides an opportunity for them to regain control before proceeding with medical interventions[42].

**Preparing children for procedures:** Preparing children with ASD for medical procedures is essential to reducing anxiety, preventing behavioral outbursts, and ensuring cooperation[34]. Proper preparation benefits both the child and the healthcare team by facilitating smoother interactions. Social stories are an effective method for explaining procedures step-by-step. These short, personalized narratives describe what will happen, why it is necessary, and how the child can cope. Social stories can be presented in written, visual, or video formats[30]. Providing visual and verbal explanations of the procedure, such as using pictures, diagrams, or videos accompanied by simple, clear verbal descriptions, can further enhance understanding[43].

Role-playing or practice sessions with toy medical equipment can help familiarize the child with the procedure. Gradually introducing the child to the medical environment and equipment in a non-threatening manner before the actual procedure can also alleviate anxiety[9]. Involving caregivers in the preparation process is another critical strategy. Caregivers can explain procedures in a familiar and reassuring manner, provide comfort, and model calm behavior, thereby easing the child's apprehension[44]. Providing clear instructions and setting expectations for behavior are equally important. Explaining what the child needs to do, how long the procedure will take, and what will happen afterward ensures the child is informed and less likely to feel overwhelmed[45]. By implementing these strategies, healthcare providers can create a supportive and effective environment, reducing stress and improving cooperation and outcomes for children with ASD in critical care settings.

### *Medical considerations for children with autism in the critical care setting*

**Pain assessment tools tailored for children with ASD:** Assessing pain in children with ASD can be particularly challenging due to their unique communication difficulties and varying pain thresholds. Standard pain assessment tools may not always be effective, highlighting the need for tailored approaches to evaluate and manage pain accurately[46]. Tools such as the Non-Communicating Children's Pain Checklist and the face, legs, activity, cry, consolability scale are valuable for assessing pain in non-verbal children or those with limited communication abilities. To identify pain, these tools rely on behavioral and physiological indicators, including facial expressions, body movements, and vocalizations[47].

When feasible, self-report tools adapted for children with ASD, such as simplified visual analog scales (VAS) or the Faces Pain Scale-Revised, can be effective. These tools should be explained using clear, concrete language supported by visual aids to enhance understanding[48]. Involving parents or caregivers in pain assessment is critical, as they can provide key insights into subtle behavioral changes that may indicate pain. Caregivers often have the best understanding of the child's typical behavior and reactions to discomfort. Consistent use of the same pain assessment tools allows for tracking pain levels over time, aiding in identifying patterns and ensuring effective management[49].

**Medication sensitivities and considerations:** Children with ASD may exhibit unique responses to medications, including heightened sensitivity to certain drugs and atypical side effects. Safe and effective pharmacological management requires careful consideration and customization. Medication dosages should be tailored based on the child's weight, age, and specific medical history. Variations in drug metabolism among children with ASD often necessitate adjustments to standard dosing regimens[50].

Monitoring for adverse effects is essential, as children with ASD may be unable to articulate discomfort or side effects. Behavioral changes, alterations in appetite or sleep patterns, and physical symptoms should be closely observed to detect potential medication-related issues[51]. Efforts should be made to minimize polypharmacy by limiting the use of multiple medications simultaneously, thereby reducing the risk of drug interactions and side effects. When polypharmacy is unavoidable, potential interactions must be carefully considered, with close monitoring for any adverse outcomes[52].

Medication guides and visual aids can improve understanding of the purpose and administration of medications for both the child and their caregivers. Clear explanations help alleviate anxiety and enhance adherence to medication regimens[53]. For children with ASD who may have atypical reactions to sedatives and anesthetics, pre-procedural planning should involve consultation with pediatric anesthesia specialists to ensure safe and effective sedation.

**Special dietary needs:** Children with ASD often have specific dietary preferences and restrictions, which can influence their nutritional status and overall health. Addressing these needs in the critical care setting is crucial for providing optimal care[54]. Thorough assessment of the child's dietary preferences, aversions, and existing dietary restrictions—including food allergies, intolerances, or specific diets such as gluten-free or casein-free—is essential[55]. Collaboration with dietitians is necessary to develop individualized nutritional plans that cater to the child's needs. This may involve modifying hospital meals, providing specialized dietary supplements, or implementing enteral feeding methods when required[56].

Sensory sensitivities related to food, such as texture, taste, and smell, should be considered to ensure the child's comfort. Providing familiar and preferred foods whenever possible can help maintain nutritional intake and reduce stress [57]. Adequate hydration should be prioritized, especially if the child has aversions to drinking water or other liquids. Offering preferred beverages and closely monitoring fluid intake are key strategies to prevent dehydration[58]. When feasible, it is beneficial to involve parents or caregivers in meal planning and preparation. Caregivers can provide invaluable insights into the child's dietary habits and preferences, ensuring the child receives appropriate and acceptable nutrition during their critical care stay[59].

### *Multidisciplinary approach for children with autism in the critical care setting*

**Importance of a multidisciplinary team:** A multidisciplinary team approach is essential for addressing the complex needs of children with ASD in critical care settings. Integrating expertise from various healthcare professionals ensures a holistic approach to care, addressing medical, behavioral, sensory, and communication challenges[59]. Collaborative efforts among team members improve the quality of care and the child's overall experience in critical care environments [60].

This approach prioritizes the physical, emotional, and psychological well-being of children with ASD. By addressing these diverse aspects, the multidisciplinary team minimizes fragmented care, reduces stress for the child and family, and fosters seamless communication and coordination among specialists[61]. Such coordinated care avoids redundancies and potential misunderstandings while aligning interventions to provide consistent and effective treatment[62].

Leveraging the diverse expertise of team members allows for creating individualized treatment plans that consider each child's unique needs and preferences. Regular and open communication within the team facilitates informed decision-making, ensuring that care is both cohesive and responsive to the child's evolving needs[62,63].

**Staff training in ASD-specific strategies:** To optimize outcomes for children with ASD, all staff members involved in their care must receive training in ASD-specific strategies. This training equips healthcare providers with the knowledge and tools required to manage the unique challenges associated with ASD, thereby enhancing the quality of care and improving the child's experience[64].

Training should provide an overview of ASD's core characteristics, including common comorbidities and the variability of symptoms across individuals. Emphasis should be placed on effective communication techniques, such as using simplified language, incorporating visual aids, and interpreting non-verbal cues. Strategies for managing behavioral challenges, such as de-escalation techniques and maintaining predictability and structure, are also critical[65, 66].

Additionally, staff should be trained to recognize and accommodate sensory sensitivities, minimizing sensory overload through adjustments in the critical care environment. Compassionate and empathetic care must remain central, with staff gaining insight into the perspectives of children with ASD and their families to foster trust and cooperation[21].

**Roles of different team members:** A multidisciplinary team for managing critical care emergencies in children with ASD typically includes various healthcare professionals, each playing a vital role in providing comprehensive care[67]. Key team members and their roles include pediatricians and intensivists, nurses, behavioral therapists, OT, SLP, dietitians, psychologists and psychiatrists, care coordinators, and family members and caregivers[68]. Pediatricians and Intensivists: Oversee the child's medical management, coordinating care plans, and making critical treatment decisions. They ensure that the medical interventions are tailored to the child's specific needs and consider any ASD-related factors[69]. Nurses provide direct care and are often the primary point of contact for the child and family. They implement care plans, monitor the child's condition, administer medications, and provide support during medical procedures. Nurses play a critical role in observing and responding to the child's needs, including recognizing signs of pain or distress[70].

Behavioral therapists, including Applied Behavior Analysis (ABA) therapists, are critical in managing and modifying challenging behaviors. They develop and implement individualized behavior management plans and provide support during interventions to reduce stress and anxiety for the child[71]. OT focus on addressing the sensory and functional needs of children with ASD. They evaluate sensory sensitivities and devise strategies to mitigate sensory overload. This may include recommending sensory tools or implementing environmental modifications to create a more supportive critical care environment[72].

SLPs address the unique communication needs of children with ASD by creating and implementing tailored communication strategies. They may introduce AAC methods to facilitate understanding and expression, ensuring the child can effectively communicate with caregivers and medical staff[73]. Dietitians ensure that the child's nutritional needs are met by considering special dietary preferences, restrictions, and sensory sensitivities. They collaborate with the multidisciplinary team to create individualized nutrition plans and provide guidance on feeding strategies to accommodate the child's specific needs[74].

Mental health professionals, including psychologists and psychiatrists, focus on supporting the emotional and psychological well-being of the child. They assess and manage co-occurring mental health conditions, such as anxiety or depression, and provide counseling and behavioral interventions to help the child cope with the critical care environment [75]. Care coordinators or case managers play a pivotal role in ensuring seamless communication among team members. They organize care plans and address all aspects of the child's needs. By acting as liaisons between the family and the healthcare team, they help families navigate the complexities of the healthcare system and ensure coordinated care[76].

Family members and caregivers are vital members of the care team. Their intimate understanding of the child's preferences, behaviors, and calming strategies provides invaluable insights for personalized care. Their involvement also ensures continuity of care and offers essential emotional support to the child during their critical care journey. The collaboration of these diverse specialists, each contributing their expertise, enables the development of personalized treatment plans that enhance outcomes for children with ASD in critical care settings[77].

### *Protocols for children with autism in the critical care setting*

Developing specific protocols for the emergency care of children with ASD is critical to addressing their unique needs effectively. These protocols establish standardized guidelines, enabling healthcare providers to deliver consistent and efficient care, thereby reducing variability in practice and improving patient outcomes[78]. Protocols should include clear guidelines for the initial assessment of children with ASD in emergency settings (Table 5)[79]. This includes identifying ASD-specific signs and symptoms, understanding the child's baseline behaviors, and gathering input from caregivers

**Table 5 Protocol that includes guidelines for the initial assessment of children with autism spectrum disorder in the emergency setting[1]**

| Protocol component | Guidelines |
|---|---|
| Recognizing ASD | Identify children with a known diagnosis of ASD from medical records or caregiver reports |
| | Observe for signs of ASD if no diagnosis is provided (*e.g.*, communication difficulties, repetitive behaviors) |
| Baseline behaviors | Gather caregiver information about the child's baseline behaviors and typical responses |
| | Note any deviations from the child's usual behavior that may indicate distress or pain |
| Communication preferences | Determine the child's preferred method of communication (*e.g.*, verbal, visual aids, sign language) |
| | Use simplified language, clear and concise instructions, and visual aids to enhance understanding |
| Involving caregivers | Involve caregivers in the assessment process to provide comfort and familiar support |
| | Ask caregivers to interpret the child's behaviors and preferences |
| Sensory sensitivities | Assess for sensory sensitivities (*e.g.*, to noise, lights, touch) based on caregiver input and observation |
| | Minimize sensory overload by reducing noise, dimming lights, and avoiding unnecessary physical contact |
| Behavioral triggers | Identify potential triggers for behavioral challenges from caregivers (*e.g.*, certain noises, activities) |
| | Avoid known triggers and implement strategies to maintain a calm environment |
| Pain assessment | Use tailored pain assessment tools suitable for children with ASD, such as the Non-Communicating Children's Pain Checklist or the face, legs, activity, cry, consolability scale |
| | Observe for non-verbal indicators of pain (*e.g.*, changes in facial expression, body movements) |
| Medical history | Obtain a detailed medical history, including any comorbid conditions, medications, and allergies |
| | Consider the child's history of reactions to medications and previous medical procedures |
| Individualized care plan | Develop an individualized care plan based on the initial assessment findings and caregiver input |
| | Ensure the care plan addresses communication needs, sensory sensitivities, and behavioral management |
| Documentation | Document all findings from the initial assessment, including baseline behaviors, communication preferences, and any identified triggers |
| | Update the care plan and share relevant information with all team members involved in the child's care |

[1]This table format helps systematically organize the guidelines for the initial assessment of children with autism spectrum disorder in an emergency setting, ensuring that each crucial aspect is covered comprehensively.
ASD: Autism spectrum disorder.

regarding effective communication and calming strategies. Effective communication is a cornerstone of care for children with ASD. Protocols should provide detailed guidance on communication techniques (Table 6)[80]. These may involve using simplified language, visual aids, and non-verbal cues to enhance understanding. Additionally, caregiver involvement in communication should be emphasized to foster cooperation and comfort for the child.

Behavioral challenges can be particularly complex in critical care settings. Protocols should offer strategies for managing these challenges, including de-escalation techniques and approaches to prevent sensory overload (Table 7)[81]. Step-by-step instructions for addressing meltdowns and maintaining a calm, predictable environment are vital to these guidelines. Tailored pain assessment tools for children with ASD are essential for proper management. Protocols should detail methods for interpreting behavioral and physiological indicators of pain and outline strategies for safe and effective pain management, with attention to potential medication sensitivities (Table 8)[82].

Developing comprehensive guidelines for the safe use of sedation and anesthesia in children with ASD is crucial. These guidelines should emphasize the importance of consulting with pediatric anesthesiologists, tailoring dosages to individual needs, and closely monitoring for atypical or adverse reactions (Table 9)[83]. Addressing the dietary needs of children with ASD requires specific protocols to manage feeding challenges and ensure nutritional adequacy (Table 10). These protocols should include assessing dietary preferences and restrictions, providing appropriate nutritional support, and involving dietitians as integral members of the care team[84].

Ensuring thorough post-emergency care is vital to the child's recovery. Follow-up protocols should be established to monitor recovery, address any ongoing medical or behavioral concerns, and support caregivers throughout the process (Table 11)[85]. Training healthcare providers in ASD-specific strategies is a foundational component of effective care. Protocols for regular staff training sessions should be implemented to ensure that all team members are equipped with the necessary knowledge and skills to care for children with ASD effectively (Figure 2, Table 12)[86].

### *Follow-up care for children with autism in the critical care setting*

Post-emergency care for children with ASD is pivotal in ensuring a smooth transition from acute care to recovery, minimizing the risk of future emergencies. After stabilization, continuous monitoring of vital signs and pain levels is

**Table 6 An example of communication protocol for children with autism spectrum disorder in the critical care and emergency setting[1]**

| Protocol component | Guidelines |
|---|---|
| Simplified language | Use clear, concise, and simple language to explain instructions |
| | Avoid medical jargon and complex phrases |
| Visual aids | Utilize visual aids, such as pictures, symbols, and written instructions, to support communication |
| | Prepare visual schedules to outline steps of procedures or routines |
| Non-verbal cues | Pay attention to non-verbal cues from the child, such as body language, facial expressions, and gestures |
| | Respond to these cues with appropriate actions or adjustments to care |
| Caregiver involvement | Involve caregivers in the communication process as they understand the child's needs and preferences best |
| | Allow caregivers to interpret and explain the child's behavior and needs |
| Repetition and patience | Repeat instructions and information as necessary to ensure understanding |
| | Be patient and give the child extra time to process information and respond |
| Clear instructions | Give step-by-step instructions for procedures, breaking down tasks into smaller, manageable parts |
| | Use positive language to explain what will happen, avoiding negative or fear-inducing terms |
| Calm and soothing tone | Maintain a calm, soothing, and reassuring tone of voice |
| | Avoid sudden changes in tone or volume that might startle the child |
| Consistency | Ensure consistency in communication methods among all staff members interacting with the child |
| | Use the same phrases and visual aids to prevent confusion and build trust |
| Personal space | Respect the child's personal space and avoid unnecessary physical contact |
| | Approach the child slowly and from the front, avoiding sudden movements |
| Preparation and explanation | Prepare the child for procedures by explaining what will happen in advance |
| | Use visual aids and simple language to describe each step of the process |
| Feedback and reassurance | Provide positive feedback and reassurance throughout interactions to build confidence and cooperation |
| | Acknowledge the child's efforts and successes in following instructions or coping with procedures |
| Crisis communication | Develop and follow specific communication strategies for managing behavioral crises or meltdowns |
| | Use calming techniques and de-escalation strategies as needed |

[1]This table organizes the guidelines for effective communication with children with autism spectrum disorder in an emergency setting.
ASD: Autism spectrum disorder.

necessary, with particular attention to behavioral and physiological indicators of distress[87]. Creating a calm and supportive environment, with dimmed lights, reduced noise, and familiar comfort items, helps reduce anxiety and fosters a sense of safety. Clear and simple communication should be used, employing visual aids and social stories to explain past events and outline the next steps[88]. Caregivers are essential in providing comfort and stability, emphasizing their involvement throughout the recovery process.

Utilizing ASD-specific pain assessment tools is critical to determine pain levels and guide appropriate management accurately. Medication plans should account for any sensitivities or adverse reactions previously experienced[11]. Upon discharge, caregivers should receive detailed, easy-to-understand instructions, including guidance on medication administration, follow-up care schedules, and early signs of potential complications. Developing a tailored emergency plan for caregivers is vital, outlining key contacts and step-by-step actions for managing future crises[90].

Supporting caregivers is a cornerstone of effective follow-up care. Offering training in ASD-specific emergency management, including recognizing early signs of distress and handling sensory sensitivities, equips caregivers with essential skills[91]. Providing resources on effective communication, behavioral management, and educational strategies fosters their ability to support the child. Emotional support through counseling services and peer support groups should be readily available to caregivers, acknowledging the psychological demands they face[92]. Encouraging caregivers to prioritize their well-being and access respite care when needed can help sustain their ability to provide quality care. Additionally, practical assistance in navigating healthcare systems, managing follow-up appointments, accessing therapies, and handling insurance or financial concerns is essential. Information about community resources, including special education services, therapy programs, and financial aid options, should also be readily accessible[93].

Long-term management involves a multidisciplinary approach to ensure holistic and continuous care. Regular follow-up appointments with pediatricians, specialists, and therapists should address the child's health, development, and any

**Table 7 Behavioral management protocols for children with autism spectrum disorder in the emergency setting[1]**

| Protocol component | Guidelines |
|---|---|
| Predictability and structure | Maintain a predictable routine to help reduce anxiety |
| | Use visual schedules to outline the sequence of events and procedures |
| Calm environment | Create a calm, quiet, and low-stimulation environment to minimize stress |
| | Reduce noise, dim lights, and limit the number of people in the room |
| De-escalation techniques | Use calm, soothing tones and slow, deliberate movements to help de-escalate heightened behaviors |
| | Avoid confrontation and allow the child space and time to calm down |
| Preparing children for procedures | Explain procedures in advance using simple language and visual aids |
| | Allow the child to ask questions and express concerns, providing clear and reassuring responses |
| Positive reinforcement | Use positive reinforcement to encourage desired behaviors |
| | Offer praise, rewards, or preferred activities for cooperation and calm behavior |
| Behavioral triggers | Identify and avoid known triggers for challenging behaviors, as informed by caregivers |
| | Develop individualized plans to prevent and manage potential triggers |
| Sensory breaks | Provide opportunities for sensory breaks and quiet time as needed |
| | Use sensory tools (*e.g.*, noise-canceling headphones, weighted blankets) to help the child self-regulate |
| Comfort items | Allow the use of familiar comfort items (*e.g.*, toys, blankets) to provide reassurance and reduce anxiety |
| Visual supports | Utilize visual supports, such as social stories and visual cues, to explain expectations and procedures |
| | Use visual timers to help the child understand the duration of activities or waiting periods |
| Crisis intervention | Develop and follow specific crisis intervention plans for managing severe behavioral crises |
| | Ensure all staff are trained in safe and effective crisis intervention techniques |
| Caregiver involvement | Involve caregivers in behavioral management strategies, as they know the child's preferences and effective calming techniques |
| | Collaborate with caregivers to develop and implement individualized behavior plans |
| Documentation | Document all behavioral incidents, triggers, and successful interventions |
| | Use this information to adjust care plans and improve future management strategies |

[1]This table organizes the guidelines for effective behavioral management of children with autism spectrum disorder in an emergency setting.

residual issues stemming from the emergency[69]. Evidence-based behavioral therapies, such as ABA, should be integrated into the child's care plan. These therapies can be complemented by individualized education plans and early intervention services to address developmental needs[94].

A collaborative multidisciplinary team—including pediatricians, neurologists, psychologists, OT, speech therapists, and social workers—should coordinate care, ensuring effective communication among members[95]. Medications should be reviewed periodically to optimize the management of comorbidities, ensuring a favorable balance between benefits and potential side effects[96]. A personalized emergency plan should be developed and regularly updated, with all caregivers, educators, and family members trained to implement it effectively[97]. Enhancing the child's quality of life is a fundamental aspect of long-term care. Efforts should promote participation in social, recreational, and educational activities, address barriers to inclusion, and foster opportunities for meaningful engagement[98].

By implementing these comprehensive follow-up care strategies, providing robust caregiver support, and prioritizing long-term management, healthcare providers can significantly improve outcomes for children with ASD who experience critical care emergencies. This compassionate, multidisciplinary approach ensures that the unique needs of these children are met with expertise, empathy, and continuity.

### *Criteria for an ideal ICU caring for children with ASD*

Designing an ideal ICU for children with ASD requires a comprehensive approach to address their distinct sensory, communication, and behavioral needs[99]. The primary objectives are to minimize sensory overload, enhance communication, ensure safety and comfort, and foster family involvement. The ICU environment should be sensory-friendly. Soft, dimmable lighting can reduce the discomfort caused by bright lights, which may overwhelm children with ASD[8]. Natural light should be incorporated wherever possible, with windows equipped with blinds or shades to allow caregivers to control light intensity. Soundproofing measures, such as noise-reducing materials and quiet alarms, should

**Table 8 Pain assessment tools, guidelines for interpreting behavioral and physiological indicators of pain, and safe and effective pain management strategies for children with autism spectrum disorder[1]**

| Protocol component | Guidelines |
|---|---|
| Pain assessment tools | |
| Non-communicating children's pain checklist | Use to assess pain in non-verbal children. Includes categories like vocal expressions, social behavior, and body/limb movements |
| Face, legs, activity, cry, consolability scale | Use for children who can't communicate their pain. Scores behaviors in five categories to determine pain level |
| Faces pain scale-revised | Use for children who can understand and point to facial expressions that correspond to their pain level |
| Visual analog scale | Use for children capable of understanding and marking a point on a line that represents their pain intensity |
| Behavioral indicators of pain | |
| Vocalizations | Moaning, crying, or screaming |
| Facial expressions | Grimacing, frowning, or tightly closed eyes |
| Body movements | Restlessness, rigidity, flinching, or guarding specific areas |
| Changes in social behavior | Withdrawal, irritability, or aggression |
| Changes in routine activities | Refusal to eat, sleep disturbances, or reluctance to move |
| Physiological indicators of pain | |
| Heart rate | Increased heart rate |
| Respiratory rate | Increased respiratory rate |
| Blood pressure | Elevated blood pressure |
| Sweating | Increased sweating (diaphoresis) |
| Muscle tension | Observed muscle tension or stiffness |
| Pain management strategies | |
| Non-pharmacological interventions | Distraction techniques (*e.g.*, videos, games), comfort items, relaxation techniques (*e.g.*, deep breathing, guided imagery) |
| Pharmacological interventions | |
| Acetaminophen | Use for mild to moderate pain, considering dosage adjustments for weight and age |
| Non-steroidal anti-inflammatory drugs (*e.g.*, ibuprofen) | Use for mild to moderate pain and inflammation, monitoring for potential gastrointestinal or renal side effects |
| Opioids | Use for severe pain, with careful monitoring for side effects and potential for dependence |
| Local anesthetics | Use topical or local anesthetics for procedural pain management |
| Alternative therapies | Consider options such as physical therapy, occupational therapy, or acupuncture as adjuncts to pain management |
| Medication sensitivities | |
| Allergies | Verify and document any known medication allergies or adverse reactions |
| Comorbid conditions | Consider the impact of comorbid conditions on medication choice and dosing |
| Drug interactions | Review all current medications to avoid potential drug interactions |
| Monitoring and reassessment | |
| Regular monitoring | Regularly reassess pain levels using appropriate tools, and adjust management strategies as needed |
| Documentation | Document pain assessments, interventions, and outcomes in the child's medical record |
| Family and caregiver input | Involve caregivers in the pain assessment and management process to provide additional insights and support |

[1]This table format provides a comprehensive approach to assessing and managing pain in children with autism spectrum disorder.

**Table 9 Sedation and anesthesia protocols for children with autism spectrum disorder in the emergency setting[1]**

| Protocol component | Guidelines |
|---|---|
| Pre-procedure assessment | |
| Medical history | Obtain a detailed medical history, including any previous reactions to sedation or anesthesia |
| | Review comorbid conditions, current medications, and allergies |
| Behavioral assessment | Assess baseline behaviors and any known triggers for anxiety or behavioral issues |
| | Consult with caregivers for effective calming strategies and past experiences with sedation |
| Preparation for sedation/anesthesia | |
| Communication | Explain the procedure to the child using simple language and visual aids |
| | Involve caregivers to help explain and reassure the child |
| Familiar items | Allow the child to have familiar comfort items during the preparation phase |
| Pre-medication | Consider using anxiolytics or mild sedatives as premedication to reduce anxiety and agitation |
| Sedation/anesthesia plan | |
| Tailored dosage | Adjust dosages based on the child's weight, age, and medical history |
| | Use the lowest effective dose to achieve the desired level of sedation or anesthesia |
| Medication choice | Select sedatives and anesthetics with a favorable safety profile and minimal side effects |
| | Avoid medications known to exacerbate behavioral issues or cause adverse reactions in children with ASD |
| Multidisciplinary Consultation | Involve a pediatric anesthesiologist and other specialists as needed to develop a comprehensive plan |
| During sedation/anesthesia | |
| Monitoring | Continuously monitor vital signs, including heart rate, respiratory rate, blood pressure, and oxygen saturation |
| | Observe for any signs of distress, adverse reactions, or changes in behavior |
| Behavioral observation | Monitor behavioral responses to sedation, noting any unusual or unexpected reactions |
| Post-procedure care | |
| Recovery monitoring | Monitor the child closely during the recovery phase for any delayed reactions or complications |
| | Ensure a calm and quiet environment to facilitate smooth recovery |
| Pain management | Provide appropriate pain relief post-procedure, considering the child's pain threshold and sensitivities |
| | Use non-pharmacological methods in conjunction with medication for effective pain management |
| Caregiver involvement | Allow caregivers to be present during recovery to provide comfort and reassurance |
| | Educate caregivers on what to expect during the recovery period and signs of potential complications |
| Documentation and follow-up | |
| Detailed documentation | Document all sedation/anesthesia process aspects, including medications used, dosages, and responses |
| | Record any adverse reactions or complications and the interventions used to address them |
| Follow-up care | Schedule follow-up appointments to monitor the child's recovery and address any ongoing concerns |
| | Provide caregivers with contact information for post-procedure questions or emergencies |

[1]This table format organizes the guidelines for sedation and anesthesia protocols for children with autism spectrum disorder in an emergency setting.
ASD: Autism spectrum disorder.

be implemented to minimize auditory stimuli from medical equipment, alarms, and conversations[100]. Communication systems should also be designed to operate quietly.

Maintaining a comfortable temperature is crucial, so adjustable temperature controls should be readily available. Walls should be painted in calming hues, such as soft blues, greens, or neutrals, to promote relaxation and avoid overstimulation[101]. Bright or highly contrasting colors should be avoided. Additionally, designated areas should be established within the ICU where children can retreat if they become overwhelmed[102]. These spaces should include sensory-friendly items such as weighted blankets, soft seating, and calming tools to provide a sense of comfort.

Private rooms or areas specifically designated for children with ASD are essential to minimize the stress and sensory overload caused by the busy ICU environment[103]. These rooms should be spacious enough to accommodate caregivers

**Table 10 Nutritional and dietary protocols for children with autism spectrum disorder in the emergency setting[1]**

| Protocol component | Guidelines |
|---|---|
| Initial assessment | |
| Medical and dietary history | Obtain a detailed medical history, including any comorbid conditions and current medications |
| | Review the child's dietary intake, food preferences, and known allergies or intolerances |
| Caregiver input | Consult with caregivers to understand the child's typical eating habits, favorite foods, and any aversions |
| Anthropometric measurements | Measure and document the child's weight, height, and BMI to assess nutritional status |
| Nutritional needs | |
| Caloric requirements | Calculate the child's caloric needs based on age, weight, and clinical condition |
| Macronutrient distribution | Ensure a balanced intake of carbohydrates, proteins, and fats according to the child's needs and preferences |
| Micronutrient needs | Monitor for any signs of micronutrient deficiencies and address them through diet or supplementation |
| Special dietary considerations | |
| Food sensitivities and allergies | Avoid known allergens and foods that the child is sensitive to, as reported by caregivers |
| Texture and consistency | Consider the child's food texture and consistency preferences, providing options that are easier to consume |
| Gastrointestinal issues | Address any gastrointestinal issues (*e.g.*, constipation, diarrhea) with appropriate dietary modifications |
| Meal planning and provision | |
| Regular mealtimes | Maintain regular meal and snack times to provide structure and predictability for the child |
| Familiar foods | Offer familiar and preferred foods to encourage intake and reduce stress |
| Nutrient-dense foods | Prioritize nutrient-dense foods to ensure adequate nutrition even with limited intake |
| Feeding strategies | |
| Positive reinforcement | Use positive reinforcement to encourage the child to try new foods or maintain healthy eating habits |
| Minimal distractions | Create a calm and distraction-free environment during meals to help the child focus on eating |
| Adaptive utensils | Provide adaptive utensils and cups if needed to facilitate independent eating |
| Nutritional monitoring | |
| Regular monitoring | Monitor the child's nutritional intake, weight, and overall health status regularly |
| Adjustments as needed | Adjust the dietary plan based on the child's evolving needs and any changes in their medical condition |
| Supplementation | |
| Vitamin and mineral supplements | Provide vitamin and mineral supplements to address deficiencies or support overall health |
| Special formulas | Consider using specialized nutritional formulas if the child has significant dietary restrictions or needs |
| Caregiver education and support | |
| Dietary guidance | Educate caregivers on the importance of balanced nutrition and how to meet their child's dietary needs. |
| Meal preparation | Provide tips and resources for preparing nutritious meals that align with the child's preferences and needs |
| Emergency planning | Develop an emergency plan for situations where usual foods are unavailable, including suitable alternatives |
| Documentation | |
| Detailed records | Document all aspects of the child's nutritional and dietary assessment, interventions, and outcomes |
| Care plan updates | Regularly update the child's care plan to reflect any dietary needs or preferences changes |

[1]This table format provides a structured approach to nutritional and dietary management for children with autism spectrum disorder in an emergency setting.

and allow for personalization. Including familiar items from home, such as toys, blankets, or family photos, can help create a comforting and secure atmosphere[28]. By incorporating these elements, an ICU can better address the unique needs of children with ASD, promoting their well-being and enabling more effective care during critical health episodes.

Effective communication is vital in caring for children with ASD in the ICU. Communication boards and visual aids should be readily available in each room, incorporating pictures, symbols, and words to enhance understanding[104]. Technology such as tablets equipped with communication apps and tools should be integrated to facilitate effective

**Table 11 Post-emergency follow-up protocols for children with autism spectrum disorder in the emergency setting[1]**

| Protocol component | Guidelines |
|---|---|
| Immediate post-emergency care | |
| Observation and monitoring | Monitor vital signs, pain levels, and overall condition immediately after the emergency event |
| | Ensure a calm and supportive environment to aid recovery |
| Reassurance and comfort | Provide reassurance to the child using simple language and visual aids |
| | Allow the child to have familiar comfort items |
| Caregiver presence | Encourage the presence of caregivers to provide emotional support and continuity of care |
| Discharge planning | |
| Clear instructions | Provide clear and simple discharge instructions to caregivers, both verbally and in written form |
| Medication management | Explain any medications prescribed, including dosages, administration times, and potential side effects |
| Follow-up appointments | Schedule follow-up appointments with relevant healthcare providers, such as primary care physicians or specialists |
| Emergency plan | Develop an emergency plan for future incidents, including contact information and steps to take |
| Ongoing monitoring and support | |
| Regular check-ins | Conduct regular follow-up calls or visits to monitor the child's progress and address any concerns |
| Behavioral and emotional support | Provide behavioral and emotional support resources, including referrals to therapists or counselors |
| Nutritional support | Ensure the child's nutritional needs are being met post-emergency, including any dietary restrictions or preferences |
| Caregiver education and resources | |
| Education on ASD-specific needs | Educate caregivers on the unique needs of children with ASD, particularly in relation to post-emergency care |
| Resource provision | Provide information on support groups, community resources, and educational materials related to ASD |
| Multidisciplinary follow-up | |
| Team coordination | Ensure coordination among all healthcare team members, including pediatricians, specialists, and therapists |
| Communication | Maintain open lines of communication among healthcare providers to share updates and coordinate care plans |
| Documentation | |
| Detailed records | Document all aspects of the post-emergency follow-up, including observations, caregiver interactions, and interventions |
| Care plan updates | Regularly update the child's care plan to reflect progress, changes in condition, and any new recommendations |
| Feedback and continuous improvement | |
| Caregiver feedback | Solicit feedback from caregivers on the effectiveness of the care and follow-up provided |
| Quality improvement | Use feedback and outcomes data to continuously improve emergency care and follow-up protocols for children with ASD |

[1]This table format provides a structured approach to post-emergency follow-up for children with autism spectrum disorder, ensuring that all critical components are addressed comprehensively.
ASD: Autism spectrum disorder.

communication for non-verbal children or those with limited verbal abilities. Additionally, information boards displaying daily schedules and upcoming procedures visually can help children anticipate and understand their environment[105]. The ICU environment should prioritize minimizing the need for physical restraints. This can be achieved by using non-invasive monitoring techniques and providing comfortable, safe furniture[106]. Equally important is creating a secure environment to prevent children from wandering while maintaining easy access for caregivers and staff. Sensory-friendly comfort items, such as weighted blankets, fidget toys, and noise-canceling headphones, should be readily available to enhance the comfort and sense of security for children with ASD[107].

Caregivers play a crucial role in the child's care, and their presence should be accommodated within the ICU. Rooms should include dedicated space for caregivers, such as a fold-out bed or comfortable recliner. In addition, family areas within the ICU should be established, providing spaces for caregivers to rest, eat, and take breaks while staying close to their children[108]. Family support services, such as counseling rooms and meeting areas for family conferences, should

**Table 12 Training and education protocols for managing children with autism spectrum disorder in the emergency setting[1]**

| Protocol component | Guidelines |
|---|---|
| Initial training for staff | |
| ASD awareness Training | Provide comprehensive training on understanding ASD, including common characteristics and behaviors |
| Sensory sensitivities | Educate staff on sensory sensitivities commonly experienced by children with ASD and strategies to minimize sensory overload |
| Behavioral management | Train staff in recognizing and managing behavioral challenges, including de-escalation techniques and positive reinforcement |
| Communication strategies | Teach effective communication methods tailored for children with ASD, such as using simplified language, visual aids, and non-verbal cues |
| Medical considerations | Educate staff on specific medical considerations, including pain assessment tools, medication sensitivities, and special dietary needs |
| Ongoing education and refreshers | |
| Regular refresher courses | Schedule periodic refresher courses to keep staff updated on best practices and new research related to ASD care |
| Case studies and simulations | Use case studies and simulation exercises to reinforce learning and improve the practical application of protocols |
| Specialized training for key roles | |
| Emergency department staff | Provide focused training for emergency department personnel on handling acute emergencies involving children with ASD |
| Nurses and paramedics | Ensure nurses and paramedics receive additional training on immediate care and transport of children with ASD |
| Anesthesiologists and surgeons | Offer specialized training on sedation, anesthesia protocols, and surgical considerations for children with ASD |
| Family and caregiver involvement | |
| Collaborative training sessions | Involve caregivers in training sessions to share insights and effective strategies for managing their child's needs |
| Educational materials | Provide caregivers with educational materials on emergency protocols and how to support their child during emergencies |
| Evaluation and feedback | |
| Competency assessments | Conduct regular competency assessments to ensure staff are proficient in applying the training protocols |
| Feedback mechanisms | Implement mechanisms for staff to provide feedback on the training program and suggest areas for improvement |
| Documentation and certification | |
| Training records | Maintain detailed records of all training sessions attended by staff, including dates and content covered |
| Certification programs | Develop certification programs to recognize staff who have completed advanced training in ASD emergency care |
| Continuous improvement | |
| Review of best practices | Regularly review and update training materials to incorporate the latest research and best practices in ASD care |
| Interdisciplinary collaboration | Foster interdisciplinary collaboration to enhance the training program and ensure comprehensive care for children with ASD |
| Resource provision | |
| Access to resources | Provide staff with easy access to resources such as guidelines, visual aids, and toolkits specific to ASD care |
| Support networks | Establish support networks within the institution for staff to share experiences and strategies related to ASD care |

[1]This table format outlines a comprehensive approach to training and education protocols for managing children with autism spectrum disorder in the emergency setting.
ASD: Autism spectrum disorder.

also be included to ensure comprehensive emotional and practical support[109].

Therapeutic activities form a key component of holistic care for children with ASD. The ICU should have spaces equipped for occupational therapy, physical therapy, and speech therapy, along with sensory-friendly tools and equipment to aid in these interventions[110]. Medical equipment should be designed or modified to reduce noise and visual stimulation. This includes using quiet infusion pumps and monitors with dimmable displays. Dedicated areas for crisis intervention should be available within the ICU. These spaces should be equipped with sensory-friendly calming tools and staffed by trained personnel[111]. Clear and accessible emergency plans tailored to the needs of children with ASD should be present in each room, incorporating visual guides to enhance understanding during emergencies.

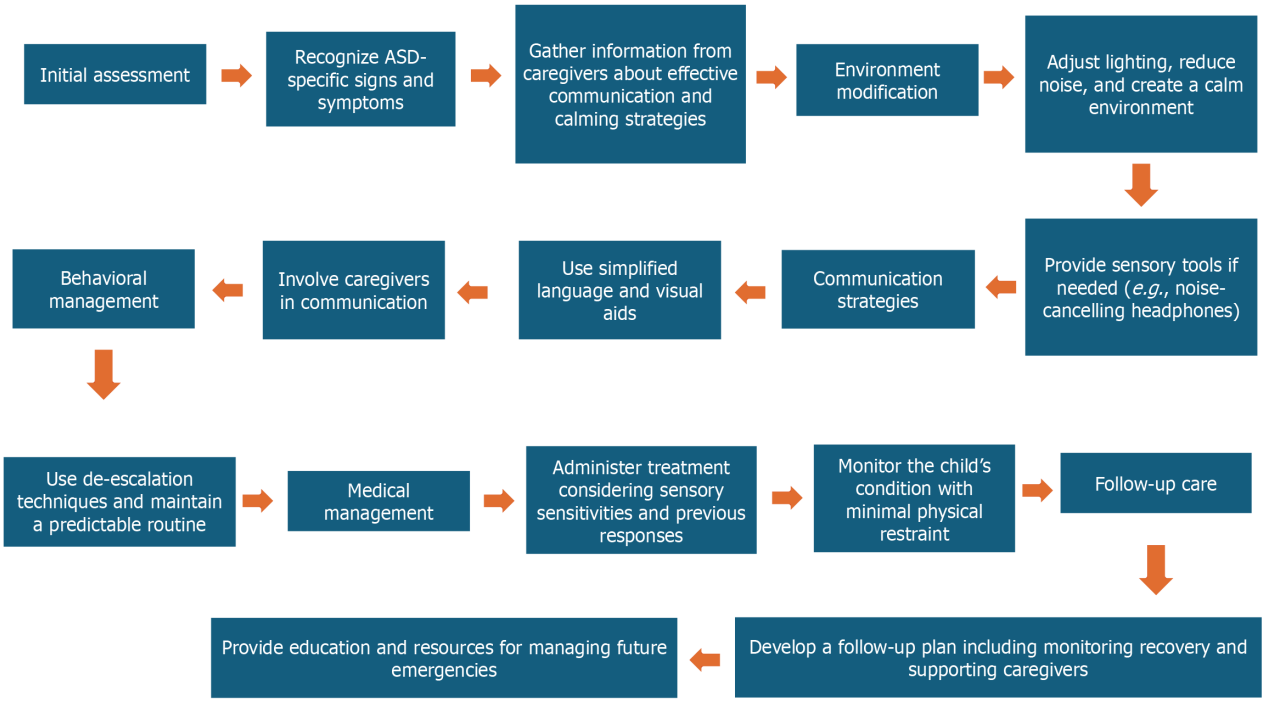


**Figure 2 A flowchart illustrating the step-by-step process for managing emergencies in children with autism spectrum disorder.** It includes initial assessment, communication strategies, sensory modifications, behavioral management, and follow-up care.

Staff training and education on ASD-specific care strategies are essential for effective care. The ICU should include dedicated spaces equipped with resources for ongoing learning and staff development[112]. Interdisciplinary team collaboration is also critical; spaces designed for team meetings and communication can facilitate seamless coordination of care[113]. By incorporating these thoughtful design elements, the ICU can provide a supportive, sensory-friendly environment tailored to the unique needs of children with ASD. This approach ensures that care is delivered compassionately, effectively, and holistically, improving outcomes and experiences for children and their families (Figure 3, Table 9 and Table 13).

### *Review of case studies and their impact on care practices*

Case studies serve as a crucial resource for understanding the challenges and successes in managing critical care emergencies in children ASD[114]. These real-world examples provide valuable insights that help refine care practices and protocols, highlighting both effective strategies and areas for improvement[115]. By illustrating specific scenarios and their management, case studies offer practical lessons that healthcare providers can relate to and implement in their practice. Through the analysis of case studies, best practices can be identified and incorporated into standardized protocols[116]. Effective strategies for communication, behavioral management, pain assessment, and other aspects of care can be shared among healthcare teams to enhance overall care quality[117]. Case studies also shed light on common challenges in managing children with ASD, such as communication barriers, sensory sensitivities, and behavioral complexities[118]. Understanding these challenges enables the development of targeted interventions and training programs tailored to the unique needs of these children.

The impact of case studies extends to the evolution of care protocols. Feedback and outcomes derived from case studies provide a basis for refining protocols, ensuring they are more responsive to the needs of children with ASD in emergency settings[119]. These studies underscore the importance of a multidisciplinary approach, showcasing the roles of various team members and the significance of collaboration and communication in achieving positive outcomes[120]. Furthermore, reviewing case studies fosters a culture of continuous improvement within healthcare settings. By encouraging providers to reflect on their practices, seek feedback, and adjust, case studies enhance care quality[121]. Documenting both successes and challenges within these studies provides a comprehensive understanding of the complexities of managing ASD in critical care, offering a balanced perspective that aids in strategy development[122].

Case studies also play a pivotal role in guiding future research. They identify knowledge gaps and areas requiring further investigation, prompting innovation and evidence-based advancements in care approaches[123]. By serving as a bridge between real-world experiences and clinical research, case studies ensure that care practices remain dynamic, informed, and responsive to the evolving needs of children with ASD.

Here are some case scenarios for children with ASD who need Emergency care (Names are not real).

**Case study 1:** Managing sensory overload during an emergency. John is an 8-year-old male with ASD with a history of bronchial asthma. John arrived at the ED in acute respiratory distress due to a severe asthma attack. His mother informed the medical team that John has significant sensory sensitivities, particularly loud noises and bright lights, which can trigger severe anxiety and behavioral outbursts. A quick, efficient assessment was conducted in a calm manner. The team

**Table 13 Ideal intensive care unit design for caring for children with autism spectrum disorder**

| Aspect | Elements | Description |
|---|---|---|
| Sensory-friendly environment | Adjustable lighting | Dimmable, soft, indirect lighting; natural light with blinds/shades |
| | Noise reduction | Soundproofing materials, quiet alarms, and communication systems |
| | Calm color scheme | Soft blues, greens, and neutrals; avoid bright, contrasting colors |
| | Controlled climate | Adjustable temperature controls |
| | Safe spaces | Designated areas with sensory-friendly items like weighted blankets and soft seating |
| Private rooms | Individualized spaces | Private rooms or areas spacious enough for caregivers |
| | Personalization | Allow familiar items from home like toys, blankets, and pictures |
| Communication enhancements | Visual supports | Communication boards and visual aids with pictures, symbols, and words |
| | Technology integration | Tablets with communication apps/tools for non-verbal/Limited verbal children |
| | Information boards | Display daily schedules and procedures visually |
| Safety and comfort | Minimal physical restraint | Non-invasive monitoring techniques; comfortable, safe furniture |
| | Secure environment | Measures to prevent wandering while allowing caregiver/staff access |
| | Comfort items | Sensory-friendly items like weighted blankets, fidget toys, noise-canceling headphones |
| Family involvement | Caregiver accommodation | Space for caregivers to stay (*e.g.*, fold-out bed, recliner) |
| | Family areas | Dedicated areas for caregivers to rest, eat, take breaks |
| | Family support services | Spaces for counseling and family conferences |
| Medical and therapeutic spaces | Therapy rooms | Spaces for occupational, physical, and speech therapy with sensory-friendly tools |
| | Medical Equipment | Quiet infusion pumps and monitors with dimmable displays |
| Emergency preparedness | Crisis intervention spaces | Areas equipped with sensory-friendly calming tools and trained personnel |
| | Emergency plans | Accessible emergency plans with visual guides for procedures |
| Collaboration and training areas | Staff training rooms | Spaces for ongoing ASD-specific care strategy training |
| | Collaboration spaces | Areas for interdisciplinary team meetings and care coordination |

ASD: Autism spectrum disorder.

used simplified language and minimal physical touch to avoid overwhelming John (initial assessment). The lights in the examination room were dimmed, and the noise levels were reduced by limiting unnecessary conversations and alarms. John was provided with noise-cancelling headphones to minimize auditory stimuli (environment modification). The team communicated with John using short, simple sentences. His mother was involved in explaining the procedures and comforting him. John's favorite toy, brought from home, was given to him for comfort (communication and comfort). Bronchodilator treatment was administered using a metered-dose inhaler with a spacer, which John is more familiar with than a nebulizer. Continuous monitoring was done with minimal physical restraint to avoid triggering further anxiety (treatment). John's condition stabilized, and he was transferred to a quieter observation area. A follow-up plan was discussed with his mother, including strategies to manage future emergencies while considering his sensory sensitivities (outcome).

**Case study 2:** Behavioral de-escalation in a pediatric ICU (PICU). Emma is a 12-year-old female with ASD. She was transferred to the PICU for post-operative recovery following appendectomy. Emma was recovering from an emergency appendectomy. She woke up agitated and disoriented, displaying signs of a meltdown, including screaming, self-injurious behavior, and resistance to medical staff.

The team reviewed Emma's behavioral plan and history of previous hospitalizations. Then, a quiet room with minimal sensory stimuli was prepared (preparation). The team used de-escalation techniques, such as speaking calmly, using low voices, and giving Emma space. Visual aids were used to explain what was happening and what would happen next, reducing her anxiety. Emma's mother was called to be with her, as her presence was calming for Emma (behavioral de-escalation). A schedule of care activities was created and displayed using visual supports. The team informed Emma before each procedure, maintaining a predictable routine (predictability and structure). Pain was assessed using a VAS tailored for children with ASD. Pain management included both pharmacological (acetaminophen) and non-pharmacological (comfort positioning) methods (medical management). Emma calmed down and cooperated with the medical team. She was closely monitored with periodic checks, and her recovery progressed smoothly. A discharge plan included strategies for managing post-operative care at home (outcome).

**Figure 3 An artificial intelligence-generated sensory-friendly intensive care unit room design for children with autism spectrum disorder.** To minimize sensory overload, the room includes soundproof doors, dimmable lighting, and noise-canceling equipment. The room features a comfortable, adjustable bed and a sensory retreat area with weighted blankets and fidget toys. A dedicated space for caregivers with a fold-out bed or recliner and storage for personal items is also included. Therapeutic activity space with occupational and speech therapy tools and interactive technology like tablets with communication apps supports the child's needs. The design incorporates environmental controls such as adjustable temperature and calming wall colors, with windows with blinds or shades to control natural light. Medical equipment is accessible but discreetly stored to reduce visual clutter. A family support area also provides private meeting space and resources on autism spectrum disorder and emergency care. This design aims to reduce anxiety, manage sensory sensitivities, and support effective medical care and family involvement.

**Case study 3:** Communication strategies during an emergency seizure. Alex is a 10-year-old male with ASD and epilepsy. The seizure types are usually generalized tonic-clonic seizures. Alex experienced a generalized tonic-clonic seizure at home. His parents called Emergency Medical Services (EMS), and he was transported to the emergency department (ED). Alex has difficulty communicating verbally, especially during stress.

Paramedics trained in ASD-specific communication strategies arrived at the house. They used a calm, soothing tone and avoided loud, sudden noises. Visual supports were used to explain the transport process to Alex's parents and Alex if he becomes aware (EMS response). On arrival at the ED, Alex was assessed using minimal physical restraint. The ED staff used simplified language and visual aids to explain procedures to Alex and his parents. His parents were involved in providing medical history and calming Alex (ED assessment). The ED environment was modified by dimming lights and reducing noise. Alex was allowed to hold a familiar object (a stuffed animal) for comfort (sensory sensitivities). Anti-seizure medication was administered, considering Alex's known sensitivities and previous responses to medication. Continuous monitoring was conducted with minimal interference to avoid sensory overload (medical management). Alex's seizure was controlled, and he regained consciousness without severe agitation. The team developed a follow-up plan, including a review of seizure triggers and preventive strategies. Alex's parents were provided with educational materials on managing seizures and when to seek emergency care (Outcome and follow-up).

**Case study 4:** Managing transition during a complex procedure. Sophie, a 9-year-old girl with ASD and a history of gastrointestinal issues, was admitted to the ED for an emergency endoscopy due to severe abdominal pain. She has a strong aversion to medical procedures and changes in routine.

Upon arrival, Sophie displayed signs of significant distress, including crying and resistance to medical staff. The team quickly assessed her baseline behaviors and noted her sensitivity to changes in routine and medical equipment (initial assessment). The examination room was prepared to minimize stress by using soft, ambient lighting and reducing noise levels. Sophie's favorite calming music was played through headphones to help soothe her anxiety. A visual schedule explained the procedure step-by-step (environment modification). Sophie's caregivers were involved in the process, explaining each step calmly and reassuringly. A familiar comfort item, a blanket, was used to provide reassurance. During the procedure, Sophie was allowed to choose a small toy to hold (communication and comfort). The endoscopy was performed with Sophie in a calm, quiet environment, and a sedative was administered with careful monitoring. The team used a gentle approach, minimizing physical restraint and ensuring clear, consistent communication (treatment).

Sophie tolerated the procedure well and was less agitated than anticipated. A follow-up plan included recommendations for managing anxiety related to future procedures and strategies for maintaining routine stability at home (outcome).

**Case study 5:** Handling severe allergic reaction in the ICU. Michael, a 6-year-old boy with ASD and known food allergies, was admitted to the PICU after experiencing an anaphylactic reaction to a food allergen. He has a limited verbal communication ability and exhibits strong food aversion.

Michael arrived in the ICU with symptoms of severe distress, including difficulty breathing and swelling. His medical history indicated a history of severe food allergies, which were crucial for managing his condition (initial assessment). The ICU team immediately implemented a low-stimulation environment by dimming lights and reducing noise. The team ensured that all potential allergens were removed from the vicinity (environment modification). Michael's caregivers provided crucial information about his allergies and preferred methods of communication. A visual aid with simple images and words explained his treatment plan. A soothing, familiar object was provided for comfort (communication and comfort). Epinephrine was administered promptly, and Michael was closely monitored for any signs of improvement or further reactions. The team maintained a calm demeanor and used clear, non-threatening language throughout the process (treatment). Michael's allergic reaction was managed effectively and stabilized with minimal additional complications. A detailed discharge plan was developed, including an updated allergy action plan and recommendations for managing allergens in future situations (outcome).

These case studies illustrate the importance of tailored approaches in managing critical care emergencies for children with ASD, focusing on sensory sensitivities, behavioral challenges, effective communication, and multidisciplinary care.

### Recommendation

Based on the review of case studies and the criteria for an ideal ICU for children with ASD, several recommendations can enhance the management of critical care emergencies in this population. Sensory-friendly modifications are essential, including adjustable, soft, and dimmable lighting, soundproofing to minimize medical equipment noise, and calming colors such as blues, greens, and neutrals. Designating sensory retreat areas equipped with items like weighted blankets and soft seating can help children manage sensory overload. Communication and comfort can be improved by providing private rooms that allow personalization with familiar items from home and supplying communication boards, visual aids, and technology like tablets with communication apps. Visual information boards displaying daily schedules and procedures can help children anticipate and understand activities. Ensuring safety and family involvement is crucial; adopting non-invasive monitoring techniques, implementing measures to prevent wandering, and providing sensory-friendly comfort items like weighted blankets, fidget toys, and noise-canceling headphones can enhance comfort and security. Including space for caregivers to stay with the child, offering dedicated family areas within the ICU, and developing spaces for family support services are also important. Integrating therapeutic and crisis intervention services involves equipping spaces for occupational, physical, and speech therapy with sensory-friendly tools and using or modifying medical equipment to reduce noise and visual stimuli. Designating areas for crisis intervention that are equipped with calming tools and staffed by trained personnel and ensuring each room has clear, accessible emergency plans tailored to the needs of children with ASD, including visual guides for emergency procedures, are also recommended. Prioritizing staff training and interdisciplinary collaboration by providing ongoing ASD-specific training for staff, creating dedicated spaces for training, and facilitating regular interdisciplinary team meetings can ensure effective communication and coordination. Promoting case study reviews and protocol development by regularly reviewing and analyzing case studies to identify best practices, common challenges, and areas for improvement and integrating these findings into care protocols and training programs can foster continuous improvement. Encouraging a multidisciplinary approach to care, emphasizing collaboration and communication among team members, and developing targeted interventions and training programs based on common challenges identified in case studies, such as communication difficulties, sensory sensitivities, and behavioral issues, can significantly improve care outcomes and experiences for children with ASD and their families.

### Limitations

Despite the numerous strategies and recommendations outlined for managing critical care emergencies in children with ASD, several limitations must be acknowledged. First, the heterogeneity of ASD means that each child's needs and responses can vary significantly, making it challenging to develop one-size-fits-all protocols. While case studies provide valuable insights, they may not capture the full spectrum of ASD manifestations, limiting the generalizability of their findings. Additionally, implementing sensory-friendly modifications and specialized equipment in ICUs can be costly and require significant financial investment and institutional commitment, which might not be feasible in all healthcare settings.

Furthermore, training healthcare staff in ASD-specific strategies demands time and resources, and ensuring consistent application of these strategies across all team members can be difficult. The reliance on caregivers to provide insights into the child's preferences and behaviors also assumes their availability and willingness to participate, which might not always be possible due to various factors such as caregiver stress or absence. The integration of multidisciplinary teams, while beneficial, can also present logistical challenges, including coordinating schedules and ensuring effective communication among diverse professionals. Lastly, while reviewing and analyzing case studies can guide practice improvements, the lack of standardized reporting and the potential for publication bias might limit the robustness of the evidence base. These limitations highlight the need for ongoing research, resource allocation, and flexible, individualized approaches to care for children with ASD in critical care settings.

## CONCLUSION

This comprehensive literature review underscores the multifaceted challenges and critical considerations involved in managing critical care emergencies for children with ASD. The evidence highlights the importance of adopting a multidisciplinary approach that integrates medical, behavioral, and sensory considerations to improve outcomes and enhance the overall experience for these children. Effective management requires tailored communication strategies, individualized care plans, and adaptations to the critical care environment to address the unique sensory sensitivities and behavioral needs of children with ASD. The review also emphasizes the value of case studies in refining care practices and protocols, revealing practical insights into successful strategies and areas for improvement. Despite advancements in protocol development and staff training, ongoing research and continuous evaluation are necessary to address the limitations identified and further optimize care. Ultimately, implementing a holistic, patient-centered approach that prioritizes both medical and emotional needs will contribute to better management of critical care emergencies in children with ASD, fostering improved health outcomes and providing a more supportive, compassionate care experience.

## FOOTNOTES

**Author contributions:** Al-Beltagi M was responsible for conceptualization, study design, drafting the manuscript, and critically revising it for important intellectual content; Saeed NK contributed to data analysis and interpretation, provided clinical expertise, and reviewed the manuscript for accuracy and clarity; Bediwy AS assisted with the literature review, data acquisition, and editing of the manuscript. Alhawamdeh R contributed to drafting specific sections, organizing references, and formatting tables and figures; Elbeltagi R reviewed the final manuscript for coherence and alignment, supported graphical content preparation, and provided administrative oversight. All authors reviewed and approved the final version of the manuscript, ensuring its integrity and quality.

**Conflict-of-interest statement:** The authors declare that they have no conflicts of interest to disclose regarding the publication of this manuscript. All authors have contributed to the work and have no financial, personal, or professional affiliations that could influence the content or interpretations presented in this study.

**PRISMA 2009 Checklist statement:** The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.



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**S-Editor:** Liu H
**L-Editor:** A
**P-Editor:** Guo X

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World Journal of Critical Care Medicine

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*World J Crit Care Med* 2025 June 9; 14(2): 101377

DOI: 10.5492/wjccm.v14.i2.101377

ISSN 2220-3141 (online)

SYSTEMATIC REVIEWS

# Driving pressure in acute respiratory distress syndrome for developing a protective lung strategy: A systematic review

Hassan A Alzahrani, Nadia Corcione, Saeed M Alghamdi, Abdulghani O Alhindi, Ola A Albishi, Murad M Mawlawi, Wheb O Nofal, Samah M Ali, Saad A Albadrani, Meshari A AlJuaid, Abdullah M Alshehri, Mutlaq Z Alzluaq

**Specialty type:** Critical care medicine

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade C
**Novelty:** Grade B
**Creativity or Innovation:** Grade B
**Scientific Significance:** Grade B

**P-Reviewer:** Tovichien P

**Received:** September 12, 2024
**Revised:** December 15, 2024
**Accepted:** January 3, 2025
**Published online:** June 9, 2025
**Processing time:** 167 Days and 23.9 Hours

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## Abstract

***BACKGROUND***

Acute respiratory distress syndrome (ARDS) is a critical condition characterized by acute hypoxemia, non-cardiogenic pulmonary edema, and decreased lung compliance. The Berlin definition, updated in 2012, classifies ARDS severity based on the partial pressure of arterial oxygen/fractional inspired oxygen fraction ratio. Despite various treatment strategies, ARDS remains a significant public health concern with high mortality rates.

***AIM***

To evaluate the implications of driving pressure (DP) in ARDS management and its potential as a protective lung strategy.

***METHODS***

We conducted a systematic review using databases including EbscoHost, MEDLINE, CINAHL, PubMed, and Google Scholar. The search was limited to articles published between January 2015 and September 2024. Twenty-three peer-reviewed articles were selected based on inclusion criteria focusing on adult ARDS patients undergoing mechanical ventilation and DP strategies. The literature review was conducted and reported according to PRISMA 2020 guidelines.

***RESULTS***

DP, the difference between plateau pressure and positive end-expiratory pressure, is crucial in ARDS management. Studies indicate that lower DP levels are significantly associated with improved survival rates in ARDS patients. DP is a better predictor of mortality than tidal volume or positive end-expiratory pressure alone. Adjusting DP by optimizing lung compliance and minimizing overdistension and collapse can reduce ventilator-induced lung injury.

***CONCLUSION***

DP is a valuable parameter in ARDS management, offering a more precise measure of lung stress and strain than traditional metrics. Implementing DP as a threshold for safety can enhance protective ventilation strategies, potentially reducing mortality in ARDS patients. Further research is needed to refine DP measurement techniques and validate its clinical application in diverse patient populations.


**Key Words:** Acute respiratory distress syndrome; Mechanical ventilation; Driving pressure; Respiratory care; Intensive care unit; Pulmonary disease



**Core Tip:** This manuscript reviews the concept of monitoring driving pressure generated by mechanical ventilation to protect the lung. The literature demonstrated that driving pressure (DP) is a valuable parameter in acute respiratory distress syndrome management, offering a more precise measure of lung stress and strain than traditional metrics. Implementing DP as a threshold for safety can enhance protective ventilation strategies, potentially reducing mortality in acute respiratory distress syndrome patients. Further research is needed to refine DP measurement techniques and validate its clinical application in diverse patient populations.

**Citation:** Alzahrani HA, Corcione N, Alghamdi SM, Alhindi AO, Albishi OA, Mawlawi MM, Nofal WO, Ali SM, Albadrani SA, AlJuaid MA, Alshehri AM, Alzluaq MZ. Driving pressure in acute respiratory distress syndrome for developing a protective lung strategy: A systematic review. *World J Crit Care Med* 2025; 14(2): 101377

**URL:** https://www.wjgnet.com/2220-3141/full/v14/i2/101377.htm

**DOI:** https://dx.doi.org/10.5492/wjccm.v14.i2.101377

## INTRODUCTION

Acute respiratory distress syndrome (ARDS) was first discussed in a 1967 case-based study that described the clinical features in critically ill adults of acute hypoxemia, non-cardiogenic pulmonary edema, decreased lung compliance, elevated work of breathing, and the need for positive-pressure ventilation[1]. Pathological specimens from patients with ARDS often reveal diffuse alveolar damage. Laboratory studies have shown both alveolar epithelial and lung endothelial injury, resulting in an accumulation of protein-rich inflammatory edematous fluid in the alveolar space[2]. An American European consensus conference in 1992 created specific diagnostic criteria for the syndrome[3]. These criteria of ARDS were updated in 2012 and were denominated as the Berlin definition. It differs from the former American European Consensus definition by eliminating the term acute lung injury; it also excluded the requirement for wedge pressure < 18

and introduced the requirement of positive end-expiratory pressure (PEEP) or continuous positive airway pressure of greater than or equivalent to 5 $cmH_2O$[4]. The ratio of oxygen in the patient's arterial blood to the fraction of the oxygen in the inspired air is used to diagnose ARDS. Partial pressure of arterial oxygen ($PaO_2$)/fractional inspired of oxygen ($FiO_2$) ratio of these patients is less than 300[5].

The Berlin definition uses the $PaO_2/FiO_2$ ratio to distinguish mild (200-300 mmHg), moderate (100-200 mmHg), and severe (≤ 100 mmHg)[5]. ARDS is an acute disorder that begins within seven days of the inciting situation and is designated by bilateral lung infiltrates and severe progressive hypoxemia in the lack of any evidence of cardiogenic pulmonary edema. In addition, the Berlin definition was created to achieve more reliable diagnostic criteria that would aid in disease recognition and help align care choices and clinical outcomes based on the severity of the disease groups. ARDS diagnosis depends on clinical criteria solely because it is not feasible to obtain direct lung injury measurements by pathological specimens of lung tissue in most cases. Accordingly, neither distal airspace nor blood samples can be used to diagnose ARDS[2].

The emphasis on viability, reliability, and relevance during definition development; the implementation of an empiric assessment method in refining the definition; and the production of explicit illustrations to utilize the radiographic and origin of edema parameters are all significant incremental advances in this ARDS definition[6]. Berlin criteria are shown in Table 1. Epidemiologic research revealed that this clinical condition had a substantial effect in the United States, with 200000 cases each year associated with increased patient morbidity and healthcare costs[1]. Moreover, cellular damage in ARDS is distinguished by inflammation, apoptosis, necrosis, and increased alveolar-capillary permeability, which leads to the development of alveolar edema[7].

ARDS appeared to be a significant public health concern worldwide in a prospective study conducted in 459 intensive care units (ICUs) in 50 countries across five regions, with some geographical variation and very high mortality of approximately 40%[8]. Also, ARDS has been reported in 10.4% of total ICUs admissions and 23.4% of all patients requiring mechanical ventilation (MV)[8]. Since its first report in 1967, several studies have addressed various clinical aspects of the syndrome (risk factors, epidemiology, and treatment) and studies addressing its pathogenesis (underlying mechanisms, biomarkers, and genetic predisposition)[9].

Despite several randomized clinical trials to control the lung inflammatory response, the only proven method to consistently reduce mortality is a protective ventilation strategy[10]. An attractive method of setting tidal volume (VT) normalized to respiratory system compliance (Crs) proposed to be a predictor of survival than VT scaled to normal lung volume using predicted body weight (PBW)[11,12]. Driving pressure (DP) represents the difference between plateau pressure (Pplat) and PEEP and might be influenced by changes in VT or PEEP or Crs. Despite the correlation of DP and death rate in patients with ARDS, this relationship is less evident to non-ARDS patients[13]. Some authors recommended that DP was a goal in itself for ARDS management, implementing DP as a threshold for safety to reduce ventilator-induced lung injury (VILI)[14].

### *Evolving approaches to protective ventilation*

When treating the underlying pathology of ARDS, MV is the most effective method of reinstating or supporting optimal oxygenation and carbon dioxide removal requirements in patients with ARDS. ARDS patients' lungs are highly susceptible to MV injury, widely known as VILI[15,16]. Consequently, an inappropriate MV approach leads to the development of VILI. The relative contributions to the development of the VILI are unclear as to the magnitude and frequency of mechanical stress and expiratory pressure[17]. This chain of events begins with mechanical injury to the lung tissue determined as the first hit by excess stress-induced strain, with subsequent barotrauma development as a response to the physical damage caused by excessive strain[18].

Thus, minimizing lung injury while ensuring adequate gas exchange (protective ventilation) is essential for ARDS to be safely managed clinically. There is currently widespread confusion concerning how best to perform protective ventilation in ARDS. Numerous strategies have been recommended and used, each with its rationale, advocates, and evidence of effectiveness[10]. Several ventilator strategies have been suggested for ARDS, such as lower VT, higher PEEP, and adjuncts such as prone positioning, neuromuscular blockade, and extracorporeal membrane oxygenation[8]. However, the lung-protective ventilation technique suggested low VT, depending on optimal body weight and appropriate amounts of PEEP. Therefore, overstress and overstrain are not permanently reduced by lowering VT according to ideal body weight[19].

Numerous studies have been performed since the ARDS Net trials were published in 2000 to establish ventilation strategies to minimize or prevent VILI in patients with ARDS. Lowering the VT to 6 mL/kg of PBW was subsequently proven to improve the outcomes and reduce VILI incidence[20]. The goal of lung-protective MV strategies is to reduce the incidence of VILI. These strategies typically focus on delivering relatively low VT of 5-8 mL/kg of PBW and restricting Pplat to 30 $cmH_2O$[20,21]. However, there is growing evidence showing that VILI can still be affected in patients with minimal aerated lung units available for ventilation, even when the VT is 6 mL/kg of PBW.

Ultimately, the Crs is linearly correlated to the "baby lung" dimensions, meaning that the ARDS lung is not "stiff" but small, with nearly normal intrinsic elasticity. Scientifically, the "baby lung" is a distinct anatomical structure in the nondependent lung regions. Nevertheless, the density redistribution in the prone position reveals that the "baby lung" is a functional and not an anatomical concept. This demonstrates conditions such as barotrauma and volutrauma and offers a rationale for the lung-protective strategy[22-24]. On the other hand, improved oxygenation has not consistently been shown to be an effective strategy for lowering mortality rates in ARDS patients[20]. However, lung stress and strain are more strongly correlated with outcomes and reflect VILI risk[22,25,26]. In 2015, the team of Amato *et al*[12] first began to seriously evaluate the effect of DP in treating ARDS patients with a meta-analysis of nine prospective trials involving 3500 patients with ARDS. The most remarkable conclusions from this data were that DP's identification as an independent paramount factor correlated with ARDS survivors. To this end, the purpose of this paper to review important

**Table 1 Berlin criteria for acute respiratory distress syndrome**

| Features | Mild | Moderate | Severe |
|---|---|---|---|
| Timing | Acute onset within one week of a known respiratory clinical insult or new/worsening respiratory symptoms | | |
| Hypoxemia | 200 < $PaO_2/FiO_2$ ≤ 300 with PEEP or CPAP ≥ 5 $cmH_2O$ | 100 < $PaO_2/FiO_2$ ≤ 200 with PEEP ≥ 5 $cmH_2O$ | $PaO_2/FiO_2$ < 100 with PEEP ≥ 5 $cmH_2O$ |
| Origin of edema | Respiratory failure is associated with known risk factors and is not fully explained by cardiac failure or fluid overload. An objective assessment of cardiac failure or fluid overload is needed if no risk factor is present | | |
| Radiologic abnormalities | Bilateral opacities | | Opacities involving at least three quadrants |
| Additional physiological derangement | N/A | | Crs < 40 mL/$cmH_2O$[1] |

[1]Respiratory system compliance.

$PaO_2$: Partial pressure of arterial oxygen; $FiO_2$: Fractional inspired of oxygen; PEEP: Positive end of expiratory pressure; Crs: Compliance; CPAP: Continuous positive airway pressure; N/A: Not applicable.

critical considerations about the effect of DP when treating ARDS patients on MV. The research question for this review was to what extent the concept of using optimal DP with ARDS patients would reduce mortality in the ICU settings. In other words, this integrative review aims to evaluate the implications of DP in ARDS management and its potential as a protective lung strategy.

## MATERIALS AND METHODS

This study employs a systematic literature review adhering to the PRISMA guidelines. We conducted comprehensive searches across electronic databases including EbscoHost, MEDLINE, CINAHL, PubMed, and Google Scholar, with the assistance of medical librarian experts. The search strategy incorporated key terms and Medical Subject Headings such as "Mechanical Ventilation", "Driving Pressure", "Acute Respiratory Distress Syndrome (ARDS)", and "Mortality". The search was confined to articles published between January 2015 and September 2024 and limited to English-language publications.

Two independent reviewers screened the titles and abstracts, with a third reviewer available to resolve any disagreements. Relevant articles were exported to EndNote (version 20.6). After removing duplicates, 23 peer-reviewed articles met the inclusion criteria. We included studies focusing on adult critical care patients using MV for ARDS or employing DP strategies with ARDS patients. Included studies must have patients on mechanical ventilator either invasive or non-invasive. Exclusion criteria encompassed studies on children, pulmonary conditions other than ARDS, pregnant or obese populations, non-full-text articles, reviews, and conference abstracts. Data were summarized and synthesized toward answering the research question. Summary of included studies provided in Table 2. PRISAM flow chart for included studies summarized in Figure 1.

## RESULTS

### *DP and mortality*

Adjustments was more strongly linked with lower mortality than improved $PaO_2/FiO_2$, making change in DP more informative about the advantage from ventilator adjustments. Since the Amato *et al*[12] in 2015 study, DP has been a significant area of concern in ARDS management in the past five years. The research had a multilevel mediation analysis that applied data from ARDS patients who participated in previously recorded randomized and controlled trials. Relatively low DP levels were significantly related to survival in ARDS patients[27], while survival was not independently associated with VT and PEEP[12]. DP has recently been suggested as a possible lung-protective ventilation goal based on multiple observational studies demonstrating associations in ARDS individuals between reduced DP levels and low mortality[12]. Facilitating active modification of the lung "mechanical scenario" through lung recruiting and PEEP selection is possible. A redistribution of VT from overextended to recruited lungs happens as the individual distribution of threshold-opening airway pressures is considered to achieve maximal recruitment. Overdistension in the upper regions can be reduced due to the more homogeneous distribution of transpulmonary pressures. After successful recruitment, the increment in lung Crs rescales the functional lung's size, eventually allowing for a further DP reduction [28]. The Crs affected the relationship between VT and strain in ARDS patients. Lung strain did not increase significantly with increasing VT between 6 mL/kg and 10 mL/kg PBW in the high Crs patients. However, among the low Crs ARDS patients, even with ventilation at a VT of 6 mL/kg PBW, the strain was high enough to induce VILI. Moreover, the strain was significantly higher in the patients with high DP compared to the patients with low DP. These results may partly validate the concept of the study of Amato and his colleagues[29]. Also, reduced DP following protocolized ventilator

**Table 2 Summary of included studies**

| Ref. | Title of the article | Objective of the article | Methodology of the article | Number of patients included in the article | Summary of the results | How driving pressure is described in the article | Mortality rate or mortality outcome mentioned in article | Effect of driving pressure on mortality |
|---|---|---|---|---|---|---|---|---|
| Gattinoni *et al*[22], 2006 | Lung recruitment in patients with the acute respiratory distress syndrome | Studying lung recruitment in ARDS | Prospective study | Not specified | Lung recruitment beneficial for ARDS | Not described | Yes | Lung recruitment beneficial for ARDS |
| Meade *et al* [16], 2008 | Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: A randomized controlled trial | To study the effect of ventilation strategy on ARDS | Randomized controlled trial | Not specified | Low tidal volumes and high PEEP beneficial for ARDS | Not described | Yes | Low tidal volumes and high PEEP beneficial for ARDS |
| Mercat *et al* [21], 2008 | Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: A randomized controlled trial | To study the effect of PEEP setting on ARDS | Randomized controlled trial | Not specified | High PEEP beneficial for ARDS | Not described | Yes | High PEEP beneficial for ARDS |
| Retamal *et al* [25], 2015 | High PEEP levels are associated with overdistension and tidal recruitment/derecruitment in ARDS patients | To study the effects of high PEEP levels on lung mechanics in ARDS patients | Prospective study | Not specified | High PEEP levels associated with overdistension and tidal recruitment/derecruitment | Not described | Yes | High PEEP levels associated with overdistension and tidal recruitment/derecruitment |
| Borges *et al* [28], 2015 | Altering the mechanical scenario to decrease the driving pressure | To study the effect of altering mechanical scenarios on DP | Prospective study | Not specified | Altering mechanical scenarios can decrease DP | Described as the difference between plateau pressure and PEEP | Yes | Altering mechanical scenarios can decrease DP |
| Bellani *et al* [8], 2016 | Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries | To study the epidemiology and outcomes of ARDS | Prospective study | 459 ICUs | High mortality rate and geographical variation in ARDS | Not described | Yes | Not specified |
| Chiumello *et al*[19], 2016 | Airway driving pressure and lung stress in ARDS patients | To study the relationship between driving pressure and lung stress in ARDS | Retrospective study | 150 patients | DP correlated with lung stress | Described as the difference between plateau pressure and PEEP | Yes | Driving pressure correlated with lung stress |
| Baedorf Kassis *et al* [31], 2016 | Mortality and pulmonary mechanics in relation to respiratory system and transpulmonary driving pressures in ARDS | To study the relationship between pulmonary mechanics and mortality in ARDS | Retrospective study | 150 patients | DP correlated with lung stress and mortality | Described as the difference between plateau pressure and PEEP | Yes | DP correlated with lung stress and mortality |
| Guérin *et al* [33], 2016 | Effect of driving pressure on mortality in ARDS patients during lung protective mechanical ventilation in two randomized controlled trials | To study the effect of DP on mortality in ARDS | Randomized controlled trial | Not specified | DP correlated with mortality in ARDS | Described as the difference between plateau | Yes | DP correlated with mortality in ARDS |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | pressure and PEEP | | |
| Xie *et al*[29], 2017 | The effects of low tidal ventilation on lung strain correlate with respiratory system compliance | To study the effects of low tidal ventilation on lung strain | Prospective study | Not specified | Low tidal ventilation correlated with respiratory system compliance | Described as the difference between plateau pressure and PEEP | Yes | Low tidal ventilation correlated with respiratory system compliance |
| Mezidi *et al* [36], 2017 | Effect of end-inspiratory plateau pressure duration on driving pressure | To study the effect of plateau pressure duration on DP | Prospective study | Not specified | Plateau pressure duration affects DP | Described as the difference between plateau pressure and PEEP | Yes | Plateau pressure duration affects DP |
| Das *et al* [10], 2019 | What links ventilator driving pressure with survival in acute respiratory distress syndrome? | To study the link between ventilator driving pressure and survival in ARDS | Computational study | Not specified | Link between DP and survival | Described as the difference between plateau pressure and PEEP | Yes | Driving pressure linked to survival |
| Collino *et al* [26], 2019 | Positive end-expiratory pressure and mechanical power | To study the effect of PEEP and mechanical power on ARDS | Prospective study | Not specified | High PEEP levels associated with overdistension and tidal recruitment/derecruitment | Not described | Yes | High PEEP levels associated with overdistension and tidal recruitment/derecruitment |
| Dai *et al* [32], 2019 | Risk factors for outcomes of acute respiratory distress syndrome patients: a retrospective study | To identify risk factors for ARDS outcomes | Retrospective study | Not specified | Identified risk factors for ARDS outcomes | Not described | Yes | Identified risk factors for ARDS outcomes |
| Bellani *et al* [37], 2019 | Driving pressure is associated with outcome during assisted ventilation in acute respiratory distress syndrome | To study the association of DP with outcomes during assisted ventilation in ARDS | Prospective study | Not specified | DP associated with outcomes during assisted ventilation in ARDS | Described as the difference between plateau pressure and PEEP | Yes | DP associated with outcomes during assisted ventilation in ARDS |
| Yehya *et al* [30], 2021 | Response to ventilator adjustments for predicting ARDS mortality: Driving pressure versus oxygenation | To compare the predictive value of DP and oxygenation on ARDS mortality | Comparative study | Not specified | DP more informative about ventilator adjustments than oxygenation | Described as the difference between plateau pressure and PEEP | Yes | DP more informative about ventilator adjustments than oxygenation |
| Dianti *et al* [17], 2021 | Comparing the effects of tidal volume, driving pressure, and mechanical power on mortality in trials of lung-protective mechanical ventilation | Comparing the effects of tidal volume, driving pressure, and mechanical power on mortality | Comparative study | Not specified | DP and mechanical power correlated with mortality | Described as the difference between plateau pressure and PEEP | Yes | Driving pressure correlated with mortality |
| Goligher *et al*[35], 2021 | Effect of lowering VT on mortality in acute respiratory distress syndrome varies with respiratory system elastance | To study the effect of lowering tidal volume on mortality in ARDS | Prospective study | Not specified | Lowering tidal volume beneficial for ARDS | Not described | Yes | Lowering tidal volume beneficial for ARDS |
| Costa *et al* [42], 2021 | Ventilatory variables and mechanical power in patients with acute respiratory distress syndrome | To study ventilatory variables and mechanical power in | Prospective study | Not specified | Ventilatory variables and mechanical power associated with ARDS outcomes | Described as the difference between plateau | Yes | Ventilatory variables and mechanical power associated with ARDS outcomes |

| | | |
|---|---|---|
| | ARDS | pressure and PEEP |

ARDS: Acute respiratory distress syndrome; PEEP: Positive end expiratory pressure; VT: Tidal volume; ICUs: Intensive care units; DP: Driving pressure.

adjustments was more strongly linked with lower mortality than improved $PaO_2/FiO_2$, producing change DP more informative about the advantage from ventilator adjustments[30].

### *Physiological bases of DP*

Transpulmonary DP, the pressure differential around the lung, must be considered when distinguishing lung from chest wall mechanics. Although measuring transpulmonary DP might be better to evaluate lung stress, an estimation of pleural pressure by using esophageal manometry is required. This measurement is not routinely implemented in most ICUs due to its laborious nature and some assumptions and limitations related to the technique[31]. Alternatively, DP is readily and promptly measured at the bedside, without the necessity for extra equipment or software. Two previous studies indicate for most patients, DP associates with transpulmonary DP and is a sufficient surrogate for lung stress[19,31].

Chiumello *et al*[19] in 2016 state that DP may vary from minimal variations (skinny patient, pneumonia) to a considerable overestimation (morbid obesity, abdominal hypertension) of transpulmonary DP. However, in the patient without spontaneous ventilatory activity, transpulmonary DP will always be lower than DP. For instance, it has been shown that DP correlates with lung stress and could be used to identify over-distension[19]. Hence, it appears logical to suspect that DP might be strongly associated with the risk of VILI so that the DP may be sufficient to detect lung overstress with acceptable accuracy[19]. Controlling VT without considering lung mechanics may be ineffective. New evidence strongly suggests that VT normalized to lung mechanics (*e.g.*, VT/C) is a better predictor of mortality than VT dosage[28]. Amato *et al*[12] in 2015 stated that DP could be measured through the difference between Pplat and PEEP, "DP = Pplat - PEEP". So, the Crs is measured as a ratio between VT and the DP. "Crs = VT/ (Pplat - PEEP) = VT/DP; DP = VT/ Crs". Thus, The DP can be formulated as the ratio between VT and Crs resembling the lung and chest wall elastance.

As the equation indicates, a change in VT or pressure will impact the respiratory system's Crs. A change in PEEP may likely minimize the stress associated with a VT (*i.e.*, increase the Crs) if it will recruit non-aerated lung previously[11]. Amato and his colleagues hypothesized that if VT could be normalized to Crs rather than PBW, the impact of tidal ventilation could be calculated in a better way. That clearly shows that the ratio of VT/Crs represents the dynamic lung strain; it could be imprecise as the available lung volume is variable with the severity of ARDS[11]. The relationship between the airway DP (Pplat-PEEP) and transpulmonary DP (the difference between end-inspiratory transpulmonary pressure and end-expiratory transpulmonary pressure) is worth mentioning. Considering the chest wall's elastance, such a variable can positively evaluate lung stress, which may be a safe technique to change MV support[19]. Therefore, adjusting VT through the available lung units by measuring DP can contribute to a more effective protective lung strategy in ARDS patients[12].

Chiumello *et al*[19] conducted a retrospective study of 150 heavily sedated and paralyzed ARDS patients recruited to a constant VT, respiratory rate (RR), and PEEP trial of 5 $cmH_2O$ and 15 $cmH_2O$. At both PEEP levels, the higher DP group had significantly greater lung stress, respiratory system, and lung elastance than the lower DP group. More importantly, DP was significantly related to lung stress (transpulmonary pressure), and DP higher than 15 $cmH_2O$ and transpulmonary DP higher than 11.7 $cmH_2O$, both measured at PEEP 15 $cmH_2O$, were correlated with critical levels of stress. The only ventilation predictor linked to survival was airway DP, which has received a lot of attention after past findings by Amato *et al*[12] in 2015. DP was used as a surrogate for cyclic lung strain because it was the most accessible and easiest to

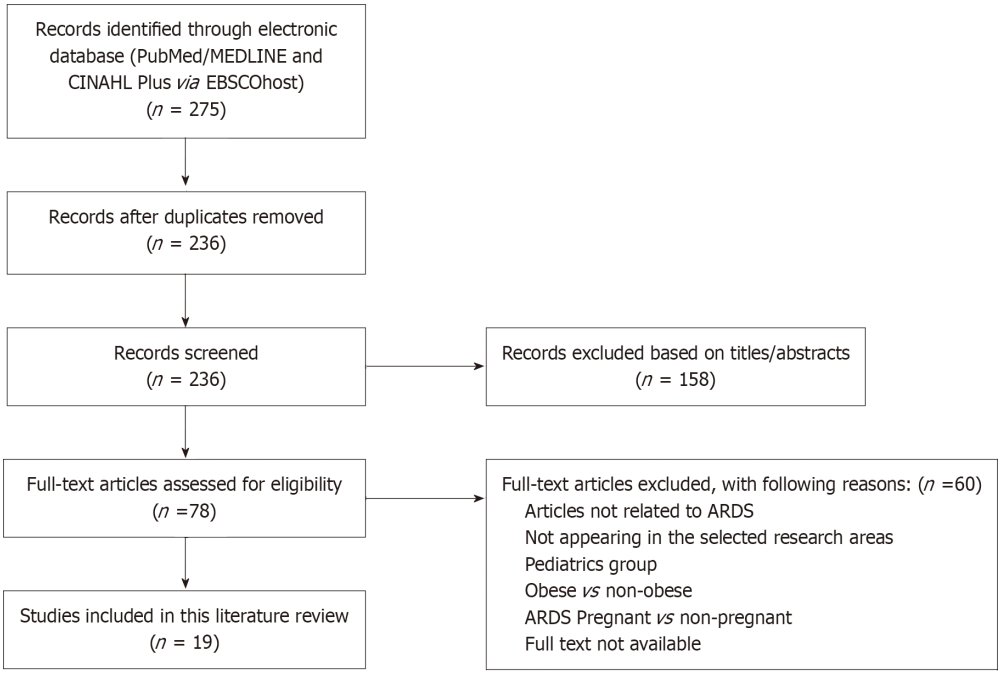


**Figure 1 PRISMA flowchart.** ARDS: Acute respiratory distress syndrome.

measure. The amplitude of cyclic stretch is more closely related to cell and tissue damage than the maximum stretch level [32].

### *Limitations and challenges of DP measurement*

In critically ill patients with ARDS, the chest wall and abdomen play an unpredictable role in pleural pressure and respiratory system mechanics. As a result, a given PEEP can facilitate significantly different degrees of lung recruitment and distension in different patients. Moreover, airway pressure alone might not be enough to conduct lung-protective PEEP titration[31]. Therefore, if PEEP increases (with a constant VT) and DP decreases, this suggests a rise in Crs, and more non-aerated lung units are recruited *via* the higher PEEP. Likewise, if the DP increases and the Crs decrease with a rise in PEEP, it signifies that increased PEEP causes the aerated lung systems to overdistention. Accordingly, titrating PEEP to reduce DP can allow the clinician to reduce possible VILI.

However, since DP is mathematically coupled with VT and elastance, "causal mediation" does not provide a clear causal relation between setting a particular DP and the outcomes. As a result, a change in elastance after an intervention suggests a change in lung dynamics beyond a specific DP value setting. As recently shown by Guérin *et al*[33], when Pplat, VT, and PEEP are set within the close ranges of protective ventilation, DP does not give any additional benefit over indices of lung mechanics such as elastance Crs or Pplat. Indeed, independently from complex statistics, the best association between outcome and DP, instead of VT/kg PBW, is self-evident considering the correlation between the two variables: Elastance and VT. DP = VT × elastance. As revealed, Guérin *et al*[33] in 2016 suggest that the impact of DP on survival may be either due to elastance (severity of the disease) or VT (degree of strain). Another study revealed that DP and lung stress were closely linked. The optimal cutoff value for the DP was 15.0 $cmH_2O$ for lung stress greater than 24 $cmH_2O$ or 26 $cmH_2O$, a level that has been associated with VILI[19]. Furthermore, other randomized controlled trials in patients with ARDS proved that besides Crs and Pplat, DP is an associated risk factor for elevated hospital mortality[33].

### *Influencing DP measurements*

In ARDS, the mortality of ventilation with lower VT ventilation varies with respiratory system elastance, indicating that lung-protective ventilation strategies should focus on DP rather than VT[14,3]. Baedorf Kassis *et al*[31] reported ventilation strategies that reduce DP and elastance are linked to decreased 28-day mortality in ARDS patients. The lung open ventilation study (2008) for 56 ARDS patients, which evaluated esophageal pressures in patients with ARDS, witnessed the use of PEEP titration to target positive transpulmonary pressures improved both elastance and DP[31].

Several studies confirmed that DP values are significantly changed by how Pplat and PEEP are measured[31-33]. As intrinsic PEEP (autoPEEP) is frequently greater than PEEP in patients with ARDS, the standard calculation will overestimate DP if total PEEP is not considered[34], higher DP may induce lung damage[35]. Mezidi *et al*[36] in 2017 confirmed that alveolar recruitment maneuvers with increased PEEP levels decrease DP in patients responding to alveolar opening. Likewise, DP increases again when the patient begins with alveolar collapse, even maintaining the same VT.

Recent evidence suggests that lung mechanics (*i.e.*, DP) should be used to titrate ventilation in ARDS patients rather than patient-based prescriptions (*i.e.*, VT based on ideal body weight)[36-38]. However, regional characteristics of lung parenchyma may locally amplify (*i.e.*, stress risers) the applied ventilation power and contribute to VILI[38]. Thus, small variations in VT or PEEP that result in a lower DP benefit can be considered protective for patients with acute respiratory failure or ARDS. The effect of DP in spontaneously breathing ARDS subjects has recently been investigated. The findings

support the effectiveness of determining DP during assisted MV, and the authors notice that subjects with lower DP and higher Crs have a greater chance of surviving[38].

### Discrepancy and conflicting data on DP

There was conflicting data regarding the additive prognostic advantage of DP beyond other pulmonary mechanics, such as Pplat and Crs, in confirmed ARDS cases. Amato *et al*[12] announced that DP was the most valuable ventilator parameter to treat ARDS because it was significantly associated with mortality. A study concluded that DP was also correlated with mortality, yet it provided the same information as Pplat[33]. Pplat predicted mortality better than DP in several studies[33]. For example, Villar *et al*[34], in their cohort of non-ARDS patients, indicated that fact. Measuring the Pplat correlated better with mortality than DP. Even in likely patients ventilated with a DP below 19 $cmH_2O$, a Pplat strictly below 30 $cmH_2O$ would enable a significant reduction in mortality, a greater effect than that of a DP below 19 $cmH_2O$ when the Pplat was already below 30 $cmH_2O$.

The PEEP level with the least overdistention and collapse does not always correspond to the best respiratory system Crs, particularly when tidal recruitment is affected by repetitive opening and closing of collapsed alveoli and small airways within atelectatic areas. Using DP separately may neglect the role of PEEP in treating and managing patients on ventilatory support. For instance, although a theoretically "safe" level of DP of 14 $cmH_2O$, it could become harmful if PEEP is 20 $cmH_2O$ or 0 $cmH_2O$[34,35]. Besides, using Crs could help clinicians easily recognize subjects at lower or higher risk of being exposed to "safe" or "unsafe" lung strain levels. However, higher DP may induce lung injury more easily in patients with low Crs[35]. Despite the possibility of reducing DP in patients with ARDS may improve survival rate, an accurate measurement of DP could be challenging in clinical settings. Furthermore, inaccuracies in ventilator pressure measurements and the role of spontaneous breathing efforts in the management of ARDS contribute to the clinical question about how to calculate and titrate DP at the bedside optimally[36].

### Clinical evidence supporting ventilation goal

In a secondary review of the lung safe study (2016), researchers investigated the predictors associated with beneficial outcomes in 2377 ARDS patients who underwent MV[37]. According to the authors, optimal DP, higher PEEP level, and lower RR were valid predictors to improve ARDS survival[37]. In another study, Pplat, DP, and Crs can be evaluated at the bedside during spontaneous breathing trials. Also, the data suggested that both higher DP and lower Crs are associated with more mortality[38].

In 2018, a systematic review and meta-analysis research observed that higher DP was associated with a significantly higher mortality rate in the meta-analysis of four studies of 3252 patients. The median DP between the higher and lower groups (interquartile range) was 15 $cmH_2O$[11]. At the same time, high DP was related to increased mortality in patients requiring pressure support ventilation mode. Non-survivors had a higher DP than survivors, but it was just one $cmH_2O$ where non-survivors had lower static Crs[39]. In adjusted analyses, a pooled database of 4549 ARDS patients who had enrolled in six randomized clinical trials and one large observational cohort of ARDS patients confirmed that DP was a significant predictor of mortality. Interestingly, during controlled MV in ARDS, mechanical power was associated with mortality, but a simplified model using DP and RR was equivalent[39].

### Impact of DP on survival in ARDS

Researchers in 2015 identified DP as an independent factor correlated with survival in patients with ARDS[12]. Their study demonstrated that lower DP levels were significantly associated with improved survival rates in ARDS patients. Similarly, another study in 2021 found that reduced DP following protocolized ventilator adjustments was more strongly linked with lower mortality than improvements in the $PaO_2/FiO_2$ ratio[30]. A meta-analysis conducted in 2018 conducted involving 3252 patients and observed that higher DP was associated with a significantly higher mortality rate[11]. Further researcherconfirmed these findings by showing that DP was a significant predictor of mortality in ARDS[40,41].

### Mechanisms of DP reduction

A study in 2015 suggested that active modification of the lung "mechanical scenario" through lung recruiting and PEEP selection could reduce DP[28]. This approach involves redistributing VT from overextended to recruited lung regions, thereby decreasing overdistension and improving lung Crs. Another retrospective study of 150 heavily sedated and paralyzed ARDS patients, finding that higher DP was significantly related to greater lung stress and mortality[19]. Additional study confirmed that DP values are significantly influenced by how Pplat and PEEP are measured[31]. Intrinsic PEEP (auto-PEEP) can overestimate DP if total PEEP is not considered. Further research reported that alveolar recruitment maneuvers with increased PEEP levels decrease DP in patients responding to alveolar opening, although DP increases again when the patient begins with alveolar collapse[28-41].

### Influence of DP on ventilation strategies

Researchers in 2015 explained that DP can be measured through the difference between Pplat and PEEP[12]. The Crs of the respiratory system is measured as a ratio between VT and DP. Adjusting VT through available lung units by measuring DP can contribute to a more effective protective lung strategy in ARDS patients. Another study stated that DP may vary from minimal variations to considerable overestimation of transpulmonary DP, depending on patient-specific factors like obesity or abdominal hypertension[19]. DP correlates with lung stress and can be used to identify overdistension. Further research showed that when Pplat, VT, and PEEP are set within close ranges of protective ventilation, DP does not provide additional benefit over indices of lung mechanics such as elastance Crs or Pplat[33]. Additional studies reiterated that DP values are significantly influenced by how Pplat and PEEP are measured, with intrinsic PEEP

potentially overestimating DP if total PEEP is not considered[31-42].

## DISCUSSION

The findings from this review highlight the critical role of DP in the management of ARDS. The review emphasizes that lower DP is significantly associated with improved survival rates in ARDS patients. The physiological basis of DP, noting that it represents the pressure differential around the lung. While measuring transpulmonary DP might offer a more accurate assessment of lung stress, it is often impractical in clinical settings due to the need for esophageal manometry. Instead, DP can be readily measured at the bedside, making it a practical surrogate for lung stress in most patients.

With regards to the relationship between DP and lung mechanics, it is indicating that DP is a better predictor of mortality than VT alone. This is because DP accounts for the Crs of the respiratory system, which varies among patients. The review highlights that controlling VT without considering lung mechanics may be ineffective, and adjusting VT based on DP can lead to more effective lung-protective ventilation strategies. Several challenges in measuring and interpreting DP are noted. For instance, intrinsic PEEP (autoPEEP) can lead to overestimation of DP if not properly accounted for. Additionally, the variability in chest wall and abdominal mechanics among critically ill patients can affect DP measurements. Also, DP is a valuable parameter, and it should not be used in isolation but rather in conjunction with other indices of lung mechanics such as elastance and Pplat.

## CONCLUSION

The clinical evidence underscores the importance of DP as a critical parameter in the management of ARDS. Lower DP is consistently associated with better survival outcomes, making it a valuable target for lung-protective ventilation strategies. While there are challenges in measuring and interpreting DP, its practical applicability at the bedside makes it a useful tool for clinicians. Future research should continue to refine our understanding of DP and its role in optimizing ventilation strategies for ARDS patients. Integrating DP with other indices of lung mechanics can enhance the precision of ventilatory support and improve patient outcomes.

## FOOTNOTES

**Author contributions:** Alzahrani HA, Corcione N, Alghamdi SM, Alhindi AO, Albishi QA, Mawlawi MM, Nofal WO, Ali SM, Albadani SA, AlJuaid MA, Alshehri AM, and Alzluaq MZ were involved in the writing of the first draft, revision of manuscript, work design, data collection, data analysis and data interpretation; and all authors thoroughly reviewed and endorsed the final manuscript.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**PRISMA 2009 Checklist statement:** The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.



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**S-Editor:** Bai Y
**L-Editor:** A
**P-Editor:** Guo X

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*World J Crit Care Med* 2025 June 9; 14(2): 99445

DOI: 10.5492/wjccm.v14.i2.99445

ISSN 2220-3141 (online)

META-ANALYSIS

# Association between neutrophil-to-lymphocyte ratio and hematoma expansion in spontaneous intracerebral hemorrhage: A systematic review and meta-analysis

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**Specialty type:** Critical care medicine

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade C

**Novelty:** Grade C

**Creativity or Innovation:** Grade C

**Scientific Significance:** Grade B

**P-Reviewer:** Lin YJ

**Received:** July 22, 2024

**Revised:** December 2, 2024

**Accepted:** December 16, 2024

**Published online:** June 9, 2025

**Processing time:** 219 Days and 12.1 Hours

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## Abstract

### *BACKGROUND*

Hematoma expansion (HE) typically portends a poor prognosis in spontaneous intracerebral hemorrhage (ICH). Several radiographic and laboratory values have been proposed as predictive markers of HE.

### *AIM*

To perform a systematic review and meta-analysis on the association of neutrophil-to-lymphocyte ratio (NLR) and HE in ICH. A secondary outcome examined was the association of NLR and perihematomal (PHE) growth.

### *METHODS*

Three databases were searched (PubMed, EMBASE, and Cochrane) for studies evaluating the effect of NLR on HE and PHE growth. The inverse variance method was applied to estimate an overall effect for each specific outcome by combining weighted averages of the individual studies' estimates of the logarithm odds ratio (OR). Given heterogeneity of the studies, a random effect was applied. Risk of bias was analyzed using the Newcastle-Ottawa Scale. The study was conducted following the Preferred Reporting Items for Systematic Review and Meta-analysis guidelines. The protocol was registered in PROSPERO (No. CRD42024549924).

### *RESULTS*

Eleven retrospective cohort studies involving 2953 patients were included in the meta-analysis. Among those, HE was investigated in eight studies, whereas PHE growth was evaluated in three. Blood sample was obtained on admission in ten studies, and at 24 hours in one study. There was no consensus on cut-off value

among the studies. NLR was found to be significantly associated with higher odds of HE (OR = 1.09, 95%CI: 1.04-1.15, $I^2$ = 86%, $P$ < 0.01), and PHE growth (OR = 1.28, 95%CI: 1.19-1.38, $I^2$ = 0%, $P$ < 0.01). Qualitative analysis of each outcome revealed overall moderate risk of bias mainly due to lack of control for systemic confounders.

***CONCLUSION***

The available literature suggests that a possible association may exist between NLR on admission and HE, and PHE growth. Future studies controlled for systemic confounders should be designed to consolidate this finding. If confirmed, NLR could be added as a readily available and inexpensive biomarker to identify a subgroup of patients at higher risk of developing HE.

**Key Words:** Neutrophil-to-lymphocyte ratio; Hematoma expansion; Perihematomal growth; Intracerebral hemorrhage; Hemorrhagic stroke



**Core Tip:** In this work, we provide an updated and concise quantitative synthesis of the literature addressing the association between neutrophil-to-lymphocyte ratio and hematoma expansion (HE) in intracerebral hemorrhage. We found an independent association between neutrophil-to-lymphocyte ratio (NLR) on admission and HE, and perihematomal growth. Our findings support the idea that NLR could be added as a readily available and inexpensive biomarker to identify a subgroup of patients at higher risk of developing HE.

**Citation:** Loggini A, Hornik J, Henson J, Wesler J, Hornik A. Association between neutrophil-to-lymphocyte ratio and hematoma expansion in spontaneous intracerebral hemorrhage: A systematic review and meta-analysis. *World J Crit Care Med* 2025; 14(2): 99445

**URL:** https://www.wjgnet.com/2220-3141/full/v14/i2/99445.htm

**DOI:** https://dx.doi.org/10.5492/wjccm.v14.i2.99445

## INTRODUCTION

Spontaneous intracerebral hemorrhage (ICH) is the most devastating type of stroke, and it is associated with high morbidity and mortality[1,2]. Initial hematoma expansion (HE) has been shown to be associated with poor outcome[3]. As such, early predictors of HE, including clinical and radiographic markers, have been extensively investigated[4,5]. Prediction scores for HE have been proposed and compared to each other[6] in an effort to best predict which patients would benefit from enrollment in trials targeted to reducing HE[7,8].

Detection of abnormal systemic inflammatory markers is a frequent encounter in the critically ill patient[9]. In acute ischemic stroke, elevated inflammatory markers have been demonstrated to have a negative prognostic significance given their role in developing secondary neurological injury[10,11]. Neutrophil-to-lymphocyte ratio (NLR) has been reported to be an independent prognostic factor in ICH, being associated with neurological deterioration, short-term mortality, and major disability at 90 days[12-16]. A meta-analysis from 2022 has failed to observe a significant association between NLR and HE[17]. However, the bulk of literature on the topic has significantly grown since then. Here we presented an updated systematic review and meta-analysis aimed at assessing the association between NLR and HE in ICH. The secondary objective was to assess the role of NLR in perihematomal (PHE) growth in ICH.

## MATERIALS AND METHODS

### *Protocol*

This systematic review was registered *via* PROSPERO (No. CRD42024549924) and conducted and presented in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement[18]. Ethical approval was not required because data was synthetized from previously published studies.

### *Study design*

This is a systematic review and meta-analysis aimed at assessing the association of NLR and HE in ICH. Additional outcome investigated was the association between NLR and PHE growth.

### *Search strategy*

Three databases (PubMed, EMBASE, and Cochrane) were searched from inception to May 22, 2024, without linguistic or geographical limitation using the following keywords "neutrophil-to-lymphocyte ratio" or "neutrophil lymphocyte ratio"

or "neutrophil-lymphocyte ratio" in conjunction with "hematoma expansion" or "hematoma growth" or "intracerebral hemorrhage" or "ICH". The search strategy is available in supplementary material. Reference lists were searched manually for additional sources.

### Eligibility criteria

All articles identified from the literature search were screened by two authors (Loggini A and Hornik J), independently, as per the following inclusion criteria: (1) Adult population with spontaneous ICH; (2) Laboratory value indicating NLR; and (3) Clinical outcome focused on HE and PHE edema growth. Randomized clinical trials and controlled observational cohort studies were included in the review. Detailed information on participants, interventions, comparisons, outcomes and types of studies are provided in Supplementary Table 1. The relevance of the studies was assessed using a hierarchical approach based on title, abstract, and full manuscript.

### Assessment of study quality

Risk of bias was computed using the Newcastle-Ottawa Scale (NOS) by two authors (Loggini A and Hornik J), independently[19]. Disagreement between quality of the study was resolved by consensus.

### Data extraction

For each included study, the following variables were extracted independently by two authors (Loggini A and Hornik J): (1) Lead author; (2) Publication date; (3) Study design; (4) Number of participants; (5) NLR and its cut-off value; (6) Time of sample collection; (7) Markers of stroke severity; (8) Clinical outcomes of HE and PHE edema; and (9) Corresponding odds ratio (OR) and 95%CI values from multivariable analyses. If any of the above variables were not available in the full text publication, further information was sought by correspondence with the lead author of the study.

### Statistical analysis

The inverse variance method was applied to estimate an overall, unconfounded, effect estimate of NLR for each specific outcome by combining weighted averages of the individual studies' estimates of the logarithm OR. A $Z$ test was carried out to assess the significance of the OR. The $I^2$ was calculated by $\chi^2$ test to assess variability due to heterogeneity rather than chance. A substantial heterogeneity was assumed with $I^2 > 50\%$. 95%CI for HE and PHE edema were calculated with the Wilson method and placed in forest plots. A $P$ value < 0.05 was considered statistically significant. Statistical analysis was performed using Review Manager 5.3[20,21].

## RESULTS

### Study selection

A total of 241 studies were identified through database searching, including PubMed ($n$ = 103), EMBASE ($n$ = 134), and Cochrane ($n$ = 4). After removing 97 duplicates, the remaining studies ($n$ = 144) were screened for eligibility. A total of 120 records were excluded by title and by abstract. As a result, 24 studies were assessed with full-text review. Among those, 13 articles were excluded due to not investigating the desired population ($n$ = 4), protocol only ($n$ = 3), reviews ($n$ = 3), lack of control group ($n$ = 2), and pilot study ($n$ = 1). Finally, this meta-analysis included 11 articles that met the inclusion criteria[22–32]. The detailed PRISMA flow diagram is shown in Figure 1.

### Study characteristics

The characteristics of the included studies are summarized in Table 1[22-32]. No randomized controlled trials were identified; all studies were single center retrospective cohort analyses. HE was evaluated in eight studies[23,25–29,31,32]. HE was defined as an increase of 33% from baseline hematoma volume or absolute growth of more than 6 mL in five study[25,26,28,31,32], increase of 33% or absolute increase of 12.5 mL from baseline hematoma volume in two study[22, 23], whereas it was not defined in one study[27]. PHE growth was evaluated in three studies[24,29,30]. All of the included studies defined PHE growth as the absolute difference in the PHE volume between follow-up and first scan. Blood sample was obtained on admission in ten studies[23–32], and at 24 hours in one study[22]. There was no consensus on cut-off value of NLR among the studies.

### Study quality

The summary of the risk of bias for each of the outcomes is listed in Supplementary Tables 1, 2 and 3[22-32]. Their overall quality was acceptable, ranging on the NOS from 8/9 to 9/9 (9/9 being the highest study quality). Specifically, ten studies had moderate risk of bias for lack of control for systemic factors (systemic infections).

The presence of publication bias was not able to be assessed through visual assessment of asymmetry of the funnel plot as there were less than 10 studies included for each outcome.

### Study outcomes

Results of study outcomes are presented in Figure 2[22-32]. NLR was associated with significant higher odds of HE (OR = 1.09, 95%CI: 1.04-1.15, $I^2$ = 86%, $P$ < 0.01). A sensitivity analysis on the HE outcome was conducted by excluding studies one by one. After removing the study of Kim *et al*[30], the heterogeneity was decreased ($I^2$ = 83%) without affecting the result (OR = 1.07, 95%CI: 1.02-1.12, $P$ < 0.01). A subgroup analysis for the HE outcome was performed, including only the

**Table 1 Characteristics of included studies**

| Ref. | Design | *N* | Sample time | Cut-off value | Outcome | Outcome definition | Factors controlled for |
|---|---|---|---|---|---|---|---|
| Mao *et al*[30], 2024 | Retrospective | 117 | Admission | - | PHE | Difference between follow up scan and admission PHE | ICH volume, GCS score |
| Pisco *et al*[29], 2023 | Retrospective | 215 | Admission | - | PHE | Difference between follow up scan and admission PHE | NIHSS, glucose, neurosurgery procedure, ICH volume, ICH location, time to first HCT |
| Kim *et al*[31], 2023 | Retrospective | 520 | Admission | 5.63 | HE | ICH growth > 6 mL or > 33% of initial volume | Age, hypertension, diabetes, prior anticoagulation, GCS, NIHSS, WBC, glucose, SBP |
| Chu *et al*[27], 2023 | Retrospective | 301 | Admission | 5 | HE | - | Sex, diabetes, GCS, time to first HCT, ICH volume, WBC |
| Alimohammadi *et al*[28], 2022 | Retrospective | 221 | Admission | - | HE | ICH growth > 6 mL or > 33% of initial volume | ICH volume, SBP, GCS, WBC |
| Zhang *et al*[32], 2022 | Retrospective | 506 | Admission | - | HE | ICH growth > 6 mL or > 33% of initial volume | GCS, blend sign, swirl sign, hypodensities on CT |
| Fonseca *et al*[25], 2019 | Retrospective | 135 | Admission | 7.8 | HE | ICH growth > 6 mL or > 33% of initial volume | Systemic infection, time to fist CT, ICH volume, use of anticoagulant |
| Pektezel *et al*[22], 2019 | Retrospective | 383 | At 24 hours | - | HE | ICH growth > 12.5 mL or > 33% of initial volume | ICH location, use of anticoagulant |
| Wang *et al*[26], 2019 | Retrospective | 123 | Admission | 6.49 | HE | ICH growth > 6 mL or > 33% of initial volume | Age, sex, GCS, WBC, ICH volume, midline shift |
| Zhang *et al*[23], 2018 | Retrospective | 279 | Admission | 14.53 | HE | ICH growth > 12.5 mL or > 33% of initial volume | Time to fist CT, hydrocephalus, IVH, GCS, ICH volume, island sign |
| Gusdon *et al*[24], 2017 | Retrospective | 153 | Admission | - | PHE | Difference between follow up scan and admission PHE | ICH volume, HE, IVH, external ventricular drain placement, GCS, time to first CT |

CT: Computed tomography; HCT: Head computed tomography; HE: Hematoma expansion; ICH: Intracerebral hemorrhage; IVH: Intraventricular hemorrhage; GCS: Glasgow Coma Scale; NIHSS: National Institute of Health Stroke Scale; PHE: Perihematomal edema; SBP: Systolic blood pressure; WBC: white blood cells.

studies that uniformly considered HE as growth > 6 mL or > 33% of initial ICH volume. The result of the meta-analysis held true (OR = 1.13, 95%CI: 1.05-1.22, $I^2$ = 86%, $P$ < 0.01). NLR was also found to be associated with PHE growth (OR = 1.28, 95%CI: 1.19-1.38, $I^2$ = 0%, $P$ < 0.01).

## DISCUSSION

### *Summary of evidence*

This systematic review and meta-analysis included eleven retrospective cohort studies involving 2953 patients with ICH. The increasing volume of published data in recent years testifies to the rapidly developing interest in this topic. Our study showed that in patients with ICH, the NLR is associated with a higher trend of HE and PHE growth.

NLR is a marker of systemic inflammation[33]. In ICH, the local inflammatory response that occurs immediately after hematoma development involves the recruitment of peripheral leukocytes, with neutrophils being the first centrally recruited[34,35]. Additionally, the systemic stress response after ICH promotes the demargination of neutrophils and suppression of lymphocytes, further imbalancing the peripheral NLR[36,37]. Elevation of neutrophils in the brain parenchyma promotes neurotoxicity and alters the permeability of the blood-brain barrier[30,38–40]. The former appears to be the leading mechanism underlying PHE growth, while the latter drives HE.

The association between NLR and HE appears robust. Among the eight studies quantitatively summarized, most were homogeneous in the definition of HE, and a subgroup analysis restricted to a uniformed definition of HE confirmed the results. An association between NLR and PHE growth was also found. However, this association needs to be considered with more caution due to the low number of studies on the topic.

HE is an independent predictor of poor prognosis in ICH patients[3]. Several radiographic and laboratory values have been investigated as predictors of HE[4,5]. Among these, inflammatory markers are inexpensive laboratory tests frequently evaluated on admission. This makes NLR an exciting, inexpensive, and reliable potential early biomarker of HE in ICH. Developing sensitive early biomarkers of HE holds potential for transforming prognostic modeling, precision

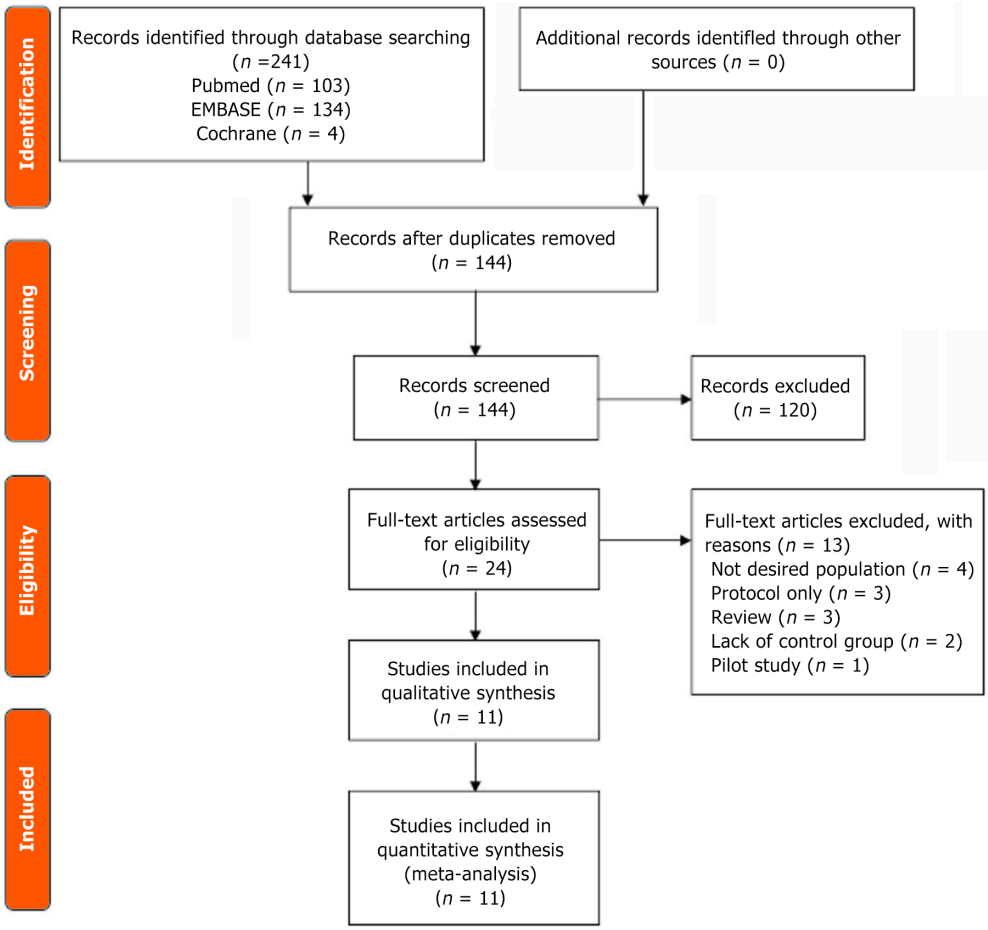


**Figure 1 Preferred Reporting Items for Systematic Review and Meta-analysis flow diagram.**

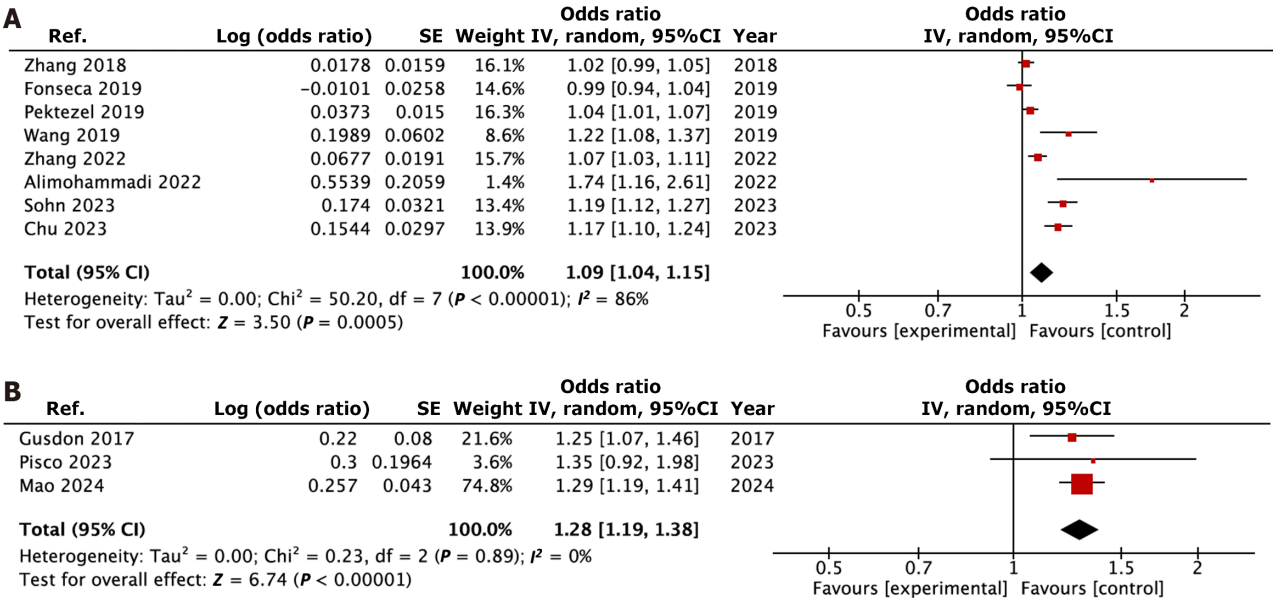


**Figure 2 Meta-analysis of the association.** A: Between NLR and hematoma expansion; B: Between NLR and perihematomal edema.

therapeutic targeting, and tailoring patient-specific treatment plans in ICH.

The association between high NLR and poor outcome has been well-documented in the literature[17]. Several studies have proven a correlation between NLR and mortality, and disability at 30 days and 90 days after ICH[12–16]. Furthermore, NLR has also been found to be associated with poor outcomes in other acute neurological conditions, such as severe traumatic brain injury[41,42]. The results of this meta-analysis, combined with the proven association with

outcomes, suggest that NLR may not simply be a bystander marker of poor outcome but could play an active role in the early development of secondary brain injuries, such as HE and PHE growth, that affect long-term outcomes.

As a nonspecific peripheral inflammatory marker, NLR has been evaluated in several diseases, such as cancer, heart failure, and infectious disease[43–45]. In the hyperacute phase, systemic infections can cause a sudden rise in the innate response alongside suppression of the adaptive response, leading to a rise in NLR[21]. While all included studies were appropriately controlled for known markers of ICH severity, only one study considered systemic infections as a covariable of interest[45].

Finally, it is important to note that the studies included in this meta-analysis were designed as retrospective cohort studies. The association between NLR and HE and PHE appears robust. However, no assumptions can be made about the effect that modulating the NLR could have on ICH outcomes.

A future large multi-center prospective study should be designed to enroll subjects from different geographical areas worldwide, sampling blood of participants at presentation, controlling for markers of ICH severity and systemic confounders, and following the temporal behavior of NLR. This would help to consolidate the available literature and clarify the association and relationship between NLR, HE, PHE, and outcomes in ICH.

### *Limitations*

The main limitation of this meta-analysis is that all included studies were retrospective cohort analyses, which are inherently subject to selection bias and confounding factors. Additionally, the definition of HE varied among the studies, and the cut-off values for NLR were not consistent. Finally, the relatively small number of studies included in this meta-analysis limited the ability to perform further subgroup analyses and assess consistency across different populations, aside from a subgroup analysis on a homogeneous definition of HE.

## CONCLUSION

The available literature suggests that a possible association may exist between NLR on admission and HE, and PHE growth. Future studies controlled for systemic confounders should be designed to consolidate this finding. If confirmed, NLR could be added as a readily available and inexpensive biomarker to identify a subgroup of patients at higher risk of developing HE.

## FOOTNOTES

**Author contributions:** Loggini A was responsible for study concept, study design, data abstraction, data analysis, and drafting the manuscript; Hornik J was responsible for study design, data abstraction, data analysis, and drafting the manuscript; Henson J and Wesler J were responsible for data abstraction and data analysis; Hornik A was responsible for critical revision and approval of the final version of the manuscript; all of the authors read and approved the final version of the manuscript to be published.

**Conflict-of-interest statement:** None of the authors has any conflict of interest or financial disclosures to declare.

**PRISMA 2009 Checklist statement:** The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.



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**S-Editor:** Luo ML
**L-Editor:** A
**P-Editor:** Zhang XD

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World Journal of Critical Care Medicine

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*World J Crit Care Med* 2025 June 9; 14(2): 96624

DOI: 10.5492/wjccm.v14.i2.96624

ISSN 2220-3141 (online)

CASE REPORT

# Thrombolysis in dysfunctional valve and stroke

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**Specialty type:** Critical care medicine

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade B, Grade C

**Novelty:** Grade B, Grade C

**Creativity or Innovation:** Grade B, Grade B

**Scientific Significance:** Grade B, Grade B

**P-Reviewer:** Arboix A

**Received:** May 11, 2024

**Revised:** January 11, 2025

**Accepted:** February 18, 2025

**Published online:** June 9, 2025

**Processing time:** 292 Days and 0.2 Hours

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## Abstract

### *BACKGROUND*

Valvular heart disease affects more than 100 million people worldwide and is associated with significant morbidity and mortality. The prevalence of at least moderate valvular heart disease is 2.5% across all age groups, but its prevalence increases with age. Mitral regurgitation and aortic stenosis are the most frequent types of valvular heart disease in the community and hospital context, respectively. Surgical valve replacement (or mitral valve repair) is the standard of care for treating heart valve disease. However, the replacement of a prosthetic heart valve can lead to complications, either in the peri-procedural phase or in the long-term follow-up period.

### *CASE SUMMARY*

We present a case of a 71-year-old female patient with a history of mitral valve replacement and warfarin anti-coagulation therapy. She was admitted to the intensive care unit due to spontaneously reperfused ischemic stroke of probable cardioembolic etiology. A dysfunctional mitral prosthesis was identified due to malfunction of one of the fixed discs. Furthermore, a possible microthrombotic

lesion was suspected. Therefore, systemic thrombolysis was performed with subsequent normalization of mitral disc opening and closing.

*CONCLUSION*
This case underscores the critical importance of a multidisciplinary approach for timely decision-making in critically ill patients with prosthetic valve complications.

**Key Words:** Mitral valve thrombolysis; Stroke; Recombinant human plasminogen tissue activator; Heart valve disease; Prosthetic valve-associated thrombosis; Thrombotic dysfunction



**Core Tip:** We describe the case of a 71-year-old woman with a history of mitral valve replacement who presented with cardioembolic stroke due to prosthetic valve dysfunction and thrombotic obstruction. Advanced imaging confirmed the diagnosis. After careful assessment by neurology, cardiology, and critical care teams, systemic thrombolysis was performed as an alternative to surgery. The intervention successfully restored valve function without complications. This case demonstrates the value of collaborative decision-making and tailored treatment strategies in optimizing outcomes for patients with prosthetic valve thrombosis and associated complications.

**Citation:** Barrios-Martínez DD, Pinzon YV, Giraldo V, Gonzalez G. Thrombolysis in dysfunctional valve and stroke. *World J Crit Care Med* 2025; 14(2): 96624
**URL:** https://www.wjgnet.com/2220-3141/full/v14/i2/96624.htm
**DOI:** https://dx.doi.org/10.5492/wjccm.v14.i2.96624

## INTRODUCTION

Heart valve disease affects more than 100 million people worldwide and is associated with significant morbidity and mortality[1]. The prevalence of at least moderate valvular heart disease is 2.5% and it increases with age. Mitral regurgitation and aortic stenosis are the most frequent types of valvular heart disease within the community and hospital settings, respectively[2]. Surgical valve replacement or mitral valve repair are the standard of care for valvular heart disease treatment[3]; however, prosthetic heart valve replacement can be associated with complications in either the periprocedural phase or in the long-term follow-up period[4]. After prosthetic implantation, transthoracic or transesophageal echocardiography can detect valve dysfunction secondary to structural damage or thrombosis[5]. Prosthetic valve-associated thrombosis is a serious complication with a high mortality rate; the most common cause is inadequate anticoagulation therapy or other associated pathogenic factors, such as type of prosthesis and atrial fibrillation[6]. Although surgical treatment is usually preferred in cases of prosthetic valve-associated thrombosis, the optimal treatment approach remains controversial. The different therapeutic modalities available for prosthetic valve-associated thrombosis (heparin therapy, fibrinolysis, surgery) are largely influenced by the presence of valvular obstruction, valve location (left or right) and the patient's clinical status[7].

We present herein the case of a 71-year-old female patient with a history of mitral valve replacement and warfarin anticoagulation therapy. She was admitted to the intensive care unit for neurological monitoring due to spontaneously reperfused ischemic stroke of probable cardioembolic etiology. A dysfunctional mitral prosthesis was documented due to malfunction of one of the fixed discs. Furthermore, a possible microthrombotic lesion was suspected, so systemic thrombolysis was considered through a multidisciplinary approach with subsequent normalization of the opening and closing of the mitral discs.

## CASE PRESENTATION

### *Chief complaints*

A 71-year-old woman consulted the emergency department with symptoms of nausea, somnolence and headache.

### *History of present illness*

The patient presented with clinical symptoms over the course of 2 hours characterized by nausea, dizziness and intense headache, which did not improve with analgesic use such as acetaminophen.

### *History of past illness*

The patient has a history of mechanical mitral valve replacement 20 years ago with regular echocardiographic follow-up, last performed a year before admission. Transthoracic echocardiograms documented a normofunctioning prosthetic with

adequate transvalvular gradients.

### *Personal and family history*

Patient with a history of atrial fibrillation, warfarin use, and two cerebrovascular events in the last 3 years.

### *Physical examination*

On presentation, the patient was in hypertensive crisis with a blood pressure of 186/90 mmHg and mitral holosystolic murmur. There were no signs of acute heart failure and no neurological findings. NIH Stroke Score, 0 points.

### *Laboratory examinations*

Blood work analysis suggested anemia (hemoglobin: 10.7 g%; normal range: 13-16 g%), leukocytosis (total leukocyte count: 13700; normal range: 4500-11000) with a shift to the left (75% neutrophils), and thrombocytosis (platelets: 4.14 × $10^5$; normal range: 1.50-4.00 × $10^5$). Liver and kidney function tests were within normal limits. The patient had a subtherapeutic international normalized ratio of 1.3 (therapeutic range: 2.0-3.0).

### *Imaging examinations*

A simple cranial computed tomography (CT) scan was performed to rule out acute ischemic events and a cerebral magnetic resonance imaging showed right temporal punctate infarcts with recanalization, in addition to several old ischemic lesions.

Transthoracic echocardiogram was initially performed and identified high transvalvular gradients, with a mean gradient of 6 mmHg. However, it did not allow for adequate visualization of the valve prosthesis. Therefore, a transesophageal echocardiogram was subsequently performed. Three-dimensional evaluation revealed a thickened prosthesis with altered mobility of one of the discs, generating an increase in transvalvular gradients and moderate insufficiency, compatible with thrombotic dysfunction (Figure 1).

## MULTIDISCIPLINARY EXPERT CONSULTATION

Cardiology assessment was requested and, together with the neurocritical care service, thrombolysis was decided.

## FINAL DIAGNOSIS

Cardioembolic etiology was suspected.

## TREATMENT

We consulted the Neurology and Critical Medicine Departments on thrombolysis as an alternative treatment to surgery. We requested a cardiology assessment, and together with the neurocritical care service decided to perform thrombolysis.

Prior to the procedure, warfarin reversal with prothrombin complex is required. We confirmed that there was no residual anticoagulant effect at the time of tissue plasminogen activator administration, which was administered at a dose of 0.9 mg/kg, the initial 10% as a bolus and the remaining infusion for 60 minutes. The infusion was completed without complications, without major bleeding nor changes in clinical status.

## OUTCOME AND FOLLOW-UP

A transesophageal echocardiogram was performed 24 hours after thrombolysis and demonstrated normalization of the opening of the hemidiscs of the mitral valve prosthesis, reduction of the transvalvular gradients and reduction of the insufficiency to mild residual (Figure 2).

An additional CT scan of the skull showed no signs of bleeding. Anticoagulation therapy was restarted the day after thrombolysis.

The patient was transferred to a general hospital with adequate neurological evolution under anticoagulation therapy with unfractionated heparin. Warfarin was started for long-term anticoagulation and management of cardiovascular comorbidities. The patient was discharged without complications.

## DISCUSSION

The worldwide incidence of prosthetic valve thrombosis is 0.03% in bioprosthetic valves, 0.5% to 8% in mechanical valves in the mitral and aortic positions, and up to 20% in mechanical tricuspid valves[8]. In contrast, a previous study found

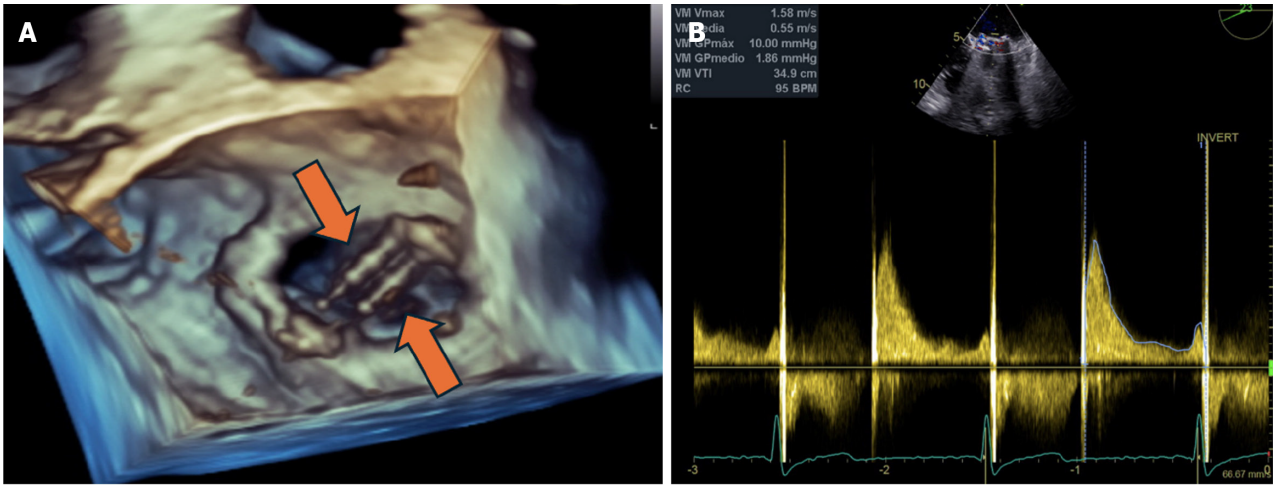


**Figure 1 Dysfunctional mitral valve prosthesis in transthoracic echocardiography.** A: Mitral valve prosthesis viewed from the atrium demonstrating the opening of only one of the two hemidiscs (arrows); B: Elevated mitral transvalvular gradient. Mean gradient of 6.4 mmHg.

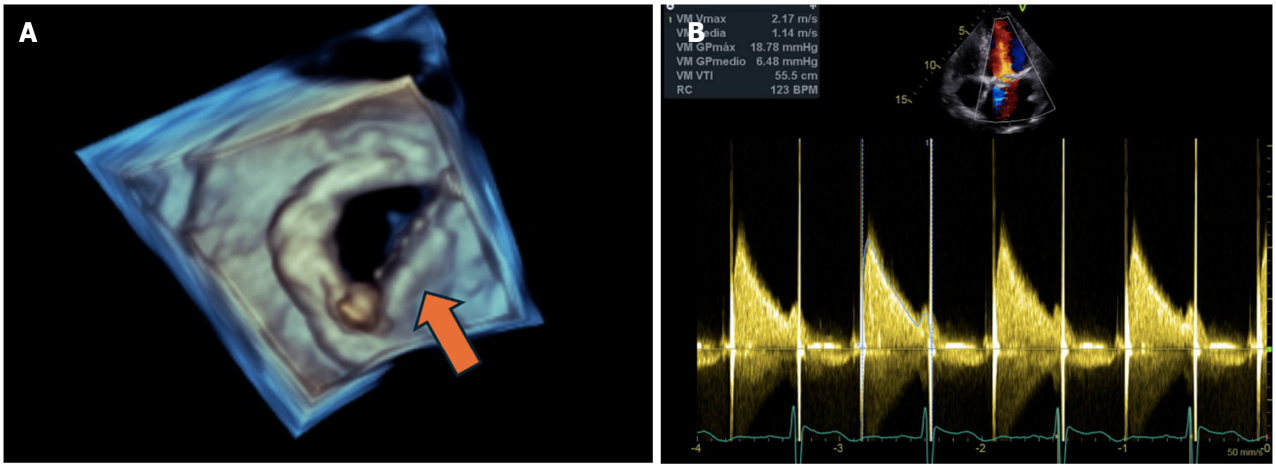


**Figure 2 Post-thrombolysis corrected mitral valve prosthesis in transthoracic echocardiography.** A: Mitral valve prosthesis viewed from the atrium with two open hemidiscs (arrows); B: Transvalvular mitral valve gradient after thrombolysis. Mean gradient of 1.8 mmHg.

that 1.2% of patients in a 402 person cohort had mitral valve disease[9]. Periprosthetic valve-associated thrombosis is not very common but is one of the most frequent complications of mechanical or biological valve prostheses. Thrombotic phenomena account for 11% of valve dysfunction[10]. Another study by the same group found that in a study of 575 patients with rheumatic mitral valve disease, acute cardioembolic phenomena occurred in 16.3% of patients[11]. Mitral valve dysfunction can occur through several mechanisms: Reduced leaflet motion, impaired leaflet coaptation, leaflet thickening, reduction or enlargement of the prosthetic orifice, leading to stenosis or insufficiency. These changes cause disruptions to the transvalvular gradients that may or may not co-occur with other associated symptoms[12]. Although inadequate anticoagulation is the main cause of this phenomenon, other comorbidities or associated factors contribute, including atrial fibrillation, mechanical prostheses, and prosthesis location. Finally, thrombin generation can be induced through tissue factor and contact coagulation pathway activation, increasing thrombotic risk through proatherogenic and proinflammatory mechanisms[13].

Patients with prosthetic valve dysfunction with or without thrombosis may present with variable symptoms ranging from progressive dyspnea and signs of heart failure or systemic embolization. It is sometimes even asymptomatic with non-obstructive thrombi. These patients are at an increased risk of developing cerebral embolism, manifesting as transient ischemic attack or stroke[13]. The preferred diagnostic tool remains transthoracic or transesophageal echocardiography. With current techniques, three-dimensional reconstruction of the prosthetic valve can aid in the assessment of disc mobility and define the etiology of prosthetic dysfunction. These assessments are important to determine the type of treatment required. It is most useful in asymptomatic patients with sub-therapeutic levels of anticoagulation. When a more detailed assessment of the valve, thrombus size and prosthetic valve body motion is required, transesophageal echocardiography and transthoracic echocardiography is recommended for hemodynamic assessment. Multimodality imaging has a class I-b indication in patients with suspected mechanical prosthetic valve thrombosis to assess valve function and presence of thrombus[14].

In this case study, our patient presented with a cardioembolic ischemic stroke. Echocardiogram analysis suggested that the stroke was caused by mitral mechanical prosthesis dysfunction with thrombotic lesion leading to mitral valve dysfunction. Left atrial thrombi are the most likely embolic source in these patients. Barbetseas *et al*[14] found that patients with ischemic stroke had a higher rate of mitral valve replacement and atrial fibrillation and increased left atrial size compared to patients with transient ischemic attack. However, none of these differences were statistically significant; the presence of left atrial thrombus, visualized by transesophageal echocardiography, was the only parameter that differentiated between patients with ischemic stroke and transient ischemic attack.

Antithrombotic treatments indicated in prosthetic valve thrombosis and thromboembolic events after prosthetic heart valve replacement can be broadly classified according to their mechanisms of action as antiplatelet-based strategies (aspirin and/or a P2Y12 receptor inhibitor) and anticoagulant-based strategies [using vitamin K antagonists (VKAs) or direct oral anticoagulants][1].

VKAs are the primary preventative treatment against thrombosis due to prosthetic valve dysfunction, with dosing adjusted to maintain INRs of 2 to 3 and 2.5 to 3.5 for mechanical heart valves implanted in the aortic and mitral positions, respectively; for bioprosthetic heart valves, anticoagulation with VKA is recommended for the 1$^{st}$ 3 months after the procedure, with a target INR between 2.0 and 3.0, regardless of prosthesis position (aortic, mitral or right)[3,15,16].

In recent years, thrombolytic therapy has become an alternative to surgery in the treatment of obstructive prosthetic valve thrombosis[4]. Fibrinolytic therapy has a success rate of over 80%[15]. The appropriate management for obstructive prosthetic valve thrombosis has remained debatable. Some guidelines [*e.g.*, European Society of Cardiology (ESC)] recommend surgery for all patients regardless of clinical status, while others (Heart Valve Disease Society) recommend thrombolytic therapy for all patients without contraindications[17,18]. However, the current update of the ESC/EACTS guidelines still considers surgery as the first-line approach[19].

Due to its high fibrin specificity, recombinant tissue-type plasminogen activator (tPA) is widely used in managing prosthetic heart valve thrombosis. However, streptokinase remains the drug of choice in low-income countries due to its relatively lower cost, while other agents such as tenecteplase and urokinase have also been used, with similar safety and efficacy compared to streptokinase[4,19].

## CONCLUSION

The ESC guidelines recommend the standard dose (recombinant tissue plasminogen activator 10 mg bolus to 90 mg over 90 minutes with unfractionated heparin) of fibrinolytic therapy (class IIa) based on a meta-analysis of seven trials[20]. The American College of Cardiology and American Heart Association guidelines recommend the use of slow infusion, low-dose (25 mg tPA over 6 hours to 24 hours without bolus) fibrinolytic therapy as a comparable initial approach (Class I)[5]. Comparison of complication rates between the study groups showed a statistically lower combined complication rate in the slow infusion low-dose tPA group[21]. The ultra-slow PROMETEE trial demonstrated that ultra-slow (25 hours) infusion of low-dose (25 mg) tPA without bolus dosing is associated with fairly low non-fatal complications and mortality without loss of efficacy, except for those with NYHA class IV[22].

For a patient with prosthetic valve thrombosis, stroke may be the initial symptom resulting in cerebral embolism or may be secondary to thrombolysis therapy, with rates as high as 5%-6% for left-sided prosthetic heart valve thrombosis[23]. The recommended RTPA dose according to the ischemic stroke guideline is 0.9 mg/kg over 60 minutes, with a bolus of 10% of the total dose over 1 minute[24].

Simple cranial CT scan is essential to exclude intracranial hemorrhage and to define the administration of thrombolytic agents[25]. There are no protocols for thrombolytic therapy in patients presenting with stroke associated with cardiac valvular prosthesis. However, accelerated thrombolytic therapy regimens may complicate treatment[25]. In their case report, Özka *et al*[24] demonstrated that prolonged low-dose infusion of thrombolytic therapy and its continuation for the treatment of acute cerebral ischemic complications induced thrombolysis and limited the risk of hemorrhage and embolization. It resulted in subsequent normal mitral valve function with no evidence of residual thrombus, as assessed by echocardiography. However, there is no consensus on the best thrombolytic therapy strategy or specific agent. Therefore, thrombolysis in ischemic stroke associated with prosthetic heart valve thrombosis may be an effective therapy in selected cases[26].

## ACKNOWLEDGEMENTS

We thank Dr. Nohra Piedad Romero Vanegas and the Echocardiography Service, Hospital Universitario Fundación Santa Fe De Bogotá, Bogotá, Colombia. We also thank the Neurology Service, Hospital Universitario Fundación Santa Fe De Bogotá, Bogotá, Colombia. During the final review and approval of the manuscript, our professor Jose del Carreño passed away. May he rest in peace.

## FOOTNOTES

**Author contributions:** Barrios-Martínez DD, Giraldo V, and Pinzon YV contributed to the conceptualization of this case report; Barrios-Martínez DD and Pinzon YV were involved in the writing and preparation of the original draft; Gonzalez G and Carreño JN contributed

to the reviewing and editing of the manuscript. All authors have read and approved the final manuscript, Professor Carreño JN passed away, when all finish the manuscript. Barrios-Martínez DD and Pinzon YV contributed equally to this work as co-first authors.

**Informed consent statement:** Informed written consent was obtained from the patient for publication of this report and any accompanying images.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).



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**S-Editor:** Qu XL
**L-Editor:** A
**P-Editor:** Zhang XD

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