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REVIEW

Mucosal COVID-19 vaccines: Risks, benefits and control of the pandemic

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Abstract

Based on mucosal immunization to promote both mucosal and systemic immune responses, next-generation coronavirus disease 2019 (COVID-19) vaccines would be administered intranasally or orally. The goal of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines is to provide adequate immune protection and avoid severe disease and death. Mucosal vaccine candidates for COVID-19 including vector vaccines, recombinant subunit vaccines and live attenuated vaccines are under development. Furthermore, subunit protein vaccines and virus-vectored vaccines have made substantial progress in preclinical and clinical settings, resulting in SARS-CoV-2 intranasal vaccines based on the previously successfully used nasal vaccines. Additional to their ability to trigger stable, protective immune responses at the sites of pathogenic infection, the

development of 'specific' mucosal vaccines targeting coronavirus antigens could be an excellent option for preventing future pandemics. However, their efficacy and safety should be confirmed.

Key Words: SARS-CoV-2; COVID-19 vaccine; Mucosal immunity; Intranasal vaccination; Oral vaccines; Resident memory T cells; Vaccine safety; Vaxart; OraPro-COVID-19 vaccine; RPS-vector system platform

Core Tip: Oral or nasal vaccination against coronavirus disease 2019 (COVID-19) would stimulate both the humoral and cellular immune responses and may exert many socioeconomic benefits. Mucosal vaccines are promising for preventing infections and reducing the transmission, morbidity and mortality of COVID-19. Mucosal vaccination may be used prophylactically in human populations at high risk for severe acute respiratory syndrome coronavirus 2. Currently, only a limited number of oral vaccines are approved for human use, and some others are included in preclinical and clinical trials to validate their efficacy and safety.

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INTRODUCTION

The current coronavirus disease 2019 (COVID-19) pandemic, characterized by the ongoing rapid spread and high mutation rate of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emphasizes the need for more efficient vaccinations to avoid preventable illness and mortality. In addition, SARS-CoV-2 is a mucosal pathogen that spreads *via* person-to-person respiratory droplets[1] and infects human respiratory epithelial cells and gastrointestinal tract by attaching to angiotensin-converting enzyme 2 *via* the spike (S) receptor-binding domain[2]. Thus, mucosal immunity will be primary for adequate and long-term viral protection[3].

To date, there are over 300 potential anti-SARS-CoV-2 vaccines at various stages of preclinical and clinical trials and 24 vaccines approved for emergency use in humans[4-6], (https://covid19.trackvaccines.org/trials-vaccines-by-country/). Approved vaccines and most of the preparations under development are intended to be administered intramuscularly to provide high levels of antibodies against systemic viral infection[7]. This method of administration is the most common immunization method. While it is not the most efficient option to protect against pathogens entering through the mucous membranes, it is still an effective method.

Thus, current vaccines against COVID-19 fail to fully prevent viral infection, which is partly due to the lack of mucosal immune activation. On the other hand, mucosal immunization has the ability to promote both mucosal and systemic immune responses[8].

Over 10 different vaccines against SARS-CoV-2 are in various stages of development, including virus-based vaccines, recombinant subunit vaccines and live attenuated vaccines[9-13]. Their development and application are encouraging because of the expected efficacy of the mucosal and systemic immune response they will elicit.

Despite the emergence of SARS-CoV-2 variants, people will prefer the next generation COVID-19 vaccine (*i.e.* intranasal immunization). This vaccine is expected to be very effective in producing both mucosal and systemic immune responses[13].

Various intranasal vaccines against SARS-CoV-2 are now being studied, even though they are not yet approved, with 12 candidates advancing to multiple stages of clinical trials, including virus-vectored vaccines, recombinant subunit vaccines and live attenuated vaccines[14].

NATURAL AND VACCINE-INDUCED MUCOSAL IMMUNITY: PRINCIPLE OF MUCOSAL VACCINES

The rationale for the need for effective COVID-19 vaccines that elicit mucosal immunity is to use early mucosal immune responses against the virus to prevent the virus from entering mucosal layers and causing infection. This is also called "sterilizing immunity"[15]. So far, the data show that people naturally infected with SARS-CoV-2 produce mucosal immunoglobulin (Ig)A antibodies (*e.g.*, saliva,

nasal swab/wash or bronchoalveolar lavage fluid) and systemic IgG antibodies[16,17].

However, firstly, when SARS-CoV-2 infiltrates the nasal and/or oral cavities, nasopharynx-associated lymphoid tissue, bronchial-associated lymphoid tissue and mucosa-associated lymphoid tissue act as the first line of defense against viral infection[18]. In addition, all components of the innate immunity of the upper respiratory tract and/or the gastrointestinal tract (phagocytic neutrophils, macrophages, dendritic cells, resident microfolded M cells, innate lymphoid cells, natural killer cells and mast cells) [19] and immune molecules (*i.e.* galectins, collectins, cytokines and others) are involved in the immune response against the virus in various ways[20]. Additionally, T helper (Th)1- and Th2 cells, IgA-switched B cells are also rapidly activated after the initial interaction of SARS-CoV-2 with the innate immunity of the host[21].

These immune cells can work together to produce an integrated system that includes pattern-recognition receptors such as toll-like receptor 7 or toll-like receptor 8[22]. They identify molecular patterns (*i.e.* single-stranded RNA) associated with viral pathogens, resulting in increased production of proinflammatory cytokines such as type I interferon. Interferons have an essential role in the early stages of viral infection[23]. However, SARS-CoV-2 possesses the ability to suppress the production of interferons. The complement system is a vital part of innate immunity against SARS-CoV-2, which contributes to acute respiratory distress syndrome and cytokine storm[24]. Therefore, it is important to consider antibody-based treatments and vaccines when developing strategies to fight SARS-CoV-2.

After the innate immune system activation through dendritic cells, T and subsequent B cells specific to SARS-CoV-2 are recruited, mainly in the systemic bloodstream[25]. However, the simultaneous expansion of CD4+ T-helper cells, CD8+ cytotoxic T cells and plasma cells is crucial for viral elimination. Specific SIgA protects against SARS-CoV-2 by neutralizing it, suppressing its adhesion ability and agglutinating. This allows for a stronger anti-inflammatory response[26].

Traditional injectable vaccines are not very effective at inducing mucosal immunity. Furthermore, the benefits of such vaccination that leads to mucosal (SIgA) and circulating (IgG and IgA) antibody formation as well as SARS-specific effector and memory T cell responses have not been demonstrated in conventional vaccines[27,28].

However, a study showed induced S1-specific neutralizing IgA and IgG responses in the nasal mucosa following BNT162b2 but not after inactivated virus vaccine[29]. Additionally, it was shown that nasal immunization after an intramuscular vaccine could induce robust mucosal immunity to prevent mucosal pathogen entrance and development. A recent animal study showed promising results for using mucosal booster immunizations after mRNA priming to elicit mucosal immunity in addition to systemic responses[30].

There is evidence that SARS-CoV-2 nasal vaccination provides protection against both ancestral and mutant strains (*i.e.* variants of concern, B.1.1.7 and B.1.351)[31]. Furthermore, the authors suggest that adenovirus (Ad)-vectored multivalent vaccination delivered *via* the respiratory mucosa is a viable next-generation COVID-19 vaccine approach for inducing overall mucosal immunity against existing and future variants of concern[31].

Similarly, a combination of mucosal prime and systemic booster vaccines has been shown to increase the lifespan of lung CD8+ resident memory T cells[32]. In addition, CD4+ resident memory T cells are essential to developing protective CD8+ memory cells and B lymphocytes[33,34]. The ability of nasal vaccinations to induce resident memory T cells in the respiratory and gastrointestinal tract considerably increases their effectiveness. The development of nasal vaccines also relies on the data that mucosal immunization can elicit a wide range of adaptive immune responses, including SIgA antibodies and resident memory T cells[35]. Nasopharynx-associated lymphoid tissue is an important location for the induction of mucosal immune responses. Th1- and Th2-polarized lymphocytes, as well as IgA-secreting B cells, proliferate there. SIgA antibodies neutralize toxins and pathogens *via* immunological exclusion, antigen excretion and intracellular neutralization[36-38].

Additionally, we must keep in mind that mucosal SIgA levels raise up rapidly in babies, and these levels reach adult levels early in the childhood[39]. This should be considered when developing vaccines for children[40]. Also, although the titers of protection are not known now, virus-neutralizing antibodies are needed to protect and control the infection[41].

Nasal vaccination successfully stimulates resident memory T cell production, and persistent antigens in the lungs and gut can support long-term memory cell maintenance[42]. Resident memory T cells (especially CD8+) in the mucosa may help protect the body against virus infection by producing cytokines that mediate tissue antiviral resistance and chemokines that attract additional immune cells [43]. It is known that resident memory T cells are more effective at protecting the lungs than circulating T cells[44]. Furthermore, these memory cells can move from the lungs to mediastinal lymph nodes *via* a mechanism known as "retrograde migration" to maintain the memory phenotype and provide long-term protection[45].

The principle of intranasal vaccines, the vaccine-induced immune responses, mucosal involvement and benefits are shown in Figure 1.

Intranasal and oral COVID-19 vaccines promise to generate both local and systemic immune responses. Fortunately, the local activation of innate antigen-presenting cells by viral antigens leads to the stimulation of adaptive immune cells and an efficient immune response against the virus. Once this occurs, this local immune response has the potential to spread to other mucosal surfaces in the

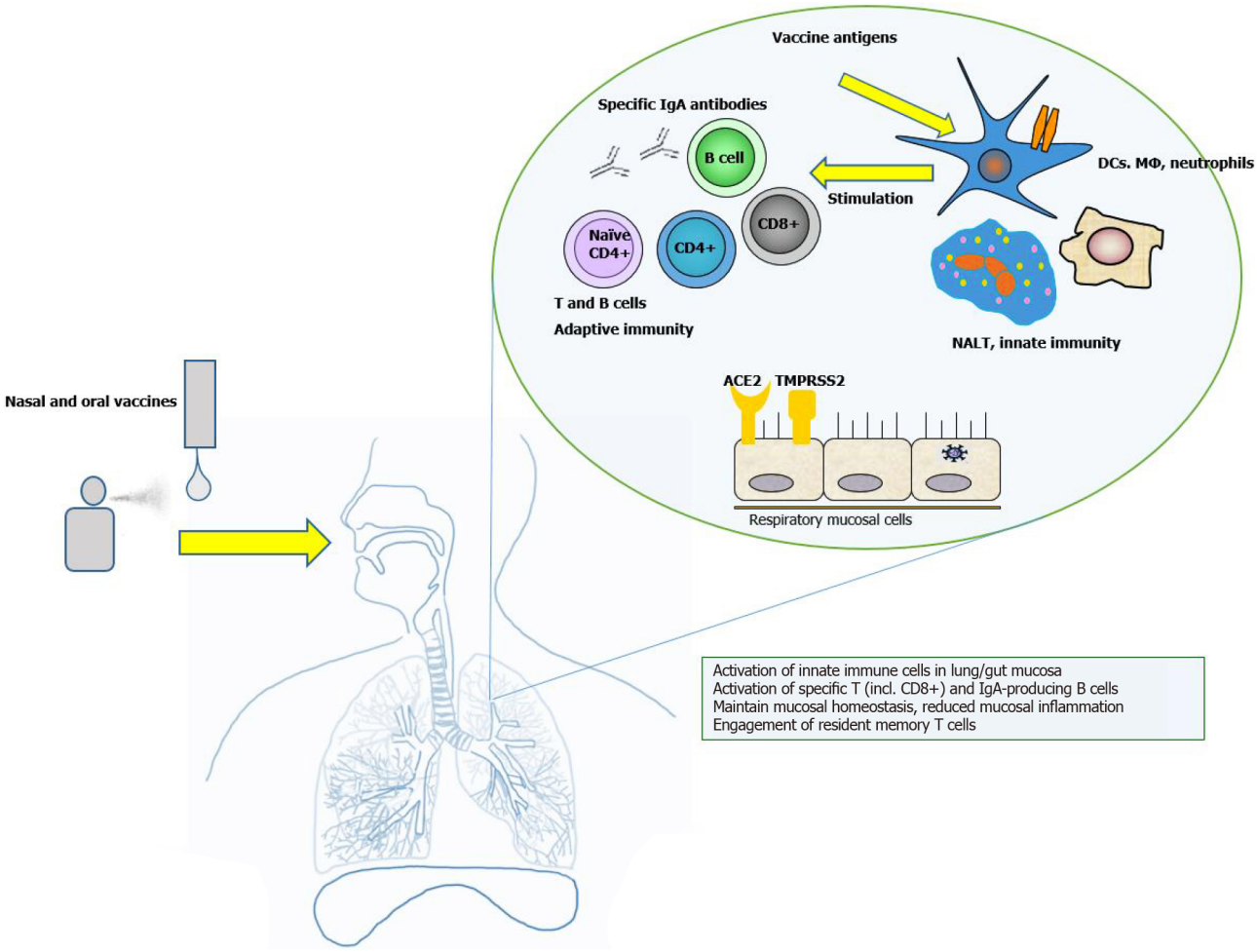

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Figure 1 Intranasal and oral coronavirus disease 2019 vaccines promise to induce both local and systemic immune responses. ACE2: Angiotensin-converting enzyme 2; DCs: Dendritic cells; Mф: Macrophages; NALT: Nasopharynx-associated lymphoid tissue; Ig: Immunoglobulin; TMPRSS2: Transmembrane serine protease 2.

organism. It is assumed that local immunity will prevent virus entry and shedding and keep low levels of inflammation in the mucous membranes. Some adaptive cells remain in the mucosa and act as effector T cells or specific IgA-plasmacytes. Some of them exert systemic antiviral effects by going to the periphery. Additionally, activated innate and adaptive immune cells can clear the virus at the infection site, leading to undetectable viral RNA in airways and gut mucosa, leading to long-term immunity.

SUCCESSFUL MUCOSAL VACCINES IN HISTORY

Humans have been licensed to eight oral and one intranasal vaccines against various mucosal infections. All of these vaccines are complete viral vaccines[1,32]. These types of vaccines are exceptionally preferred since they do not involve needles. In addition, subunit protein vaccines and virus-vector vaccines have significant advantages. Therefore, using all the scientific data and knowledge gained over the years about these types of vaccines, the scientific community is trying to create nasal vaccines SARS-CoV-2 based on already used vaccines in human history[32].

Oral vaccination can be used prophylactically in human populations at high risk for SARS-CoV-2. Thus, it could be the most cost-effective and efficient way to reduce the transmission of infection and morbidity. As we already stated, a needle-free vaccine eliminates the risk of transmitting blood-borne infections. Another benefit is that healthcare staff can perform oral vaccination without medical training. Pain and discomfort from a needle stick are avoided, as is the need to monitor side effects[32].

Type 1 and 2 monovalent oral poliovirus (OPV) vaccines (serotypes 1 or 3) and bivalent containing serotypes 1 and 3 were approved and licensed in 1961 and type 3 monovalent OPV vaccine in 1962. A trivalent OPV vaccine was approved in 1963. The World Health Organization (WHO) has announced that types 2 and 3 have been eradicated in 2015 and 2019, respectively. It turns out that OPV is the most effective and successful polio vaccine by inducing poliovirus-specific mucosal immunity[46].

The OPV contains a live poliovirus strains (Sabin). The strains are derived from wild polioviruses and have been reduced in virulence. Poliovirus is a member of the enterovirus subgroup of the Picornaviridae family. Picornaviruses are small viruses with an RNA genome, characterized by three poliovirus serotypes (type1, type 2 and type 3). Scientists have proven that immunity to one serotype does not confer significant immunity to other serotypes[47,48]. The virus enters the mouth and spreads throughout the oropharynx and gastrointestinal tract. The poliovirus is usually present in the nasopharynx for 1 wk to 2 wk and can be excreted in the feces for several weeks after infection. Even people with mild symptoms or without illness can be sources of infection[49].

In 2020, a global campaign was launched to end OPV use and switch to inactivated polio vaccination. But the last reports show that the neutralizing antibodies found in the nasopharynx of patients treated with OPV were more than those treated with inactivated polio vaccination[50].

After being ingested, the OPV vaccine replicates in the intestinal mucosa and lymphoid cells in the oropharynx and intestine. It behaves similarly to wild poliovirus. Vaccine strains are excreted in the feces of the vaccinated individual up to 6 wk after a dose, with maximum excretion occurring in the first 1-2 wk.

The OPV vaccine is very effective in protecting people from poliovirus. Interference among serotypes was observed during replication in the gut. A single dose of trivalent OPV elicits immune responses to all three vaccine viruses in half of recipients[51].

It is crucial that the OPV vaccine produces localized immunity in the intestines. This decreases the amount of virus that is shed when someone is re-infected with the same poliovirus serotype and reduces the chance of potential transmission. Subsequent vaccine doses reduce interference during gut replication. In contrast, three doses of vaccine provide immunity to all three poliovirus serotypes in more than 95% of recipients in industrialized countries. The immunity from the OPV is probably lifelong[52,53].

The OPV vaccine has been proven to have many benefits over the years, including providing non-specific protection against other infections. In addition, various studies have been conducted to research the effects of OPV and live enterovirus vaccines on the induction of non-specific immune responses, which show the non-reactogenicity and safety of vaccines[54-57].

All these studies demonstrated that cytopathic agents in the gastrointestinal tract decrease and reduce isolated infections of influenza, Ad, parainfluenza, herpesviruses, *etc.* According to these findings, OPV may offer protection against other viral respiratory infections.

In 2015, another research group conducted a retrospective cohort study in Denmark. They studied how the incidence of infection among the children with various infections changes depending on the last vaccine children received: OPV, DTap- inactivated polio vaccination-Hib (diphtheria-tetanus-acellular pertussis-inactivated poliovirus-Haemo type b) or measles, mumps, rubella (MMR)[58]. A similar study was conducted in the United States. The results show the most significant reduction in non-specific infections with live vaccines[59].

When COVID-19 cases began to rise worldwide, the researchers began studying the effects of OPV vaccines in symptomatic and asymptomatic patients because the SARS-CoV-2 virus suppresses the innate immune system, which affects adaptive immunity[60]. Suppose the damage to the innate immune system is crucial for the transmission and infection of SARS-CoV-2. In that case, it may be suggested that preparing the immune system before infection can alleviate the course of the COVID-19 disease. Furthermore, evidence suggests that the prophylactic use of OPV or other live vaccines prior to COVID-19 may activate innate immunity and strengthen the immune system for the subsequent SARS-CoV-2 infection[61-63]. Therefore, it is necessary to consider the potential benefits of the OPV vaccine and its application before or together with the available COVID-19 vaccines.

Since the start of the COVID-19 pandemic, scientists have been scrutinizing rotavirus vaccines. Rotavirus is a double-stranded RNA virus (Reoviridae family). The outer capsid contains two important proteins, VP7 (G-protein) and VP4 (P-protein), which stimulate neutralizing antibodies. It is believed that they play an important role in immune protection[64]. The scientists proved that up to 60%-70% of children with severe rotavirus gastroenteritis demonstrate rotavirus antigen and RNA in serum (antigenemia). However, the immune correlates of protection for rotavirus are still not fully understood [64].

The antibodies against VP7 and VP4 that are found in the serum and mucosa probably play a crucial role in protecting against disease. Cell-mediated immunity probably helps to protect from infection and recover from it. Unfortunately, immunity usually does not last long after a vaccine is given. Re-infection can happen at any age[64].

Two live oral rotavirus vaccines, RV5 (RotaTeq) and RV1 (Rotarix), are currently approved for use [65]. In Finland and the United States, Phase III clinical efficacy trials of the RV5 vaccine were conducted. The data proved 74% efficacy after a 3-dose series against G1-G4 rotavirus gastroenteritis and 98% against severe G1-G4 rotavirus gastroenteritis, during the first entire rotavirus season after vaccination. Furthermore, scientists observed children during the first 2 years of life in a large health care utilization study. Among them, the RV5 vaccine decreased the incidence of G1-G4 rotavirus gastroenteritis: medical visits by 86%, emergency department visits by 94% and hospitalizations by 96% [66].

In Latin America and Europe, phase III clinical efficacy trials of RV1 vaccine were conducted. This study found that the 2-dose series against severe rotavirus gastroenteritis is 85% effective to age 1 year. The European study estimated the vaccines efficacy against severe rotavirus gastroenteritis is 96% through the first rotavirus season and 87% against any rotavirus gastroenteritis. The trial data also showed that vaccinating against rotavirus resulted in a 96% reduction in the number of hospitalizations for rotavirus gastroenteritis in the second season after vaccination[67].

In the United States, several RV5 and RV1 case-control vaccine effectiveness evaluations have been conducted among children between 2 years or 3 years or younger. The scientists found that the vaccine effectiveness against the combined outcome of emergency department visits or hospital admission for rotavirus was estimated at 84% for the RV5 and 83% for the RV1 vaccine. Evaluations of vaccine effectiveness tends to increase as the severity of rotavirus disease. Both vaccines have been shown to be effective against a wide range of rotavirus genotypes[68].

The exact duration of immunity with rotavirus vaccine is still unknown. However, effectiveness has been demonstrated in the first 2 years to 3 years of life in the United States. Vaccine efficacy was generally lower in the 2nd year of life than in the 1st year in low-income countries[66,69,70].

In the last 2 years, two more vaccines have received much attention concerning COVID-19. These are the tuberculosis vaccine Bacille Calmette-Guerin (BCG) and MMR vaccine.

BCG vaccination is an effective intervention against tuberculosis, and the researchers could make an effort to create a novel BCG-based vaccine for COVID-19. However, many studies reported non-specific cross-protective effects of the vaccine against other infectious diseases. For example, in 1932 the BCG vaccine was introduced for tuberculosis prevention in Northern Sweden[71]. Later, two groups studied the protective effect of BCG and, for the first time, reported a 45% reduction in child mortality from respiratory infections in West Africa[72,73]. Other examples of BCG-mediated non-specific effects were also reported by Stensballe *et al*[74] and Wardhana *et al*[75].

Furthermore, the BCG vaccine has recently been found to protect against different virus infections such as influenza virus, herpes simplex virus, human papillomavirus, respiratory syncytial virus and virus for yellow fever[76].

With the worldwide occurrence of the SARS-CoV-2, different agencies, including the WHO, have called to explore every possible solution, even already approved therapies and vaccines, to slow transmission and reduce the effects of the COVID-19 pandemic. However, the obtained data suggest that BCG does not reduce COVID-19 mortality. Still, BCG vaccination may reduce the incidence of frequency during the COVID-19 crisis[77,78].

Only randomized controlled trials will show whether BCG reduces the frequency and severity of COVID-19. A recent study, a phase III ACTIVATE trial (NCT03296423), confirmed that adults over 65 years who have recently been vaccinated against BCG are less likely to get new virus infections. The study found that the incidence of new respiratory infections after receiving a placebo vaccine (42.3%) was different from the incidence of new respiratory infections after receiving BCG vaccine (25.0%)[78].

Another clinical trial in Brazil, BATTLE (NCT04369794), is designed to test BCG-like therapeutic vaccination. The aim is to show if it affects the elimination of SARS-CoV-2 and the degree of seroconversion and titration (IgA, IgG and IgM)[79]. In murine models, the new BCG:CoVac form, which combines BCG with the stable form of S protein, simultaneously stimulates SARS-CoV-2 and T-cell responses even at levels equivalent to or higher than expected by current vaccines[80].

In March 2020, with the rise of COVID-19 cases in the United Arab Emirates, the Emirates International Hospital Safety Committee decided to offer a BCG booster vaccination to hospital staff, which is 280 people. Seventy-one received the BCG vaccine. None of the 71 people who received the BCG booster vaccine tested positive for the SARS-CoV-2 virus. For the other 209 individuals that had not received booster BCG, there were 18 positive PCR cases of COVID-19. There were no available reports of complications with the BCG booster group[81]. In conclusion, BCG vaccination may protect medical staff who work or who are vulnerable to SARS-CoV-2 infection. Further studies are needed to determine if BCG vaccine is effective against COVID-19.

MMR (measles-mumps-rubella) vaccine is another childhood vaccine relevant to the COVID-19 pandemic. Homologies of the amino acid sequence between SARS-CoV-2 and measles, rubella and mumps viruses have been found[82,83]. A study found that there is a strong correlation between mumps IgG titers and the severity of COVID-19 in people vaccinated with the MMR vaccine in childhood[84]. There are also data that recently vaccinated MMR people had less severe COVID-19 and lower mortality rate[85].

Until the end of 2021, a placebo-controlled randomized clinical trial was conducted with 30000 individuals to investigate the protective effect of MMR vaccination after a positive test and symptomatic COVID-19[86]. A case-control study indicated that there may be a protective effect of the MMR vaccine against SARS-CoV-2 in males but not in females[87]. Several other studies have shown that recently receiving the MMR vaccine may protect against SARS-CoV-2 and/or the development of severe COVID-19[88-90]. They showed that the MMR vaccine can stimulate innate immunity inducing non-specific protection against other infections. Compared with those in the placebo group, participants who received at least one dose of MMR had a significantly decreased risk for symptomatic COVID-19 and need for treatment.

These data were used to make assumptions about the potential efficacy of COVID-19 vaccine administered live or nasal/oral. We summarize the information in Table 1.

MUCOSAL VACCINES FOR COVID-19: RISKS AND BENEFITS

Since the discovery of the first vaccine, it has always been a question about the benefits and risks of vaccines. However, over the years, vaccination programs that have been introduced and updated have managed to achieve their goals: Smallpox has been eradicated, polio and measles have been almost eradicated, and other diseases have been controlled[91].

The vaccines being administered now are given by injection. The mucosal vaccines can be superior to this process because they will elicit protective immune responses from the mucosa, blocking infection at the site of infection. The nature of the infection should be well known when developing mucosal vaccines: invasive (in intestinal pathogens), locally invasive (in shigellosis) or strictly mucosal (in cholera)[36,91,92]. This will affect the proper access of the circulating antibodies as well as the longevity of the immune response.

A large part of the population is willing to accept vaccines, but the claims about their risks have a greater impact than before. Therefore, the risks associated with a potential decision must be discussed in light of the best available scientific information.

When countries are faced with the decision to include a new vaccine in their national immunization programs, the relevant scientific, clinical, epidemiological and economic factors of the immunization program need to be considered.

Today, many vaccine production platforms vary in complexity and cost[93]. For example, the live attenuated OPV has a significantly lower cost of production. In contrast, the highly complex pneumococcal conjugate vaccine is much more expensive[94]. Financial cost-effectiveness is one of the most important factors when choosing a financial product or service. When a vaccine is cost-effective, it can help to manage both the health and financial consequences in a country. Oral vaccines offer great potential for preventing pandemics because they are very efficient, low cost, require no medical personnel and can elicit both systemic and mucosal immune responses. This type of vaccine is one of the most successful and cost-effective public health investments a country can make to improve people's health.

Oral vaccines require protection in the harsh environment of the gastrointestinal tract, where the pH is low and the proteases are present. Under normal circumstances, antigens that enter orally are treated as nutrients. If a vaccine does not trigger the appropriate danger signals, it is recognized as non-pathogenic by the intestinal tissue[95]. High doses are usually required for successful immunization, but this may increase the risk of tolerance[96]. These barriers are the main reasons there are so few effective oral vaccines.

Mucosal vaccines against SARS-CoV-2 are incredibly challenging to develop and confirm their safety. However, they will offer the ability to trigger stable, protective immune responses at the sites of pathogenic infection. Unfortunately, mortality and morbidity associated with various infectious diseases caused by mucosal pathogens have remained very high over the last 10 years.

Data so far demonstrated several attempts to develop intranasal vaccines against SARS-CoV and Middle East respiratory syndrome, based on viral vector, subunit, DNA, virus-like particle, inactivated and live-attenuated, described extensively elsewhere[97-101]. Based on our experience with mucosal vaccine platforms for SARS and Middle East respiratory syndrome, effective mucosal vaccines against SARS-CoV-2 could be developed. There are different types of correlates of protection, both humoral and cellular, that are associated with different goals of vaccination: prevention of infection at the mucosal or systemic level. However, until their efficacy and safety have been proven in clinical trials, their use is not recommended.

According to WHO data from 2020, lower respiratory tract infections are the fourth leading cause of death worldwide[102]. Developing an effective vaccine to protect against SARS-CoV-2 infection is a worthwhile endeavor. An extensive risk-benefit analysis of COVID-19 vaccines was published in 2021 [103]. The study was focused on thrombocytopenia and thromboembolism. It demonstrated that the risks of thrombocytopenia, venous or arterial thromboembolism, cerebral venous sinus thrombosis and ischemic stroke were much higher after SARS-CoV-2 infection than after vaccination.

The COVID-19 pandemic will continue and will hit low-income countries. Although there are already effective vaccines against SARS-CoV-2, mass production is still difficult, with no global coverage. The development of 'specific' mucosal vaccines targeting coronavirus antigens could be an excellent option for preventing future pandemics.

INTRANASAL AND ORAL COVID-19 VACCINES ON THE GO

As mentioned earlier, intramuscular injections are not effective at reducing viral replication or nasal secretions in the upper respiratory tract. This leads to asymptomatic or mild symptomatic disease,

Table 1 Approved vaccines that have received the attention of the scientific community concerning coronavirus disease 2019 as potential prototypes for developing mucosal coronavirus disease 2019 vaccines

Name of vaccine	Form	Immunity	Dosage	Route
OPV (oral poliovirus vaccine)	Live attenuated poliovirus (Sabin strain types 1, 2 or 3)	Poliovirus-specific mucosal immunity	2 doses	Oral
BCG (Bacille Calmette-Guerin)	Live attenuated bacteria *Mycobacterium bovis*	Mycobacterium-specific mucosal and systemic immunity	0.05 mL until 1 yr of age; 0.1 mL thereafter	Intradermal injection subcutaneous
MMR (measles, mumps and rubella vaccines)	Weakened forms of the measles, mumps and rubella viruses	Measles, mumps and rubella-specific systemic and mucosal immunity	2 doses	Subcutaneous injection
RV1 (Rotarix®)	Live-attenuated rotavirus	Rotavirus-specific mucosal immunity	2 doses	Oral
RV5 (RotaTeq®)	Live-attenuated rotavirus	Rotavirus-specific mucosal immunity	3 doses	Oral

which helps to spread the virus. On the other hand, intranasal vaccinations may generate sterilizing immunity against mucosal infections[104]. In addition, the principle of antigens exposed at the initial site of the viral infection will help to elicit a stable immune response in the mucosa[105]. The systemic immune response induced by intranasal vaccination is equivalent to or even stronger than the response caused by intramuscular immunization. This suggests that a lower dose will be needed to increase the efficacy and safety of vaccination.

Intranasal vaccination with chimpanzee Ad vector SARS-CoV-2 vaccine (ChAd-SARS-CoV-2-S) was shown to generate more significant levels of S-specific neutralizing antibodies in hamsters[106]. Such vaccination can produce pan-reactive antibodies[107], which is particularly attractive given the emergence of new SARS-CoV-2 mutants. The development of this type of vaccine would have a significant socioeconomic impact. A huge population could be vaccinated in a very short time in a global pandemic, such as COVID-19. The vaccines are supplied with nasal devices, which are preferred and convenient for patients. It is unnecessary from very low storage temperatures and a sterile environment that make them suitable for use. Furthermore, mucosal vaccination may hasten herd immunity, owing to its ease of delivery to impoverished individuals in low- and middle-income countries[98].

Because most clinical trial results have not yet been available, preclinical research is required to investigate the immunogenicity and safety of intranasal COVID-19 vaccines.

Preclinical studies of intranasal COVID-19 vaccines include a variety of mechanisms, which have been extensively described by Alu *et al*[8]. Studies on intranasal/mucosal COVID-19 vaccines, both preclinical and clinical trials[8], are shown schematically in Figure 2.

Oral mucosal COVID-19 vaccine: Vaxart

Vaxart's vaccine is an tablet vaccine that contains an adenoviral vector. The vector encodes the SARS-CoV-2 S and nucleocapsid proteins. The vaccine has progressed to a phase I trial (NCT04563702). Therefore, the film-coated tablets provide mucosal immunity by dissolving in the digestive tract. In addition, the active ingredient is protected from the aggressive action of the stomach's acidic environment by its enteric coating[7].

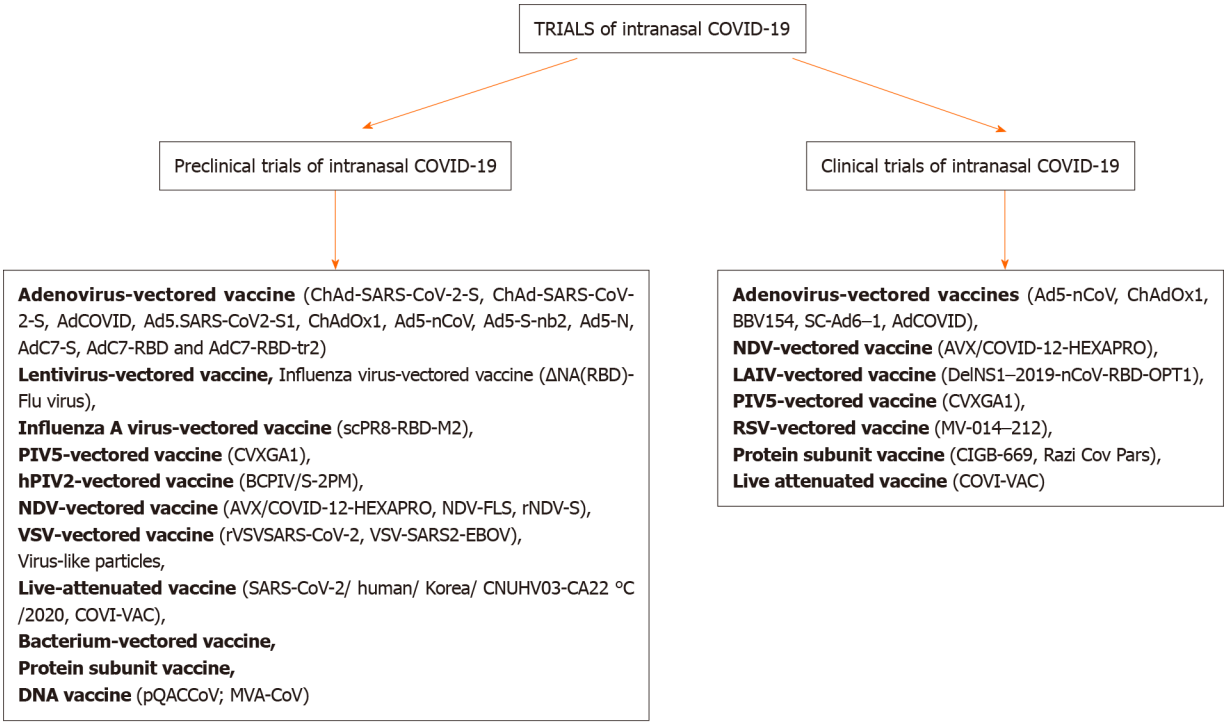
Studies show a significant increase in the titer of neutralizing antibodies against SARS-CoV-2 2 wk after the first vaccination in all animals that received the vaccine compared to the unvaccinated group [108]. Comparing the mucosal application of full-length wild-type S-protein antigens and those of the S1-domain or stabilized S-antigen, mucosal administration induced higher neutralizing antibody titers in the lungs and periphery.

Vaxart's tablet vaccine studies have shown that both low and high doses induce antigen-specific $CD4^+$ and $CD8^+$ cells. It is in the process of undergoing clinical phase evaluation[108].

OraPro-COVID-19™ vaccine - IosBio's (Sabilitech's)

Another interesting project underway is the IosBio Pharma's vaccine (United Kingdom). They also participated in the rat race for the golden choice SARS-CoV-2 vaccine by developing an oral dual-antigen COVID-19 vaccine in capsule form called OraPro-COVID-19[109]. This candidate is based on a human adenoviral vector (hAd5). It expresses modified SARS-CoV-2 S protein and nucleocapsid protein genes with enhanced T-cell stimulation domain, which is predicted to enhance major histocompatibility class II responses[110]. Gabitzsch *et al*[111] first investigated this adenoviral vector platform against various viral antigens such as influenza, HIV-1 and Lassa fever. Their previous and current results show that this immunization model both promotes humoral and cell-mediated immunity[111-114].

In investigating the role of T-cell-mediated immunity in SARS-CoV-2 infection, Sekine *et al*[115] highlighted its importance by detecting virus-specific T-cells in the serum of patients with SARS-CoV-2 negative antibodies, including asymptomatic individuals or exposed family members.



DOI: 10.5501/wjv.v11.i5.221

Figure 2 Preclinical and clinical trials on intranasal/mucosal coronavirus disease 2019 vaccines. PIV5: Parainfluenza Virus 5; hPIV2: Human parainfluenza virus 2; NDV: Newcastle disease virus; VSV: Vesicular stomatitis virus; LAIV: Live attenuated influenza vaccine; RSV: Respiratory syncytial virus; COVID-19: Coronavirus disease 2019.

Gabitzsch *et al*[116] also developed a dual vaccine model to ensure T-cell activation and more durative protective immunity. First, they studied a murine model using hAd5 S-Fusion + nucleocapsid protein genes with enhanced T-cell stimulation domain. They proved that this type of immunization elicits not only a protective humoral but also a Th1-dominant T-cell response. Furthermore, they found that if the vaccine was stored at room temperature, subcutaneous application followed by oral boost elicited both antibody-mediated and T-cell responses. In addition, they also demonstrated that applications of hAd5 S-Fusion + nucleocapsid protein genes with enhanced T-cell stimulation domain inhibited viral replication in both nasal and pulmonary mucosa within 24 h, with complete clearance 7 d after administration.

Human clinical trials are still underway to determine dose strengths and the number of vaccine applications. However, more research is needed to determine if this oral dual vaccine model is effective in managing COVID-19.

COVID-19 oral mucosal vaccine: Recombinant poliovirus Sabin 1-vector system platform

DNA vaccines have some limitations, such as the need for high doses, suitable adjuvants and unique technologies for delivering them to specific sites in the body[117,118]. So poliovirus has been used as a vaccine vector to overcome these barriers due to its safety, low cost and ability to be used orally.

One of the potential platforms for developing an effective vaccine against COVID-19 for oral mucosa is based on the Sabin-1 poliovirus cDNA-based recombinant poliovirus Sabin 1 (RPS) vector system. Sabin-1 is one of three attenuated poliovirus serotypes (OPV). The Sabin strains are safe and easy to store and manipulate experimentally. Therefore, they are ideal vaccine vectors for foreign antigen expression. There are two variants of this system: RPS-Vax and RPS-cytoplasmic transduction peptide (CTP). The RPS-Vax has the multiple cloning site and 3C-protease cutting site, which allow the cloning of a vaccine gene and the release of the vaccine protein from the viral particle during replication[119]. The RPS-CTP vector system is a modified version of the RPS-Vax vector system, which contains CTP right above the multiple cloning site.

Based on the RPS-CTP platform, the vaccine is designed to be used orally instead of parenterally or intramuscularly. In this regard, it has advantages that can make it convenient for patients with COVID-19: easy to apply and no loss during application[120]. In addition, it has also been well established that OPV can induce long T-cell and B-cell memory[121]. Therefore, OPV is an effective and preferred vaccine in most of the world because it has the potential to quickly halt viral transmission. Furthermore, it successfully mimics infection that is naturally acquired due to its oral application.

OPV also has the hypothetical ability to "vaccinate" indirectly through close contact of vaccine recipients, who spread OPV through nasopharyngeal secretions and feces[122]. These results suggest that the vector system RPS-CTP can be used to develop preventive or therapeutic mucosal vaccines against COVID-19 and other diseases.

NEXT-GENERATION RESPIRATORY MUCOSAL DELIVERY OF COVID-19 VACCINE CAN PROVIDE PROTECTION AGAINST SARS-COV-2 AND CONTROL THE PANDEMIC

Although challenging, oral vaccination has many socioeconomic benefits and stimulates both the humoral and cellular immune responses. They are easy to use, even in areas without medical staff, with relatively few side effects and lower cost. Although there are many oral vaccines currently undergoing clinical trials, only a limited number of these vaccines have been approved for human use. According to the WHO, most COVID-19 vaccines are designed to be administered by the intramuscular route[123] in order to produce high titers of neutralizing antibodies. It is well established that mucosal vaccines offer robust protective potential in pathogen infection sites. Additionally, the adaptive immunity induction at mucosal sites comprises secretory antibody production and T cell responses, preventing infection and developing disease symptoms[7]. These data support developing an oral or nasal mucosal vaccine against SARS-CoV-2, as this type of vaccine is known to activate the mucosal immune system and have been successful in protecting people from other infections in the past[124].

Identifying safe and effective mucosal adjuvants allied to innovative antigen delivery plays a crucial role in advancing mucosal COVID-19 vaccines. The complex mechanisms of innate and adaptive mucosal immunity regulation are not yet fully understood. But the significant progress that has been made in recent years will help create more effective oral vaccines. In addition, oral tablet versions of a COVID-19 vaccine will also reach regions without healthcare staff and healthcare infrastructure.

In addition, because the gut is already colonized with microorganisms, oral vaccines do not require extensive and expensive antigen purification. This simplifies the entire production process and reduces the cost. These benefits of oral vaccination may be preferred over conventional vaccination methods during pandemic situations like COVID-19.

The production of effective oral vaccines for COVID-19 must comply with high safety standards, stability and immunogenicity. When oral vaccines succeed in generating protective and therapeutic immune responses, we will be able to overcome the global COVID-19 pandemic that has changed people's lives worldwide[125].

CONCLUSION

A mucosal SARS-CoV-2 vaccine that targets the mucosal surfaces such as the nose or mouth would be ideal if it were shown to be safe. However, there are still major regulatory issues concerning stability and effectiveness. It is fascinating to see if the intranasal application of SARS-CoV-2 mRNA vaccines may induce resident memory T cells and B cells and protect the lungs and gut. Recent and ongoing studies highlight the importance of understanding local immune responses and suggest that mucosal, innate and vaccine-mediated immunity to SARS-CoV-2 has enormous therapeutic implication value.

FOOTNOTES

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REVIEW

Association of COVID-19 with hepatic metabolic dysfunction

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic continues to be a global problem with over 438 million cases reported so far. Although it mostly affects the respiratory system, the involvement of extrapulmonary organs, including the liver, is not uncommon. Since the beginning of the pandemic, metabolic comorbidities, such as obesity, diabetes, hypertension, and dyslipidemia, have been identified as poor prognostic indicators. Subsequent metabolic and lipidomic studies have identified several metabolic dysfunctions in patients with COVID-19. The metabolic alterations appear to be linked to the course of the disease and inflammatory reaction in the body. The liver is an important organ with high metabolic activity, and a significant proportion of COVID-19 patients have metabolic comorbidities; thus, this factor could play a key role in orchestrating systemic metabolic changes during infection. Evidence suggests that metabolic dysregulation in COVID-19 has both short- and long-term metabolic implications. Furthermore, COVID-19 has adverse associations with metabolic-associated fatty liver disease. Due to the ensuing effects on the renin-angiotensin-aldosterone system and ammonia metabolism, COVID-19 can have significant implications in patients with advanced chronic liver disease. A thorough understanding of COVID-19-associated metabolic dysfunction could lead to the identification of important plasma biomarkers and novel treatment targets. In this review, we discuss the current understanding of metabolic dysfunction in COVID-19, focusing on the liver and exploring the underlying mechanistic pathogenesis and clinical implications.

Key Words: COVID-19; Coronavirus; Metabolism; Metabolic syndrome; Metabolic inflammation; Hepatic dysfunction

Core Tip: In coronavirus disease 2019 (COVID-19) patients, the virus induces a complex viral-host interaction that leads to metabolic reprogramming, altered immunological responses, and a variety of clinical consequences. In metabolomic and lipidomic studies, a variety of alterations in amino acids, lipids, carbohydrates, and energy metabolism have been identified in such patients. The liver is the primary metabolic organ; thus, these metabolic alterations may have a major impact on patients with liver diseases and metabolic comorbidities that are common in COVID-19 patients. Therefore, this review article discusses the pathophysiological aspects and clinical implications of metabolic dysfunction in COVID-19 patients with a focus on the liver.

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INTRODUCTION

Patients with metabolic disorders such as obesity, hypertension, diabetes mellitus (DM), and non-alcoholic fatty liver disease (NAFLD) are more likely to develop a severe case of coronavirus disease 2019 (COVID-19)[1-5]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection *per se* is linked to the changes in numerous metabolic pathways involving glucose, lipids, and amino acids[6-8]. The metabolic reprogramming that occurs in COVID-19 patients performs several roles, including providing energy and substrates for viral replication and modulating the immunological response. Pre-existing metabolic comorbidities may fire up metabolic reprogramming more strongly due to the varying amounts of metabolites and their influence on the immune response. Untargeted metabolomic and lipidomic methods provide new insight into the host's response to COVID-19 infection. Hyperglycemia, new-onset DM, dyslipidemia, and worsening of pre-existing metabolic abnormalities have all been described in COVID-19 patients[9-11]. As the liver is a primary metabolic hub, it is crucial in orchestrating systemic metabolic alterations during infection. The angiotensin-converting enzyme 2 (ACE2) that allows SARS-CoV-2 to enter the body is normally present in the liver and is overexpressed in patients with chronic liver disease (CLD)[12,13]. Additionally, ACE2 is an integral part of the renin-angiotensin-aldosterone system (RAAS), which plays a major role in the pathophysiology of liver cirrhosis[14].

Obesity and DM have been associated with a poor disease prognosis since the outset of the COVID-19 pandemic[15,16]. As these metabolic conditions are still among the world's most common public health issues, a sizable section of the population is at risk of severe COVID-19 infection. Compelling evidence suggests that patients with metabolic comorbidities also have a higher risk of post-infection sequels[17,18]. Furthermore, NAFLD is common in subjects with obesity and DM. When compared to non-NAFLD COVID-19 patients, those with NAFLD have a higher risk of disease progression (6.6% *vs* 44.7%), a higher likelihood of impaired liver function (70% *vs* 11.1%), and a longer viral shedding period (17.5 *vs* 12.1 d)[19]. Moreover, patients with COVID-19 frequently have elevated liver enzyme levels, and this has been linked to poor clinical outcomes[20,21]. Similarly, COVID-19 has been proven to have a negative impact on the complications and outcomes of CLD patients[21].

Infections trigger a wide range of responses in the host, including inflammation, tissue injury, and healing. In this context, evidence suggests that COVID-19 has both immediate and long-term metabolic consequences associated with inflammation[4,7,17,22,23]. Immunometabolism, which is the direct link between metabolic diseases and inflammation, has recently emerged as a key study subject. Correlation analyses reveal strong links between metabolites and proinflammatory cytokines and chemokines[22,23]. In this sense, studies have found that arginine, tryptophan, and purine metabolism have a regulatory interaction with inflammation. Therefore, targeting metabolism to modulate the release of proinflammatory cytokines could be a viable method for treating cytokine storms in COVID-19 patients. This review article discusses the spectrum of metabolic dysfunctions in COVID-19 patients, their pathophysiological aspects, and clinical implications in patients with underlying metabolic comorbidities and liver disorders.

ALTERATIONS IN METABOLIC AND BIOSYNTHETIC PATHWAYS IN COVID-19

In patients with severe COVID-19, considerable changes in hepatic metabolic and biosynthetic pathways have been discovered[6-8,24-28]. Lipids, glycoproteins, amines, aromatic compounds, amino acids, steroids, and flavone metabolism were all found to be altered (Table 1). A study on liver autopsy samples of COVID-19 patients has demonstrated a significant downregulation of transcripts implicated in the metabolic pathways. The most downregulated genes were acyl-CoA dehydrogenases 11 (involved in mitochondrial β-oxidation and metabolism of long-chain fatty acyl-CoAs), *CIDEB* (a liver-specific regulator of lipids metabolism), glycine N-methyltransferase (contributes to liver steatosis and fibrosis), and glycerol-3-phosphate acyltransferase (implicated in triglyceride biosynthesis)[6,24-26]. The suppression of lipid and amino acid metabolism has resulted in the accumulation of amino acids and steroids in the sera of COVID-19 patients[7]. More than 100 Lipids were discovered to be downregulated in COVID-19 patient sera, including sphingolipids, glycerophospholipid, and fatty acids, most likely due to liver damage. Many steroid hormones, such as progesterone, androgens, and estrogens, have been found to accumulate, which can enhance immune cell activation. Increased levels of 21-hydroxypregnenolone could imply that corticosterone is protective against COVID-19[7].

In this context, many such metabolic changes aid SARS-CoV-2 replication and have been linked to the severity of COVID-19 cases. Glycolysis and glutaminolysis were found to be required for virus replication[8,27]. In this regard, glutaminolysis is a process that converts glutamine to tricarboxylic acid (TCA) cycle intermediates and is required for protein, lipid, and nucleic acid production. Inhibiting glutaminolysis has been shown to impede viral replication and production. Furthermore, patients with severe COVID-19 disease had higher glucose and mannose levels in their blood[8], and mannose was found to be a reliable biomarker for the severity of COVID-19 disease. Chen YM found that the TCA cycle and glycolytic pathways were significantly dysregulated in COVID-19 patients[28]. Significant suppression of cytochrome P450 enzymes has been observed in COVID-19 patients, suggesting a compromised hepatic detoxification capacity[6]. In a metabolomic study, Shen *et al*[7] have detected elevated levels of glucuronate, which is a bilirubin degradation product, and bile acid derivatives in severe COVID-19 patients, also indicating a decline in the liver's detoxification function. It is noteworthy that the suppressed hepatic metabolic pathways in COVID-19 patients are consistent with mitochondrial dysfunction[6]. In this regard, Scozzi *et al*[29] have reported that circulating levels of mitochondrial DNA (MT-DNA), inflammatory nucleic acids released by injured tissues, were highly elevated in patients who eventually died or required ICU admission. Thus, MT-DNA in blood could be a potential early prognostic marker for poor outcomes in COVID-19 cases. Moreover, mitochondrial dysfunction also appears to play a role in COVID-19-induced porphyrin accumulation occurring due to interference with the heme biosynthetic pathway[30]. Heme synthesis is dependent on the sequential action of eight enzymes, which are mainly expressed in the liver and erythroid cells.

ALTERATIONS IN AMINO ACIDS, LIPIDS, AND SUGAR

Amino acids

Amino acids (AAs), which are mostly synthesized in the liver, are essential for metabolism, immunological function, and redox balance[31]. The potential effects of glutamine, arginine, methionine, and cysteine on immunological function have been well documented[32]. Branched-chain amino acids (BCAAs) play an important role in metabolism and inflammation. In this sense, BCAAs stimulate the synthesis of glycogen and proteins such as albumin *via* activating the mammalian target of rapamycin complex 1 (mTORC1) signaling[33]. Serine and glycine are important components of the one-carbon cycle, which aids redox balance and several biosynthetic activities[34].

BCAA levels in the blood increase in severe COVID-19 patients[35]. Through the transcription factor NF-kB, elevated levels of BCAA increase reactive oxygen species generation and proinflammatory responses in endothelial cells[33]. Additionally, BCAAs also cause insulin resistance (IR) *via* activating mTORC1[36]. Furthermore, increased BCAA levels in the blood are linked to a higher risk of metabolic diseases, including DM. On the other hand, a decrease in the BCAA/aromatic amino acids ratio, also known as Fischer's ratio, has been linked to hepatic impairment in COVID-19 patients[37]. A metabolomics study has linked the severity of COVID-19 to a reduction in serotonin and increased plasma levels of aspartate, glutamate, phenylalanine, and succinic acid[38]. The rise in such amino acids and succinic acid could be related to a dysregulation of central carbon metabolism in the liver as well as metabolic and oxidative stress.

On another note, changes in tryptophan metabolism along the kynurenine pathway have been reported in COVID-19 patients[39]. This pathway is activated by proinflammatory cytokines such as interleukin-6 (IL-6) in response to diverse situations. Indeed, the kynurenine and tryptophan ratio (KTR) is frequently used to assess inflammation and immunological responses in a variety of disorders. In COVID-19 patients, an increased KTR was also indicative of the disease severity and progression[40]. Other alterations indicative of hepatic dysfunction in COVID-19 patients include elevated levels of taurine and ethanolamine[37]. Increased taurine levels in the blood have been identified as indicators of

Table 1 Metabolic alterations in coronavirus disease 2019 with implications

Metabolite alteration	Implications/association
Increased branched chain amino-acids	Insulin resistance, reactive oxygen species production, and pro-inflammatory responses
Decreased tryptophan; Increased kynurenine	Increased kynurenine tryptophan ratio indicates inflammatory response
Increased glutamic acid; Decreased glutamine	Lower glutamine level is associated with insulin resistance and an increased risk of diabetes
Decrease arginine; Increased ornithine	Attempt to suppress virus-specific $CD8^+$ T cell. Delayed interferon response or metabolic syndrome tend to increase arginine/ornithine ratio, causing tissues damage
Increased spermidine and spermine	Help structural assembling and genome replication
Increased serum triglycerides and VLDL; Decreased total cholesterol, HDL and LDL; Upregulation of fatty acid synthesis	Viral replication, inflammation, atherogenic risk, hepatic steatosis
Increased ketone bodies and 2-hydroxybutyric acid	Altered energy metabolism and oxidative stress
Decreased glycerophospholipid; Increased lysophospholipids	Indicates inflammation and tissue damage
increased levels of pyruvate, pyruvate kinase and lactate dehydrogenase	Indicates enhanced glucose metabolism. Increased glycolysis promotes replication of SARS-CoV-2 and cytokine storm
Increased methionine sulfoxide levels; Decreased glutathione levels	Indicative of increased oxidative stress

HDL: High-density lipoprotein; LDL: Low-density lipoprotein; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; VLDL: Very-low-density lipoprotein.

liver failure. Furthermore, glutamate and glutamine are important in energy metabolism. In this regard, glutamic acid levels are higher in COVID-19 patients; however, glutamine levels are much lower, and this is linked to IR and an increased risk of DM[41]. Low glutamine levels in COVID-19 patients may be due to an abnormal cysteine catabolism secondary to increased hepatic glutathione biosynthesis, induced by proinflammatory cytokines[42]. On another note, the hepatic urea cycle is dysregulated in severe COVID-19 patients[40]. The urea cycle, which converts ammonia to urea, is the principal metabolic pathway implicated in detoxification processes, with a fumarate shunt connecting the urea cycle and the TCA cycle[43]. In moderate and severe COVID-19 patients, an increased level of ornithine, the main metabolite of the urea cycle, is observed. This, along with increased levels of aspartate and glutamate, which are also linked to the cycle, suggests that SARS-CoV-2 disturbs the hepatic urea cycle. Moreover, ornithine and glutamate demonstrate a positive correlation with lactic acid in severe COVID-19[38].

In viral infections, modification of liver metabolism and the urea cycle may be an endogenous immunoregulatory mechanism to minimize tissue damage[44]. The reprogramming of liver metabolism that occurs after a viral infection is correlated with type I interferon (IFN-I) responses. In this sense, the IFN-I response modifies the urea cycle, resulting in lower arginine and higher ornithine concentrations in the blood, thus suppressing virus-specific CD8+ T-cell responses and reducing the liver damage[45]. However, in COVID-19 patients, the IFN-I response is frequently delayed, and this may weaken the protective response. Metabolic syndrome, which is common in COVID-19 patients, causes decreased arginine availability and an elevated arginine/ornithine ratio, which may further worsen tissue damage [46]. Furthermore, the synthesis of polyamines may be increased if ornithine metabolism is dysregulated. Metabolomics analysis has reported increased levels of spermidine and spermine in the serum of COVID-19 patients[47]. As polyamines are involved in various viral activities, including viral assembly and genome replication, blocking polyamine synthesis could be a useful antiviral strategy.

Lipids

Lipids play an important role throughout the viral life cycle, and viruses exploit host lipid metabolism to facilitate their replication. Several studies have looked at lipidomic profiling in COVID-19 patients. Even though these studies are heterogeneous, several consistent findings have been reported[48]. COVID-19 patients exhibited downregulation of several serum lipids, including sphingolipids, glycerophospholipids, and fatty acids[49]. The liver damage caused by SARS-CoV-2 infection has been linked to dyslipidemia and oxidative stress[50]. In this regard, the levels of blood triglycerides and very-low-density lipoprotein are significantly elevated, whereas the levels of high-density lipoprotein and low-density lipoprotein are much lower[37,50,51]. Notably, COVID-19-related dyslipidemia occurs primarily in patients with high severity and not in those who recover from a mild uneventful infection. Bruzzone *et al*[50] used nuclear magnetic resonance spectroscopy to determine the lipidomic serum profile of 389 COVID-19 patients, revealing a pathogenic redistribution of lipoprotein particle size and composition with atherosclerosis risk. In the same study, the metabolomics analysis revealed unusually high levels of

ketone bodies, which are produced in the liver from free fatty acids, and 2-hydroxybutyric acid, which is a marker of oxidative stress and a consequence of glutathione synthesis in the liver. Ketosis in COVID-19 patients has been associated with a longer hospitalization and increased mortality rates[52]. Furthermore, a shift to fatty acid oxidation is a common metabolic response observed during many severe illnesses, and COVID-19 is no exception[49,53]. In this regard, a reduction in sphingosine-1-phosphate (S1P), which is a sphingosine molecule that regulates a variety of biological processes such as inflammation and apoptosis, is observed in COVID-19 patients[7,54]. In a study, serum level of S1P was found to be inversely associated with COVID-19 severity[55]. Additionally, glycerophospholipid levels are also reduced, whereas the levels of the corresponding lysophospholipids are increased, indicating increased phospholipase A_2 activation[7,54,56]. Elevated levels of phospholipase A2 may be an early marker of severe COVID-19.

Glucose

On another note, SARS-CoV-2 infection is also associated with dysregulated glucose metabolism. Regardless of previous diabetes status, hyperglycemia frequently develops in COVID-19 patients, and many develop new-onset DM and diabetes ketoacidosis[9-11,57]. Furthermore, the abnormal glucose metabolism has been reported to persist even after recovery from COVID-19. In a hospitalized sample of 551 COVID-19 patients, 46% were hyperglycemic, and glycemic abnormalities were detected for at least 2 mo following COVID-19 recovery[58]. In several observational studies, more severe hyperglycemia has been linked to a worse prognosis in COVID-19 patients[2,8,9,10,59]. IR and/or decreased insulin production are the primary causes of abnormal glucose metabolism in COVID-19 patients, and proinflammatory cytokines play an essential role in this process. The increased glucose metabolism due to sustained hyperglycemia may further enhance entry of SARS-CoV-2, with exacerbated immune response[60]. In this sense, elevated glucose levels and glycolysis lead to an increase in SARS-CoV-2 replication[27,61]. Furthermore, COVID-19 causes glycemic control to deteriorate in patients with pre-existing DM, and new-onset hyperglycemia is an independent predictor of mortality in such patients[11, 62,63]. As glycemic control deteriorates, the severity of illness and the risk of mortality increases.

PATHOPHYSIOLOGY OF METABOLIC DYSFUNCTIONS IN COVID-19

The occurrence of metabolic dysfunction in COVID-19 has been well documented; however, the molecular mechanisms behind these dysfunctions are sparsely known. Infection with SARS-CoV-2 can affect several metabolic organs such as the liver, pancreas, adipose tissue, and muscles, either directly or indirectly. Proinflammatory cytokines, oxidative stress, and IR all appear to contribute to metabolic dysregulation in COVID-19, and the association between metabolism and inflammation is well-known and still being investigated. The by-products of glycolysis increase cytokine maturation and, as a result, T-cell proliferation[64]. One such glycolytic metabolite necessary for IL-1β synthesis is 3-phosphoglycerate. Moreover, alterations in the levels of fatty acids and tryptophan metabolites have been associated with inflammatory markers in COVID-19 patients[40]. A study found high-affinity interactions between the viral spike protein and toll-like receptors (TLRs), particularly TLR4[65]. TLR4 activation is known to cause inflammation and cellular metabolic alterations[66]. Additionally, hyperglycemia has been linked to delayed IFN response and cytokine storm in COVID-19 patients[67,68].

Entry of SARS-CoV-2 into host cells

The interaction between the spike protein and ACE2 allows SARS-CoV-2 to enter host cells. Virus entry is facilitated through the priming of spike proteins by specific proteases such as transmembrane serine protease 2 (TMPRSS2) and furin protease. At first, SARS-CoV-2 targets epithelial cells in the lungs; however, viral RNA has been found in a variety of organs, including the liver, suggesting that other organs could be targeted as well. ACE2 is expressed by many cells, and its expression is further upregulated in a variety of conditions, including inflammatory and liver diseases[12,69]. As a result, increased ACE2 expression could be a risk factor as well as an effect of SARS-CoV-2 infection. In particular, the delta and omicron variants of SARS-CoV-2 have an even higher affinity for ACE2 than other variants[70]. While ACE2 expression is low in healthy livers, cirrhotic livers exhibit higher levels of ACE2 expression[12]. As a result, patients with liver cirrhosis may be more susceptible to SARS-CoV-2 infection.

Alterations in the RAAS

SARS-CoV-2 infection significantly influences the RAAS since ACE2 is a key part of it[71]. The discovery of functional local RAAS in several organs, including the liver, has changed our knowledge of the RAAS[14]. Alternative RAAS pathways mediated by ACE2 in the local RAAS result in the opposite effects of classic RAAS (Figure 1). ACE2 is a major regulator in the alternative RAAS pathways, regulating the production of angiotensin 1–7 (Ang 1-7) from angiotensin II (Ang II). Additionally, ACE2 converts angiotensin I to angiotensin 1–9 (Ang 1-9), which can be further converted to Ang 1–7 by the angiotensin-converting enzyme. Importantly, the protective arm of the RAAS is made up of ACE2, Ang

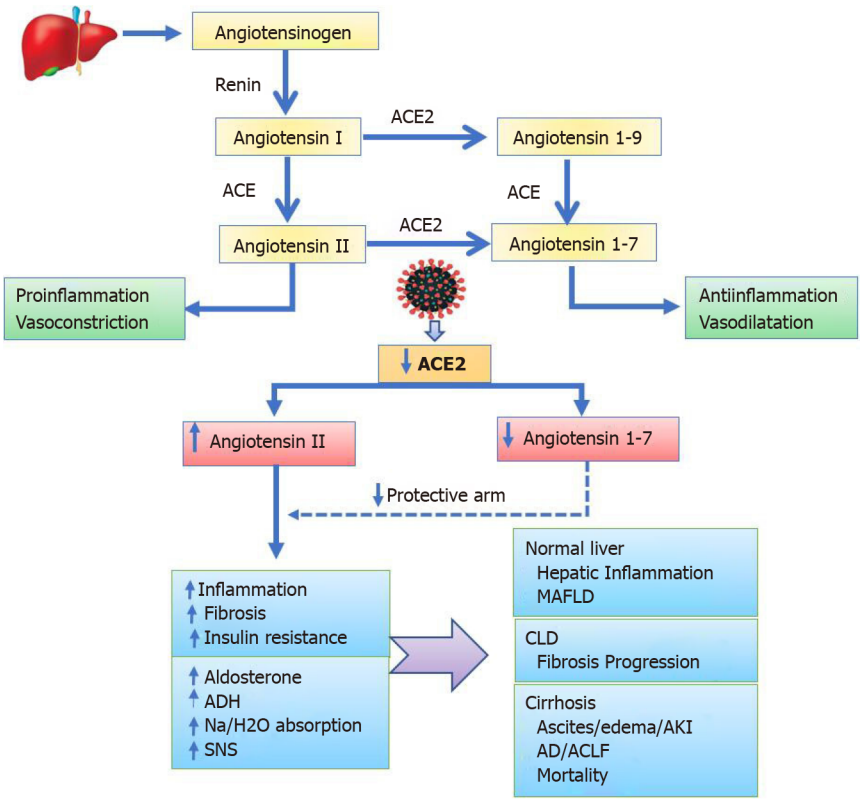

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Figure 1 Interaction between severe acute respiratory syndrome coronavirus 2 and renin–angiotensin–aldosterone system system *via* angiotensin converting enzymes 2 as receptor. The interaction between the cellular spike protein and angiotensin converting enzymes 2 (ACE2) allows severe acute respiratory syndrome coronavirus 2 to enter host cells. ACE2 mediates alternative renin–angiotensin–aldosterone system (RAAS) pathways in the local RAAS system. ACE2 regulates the production of angiotensin 1–7 from angiotensin II (Ang II) and angiotensin 1–9. ACE2 after binding to virions is internalised, reducing its availability on the cellular surface. Once ACE2 is downregulated, Ang II gets upregulated which upon binding to the Ang II receptors, causes proinflammatory, profibrotic, vasoconstrictive, and antidiuretic responses. Overactivation of the RAAS has been linked to the development of refractory ascites, hepatorenal syndrome, and circulatory dysfunction in cirrhosis. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; RAAS: renin-angiotensin-aldosterone system; ACE2: Angiotensin converting enzymes 2, CLD: Chronic liver disease, MAFLD: metabolic associated fatty liver disease, ADH: Antidiuretic hormone; Na: Sodium; H2O: Water; SNS: Sympathetic nervous system, AD: Acute decompensation, ACLF: Acute-on-chronic liver failure.

1–7, and its Mas receptor, and this results in anti-inflammatory and antifibrotic responses (Figure 1). However, when ACE2 is downregulated, Ang II gets upregulated, and upon binding to the Ang II receptors, it causes proinflammatory, profibrotic, vasoconstrictive, and antidiuretic responses that can lead to end-organ damage[71]. The plasma level Ang II rises in COVID-19 patients and is linearly associated with viral load[72]. Ultimately, SARS-CoV-2 infection causes inflammatory reactions due to the downregulation of ACE2[71-73]. Generally, ACE2 coupled to virions is internalized, reducing its availability on the cellular surface. Moreover, some unknown mechanism induces the gene expression of disintegrins and metalloproteinase domain-17 (ADAM-17)[74]. ADAM-17 is a membrane sheddase protease that releases ACE2, IL-4, and IFN from cell membranes. Finally, free IFN-γ and IL-4 suppress membrane-bound ACE2, further shifting the RAAS to a higher Ang II and lower Ang1-7 tone[71,74].

Alterations in one-carbon pathways

The one-carbon pathway is a metabolic network that include the methionine and folate cycles and is involved in many biological functions such as synthesis of amino acids, polyamines, nucleic acids, adenosine triphosphate, phospholipids and glutathione[75]. In particular, the metabolic pathways of methionine, folate, and choline have been implicated in the pathogenesis of hepatic steatosis[76]. One-carbon metabolism appears to have a crucial role in COVID-19[78-83]. In this regard, SARS-CoV-2 uses folate and one-carbon metabolism to gain a competitive advantage in replication[77]. It modifies host folate metabolism at the post-transcriptional level to enhance de novo purine synthesis. Several observational studies on COVID-19 patients have linked one-carbon metabolism to the disease severity, although mechanistic insights are still being developed[78]. The results of various studies on the link between one-carbon metabolism and COVID-19 have been varied and conflicting, except for a few metabolites such as glutathione, choline, and methionine sulfoxide, which were consistently altered by COVID-19[78]. These discrepancies could be related to the confounding effects of non-matched study subjects, variances in disease severity, and the time points at which samples were collected in different

studies.

Furthermore, metabolomic studies have ascertained that S-adenosylmethionine (SAM), the universal methyl donor, is significantly increased in severe and fatal cases of COVID-19[79,80]. As the generation of SAM requires vitamin B12-dependent methionine synthase, many symptoms of long COVID-19 are similar to those of vitamin B12 deficiency, a condition in which methylation is disturbed[81]. Multiple independent metabolic studies have reported higher serum levels of methionine sulfoxide in COVID-19 patients, implying increased oxidative stress[82,83]. Moreover, glutathione, the most important antioxidant, is consistently depleted in COVID-19 patients and is often associated with increased lipid peroxidation markers[84]. In children with mild COVID-19, higher levels of methylmalonic acid (MMA), which is a catabolic product of certain amino acids, have been found[83]. A vitamin B12-dependent enzyme further metabolizes MMA to succinic acid, which is a TCA cycle substrate. The antiviral and anti-inflammatory properties of MMA are thought to protect children from severe infection. Polyamines, including as spermidine and spermine, have been found to have a role in the replication and attachment of SARS-CoV-2, with serum levels of these compounds being greater in COVID-19 patients[47]. Overall, it appears that the virus exploits one-carbon metabolism pathways for its replicative advantages, producing metabolic disturbance in the host cells.

Pathogenesis of hyperglycemia

The pathophysiological basis of hyperglycemia in COVID-19 patients appears to be the development of IR and pancreatic β-cell dysfunction (Figure 2). Peripheral IR is caused by SARS-CoV-2-induced hyperinflammation and cytokine storm. Metaflammation, defined as a rise in TNF, IL-6, and IL-1 Levels in patients with metabolic syndrome, can further increase IR[85]. Furthermore, pancreatic damage with subsequent impairment of insulin secretion is evident in COVID-19 patients[10,86]. However, SARS-CoV-2 does not appear to infect β-cells. directly, as ACE2 and TMPRSS2 have only been detected in pancreatic microvasculature and ducts, not in β-cells[87]. Pancreatic injury caused by SARS-CoV-2 increases the release of pancreatic lipase, resulting in lipolysis and the release of unsaturated fatty acids, thus causing mitochondrial damage and inflammation[86,88]. When ACE2 is downregulated in the intestinal epithelium, SGLT1 is upregulated, resulting in hyperglycemia[89]. The unopposed action of Ang II leads to oxidative stress that triggers β-cell damage and further impairment of insulin secretion. Hyperglycemia *per se* can cause β-cell dysfunction by upregulating the Ang II receptor on β-cells and causing glucolipotoxicity[11]. Furthermore, persistent hyperglycemia may exacerbate COVID-19 by glycating ACE2, which facilitates the entry of SARS-CoV-2[10]. Recently, a circulating protein GP73, which is a glucogenic hormone that enhances hepatic gluconeogenesis, has been found in COVID-19 patients, and it appears to modulate SARS-CoV-2-induced glucose metabolic alteration[90].

CLINICAL IMPLICATIONS OF METABOLIC ALTERATIONS IN COVID-19

COVID-19 and metabolic diseases

Multiple studies have found that metabolic comorbidities are more common in COVID-19 patients and are associated with poorer outcomes. However, the pathophysiologic mechanisms that underpin this adverse metabolic interaction are still poorly understood. The proinflammatory environment in patients with metabolic disorders may aggravate immune dysregulation, inflammation, microvascular dysfunction, and thrombosis, which may intensify the essential interaction between virus and host components. Additionally, patients with metabolic illnesses are more likely to respond to infection in a proinflammatory rather than protective manner, which could contribute to increased cytokines in COVID-19 infection. Obesity[91,92], DM[2,59], hypertension[93], dyslipidemia[94,95], and metabolic-associated fatty liver (MAFLD)[5,96] have all been shown to be associated with a more severe disease course and increased mortality in COVID-19 (Table 2). A pooled data analysis of 20 studies determined that obese individuals had a 46% (Odds ratio [OR]: 1.46) higher chance of testing positive for COVID-19 than non-obese people[97]. Moreover, a history of prior bariatric surgery is associated with a reduced severity in COVID-19 patients[98]. In severe COVID-19 patients, the prevalence of DM (OR: 3.5) and hypertension (OR: 2.6) is higher than that in non-severe patients[99]. In a meta-analysis of 33 studies, including 16003 COVID-19 patients, the pooled odds ratio of mortality or severity in presence of DM was 2.16 (95%; CI: 1.74-2.68; $P < 0.01$)[59]. Poor outcome of COVID-19 associated with DM or hyperglycemia may be attributed to higher glucose levels that provide huge substrates for increased glycolysis thus producing energy and substrates for SARS-CoV-2 replication. On the other hand, improved glycemic control is associated with better outcomes in COVID-19 patients with DM[62]. Lactic acidosis has been documented frequently in severe COVID-19 patients with DM treated with metformin [100]. A meta-analysis of 7 studies (n = 6922) showed that dyslipidemia is associated with severe COVID-19 infections [RR 1.39][95].

COVID-19 and liver diseases

SARS-CoV-2 produces steatosis and lobular and portal inflammation in the liver[101]. Microthrombi have been found in the hepatic sinusoids in fatal cases due to coagulopathy and endothelial

Table 2 Meta-analyses of associations between coronavirus disease 2019 and metabolic diseases

Ref.	Metabolic condition	COVID-19 (N); Studies/Patients	Main results
Ho *et al*[91]	Obesity	61/270241	Obesity was associated with more severe disease (OR 3.13, 95%CI: 1.41-6.92) and mortality (OR 1.36, 95%CI: 1.09-1.69)
Yang *et al*[92]	Obesity	50/18 260 378	Obesity was associated with a higher risk of SARS-CoV2 infection (OR: 1.39, 95%CI: 1.25-1.54), increased disease severity (OR: 3.74, 95%CI: 1.18-11.87) and mortality (OR: 1.65, 95%CI: 1.21-2.25)
Huang *et al*[2]	DM	30/6452	DM was associated with composite poor outcome (RR 2.38 [1.88, 3.03], $P < 0.001$)
Kumar *et al*[59]	DM	33/16003	The combined corrected pooled OR of mortality or severity was 2.16 (95%CI: 1.74-2.68; $P < 0.01$)
Atmosudigdo *et al*[94]	Dyslipidemia	09/3663	Dyslipidemia was associated with poor outcome (RR 1.39 [1.02, 1.88], more so in patients with older age, male, and hypertension
Hariyanto *et al*[95]	Dyslipidemia	07/6922	Dyslipidemia was associated with severe disease (RR 1.39 (95%CI: 1.03-1.87)
Du *et al*[93]	Hypertension	24/99918	Patients with hypertension had a 1.82-fold higher risk for critical COVID-19 (OR: 1.82; 95%CI: 1.19-2.77; $P = 0.005$) and a 2.17-fold higher risk for COVID-19 mortality (OR: 2.17; 95% CI: 1.67-2.82; $P < 0.001$)
Zuin *et al*[4]	Metabolic syndrome	06/209.569	Pre-existing metabolic syndrome was associated with higher risk of mortality (OR: 2.30, 95%CI: 1.52-3.45). Meta-regression showed a direct correlation with hypertension, DM and hyperlipidaemia
Tao *et al*[5]	MAFLD	07/2141	MAFLD increased the risk of severe COVID-19 (OR: 1.80, 95%Cl: 1.53-2.13)
Pan *et al*[96]	MAFLD	06/1293	MAFLD increased the risk of disease severity, with a pooled OR of 2.93 (95%CI: 1.87, 4.60)

COVID-19: Coronavirus disease 2019; CI: Confidence interval; DM: Diabetes mellitus; RR: Relative risk, OR: Odds ratio; MAFLD: Metabolic associated fatty liver disease.

dysfunction. Despite the preponderance of ACE2 on the biliary epithelium, significant cholestasis is rare. In a histological study of patients who died of complications of COVID-19, macrovesicular steatosis was the most common finding as it was observed in 75% of patients, and PCR for viral ribonucleic acid in liver tissue was positive in 55% of patients tested[102]. Such a high frequency of hepatic steatosis suggests a role of some metabolic derangements associated with COVID infection, which in turn lead to fatty liver disease. In this regard, COVID-19 patients with NAFLD have a higher risk of developing liver injury[103], a higher risk of disease progression (44.7% *vs* 6.6%), more likelihood of impaired liver function, and a longer viral shedding time compared to those without NAFLD[19]. It is noteworthy that NAFLD is now known as MAFLD, which refers to the hepatic manifestation of metabolic health. In two meta-analyses, MAFLD was found to increase the risk of severe COVID-19 (OR: 1.8 and 2.9, respectively)[4,5]. After adjusting for confounders, the pooled OR for severe COVID-19 in NAFLD was 2.358, demonstrating that NAFLD alone, without confounding factors, may contribute to worse COVID-19 outcomes; however, the exact explanation is still unknown[104]. Therefore, further research on the impact of NAFLD in COVID-19 patients is needed.

In patients with liver cirrhosis, the RAAS plays a key role in the development of portal hypertension and ascites[14,105,106]. The hyperdynamic circulation seen in portal hypertension is caused by overexpression of ACE2 and enhanced Ang1-7 production in the mesenteric arterioles[105,106]. As per the combined SECURE-liver and COVID-Hep registries, 38% of patients with cirrhosis and COVID-19 had worsening ascites, acute kidney injury (AKI), or encephalopathy[107]. In cirrhosis, RAAS activation occurs as a compensatory response to the systemic and splanchnic arterial vasodilation, resulting in renal water and sodium retention, which contributes to the development of the complications of cirrhosis such as ascites and AKI[14,108,109]. COVID-19 can increase the risk of these complications by interacting with the RAAS. On another note, hyperammonemia has been reported in COVID-19 patients, and it could be linked to hepatic dysfunction and urea cycle interference[110]. Ammonia is a neurotoxin that affects astrocytes and plays a role in the development of cerebral edema and hepatic encephalopathy. By causing IR and pancreatic dysfunction, COVID-19 can increase the risk of hepatogenous diabetes in patients with liver cirrhosis, and it can aggravate pre-existing gut dysbiosis in cirrhosis. On the one hand, gut dysbiosis can result in the translocation of endotoxins and bacteria leading to inflammation; on the other hand, it reduces the anti-inflammatory effects by reducing the production of commensal bacterial metabolites such as butyrate, bile acid derivatives, and indole[111]. Overall, the proinflammatory environment with metabolic alterations in COVID-19 patients with liver cirrhosis leads to the development of acute decompensation, acute-on-chronic liver failure, and increased mortality[109,112].

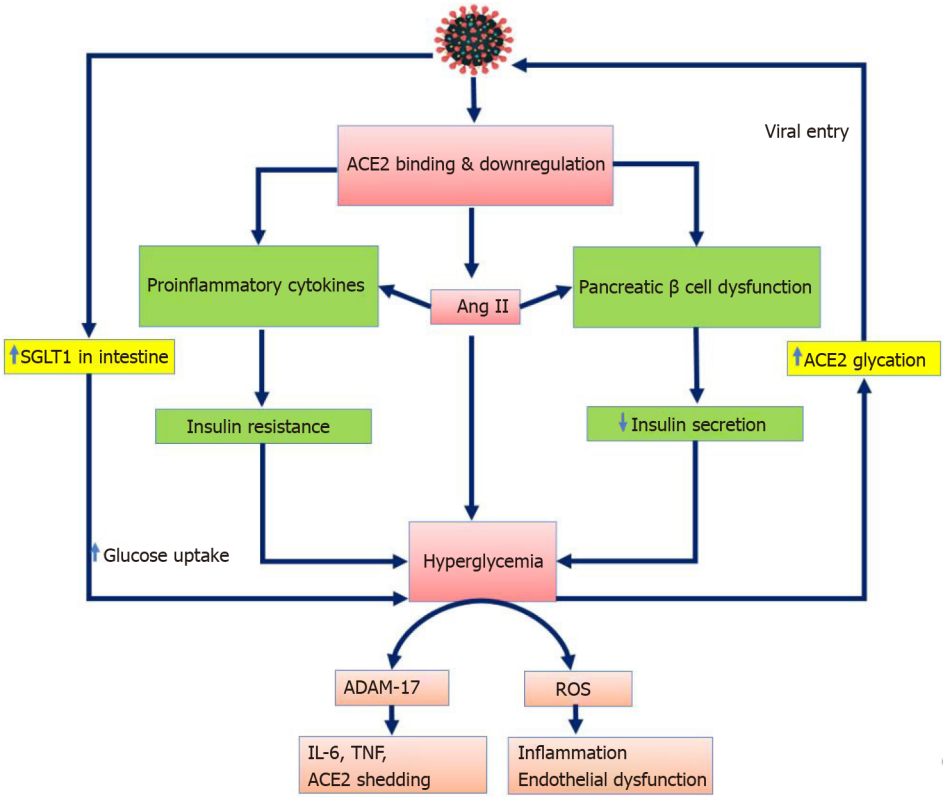

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Figure 2 The pathophysiological mechanism linking coronavirus disease 2019 with hyperglycemia. The pathophysiological basis of hyperglycaemia in coronavirus disease 2019 patients is still poorly understood but appears to be due to the development of insulin resistance and pancreatic β-cell dysfunction in which upregulation of angiotensin II, inflammation, and oxidative stress play important role. ACE2: Angiotensin converting enzymes 2; Ang II: Angiotensin II; SGLT1: Sodium glucose transport protein1; ROS: Reactive oxygen species; ADAM-17: Disintegrin and metalloproteinase domain-17; IL-6: Interleukin-6, TNF: Tumour necrosis factor.

METABOLIC CHANGES DURING AND FOLLOWING RECOVERY FROM COVID-19

During the early convalescence of COVID-19 patients, distinct profiles of metabolites and cytokines have been observed. One study reported a reduction in saturated fat palmitic acid while unsaturated fatty acids such as docosapentaenoic acid and docosahexaenoic acid were elevated[29]. These changes correspond to the prevention of hepatocyte apoptosis and facilitation of liver repair. Furthermore, a rise in tryptophan levels was observed, and this could aid in the reversal of liver injury by preserving protein synthesis activity[113]. On another note, the glycemic abnormalities persist for at least 2 mo following recovery from COVID-19[58]. A long-term follow-up study on patients who had recovered from the original SARS-CoV-1 infection found a significant prevalence of hyperlipidemia (68%) and glycemic abnormalities (60%)[114]. Given the structural similarity of the SARS-CoV-2 virus to the original SARS-CoV-1 virus, comparable outcomes can be expected; however, this remains to be seen. The metabolic abnormality appears to persist more in patients with metabolic comorbidities. In this sense, a study with 1-year follow-up following discharge reported significant abnormalities in metabolic indicators such as blood lipids, uric acid, and liver function in obese COVID-19 patients compared to non-obese ones[18]. Another study demonstrated incomplete metabolic phenorversion in post-COVID patients. Even though most metabolic markers showed a high level of normalization, plasma taurine, and lower glutamine/glutamate ratios indicated little normalization in the majority of patients, indicating probable liver and muscle injury[17]. Further research is needed to determine the long-term clinical implications of these findings. In a study published recently, MAFLD was highly prevalent after hospital discharge, indicating potential long-term metabolic health implications. The prevalence of MAFLD was 55.3% at follow-up, while it was 37.3% on admission[115]. As metabolic alterations such as dysglycemia, hyperlipidemia, and inflammation are important in the progression of MAFLD, a high prevalence of MAFLD-induced advanced CLD may be expected in the years to come.

CONCLUSION

Human SARS-CoV-2 infection triggers a complex viral-host interaction that results in metabolic

reprogramming, altered immunological response, and a variety of clinical consequences. As the liver is the metabolic hub of the body, it is targeted in this process. In metabolomics and lipidomic studies on COVID-19 patients, a variety of alterations in amino acids, lipids, carbohydrates, and energy metabolism have been identified. Although the impact of each metabolic change remains to be determined, pathophysiological alterations in the RAAS, insulin sensitivity, pancreatic functions, biosynthesis pathways, and ammonia metabolism can be used to make various extrapolations in the clinical setting. Furthermore, evidence suggests a direct link between metabolic changes and inflammatory responses in the body. Patients with underlying low-grade chronic inflammation, such as metabolic syndrome or CLD, may be particularly affected by COVID-19-induced metabolic changes. Therefore, obesity, DM, hypertension, dyslipidemia, and MAFLD in COVID-19 patients have all been associated with a more severe disease course and higher mortality. Moreover, preliminary data suggest that metabolic changes in COVID-19 can also have long-term health implications. Improved metabolic parameters such as blood glucose, blood pressure, and body weight may help control the systemic inflammatory response and reduce the severity of COVID-19 disease. Furthermore, metabolic changes may reflect the molecular profile of SARS-CoV-2-infected individuals, opening up new avenues for targeted therapeutic interventions.

FOOTNOTES

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REVIEW

SARS-CoV-2 infection and diabetes: Pathophysiological mechanism of multi-system organ failure

Bipradas Roy, Sadia Afrin Runa

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Abstract

Since the discovery of the coronavirus disease 2019 outbreak, a vast majority of studies have been carried out that confirmed the worst outcome of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in people with preexisting health conditions, including diabetes, obesity, hypertension, cancer, and cardiovascular diseases. Likewise, diabetes itself is one of the leading causes of global public health concerns that impose a heavy global burden on public health as well as socio-economic development. Both diabetes and SARS-CoV-2 infection have their independent ability to induce the pathogenesis and severity of multi-system organ failure, while the co-existence of these two culprits can accelerate the rate of disease progression and magnify the severity of the disease. However, the exact pathophysiology of multi-system organ failure in diabetic patients after SARS-CoV-2 infection is still obscure. This review summarized the organ-specific possible molecular mechanisms of SARS-CoV-2 and diabetes-induced pathophysiology of several diseases of multiple organs, including the lungs, heart, kidneys, brain, eyes, gastrointestinal system, and bones, and subsequent manifestation of multi-system organ failure.

Key Words: SARS-CoV-2; Diabetes; Neurological dysfunction; Cardiovascular complications; Renal dysfunction; Bone loss

Core Tip: There is no therapeutic approach yet that can eradicate diabetes and its complications from human life, as the etiopathology of diabetes is very complex. Before the outbreak of coronavirus disease 2019, it was almost unknown that diabetes is a leading risk factor that could fuel the pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced multi-organ dysfunction and subsequent mortality. Additionally, SARS-CoV-2-infected children and young people have been shown to develop diabetes. Therefore, identifying the precise molecular mechanisms of diabetes-induced SARS-CoV-2 susceptibility and subsequent manifestation of multi-organ dysfunction may help us to develop drugs that prevent millions of human lives.

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INTRODUCTION

Diabetes mellitus (DM) is a multi-faceted metabolic syndrome that induces or exacerbates the pathophysiology of several complications, including neuropathy, nephropathy, retinopathy, cardiovascular diseases, pulmonary dysfunction, gastrointestinal (GI) dysfunction, and osteoporosis[1]. DM and its complications are increasing day by day while decreasing life expectancy and increasing the cost of diagnosis and treatment. According to the most recent Centers for Disease Control and Prevention (CDC) report, 37.3 million Americans have diabetes, and another 96 million US population have prediabetes[2].

Recently, coronavirus disease 2019 (COVID-19) has been the most discussed topic worldwide due to its devastating physiological and socioeconomic impacts since its discovery in December 2019 in Wuhan, China. As of 21 June 2022, the World Health Organization has reported 539119771 globally diagnosed COVID-19 cases, including 6322311 COVID-19-associated mortalities (WHO Coronavirus Dashboard. Available online: https://covid19.who.int). Although the overall COVID-19 positive case numbers declined from the previous years, the post-COVID-19 impact is still increasing. As time goes by, the trend of the pathogenicity for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has shifted from acute to long-term. Many studies determined the physiological consequences of the acute phase of SARS-CoV-2 infection and the post-COVID-19 effects on human health and diseases, including diabetes. However, few studies have been carried out to characterize the long-term risks and burden of diabetes in the post-acute phase of COVID-19. A recent study in a cohort that recruited 181280 participants who tested positive for SARS-CoV-2 and a contemporary control that recruited 4118441 participants showed that people with COVID-19 exhibited an increased risk and excess burden of incident diabetes as well as increased risk of antihyperglycemic use compared with the contemporary control group[3]. Another retrospective cohort study that recruited 126710 participants with one or more nasal swabs positive for SARS-CoV-2 and 2651058 participants with no positive swab showed that SARS-CoV-2 was associated with a higher risk of incident diabetes in men but not in women, compared with no positive tests. This study further demonstrated that among hospitalized COVID-19 patients, SARS-CoV-2 was associated with a higher risk of diabetes at 120 d and the end of follow-up in men but not in women[4]. However, the exact mechanism of SARS-CoV-2-induced increase in diabetic incidence and subsequent multiorgan dysfunction is unknown. This review provides ideas about the organ-specific cellular mechanism through which SARS-CoV-2 and diabetes mellitus results in multi-system organ dysfunction.

METHODS

We searched our queries using Google Scholar, PubMed Central, ResearchGate, and the CDC databases. For this manuscript, we used articles published recently in standard peer-reviewed journals. We tried to avoid using review articles as much as possible; instead, we used research articles and case studies. We recruited research articles based on the following hierarchy: studies in humans > studies in animals > and studies in cell culture models. We thoroughly read the selected articles and picked the findings supporting our query.

SARS-CoV-2 INFECTION EXACERBATES DIABETES-INDUCED MULTI-SYSTEM ORGAN FAILURE

SARS-CoV-2 infection exacerbates diabetes-induced pulmonary dysfunction

Many studies have been carried out to determine the pathophysiology of diabetes-induced pulmonary dysfunction. For instance, a retrospective, longitudinal cohort study on 1811228 subjects showed that the prevalence of asthma, chronic obstructive pulmonary disease (COPD), fibrosis, and pneumonia was significantly higher in diabetic patients relative to their age and sex-matched non-diabetic controls[5]. Another retrospective cohort study with 1332 patients with concomitant asthma and diabetes showed that the use of metformin, a well-known diabetic drug, significantly reduced the risk of asthma[6]. Findings from this study suggest that diabetes induces the development of asthma in humans. A prospective multicenter study that employed 5334 COPD patients with or without diabetes showed that COPD patients with comorbid diabetes had a more severe profile and higher hospitalization costs[7]. A study in 162 T2DM patients without diabetes complications and 55 healthy control subjects showed that pulmonary function in T2DM patients is negatively correlated with vascular endothelial functional index, *e.g.*, flow-mediated dilation and nitric oxide (NO), whereas positively correlated with endothelin-1 (ET-1) and glycosylated hemoglobinA1c (HbA1c)[8]. This study suggests that T2DM-induced vascular EC dysfunction is an important biomarker of pulmonary dysfunction. Hyperglycemia or insulin resistance (IR)-induced diabetic ketoacidosis (DKA) is associated with reduced serum potassium levels that subsequently cause respiratory muscle weakness and culmination of acute respiratory failure[9]. Additionally, DKA may contribute to the pathogenesis of pulmonary edema results from an acute shift of a large volume of fluid into the extracellular compartment and subsequent elevation of pulmonary venous pressure (hydrostatic pulmonary edema) as well as increased pulmonary capillary permeability (non-hydrostatic pulmonary edema) due to pulmonary microangiopathy[9]. A study in 26 diabetic patients showed a significant increase in angiotensin converting enzyme-2 (ACE2) protein levels in both alveolar tissue and bronchial epithelium compared to the control subjects, independent of smoking, chronic obstructive pulmonary disease, body mass index (BMI), renin-angiotensin-aldosterone system (RAAS) inhibitor use, and other potential confounders[10]. A study in 34239 patients (with or without diabetes) with a pneumonia-related hospitalization and 342390 healthy control subjects showed that poor long-term glycemic control in T1DM and T2DM increases the risk of hospitalization with pneumonia[11]. In addition to humans, a vast majority of studies have been carried out in rodents to determine the role of diabetes in pulmonary dysfunction. For instance, streptozotocin (STZ)-induced diabetic rats showed increased pulmonary basal membrane thickness, increased inflammatory reaction due to mononuclear cell infiltration in their lungs, and increased levels of protein carbonyl content, a by-product of oxidative stress, relative to their age-matched controls[12]. Likewise, myocardial ischemia-reperfusion in STZ-induced diabetic rats demonstrated an increase in alveolar wall thickness and lung tissue damage along with increased infiltration or aggregation of neutrophils in lung tissue compared with their age-matched wild-type controls[13]. Another study in STZ-induced diabetic rats showed that the lung tissue and lamellar bodies were significantly collapsed along with a significant reduction in SOD activity and the mRNA expression and protein levels of aldehyde dehydrogenase 2, an alcohol detoxifying mitochondrial enzyme in the lung tissue of diabetic rats[14]. STZ-induced diabetic rats developed pulmonary fibrosis along with increased inflammation in the lung tissue as evaluated by increased expression and levels of several profibrotic and proinflammatory biomarkers, including fibronectin, connective tissue growth factor (CTGF), plasminogen activator inhibitor-1 and tumor necrosis factor (TNF)-α[15]. Additionally, the expression of NADPH oxidase (NOX), an important mediator of oxidative and nitrative stress, significantly increased along with increased protein nitration and upregulation of angiotensin II (Ang II) and its receptor angiotensin II type 1 (AT1) in diabetic lung tissue. This study again reported that chronic administration of Ang II in normal mice induced diabetes-like lung fibrosis and inflammation (Figure 1), and the effects of Ang II were completely abrogated with losartan treatment, a potential AT1 inhibitor[15]. All the studies I stated so far revealed mostly the association between diabetes and different types of lung dysfunction. However, the precise underlying mechanism of diabetes-induced pathophysiology of lung disease is not well understood. Hyperglycemia and hyperinsulinemia in diabetes increase oxidative stress, non-enzymatic glycation of tissue proteins, activation of protein kinase C (PKC), nuclear factor-κB (NF-κB), and polyol pathways, and eventually lead to the development of pulmonary dysfunction through autonomic neuropathy, micro/macroangiopathy in the lung, impairment in pulmonary elastin and collagen content, alteration of pulmonary connective tissue, surfactant dysfunction and malfunctioning of respiratory muscles (Figure 1)[16].

It is well established that ACE-2 is predominantly expressed in pulmonary endothelial cells and airway epithelial cells (AECs), the main cellular entry of SARS-CoV-2 to start the pathogenesis of COVID-19 manifestation. A *phenome-wide* Mendelian randomization study in 898130 T2DM subjects showed an increase in ACE2 expression in their lung tissue compared with non-diabetic healthy controls[17]. Another study in humans showed an increased expression of ACE2 and transmembrane serine protease 2 (TMPRSS2) in the upper and lower airway tissue in adults than in children. This study further showed an elevated expression of ACE2 and TMPRSS2 in the airway tissue of smokers and

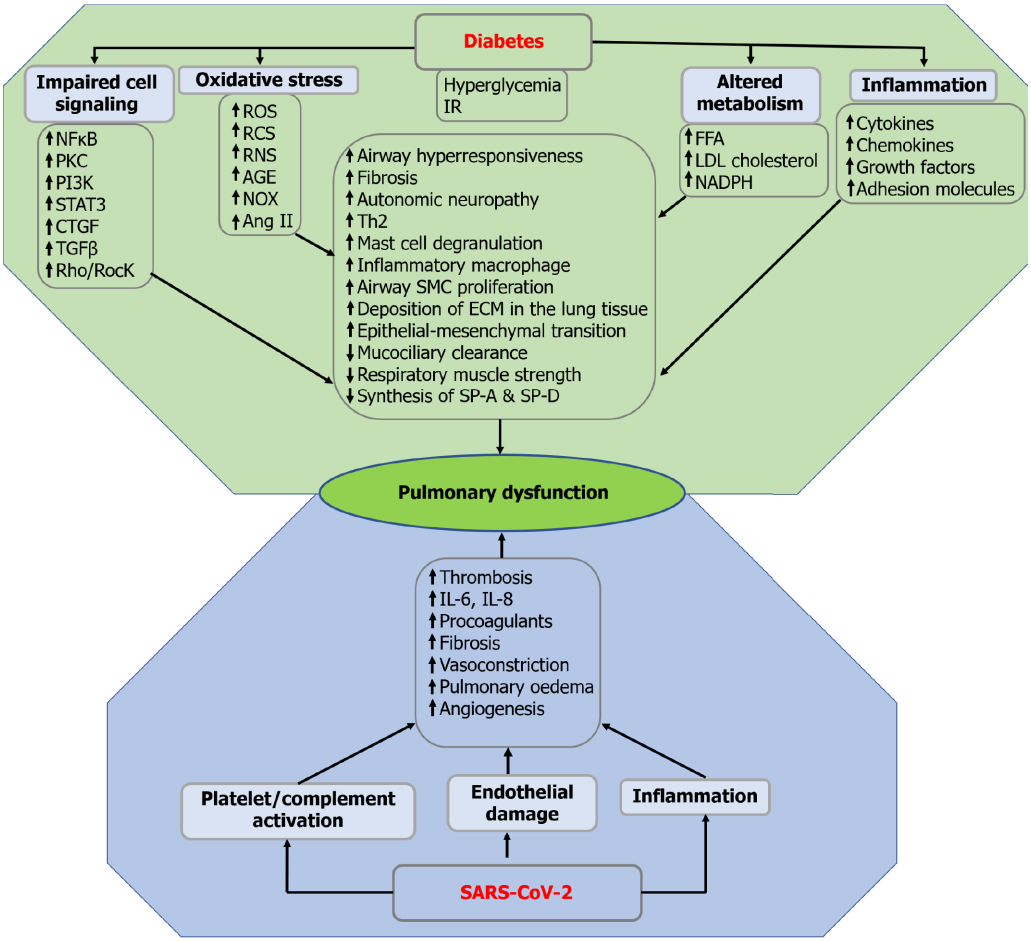

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Figure 1 Possible mechanism of diabetes and severe acute respiratory syndrome coronavirus 2-induced pulmonary dysfunction. Hyperglycemia and insulin resistance in diabetes is associated with impaired cell signaling, oxidative stress, inflammation, and altered metabolism and subsequently lead to the manifestation of pulmonary dysfunction due to increased airway hyperresponsiveness, fibrosis, autonomic neuropathy, T helper 2, mast cell degranulation, Inflammatory macrophage, airway smooth muscle cell proliferation, deposition of extracellular matrix in the lung tissue, epithelial-mesenchymal transition, whereas reduced mucociliary clearance, respiratory muscle strength and synthesis of SP-A and SP-D. On the other hand, platelet or complement activation, endothelial damage, and inflammation in severe acute respiratory syndrome coronavirus 2 infection lead to the pathogenesis of pulmonary dysfunction due to elevated thrombosis, IL-6, IL-8, procoagulants, fibrosis, vasoconstriction, pulmonary edema, and angiogenesis. IR: Insulin resistance; NFκB: Nuclear factor-κB; PKC: Protein kinase C; PI3K: Phosphoinositide 3-kinases; STAT3: Signal transducer and activator of transcription 3; CTGF: Connective tissue growth factor; TGFβ: Transforming growth factor beta; Rho/RocK: Ras homologous/Rho-associated coiled-coil kinase; ROS: Reactive oxygen species; RNS: Reactive nitrogen species; RCS: Reactive carbonyl species; AGE: Advanced glycation end products; NOX: Nitrogen oxides; Ang II: Angiotensin II; Th2: T helper 2; SMC: Smooth muscle cell; ECM: Extracellular matrix; SP-A: Surfactant proteins A; SP-D: Surfactant proteins D; FFA: Free fatty acid; LDL: low-density lipoprotein; NADPH: Reduced nicotinamide adenine dinucleotide phosphate; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

COPD patients[18]. A study in 55, 44 COVID-19 post-mortem lung samples showed increased expression of ACE2 along with increased diffuse alveolar damage, acute bronchopneumonia, and acute lung injury in severe COVID-19 patients relative to the lung samples from healthy subjects[19]. There are contradictory findings regarding the prevalence of ACE2 expression in pulmonary vascular endothelial cells *vs* airway epithelial cells/pneumocytes. Findings from a vast majority of studies confirmed that ACE2 is predominantly expressed in airway epithelial cells. For instance, a study in two cohorts in Australia showed that gene expression and protein levels of ACE2 in the lower AECs were significantly higher in older age and male sex compared with younger age and females, respectively [20]. However, another study in humans suggests that pulmonary endothelial cells express twice as many ACE2 receptors for viral entry than pneumocytes[21].

A study in lungs from patients who died from COVID-19 as well as patients who died from acute respiratory distress syndrome secondary to influenza A (H1N1) infection showed alveolar damage with perivascular T-cell infiltration along with severe endothelial injury associated with the presence of intracellular virus and disrupted cell membranes. Additionally, pulmonary vessels in patients with Covid-19 showed widespread thrombosis with microangiopathy. This study further demonstrated that the prevalence of alveolar-capillary microthrombi was nine times higher in the Covid-19 patients relative to patients with influenza[21]. Another study in the lung tissue from 11 Covid-19 deaths showed an increased loss of alveolar wall integrity, detachment of lung tissue pieces, fibroblast prolif-

eration, and extensive fibrosis[22]. SARS-CoV-2 infected human AECs showed an increased cytopathic effect which was determined through a lack of cilium beating on the surface of AECs after 96 h of inoculation. However, SARS-CoV-2 infected Vero E6, and Huh-7 cell lines did not show any cytopathic effect[23]. Another case series study employing ultrasound-guided minimally invasive autopsy (MIA-US) in 10 fatal cases of COVID-19 showed exudative/proliferative diffuse alveolar damage, intense pleomorphic cytopathic effects on the respiratory epithelium, including airway and alveolar cells, increased fibrinous thrombi in alveolar arterioles and elevation of alveolar megakaryocyte numbers. This study further showed that small thrombi formation was less frequent in other tissues, including the glomeruli, spleen, heart, dermis, testis, and liver sinusoids, compared to the lungs[24]. Findings from this study suggest that COVID-19 is a systemic disease that predominantly infects the lungs through severe epithelial injury and microthrombotic vascular phenomena, along with damage to other organs and tissues. Immunohistochemistry of the lung tissue biopsy from a 72-year-old man with a history of diabetes and hypertension showed denuded alveolar lining cells, increased reactive type II pneumocyte hyperplasia, and increased intra-alveolar fibrinous exudates, along with loose interstitial fibrosis, and chronic inflammatory infiltrates. This study further confirmed the presence of SARS-Cov-2 in alveolar epithelial cells due to the presence of SARS-CoV-2 Rp3 NP protein[25]. A study in 108 individuals showed increased alveolar type II-pneumocyte injury as confirmed by elevated plasma levels of surfactant protein D, a biomarker of alveolar type II-pneumocyte injury, along with increased interleukin (IL)-6 serum levels in critically ill COVID-19 patients[26].

Other studies also showed that the use of ET-1 receptor antagonist, Bosentan has been approved as a drug to treat pulmonary arterial hypertension in New York Heart Association functional classification II-IV and in scleroderma patients, as it decreases the systemic levels of profibrotic and proinflammatory cytokines including IL-2, IL-6, IL-8 and interferon (IFN)-γ in scleroderma patients, as well as slows down the progression of fibrosis and vascular damage[27]. The possible mechanisms of diabetes and SARS-CoV-2-induced pulmonary dysfunction are stated in Figure 1.

SARS-CoV-2 infection exacerbates diabetes-induced immune dysfunction

The complement system, a complex innate immune surveillance system, contributes to the destruction/neutralization of pathogens, including viruses and bacteria, that invade our body[28]. The complement system is composed of plasma proteins synthesized mainly by the liver or membrane proteins expressed on the cell surface, whose main functions are to promote the opsonization and phagocytosis of microorganisms and apoptotic cells through macrophages and neutrophils to induce their degradation[28,29]. A study showed that hyperglycemia inhibited complement-mediated opsonization of *S. aureus* in diabetic rats[30]. Another study reported that hyperglycemia caused direct glycosylation of proteins and altered the tertiary Structure of complement proteins, and subsequently inhibited immunoglobulin-mediated opsonization of bacteria[31].

Thrombotic microangiopathy (TMA) is a pathological condition that is associated with thrombosis in capillaries and arterioles, which leads to microangiopathic hemolytic anemia, thrombocytopenia, and organ damage, such as neurological, renal and cardiac dysfunction[32]. There are several risk factors that can contribute to the pathogenesis of TMA, including viruses, bacteria, drugs, oxidative stress, complement hyperactivation, and congenital predisposing conditions. All these factors directly or indirectly induce vascular endothelial cell damage, followed by the development of TMA. Studies showed that DM is associated with increased activation of the C3 complement component, which is a central factor of complement cascade[33,34]. Another study also showed that Insulin resistance is linked with elevated circulating complement factor C3 levels[35]. Increased C3 levels in plasma contribute to the hyperactivation of complement cascade that may lead to the development of TMA[36]. Oxidative stress-induced vascular endothelial dysfunction is an important hallmark of DM[37] and may contribute to the development of TMA[38]. Von Willebrand factor (VWF) is a clotting factor that is required for the pathogenesis of thrombotic thrombocytopenic purpura (TTP), a fatal blood disorder[39]. In pathological conditions, a multimeric form of VWF and platelets are prone to form aggregates and subsequently cause TTP[40]. A disintegrin and metalloprotease with thrombospondin type I repeats-13 (ADAMTS13), a zinc-containing metalloprotease that cleaves multimeric form of VWF and mitigates the formation of VWF-platelets aggregates[40]. The deficiency of plasma ADAMTS13 contributes to the progression of TTP[41]. A study in human subjects showed that T2DM-induced oxidative stress modifies the amino acid sequences of VWF and thereby prevents its proteolytic cleavage by ADAMTS13[42]. Another study showed that ADAMTS13 activity is significantly lower in T2DM patients compared with healthy control people[43]. Several virus strains, including SARS-CoV-2, HIV, MCV, EBV, parvovirus, rubella, and measles, have been recognized so far that can cause TTP by modulating the autoimmune process in human and animal species[44,45]. However, the exact molecular mechanism of the novel coronavirus, SARS-CoV-2-induced TTP, is completely unknown. Rapidly emerging data from clinical observations, autopsy-based findings, extrapolations from *in vitro* and *in vivo* studies, and dynamic modeling are not well enough to provide the exact pathophysiology of secondary complications associated with SARS-COV-2 infection[46]. However, a large number of patients with severe COVID-19 demonstrated TMA-like systemic coagulopathy that led to an increased number of deaths[47]. Findings from several studies reported that coagulopathy in COVID-19 patients was confirmed through the presence of elevated D-dimer, elevated lactate dehydrogenase, elevated total bilirubin, and decreased platelets[46,48]. As DM

and SARS-COV-2 both are associated with TMA-like symptoms, the mortality rate should be higher in DM patients when infected with SARS-COV-2. A single-center cross-sectional study that employed 68 patients with COVID-19, including 48 ICU and 20 non-ICU patients, as well as 13 non-hospitalized, asymptomatic controls, showed that the levels of endothelial cell and platelet activation markers, including VWF antigen and soluble P-selectin. This study further demonstrated that the mortality of ICU patients was positively correlated with concentrations of VWF antigen and soluble thrombomodulin[49].

Hemophagocytic lymphohistiocytosis (HLH) is a cytokine storm-induced inflammatory syndrome that is associated with substantial morbidity and mortality due to multiorgan failure[50,51]. Several case reports demonstrated that diabetes insipidus is associated with secondary HLH (sHLH)[52,53]. Accumulating evidence suggests that several patients with severe COVID-19 demonstrated sHLH due to cytokine storm, which is characterized by increased interleukin IL-2, IL-7, granulocyte colony-stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α[51]. Based on the findings stated above, it can be surmised that diabetes patients infected with SARS-COV-2 possess a higher risk of fatality compared with SARS-COV-2 infected non-diabetic subjects.

SARS-CoV-2 infection exacerbates diabetes-induced cardiovascular complications

The prevalence of atrial fibrillation (AF), an important hallmark of arrhythmia, is higher in DM patients. In an observational, age- and sex-matched cohort, a longitudinal study that included 34744 patients with and without diabetes showed that AF was 44% more prevalent and 38% more likely to develop in T2DM[54]. A cohort study with 421855 T2DM patients showed that there is a 35% increased risk of developing AF in T2DM patients compared with age- and sex-matched controls from the general population. This study also showed that the risk of developing AF is exacerbated in T2DM patients with poor glycemic control and renal complications[55]. There are several mechanisms that may lead to the development of AF in DM. Oxidative stress in diabetes is associated with increased formation of reactive oxygen species, carbonyl species, nitrogen species, and AGE, which in turn predisposes to the development of AF through endothelial dysfunction, increased atherogenesis and reduced coronary angiogenesis. T2DM is a leading cause of cardiovascular diseases (CVDs), including atherosclerosis, MI, HF, and cardiomyopathy. There are several mechanisms that result in the pathogenesis of diabetic cardiomyopathy, including impaired insulin signaling, mitochondrial dysfunction, increased oxidative stress, reduced NO levels, elevated AGEs levels, stiffness of extracellular matrix, impaired handling of Ca^{2+} by cardiomyocytes, inflammation, RAAS over activation, cardiac autonomic neuropathy, endoplasmic reticulum stress, microvascular dysfunction, and several cardiac metabolic abnormalities [56].

Several studies have demonstrated that hospitalization and mortality rate are significantly higher in COVID-19 patients who has preexisting arrhythmia. A study in a cohort of 153760 US veterans who survived in the first 30 d of COVID-19 has experienced different types of CVDs, including dysrhythmias, ischemic and non-ischemic heart disease, pericarditis, myocarditis, heart failure, and thromboembolic disease[57]. A multicenter study with 696 hospitalized covid-19 patients developed acute HF and multiorgan failure as well as increased mortality which had a history of AF[58]. A retrospective observational study also showed that iCOVID-19 patients with a myocardial injury (determined by increased systemic C-reactive protein levels) are positively correlated with inflammation and coagulopathy and increased hospitalization[59]. Several possible mechanisms may contribute to the pathogenesis of acute myocardial injury in COVID-19 subjects, including microvascular injury, hypoxemia, preexisting CVDs, ventricular/atrial arrhythmias, hypotension, viral myocarditis, cytokine storm, and stress-induced cardiomyopathy[60]. A systematic pathological analysis that included 40 hearts from hospitalized patients dying of COVID-19 showed that the most common pathological cause of cardiomyocyte necrosis in COVID-19 patients was microthrombi. This study further demonstrated that the composition of intramyocardial microthrombi was different between COVID-19-negative and positive subjects[61].

A study using the samples from right atrial appendage biopsies in 57 diabetics and 22 non-diabetic subjects who underwent coronary artery bypass graft surgery showed that ACE2 mRNA expression and protein levels in heart tissue, as well as serum ACE2 levels, were significantly higher in diabetic patients relative to the non-diabetic control subjects. Additionally, ACE2 levels were positively correlated with glycosylated hemoglobin (HbA1c) levels, BMI, and activation of RAAS, and negatively correlated with ejection fraction. This study further demonstrated that the expression of TMPRSS2, metalloprotease *ADAM10*, and *ADAM17* that facilitate viral-*ACE2* complex entry and degradation were increased in diabetic hearts[62]. Diabetes is associated with increased activation of RAAS and subsequent elevation of systemic Ang II levels. However, the direct association of T2DM and SARS-CoV-2 susceptibility to the human heart is still unclear. STZ-induced diabetic mice developed severe cardiovascular complications after influenza virus infection as evaluated with increased circulatory levels of serum cardiac troponin I and creatine-kinase MB, left ventricular structural changes, and right ventricular functional alterations[63]. A prospective cohort study in Germany demonstrated an elevation of myocardial SARS–CoV-2 RNA in 5 out of 12 COVID-19–positive deaths[64]. Another study by Wenzel *et al*[65] showed an increased myocardial SARS-CoV-2 RNA in patients with clinically suspected myocarditis

who were tested negative for COVID-19 in nasopharyngeal swabs. A case study in a 72-years-old male patient who died due to severe COVID-19 reported the presence of SARS-COV-2 RNA as well as SARS-COV-2 antigen in his cardiac tissue and cardiomyocyte, respectively[66]. Another study that employed endomyocardial biopsy samples from four SARS-CoV-2 infected dead patients who were diagnosed with myocarditis showed left ventricular systolic dysfunction due to cardiomyocyte injury and degenerative vacuolization of cardiomyocyte cytoplasm along with myeloid-rich inflammatory cell infiltrate. Additionally, the myocardium of each COVID-19 myocarditis subject also showed an increased expression of SARS-CoV-2 spike and nucleocapsid RNAs as well as nucleocapsid protein levels. This study further demonstrated that SARS-CoV-2 selectively infects hPSC-derived cardiomyocytes through an ACE2 and endosomal cysteine protease-dependent pathway and subsequent production of the infectious virus with peak titers on day three post-inoculation. Infecting engineered heart tissues with SARS-CoV-2 confirmed that cytokine production, myocardial sarcomere disassembly, and cardiomyocyte death were a direct consequence of cardiomyocyte infection[67]. The possible mechanisms of diabetes and SARS-CoV-2-induced cardiovascular dysfunction are stated in Figure 2.

SARS-CoV-2 infection exacerbates diabetes-induced renal complications

According to the most recent data from the CDC, around 37 million people in the united states are estimated to have chronic kidney disease (CKD)[68], and approximately 1 in 3 adults with diabetes has CKD, which is also known as diabetic kidney disease (DKD) or diabetic nephropathy. Additionally, the increased rate of mortality and associated socioeconomic and medical burden due to CKD-mediated development of end-stage renal disease is receiving more attention as a leading cause of death around the world[69]. DKD is associated with several structural changes in the kidney, including mesangial expansion, thickening of the glomerular and tubular basement membrane, glomerular sclerosis that manifests clinical symptoms including elevated blood pressure, sustained reduction in glomerular filtration rate (GFR), persistent albuminuria, increased cardiovascular events and associated mortality.

There are several possible mechanisms that contribute to the pathogenesis of DKD in diabetes, including impairment in renal hemodynamics, inflammation, abnormal glucose metabolism, oxidative stress, and overactive RAAS. Diabetes is associated with increased dilatation of afferent arteriole in the kidney due to increased generation of important vasoactive peptides, including prostaglandin and NO. A cohort study with 171 subjects showed that plasma prostaglandin E2 levels were increased in 136 T2DM patients compared with 35 non-diabetic controls[70]. Studies in humans and animals showed that poor glycemic control is associated with increased generation of NO and subsequent inhibition of tubuloglomerular feedback–mediated vasoconstriction of afferent arterioles in diabetic kidneys[71,72]. Additionally, T2DM is associated with elevated circulatory Ang II levels due to the overactivation of RAAS, which constricts efferent arteriole and subsequently results in glomerular hypertension and impaired autoregulation. A study in a cohort with COVID-19 patients (n = 89) demonstrated that regardless of their severity, circulatory PEG2 levels increased significantly in SARS-CoV-2 infection compared with age and sex-matched healthy controls. Additionally, this study showed that the entire COVID-19 cohort had an increased rate of diabetes, BMI, as well as elevated circulatory C-reactive protein levels[73], an important prognostic biomarker of COVID-19[74] and CVDs[75].

Similarly, T2DM contributes to the development of renal fibrosis, podocyte injury, and inflammation through an increased generation of renal ET-1, an important vasoconstrictor. Studies showed that pulmonary infection and hypoxia cause an elevation of circulatory ET-1 levels in humans and animals [76]. A study in a cohort showed that plasma levels of the stable precursor protein of endothelin-1, proET-1 were significantly higher in non-survivor COVID-19 patients relative to the survivor COVID-19 patients. This study also showed that plasma proET-1 levels were significantly higher in patients with community-acquired pneumonia compared with both survivors and non-survivors of COVID-19 patients. Additionally, data from this study showed that there is no significant association between proET-1 levels and mortality in a regression model adjusted for age, gender, creatinine level, diastolic blood pressure, as well as cancer and coronary artery disease[77].

Hyperglycemia contributes to the generation of ROS through mitochondrial overload and subsequently leads to podocyte dysfunction and apoptosis. Hyperglycemia and oxidative stress in diabetes mellitus increase intrarenal AGE levels that may cause morphological and functional impairments in the kidney, including modification of basement membranes, glomerulosclerosis, interstitial fibrosis, and tubular atrophy. Studies in humans and animals showed that in most cases, AGE exerts its role through the activation of the receptor for AGE (RAGE) in the kidney[78]. Studies in rodents showed that inhibition of AGE binding with RAGE using RAGE-aptamers attenuates the development and progression of diabetic nephropathy in streptozotocin-induced diabetic rats. This study further showed that continuous administration of RAGE-aptamer significantly suppressed the AGE-induced oxidative stress generation and inflammatory and fibrotic reactions in human cultured mesangial cells[79].

A single-center observational cohort study in Germany showed that serum levels of soluble RAGE (sRAGE) increased significantly with COVID-19 severity, the need for dialysis, and catecholamine support[80].

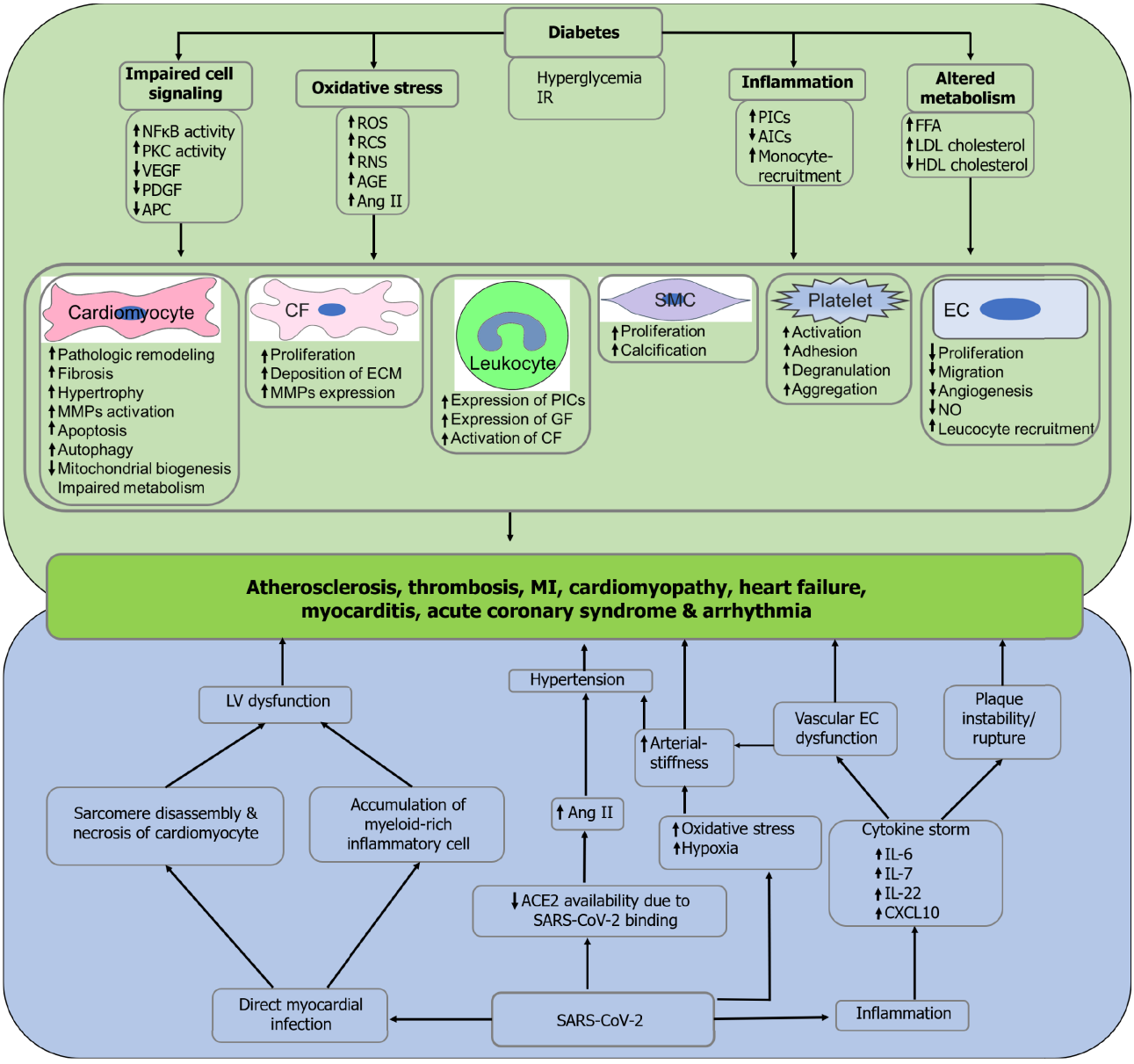

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Figure 2 Possible mechanism of diabetes and severe acute respiratory syndrome coronavirus 2-induced cardiovascular complications. Hyperglycemia and insulin resistance in diabetes is associated with impaired cell signaling, oxidative stress, inflammation, and altered metabolism and subsequently induce the pathogenesis of cardiovascular diseases, including atherosclerosis, thrombosis, myocardial infarction, cardiomyopathy, heart failure, myocarditis, acute coronary syndrome and arrhythmia due to impaired functioning of cardiomyocytes, cardiac fibroblasts, smooth muscle cells, endothelial cells and endothelial cells, leukocytes, and platelets. On the other hand, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directly infects the myocardium and subsequently induces left ventricular dysfunction due to sarcomere disassembly, necrosis of cardiomyocytes, and infiltration of myeloid-rich inflammatory cells. Additionally, SARS-CoV-2 infection reduces the availability of angiotensin converting enzyme-2 numbers, which results in elevated angiotensin II levels and subsequent manifestation of hypertension. SARS-CoV-2 infection is also associated with increased oxidative stress and hypoxia that may manifest hypertension due to arterial stiffness. Finally, inflammation in SARS-CoV-2 infection leads to cytokine storm and eventually induces vascular endothelial cell dysfunction and thrombotic plaque instability. Left ventricular dysfunction, hypertension, arterial stiffness, vascular endothelial cell dysfunction, and plaque instability induce the pathophysiology of cardiovascular diseases. IR: Insulin resistance; NFκB: Nuclear factor-κB; PKC: Protein kinase C; VEGF: Vascular endothelial growth factor; PDGF: Platelet-derived growth factor; APC: Adenomatous polyposis coli; ROS: Reactive oxygen species; RNS: Reactive nitrogen species; RCS: Reactive carbonyl species; AGE: Advanced glycation end products; Ang II: Angiotensin II; PICs: Pro-inflammatory cytokines; AICs: Anti-inflammatory cytokines; FFA: Free fatty acid; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; CF: Cardiac fibroblast; ECM: Extracellular matrix; GF: Growth factor; SMC: Smooth muscle cell; EC: Endothelial cell; NO: Nitric oxide; LV: Left ventricle; ACE2: Angiotensin converting enzyme-2; IL-6: Interleukin-6; IL-7: Interleukin-7; IL-22: Interleukin-22; CXCL10: C-X-C motif chemokine ligand 10; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Being a pleiotropic receptor, RAGE also interacts with a wide range of ligands in the S100 family, including S100A8/MRP8, S100A9/MRP14, S100A11, S100A12, S100B, high-mobility group box 1 (HMGB1). A study in Wuhan, China, showed that expression of S100A8, S100A9, S100A11, and S100A12 are significantly elevated in the lung tissue and serum of fatal COVID-19 patients compared to less severe cases of COVID-19[81]. Some other studies also demonstrated a positive association between

COVID-19 severity/fatality and plasma levels of S100A8[82], S100A9[82], HMGB1[82], S100A12[83] and S100B[84]. Additionally, an *in vitro* study revealed that HMGB1 epigenetically upregulates the expression of ACE2 in Vero-E6 cells and subsequently increases the susceptibility to SARS-CoV-1, SARS-CoV-2, and NL63 infection[85].

Prolonged hyperglycemia in diabetes is a renowned risk factor for kidney injury leading to proteinuria in humans[86,87]. A prospective, multicenter study in France showed that 60% of COVID-19 patients developed proteinuria as determined by urinary protein to creatine ratio. Additionally, this study also showed that proteinuria was significantly elevated in severe COVID-19 patients who required ICU admission[88].

The prevalence of obstructive sleep apnea (OSA) is relatively high in T2DM[89]. A multicenter, observational, cross-sectional study using 214 DKD patients showed that UACR was higher in DKD with severe OSA relative to moderate OSA, mild OSA, or non-OSA subjects. Additionally, this study showed that the estimated GFR (eGFR) decreased in an OSA severity-dependent manner[90]. OSA-induced intermittent hypoxia and increased sympathetic nerve activity are associated with increased vascular complications, including endothelial damage and hypertension that leads to renal dysfunction [91]. A study using 445 COVID-19 patients where 8.5% had OSA showed that OSA is an independent risk factor of severe COVID-19 that requires hospitalization[92]. Findings from the studies above, it can be surmised that T2DM-induced OSA may contribute to the pathogenesis of DKD and subsequent fatality in severe COVID-19 patients.

A retrospective study in 2345 children having both type-1 diabetes and albuminuria demonstrated that the development of acute kidney injury is positively associated with the episodes of DKA[93]. A study that included 658 hospitalized patients with confirmed COVID-19 showed an increase in ketoacidosis in both diabetic and non-diabetic COVID-19 patients regardless of their age and sex[94]. In an observational study with 3993 hospitalized COVID-19 patients without any history of end-stage kidney disease end-stage kidney disease (ESKD) prior to admission, 1835 (46%) patients developed AKI [95]. Another retrospective cohort study that employed 89216 patients who were 30-d survivors of COVID-19 and 1637467 non-infected controls showed that 30-d survivors of COVID-19 exhibited a higher risk of AKI, declined eGFR, ESKD and major adverse kidney events[96].

Hyperglycemic osmotic diuresis in DKA contributes to the progression of dehydration, hypovolemia, and, ultimately, a reduction in the GFR[97]. Sepsis and hypovolemia are two of the major risk factors that contribute to the pathogenesis of AKI[98]. A vast majority of COVID-19 patients experienced several complications, including fever, malaise, nausea, vomiting, and diarrhea for several days before seeking medical care and subsequently developed hypovolemia[99]. A prospective case-control study showed that COVID-19 patients with AKI are associated with reduced renal blood flow compared with healthy controls, which are independent of left/right cardiac dysfunction[100]. Reduced renal blood flow is a common pathophysiological mechanism of subsequent reduction of GFR and culmination of AKI[101]. Hypercoagulability is a common feature of diabetes. A study in humans showed significantly elevated platelet activity as well as more severe blood clots in patients with concomitant diabetes and renal dysfunction compared with healthy controls and patients with renal dysfunction but no diabetes [102]. The possible mechanisms of diabetes and SARS-CoV-2-induced renal dysfunction are stated in Figure 3.

SARS-CoV-2 infection exacerbates diabetes-induced neurological complications

Approximately one-third of COVID-19 patients have been shown to develop neurological symptoms, including headache, disturbed consciousness, paresthesias, brain tissue edema, stroke, neuronal degeneration, and neuronal encephalitis[103]. Plenty of studies determined the association between COVID-19 and brain dysfunction. However, very little is known about the exact pathophysiology of SARS-CoV-2-induced neurological dysfunction. A recent study by Douaud *et al*[104] recruited 785 participants of UK Biobank who went through the magnetic resonance imaging (MRI) twice, including 401 cases which tested positive for SARS-CoV-2 infection on an average of 141 d before the second scan and 384 controls. Contrary to the first scan, data from the second scan of the SARS-CoV-2 positive cases revealed several striking features associated with brain dysfunction, including a reduction in grey matter thickness and tissue contrast in the orbitofrontal cortex and parahippocampal gyrus, significant alteration in the presence of tissue damage markers in regions that are functionally connected to the primary olfactory cortex; and a significant reduction in global brain size in the SARS-CoV-2 cases[104]. A study by Reiken *et al*[103] showed that SARS-CoV-2 infection is associated with Alzheimer's disease-like phenotypes, which are characterized by the upregulation of TGF-β signaling and hyperphosphorylation of tau protein and leaky phenotype of the ryanodine receptor in the brain. STZ-induced diabetic mice exhibited mild hyperphosphorylation of tau protein after 10, 20, and 30 d of STZ injection, and massive hyperphosphorylation of tau protein was observed after 40 d of STZ injection[105]. There are several studies that confirmed the direct involvement/ entry of SARS-CoV-2 in the brain. For instance, a study using the autopsy samples of olfactory nervous tracts and defined CNS regions from 33 individuals with COVID-19 showed the presence of SARS-CoV-2 RNA in olfactory mucosa, its nervous projections, and distinct CNS regions[106].

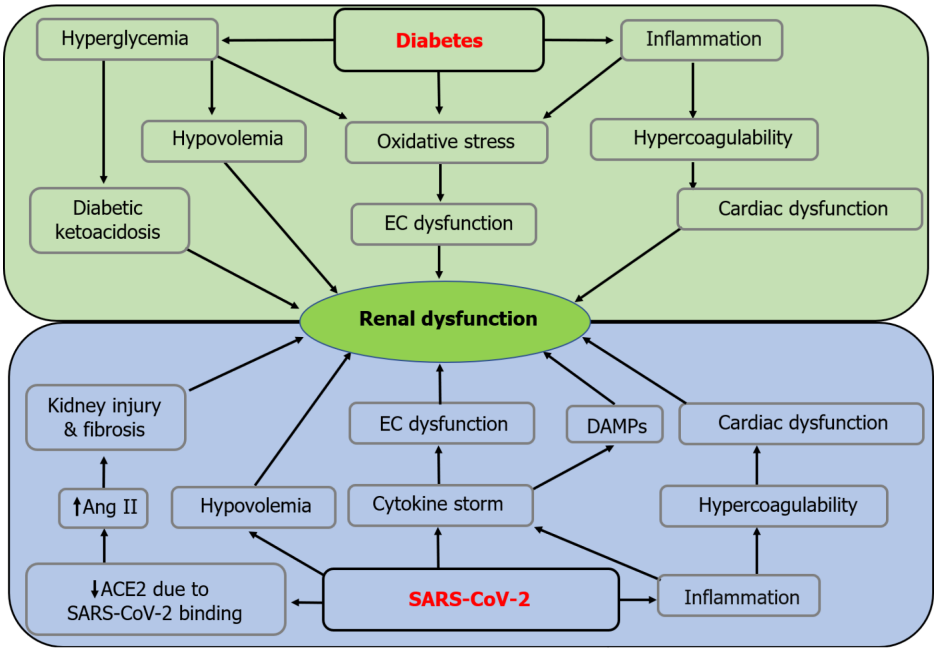

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Figure 3 Possible mechanism of diabetes and severe acute respiratory syndrome coronavirus 2-induced renal dysfunction. Hyperglycemia in diabetes is associated with increased oxidative stress mediated endothelial cell (EC) dysfunction, hypovolemia, and diabetic ketoacidosis that subsequently induces renal dysfunction. Likewise, inflammation in diabetes is associated with increased oxidative stress mediated EC dysfunction and hypercoagulability mediated cardiac dysfunction that subsequently leads to renal dysfunction. On the other hand, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection reduces the availability of angiotensin converting enzyme-2 numbers, which results in elevated serum angiotensin II and subsequent kidney injury and fibrosis due to hypertension. Additionally, hypovolemia in SARS-CoV-2 infection induces renal dysfunction. Finally, inflammation in SARS-CoV-2 infection is associated with cytokine storm mediated endothelial cell dysfunction and upregulation of damage-associated molecular patterns, hypercoagulability mediated cardiac dysfunction results in renal dysfunction. EC: Endothelial cell; Ang II: Angiotensin II; ACE2: Angiotensin converting enzyme-2; DAMPs: Damage-associated molecular patterns; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Encephalopathy refers to brain disorders that alter brain function or Structure. Acute encephalopathy is a rare but fatal complication caused by several factors, including metabolic diseases (*e.g.*, diabetes) and pathogen infection. The pathogenesis of encephalopathy caused by diabetes-induced microvascular dysfunction in the brain is called diabetic encephalopathy (DE). DE is a chronic microvascular complication of diabetes mellitus that is characterized by impaired cognitive functions and electrophysiological, neurochemical, and structural abnormalities[107,108]. A case study showed that there is a possible association between T1D and autoimmune neurologic disorders due to elevated systemic levels of glutamic acid decarboxylase antibody, an important biomarker of limbic encephalopathy[109].

One of the most frequent neurological complications in COVID-19 is acute encephalopathy. Several studies have been conducted to understand the neuropathogenesis of COVID-19-induced acute encephalopathy. For instance, a study by Uginet *et al*[110] that recruited 707 COVID-19 hospitalized patients showed that the severity of the pneumonia was not associated with the severity of the COVID-19 encephalopathy. Additionally, increased MRI abnormalities, intracranial vessel gadolinium enhancement, and disruption of BBR disruption were observed in maximum COVID-19 patients who had no history of acute encephalopathy and other neurological disorders. A case study that employed a SARS-CoV-2 positive middle-aged woman who presented to the emergency department of a tertiary care hospital with an episode of generalized tonic-clonic seizures primarily showed neuropsychiatric manifestations, including viral encephalitis rather than the most common COVID-19 symptoms[111]. Another single-center retrospective study that comprised 1683 patients with COVID-19 showed that 23 (1.4%) patients developed cerebrovascular disease. Out of these 23 patients, 17 developed cerebral ischemia, five developed intracerebral hemorrhages, and one developed leukoencephalopathy of posterior reversible encephalopathy type. This study further showed that elevated ferritin levels were observed in hemorrhagic patients at the time of stroke along with subarachnoid hemorrhage, parieto-occipital leukoencephalopathy, microbleeds, and single or multiple focal hematomas, thrombotic microangiopathy, and endothelial injury, with no evidence of vasculitis or necrotizing encephalitis [112]. A study that employed both the human and animal brains showed that the hypothalamus and associated regions express ACE2 and transmembrane proteinase, serine 2, which mediate SARS-CoV-2 cellular entry, along with several genes or pathways involved in physiological functions or viral pathogenesis[113]. A multicenter study employing 25 COVID-19 patients with encephalitis developed acute demyelinating encephalomyelitis and limbic encephalitis along with hyper proteinopathies and/or pleocytosis in the CSF[114]. Another study that recruited 13 encephalitis patients with COVID-

19, 21 encephalitis patients without COVID-19, and 18 healthy controls, showed that CSF from the encephalitis patients with COVID-19 was negative for SARS-CoV-2, whereas the levels of IL-6, IL-8, TNF-α, β2-microglobulin and glial markers including glial fibrillary acidic protein, soluble triggering receptor expressed on myeloid cells 2, and chitinase-3-like protein 1 (YKL-40) were significantly elevated compared with the encephalitis patients without COVID-19[115].

The blood-brain barrier (BBB) is a highly selective semipermeable border that mediates the communication between the periphery and the central nervous system (CNS), composed of endothelial cells, neurons, astrocytic end-feet, pericytes, and a thick basement membrane[116]. This BBB allows the transport of various nutrients, ions, glucose, water, amino acids, and hydrophobic molecules, including O_2, CO_2, and hormones[116], whereas it restricts the entry of pathogens, peripheral inflammatory mediators (*e.g.*, cytokines and antibodies) as well as large or hydrophilic molecules into the CNS[117]. Tight junctions (TJs) form a diffusion barrier between cerebral endothelial cells and prevent blood-borne substances from entering the brain[118].

DM-induced hyperglycemia upregulates the expression and activation of proangiogenic factors, including hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VRGF), and subsequently increases capillary formation at the BBB. Additionally, hyperglycemia downregulates the expression of inter-endothelial tight junction proteins, including occludin, claudin-5, ZO-1, and JAM-1, and subsequently increases tight junction malfunctioning[119]. DM-induced formation of advanced glycation end-products contributes to the loss of BBB integrity through the upregulation of matrix metalloproteinases 2 in BBB ECs. Oxidative stress-induced formation of ROS[120] may disrupt the BBB through increasing systemic inflammation in diabetes[121]. Increased hypoxia associated with severe COVID-19 may increase capillary density in the BBB through the upregulation of HIF-1α and VRGF. Increased capillary formation and malfunctioning/disruption of TJs facilitate the invasion of inflammatory factors, neurotoxins, and pathogens into the CNS[122]. Since the BBB is the only route for the pathogens and systemic proinflammatory cytokines/chemokines to enter inside the brain, pathogens including SARS, MERS, SARS-CoV, and SARS-CoV-2 and proinflammatory cytokines in the systemic circulation generated due to cytokine storm may easily penetrate inside the CNS of a diabetic person through the damaged BBB. Since the human brain tissue is known to express ACE2 receptors[123], SARS-CoV-2 may infect the brain tissue, followed by the expression of several pathophysiological symptoms associated with the CNS infection. For instance, a study that recruited 8 COVID-19 patients exhibited an elevation of anti-SARS-CoV-2 antibodies in the CSF of comatose or encephalopathic patients suggesting intrathecal IgG synthesis or BBB disruption. BBB disruption may facilitate the entry of proinflammatory cytokines and inflammatory mediators into the CNS and subsequent neuroinflammation and neurodegeneration[124]. A study that recruited 15 hospitalized COVID-19 patients with neurological manifestations exhibited lymphocytic pleocytosis, cranial neuropathy with meningopolyradiculitis, brainstem encephalitis, and delirium[125]. The possible mechanisms of diabetes and SARS-CoV-2-induced neurological dysfunction are stated in Figure 4.

SARS-CoV-2 infection exacerbates diabetes-induced eye diseases

Diabetic retinopathy (DR) is prevalent in diabetic patients and is one of the leading causes of blindness worldwide[126]. In 2020, the number of adults worldwide with DR, vision-threatening DR, and clinically significant macular edema was estimated to be 103.12 million, 28.54 million, and 18.83 million, respectively, and projection speculated that this number would increase to 160.50 million, 44.82 million, and 28.61 million, respectively in 2045[127]. The manifestation of DR is characterized by microaneurysms, retinal hemorrhages, intraretinal microvascular abnormalities, preretinal neovascularization, venous caliber changes, and lipid exudates from the damaged vasculature, capillary nonperfusion with accompanying neuronal infarcts and diabetic macular edema[128]. There are several possible mechanisms that may contribute to the pathogenesis of DR, including hyperglycemia-induced microangiopathy, inflammation, and retinal neurodegeneration[129]. Hyperglycemia has been implicated in the pathogenesis of retinal microvascular dysfunction through the impairment of several metabolic pathways, including the polyol pathway, formation of AGEs, the PKC pathway, and the hexosamine pathway[129]. Hyperglycemia is a well-known factor in pericyte and endothelial dysfunction mediated microaneurysm formation, impairment of blood-retinal barrier (BRB), capillary occlusion, and ischemia in DR[126]. Additionally, ischemia in diabetic eyes upregulates the expression of VEGF through the activation of HIF1[130] and phospholipase A2[131] and subsequently induces the pathogenesis of proliferative DR and diabetic macular edema by increasing vascular permeability. An *in vitro* cell culture study showed that VEGF-A mediates the early glucose-induced damage in human retinal endothelial cells through the activation of the ERK1/2/PLA2 signaling pathway[132]. A retrospective cohort study comprising 241196 DM patients showed that the prevalence of retinal artery occlusion is 2.30-times higher in DM patients compared to their age and sex-match healthy controls[133]. Leucocyte plays an important role in the pathogenesis of DR through the leukostasis-mediated retinal occlusion. A study in humans showed that subjects with central retinal vein occlusion were characterized by elevated levels of monocyte chemotactic protein-1, macrophage inflammatory protein-1alpha (MIP-1α), and MIP-1β that regulate the activation and binding of leukocytes[134]. STZ-induced diabetic mice showed retinal inflammation, which was characterized by leukostasis, increased expression of ICAM-1 on the luminal surface of the vascular endothelium, elevated retinal IL-6, CXCL1 expression, and superoxide

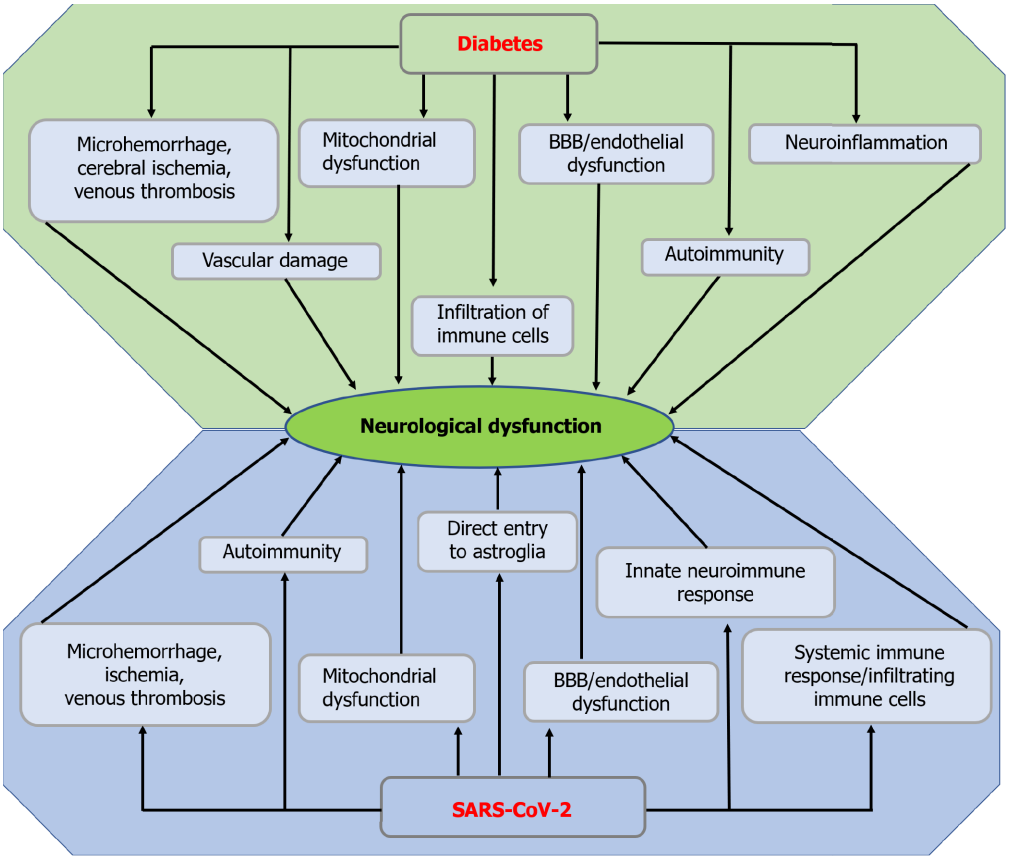

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Figure 4 Possible mechanism of diabetes and severe acute respiratory syndrome coronavirus 2-induced neurological dysfunction. Microhemorrhage, cerebral ischemia, venous thrombosis, mitochondrial dysfunction, endothelial or blood-brain barrier dysfunction, vascular damage, autoimmunity, infiltration of immune cells, and neuroinflammation in diabetes result in neurological dysfunction. On the other hand, microhemorrhage, ischemia, venous thrombosis, autoimmunity, mitochondrial dysfunction, endothelial or blood-brain barrier dysfunction, innate neuroimmune response, systemic immune response or infiltration of immune cells, and direct entry to astroglia lead to neurological dysfunction. BBB: Blood-brain barrier; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

generation[135]. Another preclinical study in STZ-induced diabetic rats showed that leukocytes lead to the pathogenesis of DME through Fas-FasL-dependent retinal endothelial cell apoptosis and subsequent dysfunction of BRB[136]. A prospective study that employed 22 DR patients and 28 non-diabetic subjects showed that inflammatory cytokines such as TNF-α, IL-6, IL-8, and IL-1β were significantly upregulated in the vitreous samples from DR patients and their levels were proportional to the severity of DR[137]. Some other studies demonstrated that retinal Müller glial cells and microglia as the initiators of retinal inflammation and subsequent pathogenesis of DR. For instance, a study by Portillo *et al*[138] showed that STZ-induced diabetic mice with overexpressed CD40 in Müller cells upregulated retinal expression of TNF-α, IL-1β, ICAM-1, and nitric oxide synthase (NOS2), developed leukostasis and capillary degeneration. This study further showed that overexpression of CD40 did not cause TNF-α or IL-1β secretion in Müller cells. Rather, TNF-α was upregulated in macrophages/microglia in the retina. The CD40 overexpressing Müller cells induced PLC–dependent ATP release and subsequent $P2X_7$-dependent production of TNF-α and IL-1β by macrophages. Findings from this study suggest that CD40 in Müller cells is sufficient to upregulate retinal inflammatory markers and appears to promote experimental DR through the activation of the CD40-ATP-$P2X_7$ pathway[138]. Hyperglycemia in diabetes is also implicated in mitochondrial dysfunction mediated apoptosis of retinal neurons and subsequent pathogenesis of DR. An *in vitro* cell culture study showed that rat retinal Müller cells grown in a high-glucose medium developed mitochondrial dysfunction that may contribute to retinal Müller cell loss and subsequent pathogenesis of DR[139]. Retinal neurodegeneration is a hallmark of the pathogenesis of early DR. Recent studies have reported that vascular changes are preceded by the damage and loss of retinal neurons due to apoptosis or autophagy. According to Silva *et al*[140] STZ-induced diabetic rats started to show DR symptoms after one month of STZ injection.

STZ-induced diabetic mice showed loss of rod cells, reduced thickness of the outer and inner synaptic layers along with the upregulation of autophagic proteins, including Beclin-1 and Atg5. Findings from this study suggest that the pathogenic pathways leading to cell death develop with the initial dysregulation of autophagy and subsequent vascular damage[141]. For instance, STZ-induced diabetic mice increased ERK activation and subsequent reduction of synaptophysin and depletion of a brain-derived neurotrophic factor in the diabetic retina after one month of STZ injection[142].

Although the respiratory tract is considered the predominant route of SARS-CoV-2 infection, several studies hypothesized that the conjunctiva could be contaminated by SARS-CoV-2 droplets and dirty hands, thereby initiating the viral entry into the body[143]. A study using 14 retinal biopsies (RB) samples and 13 optic nerve biopsy (ONB) samples collected from COVID-19 deaths showed that 7 out of 14 RB samples and 10 out of 13 ONB samples contained the SARS-CoV-2 RNA[144]. Similarly, a study in 91 hospitalized COVID-19 patients showed the presence of SARS-CoV-2 RNA on the ocular surfaces of 52 patients (57.1%). This study further showed that the virus was detected on the ocular surface in 10 out of 17 patients whose nasopharyngeal swab was negative[145]. However, the mechanism of direct eye infection by SARS-CoV-2 is still unknown. A study using human post-mortem eyes and surgical specimens showed the expression of both ACE2 and TMPRSS2 in conjunctiva, limbus, and cornea[146]. A study by Menuchin-Lasowski *et al*[147] showed that SARS-CoV-2 infected human stem cell-derived retinal organoids increased the production of several inflammatory genes associated with acute COVID-19 and retinal degeneration, including IL-33, CXCL2, and CXCL10. This study further showed that the inhibition of ACE2 activity with antibody significantly reduced SARS-CoV-2 infection of retinal organoids, indicating that SARS-CoV-2 infects retinal cells in an ACE2-dependent manner[147].

Conjunctivitis is the most common ophthalmic manifestation documented in COVID-19 patients [148]. A retrospective cross-sectional, single-center study using 127 COVID-19 patients with mild symptoms showed that 11 out of 127 (8.66%) patients had conjunctivitis[149]. Another study that recruited 535 COVID-19 patients showed that 27 patients (5.0%) presented with conjunctival congestion, which may result from direct hand contact with the eyes[150]. However, the mechanism of SARS-CoV-2-induced conjunctivitis is poorly understood. A case study in a 53-year-old man showed viral conjunctivitis along with the presence of SARS-CoV-2 RNA in the left eye after ten days of COVID-19 onset. The symptoms of the left eye conjunctivitis were completely cured in 5 d with proper medications. However, the patients experienced viral keratoconjunctivitis with progressive spot staining observed at the periphery of the corneal epithelium in both eyes; after five days, the symptoms in the left eye were completely cured. At this stage, the patient also showed an elevation of IL-6 levels in both eyes as well as in the circulation[151]. Findings from this study suggest that SARS-CoV-2-induced cytokine storm may contribute to the pathogenesis of conjunctivitis and keratoconjunctivitis. A population-based case-control study in 16 193 adults showed that diabetes is a risk factor for acute infectious conjunctivitis[152].

SARS-CoV-2 infection exacerbates diabetes-induced bone loss

DM is an important risk factor for osteoporosis. A single-center cross-sectional study that enrolled 388 Japanese patients with a history of T1D showed that long-term hypoglycemia is significantly associated with a higher risk of bone fracture[153]. A prospective and retrospective cohort study demonstrated that DM patients had a greater risk of total hip, upper arm, and ankle fractures, and this risk was pronounced in T1DM patients than T2DM patients[154]. Several mechanisms may contribute to the pathogenesis of DM-induced osteoporosis. Hyperglycemia and/or IR in DM are associated with increased production of proinflammatory cytokines, including IL-1, IL-6, and TNF-α, and vasoactive peptides, including Ang II. In contrast, it decreases the levels of vitamin D, which may downregulate osteoblast number/activity and upregulate osteoclast number/activity. Decrease in osteoblast/osteoclast ratio results in increased bone resorption and subsequent osteoporosis[155].

COVID-19 has been recognized to induce osteo-metabolic complications that are characterized by hypocalcemia, chronic hypovitaminosis D, and a high prevalence of bone fragility[156,157]. The presence of SARS-CoV-2 in bone cells has not been identified so far; however, the expression of ACE2 in the bone cells has been identified as a positive regulator of bone health. For instance, cell culture and human gingival bone samples have been shown to express ACE2 in osteoblast and osteoclast. Using both *in vitro* and *in vivo* models, this study further demonstrated that pharmacological activation of ACE2 with diminazene aceturate, an essential activator of ACE 2, significantly decreased alveolar bone loss through the improvement of osteoblast/osteoclast ratio[158]. Since SARS-CoV-2 bindings with the ACE2 receptors result in a decrease in ACE2 numbers, SARS-CoV-2 infection may increase bone loss. A study by Awosanya *et al*[159] has shown that human ACE2 expressing mice (TG) developed severe health problems and a significant reduction in trabecular bone volume due to an increase in the number and surface area of osteoclasts after 14 d of SARS-CoV-2 infection. However, more studies are required to confirm this finding. Cytokine storm upon SARS-CoV-2 infection is associated with increased circulatory levels of CXCL-10, TNF-α, IL-1β, and IL-6[160], whereas decreased reduced vitamin D levels are associated with increased infection and severity of COVID-19[161]. Many COVID-19 patients have experienced conjunctivitis in their eyes[148]. Therefore, it can be surmised that the possibility of fall-mediated bone fracture in COVID-19 patients who has conjunctivitis should be higher than the healthy people.

SARS-CoV-2 infection exacerbates diabetes-induced gastrointestinal complications

A study in a cohort including 59 patients with COVID-19 showed that 15 patients had GI dysfunction, and nine patients had stool containing SARS-CoV-2 RNA. This study also conducted a meta-analysis comprising 4243 COVID-19 patients showed that the prevalence of GI symptoms in COVID-19 patients was 17.6%, and 48.1% of COVID-19 patients exhibited the presence of SARS-CoV-2 RNA in their stool

samples, although 70.3% of those samples were collected after the loss of virus from respiratory specimens tested positive for the virus[162]. The expression of ACE2 in the human GI tract has been confirmed through several studies[163,164]. Several studies demonstrated the direct infection of SARS-CoV-2 in the GI tract. For instance, an *in vitro* study using gastric organoids from fetal, pediatric, and adult biopsies showed that pediatric and late fetal gastric organoids are susceptible to SARS-CoV-2 infection, while viral replication is significantly lower in undifferentiated organoids of early fetal and adult origin. Through transcriptomic analysis, they further showed that SARS-CoV-2 infected stomach sample elicits a moderate innate antiviral response and a lack of differentially expressed genes belonging to the interferon family. Findings from this study suggest that SARS-CoV-2 can efficiently infect the gastric epithelium, suggesting that the stomach might have an active role in fecal-oral SARS-CoV-2 transmission[165]. A retrospective, single-center study comprising 95 cases with SARS-CoV-2 infection demonstrated that GI symptoms, including diarrhea, anorexia, and nausea, were observed in 58 cases[166]. Findings from another retrospective cohort study comprising 104 patients with COVID-19 demonstrated that GI infection with SARS-CoV-2 prolongs the duration of SARS-CoV-2 shedding and hospitalization in the patients with COVID-19[167].

Diabetic patients are implicated in developing several GI complications, including gastroparesis, intestinal enteropathy, non-alcoholic fatty liver disease (NAFLD), pancreatitis, and peptic ulcer disease. There are clinical and preclinical studies that confirmed the association of diabetes with GI abnormalities. For instance, a study that recruited 50 DM patients and 20 non-DM healthy controls showed that patients with long-term DM exhibited lower maximal squeeze pressure, a higher mean threshold of minimal rectal sensation, and enhanced features of dyssynergic defection compared with the control group. Findings from this study suggest that DM patients demonstrated an impaired function of the external anal sphincter, enhanced features of dyssynergic defecation as well as impaired visceral sensation[168]. A case study that comprised ten patients with maternally inherited diabetes and deafness syndrome (MIDD) showed that GI symptoms, including constipation and diarrhea along with the mucosal accumulation of normal mitochondria and lipid droplets, are frequent in MIDD[169]. A study using the GI mucosal biopsy samples from subjects with and without type 2 diabetes exhibited that taste signaling molecules that modulate the upper GI function and energy intake are decreased in diabetic subjects with elevated blood glucose concentration and decreased by luminal glucose in mice [170]. A cohort study that recruited 5699 T2DM patients and 11226 age and sex-matched non-diabetic controls showed that in a 7-year follow-up period, T2DM patients had a significantly higher cumulative hazard of peptic ulcer bleeding than the controls with adjusted age, sex, and comorbidities[171]. Another study that recruited healthy subjects and peptic ulcer patients with or without T2DM showed that the number of circulating EPCs and their colony-forming ability, essential prerequisites for vascular repair and angiogenesis, was significantly reduced in peptic ulcer patients with T2DM[172]. There are findings from many preclinical and clinical studies that confirm diabetes as a significant risk factor for NAFLD[173-175]. A 14-years follow-up study by Han *et al*[176] that recruited 3047 subjects without underlying DM showed that NAFLD could be used as a biomarker better than BMI in predicting incident DM.

DISCUSSION AND FUTURE DIRECTIONS

Diabetes is a chronic metabolic disease that differentially induces the pathogenesis of several complications associated with different organs, including the brain, eyes, bone, GI tract, kidneys, heart, immune system, and lungs (Figure 5). On the other hand, SARS-CoV-2 infection has both acute and chronic effects on the manifestation of all diseases (Figure 5). In addition to their independent mechanisms for the pathogenesis of any disease, the coexistence of diabetes and SARS-CoV-2 infection exacerbates the disease severity and subsequent fatality (Figure 5). There are several approaches, including medications, diet and exercise that can reduce the blood glucose levels in both type 1 and type 2 DM patients. Insulin therapy and amylinomimetic drugs are used to reduce bold glucose levels in type 1 DM patients. Similarly, biguanides (*e.g.*, metformin), dopamine agonist (*e.g.*, bromocriptine), dipeptidyl peptidase-4 inhibitors (*e.g.*, alogliptin), glucagon-like peptide-1 receptor agonists (*e.g.*, albiglutide), meglitinides (*e.g.*, nateglinide), sodium-glucose transporter 2 inhibitors (*e.g.*, dapagliflozin), sulfonylureas (*e.g.*, glimepiride), and thiazolidinediones (*e.g.*, rosiglitazone) are well known type 2 DM medications[177]. However, there is no effective treatment that can completely cure diabetes or diabetic complications. On the other hand, there are several approaches that can prevent the transmission as well as the severity of SARS-CoV-2 infection, including mRNA vaccines (*e.g.*, Pfizer-BioNTech covid-19 vaccine), and antiviral drugs (*e.g.*, remdesivir) and monoclonal antibodies (*e.g.*, bebtelovimab)[178]. However, there is no effective therapy yet that can completely prevent the transmission of SARS-CoV-2 and cure COVID-19 without any side effects. Since SARS-CoV-2 is still circulating among the community, new variants like delta and omicron are evolving that can be even more transmissible and lethal than the existing variants. Because of these new mutant variants, COVID-19 is out of control despite widespread vaccination in the United States as well as other countries. There are some drugs that can prevent viral entry into the host cells as well as decrease blood glucose levels. For instance, Camostat mesylate, a

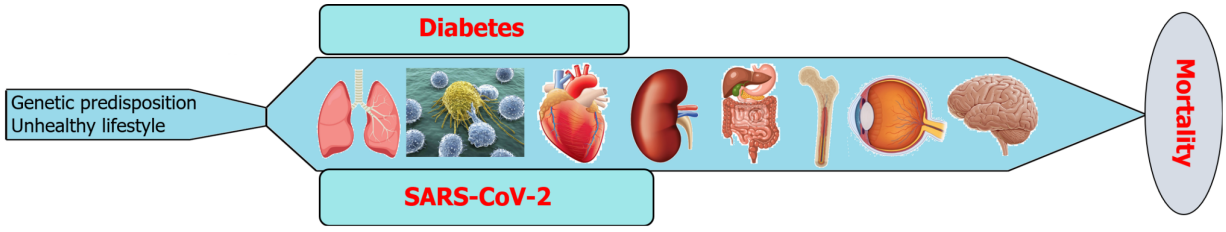

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Figure 5 Role of diabetes and severe acute respiratory syndrome coronavirus 2 co-existence in multi-system organ failure. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

serine protease inhibitor used primarily for treating postoperative reflux esophagitis and chronic pancreatitis. However, studies showed that blocking TMPRSS2 with Camostat mesylate and its metabolite 4-(4-guanidinobenzoyloxy) phenylacetic acid can prevent upper respiratory tract infection by SARS-CoV-2[179]. Chloroquine and hydroxychloroquine are glucose-lowering drugs and have been used extensively to treat COVID-19 due to their antiviral properties. However, these drugs have adverse health effects. Therefore, patients with DM and/or other underlying health conditions should be aware that SARS-CoV-2 infection can elevate blood glucose levels, and, as such, they should follow clinical guidelines for the management of DM more strictly.

CONCLUSION

People with diabetes possess a higher risk of SARS-CoV-2 infection and subsequent severe COVID-19 manifestation. On the other hand, the prevalence of SARS-CoV-2 infection-mediated manifestation of diabetes is also increasing. It is more likely to develop severe consequences due to the global increase in diabetic patients and the co-existence of diabetes and SARS-CoV-2. Still, we need to wait longer, and more research should be conducted to see the long-term effects of post-COVID-19 manifestation. To prevent or cure the long-term coexistence of diabetes and COVID-19 in the human body, we should more adhere to standardized prevention and control, cutting the transmission chain of the virus and blocking it to a minimum. Maintaining a healthy lifestyle with a healthy diet, regular exercise, and proper hygiene can reduce the risk of developing diabetes as well as the number of SARS-CoV-2 infection.

FOOTNOTES

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MINIREVIEWS

Hepatitis B virus infection reactivation in patients under immunosuppressive therapies: Pathogenesis, screening, prevention and treatment

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Abstract

With a 5.3% of the global population involved, hepatitis B virus (HBV) is a major public health challenge requiring an urgent response. After a possible acute phase, the natural history of HBV infection can progress in chronicity. Patients with overt or occult HBV infection can undergo HBV reactivation (HBVr) in course of immunosuppressive treatments that, apart from oncological and hematological diseases, are also used in rheumatologic, gastrointestinal, neurological and dermatological settings, as well as to treat severe acute respiratory syndrome coronavirus 2 infection. The risk of HBV reactivation is related to the immune status of the patient and the baseline HBV infection condition. The aim of the present paper is to investigate the risk of HBVr in those not oncological settings in order to suggest strategies for preventing and treating this occurrence. The main studies about HBVr for patients with occult hepatitis B infection and chronic HBV infection affected by non-oncologic diseases eligible for immunosuppressive treatment have been analyzed. The occurrence of this challenging event can be reduced screening the population eligible for immunosuppressant to assess the best strategies according to any virological status. Further prospective studies are needed to increase data on the risk of HBVr related to newer immunomodulant agents employed in non-oncological setting.

Key Words: Hepatitis B Virus infection; Reactivation; Occult B infection; Chronic B infection; Immunosuppression; Disease-modifying antirheumatic drugs

Core Tip: Hepatitis B Virus (HBV) is a major public health challenge requiring an urgent response. Patients with overt or occult HBV infection can undergo HBV reactivation (HBVr) in course of immunosuppressive treatments, also used in rheumatologic, gastrointestinal, neurological and dermatological settings and to treat Sars severe acute respiratory syndrome coronavirus 2 infection. The aim of the present paper is to investigate the risk of HBVr in those not oncological settings in order to suggest strategies for preventing and treating this occurrence. The occurrence of this challenging event can be reduced screening the population eligible for immunosuppressant to assess the best strategies according to any virological status.

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INTRODUCTION

Hepatitis B Virus (HBV) is a major public health challenge requiring an urgent response. According to the Global Hepatitis Report endorsed by World Health Organization (WHO) in 2017, the proportion of children 5 years old become chronically infected felt to 1.3% in 2015, compared with 4.7% of the pre-vaccine era, ranging 1980s to 2000s worldwide[1]. The spread of HBV vaccination during the childhood reduced the incidence of new HBV infections and the related possible chronicity[1]. However, it is estimated that about 3.5% of the global population (257 million people) in 2015 are affected by chronic HBV infection, most of them born before the availability of HBV vaccination: 68% of them are localized in Africa and in Western Pacific Region[1]. About 2.7 million of persons are co-infected with HBV, HDV and HIV and, among those with hepatitis, the estimated cumulative 5 years incidence of progression is estimated around 8%-20%[2] and 5%-15% of cirrhotic patients develop hepatocellular cancer (HCC) during the lifetime[2].

HBV belongs to the Hepadnaviridae family. It is a double stranded DNA virus with a lipoprotein envelope and a high hepatic tropism. Its transmission happens through the vertical route or intra-family contacts among infants and by sexual or parenteral contact. The first case is typical in regions with the highest prevalence determining the high endemicity described in these areas and the associated high rate of chronicization. The second case is common in regions with low prevalence among adults; nevertheless, high Hepatitis B surface antigen (HBsAg) prevalence there, can be encountered among immigrants from high HBV endemic area, People Who Inject Drugs (PWID), Men who have Sex with Men and People Living With HIV[3]. After a possible acute phase, the natural history of HBV infection can progress in chronicity, which consists of 5 phases, based on the HBeAg serostatus, the viral load, the transaminases levels and the grading/staging of the liver disease[4-6]. During the first one, once known as "immunotollerant phase" and currently named "HBeAg positive chronic infection", the immune response against the virus is limited or absent: Thus, there is a high viral replication with HBeAg positivity, unchanged transaminases and liver parenchyma. The second phase, called "HBeAg positive chronic hepatitis" is characterized by the production of active immune response of the host against viral antigens, with a reduction of viral load and an increase of transaminase levels along with liver inflammation. In case of immune response's control of the infection, the infection moves to the third phase, known as "HBeAg negative chronic infection" with HBeAg sero-clearance, low viral replication (HBV-DNA < 2000 IU/mL), normalization of transaminase levels and mild liver inflammation. However, severe liver inflammation and rapid progression of disease can still occurs, despite the presence of HBeAb, in case of mutation of the pre-core or basal core promoter regions. The fourth phase is the "HBeAg negative chronic hepatitis" one, with detectable anti HBe, moderate levels of serum HBV-DNA and ALT with hepatic necroinflammation. The last phase is HBsAg negative phase, with serum negative HBsAg and positive anti HBc with or without anti HBs. This phase is also called "occult hepatitis B virus infection" (OBI) defined as the replication of competent HBV DNA in the liver and blood in the absence of detectable HBsAg that contributes to the advancement of liver fibrosis and development of HCC. Patients with overt or occult hepatitis B virus infection can undergo HBV reactivation (HBVr) in course of immunosuppressive treatments. Apart from oncological and hematological diseases, immunosuppressants are also used in rheumatologic, gastrointestinal, neurological and dermatological settings, as well as to treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The aim of the present paper is to investigate the risk of HBVr in those not oncological settings in order to suggest strategies for preventing and treating this occurrence. HBVr can be defined as the novo detection of HBV DNA or a ≥ 10 fold increase in HBV DNA level compared to its baseline value in HBsAg positive subject and seroreversion to HBsAg positive status in previously negative patients[7]. The viral genome can be detected as cccDNA in hepatocites. The HBVr following immunosuppressive

treatments is commensurate to patient's characteristics and the kind of immunosuppressive agent employed. As regards as host characteristics, apart from the male gender[8], the old age[9] and any underlying lymphoproliferative diseases[10], the serostatus during immunosuppression is crucial. In fact, patients affected by chronic HBV infection have a greater risk of reactivation compared to those with OBI. Moreover, the presence of anti HBs among HBsAg negative subjects, is related to a lower risk of reactivation even in hematologic setting, according to Seto *et al*[11]. Regarding immunosuppressant, the risk of related HBVr can be classified as high, with frequency of reactivation > 10% without prophylaxis[7]; medium, with frequency of reactivation 1%-10%[12] or low, with frequency of reactivation < 1%[13]. A high risk of reactivation is described with the administration of B cell depleting agents[14], anthracycline derivatives[15] and corticosteroids at high dose, for treatments of more than 4 wk[7], along with inhibitors of cytokine, integrin[16], tyrosine kinases[17] and JAK kinases inhibitors[18].

The risk of HBVr is related to the immune status of the patient and the baseline HBV infection condition. The risk of developing HBVr is quite low for HBsAg positive or negative patients under csDMARDs and short low dose cortisone based therapy. The same risk is however higher for patients under anti-TNFs and tyrosine kinase inhibitors: when in combination, the risk is the highest.

Here reported are the main studies about HBVr for patients with OBI and chronic HBV infection affected by non-oncologic diseases eligible for immunosuppressive treatment.

RISK OF HBVR IN PATIENTS AFFECTED BY CORONAVIRUS DISEASE 2019

The ongoing SARS-CoV-2 pandemic, responsible for more than 50 million cases from 2020, still represents a challenge for the scientific community, not only regarding its pathogenesis but mostly its treatment. In fact, despite there is no available curative option yet, several immunosuppressive and immunomodulating agents have been proposed for the treatment of coronavirus disease 2019 (COVID-19) pneumonia in those last two years. Corticosteroids are currently recommended by the WHO for severe COVID-19; other employed immunosuppressive agents are interleukin 6 inhibitors (such as tocilizumab), JAK inhibitors (such as baricitinib, tofacitinib and ruxolitinib) associated with risk of HBVr in other settings[19]. Apart from a couple of retrospective studies reporting HBVr among patients receiving methylprednisolone[20] and tocilizumab[21], no data are already available in literature about the risk of HBVr among patients with COVID-19 treated with immunosuppressants. The short duration of immunosuppressive treatment in this specific setting probably limits the risk of HBVr. However, all the patients with COVID-19 pneumonia eligible for corticosteroid or immunosuppressants are routinely screened for HBV infection according to national and international guidelines to evaluate the risk of HBVr prior to prescribe those above mentioned drugs and start antiviral prophylaxis when needed.

HBVR IN RHEUMATOLOGIC SETTING

The spread of rheumatic diseases in Western Countries resulted in a greater interest of the scientific community engaged in research of efficacious therapeutic options. Giving that recognize an autoimmune pathogenesis, therapeutic committed strategies are based on immunosuppression and include Corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), analgesic drugs and disease-modifying antirheumatic drugs (DMARDs) which can be divided into conventional synthetics (csDMARDs) and biological drugs (bDMARDs). The csDMARDs include leflunomide, azathioprine, sulfasalazine, hydroxychloroquine; gold salts, methotrexate and minocycline[22]. The bDMARDs can be instead divided into IL-1 inhibitors (canakinumab and anakinra), TNF inhibitors (infliximab, adalimumab, etanercept, certolizumab and golimumab), inhibitors of IL-17 (ixekizumab and secukinumab), IL-6 and IL-6R inhibitors (respectively, tocilizumab and sarilumab), IL-23 inhibitors (guselkumab and ustekinumab), and JAK kinase inhibitors (peficitinib, tofacitinib, filgotinib, upadacitinib and baricitinib) based on their mechanism of action[23,24].

HBVr is quite common among unvaccinated people with rheumatic diseases (RD); Canzoni *et al*[25] reports that 2% of this study population (292 patients) affected by RD had a prevalence of HBsAg positivity and any kind of HBV infection markers retrieved in 24% of cases (70 patients): At least, 30% of those tested positive patients were unaware of their condition[25]. Despite European Association for the Study of Liver (EASL)[4] and AASLD[23] indication about HBV routine screening schedule before starting immunosuppressive therapies, the coverage still appears inadequate as in 2015 Lin *et al*[27] demonstrated in a retrospective cross national comparison of hepatic testing in rheumatic arthritis (RA) patients eligible to DMARD between the US and Taiwan[26]. The authors found that only 20.3% of patients in the US and 24.5% of patients in Taiwan were tested for HBV infection[27]. Similar results were found in Japan[28] where laboratory test for HBsAg, anti HBs and anti HBc were performed only in 28.33%, 12.52% and 14.63% of patients with RA, at baseline[28]. The deleterious role of HBV infection in recovery of patients with RA has been investigated by Chen *et al*[29]: Their case control study evaluated 32 patients with RA and chronic HBV infection, eligible to glucocorticosteroids, DMARDs and biologics. The study records, in a year, a worsening of hepatopathy of patients with chronic HBV

infection under immunosuppressant with no antiviral intervention; moreover patients failed in achieving the therapeutic target in 6 mo. HBVr was reported in 34% of patients at one year follow up. Among those 32 studied patients, 14 were treated with prophylaxis with lamivudine, adefovir or entecavir: 4 of them developed HBVr and 2 of them also a hepatitis flare. The remaining 18 patients enrolled did not received antiviral prophylaxis and 7 of them experienced HBVr.

HBVR IN DERMATOLOGIC SETTING

cDMARDs such as acitretin, methotrexate and cyclosporin A along with bDMARDs including etanercept, infliximab, golimumab, certolizumab, adalimumab and secukinumab are currently used in several different dermatologic diseases, like psoriasis. The safety of those immunosuppressive drugs is not properly investigated, since trials conceived to explore new efficient drugs barely involve HBV patients. However, the reactivation risk of HBV in 14 (11 HBsAg positive, 3 HBsAg negative/HBcAb positive) patients with psoriasis eligible for ustekinumab based therapy has been evaluated by Chiu *et al* [30]. No reactivation was observed among all the HBsAg negative HBcAb positive patients, while HBVr was registered among two of the HBsAg positive patients under ustekinumab not receiving prophylaxis [30]. The incidence rate of annual HBVr was calculated by Ting *et al*[31] in a retrospective cohort study including 54 inactive HBV carrier patients without prophylaxis and occult hepatitis B virus infection: only 1.5% of OBI patients developed HBVr, while 17.4% of inactive HBV carriers experienced it, under ustekinumab. According to the available evidence, HBsAg positive patients under immunosuppressive drugs at moderate risk of HBVr should be prevented with antiviral based prophylaxis, while HBsAg negative/HBcAb positive patients eligible for immunosuppressant should be close monitored in order to prescribe pre-emptive therapy, when needed.

RISK OF HBVR IN GASTROENTEROLOGICAL SETTING

The use of immunosuppressants is often required for patients affected by autoimmune, inflammatory gastroenterological disorders like Crohn disease and ulcerative colitis. The drug selected depends on the disease severity and the relapsing or remitting cause of the inflammatory bowel disease (IBD). Corticosteroids, immunomodulatory agents (methotrexate, azathioprine, mercaptopurine), anti IL12/23 p40 antibodies, JAK inhibitors, anti-adhesion therapies and biological therapies such as TNF inhibitors are widely used. Studies performed to evaluate the risk of HBVr in HBsAg positive patients with gastroenteric diseases under immunosuppressive agents clearly demonstrated that the use of more than two immunosuppressive agents is an independent predictor of HBVr[32]. A lower rate of reactivation has been registered for patients treated with antiviral prophylaxis[33]. Few cases of HBVr have been reported among HBsAg negative/HBcAb positive patients with IBD under immunosuppressants[34-37]. Thus, a complete serology for HBV is required in IBD patients to determine the active/inactive carrier status of IBD patients eligible for immunosuppressants in order to determine whether to treat, prescribe prophylaxis or monitor them, according to their HBV profile. HBsAg positive patients with IBD should undergo prophylaxis with nucleotide or nucleoside analogues before starting moderate or high doses steroids for more than 4 wk, anti TNF drugs, azathioprine or ustekinumab. This prophylaxis should last for at least one year after discontinuing immunomodulants. No standardized approach exists for HBsAg negative/HBcAb positive patients with IBD. In fact, while the American Gastroenterology Association recommends antiviral prophylaxis for this population under anti TNF or corticosteroids at moderate/high doses[38], the EASL and The European Crohn and Colitis Organization both recommend close monitoring of this population and the use of antiviral agents only after detection of HBV DNA viremia or seroreversion to HBsAg positivity[4,39].

HBVR RISK IN NEUROLOGICAL SETTING

Among neurodegenerative diseases requiring disease modifying drugs to be treated, multiple sclerosis (MS) is one of the most frequent. MS causes chronic inflammation of the central nervous system, demyelination and disability. Apart from glucocorticoids, widely used in the acute phase of MS, DMD such as anti CD52 antibodies (alemtuzumab), anti CD20, a4b1 integrin inhibitor, sphingosine 1 phosphate inhibitors and its modulators (namely, fingolimod and siponimod), anti CD20 monoclonal antibodies[40] are employed to treat MS. Since limited data concerning the risk of HBVr in neurological setting are available from literature, there is no clear, definitive consensus on the best strategies to prevent HBVr in subjects with neurologic diseases requiring immunosuppressive drugs[41]. However, HBVr in a patient with a story of HBV infection and no proper prohylaxis, under ocrelizumab treatment for MS, has been reported by Ciardi *et al*[42], highlighting the need for antiviral prophylaxis in this setting.

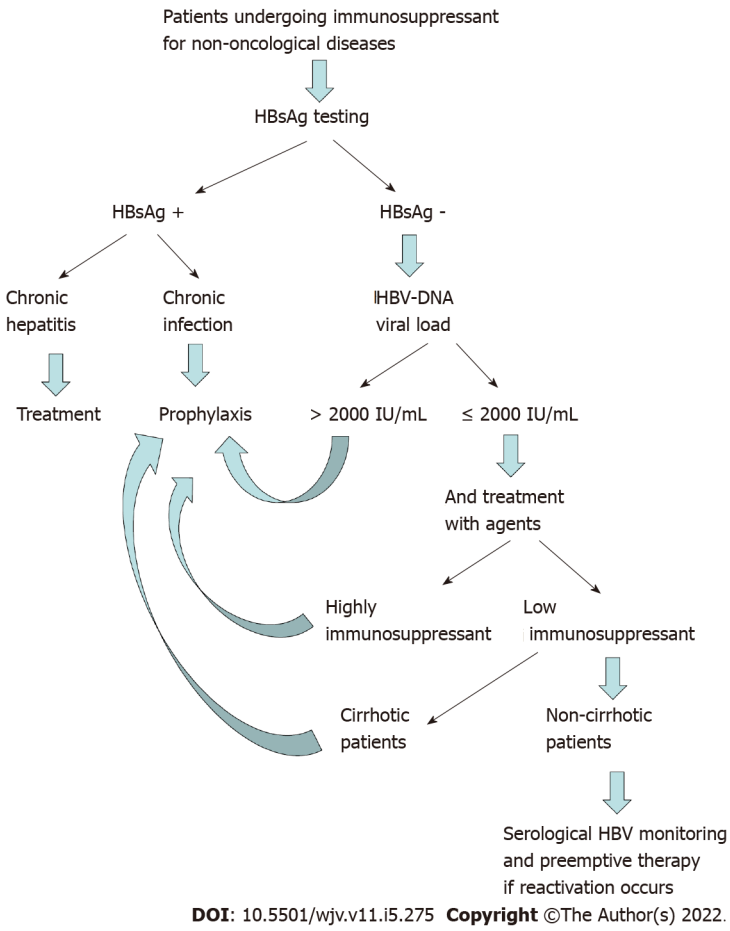

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Figure 1 Algorithm of hepatitis B virus reactivation diagnosis and management in patients eligible for immunosuppressant in non-oncological setting. HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen.

PREVENTION AND TREATMENT OF HBVR

The risk of HBVr following immunosuppressive treatments depends mostly on type, duration and intensity of the iatrogenic immunosuppression. It is necessary to modulate any kind of therapeutic strategies to avoid HBVr, according to the risk profile of reactivation itself. Close monitoring of liver function test and qualitative/quantitative HBV DNA viral load is necessary at baseline, during and after the discontinuation of immunosuppressive therapy, taking into account that HBVr can still occur after the interruption of immunosuppressants. The management of HBVr in patients under immunosuppressant for non-oncological diseases depends, firstly, on HBsAg laboratory tests. In fact, in case of HBsAg positive value, patients with chronic hepatitis must undergo treatments of HBV with high genetic barrier nucleo(t)side analogues (entecavir, tenofovir, tenofovir alafenamide)[4,38,43-45], while those with chronic infection must be considered for prophylaxis with lamivudine in case of undetectable HBV DNA or in case of expected duration of prophylaxis less than 6 mo[38]. Otherwise, because of emergence of resistance to lamivudine in patients requiring therapy for more than 6 mo long duration, the above mentioned newer nucleoside agents can represent an effective option for antiviral prophylaxis in this setting. In case of HBsAg negative and HBcAb positive laboratory test results, the HBV DNA viral load can guide physicians in determining if the patient requires prophylaxis or clinical and laboratory's close monitoring, followed, where appropriate, by preemptive therapy[4,38]. In fact, in case of HBV DNA positivity or in case of HBV DNA negativity occurred in patients under agents at moderate or high risk of immunosuppression, or affected by liver cirrhosis, a trimestral monitoring of HBsAg/HBsAb and HBV DNA is enough, and a preemptive therapy can be considered in case of reactivation[4,38]. The prophylaxis must be started before the immunosuppressive regimen and continued up to 12-18 mo after the end of the immunosuppressive treatment[38,46-48]. In Figure 1 briefly is summarized the algorithm of HBVr diagnosis and management in patients eligible for immunosuppressant in non-oncological setting.

CONCLUSION

The widespread use of immunosuppressive and immunomodulant therapies in non-oncological setting highlighted the risk of HBVr in patients with overt or occult hepatitis B virus infection. The occurrence of this challenging event can be reduced screening the population eligible for immunosuppressant to assess the best strategies according to any virological status. Further prospective studies are needed to increase data on the risk of HBVr related to newer immunomodulant agents employed in non-oncological setting, in order to better prevent and treat HBVr recurrence.

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FOOTNOTES

Author contributions: Spera AM study conception and design; data collection; analysis and interpretation of results; draft manuscript preparation; Spera AM finally reviewed the results and approved the final version of the manuscript.

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MINIREVIEWS

Acute kidney injury and electrolyte disorders in COVID-19

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Abstract

Acute kidney injury (AKI) and electrolyte disorders are important complications of hospitalized coronavirus disease 2019 (COVID-19) patients. AKI is thought to occur due to multiple pathophysiological mechanisms, such as multiple organ dysfunction (mainly cardiac and respiratory), direct viral entry in the renal tubules, and cytokine release syndrome. AKI is present in approximately one in every ten hospitalized COVID-19 patients. The incidence rates of AKI increase in patients who are admitted to the intensive care unit (ICU), with levels higher than 50%. Additionally, renal replacement therapy (RRT) is used in 7% of all AKI cases, but in nearly 20% of patients admitted to an ICU. COVID-19 patients with AKI are considered moderate-to-severe cases and are managed with multiple interdisciplinary conducts. AKI acts as a risk factor for mortality in severe acute respiratory syndrome coronavirus 2 infection, especially when RRT is needed. Electrolyte disorders are also common manifestations in hospitalized COVID-19 patients, mainly hyponatremia, hypokalemia, and hypocalcemia. Hyponatremia occurs due to a combination of syndrome of inappropriate secretion of antidiuretic hormone and gastrointestinal fluid loss from vomiting and diarrhea. When it comes to hypokalemia, its mechanism is not fully understood but may derive from hyperaldosteronism due to renin angiotensin aldosterone system overstimulation and gastrointestinal fluid loss as well. The clinical features of hypokalemia in COVID-19 are similar to those in other conditions. Hypocalcemia is the most common electrolyte disorder in COVID-19 and seems to occur because of vitamin D deficiency and parathyroid imbalance. It is also highly associated with longer hospital and ICU stay.

Key Words: COVID-19; SARS-CoV-2; Acute kidney injury; Electrolyte disorders; Renal dialysis

Core Tip: Acute kidney injury and electrolyte disorders are frequent clinical complications in hospitalized patients with coronavirus disease 2019, being directly related to the severity of the disease and increasing the mortality.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak initiated in the first months of 2020. It corresponds to an illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although frequently asymptomatic, the malady is known for its wide variety of clinical signs and symptoms. These can range from pulmonary manifestations, such as dyspnea and cough, to extrapulmonary ones, which include fever, anosmia, ageusia, diarrhea, and myalgia[1-3]. This heterogeneity of clinical features is an indicative of the systemic character of COVID-19.

COVID-19 had an outstanding impact in the nephrology community. With over 4 million chronic kidney disease patients on maintenance dialysis at risk, the pandemic caused profound changes to the sector[4,5]. The kidney was also a commonly affected organ by COVID-19; one in every four patients presented abnormal renal function at hospital admission[6]. According to the classification proposed by the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, acute kidney injury is defined as any of the following situations: Increase in serum creatinine (SCr) by ≥ 0.3 mg/dL within 48 h; or increase in SCr ≥ 1.5 times baseline from 7 d prior; or urinary volume < 0.5 mL/kg/h for a period of 6 h. The KDIGO guidelines also propose a stratification of AKI in three stages, numbered from 1 to 3 in crescent order of injury severity[7].

In primary analyses of patients with COVID-19, it was also noticed that, among the various systemic complications caused by the SARS-CoV-2, changes in electrolyte concentrations are not only present, but also independently associated with a poor outcome[8,9].

In this review, we discuss the pathophysiology, epidemiology, clinical history, risk factors, management, and prognosis of COVID-19 associated acute kidney injury (AKI) and the most reported electrolyte disorders in COVID-19, which are hyponatremia, hypokalemia, and hypocalcemia.

ACUTE KIDNEY INJURY

The mechanism of AKI in COVID-19 is most likely multifactorial. Some of the proposed alterations induced by the viral disease that could damage the kidneys can be seen in Figure 1[10].

Coronaviruses have high affinity for the angiotensin-converting enzyme 2 (ACE2), a metallopeptidase often bound to cell membranes that is responsible for catalyzing the conversion of angiotensin 2 to angiotensin 1-7[11-13]. The transmembrane protease serine 2 contributes to the entry of SARS-CoV-2 in the cell by cleaving and activating the spike (S) protein[14]. After entry, followed by endocytosis, coronavirus infection causes upregulation of PAK1, a kinase that mediates inflammation and is associated with risk factors for mortality. Increased PAK1 levels also suppress the adaptive immune response, facilitating viral replication[15]. It was previously shown that SARS-CoV could bind to ACE2 *via* the virus' S protein[16]. Being structurally similar to SARS-CoV, SARS-CoV-2 also uses ACE2 in order to enter the host cell and replicate in its cytoplasm[17]. This enzyme is distributed across multiple tissues, such as the vascular endothelium, alveolar epithelium, proximal tubular cells of the kidney, and glomerular epithelium[18].

The fact that kidney cells express ACE2 explains how they also act as host cells of the novel coronavirus, a piece of information that was shown in autopsy studies. Histopathological examination found out varying degrees of tubular injury, such as diffuse proximal tubule injury with loss of the brush border, vacuolar degeneration, necrosis, hemosiderin granules, and pigment casts[19-21]. RNA *in situ* hybridization and electron microscopy also found evidence that SARS-CoV-2 directly infects the renal tubules[20,21]. A small number of patients with AKI may present virus in urine samples, which also supports a direct viral cytopathic effect hypothesis. These patients may have a greater predilection for proteinuria[22].

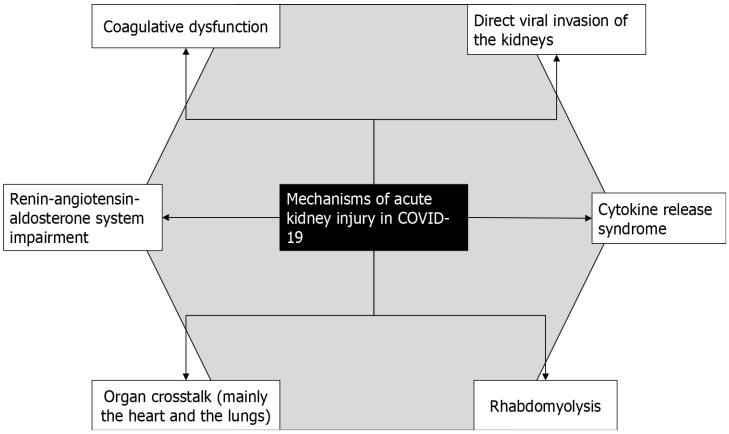

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Figure 1 Pathophysiological mechanisms of acute kidney injury in coronavirus disease 2019.

Due to the binding of SARS-CoV-2 to ACE2, the expression of this molecule is downregulated, which leads to increased activity of angiotensin 2 that is unopposed by angiotensin 1-7[23,24]. In normal conditions, angiotensin 1-7 has anti-thrombotic, anti-inflammatory, and vasodilator effects that counter the actions of angiotensin 2 through activation of Mas receptors[25-27]. It is suggested that the overactivation of angiotensin type 1 receptors may contribute to AKI onset mostly due to hemodynamic alterations, such as hypoxia, hypertension-induced proteinuria, and oxidative stress[27,28].

Furthermore, a hypercoagulative state induced by the lack of anti-thrombotic effects of angiotensin 1-7 could cause renal microangiopathy capable of causing AKI[29]. Rhabdomyolysis is also a frequent cause of COVID-19 associated AKI, being responsible for around 7% of the cases[30]. The occurrence of skeletal muscle injury is present in up to one in every five COVID-19 patients, which explains the occurrence of rhabdomyolysis nephropathy in this disease[29].

Cytokine release syndrome consists of an extreme rise of inflammatory cytokines, frequently called a "cytokine storm", caused by a systemic response that can be triggered by a wide variety of conditions [31,32]. It has been implied that cytokine storm is a significant component of the disease course of severe cases of COVID-19[33]. The binding of SARS-CoV-2 to ACE2 promotes an inflammatory response with a prominent release of inflammatory cytokines, such as IL-6, IL-8, IL-22, and TNF-α, and chemokines, like CCL2, CCL3, and CCL5[29,34,35]. Lymphopenia, a common feature of SARS-CoV-2 infection, also contributes to the rise of inflammatory cytokines[36].

The crosstalk between the kidneys, lungs, and cardiovascular system seems to be significant for the development of AKI. Cases of acute respiratory distress syndrome (ARDS) are knowingly associated with a greater risk of AKI onset, including those related to SARS-CoV-2 infection[37-39]. This is likely a result of renal damage triggered by inflammatory mediators that cause tubular injury, which by itself culminates in IL-6 upregulation that harms the lungs[39,40].

The cardiovascular system is another important topic regarding AKI in COVID-19. Acute viral myocarditis and cytokine cardiomyopathy can induce a reduction of the estimated glomerular filtration rate (eGFR) through hemodynamic changes. Type 1 cardiorenal syndrome (CRS) can occur due to a cytokine storm or myocarditis and type 3 CRS can occur after the onset of AKI. Furthermore, upon the onset of sepsis, type 5 CRS can occur[41,42]. Right ventricular failure caused by pneumonia induced by SARS-CoV-2 and reduction of cardiac output due to left ventricle failure are also possible mechanisms of eGFR diminishment and AKI[43,44].

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

Data available refers to hospitalized patients, since AKI is a complication typical of moderate and severe cases of COVID-19 that require inpatient healthcare[45-50]. The incidence of AKI in COVID-19 is highly variable depending on the study analyzed. Our review found results between 5% and 75%, and the article with the largest sample size indicated a frequency of approximately 36%, whilst a systematic review of observational studies found an incidence of AKI of 11%[30,45-49,51-53].

A multicenter study showed that about 45% of the patients had no significant kidney injury caused by the viral illness; that 34% developed AKI without need for renal replacement therapy (RRT); and that 26% developed COVID-19 AKI with need of RRT (AKI-RRT)[44]. In contrast, a systematic review found that RRT was used in only 7% of COVID-19 cases with renal manifestations[51]. The modality of first choice is usually continuous renal replacement therapy, mostly because it is a suitable modality for hemodynamically unstable patients[54].

In a Chinese cohort study, three quarters of the patients had developed renal symptomatology, including proteinuria and/or hematuria, but only one in every ten patients had an AKI onset[55]. Out of all renal clinical findings, the most common ones were proteinuria, hematuria, elevated SCr and blood urea nitrogen, reduction of eGFR, and AKI[46,47,55-57]. One study found that three in every four patients that were at least moderately ill had renal involvement to some extent. These levels were as low as 62% in moderately (3.5% being AKI) ill patients and as high as 91% in critically ill patients (43% being AKI). It is suspected that most cases of AKI in COVID-19 occur due to intrinsic rather than prerenal mechanisms[55].

A multicenter American study found that patients who developed AKI because of SARS-CoV-2 infection were older and predominantly male individuals with higher levels of comorbidities associated with more severe cases of COVID-19, such as systemic arterial hypertension, diabetes mellitus, and heart failure. Additionally, the same article shows that patients who developed AKI were usually admitted to an intensive care unit (ICU) and were more likely to be on use of vasopressors (52.6% *vs* 3.4%) as well as mechanical ventilation (89.7% *vs* 21.7% in nonventilated patients), indicating that patients who developed AKI were critically ill. In that sample of AKI patients, about one third of patients died[46]. Independent risk factors for the development of COVID-19 associated AKI include pre-existing renal impairment (such as chronic kidney disease), hypertension, and inpatient diuretic use [45,51,52,57].

It is also known that there is an association between ARDS and AKI in general and it also applies to COVID-19 due to the release of inflammatory cytokines, especially IL-6[37-40]. This is clinically notable as well, since patients on mechanical ventilators are more likely to develop AKI with or without need of RRT[45-47]. Additionally, abnormal serum urea and serum creatinine values were associated in a bivariate Cox regression model with either ARDS development or progression from ARDS to death[58].

Laboratory examinations show that most AKI patients are admitted with abnormal kidney function, represented by high levels of SCr and low eGFR. Patients who do not develop AKI are admitted with higher levels of SCr and lower eGFR than at discharge, while AKI patients are discharged with worsened kidney function[45-47]. Patients who develop stage 3 AKI are usually discharged with a median SCr of 4.0 mg/dL and median eGFR of 14.0 mL/min/1.73 m², as opposed to a median SCr of 1.19 mg/dL and median eGFR of 62 mL/min/1.73m² at admission[46].

MANAGEMENT AND PROGNOSIS

The management of COVID-19 associated AKI is a largely discussed theme among intensive care professionals. The 25th Acute Disease Quality Initiative Workgroup defined a few strategies for dealing with COVID-19 associated AKI[54]. The standard measures that have an evidence level of 1B or above include:

Measurement of kidney function through serum creatinine and urine output[56].

Use of dynamic assessment of cardiovascular status to mitigate the risk of AKI and ARDS, avoiding hemodynamic imbalance[56].

Volume expansion with balanced crystalloids to decrease the chances of developing AKI, unless there are indications for the use of other kinds of fluids[56].

Limit the patients' exposure to nephrotoxins whenever possible and monitor their kidney functionality when the use of nephrotoxins is necessary[56].

When contrast media are required, optimize intravascular volume as a means to prevent AKI[56].

The prognosis of COVID-19 associated AKI and AKI-RRT is arguably poor. AKI was associated with a longer median hospital stay, which was approximately twice as long when compared to non-AKI patients[59]. One study found that mortality is about ten times higher in patients with moderate-to-severe COVID-19 who developed AKI in comparison to those who did not[55]. Another observational study concluded that AKI is almost 2.5 times more frequent in non-survivors than in survivors of critical COVID-19 cases[60]. It is also stated that AKI is an independent risk factor for 30 d mortality among COVID-19 patients[52].

Although remission from proteinuria and hematuria is a common outcome for patients with renal COVID-19 manifestations, less than half of AKI patients recover their kidney function[55]. Mortality rates were as high as 35% of AKI patients and use of RRT increases the lethality of the disease to levels over 60%. Furthermore, approximately one in every three RRT patients that were discharged remained RRT-dependent[46,47].

ELECTROLYTE DISORDERS

Patients with COVID-19 may experience diverse electrolyte disturbances with clinical impact. The main disorders are hyponatremia, hypokalemia, and hypocalcemia. The pathophysiological mechanisms are diverse and imply changes in the renin angiotensin aldosterone system as well as immuno-inflammatory phenomena underlying the coronavirus, which are generally associated with kidney and/or

gastrointestinal damage[61]. Table 1 gives a general overview of the pathophysiology of the most frequent electrolyte disorders associated with COVID-19.

HYPONATREMIA

Hyponatremia is the most frequent electrolyte disorder in clinical practice, with a prevalence of 20% to 30% in hospitalized patients, and is defined by serum sodium levels below 135 mEq/L[62]. The association between pneumonia and hyponatremia was firstly described in 1962, mainly related to community-acquired pneumonia, which was later reported in other respiratory infections[63]. Thus, with the emergence of the COVID-19 pandemic, preliminary studies indicated that hyponatremia was one of the possible complications caused by the viral disease[64]. In general, COVID-19 patients with hyponatremia have more severe forms of the disease, with higher levels of hospitalization, when compared to normonatremic patients, both in infirmary and ICU beds. Most of these patients also have other markers of severity, such as higher levels of C-reactive protein (CRP), ferritin, and IL-6; consolidation lesions more present on chest CT; and greater need for oxygen support[65].

The pathophysiology of hyponatremia in patients with COVID-19 is considered multifactorial, but the main cause is the syndrome of inappropriate antidiuresis (SIAD). SIAD is characterized by hyponatremia (serum sodium less than 135 mEq/L) and elevated urinary osmolarity (> 100 mOsm/kg) compared to plasma osmolarity (< 280 mOsm/kg) in euvolemic patients that have normal renal, thyroid, hepatic, cardiac, and adrenal functions and are not on use of diuretics[66]. Despite its mechanism not being fully understood, SIAD in patients with COVID-19 is apparently related to elevated levels of IL-6, which induce the non-osmotic release of antidiuretic hormone. In addition, these cytokines can damage lung tissue and alveolar cells, generating hypoxic pulmonary vasoconstriction, which may induce SIAD[67]. Evidence demonstrates a directly proportional relationship between the serum sodium level and the PaO_2/FiO_2 ratio and an inversely proportional relationship between the serum sodium level and the IL-6 level[68]. Furthermore, some other factors may contribute to the secretion of this hormone, such as patients who experience fluid loss from vomiting and diarrhea (reported symptoms of COVID-19)[69].

HYPOKALEMIA

Hypokalemia corresponds to the most frequent potassium disorder and is characterized by a serum concentration of potassium below 3.5 mEq/L. The presence of hypokalemia can be variable and data in the literature point to an incidence between 10% and 41% of patients who were hospitalized for COVID-19[70,71]. Furthermore, in another study carried out in Italy, hypokalemia was associated with a longer hospital stay[71].

There are many factors that can generate hypokalemia, so a precise mechanism for this complication in patients with COVID-19 has not yet been determined. However, some hypotheses can be taken into consideration, such as: (1) Viral interaction with its input receptor (ACE2), altering the classic renin-angiotensin-aldosterone pathway and stimulating the release of aldosterone, thus increasing potassium secretion in the urine; (2) Volume loss due to gastrointestinal symptoms caused by the viral infection, mainly diarrhea; and (3) Being secondary to the use of medications, such as diuretics and glucocorticoids[9,71].

The clinical manifestations of symptomatic hypokalemia include muscle weakness and fatigue. However, in more severe cases, low levels of potassium can cause cardiac arrhythmias with alterations on the electrocardiogram tracing, and respiratory muscular weakness[72]. Therefore, it is correct to say that hypokalemia can increase respiratory stress and the risk of cardiac injury[61]. Regarding coronaviruses, hypokalemia was reported upon the onset of SARS-CoV-1 infection, back in 2003, and was also described in some preliminary studies during the beginning of the COVID-19 pandemic[71].

HYPOCALCEMIA

Calcium plays an important role in the mechanism of entering a host cell and viral replication, something that was already reported in the pathophysiology of Ebola and SARS-CoV-1 viruses[73,74]. In addition, hypocalcemia represents an independent factor for increased mortality among critically ill patients with long hospital stay[75].

In a study carried out in China, the incidence of hypocalcemia in COVID-19 patients was 62.6%. Other laboratory findings included lymphocytosis and higher levels of CRP, D-dimer, and IL-6 when compared to the normocalcemic group. In addition, in that same study, the hypocalcemia group was more likely to have a poor outcome in comparison to the normocalcemic group (47.8% *vs* 25%, respectively)[76]. In another study carried out in Italy, the incidence of hypocalcemia in patients with

Table 1 Pathophsyiology of the most common electrolyte disorders in coronavirus disease 2019

Electrolyte disorder	Pathophysiological mechanisms
Hyponatremia	Syndrome of inappropriate secretion of antidiuretic hormone
Hypokalemia	Excessive aldosterone liberation, volume loss, and use of diuretics and glucocorticoids
Hypocalcemia	Vitamin D deficiency and parathyroid imbalance

COVID-19 was 78.6%, and this electrolyte imbalance also had a strong association with ICU admissions and death when compared to patients with normal calcium levels[77].

Parathyroid hormone and vitamin D play a key role in calcium metabolism. Patients with chronic hypovitaminosis D and who are affected by COVID-19 are more predisposed to hypocalcemia, as this vitamin alters calcium metabolism by reducing the intestinal absorption of calcium and phosphorus. These patients may have a compensatory tendency to secondary hyperparathyroidism, but this is not always sufficient to prevent hypocalcemia[78].

COVID-19 hypocalcemia has been associated with higher mortality rates when compared to other patients with respiratory conditions that have similar clinical manifestations. Hypocalcemia is also more incident and quantitatively significant in COVID-19 than in other infections. The main factors responsible for hypocalcemia in hospitalized patients include low dietary intake, hypoparathyroidism, hypoproteinemia, vitamin D deficiency, and drug interaction. However, when it comes to COVID-19, vitamin D deficiency and parathyroid imbalance are identified as the main causes of said electrolyte disorder[75]. Parathyroid gland function can be impaired during critical systemic illness and inflammatory response with increased circulating cytokines[78].

CONCLUSION

Besides the respiratory complications caused by the SARS-CoV-2 virus, infected patients are also subject to manifestations regarding other systems, such as the renal system. AKI is a multifactorial and fairly common complication in moderate-to-severe COVID-19. Patients that develop AKI due to COVID-19 are usually older males with other comorbidities and are usually admitted to ICUs. Clinical management involves measurement of kidney function, cardiovascular status assessment, volume expansion, and nephrotoxin exposure limitation, as well as standard AKI care measures. AKI also acts as a risk factor for death in SARS-CoV-2 infected patients, specially concerning those on RRT.

Hyponatremia, hypokalemia, and hypocalcemia are the most relevant electrolyte disorders in hospitalized patients with COVID-19. The cause of these laboratory alterations is multifactorial and may be secondary to renal and gastrointestinal lesions caused by inflammatory response, or even by pathophysiological alterations caused by the entry mechanism of the virus. In patients with COVID-19, electrolyte disorders are associated with worse outcomes, with increased hospitalization length and mortality.

FOOTNOTES

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MINIREVIEWS

Rhino-orbital-cerebral mucormycosis as a complication of coronavirus disease 2019

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Abstract

Coronavirus disease 2019 is a highly contagious respiratory disease caused by severe acute respiratory syndrome coronavirus 2. This disease as well as its various treatments like steroids, antivirals, and antibacterials can alter the immune state of the affected individuals and result in secondary infections such as mucormycosis. Mucormycosis is a well-known opportunistic fungal infection that affects immunocompromised subjects, particularly those with diabetes mellitus, prolonged antibiotic or steroid use, and patients with organ transplantation, neutropenia, and hematological malignancies. Rhino-orbital-cerebral mucormycosis is an aggressive disease owing to its ability to invade the blood vessels by fungal hyphae, leading to necrosis of the involved structures. Large cases were reported from India, indicating that this clinical entity shows a geographical variation. The affected patients are suffering on a clinical spectrum depending on the stage of the disease. Radiological assessment, including computerized tomography and magnetic resonance imaging, is necessary to evaluate the stage of the disease and choose the appropriate surgical treatment. A multidisciplinary approach is required to treat rhino-orbital-cerebral mucormycosis and includes local or intravenous antifungal drugs, debridement of the dead tissues, and appropriate management of any predisposing conditions. The disease has a very poor prognosis with a death rate of 50%. This review aimed to sum-marize the demographic and clinical risk factors, investigations, treatments, and outcomes of coronavirus disease 2019 patients with rhino-orbital-cerebral mucormycosis.

Key Words: Rhino-orbital-cerebral mucormycosis; Mucormycosis; Nose and paranasal sinuses; Orbit; Cerebrum; COVID-19

Core Tip: Rhino-orbital-cerebral mucormycosis is an aggressive, opportunistic fungal infection. There is an increment in cases of this condition in the era of coronavirus disease 2019, particularly in India. It usually affects the severe or critical types of the COVID-19 and those with a history of diabetes mellitus, corticosteroid therapy, and mechanical ventilation. Early diagnosis with prompt treatment carries a better outcome. The treatment consists of intravenous or local amphotericin B, surgical debridement, and reversal of any immunocompromised conditions. However, this disease has a poor prognosis with a high rate of morbidity and mortality.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a peculiar disease owing to having many characteristics. First, although the disease affects mainly the respiratory system, it can affect any part of the body. Therefore, there is a diversity of clinical manifestations. These manifestations are either classical (fever, cough, headache, dyspnea, and olfactory and gustatory abnormalities) or non-classical (gastrointestinal symptoms, dysphonia, facial palsy, *etc*). Second, long-standing features, either due to the disease itself or its treatment, such as parosmia, dysphonia, sudden sensorineural hearing loss, and mucormycosis are debilitating manifestations of the disease. Third, there is a geographical variation of the COVID-19 manifestations such as rhino-orbital-cerebral mucormycosis (ROCM) that affects mainly the Indian population. Fourth, the clinical features might be related to the pandemic wave and a variant of the virus as ROCM appeared in the second wave in India and was caused by the delta variant[1,2].

COVID-19 can impair the immune status of the patients. This process is aggravated more in patients with a history of other immunocompromised conditions like diabetes mellitus (DM) or those who are on long-term steroids or antibiotic therapy. Furthermore, COVID-19 subjects are more prone to get superadded infections in certain patients with low pulmonary preserve or who need mechanical ventilation[3]. It was reported that secondary bacterial and fungal infections in hospitalized patients were approaching the rate of 8%[3,4]. Moreover, fungal infections were occurring more in a severe or critical COVID-19 stage[5].

One of the fungal-related COVID-19 infections is mucormycosis. It occurs mainly in the region of the head and neck, and the most common site is rhino-orbital-cerebral. It is an aggressive disease and carries a high death rate (approximately 50%) even if it is treated early[6]. The aim of this narrative review was to summarize the demographic and clinical characteristics, diagnostic tools, treatments, and outcomes in patients with ROCM-related COVID-19.

EPIDEMIOLOGY

Geographical distribution

In the pre-COVID-19 period, the incidence of mucormycosis in India (0.14/1000 population) was 80 times higher than what was reported in the world (0.005-1.7/million population)[7]. This means that India is the highest-burden country on the healthcare services regarding mucormycosis[8]. Despite India being the second country regarding the number of COVID-19 patients (43088118) (WHO Coronavirus COVID-19 Dashboard on 5-5-2022, https://covid19.who.int/table), most of the large case series of ROCM-related COVID-19 came from India[1,2,9]. Small case series or reported cases came from other countries like Turkey[10], Egypt[11], Iran[12,13], Honduras[14], and Peru[15]. This indicates that mucormycosis is an endemic disease in India in pre- and during COVID-19 periods.

Age

ROCM-related COVID-19 could affect any age. The median age is mostly in the sixth decade[1].

Gender distribution

Males are two to three times more affected than females[1,9].

CAUSATIVE AGENTS

Mucormycosis, previously known as zygomycosis, is a group of diseases caused by a fungal infection. The causative agent belongs to the order *Mucorales*. The *Rhizopus* specie is the commonest type[7] followed by, in descending order, *Mucor, Cunninghamella, Apophysomyces, Lichtheimia* (formerly *Absidia), Saksenaea, Rhizomucor*, and other species[10]. These fungi release a huge amount of spores into the surrounding air. Even though all human beings inhale these fungi, only individuals with impaired immunity from DM, organ transplantation, prolonged use of steroids or antibiotics, cytotoxic drugs, and malignancies are affected by the disease[16]. The disease is characterized by rapid progression from the nose to the orbit and then to the brain owing to the direct invasion of the blood vessels, which results in tissue necrosis[10].

PREDISPOSING FACTORS

Patients with any medical condition or those who use certain drugs such as steroids, which affect the immune system, are capable of initiating opportunistic infections like mucormycosis[17]. A history of DM and corticosteroid therapy are among the commonest predisposing factors of ROCM-related COVID-19[1,9,18]. Around 70% of patients with this disease have a history of DM.

PATHOPHYSIOLOGY

The correlation between COVID-19 and ROCM is well established in the literature[1,10]. There are several mechanisms by which COVID-19 enhances the possibility of mucormycosis. First of all, there is a dramatic reduction in T cells, including CD4+ and CD8+, particularly in the severe form of COVID-19. As a result, the immunocompromised condition will develop that might predispose to mucormycosis [19].

Second, in the severe COVID-19 state, there is a sudden rise in certain inflammatory markers like IL-6, IL-10, IL-2R, and TNF-alpha that results in a "cytokine storm"[19]. This storm increases ferritin levels and decreases iron export. Therefore, iron deposits inside cells. The high level of iron causes tissue necrosis and the free iron passes to the blood. The high environmental level of iron is a good medium for mucormycosis because the iron is essential for the growth of the fungi and spreading in the body [20].

Third, there is a higher prevalence of DM and diabetic ketoacidosis in patients with COVID-19 in comparison with the general population[21]. There are two causes of new-onset DM due to COVID-19; the use of steroids and the disease itself are similar to the severe acute respiratory syndrome coronavirus 1[22]. Also, there are two reasons for the diabetogenic nature of COVID-19: expression of angiotensin-converting enzyme 2 receptors in the pan-creatic islets as well as increased insulin resistance due to the cytokine storm[23]. There is more iron released into the circulation because the excessive glucose occupies the iron-binding site of ferritin and transferrin in patients with hyperglycemia and diabetic ketoacidosis allowing more iron to reach the blood. The high tissue iron level is a favorable medium for the growth of the fungi[24].

Lastly, endotheliitis as a sequel of COVID-19 might increase the risk of mucormycosis[25]. Damage to the endothelial tissue enhances angio-invasion and dissemination of mucormycosis. Besides, low pH in COVID-19 induces hyperglycemia, and high iron concentration contributes to the expression of two receptors: glucose regulatory protein 78 of endothelium cells and fungal ligand spore coating homolog protein. These mediate the adhesion and penetration of *Mucorales* into the tissues[26].

CLINICAL FEATURES

The onset of the ROCM from the time of COVID-19 diagnosis ranged from 0 to 90 d with 56% of the cases presenting within 14 d[1]. Hence, it is necessary to advise the liable patients with this disease to look for any of the warning symptoms (nasal stuffiness or obstruction, bad odor smell, epistaxis, mucopurulent or blood-stained nasal discharge, pain in the teeth, sinuses, or orbit, worsening headache, facial pain, diplopia, proptosis, fever, facial paresthesia or anesthesia, facial palsy, sudden loss of vision, sudden ptosis, altered conscious level, and focal seizures) to catch the diagnosis early[27]. These symptoms occur almost always on one side. Fever could be a warning sign during or following the course of COVID-19 if the cause of the fever is not obvious or not detected. In such cases, a nasal examination is important to detect if there is a possibility of an early stage of mucormycosis or not.

Thereafter, a thorough examination is essential and should include endoscopic nasal, ophthalmological, and neurological examinations. In a large case series of 2826 patients with this disease, the authors reported the following signs: periocular/facial edema (33%); loss of vision (21%); ptosis (12%);

proptosis (11%); nasal discharge (10%); nasal ulcer/eschar (5.7%); diplopia/ocular movement restriction (3%); periocular/facial discoloration (2.3%); periocular hypoesthesia (1.3%); oral or palatal ulcer/eschar (0.6%); facial palsy (0.2%); and altered sensorium (0.1%)[1].

STAGING SYSTEM

Adopting a staging system is crucial in the management of ROCM-related COVID-19. Owing to the huge number of cases found in India, the Indian ophthalmologist Honavar create a very useful staging system[27]. It is a simple system and depends on anatomical location from the starting point in the nose, then to the paranasal sinuses, orbit, and intracranial structures. In addition, the system considers the severity of each site. Furthermore, this system contains the specific symptoms and signs and useful investigations for each stage. As a next step, it is logical to check its validity, suggest the best option of treatment for each stage, and estimate the treatment outcomes.

DIAGNOSIS

A high index of clinical suspicion is crucial for early diagnosis. Involved tissue biopsy and potassium hydroxide mount fungal staining is the cornerstone of the diagnosis. Culture and sensitivity are used to determine the fungal species. However, it is necessary to start with amphotericin B until the laboratory result is achieved. Radiological imaging in the form of computerized tomography and magnetic resonance imaging of the nose and paranasal sinuses is used to support the diagnosis and to evaluate the stage of the disease[1].

TREATMENT

It is of utmost importance in the management of ROCM-related COVID-19 to use a multidisciplinary team including a specialist doctor in infectious diseases, internal medicine, intensive care, otolaryngology, ophthalmology, neuromedicine, and/or neurosurgery[2].

In general, the treatment consists of three steps: intravenous or local antifungals therapy; appropriate surgical debridement; and reversal of the immunosuppressive conditions[28].

Initiation of antifungal therapy within the first 5 d of the diagnosis improves the survival rate to 83%, which is much larger than the survival rate of 49% if the antifungal treatment started at ≥ 6 d[29]. Amphotericin B is considered the drug of choice as a monotherapy, while posaconazole or isavuconazole can be used as a salvage antifungal drug. A combination of amphotericin B and posaconazole can be used in refractory cases of mucormycosis[4]. In the largest case series in the world from India of 2826 patients with ROCM-related COVID-19, intravenous amphotericin B was used in 73% and intraorbital injection of amphotericin B in 22% of the patients. The study showed a satisfactory result with the use of amphotericin B[1]. Also, in another study from India of 58 patients, parenteral amphotericin B and surgical debridement were used in all patients[9]. In a case report study from Peru, isavuconazole was used, owing to the unavailability of amphotericin B, in a 66-year-old woman with this disease. The study revealed that the isavuconazole was effective and without adverse effects over 10 mo[15].

Of note, antifungal therapies have several shortcomings such as adverse effects related to infusion, optimal dosage, and nephrotoxicity. Nowadays, nanomedicine is an alternative promising solution, in which the intravenous route of the amphotericin B is shifted to other routes like through the mouth, local, and pulmonary routes. This system is under further development[30].

Surgical debridement has two advantages. It reduces the fungal load as well as provides sufficient tissue for histopathological evaluation. The process of debridement continues until the appearance of normal tissue that bleeds profusely. Removal of the palate, endoscopic nasal approach, and orbital decompression or exenteration are undertaken depending on the stage of the disease[28].

Correction of the hyperglycemic state, hypoxia, acidosis, and electrolyte disturbances are essential. We must take the opinion of relevant specialists concerning decreasing or discontinuing immunosuppressive or antibiotic therapy. Furthermore, the use of granulocyte colony-stimulating factors might increase the white cell count and improve host immunity[28].

PREVENTION

A golden rule in medicine is that "prevention is better than treatment." This is particularly true in serious diseases like mucormycosis. Many measures should be taken to avoid such a sinister pathology:

judicious and supervised use of systemic corticosteroids in compliance with the current preferred practice guidelines; judicious and supervised use of tocilizumab in compliance with the current preferred practice guidelines; strict monitoring and control of DM; aggressive aseptic precautions while administering oxygen (sterile water for the humidifier, daily change of the sterilized humidifier and the tubes); personal and environmental hygiene: use of betadine as a mouth gargle, barrier mask covering the mouth and nose, and consideration of prophylactic oral posaconazole in high-risk subjects (> 3 wk of mechanical ventilation, > 3 wk of supplemental oxygen, > 3 wk of systemic corticosteroids, poorly or uncontrolled DM with or without ketoacidosis, history of chronic rhinosinusitis, and immunocompromised conditions)[27].

PROGNOSIS

Although ROCM-related COVID-19 is a relatively uncommon condition, it is an aggressive disease with a high rate of morbidity and mortality[17]. One of the disaster complications is a loss of vision. In a large retrospective observational study from India of 2826 COVID-19 patients, there were 289 (16%) cases that ended with orbital exenteration[1]. The death rate is approaching 50%[18]. A recent study from Egypt reported a mortality rate of 21.4% (3/14)[31], which was considered low if one compares it with the mortality rate from India (31% to 49%)[32,33]. The fatality rate might range from 30% to 90% in patients with cerebral involvement[34]. It is of utmost importance to consider the staging system of the ROCM-related COVID-19 adopted by Honavar to determine the severity of the disease and survival rate[27]. It was reported in the literature that the delay in starting treatment even 6 d increases the 1-mo fatality from 35% to 66%[35]. Comorbidities and the immunosuppressive state of the patients will increase the aggressiveness of the disease and increase the morbidity and mortality rates. Early diagnosis and prompt treatment improve the outcomes.

CONCLUSION

ROCM-related COVID-19 is an opportunistic serious fungal infection. The commonest causative agents are from the *Rhizopus* specie. It occurs as one of the complications of COVID-19, particularly in diabetic patients and those on corticosteroid therapy or mechanical ventilation. The disease affects mostly the Indian population. Angio-invasion with tissue destruction is the hallmark of the disease. A high index of clinical suspicion, early diagnosis, intravenous or local amphotericin B, and surgical debridement lead to better outcomes. However, it carries a high rate of morbidity and mortality.

FOOTNOTES

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MINIREVIEWS

Role of high dose vitamin C in management of hospitalised COVID-19 patients: A minireview

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as one of the most dreadful viruses the mankind has witnessed. It has caused world-wide havoc and wrecked human life. In our quest to find therapeutic options to counter this threat, several drugs have been tried, with varying success. Certain agents like corticosteroids, some anti-virals and immunosuppressive drugs have been found useful in improving clinical outcomes. Vitamin C, a water-soluble vitamin with good safety profile, has been tried to reduce progression and improve outcomes of patients with coronavirus disease 2019 (COVID-19). Because of its anti-oxidant and immunomodulatory properties, the role of vitamin C has expanded well beyond the management of scurvy and it is increasingly been employed in the treatment of critically ill patients with sepsis, septic shock, acute pancreatitis and even cancer. However, in spite of many case series, observational studies and even randomised control trials, the role of vitamin C remains ambiguous. In this review, we will be discussing the scientific rationale and the current clinical evidence for using high dose vitamin C in the management of COVID-19 patients.

Key Words: Ascorbic acid; COVID-19; SARS-CoV-2; Vitamin C

Core Tip: Vitamin C has several biochemical effects including anti-oxidant, anti-inflammatory, immuno-modulatory, and anti-viral properties which could make it a possible low-risk, add on to the current therapeutic options for managing coronavirus disease 2019 (COVID-19) patients. As it is a water-soluble vitamin, even high doses have been shown to be safe and only rarely, complications have been reported. In the last couple of years, many case series, observational studies and even randomised control trials have been conducted to evaluate the role of vitamin C in COVID-19, but have shown conflicting results. Hence, as per the current clinical evidence, the role of vitamin C remains ambiguous and it cannot be recommended as a part of routine therapeutic regimen for managing COVID-19 patients.

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INTRODUCTION

Viruses have always been potential threats and posed challenges to human health. Historically, various respiratory viruses like severe acute respiratory virus (SARS-CoV) in 2002, H1N1 influenza virus in 2009 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 have created havoc and wrecked human life. In December 2019, in Wuhan, China, the first pneumonia outbreak secondary to COVID was reported. It was given an interim name of 2019-nCoV by the World Health Organisation and was later renamed SARS-CoV-2 by the International Committee on Taxonomy of Viruses.

SARS-CoV-2 is one of the most dreadful viruses faced by mankind which not only led to the COVID outbreak in China but also spread throughout the world infecting more than 528 million people with more than 6.3 million deaths worldwide[1]. This virus led to a disease with a varied clinical spectrum ranging from asymptomatic viral carriers to severe disease characterised by acute respiratory distress syndrome (ARDS)[2,3]. The majority of affected individuals had mild symptoms especially in the initial stages of infection but many patients developed life threatening complications in the later stages with ARDS and consequent multiorgan failure leading to mortality of 7%-10%, especially in the elderly and those with pre-existing comorbidities[2-4].

The primary mechanism by which the virus caused severe disease was the initiation and propagation of a hyperimmune response, which increased pro-inflammatory cytokines and serum biomarkers[5]. The initial viral cytopathic effects were later complicated by a cytokine storm which led to ARDS and other systemic organ involvement[6]. In lieu of this cytokine storm, various anti-inflammatory and immune-modulating medications like corticosteroids, interleukin-6 (IL-6) inhibitors, and Janus kinase (JAK) inhibitors have been tried to prevent, as well as treat this life threatening complication.

Vitamin C was one of the most commonly prescribed medications for all patients of COVID-19, irrespective of the severity of the disease. Vitamin C is an essential water-soluble vitamin which is required in humans for collagen synthesis, wound healing, bone development, various biochemical functions, redox reactions, synthesis of carnitine, adrenal steroids and catecholamines and metabolism of amino acids and cholesterol[7]. Over the years, its clinical role has expanded and is now commonly prescribed to treat myriad of severe diseases including sepsis, septic shock, acute pancreatitis and even cancer[8-10]. However, its role in these disease conditions remain controversial. Vitamin C has also been suggested as a potential therapeutic option in managing COVID-19 patients, with a few reports showing a beneficial role[11]. However, larger trials have reported variable outcomes, precluding definitive conclusions on vitamin C use in COVID-19 patients[12-14].

RATIONALE

The pathophysiology of COVID-19 remains incompletely understood. However, some patho-physiological changes, cytokine storm, micro thrombosis and immune-paralysis, have been described, which may lead to multi-organ dysfunction and death attributable to COVID-19. Another important phenomenon is release of oxygen free radicals (OFRs), causing oxidative damage and end-organ failure. These pathophysiological changes are similar to those seen with sepsis and septic shock, and hence, it was postulated that the use of vitamin C might be clinically beneficial in managing COVID-19.

Vitamin C deficiency

The normal plasma levels of vitamin C have been described above 50 μmol/L[15]. It is further suggested that although these levels may be sufficient to prevent scurvy, higher levels may be required to

strengthen the immune system[16]. However, these levels quickly fall in patients with acute illness, and vitamin C deficiency, defined as levels below 11 μmol/L, is commonly reported among hospitalized patients[17-19].

Studies in critically ill COVID-19 patients have also shown low mean vitamin C levels. In addition, levels were significantly lower among non-survivors as compared with survivors[20]. In a single center study of patients with COVID-19 associated ARDS, more than 90% had almost undetectable serum vitamin C levels[21]. It is postulated that the reason for vitamin C deficiency observed in acute illnesses like infections, trauma, and surgery is the increase in metabolic consumption[22].

Anti-oxidant properties

Vitamin C has well described anti-oxidant properties, which may help in scavenging OFRs by increasing nitric oxide levels. It also prevents production of nitrogen species, improving capillary blood flow[23].

Anti-inflammatory properties

Vitamin C has several anti-inflammatory effects, potentially having clinical benefits in managing COVID-19 induced cytokine storm. It inhibits tumor necrosis factor-α (TNF-α), suppresses activation of nuclear factor kappa-B (NF-kB), reduces pro-inflammatory cytokines and lowers histamine levels[24].

Immune enhancing properties

By affecting lipid synthesis and reinforcing the maintenance of the alveolar epithelial barrier, vitamin C helps in improving innate immunity. Vitamin C potentially helps in immunomodulation by increasing the immunoglobin and complement levels[25]. It also exhibits immunomodulatory properties by promoting T-cell maturation and modulation, improving neutrophil chemotaxis and phagocytosis and by enhancing oxidative killing. In addition, it also promotes lymphocytic proliferation, interferon production and increases antibody production[23,24].

Prevention of micro and macro vascular dysfunction

Vitamin C acts as a co-factor for synthesis of catecholamines (epinephrine, norepinephrine), and vasopressin and increases the sensitivity of vascular musculature to these compounds. Vitamin C also causes inhibition of inducible nitric oxide synthase (iNOS) expression, thereby preventing vasoconstriction. These effects may be particularly helpful in patients with shock and may improve end-organ perfusion[23,24].

Anti-viral properties

Vitamin C has been shown to have direct and indirect effects on viral replication and can inactivate several viruses *in vitro*[26]. High-dose vitamin C may cause viral inactivation by oxidation of viral nucleic acids and damage to viral capsids. Vitamin C can also have indirect effects by promoting interferon production, which may, in-turn affect viral replication by binding to the cell surface. Interferons may also aid in immune-stimulation leading to virus inactivation[27]. Because of these anti-viral properties, vitamin C has been used clinically to manage viral illnesses ranging from common cold to viral ARDS secondary to wide range of viruses like enterovirus/rhinovirus, H1N1, and CHIKV[28-31].

Other miscellaneous effects

By reducing oxidation injury and apoptosis vitamin C plays a role in prevention of mitochondrial dysfunction. In addition, it also prevents septic cardiomyopathy by reducing oxidation injury and apoptosis and by increasing carnitine synthesis[23,24]. Hence, it may prove useful in managing viral myocarditis and improving cardiac dysfunction.

CLINICAL EVIDENCE

The first large randomized clinical trial (RCT) to evaluate the effect of vitamin C in COVID-19 patients was the COVID A to Z trial. It was a multicentre open label RCT which aimed to assess the effect of high dose zinc (50 mg), high dose ascorbic acid (8000 mg per day in 2-3 divided doses, orally) or a combination of both zinc and ascorbic acid on the duration of symptoms of SARS-COV-2. A total of 214 patients were enrolled in the study and randomised equally into 4 groups to receive a 10-d course of either zinc gluconate, ascorbic acid, both or only standard of care. The study's primary end point was the number of days required for a reduction in symptoms (fever, cough, shortness of breath, and fatigue) by 50%. The results of the study did not show any significant decrease in the duration of symptoms as compared to standard of care. Additionally, there was no statistically significant difference in the need for hospitalisation and mortality[32].

Even though vitamin C is widely prescribed in the management of COVID-19 patients, the scientific evidence is primarily derived from case series and retrospective studies (Table 1)[11,14,33-42]. Only a few RCTs have been conducted to evaluate the role of high dose intravenous vitamin C (HDIVC) in hospitalised COVID-19 patients[12,13,43,44]. The largest RCT was a Pakistani study, which included 150 patients, 75 each in study and control groups. Patients in the study group were given 50 mg/kg/d of IV vitamin C and compared to those who received only the standard therapy. The authors reported that the patients who received IV vitamin C became symptom-free earlier and had reduced hospital length of stay (LOS)[13]. However, there was no significant difference in the need for invasive mechanical ventilation (IMV) and mortality. Other RCTs also failed to show any difference in the need for IMV or reduction in mortality rates (Table 1)[12,43,44].

A few studies showed a reduction in inflammatory markers[11,33,35,36,38] but these results were neither consistent nor translated in to improved clinical outcomes[33]. One small retrospective cohort study even reported increased mortality in COVID-19 patients treated with IV vitamin C 1.5 gm every 6th hourly for four days[37].

A few meta-analyses have also been published evaluating the role of vitamin C in COVID-19 (Table 2)[45-47]. Rawat *et al*[47] performed a meta-analysis on the impact of Vitamin C on major clinical outcomes such as mortality, intensive care unit (ICU) admission, duration of hospital stay and need for mechanical ventilation in patients diagnosed with COVID-19. They included 6 RCTs in their analysis encompassing 572 patients. Amongst the 6 studies, 2 were multicenter RCTs, and 4 were single centre studies. Two studies were conducted on non-severe patients, while 4 studies were conducted on severe cases of COVID-19. Both oral (2 studies) and intravenous vitamin C (4 studies) were used, and the dosage ranged from 50 mg/kg/d to 24 g per day of vitamin C. The meta-analysis did not show vitamin C to reduce any major outcomes in COVID-19 patients. Even in a subgroup analysis based on the dose, route of administration and severity of illness, no significant benefit was observed. However, this meta-analysis had multiple limitations including heterogeneity in the study population, variable doses of vitamin C and differences in route of administration. In defense, the subgroup analysis also revealed similar results. Moreover, some studies used combination of vitamin E and melatonin, which may have confounded the results. Also, the standard treatment used in the control groups differed and the data on the adverse effects of vitamin C was lacking[47].

A recently published meta-analysis analysed data from five trials in which only HDIVC, defined as IV vitamin C ≥ 2 gm/d, was prescribed to hospitalised COVID-19 patients. Among the included studies, three were RCTs, and two were retrospective studies, including 374 patients. The authors could not find any statistically significant difference in terms of hospital LOS, mortality or adverse effects when patients were treated with HDIVC[46].

Another larger meta-analysis, including seven trials and 807 patients analysing the role of HDIVC, also failed to show any beneficial results in terms of mortality, hospital or ICU LOS or need for IMV in COVID-19 patients. The authors further noted that all the included trials were of high quality but different dosing regimens were used ranging from 2-24 gm of IV vitamin C per day for 3-7 d[45].

Recognising the lack of clinical evidence, the current National Institutes of Health (NIH) guidelines also does not make any recommendation for or against the use of vitamin C in the management of outpatient or hospitalised COVID-19 patients[48].

DOSING

Both oral and intravenous formulations of vitamin C have shown similar clinical efficacy, but intravenous route is generally preferred in critically ill patients[49,50]. It is suggested that higher doses of vitamin C, 2-3 gm/day, may be required to maintain the normal serum concentrations in patients with acute viral infections[51]. High doses of up to 100 g/d have been tried in the management of sepsis patients[52]. Although there is no consensus, any dose above 2 g/d is arbitrarily considered as high dose[46].

Even though several different dosing regimens have been tried in patients with COVID-19, data regarding dosing regimens are generally extrapolated from the trials on sepsis patients. Six hourly dosing have been shown to rapidly improve serum vitamin C levels, achieve a steady state and maintain therapeutic levels[53,54]. However, no consensus presently exists on the recommended daily dosage regimen for HDIVC.

ADVERSE EFFECTS

Even when used in high doses, vitamin C is considered harmless as it is a water-soluble vitamin. The major trials have mainly concentrated on the efficacy of vitamin C, and the data regarding adverse effects are primarily derived from case reports and series[55]. Most reported adverse effects are mild and reversible (Table 3)[55-57]. Rarely, patients may develop serious adverse effects, including haemolysis, disseminated intravascular coagulation and acute kidney injury (AKI). Adverse effects have

Table 1 Different studies evaluating the role of high dose intravenous Vitamin C in COVID-19

S. No.	Title	Year of publication	Country of origin	Study design	Sample size in the control arm	Sample size in the intervention arm	Intervention summary	Results in brief
1	Effect of high-dose intravenous vitamin C on prognosis in patients with SARS-CoV-2 pneumonia[14]	2022	Turkey	Retrospective study	170 patients	153 patients	2 g/d IV	No difference in mortality
2	High-dose intravenous vitamin C decreases rates of mechanical ventilation and cardiac arrest in severe COVID-19[33]	2022	USA	Retrospective cohort study	75 patients	25 patients	3 gm 6 hrly for 7 d IV	HDIVC group had a prolonged hospital stay, prolonged ICU stay, and prolonged time to deathCRP levels were lower in the HDIVC group while other inflammatory markers (d-dimer and ferritin) were similar in both groups.HDIVC patients had significantly lower rates of IMV and cardiac arrest
3	Efficacy of High Dose Vitamin C, Melatonin and Zinc in Iranian Patients with Acute Respiratory Syndrome due to Coronavirus Infection: A Pilot Randomized Trial[43]	2021	Iran	RCT	11	10	IV vitamin C (2 g, q6hr), oral; melatonin (6 mg, 6 hourly), and oral zinc sulfate (50 mg, 6 hourly) for 10 d	No differences in PaO2/FiO2, CRP, ESR or LDH levels and ICU LOS
4	Pilot trial of high-dose vitamin C in critically ill COVID-19 patients[12]	2021	China	Multi center RCT	29 in control	27 treatment group	12 g of vitamin C/50 ml every 12 h for 7 d at a rate of 12 mL/h IV	No difference in IMV free days at D28; no difference in 28-d mortality. Steady rise in the PaO_2/FiO_2 in vitamin C group
5	No significant benefit of moderate-dose vitamin C on severe COVID-19 cases[34]	2021	China	Retrospective cohort study	327	70	2-4 gm/d	No significant difference in clinical improvement or mortality rate
6	Beneficial aspects of high dose intravenous vitamin C on patients with COVID-19 pneumonia in severe condition: a retrospective case series study[35]	2021	China	Retrospective case series		12 patients	71 to 350 mg/kg/d for 3 d IV	Reduction in CRPImproved PaO_2/FiO_2 and SOFA score
7	High Dose Intravenous Vitamin C for Preventing The Disease Aggravation of Moderate COVID-19 Pneumonia. A Retrospective Propensity Matched Before-After Study[36]	2021	China	Retrospective before-after study	55 patients	55 patients	100 mg/kg/d IV for 7 d	Significant reduction in progression to severe disease.Reduced levels of CRP, D-dimer and APTT
8	Safety and effectiveness of high-dose vitamin C in patients with COVID-19: A randomized open-label clinical trial[44]	2021	Iran	Randomised open-label study	30 patients	30 patients	6 g/d IV	Reduced temperature and improved SaO2 in HDIVC group. No difference in ICU or hospital mortalityLonger hospital LOS in HDIVC group
9	Use of Intravenous Vitamin C in Critically Ill Patients With COVID-19 Infection[37]	2021	USA	Retrospective cohort study	24 patients	8 patients	1.5 grams IV vitamin C every 6 h for up to 4 d	HDIVC group had higher rates of hospital mortality and mean SOFA scores post-treatment. No difference in daily vasopressor requirement or ICU LOS
10	High-dose intravenous vitamin C attenuates hyperinflammation in severe coronavirus disease 2019[38]	2021	China	Retrospective cohort study	151	85	100 mg/kg every 6 h for day 1 followed by 100 mg/kg evry 12 h for the next 5 d	Significantly reduced inflammatory markers (hs-CRP, IL-6, TNF-alpha)
11	The efficiency and safety of high-dose	2021	China	Retrospective	30	46	6 g twice a day on day 1	Reduced 28 d mortality. No change in oxygen support

	vitamin C in patients with COVID-19: A retrospective cohort study[39]			cohort study			followed by 6 gm once a day for 4 d IV	
12	High-dose vitamin C ameliorates cardiac injury in COVID-19 pandemic: A retrospective cohort study[40]	2021	China	Retrospective cohort study	62	51	100 mg/kg every 6 h for day 1 followed by 100 mg/kg evry 12 h for the next 5 d	HDIVC can ameliorate cardiac injury through alleviating hyperinflammation
13	The Role of Vitamin C as Adjuvant Therapy in COVID-19[13]	2020	Pakistan	RCT	75 patients	75 patients	50 mg/kg/day of intravenous (IV)	Earlier resolution of symptoms and reduced hospital LOS. No significant difference in the need for IMV and mortality
14	Activities of serum ferritin and treatment outcomes among COVID-19 patients treated with vitamin c and dexamethasone:An uncontrolled single-center observational study[41]	2020	India	Prospective, observational study		50 patients	NA	Mortality 6%
15	The use of IV vitamin C for patients with COVID-19: A case series[11]	2020	USA	Case series		17 patients	1 g every 8 h for 3 d IV	Significant decrease in inflammatory markers. Mortality 12%
16	Application of methylene blue -vitamin C - N-acetyl cysteine for treatment of critically ill COVID-19 patients, report of a phase-I clinical trial[42]	2020	Iran	Phase I clinical trial	25 ICU COVID-19 patients. 5 received MCN as last resort	25 healthy individuals	Methylene blue (1 mg/kg) along with vitamin C (1500 mg/kg) and N-acetyl Cysteine (1500 mg/kg) orally or intravenously	Reduced methhemoglobin levels, survival of 4/5 patients

IV: Intravenously; HDIVC: High dose intravenous vitamin C; ICU: Intensive care unit; CRP: C-reactive protein; RCT: Randomised control trial; ESR: Erythrocyte sedimentation rate; LDH: Lactate dehydrogenase; LOS: Length of stay; IMV: Invasive mechanical ventilation; SOFA: Sequential organ failure assessment; APTT: Activated prothrombin time; IL: Interleukin; TNF: Tumour necrosis factor; MCN: Methylene blue; USA: United states; COVID-19: Coronavirus disease 2019; RCT: Randomised control trial; NA: Not available.

been reported with both oral and intravenous preparations and the use of normal doses and high doses of vitamin C. Patients with underlying renal dysfunction and glucose-6-phosphate dehydrogenase (G6PD) deficiency are especially more prone to develop side effects like AKI and haemolysis[55].

FUTURE DIRECTIONS

Almost 50 trials are presently being conducted to evaluate the role of vitamin C in patients with COVID-19 disease. These trials are being conducted in patients with different severity of disease and are trying to assess different clinical outcomes ranging from the need for hospitalisation, resolution of symptoms, need for organ support, need for IMV and mortality. Role of vitamin C is also being explored in combination with other therapies like zinc, quercetin, and curcumin and comparison to other anti-oxidants like vitamin E, melatonin, pentoxifylline, and N-acetyl cysteine. These trials may help us better understand vitamin C's clinical efficacy and safety profile and clarify its potential role in the management of COVID-19 patients. Also, these studies may shed light on the dosing of HDIVC, as most of the studies performed till now have used different dosing regimens, which might have affected their results.

Table 2 Meta-analyses evaluating the role of Vitamin C in COVID-19

S. No.	Title	Year of publication	Country of origin	Included studies	Included sample size	Results in brief
1	Intravenous vitamin C use and risk of severity and mortality in COVID-19: A systematic review and meta-analysis[45]	2022	China	7 studies (3 RCTs, 4 observational studies)	807 patients	IV vitamin C treatment did not affect disease severity or mortality
2	The effectiveness of high-dose intravenous vitamin C for patients withcoronavirus disease 2019: A systematic review and meta-analysis[46]	2022	Korea	5 studies (3 RCTs, 2 retrospective trials)	374 patients (186 HDIVC and 184 control group)	No difference in hospital LOS or mortality
3	Vitamin C and COVID-19 treatment: A systematic review and metaanalysis of randomized controlled trials[47]	2021	India	6 RCTs	572 patients	Vitamin C treatment didn't reducemortality, ICU LOS, hospital LOS or need for invasive mechanical ventilation

RCT: Randomised control trial; IV: Intravenously; HDIVC: High dose intravenous vitamin C; LOS: Length of stay; ICU: Intensive care unit.

Table 3 Adverse effects reported with vitamin C

Item	Description
General	Interference with laboratory tests, phlebitis, nausea, vomiting
Neuro-muscular	Lethargy, fatigue, muscle cramps, headache, altered mental status
Metabolic	Hyperglycemia, hypernatremia
Haematological	Haemolysis, disseminated intravascular coagulation, methemoglobinemia
Renal	Oxalosis, renal stones, acute kidney injury

CONCLUSION

Vitamin C is a relatively safe therapeutic option, and there may be scientific rationale which theoretically may help in the recovery of COVID-19 patients. Many observational studies and some RCTs have been conducted to evaluate its role in COVID-19. However, presently there is dearth of clinical evidence showing its utility in the management of COVID-19 patients; hence, it cannot be recommended for routine use in these patients. Further larger multi-center RCTs are warranted to prove its safety and potential role.

FOOTNOTES

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MINIREVIEWS

COVID-19 and hemolysis, elevated liver enzymes and thrombocytopenia syndrome in pregnant women - association or causation?

Prashant Nasa, Deven Juneja, Ravi Jain, Ruchi Nasa

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Abstract

Pregnant women are among the high-risk population for severe coronavirus disease 2019 (COVID-19) with unfavorable peripartum outcomes and increased incidence of preterm births. Hemolysis, the elevation of liver enzymes, and low platelet count (HELLP) syndrome and severe preeclampsia are among the leading causes of maternal mortality. Evidence supports a higher odd of pre-eclampsia in women with COVID-19, given overlapping pathophysiology. Involvement of angiotensin-converting enzyme 2 receptors by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for the entry to the host cells and its downregulation cause dysregulation of the renin-angiotensin-aldosterone system. The overexpression of Angiotensin II mediated *via* p38 Mitogen-Activated Protein Kinase pathways can cause vasoconstriction and uninhibited platelet aggregation, which may be another common link between COVID-19 and HELLP syndrome. On PubMed search from January 1, 2020, to July 30, 2022, we found 18 studies on of SARS-COV-2 infection with HELLP Syndrome. Most of these studies are case reports or series, did not perform histopathology analysis of the placenta, or measured biomarkers linked to pre-eclampsia/HELLP syndrome. Hence, the relationship between SARS-CoV-2 infection and HELLP syndrome is inconclusive

in these studies. We intend to perform a mini-review of the published literature on HELLP syndrome and COVID-19 to test the hypothesis on association *vs* causation, and gaps in the current evidence and propose an area of future research.

Key Words: SARS-CoV-2; Preeclampsia; Hypertension; Pregnancy-induced; Liver dysfunction; Pregnancy-induced

Core Tip: Observational studies showed an increased prevalence of preeclampsia and hemolysis, elevated liver enzymes and low platelet (HELLP) syndrome in pregnant women with coronavirus disease 2019 (COVID-19). Despite a possible pathophysiology linkage between COVID-19 and HELLP syndrome, the evidence on temporality to prove a causal association between infection with severe acute respiratory syndrome coronavirus 2 and HELLP syndrome is lacking.

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INTRODUCTION

With immense knowledge on the pathogenesis of coronavirus disease 2019 (COVID-19), the viral-host immune interaction plays a critical role in multi-system presentation of the disease. Most of the patients, infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), develop a non-severe illness. However, those patients with specific comorbidities are predisposed to advanced stages of severe COVID-19 infection. Some of the prevalently-reported comorbidities are as follows; age above 75 years, male gender, pre-existing cardiovascular disease, chronic lung, kidney or liver disease, sickle cell disease, diabetes, active cancer, severe obesity and pregnancy[1,2]. The risk factors that aggravate the development of severe COVID-19 among pregnant women include obesity, smoking history, pre-eclampsia and diabetes mellitus[3]. Though pregnancy, per se, does not increase the susceptibility to SARS-CoV-2 infection, pregnant women are highly prone to developing severe illnesses with SARS-CoV-2 infection compared to non-pregnant women. Further, they are also associated with adverse pregnancy and perinatal outcomes[4].

Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP) syndrome is an uncommon yet deadly complication that is associated with severe pre-eclampsia. Early diagnosis and termination of pregnancy only have been proved to be effective in treating HELLP syndrome[5]. A meta-analysis, conducted recently, inferred that COVID-19 infected women recorded high levels of pre-eclampsia and HELLP syndrome odds[6]. However, abnormal liver enzymes, thrombocytopenia and hemolysis are not only associated with HELLP syndrome, but are observed in many of the critically-ill patients, as a component of multi-organ dysfunction. This phenomenon occurs especially in case of certain infectious diseases and other pregnancy-related liver disorders, for instance, acute fatty liver of pregnancy[7]. Substantial evidence infers that some of the viral infections, for instance SARS-CoV-2, tend to mimic HELLP syndrome among women during pregnancy[8,9].

Hence, the overlapping laboratory features of SARS-CoV-2 infection and HELLP syndrome may increase the possibilities of misdiagnosis than a causal association. The current review discusses about the pathogenetic linkage between COVID-19 and HELLP syndrome, reviews the evidences available on association or causation between the variables and proposes novel suggestions for future research.

PATHOGENESIS OF PRE-ECLAMPSIA AND HELLP SYNDROME

Pre-eclampsia is a multi-system disorder characterized by *de novo* hypertension that occurs after 20 wk of gestation. Recently, the International Society for the Study of Hypertension in Pregnancy provided a new definition for pre-eclampsia as given herewith; new onset of hypertension (systolic > 140 mmHg and diastolic > 90 mmHg) accompanied by at least one feature as listed below and is developed either at or after 20 wk of gestation: (1) Proteinuria; (2) Maternal organ dysfunction (like liver, kidney, neurological and haematological); and (3) Evidence of uteroplacental dysfunctions like fetal growth restriction or abnormal Doppler waveform findings of uteroplacental blood flow or stillbirth[10].

The exact pathogenesis of pre-eclampsia remains uncertain. However, the termination of pregnancy by removing the placenta seems to be an effective therapeutic measure. This method confirms the importance of placenta in the pathophysiology of pre-eclampsia. Two pathogenic phenotypes are established such as early and late pre-eclampsia. The major cause of early pre-eclampsia is placental in nature whereas the late pre-eclampsia is a result of interactions that occur between placental senescence and other factors such as genetics, obesity and nutrition or environmental factors. The oxidative stress upon syncytiotrophoblast, a cell that covers the placental villi on the maternal side, plays a crucial role by getting released into maternal circulation factors like inflammatory cytokines, cell-free fetal DNA, exosomes, and anti-angiogenic agents. This results in the endothelial dysfunction and hypertensive syndrome[11].

Oxidative stress occurs as a result of either uteroplacental hypoperfusion from the defective remodelling of uterine spiral arteries (*i.e.*, early pre-eclampsia) or due to a mismatch between supply and demand in maternal perfusion and placental or foetus requirements (*i.e.*, late pre-eclampsia). Placental stress results in the dysfunction of vascular endothelium which in turn releases the placental factors that cause systemic manifestations of pre-eclampsia. The pathways proposed earlier for the above discussed phenomenon include an increased release of pro-inflammatory cytokines, cell-free fetal DNA, p38 Mitogen-Activated Protein Kinase (MAPK), placental apoptotic debris, soluble receptor for Vascular Endothelial Growth Factor, and soluble fms like tyrosine kinase (sFlt-1)/Placental Growth Factor (PlGF) ratio (Figure 1)[11,12].

The role played by Renin-Angiotensin-Aldosterone System (RAAS) in placenta homeostasis is crucial since it regulates the proliferation of trophoblasts, angiogenesis and blood flow. When RASS is not regulated, it creates an imbalance of vasoactive peptides due to high production of angiotensin II (ATII) and low vasodilatory angiotensin 1-7. ATII is a pro-inflammatory, pro-thrombotic element that induces vascular constriction, endothelial injury and vascular smooth cell proliferation which altogether contribute to pre-eclampsia[13]. Recent evidence suggests that ATII actions are mediated through the MAPK pathway. MAPK is a cellular signaling pathway existing in three forms, p38 MAPK, extracellular signal-regulated kinase, and Janus kinase. p38 MAPK critical component in immune functions as well as stress response pathways, mediates the cellular response to pathogenic microbes, pro-inflammatory cytokines and environmental stress (oxidate stress). p38 MAPK can be stimulated by intrauterine oxidate stress, with exact function unknown. Available evidence supports p38 MAPK is linked to normal embryonic development and maintaining parturition, and premature activation, or overexpression may lead to adverse perinatal and pregnancy outcomes[14]. The upregulated p38 MAPK pathway is linked with increased pro-inflammatory cytokines like NF-κB, Tumour Necrosis Factor (TNF)-α, interleukin (IL)-6 and IL-1β, and COX-2. The activation of NF-κB with p38 MAPK overexpression is found in various tissues, but in uterine tissue, its role is unclear. On the other hand, Angiotensin 1-7 is vasodilatory, attenuate this inflammation, atrophy, and fibrosis by simulating the Mas receptor. Hence, the dysregulation of RASS and high ATII levels lead to uninhibited feedback loop to p38 MAPK pathway which in turn causes untamed inflammation observed in pre-eclampsia[15,16].

The association between pre-eclampsia and HELLP syndrome is unclear. According to a few experts, HELLP syndrome is nothing but an extended manifestation of severe pre-eclampsia. However, a few others argue that HELLP syndrome is an independent entity since it exists without the classical features of pre-eclampsia like proteinuria and oedema. A few resemblances exist between the pathogenesis of pre-eclampsia and HELLP syndrome such as endothelial dysfunction, platelet aggregation and consumption, vasospasm, and end-organ ischemia. However, immune dysregulation with maternal immunological intolerance to fetal tissues is considered as a prominent pathway in HELLP syndrome. This immunological maladaptation has been proved in literature *via* the high levels of fetal mRNA and HLA-DR in the blood of women with HELLP syndrome, who was compared with women with pre-eclampsia[16,17]. One of the recent studies demonstrated that those patients with HELLP syndrome, had a high titer of agonist antibodies to Type I ATII receptor (AT1r-AA), when compared with patients with pre-eclampsia. The agonist antibodies can simulate the ATII effect upon the receptor[18].

Women with HELLP syndrome possess high levels of other types of anti-angiogenesis factors such as endoglin and Fas ligand than the women with pre-eclampsia. These two factors are responsible for vascular endothelial injury and intense inflammation in HELLP syndrome. The role played by p38 MAPK pathway, in the pathogenesis of HELLP syndrome, is hypothesized to be an angiogenic response for environmental hypoxia. The elevated serum levels of p38 MAPK increase the serum vascular permeability and it has the potential to aggravate edema in different tissues including the brain. A recent study that compared the serum levels of p38 MAPK among patients with HELLP syndrome and pre-eclampsia found that the serum levels were significantly higher in HELLP syndrome patients than their counterpart. The authors also recommended to use serum p38 MAPK in the diagnosis of HELLP syndrome[19]. As per the literature, patients with HELLP syndrome exhibit high serum levels of p38 MAPK and low expression in placental p38 MAPK[20,21]. The future researchers must explore this relationship which may shed more insights about the role played by p38 MAPK in the pathophysiology of HELLP syndrome. Furthermore, the activation of immune complexes, $C_{5b\text{-}9}$complement pathway, anaphylatoxins like C3a and C5a and the release of inflammatory cytokines, TNF-α and active von Willebrand factor from leucocytes, macrophages and platelets also cause endothelial injury. In turn, endothelial injury contributes to multiple activities such as hemolysis, platelet aggregation and

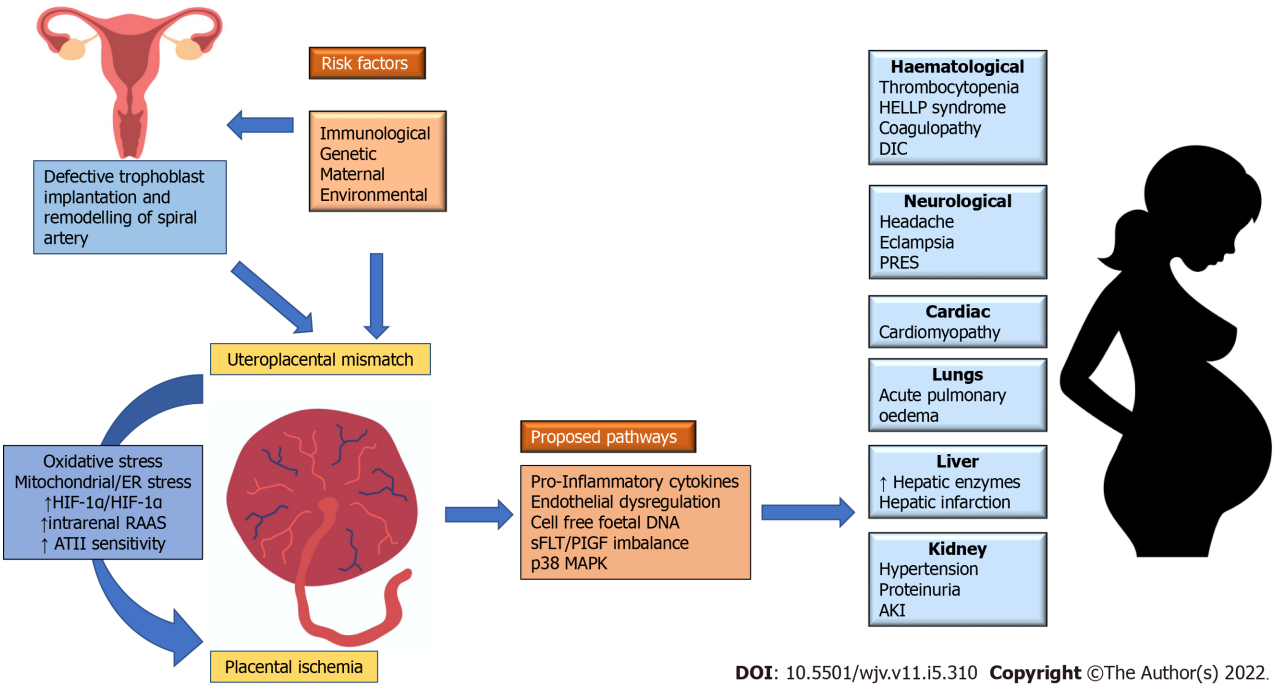

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Figure 1 Pathogenesis of hemolysis, elevated liver enzymes and low platelet syndrome. Placenta ischemia is central mechanism which is suspected to play a central role in hemolysis, elevated liver enzymes and low platelet (HELLP) syndrome. Abnormal trophoblast implantation and remodelling of uterine arteries along with genetic, environmental, nutritional, or maternal risk factors cause uteroplacental perfusion mismatch. Various pathways proposed for systemic manifestations of HELLP syndrome include, releases of inflammatory cytokines, endothelial dysfunction, release of cell-free fetal DNA, imbalance of soluble fms-like tyrosine kinase to placental growth factor ratio (sFLT/PIGF ratio). HELLP: Hemolysis, elevated liver enzymes and low platelet; ATII: Angiotensin II; HIF: Hypoxia inducible factor 1 alpha; RAAS: Renin angiotensin aldosterone system; sFlt/PlGF: Soluble fms-like tyrosine kinase and platelet growth factor ratio; ↑: Increased.

consumption (causing thrombocytopenia), intraluminal fibrin deposition, vasospasm and end-organ ischemia (causing hepatitis) that are generally observed in HELLP syndrome[21].

Conventional pre-eclampsia screening includes a periodic assessment and an early detection of hypertension and proteinuria. But, the precision of pre-eclampsia screening has increased tremendously, thanks to the measurement of circulating biomarkers and Doppler assessment of uteroplacental circulation. sFlt-1/PlGF ratio is a potential and a highly-accurate marker that can be used in the prediction of pre-eclampsia and fetal growth restriction[22]. In the prediction of early pre-eclampsia and the complications associated with it, a combination of multiple factors such as demographic risk factors with periodic blood pressure measurement, doppler assessment of uterine artery and the measurements of biomarkers is found to be highly accurate[23].

PATHOGENESIS OF COVID-19

The internalization of SARS-CoV-2, within the host cell, occurs by binding the S-spike protein of the virus with Angiotensin-Converting-Enzyme 2 (ACE2) present on the cell surface and is supplemented by Transmembrane Serine Protease 2 (TMPRSS2) on the host cell. Though ACE2 is found in multiple tissues, it is predominantly expressed in lung and heart tissues. This phenomenon may explain the high incidence of acute respiratory distress syndrome and myocarditis among patients with COVID-19 and the primary cause behind the high mortality rate. ACE2 is an integral part of RAAS and is directly associated in the conversion of ATII to Angiotensin 1-7. Like SARS-CoV, when SARS-CoV-2 interacts with ACE2 receptor, the receptor gets downregulated, thus potentiating RAAS and ATII. All three MAPK pathways are involved in the pathogenesis of COVID-19. The interaction between SARS-CoV-2 and ACE2, like many other viruses, is associated with upregulation of p38 MAPK through the interaction with ACE2 receptors and its direct activation[16,24]. The upregulated ATII through its effect on ATII Type 1 receptor causes an intense vasoconstriction and inflammation. As discussed earlier, the effect of ATII in heart and lung tissues are mediated by p38 MAPK pathway. The crosstalk between p38 MAPK and NF-κB is also found to be involved in the pathophysiology of COVID-19. SARS-CoV and SARS-CoV-2 infection activates p38 MAPK pathway and induces phosphorylation of various down-stream proteins involved in the transcription of various inflammatory cytokines. The upregulation of p38 MAPK is linked with excessive vasoconstriction, production of pro-inflammatory cytokines such as IL6, TNF-α and IL-1β. Hence, an unrestrained p38 MAPK results in hyperinflammation, vasoconstriction

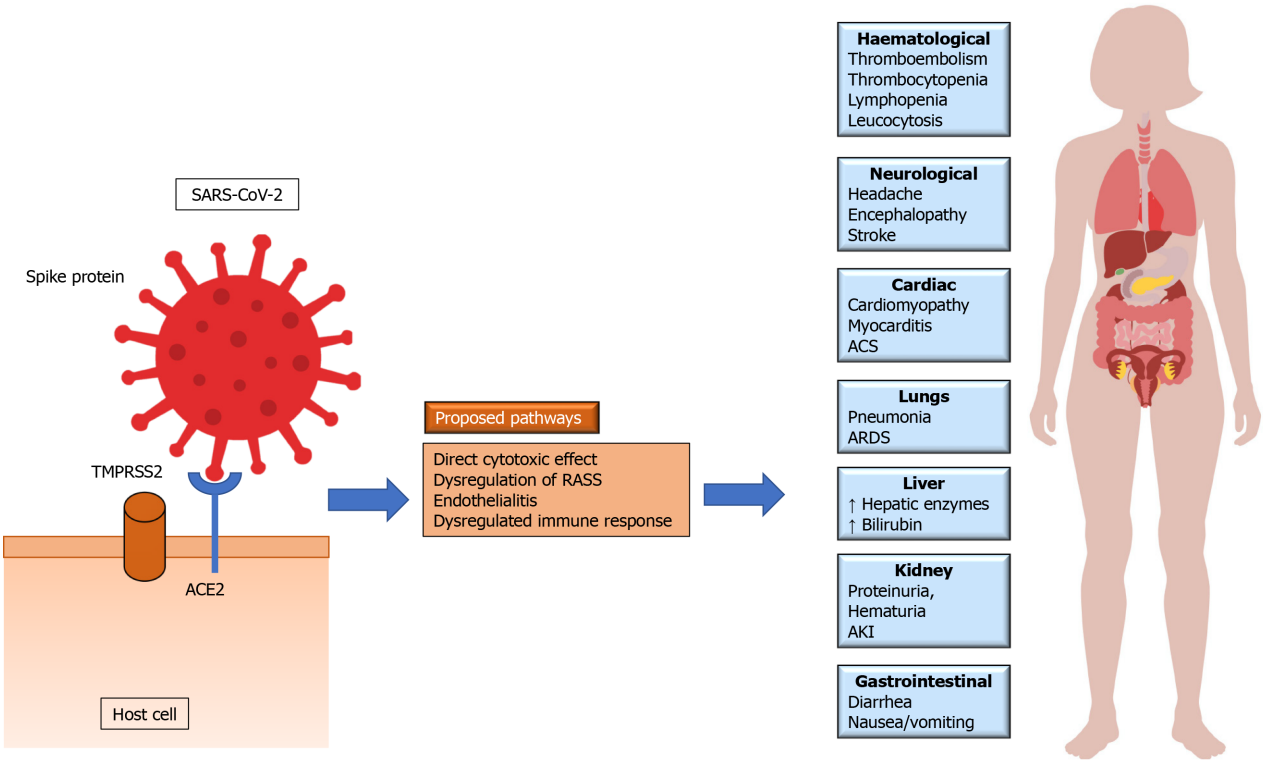

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Figure 2 Pathogenesis of coronavirus disease 2019. Severe acute respiratory syndrome coronavirus 2 entry into the host cell is mediated through its binding with angiotensin converting enzyme 2 receptor and transmembrane serine protease 2 enzyme. The pathogenetic pathways include direct cytotoxicity, endothelialitis, (endothelial damage), dysregulated host-immune response and renin-angiotensin aldosterone system. Respiratory system is the primary target organ, but other systems are involved either with direct invasion or in response of systemic dysregulated immune response. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ACE2: Angiotensin converting enzyme 2; TMPRSS2: Transmembrane serine protease 2; RAAS: Renin angiotensin aldosterone system; ACS: Acute coronary syndrome; AKI: Acute kidney injury.

and thrombosis, a hallmark of COVID-19 (Figure 2)[16]. Recently, various agents like emetine, chelerythrine and papaverine regulating the p38 MAPK signaling pathway are found to have therapeutic potential in the management of COVID-19[25-27].

The role played by virus-host immune interplays is crucial in the pathogenesis of COVID-19. Various pro-inflammatory cytokines like IL-6, IL-10, TNF-α, granulocyte-colony stimulating factors and monocyte chemoattract protein 1 mediate lungs and other systemic manifestations of SARS-CoV-2 infection. Though respiratory system is the primary target site of SARS-CoV-2 infection, COVID-19 can be characterized as a multi-system disease that affects heart, kidneys, brain, liver, gastrointestinal and haematological systems and skin (Figure 2)[28].

COVID-19 patients generally exhibit different biochemical manifestations of pre-eclampsia and HELLP syndrome such as thrombocytopenia, raised liver enzymes, proteinuria, coagulopathy, acute kidney injury, and increased lactate dehydrogenase[8,29]. Mild thrombocytopenia (the count of platelets stands at 100-150 × 10^9/L) is observed among 20%-36% patients with COVID-19 whereas severe thrombocytopenia (< 50 × 10^9/L) is uncommon[30].

EVIDENCE ON COVID-19 AND HELLP SYNDROME

A total of 11 studies was found by the authors when PubMed database was mined using the following keywords; "COVID-19" OR "SARS-CoV-2" AND "HELLP syndrome" between 01st January 2020 to 30th July 2022. When a broader keyword *i.e.*, "HELLP syndrome" was used within the same period, a total of 361 studies was found. Out of the total studies filtered, 18 studies were finalized and critically analyzed after excluding non-COVID-19 studies and non-English literature (Table 1)[6,31-47].

Inference from the evidence

Out of the 18 studies considered for final analysis, 13 were case reports or series in which 23 patients were included[31-38,40,42,44,45,47]. Maternal and fetal mortality rates were 8.6% (2) and 21.7% (5) respectively, with the development of severe COVID-19 in three patients. Mendoza *et al*[31] authored a case series in which five patients were suspected with pre-eclampsia and HELLP syndrome whereas

Table 1 Published studies on coronavirus disease 2019 and hemolysis, elevated liver enzymes, and low platelet count syndrome

Ref.	Type of study	Age (yr), gestation (wk)	Number of patients	Main results	Conclusion
Mendoza *et al* [31], 2020	Case series		5 cases with severe PE and/or HELLP syndrome	Out of 8 cases with severe COVID-19, 5 developed PE, proteinuria, elevated liver enzymes and hypertension. One developed platelet less than 150000. However, only one patient had PE based on the uterine artery pulsatility index, sFlt-1/PlGF ratio and LDH	PE like clinical features can develop with severe COVID-19. It can be distinguished from true by PE by sFlt-1/PlGF, LDH and UtAPI measurement
Braga *et al*[32], 2020	Case report	31, 31	1	Multiple pregnancy (dichorionic twins) with PE and partial HELLP syndrome. Moderate COVID-19 with HRCT showing ground-glassing. Underwent caesarean delivery for HELLP syndrome. One of the foetus died on day 16 due to intracranial hemorrhage. Both women and other foetus survived	There is a possible synergism between the pathophysiology of COVID-19 and PE/HELLP syndrome
Federici *et al* [33], 2020	Case report	33, 23.5	1	Multigravida, severe COVID-19 with ARDS requiring mechanical ventilation develop features of PE and HELLP syndrome. The serum sFlt-1/PlGF ratio was normal. Pregnancy continued and laboratory abnormalities resolved spontaneously with removal of mechanical ventilation after 10 d and discharge on day 19. Mother delivered spontaneously a live foetus at 33.4 wk	Severe COVID-19 can mimic PE and HELLP syndrome. Pregnancy can be continued in absence of complications with strict surveillance
Ahmed *et al* [34], 2020	Case report	26, 37	1	Family history of PE, atypical HELLP syndrome with acute kidney injury. Vaginal delivery with induction Postpartum day 3, developed abdominal hematoma requiring laparotomy and blood transfusions. Moderate respiratory symptoms with foetus and mother survived	Severe SARS-CoV-2 infection may be a risk factor for hypertensive disorders of pregnancy
Ronnje *et al* [35], 2020	Case report	26, 32.6	1	Underwent emergency caesarean. Both mother and foetus survived	Possible association of HELLP syndrome and COVID-19 was proposed
Coronado-Arroyo *et al* [36], 2021	Case series	Mean: 29 yr, gestation 31 wk	14 out of 20 patients with severe PE including 5 with HELLP syndrome	One out of 5 women was multipara. Two were asymptomatic and remaining had mild severity COVID-19. Four required caesarean delivery and two had still-birth. No maternal mortality	SARS-CoV-2 infection, can predisposes pregnant female to a greater severity of PE, irrespective of the severity of respiratory symptoms
Norooznezhad *et al*[37], 2021	Case report	24, 29	1	Primigravida, emergency caesarean for HELLP syndrome. Ostelmavir, lopinavir/ritonavir, chloroquine and 0.5 gm/d of methylprednisolone was used. Moderate respiratory symptoms. Both foetus and mother survived	Association between COVID-19 and HELLP syndrome cannot be concluded but deliver and methylprednisolone caused improvement in the condition
Farahani *et al* [38], 2021	Case report	28, 38	1	Multigravida, vaginal delivery for HELLP syndrome. Postpartum developed seizure, lopinavir/ritonavir and dexamethasone was used for treatment. Moderate respiratory symptoms. Both mother and foetus survived	COVID-19 in pregnant women can resemble PE and with possible CNS involvement
Aydın *et al*[39], 2021	Observational retrospective study	Case 1: 22, 31 Case 2: 25, 28	167 pregnant with COVID-19. 20 patients had PE and two (1.2%) had HELLP syndrome.	Case 1: Pregnancy with IVF. Need invasive mechanical ventilation, underwent caesarean delivery for HELLP syndrome and postpartum developed arterial thrombosis. Case 2: Vaginal delivery with preterm foetus. Both patients survived	No significant difference was observed in adverse pregnancy outcomes such as PE, preterm birth, and foetal growth restriction, gestational diabetes mellitus and HELLP syndrome according to the gestational age
Vaezi *et al*[40], 2021	Case series	36, 28	24 patients, 1 with HELLP syndrome	Delivery by caesarean section, performed for HELLP syndrome, preterm foetus admitted to NICU. Both mother and foetus survived	-
Jering *et al*[41], 2021	Retrospective cohort study		406 446 women hospitalized for childbirth. Among women with HELLP syndrome, 989 (0.2%) were without COVID-19 and 33	Unadjusted and adjusted OR for HELLP syndrome with COVID-19 was 2.10 (95%CI-1.48-2.97) and 1.96 (1.36-2.81), $P < 0.001$	In large US cohort of women admitted for childbirth during the pandemic, patients with COVID-19 had higher risk of in-hospital mortality, pre-eclampsia, VTE and HELLP syndrome

			(0.5%) with COVID-19		
Bhardwaj *et al* [42], 2022	Case report	33, 36	1	Underwent caesarean delivery. Both mother and foetus survived	COVID-19 and HELLP overlap and associations are puzzling to clinicians
Conde-Agudelo *et al* [6], 2022	Meta-analysis of observational studies		28 studies, 790954 patients including One study for HELLP syndrome	SARS-CoV-2 infection during pregnancy was associated with significant increase in the odd ratio of PE (1.58, 95%CI- 1.39-1.8), severe PE (1.76, 95%CI 1.18-2.63), eclampsia (1.97, 95%CI 1.01-3.84) and HELLP syndrome (2.76, 95%CI 1.48-2.97)	SARS-CoV-2 infection during pregnancy is associated with significantly higher odds of PE
Madaan *et al* [43], 2022	Case series	Case 1: 32, 34 Case 2: 29, 37 Case 3: 26, 39	3	All three cases had HELLP syndrome and ground glassing opacities on HRCT with RT-PCR positive for SARS-COV-2. Case 1: Severe COVID-19, mother survived, baby still born by caesarean section. Case 2: Patient developed eclampsia and required mechanical ventilation, died on day -8, baby delivered vaginally Case 3: Patient survived and discharged day 15, baby delivered alive by caesarean section due to transverse lie	Authors proposed a synergism in the pathophysiology of COVID-19 and HELLP Syndrome. and combination of both can cause morbidity or mortality risk to fetus and the mother
Takahashi *et al* [44], 2022	Case report	27, 37	1	Underwent caesarean delivery for infection control measures. Postpartum HELLP syndrome. Both mother and foetus survived	Overlap of clinical features with COVID-19 and HELLP syndrome is plausible explanation
Guida *et al*[45], 2022	Nested case-control analysis	-	203 women with COVID-19, including 21 with PE and 2 HELLP syndrome	There was no difference in the rate of PE and HELLP syndrome in women with or without COVID-19. However, imminent eclampsia was more frequent complication and overall maternal perinatal outcomes were worse with patients with PE and COVID-19	Prevalence of PE among women with COVID-19 was around 10%. Chronic hypertension and obesity were more likely associated with PE. High caesarean rate and NICU admissions due to prematurity in women with COVID-19
Snelgrove *et al* [46], 2022	Retrospective cohort study	-	157779 patients during the pandemic compared to 563859 patients delivered between March 2015-september 2019 (historical group)	There was no difference in the rate of PE/HELLP (879, 0.6%) syndrome and severe maternal morbidity (SMM) between the pandemic and historical group (3119, 0.6%). No difference between primiparous and multiparous on severe maternal morbidity and risk of PE/HELLP syndrome. Maternal age, rurality, preexisting comorbidities and use of artificial reproduction therapy were associated with increased risk of PE/HELLP syndrome	Changes in obstetrical care during the pandemic have not increased the risk the PE/HELLP syndrome and adverse maternal outcomes
Arslan[47], 2022	Case report	30, 32	1	Mutigravida pregnancy, emergency Caeserian delivery. Foetus tested positive for SARS-CoV-2 and died 5 d after delivery. Mother had severe COVID-19, required invasive mechanical ventilation and died, 10 d after delivery	Severe COVID-19 as etiological causation of HELLP syndrome is presumptive

COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; HELLP: Hemolysis, elevated liver enzymes, low platelet count; PE: Pre-eclampsia; LDH: Lactate dehydrogenase; HRCT: High-resolution computed tomography; OR: Odds ratio; CI: Confidence intervals; ARDS: Acute respiratory distress syndrome; NICU: Neonatal intensive care unit; IVF: *In vitro* fertilization.

only one had actual pre-eclampsia features based on the Doppler assessment of uterine artery pulsatility index, sFlt-1/PlGF ratio and lactate dehydrogenase. However, another case report failed to find the elevated sFlt-1/PlGF ratio in a patient who exhibited the biochemical features of HELLP syndrome. The patient was managed conservatively and her biochemical abnormalities were resolved spontaneously while the patient achieved a good perinatal outcome[33]. Most of the studies confirmed the existence of a linkage between HELLP syndrome and COVID-19. However, the inference from individual cases without a case-control remains highly biased. Two retrospective cohort studies, in which women with and without COVID-19 were compared, reported conflicting results on the increased incidence of HELLP syndrome with COVID-19[41,46]. In a population-based study authored by Snelgrove JW *et al* [46], no increased incidence of pre-eclampsia and HELLP syndrome was observed among women infected with SARS-CoV-2 compared to historical controls. On the other hand, in a large registry developed upon hospitalized women for childbirth in the United States, highly-adjusted odds of pre-eclampsia [1.21, 95% confidence interval (CI) 1.11-1.33] and HELLP syndrome (1.96, 95%CI 1.36-2.81) were found in pregnant women with COVID-19 compared to those without COVID-19, during the same duration[41]. A recent meta-analysis, in which 28 studies were included which covered a total of 790954

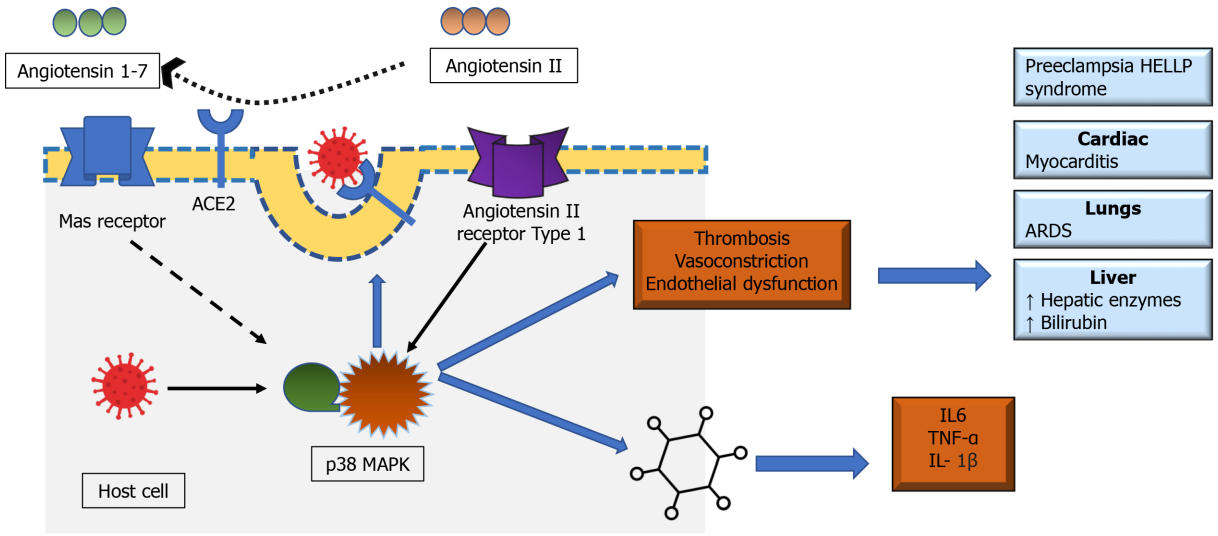

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Figure 3 Pathophysiological linkage between coronavirus disease 2019 and Hemolysis, elevated liver enzymes and low platelets syndrome. The binding of severe acute respiratory syndrome coronavirus 2 to angiotensin converting enzyme 2 (ACE2) allows its entry to host cells and, subsequently, downregulation. ACE2 also converts angiotensin II (ATII) to angiotensin 1-7. The downregulation of ACE2 increases the concentration of AT II, which causes activation of the p38 mitogen activated protein kinase (MAPK) pathway. p38 MAPK stimulates the production of inflammatory cytokines, platelet aggregation and thrombosis. Renin-angiotensin-aldosterone system and ATII are also involved in the pathogenesis of pre-eclampsia and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. Serum levels of p38 MAPK are elevated in the HELLP syndrome. ACE2: Angiotensin converting enzyme 2; IL: Interleukin; TNF: Tumour necrosis factor; HELLP: Hemolysis, elevated liver enzymes, and low platelet count;ARDS: Acute respiratory distress syndrome. Solid black arrow- stimulation (positive feedback), Dashed black arrow- inhibition (negative feedback), blue arrow: Effects of p38 MAPK overexpression.

pregnant women, reported a significantly-high risk of pre-eclampsia (pooled odd ratio (OR) 1.62, 95%CI 1.45-1.82, $P < 0.00001$, 26 studies) with SARS-CoV-2 infection compared to non-infected individuals[6]. A single study outcomes from Jering *et al*[41], reported highly-unadjusted odds of HELLP syndrome (2.10, 95%CI 1.48-2.97), in pregnant women with SARS-CoV-2 infection.

Pathophysiology linkage between COVID-19 and HELLP syndrome

Recent evidences confirm the worst clinical outcomes for pregnant women with COVID-19 in terms of high incidence of pre-eclampsia, preterm birth and the need for caesarean delivery[48,49].

ACE2 receptors and TMPRSS2, which are required for the entry of SARS-CoV-2 into human cells, are expressed in placental components including villous cytotrophoblasts, syncytiotrophoblasts and extravillous trophoblasts[50]. This makes the placenta, predisposed to SARS-CoV-2 infection. When S-spike protein of SARS-CoV-2 binds with ACE2 receptor, it results in the downregulation of the receptor, dysfunction of RAAS and triggering of local placental inflammation. Further, ATII type I -receptor and sFlt-1 are also heavily produced from the infected placenta. The increased serum levels of AT1r-AA, found in cases of SARS-CoV-2 infection, can be observed in pre-eclampsia and HELLP syndrome too[7].

Some evidence supports the presence of high levels of placental ACE2 in women with COVID-19. This may explain the increased association between pre-eclampsia and preterm birth[51]. Another study showed that ACE2 receptors and the expression of protease are dependent upon each other during gestational age. The increased levels of expression is prevalent during the first trimester compared to the rest of the trimesters in pregnancy[52]. In a molecular linkage study by Beys-da-Silva *et al*[53], SARS-CoV-2 infection was found to interact with multiple pathways that are involved in pre-eclampsia and HELLP syndrome pathogenesis like upregulation of sFlt-1 and endoglin, angiogenesis, the balance between vasoconstrictive peptides and nitric oxide modulators, hypoxia and inflammation and prothrombotic-related molecules.

There exist a few similarities in the pathophysiology of COVID-19 and HELLP syndrome. The interaction between ATII and p38 MAPK is a plausible linkage among COVID-19, preeclampsia and HELLP (Figure 3)[16]. The upregulation of p38 MAPK pathway is also linked with endothelial injury which in turn causes platelet aggregation and arterial thrombosis. This scenario reveals the systemic manifestations of COVID-19 like thrombocytopenia and raised liver enzymes[54]. However, it is still unclear whether the above-discussed biochemical abnormalities are manifestations of COVID-19 or HELLP syndrome. There is a lack of temporal studies in this domain that can establish a causal relationship between COVID-19 and HELLP syndrome. The studies conducted earlier that can prove that exposure occurred before the outcome (HELLP syndrome) establishing the temporality are missing. So, it is crucial to identify the causal association since immediate termination of the pregnancy is the only successful treatment used for HELLP syndrome, a predominant placental pathology, so far.

However, an expectant and a watchful continuation of pregnancy with better perinatal outcomes may be considered in selected cases of COVID-19[33].

Future studies should explore this linkage using the principle of temporality and circulatory biomarkers like serum p38 MAPK, sFlt-1/PIGF ratio and/or doppler assessment of uteroplacental hypoxia to identify any causal association between COVID-19 and HELLP syndrome.

CONCLUSION

There exists an association among SARS-CoV-2 infection during pregnancy, pre-eclampsia and HELLP syndrome. Evidence accepts the plausible overlap in the pathogenesis of COVID-19 and HELLP syndrome through ACE2 and RAAS dysregulation that involve ATII and p38 MAPK pathways. However, no prospective studies are available based on screening biomarkers and temporality to prove the causal relationship in this domain. Future studies should establish a temporal relationship between SARS-CoV-2 infection and the development of HELLP syndrome including circulatory biomarkers and tissue or radiological documentation of uteroplacental insufficiency.

FOOTNOTES

Author contributions: Nasa P conceptualized and designed the article; Nasa P, Juneja D, Jain R, and Nasa R performed acquisition of data, analysis and interpretation of data, and drafted the article; Juneja D and Jain R revised the article; all authors have read and approve the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Manifestations of COVID-19 infection in children with malignancy: A single-center experience in Jordan

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Abstract

BACKGROUND

The coronavirus disease 2019 (COVID-19) has been the cause of a global health crisis since the end of 2019. All countries are following the guidelines and recommendations released by the World Health Organization to decrease the spread of the disease. Children account for only 3%-5% of COVID-19 cases. Few data are available regarding the clinical course, disease severity, and mode of treatment in children with malignancy and COVID-19.

AIM

To evaluate the treatment plan and outcome of children with malignancy who contracted COVID-19.

METHODS

A retrospective study of the medical files of patients with malignancy who contracted COVID-19 between July 2020 and June 2021 was performed. The following data were reviewed for all patients: primary disease, laboratory data, admission ward, clinical status upon admission, disease course, treatment plan, and outcome. Eligible patients were those with malignancy who tested positive for COVID-19 by reverse transcription polymerase chain reaction.

RESULTS

A total of 40 patients who had malignancy contracted COVID-19 from July 1, 2020 to June 1, 2021. Their primary diseases were as follows: 34 patients (85%) had hematological malignancies (30 had acute lymphoblastic leukemia, 2 had acute myeloblastic leukemia, and 2 had Hodgkin lymphoma), whereas 6 patients (15%) had solid tumors (2 had neuroblastoma, 2 had rhabdomyosarcoma, and 2 had central nervous system tumors). Twelve patients (30%) did not need hospitalization and underwent home isolation only, whereas twenty-eight patients (70%) required hospitalization (26 patients were admitted in the COVID-19 ward and 2 were admitted in the pediatric intensive care unit).

CONCLUSION

COVID-19 with malignancy in the pediatric age group has a benign course and does not increase the risk of having severe infection compared to other children.

Key Words: COVID-19; Malignancy; Disease severity score; Children; Jordan

Core Tip: Coronavirus disease 2019 (COVID-19) has caused a global health crisis since the end of 2019. This retrospective study describes the manifestation of COVID-19 in our oncology patients who were treated at Queen Rania Children's Hospital between July 2021 and June 2021, focusing on the initial presentation, clinical course and management plan and comparing these results with the international data worldwide to determine the optimal way to care for oncology patients during the COVID-19 crisis.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) has caused a global health crisis since late 2019[1]. As there were more than 2 million cases of COVID-19 worldwide, the World Health Organization (WHO) declared COVID-19 a pandemic in March 11, 2020[2,3]. By June 1, 2021, a total of 170448610 cases of COVID-19, including 3663570 deaths, had been reported worldwide. In Jordan, a total of 737284 cases of COVID-19 and 9472 deaths had been reported by June 1, 2021[4].

The incubation period of the virus is between 2 and 14 d with an average of 5 d[5,6].The main routes of virus transmission are droplets and close contact[7]. COVID-19 affects all age groups; however, the pediatric population accounts for only 3%-5% of total cases[8]. Oncology patients generally shed respiratory viruses for longer than immunocompetent people and this is mostly true for COVID-19 as well[9]. In children, most cases of COVID-19 are asymptomatic, and studies have revealed that children have less severe symptoms compared to adults[10-12]. However, some patients develop life-threatening complications such as acute respiratory distress syndrome, thrombosis, and multiorgan failure[13-15]. Children with malignancy are frequently immunocompromised because of the therapy they receive, putting them at high risk for severe infections, which are the major cause of mortality in these patients [16-18]. However, there is growing evidence that the mortality rate in pediatric cancer patients with COVID-19 is extremely low[19,20]. The international pediatric oncology community acted quickly in response to the COVID-19 pandemic and made many recommendations to decrease the risk of infection in pediatric cancer patients[21,22].

This study analyzed and evaluated the treatment plans and outcomes of children with malignancy who contracted COVID-19 in Queen Rania Children's Hospital (QRCH; Amman, Jordan), and compared our results with the international results.

MATERIALS AND METHODS

This retrospective study was approved by the ethics committee of the Jordanian Medical Services. The medical records were reviewed of patients at QRCH who had malignancy and tested positive for

COVID-19 between July 2020 and June 2021.

All pediatric oncology patients under 14-years-old who had received anticancer treatment and were diagnosed with COVID-19 by polymerase chain reaction (PCR) nasopharyngeal swab were eligible for this study. The primary endpoint was death, discharge from the hospital, or end of active care for COVID-19 for patients who needed further treatment of their primary disease in the hospital, or 14 d after initial diagnosis of COVID-19 in patients who did not need hospitalization.

Data were collected on primary disease, age, white blood cell count, absolute neutrophil count, lymphocyte count, place of admission, clinical status on admission, mode of treatment, radiological findings, and outcome.

PCR for COVID-19 was done for symptomatic patients, patients who had close contact with a confirmed case of COVID-19, and before any admission to the hospital, as our hospital guidelines recommend PCR for COVID-19 for any patient who needs admission, whatever the cause of admission.

Detailed clinical histories including primary disease, status of the disease, comorbidities, and detailed chemotherapy history were taken from all of our patients. We also performed full physical examinations, investigations, and chest X-rays, and if indicated, a high-resolution chest computed tomography (CT) scan was performed. After obtaining all of these data, researchers assigned patients a "disease severity score" categorizing the severity of their disease into the following categories: asymptomatic, mild, moderate, and severe disease (as described in Table 1).

For patients who needed admission, they were admitted in an isolation room in a specialized ward in the hospital (COVID-19 ward). When they met the criteria for discharge, they were discharged home with precautions and remained in home isolation until 14 d from the day of their COVID-19 diagnosis.

COVID-19 recovery was defined by the disappearance of the clinical symptoms in symptomatic patients or 14 d from the diagnosis of COVID-19 in asymptomatic patients.

RESULTS

About 400 oncology patients were seen in QRCH during the study period between July 2020 and June 2021. A total of 40 oncology patients tested positive for COVID-19 during the same period. Twenty-four patients (60%) were males and sixteen (40%) were females. Twenty-eight patients were below the age of 6 years; they accounted for the majority of our patients in this study (70%). Five patients (12.5%) were between the ages of 6-years-old and 12-years-old whereas seven patients (17.5%) were between the ages of 12-years-old and 14-years-old. Hematological malignancies were the predominant primary disease in this study, as they accounted for about (85%) of the cases. The patients' characteristics are summarized in Table 2.

Upon presentation, full investigations were done for the patients in addition to chest X-rays. A high-resolution chest CT scan was done if there were any chest X-ray abnormalities or moderate to severe respiratory symptoms. Only 10 patients required a chest CT scan. Laboratory and radiological findings are summarized in Table 3.

According to the disease severity score, 10 patients (25%) were asymptomatic, 20 patients (50%) had mild symptoms, and 8 patients (20%) had moderate symptoms whereas just 2 patients (5%) had severe symptoms. Of these patients, 12 (30%) were kept in home isolation whereas 28 patients were treated in the hospital, where 26 patients (65%) were treated in the COVID-19 ward and 2 patients (5%) were treated in the pediatric intensive care unit (PICU). The solid tumor patients were asymptomatic or had mild symptoms, whereas the moderate and severe symptoms were found only in patients with hematological malignancies; however, some patients who had hematological malignancies were asymptomatic or had mild symptoms. The hospital management was case by case and the treatment plan comprised intravenous (IV) antibiotics, azithromycin, dexamethasone, oxygen support, IV immunoglobulin (IVIG) for patients with hypogammaglobulinemia, and vitamins. Details about the clinical course of COVID-19 are summarized in Table 4.

DISCUSSION

Few data are available worldwide regarding the effect of COVID-19 on pediatric oncology patients; however, multiple studies have been published on the COVID-19 clinical course in these patients. In our center, 10% of our oncology patients contracted COVID-19 between July 2020 and June 2021. This percentage of COVID-19-infected oncology patients was higher than that reported in the general pediatric population in Jordan in the same period, which was about 5%-6%[4]. This increase in the percentage of COVID-19 among our oncology patients can be explained by the frequent testing of these patients for COVID-19 even if they were asymptomatic, as they require recurrent admissions to the hospital for different reasons including chemotherapy, fever, blood, and platelet transfusions and surgeries. Screening for COVID-19 was done before each admission as part of our hospital protocol regarding admissions during the era of COVID-19. However, this was not the case for healthy pediatric patients. Screening for COVID-19 was not done for healthy children who did not need hospital

Table 1 Coronavirus disease 2019 disease severity score

Disease severity	Definition
Asymptomatic	No symptoms at all during the course of COVID-19
Mild disease	Symptoms that did not require hospital admission; if hospitalization was required, the indication was for a cause other than the management of COVID-19 associated symptoms or signs
Moderate disease	Symptoms that required inpatient management of COVID-19 associated symptoms, but without the need for PICU care
Severe disease	Symptoms that required PICU care for COVID-19 related signs and symptoms

COVID-19: Coronavirus disease 2019; PICU: Pediatric intensive care unit.

Table 2 Characteristics of pediatric oncology patients with coronavirus disease 2019

Patient characteristics	Number	Percentage (%)
Sex		
Male	24	60
Female	16	40
Age		
1-6 yr	28	70
6-12 yr	5	12.5
12-14 yr	7	17.5
Primary disease		
Acute lymphoblastic leukemia	30	75
Acute myeloid leukemia	2	5
Neuroblastoma	2	5
Rhabdomyosarcoma	2	5
CNS tumors	2	5
Hodgkin lymphoma	2	5

CNS: Central nervous system.

admission unless they were symptomatic or in close contact with a confirmed COVID-19 case.

The median age of our oncology patients at the time of COVID-19 diagnosis was 5 years (range between 1.5 years and 13.5 years). This is similar to what was reported by Millen *et al*[23] in a study done in the United Kingdom involving 54 patients under the age of 16 years with malignancy. The median age in our study was less than that reported by Al Odda *et al*[24] in a study done in al Sulaimani-Kurdisan involving 54 malignancy patients and by Dong *et al*[25] in a Chinese study involving 2143 patients with malignancy, as the median age for these two studies was 7 years. We also reported that the majority of our patients were less than 6 years (70%), followed by patients who were more than 12 years (17.5%), consistent with the study by Navaeian *et al*[26] that was conducted in Iran in 20 oncology patients.

In our study, 24 patients were males (60%) and 16 patients were females (40%). This male predominance was reported in a study done in our center about patients who underwent hematopoietic stem cell transplantation and had COVID-19 infection post-transplant; all of them were males[27]. Madhusoodhan *et al*[28] also reported male predominance in a multicenter retrospective study involving 578 pediatric oncology patients in the New York-New Jersey region; 70% of their patients were males.

The majority of our cases had hematological malignancies (85%); 30 patients (75%) had acute lymphocytic leukemia (ALL), 2 patients (5%) had acute myeloid leukemia, and 2 patients had Hodgkin lymphoma. Solid tumors accounted for a smaller percentage (20%) of the cases. Similar results were reported by most of the international studies done worldwide[10,20,29,30]. This predominance of hematological malignancies among oncology patients who had COVID-19 can be explained by the fact

Table 3 Laboratory and radiological details for coronavirus disease 2019 in our oncology patients

Parameters	Numbers	Percentage (%)
WBC count		
Leukopenia < 4000	16	40
Normal WBC count	20	50
Leukocytosis > 16000	4	10
Lymphocytes count		
Lymphopenia	23	57.5
Normal count	17	42.5
Lymphocytosis	0	0
Neutrophil count		
Severe neutropenia	10	25
Mild-Moderate neutropenia	10	25
Normal count	16	40
Neutrophilia	4	10
CRP titer		
Negative < 6	3	7.5
Positive 6	37	92.5
D-Dimer		
Positive	6	15
Negative	34	85
IgG level		
< 700 mg/dL	9	22.5
> 700 mg/dL	31	77.5
Chest X-ray findings		
Normal chest X-ray	18	45
Perihilar infiltrates	12	30
Bilateral patchy consolidation	10	25
High-resolution chest CT scan findings		
Bilateral infiltration > 25%	8	20
Bilateral infiltration 25%-50%	2	5
Bilateral infiltration > 50%	0	0

CRP: C-reactive protein; CT: Computed tomography; IgG: Immunoglobulin G; WBC: White blood cell.

that hematological malignancies are the most common malignancies in pediatric age groups, and they require longer duration of treatment, especially for ALL patients. Furthermore, the hematological malignancies themselves and the chemotherapy used for the treatment of these types of malignancies have a greater effect on T lymphocyte function compared to solid tumors[31,32].

Regarding our patients, fever was the most common presenting symptom, as 24 patients (60%) had a temperature higher than 37.8 axillary at the time of the COVID-19 test. All of these patients were admitted to the COVID-19 ward in our hospital and were treated with IV antibiotics, as bacterial infection cannot be ruled out and has to be covered by IV antibiotics, especially in neutropenic patients.

Most of the international studies also reported that fever was the most common presenting symptom of COVID-19 in oncology patients[33,34].

Most of our patients had mild symptoms (50%), whereas just 2 patients (5%) had severe symptoms. The moderate and severe symptoms were found exclusively in patients who had hematological malignancies, whereas the patients who had solid tumors were asymptomatic or had mild symptoms.

Table 4 Details of the clinical course of coronavirus disease 2019 in oncology patients

Parameters	Number	Percentage
Presenting symptoms		
Fever	24	60
Cough	15	37.5
Sore throat	3	7.5
Dyspnea	2	5
Diarrhea	2	5
Disease severity		
Asymptomatic	10	25
Mild disease	20	50
Moderate disease	8	20
Severe disease	2	5
Place of care		
Home isolation	12	30
COVID-19 ward	26	65
PICU	2	5
Treatment required		
No treatment	10	25
IV antibiotic	24	60
Azithromycin	30	75
Vitamins	30	75
Dexamethasone	26	65
Oxygen support	4	10
CPAP	2	5
IVIG	9	22.5

COVID-19: Coronavirus disease 2019; CPAP: Continuous positive airway pressure; IVIG: Intravenous immunoglobulin; PICU: Pediatric intensive care unit.

This can be explained by the fact that the hematological malignancies themselves and the chemotherapy used for the treatment of these types of malignancies have a greater effect on T lymphocyte function compared to solid tumors[31,32], in addition to the role of granulocyte-colony stimulating factor (G-CSF) administration after completing chemotherapy in solid tumor patients, which prevents the development of severe neutropenia.

Asymptomatic patients and patients with mild symptoms except fever were discharged home with instructions for strict home isolation and were followed by video and phone calls.

The patients with severe symptoms were treated in the PICU as they required the use of continuous positive airway pressure (CPAP) to maintain oxygen saturation of more than 94%. The primary disease for these 2 patients with severe symptoms was ALL. Both of them were in remission and in the consolidation phase of their treatment; however, these 2 patients had severe neutropenia at the time of COVID-19 infection. The treatment plan for these 2 patients was IVIG, dexamethasone, azithromycin, and IV antibiotics in addition to the CPAP, which was needed for 2 d for the first patient and 3 d for the second patient. Gradual improvement in clinical status was noticed for both of them and they were discharged home without any complications after about 2 wk of admission. As severe neutropenia might have played a major role in the development of severe symptoms of COVID-19 in these 2 patients, modifications of the chemotherapy doses for all of our patients in the hospital were made to prevent severe bone marrow suppression, especially severe neutropenia. Furthermore, we administered G-CSF at 48 h after finishing the chemotherapy protocol for non-hematological malignancies to perform bone marrow rescue.

Patients with moderate symptoms were admitted to the COVID-19 ward and they received dexamethasone and azithromycin. IV antibiotics were also given for patients with fever. IVIG was given

for patients with secondary hypogammaglobulinemia, which may have occurred due to chemotherapy; only 9 of our patients (22.5%) received IVIG.

These results are similar to what was reported by Millen *et al*[23], who reported that 6.6% of their oncology patients had severe symptoms of COVID-19. On the other hand, our results are higher than what was reported by Madhusoodhan *et al*[28], as they reported that only 17 of 578 oncology patients (3%) developed severe symptoms of COVID-19.

However, studies done on COVID-19 in the general pediatric population have shown similar rates of severe symptoms of COVID-19 among children who tested positive for COVID-19. Bellino *et al*[35] reported in a study done in Italy that 4.3% of patients who had COVID-19 developed severe symptoms. Meena *et al*[36] reported in their systematic review and meta-analysis that 4% of pediatric patients who had COVID-19 developed severe symptoms.

These similar results of severe symptoms of COVID-19 among oncology patients compared to the general pediatric population suggest that, even though the oncology patients have more risk factors for developing severe symptoms of COVID-19, children with malignancy who have COIVD-19 are not at greater risk of having severe symptoms of COVID-19.

None of our patients died or developed any of the chronic complications of COVID-19, including multisystem inflammatory syndrome in children, after recovering from the infection. These results may be explained by the role of chemotherapy-related immune suppression in the protection against the development of cytokine release storm[37]. The mortality rate in our study is comparable to the overall death rate reported by Verity *et al*[38], as the estimated rate in their study was 0.66% and decreased to 0.0016% in children under the age of 9 years.

For all of our patients who tested positive for COVID-19, chemotherapy was withheld for at least 10 d, even in asymptomatic patients. We did not notice any increase in the malignancy-related morbidity nor mortality due this delay of chemotherapy.

On the other hand, we did not notice an increase in the incidence of any malignancy groups during the COVID-19 era, which indicates that the virus is not an oncogenic virus, at least in the short term.

As there is a risk of exposure to COVID-19 in both the community and hospital settings, resulting in extreme anxiety in the families of patients with malignancies, standard precautions for basic and respiratory hygiene must be strictly applied to reduce the risk of transmission of COVID-19.

One limitation of this study was the small number of cases, as it included just one institution's experience in a short period of time. Another limitation was the short follow-up period of these patients, which prevented us from detecting the possible long-term complications.

CONCLUSION

Patients with malignancies are more likely to be infected with COVID-19, especially patients with hematological malignancies. However, these patients are not more likely to develop severe symptoms of COVID-19 compared to children in general. Furthermore, mortality and morbidity due to COVID-19 infection are not increased in patients with malignancies. Therefore, chemotherapy should be continued for patients with cancer during the era of COVID-19, provided that the WHO recommendations are strictly applied and that patients are not severely suppressed and have tested negative for COVID-19. However, the prevention of severe neutropenia by administering G-CSF as a bone marrow rescue is mandatory to prevent the moderate to severe symptoms of COVID-19 in malignancy patients.

ARTICLE HIGHLIGHTS

Research background

The coronavirus disease 2019 (COVID-19) has been the cause of a global health crisis since the end of 2019. All countries are following the guidelines and recommendations released by the World Health Organization to decrease the spread of the disease. Children account for only 3%-5% of cases of COVID-19. Few data are available regarding the clinical course, the severity of the disease, and mode of treatment in children with malignancy and COVID-19.

Research motivation

COVID-19 has caused a global crisis worldwide, with few data available on this new health crisis. Patients with comorbidities are more susceptible to COVID-19 complications, especially oncology patients who are receiving different modalities of treatment making them immunocompromised most of the time. We would like to share our experience in these patients to compare it with the published data worldwide.

Research objectives

The main objective of this study was to evaluate the outcome of oncology patients who contracted COVID-19, compare it with the results of the healthy population in the same age group, and compare the outcomes among different malignancy groups. Also we compared our patients' outcome with the international data published worldwide to share our experience and try to improve our management plan for these patients to provide the best care for them during this health crisis.

Research methods

A retrospective review of the medical files of patients who have malignancy and developed COVID-19 between July 2020 and June 2021 was performed. The following data were reviewed for all patients: primary disease, laboratory data, admission ward, clinical status upon admission, disease course, treatment plan, and outcome. Eligible patients were patients who had malignancy and tested positive for COVID-19 by reverse transcription polymerase chain reaction.

Research results

A total of 40 patients with malignancy who contracted COVID-19 from July 1, 2020 to June 1, 2021. Their primary diseases were as follows: 34 patients (85%) had hematological malignancies (30 of them had acute lymphoblastic leukemia, 2 had acute myeloblastic leukemia, and 2 had Hodgkin lymphoma), whereas 6 (15%) had solid tumors (2 had neuroblastoma, 2 had rhabdomyosarcoma, and 2 had central nervous system tumors). Twelve patients (30%) did not need hospitalization and underwent home isolation only, whereas 28 patients (70%) required hospitalization (26 patients were admitted in the COVID-19 ward and 2 patients were admitted to the pediatric intensive care unit).

Research conclusions

Children with malignancy who contracted COVID-19 have a benign course and do not have increased risk of severe infection compared to healthy children.

Research perspectives

The findings of this study will help us share our experience worldwide and give an idea of what is occurring in developing countries during this health crisis, especially in oncology patients who need special care.

FOOTNOTES

Author contributions: Qatawneh MA, Jazazi M, and Mutafa M substantially contributed to the conception and design of the work; Altarawneh M, Jazazi M, and Shorman A substantially contributed to the data collection; Alhazaimeh R, Shorman A, and Alsadah L substantially contributed to the acquisition, analysis, or interpretation of the data; Qatawneh MA, Alhazaimeh R, and Jarrah O contributed to drafting or revising the manuscript critically for important intellectual content; Qatawneh MA, Altarawneh M, and Mustafa M gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Effect of age on computed tomography findings: Specificity and sensitivity in coronavirus disease 2019 infection

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) is a pandemic caused by the severe acute respiratory syndrome coronavirus in 2019. Although the real-time reverse transcription PCR test for viral nucleic acids is the gold standard for COVID-19 diagnosis, computed tomography (CT) has grown in importance.

AIM

To evaluate the sensitivity and specificity of thoracic CT findings of COVID-19 pneumonia according to age groups.

METHODS

PCR and CT results from 411 patients were reviewed. The diagnosis of COVID-19 pneumonia was made by three radiologists. Lymphadenopathy, pericardial effusion, pleurisy, pleural thickening, pleural effusion, location features of the lesions, ground glass, consolidation, air bronchogram, vascular enlargement, bronchial dilatation, halo finding, inverted halo sign, nodularity, air bubble,

subpleural band (curvilinear density), reticular density, crazy paving pattern, and fibrosis findings were recorded. The patients were divided into nine groups by decades while calculating the sensitivity, specificity, and diagnostic efficacy for CT positivity.

RESULTS

The mean age of the cases was 48.1 ± 22.7 years. The CT finding with the highest diagnostic power was ground glass. Vascular enlargement and bronchial dilatation followed ground glass. Pericardial effusion was the finding with the lowest diagnostic accuracy. The incidence of lymphadenopathy, pleurisy, pleural thickening, peripheral localization, bilateral, ground glass, vascular enlargement, bronchial dilatation, subpleural band, reticular density, crazy paving appearance, and fibrosis all increased increase significantly with age in patients with positive real-time reverse transcription PCR test.

CONCLUSION

There are few publications comparing sensitivity and specificity of thoracic CT findings according to age. In cases of COVID-19 pneumonia, there is an increase in the variety and frequency of CT findings with age, and parallel to this the sensitivity and specificity of the findings increase. COVID-19 cases in the pediatric age group have fewer lung findings than adults, and this situation decreases the diagnostic value of CT in pediatric patients.

Key Words: Thoracic computerized tomography; SARS-CoV-2; COVID-19; Diagnosis; Pediatric age

Core Tip: Despite its high sensitivity for identifying coronavirus disease 2019 (COVID-19) pneumonia, the diagnostic potential of computed tomography findings has not been thoroughly investigated, particularly in relation to age subgroups. It is worth noting that the prevalence of COVID-19 pneumonia can vary by age. Even common results, such as ground glass opacities, can be reduced in younger individuals, particularly in the pediatric population. Additionally, the findings of this study may raise awareness about the proper use of computed tomography scans in children and contribute to radiation protection by limiting computed tomography scans in age groups with low sensitivity.

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INTRODUCTION

The World Health Organization has declared coronavirus disease 2019 (COVID-19) a pandemic caused by severe acute respiratory syndrome coronavirus 2[1,2]. Although fever and cough are the most common clinical symptoms, other symptoms such as fatigue, shortness of breath, and headache may also be present[3]. However, because all of these symptoms are not unique to the disease and because the disease can progress quickly to severe pneumonia, diagnostic tests are required.

Although the real-time reverse transcription (RT)-PCR test for viral nucleic acids is the gold standard in the diagnosis of COVID-19, computed tomography (CT) has become increasingly important in the diagnosis due to false negative results and the inability to obtain results quickly[4]. Because CT has a sensitivity of 97 %, it is frequently used, and algorithms are developed accordingly[5]. Even if the RT-PCR is negative, treatment and filiation are initiated in close contacts[6]. However, because CT contains ionizing radiation, there is a risk of unintentional use. The expected harms of ionizing radiation are greater in children than in adults. Seeing that, we aim to define the change of the CT findings as well as the sensitivity and the specificity of these findings according to age.

MATERIALS AND METHODS

Study design

The local (33216249-50.01.02-E.25467) medical ethics committee approved this study. The ethics committee waived informed consent as a result of the retrospective nature.

The study included 411 patients with suspected COVID-19 who applied to a tertiary healthcare center. The registration period began on March 15, 2020 and ended on May 15, 2020. All patients had laboratory RT-PCR testing of respiratory secretions obtained *via* nasopharyngeal or oropharyngeal swab. Clinical data from electronic medical records were reviewed.

All patients had a CT scan without intravenous contrast material on the day they were admitted to the hospital (Siemens SOMATOM Sensation 16, Forchheim, Germany). All patients were scanned in the supine position using an adult CT protocol; reconstruction images of the 1.5 mm lung window were obtained using tube voltage = 130kV, effective mAs = 70, slice thickness = 5 mm, collimation = 16 × 1.2, pitch = 0.8. In children, reconstruction images of the lung window of 1.5 mm were obtained with protocol tube voltage = 110kV, effective mAs = 60, slice thickness = 8 mm, collimation = 16 × 1.2, pitch = 0.8 (14 years and younger).

All CT images were reviewed by three thorax imaging experts who were not aware of the RT-PCR test results, and the final decision was reached by consensus. The North American Society of Radiology Expert Consensus Statement on Reporting of Lung CT Findings Related to COVID-19[7] (Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19) was followed in the evaluation for pneumonia caused by COVID-19. Typical and indeterminate appearance were considered positive for COVID-19 infection, whereas atypical appearance and negative for pneumonia were considered negative for infection. Lymphadenopathy, pericardial effusion, pleurisy, pleural thickening, pleural effusion, lesion location features (peripheral-central-diffuse, posterior, bilateral-unilateral, *etc*), ground glass, consolidation, air bronchogram, vascular enlargement, bronchial dilatation, halo sign, reverse halo sign, nodularity, air bubble, subpleural band (curvilinear density), reticular density, crazy paving pattern, and fibrosis findings were recorded.

The patients were divided into nine groups by decades when calculating the sensitivity, specificity, and significance for CT positivity. The ninth group was defined as people aged 80 and up. To avoid decreasing statistical power, the sensitivity, specificity, and significance of the CT findings were divided into three groups determined by the World Health Organization (age group 1: 0-18, age group 2: 18-60, age group 3: 60 and above).

Statistical analysis

IBM SPSS 22 was used for statistical analyses (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, United States: IBM Corp.). The Kolmogorov-Smirnov test was used to determine whether the data conformed to a normal distribution. Numerical variables with a normal distribution were represented as mean and standard deviation values, variables without a normal distribution as median (minimum-maximum) values, and categorical variables as number (*n*) and percentage values (percent) When calculating CT diagnostic accuracy measures, RT-PCR was used as the gold standard. CT sensitivity and specificity were reported along with their 95% confidence intervals. Exact Clopper-Pearson confidence intervals for sensitivity and specificity were calculated. A *P* value of less than 0.05 was considered as statistically significant.

RESULTS

The average age of the 411 cases was 48.1 ± 22.7 years (median: 49, range: 0-99), with 241 (58.8%) males and 170 (41.4%) females. Figure 1 depicts the distribution of the number of patients by decade, while Figure 2 depicts the distribution by group. There were 181 positive RT-PCR results and 230 negative RT-PCR results out of 411 patients, for a positive rate of 41% (181/411). There was no statistically significant difference in age or gender between patients with positive and negative RT-PCR results ($P > 0.05$). There were 141 positive and 40 negative CT findings in 181 cases, for a positive rate of 77.9% (141/181). The overall and age-segregated sensitivity and specificity of CT were calculated and reported based on RT-PCR results. CT sensitivity was found to be 77.9% (95% confidence interval: 71.15 to 83.72) for all patients. However, when the sensitivity value was stratified based on age, it was discovered that it had changed. The findings revealed that the sensitivity of CT increased with age (Table 1, Figures 3 and 4).

Table 2 showed the diagnostic accuracy of the findings recorded in RT-PCR test negative and positive cases across the entire population. According to these findings, ground glass opacity had the highest diagnostic accuracy of 62.5 % (sensitivity 84.4%, specificity 33.7%), followed by vascular enlargement at 58.5% and bronchial dilatation at 58.3% (Figure 5A). With a diagnostic accuracy of 40.0%, pericardial effusion is the finding with the lowest diagnostic accuracy.

Table 1 Diagnostic accuracy measures of the computerized tomography according to age

Age		CT	RT-PCR		Sensitivity, % (95%CI)	Specificity, % (95%CI)
			COVID-19 negative	COVID-19 positive		
Age categories	0-9	Negative	3	8	11.11 (0.28-48.25)	23.08 (5.04-53.81)
		Positive	10	1		
	10-19	Negative	0	3	50.00 (11.81-88.19)	0.00 (0.00-28.49)
		Positive	11	3		
	20-29	Negative	10	9	60.87 (38.54-80.29)	25.64 (13.04-42.13)
		Positive	29	14		
	30-39	Negative	5	10	66.67 (47.19-82.71)	18.52 (6.30-38.08)
		Positive	22	20		
	40-49	Negative	9	2	91.30 (71.96-98.93)	32.14 (15.88-52.35)
		Positive	19	21		
	50-59	Negative	4	3	90.32 (74.25-97.96)	13.33 (3.76-30.72)
		Positive	26	28		
	60-69	Negative	3	2	92.59 (75.71-99.09)	8.82 (1.86-23.68)
		Positive	31	25		
	70-79	Negative	4	3	81.25 (54.35-95.95)	11.11 (3.11-26.06)
		Positive	32	13		
	80+	Negative	4	0	100.00 (79.41-100.0)	33.33 (9.92-65.11)
		Positive	8	16		
Overall		Negative	42	40	77.90 (71.15-83.72)	18.26 (13.49-23.87)
		Positive	188	141		

Diagnostic accuracy measures (sensitivity and specificity) were calculated for computed tomography when real-time reverse transcription PCR was gold standard. CT: Computed tomography; RT-PCR: Real-time reverse transcription PCR; COVID-19: Coronavirus disease 2019; CI: Confidence interval.

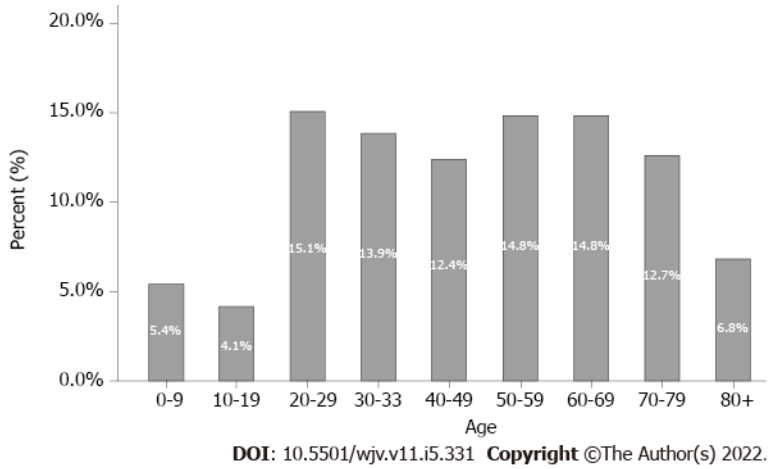

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Figure 1 Age distribution.

Table 3 showed the frequency of findings in cases with positive RT-PCR tests based on age groups. Lymphadenopathy, pleurisy, pleural thickening, peripheral localization, bilateral, ground glass, vascular enlargement, bronchial dilatation, subpleural band, reticular density, crazy paving appearance, and fibrosis all increased with age ($P < 0.05$) (Figure 5B). Although there was a significant difference in consolidation, air bronchogram, and air bubble findings between age groups, it was not related to

Table 2 Diagnostic accuracy of findings across the entire population

Findings	Sensitivity, %	Specificity, %	Diagnostic accuracy, %
Lymphadenopathy	60.3	44.7	46.9
Pleurisy	78.3	45.6	48.0
Pericardial effusion	80.0	40.0	40.0
Pleural thickening	19.3	86.1	48.0
Peripheral location	46.5	53.6	49.6
Posterior location	65.1	22.0	48.5
Bilateral location	69.3	22.0	51.4
Ground glass	84.4	33.7	62.5
Consolidation	45.9	71.1	56.7
Air bronchogram	31.2	81.3	52.8
Vascular enlargement	53.2	65.7	58.5
Bronchial dilatation	50.5	68.7	58.3
Halo sign	28.9	75.3	48.9
Reverse halo sign	1.4	95.8	42.1
Nodularity	37.2	68.1	50.5
Air bubble	16.1	87.3	46.8
Subpleural band	27.1	70.5	45.8
Reticular density	11.9	88.6	45.0
Crazy paving appearance	11.0	97.6	48.4
Fibrosis	15.6	90.3	47.7

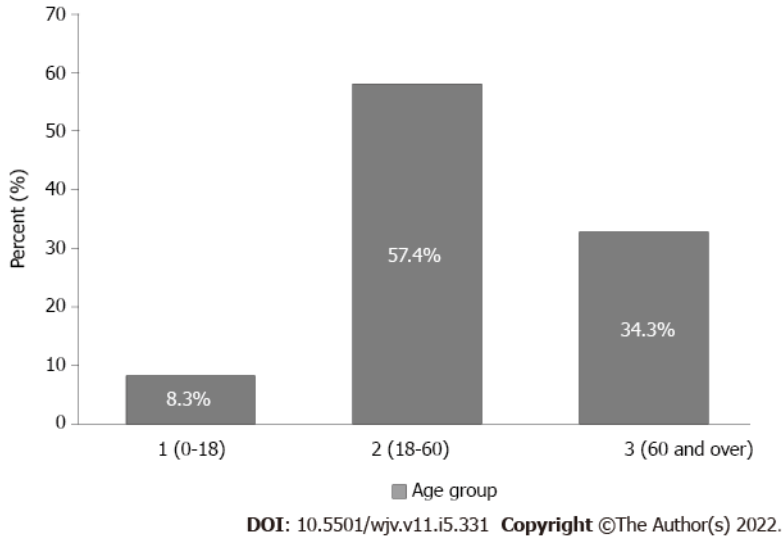

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Figure 2 Age group distribution.

patient age (Figure 5C). There was no significant difference in the rates of bilateral involvement, posterior location, pericardial effusion, halo, reverse halo, and nodularity between the three groups (P > 0.05) (Figure 5D).

Table 3 Frequency of findings according to age groups

Findings	Age group 1, %	Age group 2, %	Age group 3, %	*P* value
Lymphadenopathy	0	8.1	29.8	0.001
Pleurisy	0	2.2	20.8	0.002
Pericardial effusion	0	0.5	3.1	0.092
Pleural thickening	3.0	12.7	27.5	0.005
Peripheral location	36.4	61.5	65.1	0.04
Posterior location	59.1	67.1	74.6	0.09
Bilateral location	50.0	62.1	88.5	0.07
Ground glass	51.5	69.1	94.7	0.007
Consolidation	39.4	29.5	52.7	0.02
Air bronchogram	36.4	18.2	35.1	0.001
Vascular enlargement	30.3	38.2	59.5	0.03
Bronchial dilatation	30.3	36.7	53.4	0.005
Halo sign	24.2	26.8	24.2	0.055
Reverse halo sign	0	2.3	3.8	0.06
Nodularity	36.4	34.1	35.9	0.067
Air bubble	0	0	0.8	0.04
Subpleural band	12.1	21.8	42.8	0.002
Reticular density	0	9.1	18.3	0.001
Crazy paving appearance	3.0	4.1	13.0	0.02
Fibrosis	0	2.7	33.8	0.001

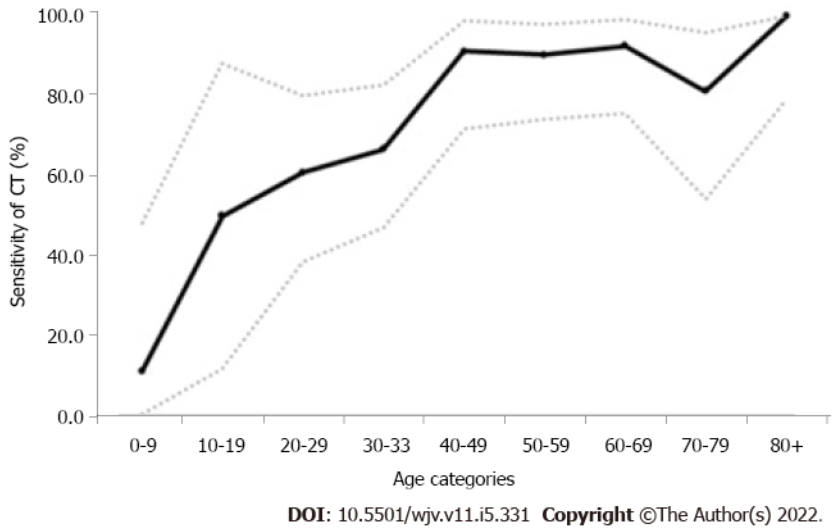

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Figure 3 Sensitivity of computed tomography by age groups. Sensitivity values and their 95% confidence intervals were shown on the graph. CT: Computed tomography.

DISCUSSION

On March 11, 2020, the World Health Organization declared COVID-19 a global epidemic. The disease's high contagiousness necessitated the development of a rapid and highly sensitive test. In addition to the low sensitivity of the gold standard RT-PCR test, test results were provided within days or weeks due to a lack of testing centers, particularly in the 1st months of the pandemic. This circumstance has resulted in a more rapid and accessible test requirement. The impact of COVID-19 infection on the lower

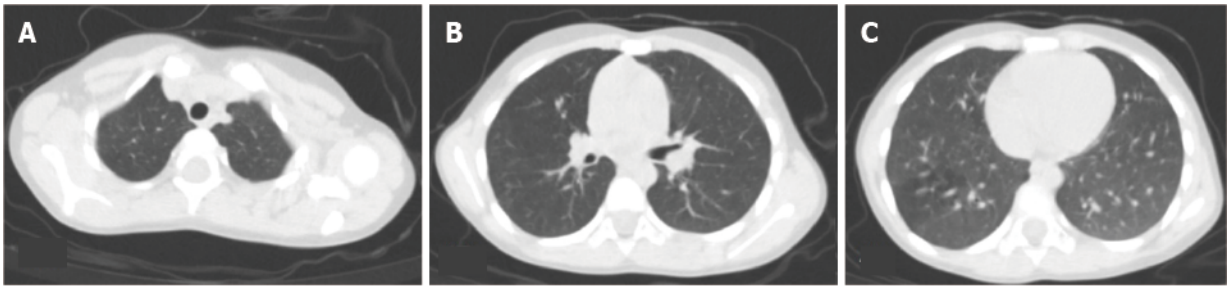

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Figure 4 A thoracic computed tomography scan in a 5-year-old female patient. There were no pathological findings in the sections that passed through the upper (A), middle (B), and lower (C) zones.

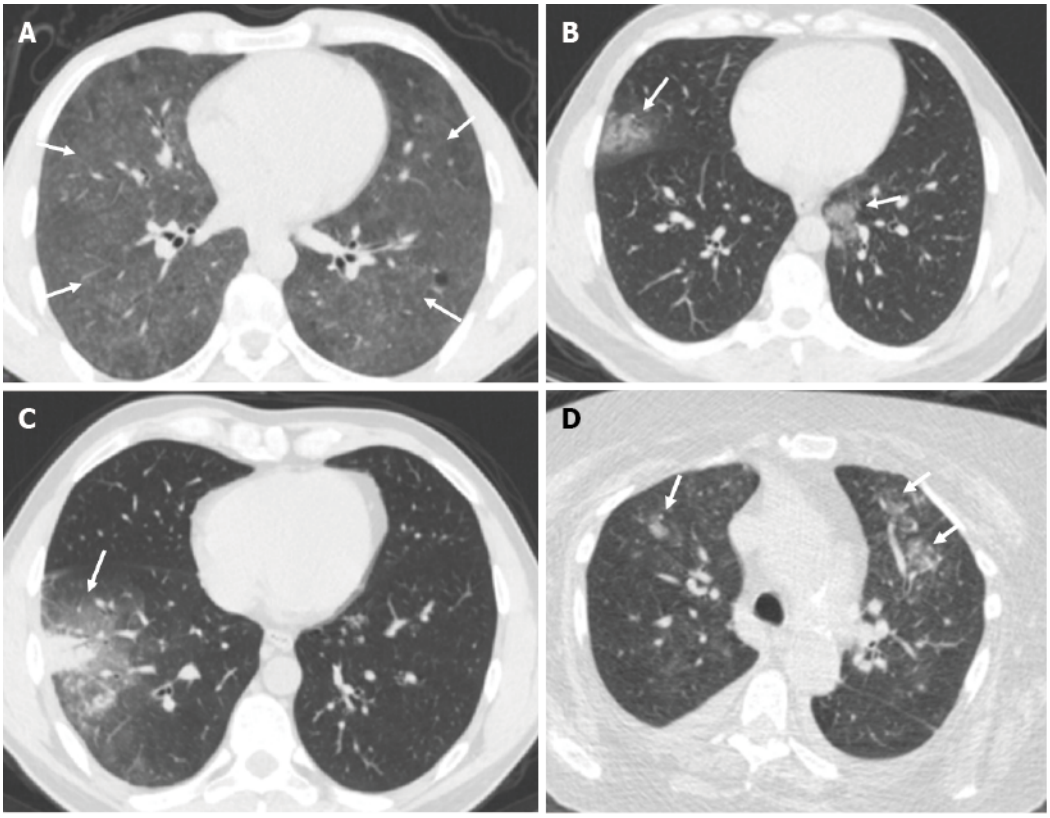

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Figure 5 Thoracic computed tomography scans in patients. A: A 45-year-old male patient underwent a thoracic computed tomography (CT) scan. Sections passing through the middle zones showed diffuse ground-glass infiltration areas with preservation of subpleural areas in both lungs (arrows); B: A 44-year-old female patient underwent a thoracic CT scan. In the sections passing through the lower zones, infiltration areas of peripheral ground glass density with a mild halo were observed in the medial basal segment on the right and in the upper lobe inferior lingular segment on the left (arrows); C: A 35-year-old male patient underwent a thoracic CT scan. A subpleural consolidation area with air bronchogram and ground-glass density halo could be seen in the lateral basal segment of the right lung lower lobe in sections passing through the lower zones (arrow); D: A 77-year-old female patient underwent a thoracic CT scan. In the sections passing through the upper zones, centrilobular nodular infiltrating areas in the form of a budded tree pattern were observed in the anterior segments of the upper lobes of bilateral lungs, particularly on the left (arrows).

respiratory tract has brought thoracic CT examination to the forefront. Thoracic CT is useful for detecting viral lung infection, determining the nature and extent of pulmonary lesions, and monitoring disease activity[8-11]. In addition, the latest studies revealed that CT perfusion examinations can reveal perfusion deficits in COVID-19 pneumonia[12]. In these circumstances, in addition to the potential for rapid diagnosis of COVID-19 by thoracic CT, identification of pulmonary changes and base images of the cases to be followed may be an added benefit.

Multiple, peripheral, bilateral, irregular, subsegmental or segmental ground glass opacities, mostly bronchovascular bundles, and areas of consolidation scattered throughout the subpleural space are typical COVID-19 chest CT imaging features. The presence of associated intralobular septal thickening in areas of ground glass opacity, crazy paving appearance, consolidation, and air bronchograms with

areas of bronchial wall thickening and less frequently thickening of the adjacent or interlobar pleura as well as a small amount of pleural effusion are also COVID-19 chest CT imaging features[7,13,14]. When all cases were considered in our study, the findings of ground glass density, vascular enlargement, bronchial dilatation, consolidation, and bilaterality stood out for diagnostic accuracy.

In limited studies, pediatric patients with COVID-19 have relatively mild clinical symptoms, a higher prevalence of negative CT scans, and atypical, peribronchial distribution of lung opacities and bronchial wall thickening are more common[15,16]. The incidence of any finding other than an air bronchogram and nodular appearance is not higher in this age group than in other age groups. Posterior location, bilaterality, and ground glass density are the most common findings. Among these findings is that the prevalence of ground glass density is significantly lower in this age group than in other age groups. The sensitivity of CT diagnosis in the 0-9 age group was found to be quite low in our study.

For the diagnosis of COVID-19, various algorithms have been developed. Due to the large number of cases, doctors from fields other than chest diseases or infectious diseases had to play an active role in disease diagnosis in many hospitals. Due to a lack of experience in physical examination, doctors from various fields frequently rely on thoracic CT exam-ination, with the tendency to deviate from algorithms and make an easy and quick diagnosis. RT-PCR may be negative in the early stages of the disease and due to other variants as well as the inadequacy of the RT-PCR test contributes to the overuse of thoracic CT[17,18]. Routine thoracic CT screening for COVID-19 is not recommended, and confirmatory diagnosis is based on RT-PCR. When a low-dose CT scan is required, it is preferable for the pediatric population. Follow-up imaging is only necessary in cases of clinical deterioration and should be kept to a minimum.

The study's most significant limitation is the small number of cases in the 0-18 age range. The main reason for this is that clinical symptoms in this age group are unclear, and pediatricians in our hospital are actively treating patients with suspected COVID-19.

CONCLUSION

Despite its high sensitivity for identifying COVID-19 pneumonia, the diagnostic potential of CT findings has not been thoroughly investigated, particularly in relation to age subgroups. It is worth noting that the prevalence of COVID-19 pneumonia can vary by age. Even common results, such as ground glass opacities, can be reduced in younger individuals, particularly in the pediatric population. Additionally, the findings of this study may raise awareness about the proper use of CT scans in children and contribute to radiation protection by limiting CT scans in age groups with low sensitivity.

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease 2019 (COVID-19) is a pandemic caused by the severe acute respiratory syndrome coronavirus in 2019. Although the real-time reverse transcription (RT)-PCR test for viral nucleic acids is the gold standard for COVID-19 diagnosis, computed tomography (CT) has grown in importance.

Research motivation

There is a risk of unintentional use because CT contains ionizing radiation. Ionizing radiation is expected to cause more harm to children than to adults.

Research objectives

We aim to define the change of the CT findings as well as the sensitivity and the specificity of these findings according to age.

Research methods

The study included 411 patients with suspected COVID-19 who sought treatment at a tertiary healthcare facility. RT-PCR testing of respiratory secretions obtained *via* nasopharyngeal or oropharyngeal swab was performed on all patients. Clinical information from electronic medical records was examined. On the day they were admitted to the hospital, all patients had a CT scan without intravenous contrast material. Three thorax imaging experts who were not aware of the RT-PCR test results reviewed all CT images, and the final decision was reached by consensus. When calculating the sensitivity, specificity, and significance for CT positivity, the patients were divided into nine groups based on decades. The group was defined as people aged 80 and up for the ninth group. The sensitivity, specificity, and significance of CT findings into three groups (age group 1: 0-18, age group 2: 18-60, age group 3: 60 and above) was determined.

Research results

There were 181 positive RT-PCR results and 230 negative RT-PCR results out of 411 patients, for a positive rate of 41% (181/411). There were 141 positive and 40 negative CT findings in 181 cases, for a positive rate of 77.9 % (141/181). CT sensitivity was found to be 77.9 % (95% confidence interval: 71.15 to 83.72) for all patients. The findings revealed that the sensitivity of CT increased with age. Ground glass opacity had the highest diagnostic accuracy of 62.5 %, followed by vascular enlargement at 58.5% and bronchial dilatation at 58.3%. Lymphadenopathy, pleurisy, pleural thickening, peripheral localization, bilateral, ground glass, vascular enlargement, bronchial dilatation, subpleural band, reticular density, crazy paving appearance, and fibrosis all increased with age ($P < 0.05$).

Research conclusions

Due to the large number of cases, doctors from various fields frequently rely on thoracic CT examination, with the tendency to deviate from algorithms and make an easy and quick diagnosis. The inadequacy of the RT-PCR test contributes to the overuse of thoracic CT. The sensitivity of CT diagnosis in the 0-9 age group was found to be quite low in our study. When a low-dose CT scan is required, it is preferable for the pediatric population. Follow-up imaging is only necessary in cases of clinical deterioration and should be kept to a minimum.

Research perspectives

Further research should be conducted to determine the diagnostic potential of COVID-19 CT findings in relation to age subgroups. Additionally, the findings of this study may raise awareness about the proper use of CT scans in children and contribute to radiation protection by limiting CT scans in age groups with low sensitivity.

FOOTNOTES

Author contributions: Karavaş E and Ünver E were responsible for the conceptualization, methodology, and project administration; Karavaş E did the writing-review & editing; Karavaş E, Aydin S, Yalçin GS, Fatihoglu E, Kuyrukluyildiz U, and Yazici M were responsible for the investigation and resources; Aydin S wrote the original draft; Aydin S and Arslan Y performed the data curation and formal analysis.

Institutional review board statement: The study was reviewed and approved by the Erzincan Binali Yildirim University Institutional Review Board (Approval No: 22/06/2020-06/04).

Informed consent statement: The Institutional Ethical Review Board waived informed consent due to the retrospective nature of the study procedure.

Conflict-of-interest statement: The authors whose names are listed immediately above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Observational Study

Validity of the patient health questionnaires (phq-2 and phq-9) for screening depression among human immunodeficiency virus patients in Lahore, Pakistan

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Abstract

BACKGROUND

Many human immunodeficiency virus (HIV) infected patients suffer from depression, but a little focus is given to detecting and treating depression in primary health care. Detection of depression can be improved by introducing short, reliable, and valid screening instruments.

AIM

To determine the psychometric properties of the patient health questionnaire-2 (PHQ-2) and patient health questionnaire-9 (PHQ-9) for depression screening and diagnosis, and the sensitivity and specificity of the PHQ-2 in HIV infected patients.

METHODS

A cross-sectional study was conducted on 158 HIV-infected patients aged 18 years and above in Lahore, Pakistan. PHQ-2 was implemented to screen depression. PHQ-9 was implemented to diagnose major depressive disorder as a reference standard. Reliability, Validity tests and receiver operating characteristic curve were computed.

RESULTS

The Cronbach's alpha of PHQ-2 and PHQ-9 were 0.732 and 0.759, respectively. The study results showed that the score of 2 on PHQ-2 indicates the highest

Youden's index of 0.924, with both sensitivity and specificity of 0.96, and the area under the curve for PHQ-2 was 0.98 (95%CI: 0.953-0.998).

CONCLUSION
Good psychometric properties for the PHQ-2 and PHQ-9 indicated their significant potential as tools for depression screening and diagnosis in the HIV-infected population.

Key Words: Depression; Validity; Patient health questionnaire-9; Patient health questionnaire-2; HIV/AIDS; Lahore; Pakistan

Core Tip: Many human immunodeficiency virus patients suffer from depression, but a little focus is given to detecting and treating depression in primary healthcare settings. The study aims to assess the psychometric properties of the patient health questionnaire-2 (PHQ-2) and Patient health questionnaire-9 for depression screening and diagnosis and estimate the sensitivity and specificity of the PHQ-2 for depression screening in human immunodeficiency virus infected patients. The study results showed that the score of 2 on PHQ-2 indicates the highest Youden's index of 0.924, with both sensitivity and specificity of 0.96, and the area under the curve for PHQ-2 was 0.98.

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INTRODUCTION

People living with human immunodeficiency virus (HIV) infection (PLWHA) seem to be more vulnerable to psychiatric morbidity than the overall population[1,2], with major depressive disorder seems to be the most prevalent psychiatric diagnosis. Suicidal thinking, anxiety, post-traumatic stress disorder, and drug/alcohol use disorders are also frequently documented psychiatric morbidities in HIV patients[3,4]. Around 3.8 percent of the world's population suffers from depression, including 5.0 percent of adults and 5.7 percent of people over 60. Depression affects around 280 million people worldwide[5]. The global HIV/AIDS 2020 research estimated that 37.7 million people were infected with HIV infection. Sub-Saharan Africa was linked to about two-thirds of the world's HIV-positive individuals[6]. In Pakistan, an estimated 183705 people infected with HIV by 2020[7]. Even though the expected prevalence of HIV infection in Pakistan's general population is less than 0.1 percent in 2019, it remains a major public health issue[8].

Depression is a mental health condition defined by a depressed mood, low mood, difficulty concentrating, self-blame or poor self-worth, sleeping or eating difficulties, and impaired focus[9-11]. Depression is associated with several clinical and socio-demographic factors in HIV patients. Some clinical factors, such as AIDS-related stigma, compromised immune status (low CD4 counts), and opportunistic infections[12,13] could be distinctive to HIV patients; however, socio-demographic factors such as gender, low levels of education, and unemployment were linked to depression including both HIV positive and negative populations[14]. Untreated depression causes rapid HIV infection advancement and increases deaths[15]. Inflammatory pathway indicators, such as monocytes and pro-inflammatory cytokines, are recognized as contributing to the higher prevalence of depression in HIV-positive individuals[16]. When a person has HIV infection, their body releases more of the pro-inflammatory cytokines interleukin-6 and tumour necrosis factor. These cytokines promote the spread of viruses and the depletion of CD4 cells[17].

Antidepressants were the most frequently recommended drugs, followed by anxiolytics, antipsychotics and psycho-stimulants[18]. Non-invasive brain stimulation (NIBS) techniques such as repeated trans-cranial magnetic stimulation and trans-cranial direct current stimulation are increasingly being used to improve cognitive function and reduce depressive symptoms in a variety of settings[19]. Given that severe depression is typically associated with cognitive impairments, the NIBS method may be beneficial in enhancing cognition in depressed people[20]. More than half of the patients with a serious depressive illness did not use antidepressants. Effective depression treatment may be crucial for increasing HIV medication adherence and clinical outcomes, possibly in combination with adherence supports[21].

Despite successful pharmacological and psychological treatments, a high proportion of individuals suffering from depression in HIV-infected patients is frequently undiagnosed clinically and is frequently untreated in primary health care settings[22,23]. Several screening questionnaires have been developed as instruments to assist in the timely identification of depression and clinical judgment[24-28]. To generate accurate clinical results, the validity and reliability of the depression screening tools should be good. Screening tools should be easy and quick for successful practical application[29-31]. The Patient Health Questionnaire [patient health questionnaire-2 (PHQ-2) and patient health questionnaire-9 (PHQ-9)] were designed especially as depression screening and diagnostic tools for primary care settings to promote the delivery of evidence-based psychiatric care intervention strategies in regions where specially trained mental health providers are scant[32-34].

A cross-culturally applicable form of PHQ-9 and PHQ-2 is available, but its psychometric properties are still to be validated formally. In many studies, the accuracy of PHQ-9 has been tested by applying it to many chronic disease populations[35-40]. However, the PHQ-9 and PHQ-2 have not yet been validated in HIV patients in Pakistan. Therefore, the present study aimed to measure the (1) psychometric properties of the PHQ-9 and PHQ-2 for the diagnosis of depression; and (2) to estimate PHQ-2 screening accuracy by using PHQ-9 as the reference standard in patients of HIV infection in Lahore, Pakistan.

MATERIALS AND METHODS

Study setting

The study was carried out in the HIV clinic of Jinnah hospital Lahore, Pakistan, from January 2019 to March 2019. HIV clinic in Jinnah hospital Lahore works from Monday to Saturday and serves around 20 to 30 patients per day. The population of Lahore is 11126285, and it is one of the most populated cities in Punjab Province[41]. The current study comprises finding active cases of depression by the use of PHQ-2 for screening, followed by the use of PHQ-9 to detect depression. Patients with a PHQ-9 score of nine or higher were referred to a psychiatrist to confirm the diagnosis of depression.

Study design

An analytical cross-sectional study design was executed to assess the validity and reliability of the Patient Health Questionnaire among HIV patients.

Participants

One hundred and fifty-eight study participants were recruited from the HIV clinic of Jinnah hospital, Lahore, through a non-probability convenience sampling technique. All participants were agreed to participate in the study. Eligibility criteria for study subjects included age more than 18 years, capability to correspond, understand Urdu language, patients must have a diagnosis of HIV based on positive test on an ELISA for HIV anti-bodies, were attending the HIV clinic for medical care, and were available for a 20 min interview. Participants who had other medical disorders unrelated to HIV, such as renal failure, chronic hepatitis, and malignancy determined on history and clinical examination, were excluded.

Measures

PHQ-9: It is a nine-component criterion-based diagnostic instrument for the evaluation of depression that identifies the presence and frequency of nine major symptoms of depression in the participant (as recommended by DSM-IV) for two weeks. PHQ-9 is applied frequently in the western world and in sub-Saharan Africa[35,40]. Scoring varies from 0 to 27, and the patient who scores ten or more on PHQ-9 is said to be suffering from depression and should be treated for it to avoid severe consequences. Studies provide evidence that PHQ-9 is designed for self-administration, but it gives the same outcomes when the researcher takes interviews based on this questionnaire[42].

PHQ-2: It comprises the first two PHQ-9 questions and evaluates the frequency of past two week's spells of despair, boredom, and happiness. Questions are valued from 0-3 (4-point scale), where zero represents the complete absence of symptoms and three shows symptoms of depression on each day of the last two weeks with a total score ranging from zero to six[43]. A cutoff value of 3 or more indicates the presence of depression and is associated with a high level of sensitivity and specificity for screening depression[40]. It is easy to use and can be easily applied by healthcare staff of over-burdened health facilities.

Data collection and study procedures: Prior to the start of data collection, study participants were informed about the study's objective, and verbal informed consent was obtained. The researcher did a face-to-face interview with the PHQ-2 depression screening questionnaire after receiving informed consent. To obtain socio-demographic information, the clinic file of the patient was examined. Due to the study population's poor literacy level, the survey was administered by the interviewer, and

responses were written down. After the screening interview, participants answered the PHQ-9 questionnaire with a second research staff member who was blind to the PHQ-2 results. The interview was conducted by local health care practitioners who had been trained in the use of the PHQ-9 questionnaire. The PHQ-9 was given in the same language as the screening interview, with the help of an interpreter if needed. A good sample size of 200 was chosen due to the restricted availability of staff who can diagnose depression. 158 (79%) of the study participants completed the interview. PHQ-2 items were used to calculate total depression screening scores, and the PHQ-9 items were used to calculate total depression diagnosis scores. Patients with a PHQ-9 score of 9 or above are referred to a psychiatrist to confirm the diagnosis of depression.

Ethical considerations: Ethical approval was obtained from the research ethical review board of the Jinnah hospital Lahore, Pakistan. Before the data collection, informed verbal consent was obtained from each study participant.

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Statistical analysis

IBM SPSS version 24 software (Chicago, IL, United States) and the statistical software MedCalc were used to analyze the data. To describe the sociodemographic characteristics of the study participants, descriptive statistics were used. The mean (standard deviation [SD]) was employed to represent continuous data, and the two-sample *t*-test was applied to compare groups. Where applicable, categorical data were evaluated using Pearson's χ^2 test. The overall Cronbach's alpha coefficient was used to assess the internal consistency of PHQ-2 and PHQ-9. Cronbach's alpha was also calculated with each item removed. The criterion validity of PHQ-2 was determined using receiver operating characteristic (ROC) analysis. Using the PHQ-9 as the reference standard, we employed MedCalc 14.8 to evaluate the sensitivity, specificity, and positive and negative predictive values of the PHQ-2 as a screening tool. Statistical significance was evaluated for all tests using a *P* value of 0.05. The area under the curve (AUC) determines the performance of a test, and an AUC of 0.5 indicates a non-discriminating test. In contrast, the value of AUC of 1.0 specifies perfect diagnostic accuracy. In sensitivity analyses, cutoffs scores balancing sensitivity and specificity were found out utilizing the point of convergence between sensitivity and specificity and Youden's index, which was calculated by (sensitivity + specificity– 1)[44,45].

RESULTS

Participant characteristics

In total, 158 study participants were completed the PHQ-2 and PHQ-9. The background characteristics of the study participants are mentioned in Table 1. According to the study results, study participants ranged from 18 to 54 years with a mean age of 30.42 ± 7.11 years (± SD). One hundred and thirty-five study participants (85.4%) were male, while twenty-three (14.5%) were female. The total score of PHQ-9 ranged from 0 to 22, with the mean PHQ-9 score being 9.92 (SD = 4.648). By the present study result, PHQ-9 scores were higher in depressed individuals (mean = 12.81) compared to those without depression (mean = 8.41). In most socio-demographic characteristics, no statistically significant differences were found as evaluated by chi-square and *t*-test for gender, education, residence, and religion by depression. However, age, marital status, and monthly family income of HIV patients showed a statistically significant difference with the depression ($P < 0.05$).

Reliability and item analysis of PHQ-2 and PHQ-9

The reliability coefficient, Cronbach's alpha for PHQ-9 total score was 0.759, indicating a strong internal consistency. The bivariate correlation between nine items of the PHQ-9 was shown in Table 2, with coefficient ranging from 0.559 to 0.301, and all correlations were statistically significant (all 2-tailed *P* values < 0.01). Thoughts that harming yourself or dying would be better and moving and feeling bad about yourself or that you are a failure were the two most frequently endorsed items. On the contrary, Feeling down, depressed, or hopeless was the item least frequently endorsed by HIV patients (Table 2). The PHQ-2 had a Cronbach's alpha of 0.732, indicating that the items of the PHQ-2 were consistent. The corrected inter-total correlation was 0.574 and 0.574, respectively.

Sensitivity and specificity for PHQ-2

Table 3 showed the sensitivity, specificity, predictive values, and Youden's index at different cutoff scores of the PHQ-2 for depression screening. The study results showed that the score of 2 on PHQ-2 indicates the highest Youden's index of 0.924, with a sensitivity and specificity of 0.96. The area under

Table 1 Socio demographic characteristics of human immunodeficiency virus positive patients (*n* = 158)

Variables	Non-depression, *n* (%)	Depression, *n* (%)	*P* value
	104 (65.8)	54 (34.1)	
Age (yr)			
mean ± SD	30.42 ± 7.11	43.91 ± 5.133	**0.001**[a]
Gender			
Male	89 (56.3)	46 (29.1)	0.947
Female	15 (9.5)	8 (5.1)	
Education			
No education	62 (39.2)	27 (17.1)	0.377
Up to primary school	11 (7.0)	6 (3.8)	
Up to secondary school	23 (14.6)	14 (8.9)	
Up to college	4 (2.5)	6 (3.8)	
Up to University	4 (2.5)	1 (0.6)	
Marital status			
Married	51 (32.3)	42 (26.6)	**0.001**[a]
Unmarried	47 (29.7)	4 (2.5)	
Separated	1 (0.6)	5 (3.2)	
Divorced	4 (2.5)	2 (1.3)	
Widowed	1 (0.6)	0 (0.6)	
Monthly family income			
Less than 20000 Rs	66 (41.8)	17 (10.8)	**0.001**[a]
Between Rs. 20000-30000	29 (18.4)	25 (15.8)	
More than Rs. 30000	9 (5.7)	12 (7.6)	
Residential status			
Rural	36 (22.8)	25 (15.8)	0.153
Urban	68 (43.0)	29 (18.4)	
Religion			
Muslim	101 (63.9)	50 (31.6)	0.190
Non-Muslim	3 (1.9)	4 (2.5)	

[a]*P* value < 0.05.

the curve for PHQ-2 was 0.98 (95%CI: 0.953-0.998) (Figure 1), which indicates excellent criterion validity of PHQ-2 in distinguishing between HIV/AIDS patients with and without major depression with a PHQ-9 diagnosis of depression. The optimum cutoff for detecting depression was found to be a PHQ-2 score of 2, according to study (Table 3).

Comparison of internal consistency between PHQ-9 and PHQ-2

According to the present study results, Cronbach's alpha was similar but quite greater for PHQ-9 than in PHQ-2. In ROC curve analysis, The AUC (0.98) was in PHQ-2. The score of 2 on PHQ-2 indicates the highest Youden's index of 0.924, with a sensitivity and specificity of 0.96. When the score of 2 for PHQ2 was assumed, 35.5% of study subjects were diagnosed with probable depression.

Table 2 Item analysis of patient health questionnaire-9

PHQ-9	Mean	SD	Item-total correlation	α if item deleted
Little interest or pleasure in doing things	1.06	1.005	0.432	0.738
Feeling down, depressed, or hopeless	1.01	1.003	0.301	0.761
Trouble falling or staying asleep, or sleeping too much	1.06	0.975	0.422	0.739
Feeling tired or having little energy	1.27	0.803	0.414	0.740
Poor appetite or overeating	1.15	0.797	0.460	0.733
Feeling bad about yourself — or that you are a failure or have let yourself or your family down	1.07	0.775	0.518	0.726
Trouble concentrating on things, such as reading a newspaper or watching television	1.13	0.799	0.381	0.745
Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	1.11	0.834	0.496	0.728
Thoughts that you would be better off dead or of hurting yourself in some way	1.06	0.926	0.559	0.716

PHQ-9: Patient health questionnaire-9.

Table 3 Sensitivity, specificity, predictive values, at various cut-off scores of the patient health questionnaire-2

PHQ-2 score	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	Youden's index
≥ 1	100.00 (93.4-100.0)	59.62 (49.5-69.1)	21.6 (17.9-25.8)	100.0 (93.4-100.)	**59.62**
≥ 2	96.30 (87.3-99.5)	96.15 (90.4-98.9)	73.6 (51.5-87.9)	99.6 (98.4-99.9)	**92.45**
≥ 3	66.67 (52.5-78.9)	100.(96.5-100.0)	100.0 (96.5-100.0)	96.4(94.9-97.5)	**66.67**
≥ 4	31.48 (96.5-100.0)	100.0 (96.5-100.0)	100.0 (96.5-100.0)	92.9 (91.6-94.0)	**31.48**
≥ 5	14.81 (6.6-27.1)	100.0 (96.5-100.0)	100.0 (96.5-100.0)	91.4 (90.4-92.2)	**14.81**

PHQ-2: Patient health questionnaire-2; PPV: Positive predictive value; NPV: Negative predictive value.

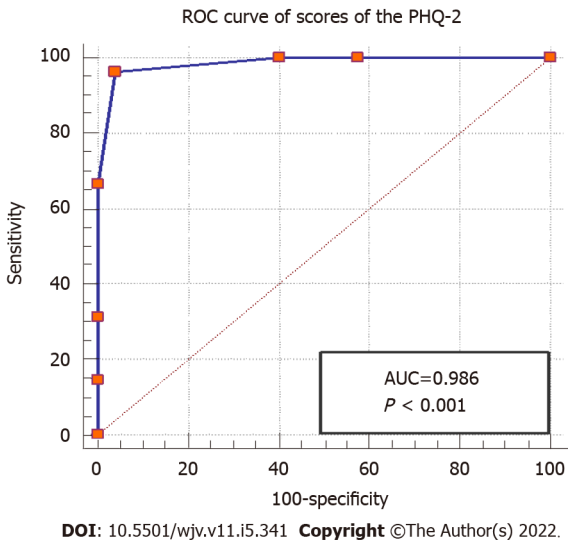

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Figure 1 Receiver operating characteristic curve of Patient Health Questionnaire-2 for depression screening. AUC: Area under the curve.

DISCUSSION

Key findings

The current study concludes that PHQ-9 and PHQ-2 are useful tools for detecting depression in people

affected by HIV living in Lahore, Pakistan. Cronbach's alpha was similar but quite greater for PHQ-9 than in PHQ-2. In ROC curve analysis, The AUC (0.98) was in PHQ-2. The score of 2 on PHQ-2 indicates the highest Youden's index of 0.924, with a sensitivity and specificity of 0.96.

Validity and reliability of PHQ-2 and PHQ-9

Based on analysis of indicators like Youden's index, sensitivity, specificity, and AUC, a cutoff score of 2 for PHQ-2 was suggested. Anyhow there are a small number of studies assessing the cutoff of depression based on its severity categories[45,46]. However, there is highly recommended to determine the cutoff scores of depression based on severity categories amid different populations[47,48]. According to the best of our knowledge, this is the first-ever study on validation and calibration of PHQ-2in the Lahore, Pakistan. Patel *et al*[15] suggested that the best cutoff score was designed by considering the best balance between sensitivity and PPV and is required for its suitability to person-based location and use. Such an instrument is especially significant for routine application in developing regions where healthcare staff is over-burdened.

The current research showed a cutoff score of 2 while using PHQ-2, sensitivity and specificity were 0.96, but this result was different from already done studies[49-51]. A score of 2 is suggested to suspect a patient is suffering from depression in patients of HIV infection when using the PHQ-2 questionnaire based on current and previous studies. The sensitivity value of our study for PHQ-2 is found to be lower than previous studies when a cutoff value of 3 or more is employed along with a documented reference standard. This result can be clarified because we used a sample of patients enrolled consecutively or by chance. One limitation is the design of the study, which is cross-sectional. For acquiring the required sensitivity, we need longitudinal studies. Enrollment of recently diagnosed HIV patients in our study can make the study prone to bias by increasing the estimation of detection of depression with precision[52].

The internal consistency or alpha coefficient for PHQ-9 was 0.759. The value of Cronbach's alpha must be at least 0.70 or higher for a self-administered questionnaire to be reliable[53,54]. The value of the alpha coefficient of PHQ-9 for our study was lesser than previous studies, where its value was 0.79-0.89, respectively[55,56]. As far as Cronbach's alpha of PHQ-2 is concerned, it is found to be 0.73, which is remarkably good. This value is also in line with the studies done in various populations[49,57].

Prevalence of depression

PHQ-2 outcomes showed the frequency of depression to be 35%. This value is higher when compared with previous studies which also used PHQ-2[48]. This high prevalence of depression in our study participants is consistent across various measures in the results of both instruments, and this concludes that the prevalence of depression in HIV patients in Pakistan can be remarkably higher than the previous estimate. Hence validation with a reliable diagnostic instrument is required to detect the real prevalence of depression[58]. As already discussed in different studies, it is suggested that the first two questions of PHQ-9 may not be able to detect symptoms of depression experienced by HIV patients accurately. It reveals that a remarkable number of HIV patients could not be detected without employing a full PHQ-9 instrument. So it is recommended that PHQ-2 be used for the initial evaluation of patients, but we cannot reach a true conclusion without applying PHQ-9[58].

Strengths and limitations of the study

It was the first-ever research done to evaluate the diagnostic accuracy of PHQ-2 for screening major and minor depression in HIV patients by using PHQ-9 as a reference standard. We used a standard instrument that is smaller than other analytical instruments to recognize patients with depression, and it is crucial in primary healthcare settings. PHQ-9 has remarkable properties for the detection of depression and has good capability for assessing the severity of depression.

Especially for evaluation of severity, the PHQ-9 and PHQ-2 offers locally adapted thresholds and follows suggestions to adjust the tool to the background and location when it is intended for application. Because of its shortness, simplicity, and ease of application and interpretation, the use of this instrument is continuously increasing in epidemiological research.

There are a few limitations or constraints in our research. The data were obtained from only one clinic, and hence results cannot be generalized to the population. Because of some reasons, we could not perform test-retest reliability in participants. The study used the cross-sectional design the study, and because of this, we could not establish causation between variables used in our research. Another drawback of this study was that information on participants' mental and physical disabilities was not gathered.

Second, we evaluated the PHQ-2's sensitivity and specificity as a depression screening tool using the PHQ-9 as the reference standard. Therefore, a study utilizing a different diagnostic tool than the PHQ-9 is recommended if the sensitivity or specificity of the PHQ-9 is insufficient as it may bias our estimates of the sensitivity and specificity of the PHQ-2. We propose modifying the PHQ-9 to the local context and literacy level of the population because several participants misunderstood a number of the PHQ-9 items.

CONCLUSION

HIV patients are more likely than the general population to develop depression. The PHQ-2 and PHQ-9 showed good psychometric properties, implying that they could be useful as depression screening tools. Due to the substantial health and social burden of depression and need for relatively short, organized, reliable, and valid tools to help healthcare professionals evaluate patients for depression, the PHQ-2 and PHQ-9 would be useful and valuable tools for screening and diagnosing depression in HIV-infected individuals. Moreover, to lessen the global prevalence of psychiatric disorders and improve patient well-being, the instruments can be used in combination with increased access to adequate mental healthcare and therapeutical and non-pharmacological treatments, which are effective in these settings.

ARTICLE HIGHLIGHTS

Research background

People living with human immunodeficiency virus (HIV) infection (PLWHA) seem to be more vulnerable to psychiatric morbidity than the overall population, with major depressive disorder seems to be the most prevalent psychiatric diagnosis. Suicidal thinking, anxiety, post-traumatic stress disorder, and drug/alcohol use disorders are also frequently documented psychiatric morbidities in HIV patients

Research motivation

Many HIV-infected patients suffer from depression, but a little focus is given to detecting and treating depression in primary health care. Detection of depression can be improved by introducing short, reliable, and valid screening instruments.

Research objectives

The current study assessed the psychometric properties of the patient health questionnaire-2 (PHQ-2) and patient health questionnaire-9 (PHQ-9) for depression screening and diagnosis and estimated the sensitivity and specificity of the PHQ-2 for depression screening in HIV-infected patients.

Research methods

A cross-sectional study was conducted on 158 HIV-infected patients aged 18 years and above in Lahore, Pakistan. PHQ-2 was implemented to screen depression. PHQ-9 was implemented to diagnose major depressive disorder as a reference standard. Reliability, Validity tests and receiver operating characteristic curve were computed.

Research conclusions

Due to the substantial health and social liability of depression and need for brief, organized, reliable, and valid tools that can help medical practitioners better assess patients for depression, the PHQ-2 and PHQ-9 would indeed be useful and beneficial instruments for screening and diagnosing depression in HIV-infected persons. Moreover, to lessen the global prevalence of psychiatric disorders and improve patient well-being, the instruments can be used in combination with increased access to adequate mental healthcare and therapeutical and non-pharmacological treatments, which are effective in these settings

Research results

The Cronbach's alpha of PHQ-2 and PHQ-9 were 0.732 and 0.759, respectively. The study results showed that the score of 2 on PHQ-2 indicates the highest Youden's index of 0.924, with both sensitivity and specificity of 0.96, and the area under the curve for PHQ-2 was 0.98 (95%CI: 0.953-0.998).

Research perspectives

HIV patients are more likely than the general population to develop depression. The PHQ-2 and PHQ-9 demonstrated good psychometric properties, implying that they might be helpful as depression screening tools.

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FOOTNOTES

Author contributions: All authors contributed to the concept of this study; Junaid K, Akram I conceived the study; Daood M carried out the literature searches; Junaid K distributed the questionnaires and extracted the data; Daood M assessed the study quality; Junaid K and Khan A performed the statistical analysis; Junaid K and Daood M wrote the manuscript; Khan A revised the manuscript; all the authors read the published version of the manuscript and gave their consent.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of Jinnah hospital Lahore, Pakistan.

Informed consent statement: Informed consent was obtained from all patients for being included in the study.

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SYSTEMATIC REVIEWS

Mortality rate of COVID-19 infection in end stage kidney disease patients on maintenance hemodialysis: A systematic review and meta-analysis

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) has been the most talked-about disease of the past few years. Patients with significant comorbidities have been at particular risk of adverse outcomes. This study looked at the outcomes and risk factors for adverse outcomes among patients on chronic hemodialysis for end-stage renal disease, a group of patients known to be particularly susceptible to infectious complications.

AIM

To assess outcomes and risk factors for adverse outcomes of COVID-19 infection among patients on chronic hemodialysis.

METHODS

We searched PubMed/MEDLINE, EMBASE, *Reference Citation Analysis* (https://www.referencecitationanalysis.com/) and Web of Science databases for relevant

terms and imported the results into the Covidence platform. From there, studies were assessed in two stages for relevance and quality, and data from studies that satisfied all the requirements were extracted into a spreadsheet. The data was then analyzed descriptively and statistically.

RESULTS

Of the 920 studies identified through the initial database search, only 17 were included in the final analysis. The studies included in the analysis were mostly carried out during the first wave. We found that COVID-19 incidence among patients on hemodialysis was significant, over 10% in some studies. Those who developed COVID-19 infection were most likely going to be hospitalized, and over 1 in 5 died from the infection. Intensive care unit admission rate was lower than the infection lethality rate. Biochemical abnormalities and dyspnea were generally reported to be associated with adverse outcomes.

CONCLUSION

This systematic review confirms that patients on chronic hemodialysis are very high-risk individuals for COVID-19 infections, and a significant proportion was infected during the first wave. Their prognosis is overall much worse than in the general population, and every effort needs to be made to decrease their exposure.

Key Words: COVID-19; End stage kidney disease; Mortality; Maintenance hemodialysis; Infection; Systematic review

Core tip: This is a systematic review to find out the mortality of coronavirus disease 2019 (COVID-19) infection in end stage kidney disease patients that are on regular maintenance hemodialysis. We found that COVID-19 incidence among patients on hemodialysis was significant, over 10% in some studies. Those who developed COVID-19 infection were most likely going to be hospitalized, and over 1 in 5 died from the infection. Intensive care unit admission rate was lower than the infection lethality rate. Biochemical abnormalities and dyspnea were generally reported to be associated with adverse outcomes.

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INTRODUCTION

Since early 2020, the coronavirus disease 2019 (COVID-19) pandemic has caused hundreds of thousands of deaths in the United States and millions worldwide, alongside unprecedented disruptions in everyday life. Elderly and patients with significant comorbidities are known to be more susceptible to severe forms of both viral and bacterial respiratory infections, and the same has been shown to be true with COVID-19[1-3]. Chronic kidney disease (CKD) is one of the most prevalent chronic conditions in the United States[4]. The high prevalence of diseases that frequently lead to CKD, such as cardiac disease, hypertension, and diabetes, likely means that the prevalence of CKD will remain high in years to come.

Patients with end-stage renal disease (ESRD) requiring hemodialysis are likely to be especially susceptible to infections. Infection-related complications in those patients exceed 40 in 100 patients per year[5]. Patients with ESRD often undergo in-center hemodialysis, making it more difficult to physically separate for infection control purposes. Also, frequent visits to healthcare facilities for routine check-ups may contribute to infection spread. Additionally, this group's comorbidities make them immunodeficient, increasing their risk of infection[6].

Furthermore, evidence suggests a high frequency of acute kidney injury (AKI) development among patients hospitalized with COVID-19, which is associated with significant mortality[7,8]. AKI is also a known risk factor for CKD development and progression[9].

All these factors make it plausible that COVID-19 would be an especially severe disease in patients with end-stage renal disease on hemodialysis. Due to the high prevalence of ESRD requiring HD and the number of COVID-19 infections worldwide, determining the actual impact COVID-19 has on this

population could enable clinicians to target the factors associated with increased mortality and, subsequently, improve the care they provide are delivering.

This systematic review will attempt to determine the prognosis of end-stage renal disease patients on hemodialysis who test positive for COVID-19 and any clinical or laboratory findings associated with adverse outcomes.

MATERIALS AND METHODS

Data sources and literature search

The databases used for our systematic review were PubMed/MEDLINE, EMBASE, *Reference Citation Analysis* (https://www.referencecitationanalysis.com/) and Web of Science, up to date as of April 10, 2022. The review aims to follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search strategy for the PubMed database was: ("COVID-19"[Mesh] OR "SARS-CoV-2"[Mesh] OR "COVID-19" OR "COVID19" OR "novel coronavirus" OR "coronavirus 2019" OR "COVID" OR "SARS-CoV-2") AND ("Kidney Failure, Chronic"[Mesh] OR "CKD" OR "chronic kidney disease" OR "end-stage renal disease" OR "ESRD" OR " end stage kidney disease (ESKD) " OR "end-stage kidney disease" OR "end-stage renal disease" OR "end-stage kidney disease") AND ("Renal Dialysis"[Mesh] OR "renal dialysis" OR "hemodialysis" OR "dialysis") AND ("Prognosis"[Mesh] OR "Mortality"[Mesh] OR "Survival"[Mesh] OR "prognosis" OR "lethality" OR "mortality" OR "survival"). The search strategy for Web of Science and Embase was: ("COVID-19" OR "COVID 19" OR "novel coronavirus" OR "coronavirus 2019" OR "COVID" OR "SARS-CoV-2") AND ("CKD" OR "chronic kidney disease" OR "end-stage renal disease" OR "ESRD" OR "ESKD" OR "end-stage kidney disease" OR "end-stage renal disease" OR "end-stage kidney disease") AND ("renal dialysis" OR "hemodialysis" OR "dialysis") AND ("prognosis" OR "lethality" OR "mortality" OR "survival").

Articles were then imported into the Covidence platform, which automatically removed duplicates. Two reviewers then independently screened titles and abstracts for relevance. Conflicts were resolved through direct communication between the two reviewers. Where consensus could not be reached, the third reviewer made the decision.

Afterward, full texts were obtained and screened for relevance. Those that were deemed relevant were assessed for quality using the National Institute of Health scoring systems according to the type of study in question, and only those studies that scored no less than three points below the maximum were included in the final review.

Eligibility criteria

We included prospective and retrospective observational studies as well as clinical trials if they involved at least 100 adult patients with end-stage renal disease on chronic hemodialysis who developed COVID-19 infection. We excluded case reports, case series, all review articles, conference abstracts, letters, communications, and editorials. We also excluded studies that were written in languages other than English and those that could not be retrieved. Equally, we excluded studies that pertained to pediatric patients and those that involved patients on peritoneal dialysis.

Data extraction and quality assessment

A spreadsheet was created and used as a data extraction tool. The following data were extracted for all the studies: authors, title, quality assessment score, number of patients who were studied, the incidence of COVID-19 among patients on hemodialysis, number of patients who required intensive care unit (ICU) level of care, number of deaths, as well as any findings that were found to be associated with increased risk of death or severe disease.

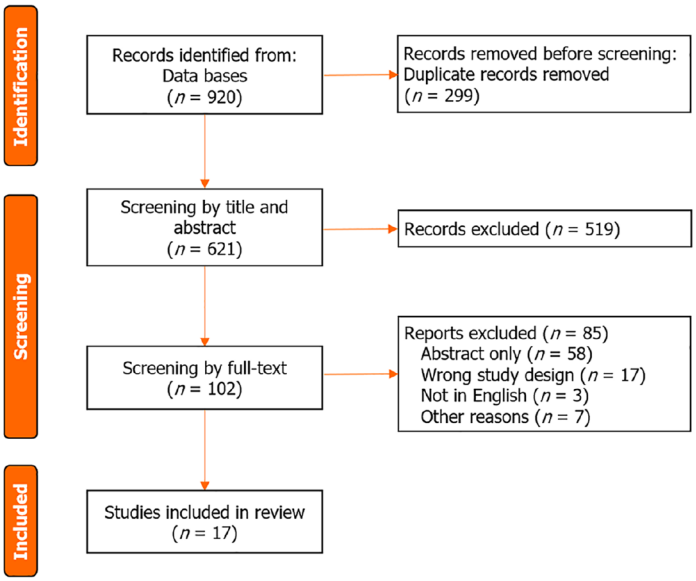
Statistical analysis

Data were entered into the spreadsheet and analyzed descriptively. Afterward, statistical analysis was done using SPSS software, and the results were presented in the form of a forest plot.

RESULTS

We found 920 articles through databases search. The 299 duplicate articles were automatically removed by the Covidence platform. The authors screened the titles and abstracts of 621 articles for relevance. The 519 articles were excluded at that stage. A total of 102 full texts were assessed for quality and relevance, and 85 of them were excluded. A total of 17 articles were included in our analysis, comprising a total of 37280 patients (Figure 1).

The number of ICU admissions was reported in 9 studies. The pooled analysis showed incidence of ICU admission of 17.4% (95%CI: 0.114-0.235) with high heterogeneity (I^2 = 95.59%, P < 0.001) (Figure 2A).



DOI: 10.5501/wjv.v11.i5.352

Figure 1 PRISMA image.

The number of hospital admissions was reported in 5 studies. The incidence of hospitalization after COVID-19 infection among patients included in those studies is 64.4% (95%CI: 0.521-0.767) with high heterogeneity (I^2 = 97.18%, P < 0.001) (Figure 2B).

All 17 studies reported mortality. The pooled estimate showed the incidence of mortality to be 23.3% (95%CI: 0.205-0.261) with significant heterogenicity I^2 = 88.52%, P < 0.001) (Figure 2C).

DISCUSSION

COVID -19 incidence

Not all the studies that were included in this review analyzed both the incidence and prognosis of COVID-19 patients on chronic hemodialysis. The incidence of COVID-19 is very difficult to analyze, considering that different studies looked at very different patient populations and different periods. However, several studies looked at the incidence in 2020, before vaccines were available. Lugon *et al*[10] reported that 741 out of 9877 Brazilian patients developed COVID-19 in 2020. Savino *et al*[11] reported the incidence of 4408 out of 22415 in England, Wales, and Northern Ireland; however, their study included the month of January 2021, when the United Kingdom was averaging tens of thousands of cases per day, the highest recorded up to that point in time[11,12]. De Meester *et al*[13] and Keller *et al*[14] reported a lower incidence, but their study period ended in May 2020, only including the infections that occurred during the first wave. Marino *et al*[15], however, reported a relatively low incidence of only 256 out of 4942 with their study period extending to November 2020 but still not taking into account the spike in winter 2020/2021, unlike Savino *et al*[11]. Ozturk *et al*[16] reported the incidence of 148 out of 746 until 05/11/2020 only in a single center in London, which is notably higher than in other studies covering the same study period.

The reported incidence of COVID-19 in patients on chronic hemodialysis is higher than in the general population, where the overall incidence in the first wave was relatively low despite the havoc it caused [12,17]. Cases started rising significantly in the winter of 2020/2021, but only Savino *et al*[11] covered the majority of that wave[12,17]. It needs to be said, however, that part of the explanation for the low incidence of COVID-19 during the first wave can be explained by the scarcity of testing for the general public, while patients on chronic hemodialysis would likely have been among the first ones to get tested, skewing the incidence numbers. It is also true that patients on chronic hemodialysis clearly have been in a very precarious and vulnerable position early in the pandemic. They were required to spend significant amounts of time in health care facilities when both tests and personal protective equipment were not widely available. Overall, while it is likely that the results were skewed by a difference in the availability of tests between hemodialysis patients and the general public, it is still likely that the incidence of COVID-19 infections among them was higher.

COVID-19 prognosis

There are multiple ways to look at the COVID-19 prognosis. In terms of the risk of hospitalization, it is significant among patients with end-stage renal disease. However, it is important to note that hospital-

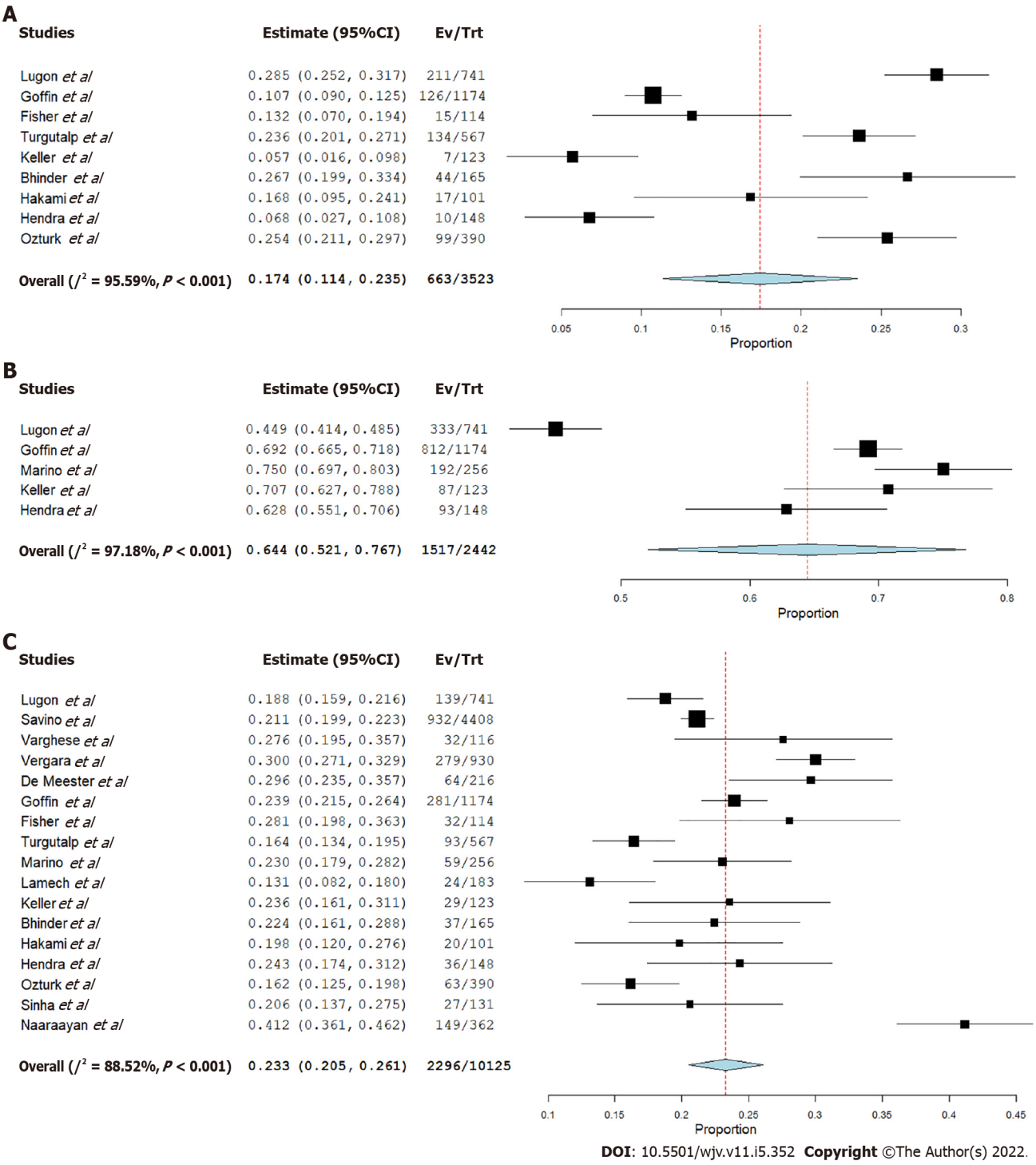


Figure 2 Forest plot. A: Incidence of intensive care unit admission; B: Incidence of hospital admission; C: Incidence of death.

ization criteria vary between institutions, and if, for example, desaturation is required to admit a patient without significant comorbidities, a far lower threshold may be employed for patients with ESRD. Furthermore, some of the studies only looked at hospitalized patients, possibly skewing numbers. In addition, most of the studies were done early in the course of the pandemic when the criteria were less clear, and there was a significant scarcity of ICU beds. That probably explains why in some of the studies, the incidence of death was higher than the incidence of ICU admission. While determining the exact COVID-19 Lethality is difficult due to the unknown number of cases that are undetected, what is undoubtedly true is that prognosis of COVID-19 infection is significantly worse in ESRD patients compared to the general public. In the studies involved in this systematic review, almost two-thirds of all the patients infected by COVID-19 were hospitalized, with 17.4% (95%CI: 0.114-0.235) $P < 0.001$ requiring ICU admission and 23.3% (95%CI: 0.205-0.261) $P < 0.001$ ultimately succumbing to the infection. There are no major outliers in terms of mortality, but it should be noted that studies such as Ozturk *et al*[16], Fisher *et al*[18], Turgutalp *et al*[19], Bhinder *et al*[20], Hakami *et al*[21], Sinha *et al*[22],

and Naaraayan *et al*[23] only reported cases that led to hospitalization so the mortality rates in those articles may be less representative unless a way to adjust them for hospitalization rate was found. A possibly relevant study to point to is Lamech *et al* which reported that close to one-third of all patients who tested positive for COVID-19 required mechanical ventilation[24]. HD itself may be an independent risk factor for mortality because, despite the required immunosuppressive treatment, Goffin *et al*[25] found mortality significantly lower among kidney transplant recipients than patients with HD. At the same time, De Meester *et al*[13] found that overall mortality among HD patients did not increase compared to pre-pandemic levels. That finding is surprising given that both Lugon *et al*[10] and Savino *et al*[11] found that a very significant proportion of HD patients developed COVID-19, and almost all the studies showed that those who do get infected are at significant risk of mortality. That would ordinarily raise the question about a possible selection bias in De Meester *et al*[13]; however, the study included the entire hemodialysis population of a region in Belgium, so barring a significant environmental confounder in that particular region, the study should be generalizable.

Risk factors for mortality

We looked at a number of risk factors that may be associated with mortality among hemodialysis patients who got infected by COVID-19. A number of prior studies suggest that diabetes worsens the prognosis of COVID-19[26]. Lugon *et al*[10] found a statistically significant association between diabetes and COVID-19 mortality among HD patients with an HR of 1.52 (1.05–2.19) $P = 0.026$. Hakami *et al*[21], Sinha *et al*[22], and Varghese *et al*[27] similarly found diabetes to be associated with COVID-19 mortality. Savino *et al*[11], Fisher *et al*[18], Turgutalp *et al*[19], Marino *et al*[15], Lamech *et al*[24], and Hendra *et al*[28] found no statistically significant difference in mortality among those with diabetes. While it can be assumed that this can be explained by sample sizes alone, that is not the case since the Savino *et al*[11] study included 4408 patients. Overall, those findings are difficult to interpret. Diabetes is a common cause of end-stage renal disease that also seems to worsen COVID-19 outcomes in the general population; however, it needs to be noted that all ESRD patients have significant comorbidity at baseline, and it remains unclear whether diabetes is uniquely associated with COVID-19 mortality compared to other conditions which also lead to ESRD.

Several studies looked at the association between common laboratory values and COVID-19 mortality. White blood cell (WBC) count and C-reactive peptide (CRP) were commonly reported as they normally correlate with the severity of infections. Varghese *et al*[27] and Hendra *et al*[28] found both to be associated with mortality, with CRP difference between those who died and those who survived being reported as 78.82 ± 89.16 *vs* 40.49 ± 43.16 ($P = 0.002$) by Varghese *et al*[27] and 128.0 (75.0-261.8) *vs* 40.5 (23.0-108.8) $P < 0.0001$ by Hendra *et al*[28] and WBC count difference 14.14 ± 8.88 *vs* 6.03 ± 2.37 ($P = 0.001$) reported by Varghese *et al*[27] and 7.45 (5.6-9.8) *vs* 5.40 (4-7) $P = 0.0007$ by Hendra *et al*[28]. In the study done by Keller *et al*[14], CRP was found to be associated with mortality [14.2 (10.2-27) *vs* 9.3 (3.8-18.9) $P = 0.005$], while WBC count was not [6.7 (4.7-9.5) *vs* 5.5 (3.9-7.6) $P = 0.6$]. Hakami *et al*[21] and Sinha *et al*[22] only reported the WBC difference as follows: 9.1 ± 1.3 *vs* 6.3 ± 0.4 $P = 0.04$ reported by Hakami *et al*[21] and 11.059 ± 5929 *vs* 7022 ± 2935 $P < 0.001$ reported by Sinha *et al*[22]. Keller *et al*[14] only reported the CRP difference and found it to be statistically significant: 95 (49-192) *vs* 44.5 (19-92) $P = 0.0003$.

Overall, it does appear that elevations in both CRP and WBC count are associated with worse outcomes. A meta-analysis by Malik *et al*[29] also reported that CRP elevation is associated with adverse outcomes in COVID-19 in the general population. It is worth noting that a number of conditions and treatments other than COVID-19 can be associated with CRP and WBC elevations. For example, corticosteroids can lead to elevated WBC counts, and corticosteroids are a common treatment for both severe COVID-19 and a number of conditions that may ultimately lead to ESRD. Further subgroup analysis would be required to evaluate further whether a significant confounder exists.

Varghese *et al*[27] also found hyponatremia and hyperkalemia to be associated with poor outcomes, while studies by Hakami *et al*[21] and Sinha *et al*[22] found no significant difference in outcomes based on sodium or potassium levels. Electrolyte abnormalities would, in general, be expected among patients on hemodialysis, especially on days when dialysis sessions are not scheduled. However, other studies have found that both sodium and potassium abnormalities are associated with worse COVID-19 outcomes in the general population[30,31]. It is almost undeniably true that every effort should be made to keep electrolytes within reference ranges, whether hyponatremia and hyperkalemia at presentation are associated with increased COVID-19 severity or simply a consequence of the dialysis schedule.

Ferritin is both an inflammatory marker and a relevant marker of iron stores in the body. Five of the studies included in this analysis looked at the significance of ferritin in determining the prognosis of COVID-19, and all found ferritin to be significantly higher among hemodialysis patients who succumb to COVID-19 in comparison to those who survive[18,19,21,27,28]. It is notable, however, that average ferritin levels varied widely between studies, and while in each study, patients with higher ferritin were more likely to die, in some studies, even the levels among those who survived were notably higher than those of those who died in a different study. Moreover, it needs to be remembered that patients with ESRD are likely to be anemic at baseline. Therefore, even though all the studies point towards an association between higher ferritin and mortality, it is difficult to interpret clinically.

Finally, dyspnea is one of the most common symptoms of severe respiratory infection, and decreased oxygen saturation is a marker of worsening respiratory status. The same has generally held true for COVID-19 throughout the pandemic, and oxygen saturation level is frequently used as one of the main criteria for the hospital admission. As would be expected, both dyspnea and oxygen saturation were associated with mortality. Of the five studies that analyzed the association between dyspnea and COVID-19 mortality in HD patients, all 5 showed statistical significance, with a *P* value never reaching 0.03[15,19,21,22,27]. Studies by Varghese *et al*[27] and Fisher *et al*[18] found a significant association between lower SpO_2 and mortality. Keller *et al*[14] and Hendra *et al*[28] failed to find a significant association. It should be noted that all 4 of the aforementioned studies had relatively small sample sizes, and oxygen saturation generally falls within a narrow range, likely impacting some of the findings. Moreover, patients tend to desaturate later in the course of the disease, and if HD patients were admitted to the hospital early due to their pre-existing comorbidities, it is possible that this could make SpO_2 at presentation less reliable as an indicator of COVID-19 severity in those patients.

Limitations

The study has several notable limitations. Firstly, most of the studies only looked at COVID-19 prognosis in the early phases of the pandemic when treatment options were also more limited, and no vaccines were available. Secondly, we excluded three as they were written in languages other than English. The way data was reported varied across studies, limiting the number of studies that reported each variable. Finally, hospital and ICU admission criteria vary between institutions, so they may not be a perfect indicator of disease severity.

CONCLUSION

Patients on chronic hemodialysis due to end-stage renal disease are among the most vulnerable members of society at increased risk of both catching and succumbing to COVID-19 infection. We found that the incidence of COVID-19 in hemodialysis patients was significant, and in some studies, more than one-tenth caught COVID-19 during the first wave. The prognosis was overall much poorer than in the general population, with the majority requiring hospitalization and more than one in five deaths. Generally, biochemical abnormalities and early dyspnea were associated with a higher degree of mortality. It would be interesting to see how much the numbers would change if the same studies were done during subsequent COVID-19 waves.

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease 2019 (COVID-19) has been the most talked-about disease of the past few years. Patients with significant comorbidities have been at particular risk of adverse outcomes. We looked at the outcomes and risk factors for adverse outcomes among patients on chronic hemodialysis.

Research motivation

The authors assess outcomes and risk factors for adverse outcomes of COVID-19 infection among patients on chronic hemodialysis.

Research objectives

The objective of this study is to assess outcomes and risk factors for adverse outcomes of COVID-19 infection among patients on chronic hemodialysis.

Research methods

The authors searched PubMed/MEDLINE, EMBASE, *Reference Citation Analysis* (https://www.referencecitationanalysis.com/) and Web of Science databases for relevant terms and imported the results into the Covidence platform. From there, studies were assessed in two stages for relevance and quality, and data from studies that satisfied all the requirements were extracted into a spreadsheet. The data was then analyzed descriptively and statistically.

Research results

Of the 920 studies identified through the initial database search, only 17 were included in the final analysis. The studies included in the analysis were mostly carried out during the first wave. The authors found that COVID-19 incidence among patients on hemodialysis was significant, over 10% in some studies. Those who developed COVID-19 infection were most likely going to be hospitalized, and over 1 in 5 died from the infection. ICU admission rate was lower than the infection lethality rate. Biochemical

abnormalities and dyspnea were generally reported to be associated with adverse outcomes.

Research conclusions

This systematic review confirms that patients on chronic hemodialysis are very high-risk individuals for COVID-19 infections, and a significant proportion was infected during the first wave. Their prognosis is overall much worse than in the general population, and every effort needs to be made to decrease their exposure.

Research perspectives

Further research can be done to assess the efficacy of protective measures and vaccines against COVID-19 among dialysis patients.

FOOTNOTES

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SYSTEMATIC REVIEWS

Anatomophysiological relationships and clinical considerations of taste and smell loss in patients with COVID-19

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Abstract

BACKGROUND

There are numerous conflicting discussions about the outbreak of the new coronavirus 2019 (COVID-19).

AIM

To present some anatomical and physiological considerations about two of the symptoms reported by patients: The loss or reduction of smell and taste.

METHODS

The loss or reduction of smell and taste is presented in a peculiar way, with some cases of persistence even after COVID-19. For this, it was searched in three databases, PubMed/MEDLINE, Web of Science, and Scopus, using the following keywords: "Smell", "Taste", "Smell AND COVID-19", "Taste AND COVID-19", with no publication time restriction, only in English with full text available, excluding also brief communications, letters to the editor, editorials, reviews, comments, and conference abstracts.

RESULTS

The search found 776 articles in the PubMed/MEDLINE database, 1018 in the Web of Science database, and 552 in the Scopus database, from which duplicates were removed (104 articles). Finally, 17 studies were selected for detailed analysis

within the eligibility criteria, with titles and abstracts related to central nervous system lesions responsible for smell and taste. This review suggests that viral mechanisms of action may be related to lesions both at the local level and at the level of the central nervous system, lasting up to 3 to 4 wk. It is considered persistent if it exceeds this period, as reported in one case in this review. There are still few studies about the treatment, and among those addressed in this review, only two studies reported possible treatments and emphasized the scarcity of data, with the best option being treatments that do not cause harm, such as gustatory and olfactory physiotherapy

CONCLUSION

Given the scarcity of data, this review emphasizes the importance of prevention, through the correct use of personal protective equipment by health professionals and respect for local behavioral indications. It is also emphasized, through five studies, that there is a predominance of such symptoms in patients with COVID-19, which can be a tool to control dissemination, through the early isolation of patients until the results are ready.

Key Words: SARS-CoV-2; COVID-19; Coronavirus; Olfactory nerve; Smell; Taste

Core Tip: We discuss the anatomical and physiological considerations about two of the symptoms reported by patients: The loss or reduction of smell and taste. There are still few studies about the treatment, and among those addressed in this review, only two studies reported possible treatments and emphasized the scarcity of data, with the best option being treatments that do not cause harm, such as gustatory and olfactory physiotherapy. Given the scarcity of data, this review emphasizes the importance of prevention, through the correct use of personal protective equipment by health professionals and respect for local behavioral indications. It is also emphasized, through five studies, that there is a predominance of such symptoms in patients with coronavirus disease 2019, which can be a tool to control dissemination, through the early isolation of patients until the results are ready.

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INTRODUCTION

In December 2019 in Wuhan (China), the emergence of an acute respiratory syndrome caused by severe acute respiratory syndrome coronavirus 2 CoV (SARS-CoV-2), with a peculiar and highly contagious behavior, was reported[1]. Thus, the World Health Organization decreed on March 11, 2020 a state of pandemic, considering the condition of community transmission of human infection by the virus[2]. In the current world scenario, there are already approximately 493 million infected and 6.1 million dead people. In Brazil, there are approximately 30.1 million infected and 661 thousand dead ones[2]. Such global and national data are alarming and may be related to the high speed of dissemination, high mortality rate in people with comorbidity, and the coping strategies of each country, as well as socioeconomic and health conditions[3,4].

The clinical manifestations of the new coronavirus (COVID-19) are very varied, with the most common symptoms being fever (74%), cough (79%), fatigue (75%), headache (78%), gastrointestinal disorders (57%), and loss of smell (63%) and taste (65%). These symptoms, when present, lead to the diagnostic suspicion of COVID-19, until confirmed by examinations[5,6]. The sensory pathway of smell is initially given by the nerve endings of the olfactory nerve, the primary olfactory neuron, located in the upper third of the nasal cavity and nasal septum, stimulated by chemical substances from the air that are transformed into action potential[7-9]. This stimulus travels through the primary neuron crossing the cribriform plate of the ethmoid bone through its foramina[8]. Upon accessing the anterior cavity of the skull, they synapse with the secondary neuron. The olfactory nerve impulses terminate in the primary cortical projection area and travel to the thalamus, which proceeds to the orbitofrontal and rectus olfactory gyrus (Figure 1). There is also an association of some odors with the limbic system, causing reactions of pleasure or aversion[8-11] (Figures 2 and 3).

Taste is provided by the specialized sensitivity of the tongue, *via* the glossopharyngeal nerve (IX cranial nerve) in the posterior third, vagus nerve (X cranial nerve) with few branches at the base of the

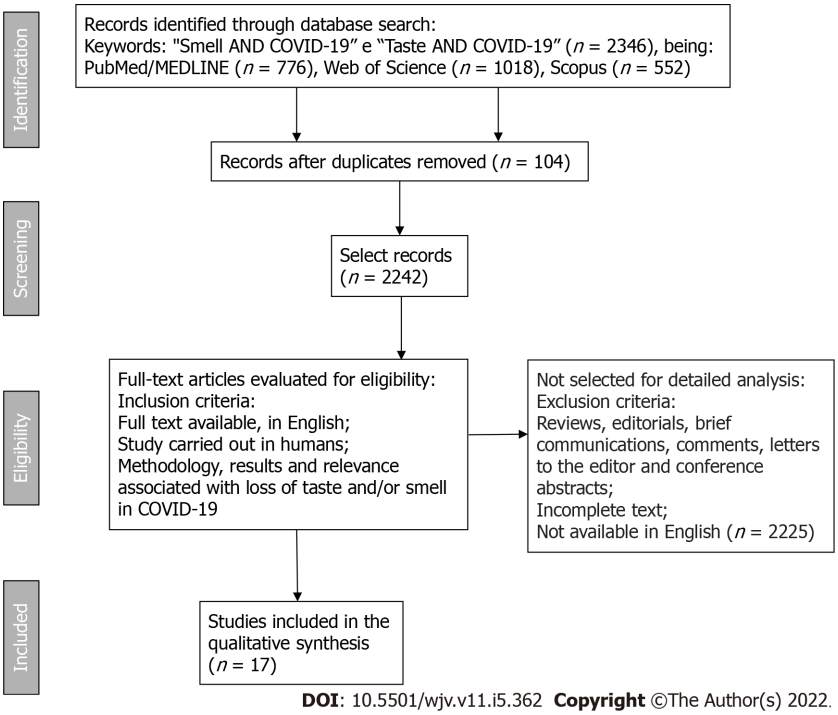

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Figure 1 Flow diagram showing the selection of articles in the PubMed/MEDLINE, Web of Science, and Scopus databases. COVID-19: The new coronavirus 2019.

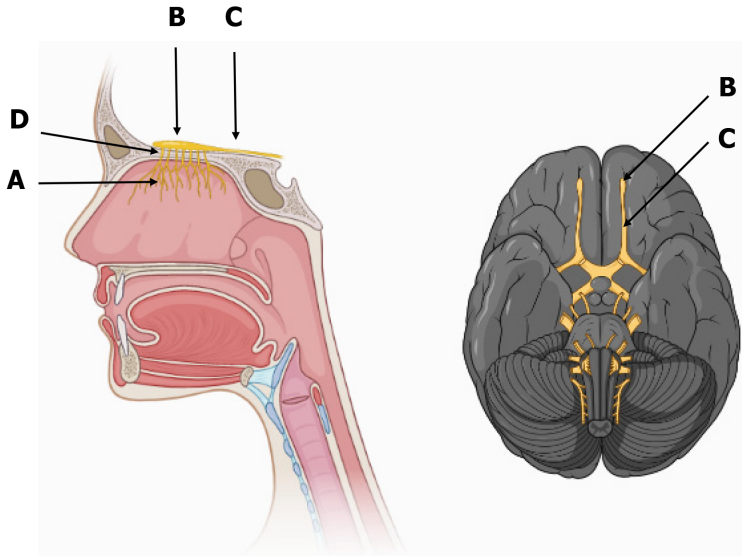

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Figure 2 Olfactory pathway and its components. A: Fillets of the olfactory nerves, the first pair of cranial nerves, inside the nasal cavity in the upper third of the nasal septum; B: Olfactory bulb; C: Olfactory tract; D: Cribriform plate of the ethmoid bone, which communicates the nasal cavity with the anterior cranial fossa.

tongue and epiglottis, and chorda tympani nerve (branch of the VII cranial nerve, the facial-intermediate nerve) in the anterior two thirds of the tongue[7,8]. They receive the stimulus through taste buds that are made up of epithelial cells that have different receptors for each type of flavor, distributed throughout the tongue[12]. From there, the stimuli travel through the primary afferent fibers of the respective gustatory sensory nerves to the solitary tract in the medulla, then to the thalamus, passing to the cortex[8] (Figures 4 and 5).

Given this context, research has sought strategies in order to clarify the sensory alterations of loss of smell and taste, the possible mechanism of action of the virus in these nerves, and its treatment. Thus, the present study aimed to review the anatomy and physiology of the olfactory and gustatory pathways, and their relationship with symptomatology in patients with COVID-19.

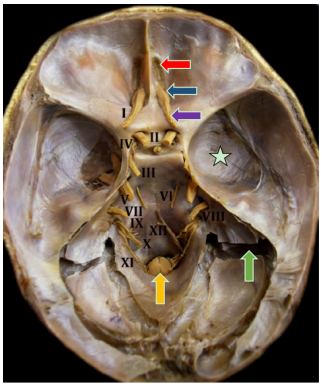

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Figure 3 Endocranial view of the 12 pairs of cranial nerves in a natural anatomical piece. I: Olfactory nerve; II: Optic nerve; III: Oculomotor nerve; IV: Trochlear nerve; V: Trigeminal nerve; VI: Abducens nerve; VII: Facial and intermediate nerve; VIII: Vestibulocochlear nerve; IX: Glossopharyngeal nerve; X: Vagus nerve; XI: Accessory nerve; XII: Hypoglossal nerve. Red arrow indicates the cribriform plate of the ethmoid bone; blue arrow indicates the olfactory bulb; purple arrow indicates the olfactory tract; yellow arrow indicates the beginning of the spinal cord at the level of the foramen magnum; green arrow indicates the sigmoid sinus; white star indicates the cranial dura mater.

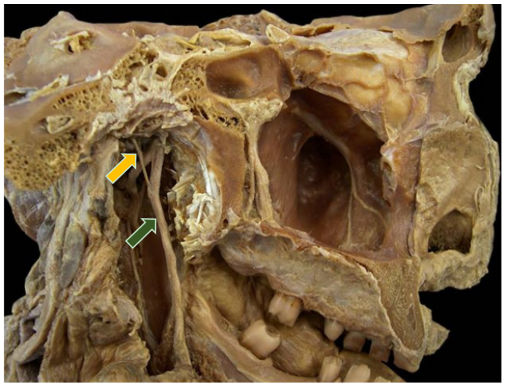

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Figure 4 Natural anatomical piece in midsagittal section (medial view). Yellow arrow represents the chorda tympani nerve, a branch of the intermediate nerve; green arrow represents the lingual nerve, a branch of the mandibular division of the trigeminal nerve.

MATERIALS AND METHODS

For this study, PubMed/MEDLINE, Web of Science, and Scopus databases were searched, using the following terms as keywords: "Smell", "Taste", "Smell AND COVID-19", "Taste AND COVID -19", without publication time restriction and only in the English language. Works that present titles and abstracts related to the topic of the initial research were verified, using the variables taste and/or smell and COVID-19. Subsequently, the text was evaluated of the articles previously selected by the abstract. The methodology, results, and relevance were considered to list the choice of articles. For inclusion in the research, the articles must necessarily be accessed in their full content (Figure 1).

The inclusion criteria were: Description of changes in smell and taste due to COVID-19; Human studies; Publications in English only; Publications that allow full access to the text. The exclusion criteria were: Articles that have been duplicated; Animal studies; The title was not related to the objective; There was no loss of taste; There was no loss of smell; Other languages (except English); Access to the full text has not been obtained; Brief communications, letters to the editor, editorials, reviews, comments, and conference abstracts.

RESULTS

The search found 776 articles in the PubMed/MEDLINE database, 1018 in the Web of Science database, and 552 in the Scopus database, from which duplicates were removed (104 articles), then editorials, review articles, brief communications, letters to the editor, comments, conference abstracts, and articles without full text available or not produced in English were excluded, as they are outside the eligibility criteria. Seventeen studies that met the eligibility criteria were selected (Table 1).

Table 1 Seventeen studies that meet the eligibility criteria

Database	Title	Ref.	Sample/study type	Conclusion	Anatomophysiological relationship
PubMed/MEDLINE and Web of Science	A structural equation model to examine the clinical features of mild to moderate coronavirus disease 2019 (COVID-19): An Italian multicenter study	Barillari *et al* [15], 2021	294 patients/multicenter study	It has been reported that anosmia should be considered as a specific symptom for COVID-19, especially when the patient is "suspected" or untested	Inflammation in the olfactory epithelium or damage to olfactory receptor neurons, since the cells that make up this tissue have high expression of ACE2 and TMPRSS2, which have a strong capacity to bind the virus, being particularly susceptible to infection
PubMed/MEDLINE and Web of Science	Acute loss of smell and taste among patients with symptoms compatible with COVID-19	Bodnia and Katzeinstein [20], 2020	95 patients/cross-sectional study	There was persistence of mild olfactory and/or taste changes even after the other symptoms of COVID-19 had disappeared. In addition, loss of smell and taste was reported in 50% of patients with COVID-19, especially in adults	Human angiotensin-converting enzyme 2 is the main receptor of the SARS-CoV-2 host cell, present in nasal and olfactory respiratory epithelial cells. In addition, ACE2 is expressed in the oral cavity
PubMed/MEDLINE	Anosmia in COVID-19 associated with olfactory bulb lesion evidenced on MRI	Aragão *et al* [19], 2020	5 patients/retrospective study	This study documented for the first time, through neuroimaging, a type of lesion of the olfactory bulb in patients with COVID-19, demonstrating that the possible mechanism of action that causes olfactory dysfunction, either through the olfactory bulbs or intracranially, by a microvascular phenomenon	Intracranial olfactory bulb lesion, studied and documented by magnetic resonance imaging
PubMed/MEDLINE	COVID-19 viral load in the severity and recovery of olfactory and gustatory dysfunction	Cho *et al* [21], 2020	143 patients/Prospective cross-sectional cohort study	Symptom severity is not correlated with SARS-CoV-2 viral load, and there is a high prevalence of olfactory and gustatory dysfunction in COVID-19	The virus has affinity for ACE2 receptors that are found in the nasal and olfactory epithelium, causing peripheral neuropathy, which affects the functions of smell and taste. The virus is also able to invade the central nervous system through the olfactory bulb
PubMed/MEDLINE and Scopus	Evolution of olfactory disorders in patients with COVID-19	Gorzkowski *et al*[14], 2020	229 patients/Cross-sectional study	Olfactory and taste disturbances can be an isolated symptom of COVID-19, being reported in two-thirds of COVID-19 patients. Knowledge of these symptoms and their evolution can be useful in creating therapeutic strategies for cases of persistence even after the resolution of other symptoms of COVID-19	Mechanisms of olfactory disorders related to SARS-CoV-2 infection are still unknown, but it is likely to be associated with the outcomes of various patterns, such as nasal mucosa edema, olfactory epithelial damage (including neural and non-neural epithelium), and even involvement of olfactory pathways
PubMed/MEDLINE and Web of Science	Frequency and outcome of olfactory impairment and sinonasal involvement in hospitalized patients with COVID-19	Jalessi *et al* [22], 2020	100 patients/prospective descriptive study	In patients with COVID-19, there is a high prevalence of sudden temporary olfactory loss and upper airway infection symptoms. However, among all these symptoms, there was a predominance of olfactory loss, showing that this symptom is not associated with the generalized mucosal edema that occurs during an upper respiratory infection with common coronaviruses	Binding between ACE2 receptors and SARS-CoV-2 spike protein on target cells. In addition, infected cells secrete pro-inflammatory cytokines and chemokines, which can generate localized edema
PubMed/MEDLINE	Importance of anosmia in SARS-CoV-2: from phenomenology for neurobiology	Pallanti[13], 2020	2 patients/descriptive study	Anosmia and hypogeusia among respiratory symptoms can be considered a symptom of COVID-19 infection, if confirmed; these symptoms	The neuroinvasive potential of SARS-CoV-2 was highlighted: When penetrated transnasally, it may access the brain, possibly *via* the olfactory torsion nerves, and

				could represent early markers or signs of SARS-CoV-2 infection to trigger quarantine. These symptoms go beyond sensory aspects, involving extensive neural circuits	from there rapidly spread to some specific brain areas, including the thalamus and brainstem
PubMed/MEDLINE and Web of Science	Loss of smell in COVID-19 patients: MRI data reveal transient swelling of the olfactory clefts	Eliezer *et al* [16], 2020	20 patients/prospective, mono-centric, case-controlled study	Olfactory clefts were evaluated, as well as olfactory function in a cohort study of patients with SARS-CoV-2 infection with loss of olfactory function, which was present in the initial phase of the disease, with improvement at 1-mo follow-up, supporting the hypothesis that this loss, in patients infected with SARS-CoV-2, is caused, at least in part, by reversible inflammatory changes in the olfactory epithelium	SARS-CoV-2 infects cells through interactions between its S protein and ACE2 protein on target cells. Furthermore, it is suggested that SARS-CoV-2 could invade the brain through the cribriform plate near the medulla and olfactory epithelium, causing some structural changes in the olfactory bulb
PubMed/MEDLINE and Web of Science	Olfactory dysfunction and sinonasal symptomatology in COVID-19: prevalence, severity, time and associated characteristics	Speth *et al* [17], 2020	103 patients/prospective, cross-sectional	Olfactory dysfunction is very prevalent during COVID-19, often in conjunction with loss of taste. This dysfunction is negatively associated with advanced age and positively associated with female sex	SARS-CoV-2 has great affinity with the host cell surface receptor, ACE2, located in the nasal mucosa, in particular in the ciliated epithelium and goblet cells. In addition, the virus appears to have neurotropism in which olfactory neurons are susceptible to infection
PubMed/MEDLINE	Histopathological findings of the olfactory epithelium reported anosmia due to long-term coronavirus disease 2019	Vaira *et al* [18], 2020	1 patient/case report	3 mo after the onset of COVID-19 anosmia, a biopsy was performed, which showed massive rupture of the olfactory epithelium, changing the focus of invasion of the olfactory bulb, encouraging further studies of treatments aimed at the superficial epithelium	The epithelium showed thinning with loss of the characteristic three-layer structure, and reduction in the number of olfactory receptor cells, while those that were present had no cilia. There was also an irregular regeneration of the olfactory epithelium interspersed with the respiratory epithelium and, in some cases, the olfactory epithelium was replaced by metaplastic squamous epithelium
PubMed/MEDLINE, Web of Science and Scopus	Psychophysical assessment of chemosensory functions after 5 weeks of olfactory loss due to COVID-19: a prospective cohort study in 72 patients	Le Bon *et al* [23], 2021	72 patients/prospective cohort study	Possibly, SARS-CoV-2 mainly affected odor thresholds, suggesting that the main cause of the loss of smell is at the level of the olfactory neuroepithelium rather than the central nervous system	The loss of taste may be related to a direct injury to the taste organ, and ACE2 receptors have been identified in the mouth and, in particular, on the tongue. ACE-2 receptors are also found in olfactory tissue, inducing olfactory loss at the peripheral rather than the more central nervous level. There is thickening of the olfactory cleft mucosa during COVID-19, reporting olfactory neuritis during COVID-19. There may also be viral spread to the central nervous system that started in the olfactory neuroepithelium
PubMed/MEDLINE	Head and neck symptomatology in coronavirus disease (COVID-19): A possible neuroinvasive action of SARS-CoV-2	Freni *et al* [24], 2020	50 patients/ prospective descriptive study	The authors tried to confirm the theories about the neuroinvasiveness of the virus, from a clinical point of view, so the coronaviruses are neurotropic since the neural cells express the ACE2 entry protein, being able to enter the CNS by several routes, mainly by intranasal inoculation and by peripheral nerve pathway using trans-synaptic pathways. In addition, anosmia, dysgeusia, and xerostomia are the first symptoms of COVID-19, which can be exploited for early quarantine and a	SARS-CoV-2 has neuroinvasive and neurotropic properties. First, there is infection of the neuronal olfactory receptor in the olfactory mucosa, then the virus is transported antegrade to the olfactory bulb, and then there is diffusion through channels formed by cells of the olfactory envelope, which form an open connection with the central nervous system

				limitation of viral contagion	
PubMed/MEDLINE	Trends in olfactory and gustatory dysfunction in quarantined COVID-19 patients	Seo *et al*[25], 2020	62 patients/prospective surveillance study	The prevalence of olfactory and gustatory dysfunction was 24.2% in patients with mild COVID-19, which may be characteristic indicators in these cases. All patients had hyposmia due to sensorineural olfactory dysfunction, confirmed by validated methods of olfactory and gustatory assessment and endoscopic examinations	It may involve olfactory neurons related to the central nervous system or non-neuronal olfactory epithelial cells. When viral infection occurs in olfactory neurons, permanent olfactory dysfunction may occur, and even if there is recovery, it may take a long time. Therefore, the location of olfactory neurons with sensorineural olfactory dysfunction can be inferred from the clinical course
Web of Science	Taste and smell disorders in COVID-19 patients: role of interleukin-6	Cazzolla *et al*[26], 2020	125 patients/observational study	This study based on clinical evidence and laboratory data highlighted the importance of IL-6 in the pathogenesis of chemosensitive disorders	Action of local inflammatory phenomena on the receptors of olfactory and gustatory cells, rather than permanent cell damage linked to the action of the virus. The dysfunctions may be linked to the peripheral action of IL-6 at the level of cell receptors infected by the virus and to the central action of IL-6 at the level of intermediate taste stations and olfactory pathways, especially in the thalamus
Scopus	Brain metabolic correlates with persistent olfactory dysfunction after SARS-Cov-2 infection	Donegani *et al*[27], 2021	22 patients/cross-sectional study	The study provided a group analysis on brain metabolism of patients with persistent olfactory dysfunction after infection with SARS-CoV-2 for the first time proven by olfactory test. It highlighted the confusion of the subtle sequelae of SARS-COV-2 infection and its reflection on PET and other biomarkers	The virus can enter the central nervous system through the first neurons of the olfactory pathway located in the olfactory mucosa. Post-infectious olfactory dysfunction is thought to be caused by damage to the olfactory epithelium or central olfactory processing pathways, with current evidence that hypometabolism in two symmetrical and similar regions within the limbic cortex may support the occurrence of distal olfactory pathway involvement
Scopus	Olfactory function and chest CT findings in COVID-19: is there any correlation?	Mangia *et al* [28], 2021	57 patients/cohort-nested cross-sectional study	Olfactory dysfunction does not correlate with radiological lung involvement in hospitalized patients with COVID-19	The nasal mucosa is an important entry site for SARS-COV-2, as it has a predilection for this neuroepithelium, in addition to having neurotrophic properties. The smell disorder in COVID-19 would not arise from local edema and nasal secretion, preventing odor molecules from reaching the olfactory neuroepithelium
Scopus	Structural and metabolic brain abnormalities in patients with sudden loss of smell with COVID-19	Niesen *et al* [29], 2021	12 patients/prospective descriptive study	This PET-MR study suggests that the sudden loss of smell in COVID-19 is not related to central involvement due to SARS-CoV-2 neuroinvasiveness. Loss of smell is associated with subtle brain metabolic changes in high-order central and cortical olfactory areas, likely related to combined processes of deaeration and active functional reorganization secondary to lack of olfactory stimulation	Considering that the metabolic abnormalities were not associated with any MRI signal abnormalities, they likely do not represent neuroimaging evidence supporting the neuroinvasive potential of SARS-CoV-2, but rather functional brain markers of olfactory deficit

ACE2: Angiotensin-converting enzyme 2; COVID-19: Coronavirus 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; MRI: Magnetic resonance imaging; PET: Positron emission tomography; CT: Computed tomography.

DISCUSSION

The present study aimed to select and evaluate articles that elucidate the anatomophysiological relationships of the olfactory and gustatory pathways with the loss of smell and taste as the main symptoms in patients with COVID-19[13,14]. This knowledge can help in the therapeutic approach

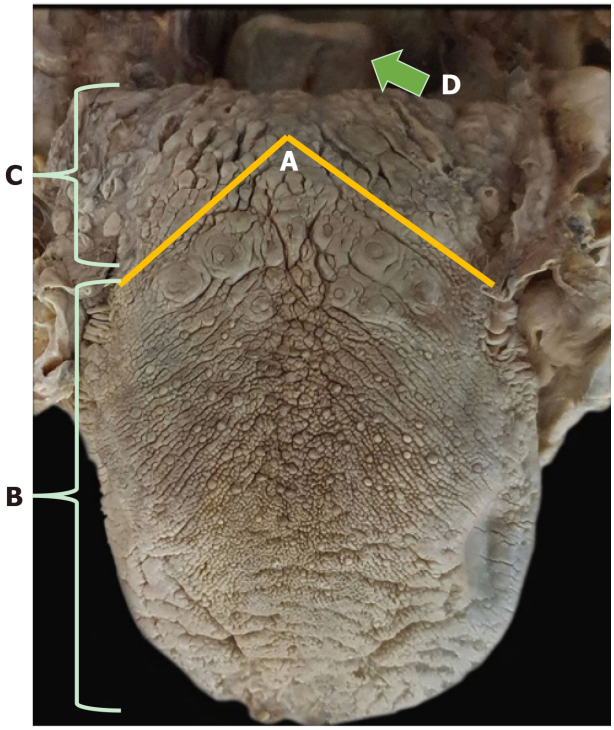

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Figure 5 Dorsal region of the tongue. A-C: Yellow line indicates the terminal sulcus, which separates the tongue into body or two anterior thirds and root or posterior third; D: Green arrow indicates the epiglottis cartilage of the larynx, where taste is made by the vagus nerve.

during infection and in persistent post-infection cases. In addition, by giving due relevance to this symptomatology, which has a high incidence in patients with COVID-19, isolation is possible of patients with this symptomatology, even before the test results, thus decreasing the transmissibility of SARS-CoV-2[13,14].

Among all the articles selected, through the methodology used, the presence of a very variable number of patient samples was found, in addition, there was a variability in the anatomical structure placed as the focus of the discussion, which were studied and evaluated by different parameters. Six articles[15,18,20,22,23,28] focused on the olfactory and gustatory epithelium as the main responsible for the loss of smell and taste, due to the fact that they have angiotensin-converting enzyme 2 (ACE2) receptors, which at the time of the entry of SARS-CoV-2 alter and damage this mucosa, making it unable to act as local chemoreceptors. Eleven articles[13,14,16,17,19,21,24-27,29] in addition to highlighting ACE2 receptors as a gateway, indicate the olfactory pathways as the access pathways to the central nervous system by SARS-CoV-2, due to its neurotropic properties, which intracranially, are capable of injuring regions responsible for these senses.

Some studies concluded that there is a high prevalence of loss of smell and taste in patients with COVID-19, there was a variation in the ages studied and the degree of severity of the patient's disease [13-17], but due to the strong correlation of the symptomatology with the COVID-19 is considered a specific symptom of the disease[13,14]. These symptoms usually resolve in approximately 1 mo[17]; however, there are cases of persistent loss of smell and taste[18], which was observed by Vaira *et al*[18]. After biopsy of the nasal mucosa, there was alteration of the olfactory epithelium, which in some places, instead of forming normal tissues, formed metaplastic tissue, which is a possible explanation for the persistence in some cases.

Most articles[13,14,16,17,19,21,24-27,29] highlighted the neurotropic activity of SARS-CoV-2, allowing access and changes in the central nervous system. In the study carried out by Aragão *et al*[19], a microvascular lesion in the olfactory bulb in a patient with COVID-19 and loss of smell and taste were documented through magnetic resonance imaging (MRI), demonstrating a possible mechanism of action of the virus in addition to its action on the olfactory epithelium.

The study by Izquierdo-Dominguez *et al*[30], not included in this study because it is a systematic review, confirms the change in smell and taste due to the presence of ACE2 receptors in the respective mucosa and the fact that SARS-CoV-2 has affinity for these receptors. In addition to these sites, ACE2 can be found in various types of tissues, such as those of the central nervous system, which may also represent one of the causes of loss of smell and taste, if damaged. Studies that performed the autopsy of patients with COVID-19 and found hyperemic, swollen brain tissue and some sites with degenerated neurons were also discussed in this article, and also detected the presence of SARS-CoV-2 nucleic acid in the cerebrospinal fluid[30].

Among the main questions on the subject, in addition to the cause of the loss of smell and taste, as well as its anatomophysiological relationships, there are also discussions on whether there are possible preventions and what therapeutic measures can be carried out in the treatment in cases of persistent losses. Among the selected articles, there are no reports of possible preventive measures for loss of smell and taste, but Xu *et al*[31] raised the hypothesis that the use of vitamin D, as it has several independent neuroprotective mechanisms, can generate protection of central and peripheral nervous tissues, through neurotrophins. The authors hypothesized that the neuroprotective potential could prevent the neurological complications of COVID-19[31].

Regarding therapeutic measures, we selected the study by Vaira *et al*[18] who cited the existence of evidence of the use of steroid rinses and a pilot study with submucosal injection of platelet-rich plasma into the epithelium, obtaining relevant improvement, but they need more studies to reach significant conclusions and be indicated as clinical treatments for lesions[18]. The study by Kanjanaumpor *et al*[32], not addressed in our study because it is a systematic review, argued that there is still no significant evidence to recommend any type of pharmacological treatment; however, olfactory training, without contraindications but with low cost and evidence of improvement, is an interesting therapy in patients with persistent loss of smell and taste with COVID-19[32].

About prognosis, Kanjanaumpor *et al*[32] revealed that in about 32-66% of patients, there is spontaneous recovery and that a US study reported improvement in the loss of smell and taste in 74% of infected patients correlating with the overall resolution of clinical symptoms. Jalessi *et al*[22] mentioned recovery of smell in 44.0% of patients in the short term (2 wk) and Vaira *et al*[18] reported that about 66% of patients achieved complete recovery in an average of 19.3 d from the onset of symptoms.

Regarding preventive measures against COVID-19 and its symptoms, such as loss of smell and taste, the importance of using personal protective equipment (PPE) is found in the literature, as in the study by Kim *et al*[34]. Limited access to this equipment (mask, lab coat, new gloves, and face shield) was significantly associated with a higher risk of developing symptoms of COVID-19, in addition to being associated with more severe disease, with moderate or severe symptoms[34].

Adequate access to PPE by health professionals, especially those on the front line, is associated with a lower chance of contracting the disease, and even if PPE fails, there is an association with less severe and shorter forms[34].

There are numerous studies in progress, including a study by da Fonseca Orcina *et al*[36], who proposed the therapeutic use of a phthalocyanine-derived mouthwash, which is able to reduce the severity of the disease locally, the viral load in the oral cavity, and consequently the clinical symptoms, such as sore throat, cough, and mouth ulcers. It can thus also reduce the severity of the general disease by reducing the viral load and dissemination, since the oral cavity and oropharynx are an important means of dissemination of SARS-CoV-2[35,36]. The authors emphasized the need for more randomized clinical trials for further conclusions[36].

Regarding therapeutic measures in the loss of smell and taste, there are ongoing research testing several drugs; among them, the therapy with sprays and topical rinses based on corticosteroids has obtained good results, in addition to presenting a high safety profile, being appropriate for post-infection patients with persistent loss of these senses[37]. However, smell and taste training is the only specific therapy with proven efficacy. Although the exact mechanism of action is not known, it is believed that through repeated stimulation, there is an increase in the neuroplastic and regenerative capacity of the brain. Thus, it is an important therapy indicated at first in patients with a persistent condition[37-39].

There are difficulties in quantifying the prevalence and incidence of gustatory and olfactory dysfunction in the general population, due to causes such as analysis and evaluation methods, sample size and area, and the correct definitions of dysfunctions[40]. Multicentric research from Europe, in the year 2020, showed interesting data: 85.6% of patients with COVID-19 reported olfactory loss. It was also one of the pioneering studies in the identification of taste loss, which at the time was 88.0% in patients with COVID-19. In addition, that study described that infected patients could experience this loss in the absence of other significant symptoms[40].

With the emergence of coronavirus variants, infections caused by Omicron can currently be highlighted, which resulted in mild disease, mainly due to the discovery and use of vaccines. Compared to other strains such as Delta, Omicron infections were more often associated with symptomatology and upper respiratory tract infections, and have lower viral loads, less dysregulated immune cell profiles, and lower levels of pro-inflammatory cytokines[41].

A study, through questionnaires, evaluated the clinical profile of patients who developed COVID-19 after full vaccination, in symptomatic patients. The most frequent symptoms were asthenia (82.4%), chemosensory dysfunction (63.4%), headache (59.5%), coryza (58.2%), muscle pain (54.9%), loss of appetite (54.3%), and nasal obstruction (51.6%). However, 62.3% and 53.6% of survey participants reported olfactory and gustatory dysfunction, respectively. Symptom severity was mild or moderate in almost all cases. Chemosensory dysfunction is still a frequent symptom, even in people who contracted the infection after full vaccination. In this way, the sudden loss of smell and taste may continue to represent a useful and specific diagnostic aid in suspected COVID-19, even in vaccinated individuals [42].

As limitations of this study, one can consider the rapid change in the literature on COVID-19, as well as the emergence of new variants, with different symptoms from the initial versions.

CONCLUSION

Most of the articles studied reported that possible anatomophysiological mechanisms related to the loss of smell and taste, are local lesions in the olfactory and gustatory tissue due to having ACE-2 receptors, with the SARS-CoV-2 gateway being the oral and nasal cavity. In addition to local lesions, there are central changes in the tissues of the nervous system related to taste and smell, which are also damaged by the neurotropic capacity of SARS-CoV-2. The duration, in most cases, can extend from 3 to 4 wk, and it is considered persistent after 1 mo.

Therapeutic conducts in persistent cases with better initial results, which could be indicated by the doctor, are the use of steroid-based sprays and rinses and, mainly, the training of the senses of smell and taste. Likewise, the best measure to be taken is prevention, with the correct use of PPE by health professionals, and respect for local health recommendations determined in order to reduce viral spread.

ARTICLE HIGHLIGHTS

Research background

There are numerous conflicting discussions about the outbreak of the new coronavirus (COVID-19).

Research motivation

Describe the anatomy and physiology relationships of taste and smell losses due to COVID-19

Research objectives

To present some anatomical and physiological considerations about two of the symptoms reported by patients: the loss or reduction of smell and taste.

Research methods

Since, these symptoms are presented in a peculiar way, with some cases of persistence even after COVID-19. For this, it was searched in three databases, PubMed/MEDLINE, Web of Science and Scopus, using the following keywords: "Smell", "Taste", "Smell AND COVID-19", "Taste AND COVID-19", no publication time restriction, only in English with full text available, excluding also brief communications, letters to the editor, editorials, reviews, comments and conference abstracts.

Research results

The search found 776 articles in the database PubMed/MEDLINE, 1018 in the Web of Science database, and 552 in the Scopus database, from which duplicates were removed (104 articles). Finally, 17 studies were selected for detailed analysis within the eligibility criteria, with titles and abstracts related to central nervous system lesions responsible for smell and taste. This review suggests that viral mechanisms of action may be related to lesions both at the local level and at the level of the central nervous system, lasting up to 3 to 4 wk. It is considered persistent if it exceeds this period, as reported in one case in this review. There are still few studies about the treatment, and among those addressed in this review, only two studies reported possible treatments and emphasized the scarcity of data, with the best option being treatments that do not cause harm, such as gustatory and olfactory physiotherapy

Research conclusions

Most of the articles studied reported that possible anatomophysiological mechanisms related to the loss of smell and taste, are local lesions in the olfactory and gustatory tissue due to having ACE-2 receptors, with the SARS-CoV-2 gateway being the oral and nasal cavity. In addition to local lesions, there are central changes in the tissues of the nervous system related to taste and smell, which are also damaged by the neurotropic capacity of SARS-CoV-2. The duration, in most cases, can extend from 3 to 4 wk, and it is considered persistent after 1 mo. Therapeutic conducts in persistent cases with better initial results, which could be indicated by the doctor, are the use of steroid-based sprays and rinses and, mainly, the training of the senses of smell and taste. Likewise, the best measure to be taken is prevention, with the correct use of PPE by health professionals, and respect for local health recommendations determined in order to reduce viral spread.

Research perspectives

Future studies should further describe the relationships between the anatomy and physiology of taste and smell losses due to COVID-19.

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FOOTNOTES

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SYSTEMATIC REVIEWS

Utility of cardiac bioenzymes in predicting cardiovascular outcomes in SARS-CoV-2

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Abstract

BACKGROUND

Cardiovascular complications have been increasingly recognized in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) associated coronavirus disease 2019 (COVID-19). Cardiac biomarkers are released because of this ongoing cardiovascular injury and can act as surrogate markers to assess the disease severity.

AIM

To review the variation and utility of these biomarkers in COVID-19 to ascertain their role in diagnosis, prognosis and clinical outcomes of the disease.

METHODS

We performed a literature search in PubMed, Medline and the Reference Citation Analysis (RCA), using the search terms "COVID-19" and "cardiac bioenzymes" or "cardiac biomarkers". Additionally, we also used the latest reference citation analysis tool to identify more articles.

RESULTS

Cardiac troponin has been consistently elevated in patients with COVID-19 associated myocarditis, and strongly correlated with adverse prognosis. Natriuretic peptides including brain natriuretic peptide (BNP) and pro-BNP is elevated in patients with COVID-19 associated cardiac injury, irrespective of their prior

heart failure status, and independently correlated with worst outcomes. Alongside these traditional biomarkers, novel cardiac bioenzymes including presepsin, soluble ST2 and copeptin, are also increasingly recognized as markers of cardiovascular injury in COVID-19 and can be associated with poor outcomes.

CONCLUSION

Assessment of cardiac bioenzymes at admission and their serial monitoring can help assess the severity of disease and predict mortality in patients with SARS-CoV-2 infection. Future studies are needed to elude the critical importance of novel biomarkers.

Key Words: SARS-CoV-2; Troponin; Brain natriuretic peptide; Prognosis; Outcomes; Heart failure

Core Tip: Cardiac bioenzymes act as surrogate markers for various cardiovascular complications associated with coronavirus disease 2019 (COVID-19). Cardiac bioenzymes at admission and their serial monitoring can help assess the disease severity and predict mortality in patients with COVID-19. This review summarizes the role of these bioenzymes in diagnosis, prognosis and clinical implications on outcomes of various cardiovascular complications associated with COVID-19.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has since infected nearly 500 million people across 200 different countries and killed more than six million people worldwide. Lung injury is the most common presentation seen; however, cardiac injury is another dreaded consequence of this viral disease. Multiple mechanisms of injury have been hypothesized that culminate in widespread inflammation and cytokine storm causing significant cardiovascular dysfunction. A few authors have hypothesized that the inciting events for this injury include microvascular damage in the heart, causing perfusion defects, vessel hyperpermeability, and vasospasm[1-5]. Cardiac biomarkers are released because of this ongoing cardiovascular injury and can act as surrogate markers to assess the disease severity. These biomarkers can be elevated in many cardiac conditions, including acute Myocardial infarction (AMI), heart failure (HF), arrhythmias and cardiomyopathies. Among the available biomarkers, cardiac troponin (cTn) and natriuretic peptides including brain natriuretic peptide (BNP) and N terminal pro-BNP (NT-proBNP), have been extensively studied. Numerous reports from China have noted elevated cTn in COVID-19 patients[6,7]. A major review on cardiac biomarkers in HF emphasized the importance of negative NPs in ruling out HF[8]. In addition, novel biomarkers including soluble ST2 (sST2), Galectin-3 (Gal-3), and copeptin have also been studied. In this review, we aimed to study in detail the various cardiac biomarkers that have been reported in the literature in patients with COVID-19. We also aimed to identify the role of these cardiac biomarkers in diagnosing the impact of cardiac injury and their role in prognostication of morbidity and mortality among patients with COVID-19.

MATERIALS AND METHODS

We conducted an extensive review of the literature of all the studies on patients with COVID-19 associated cardiac injury and cardiac bioenzymes. We screened for articles on cardiac biomarkers in patients with COVID-19 in the MEDLINE/PubMed database. Published articles between November 2019 and March 2022 were reviewed. Keywords for the search criteria included "Coronavirus disease 2019", OR "COVID-19", OR "Severe Acute Respiratory Syndrome Coronavirus-2", OR "cardiac bioenzymes", OR 'biomarkers", OR "prognosis", OR "heart failure", OR "myocarditis" OR "outcome", OR "morbidity", and "mortality". We also used the related article search feature and manual search of references to identify further articles. Additionally, we used the latest reference citation analysis tool to screen for more articles. Two independent trained physician reviewers were involved in screening and

reviewing relevant articles. As of March 2022, a total of 560 papers were identified. Among them, only 61 papers were eligible to be included (Figure 1). All articles with details on COVID-19 patients with cardiac injury and measured cardiac biomarkers were eligible to be included in this review. We included all articles published in English from all over the world. Independent reviews, editorials, letters, abstracts, preprints, and opinions were excluded. Most studies reporting cardiac biomarkers in patients with COVID-19 were from China, North America, and Europe. The reporting of study design, methodology, data collection, biomarker levels, and measured outcomes were not consistent across all the studies. To simplify the role of each cardiac biomarker with regard to COVID-19 disease diagnosis, prognosis, and mortality, we subdivided this review into three principal sections. The three sections were (1) Studies on the role of cardiac troponin in diagnosing and prognosticating COVID-19 associated myocardial injury and mortality; (2) Studies on the role of natriuretic peptides in diagnosing and prognosticating COVID-19 associated myocardial injury and mortality; and (3) Studies on the role of other biomarkers and novel cardiac biomarkers in diagnosing and prognosticating COVID-19 associated myocardial injury and mortality.

Cardiac troponin

Pathophysiology: cTn include troponin T (cTnT) and troponin I (cTnI), which are universally accepted markers of cardiac injury[9]. Cardiac troponin, a regulatory protein complex with three units, is located at the sarcomere thin filament. The inhibitory unit cTnI and a tropomyosin binding unit cTnT are responsible for maintaining a relaxed state when intracellular Ca2+ concentrations are low in diastole. In systole, the rise in intracellular Ca2+ leads to Ca2+ binding to cardiac troponin C (cTnC), releasing inhibition and promoting contraction and ejection[10].

Troponin as a diagnostic marker of cardiovascular injury in COVID-19: In the early phases of the pandemic caused by SARS-CoV-2, the emphasis was on lung damage and treatment of the same. Guidelines from AHA had recommended against the determination of cTnT and cTnI. However, this notion changed in 2020, when Chapman *et al*[11] published a statement strongly supporting the determination of serum cTnI and cTnT, emphasizing their role as biomarkers for cardiac injury in COVID-19 infected patients. Initially, the exact mechanism leading to serum elevations of these biomarkers was unclear, with several theories being proposed. Recent evidence showed direct infection of cardiac myocytes by SARS-CoV-2[12], leading to a decrease in Angiotensin-converting enzyme 2 (ACE2) and an increase in Angiotensin II (AngII). The dysfunctional signaling leads to necrosis or membrane instability, causing the leak of the bioenzymes[13]. Multiple additional studies[14-16] have reiterated the importance of cardiac troponin as a diagnostic tool and have been summarized in Table 1. Cardiac troponins have been reported to be elevated irrespective of the pattern of cardiac injury and clinical presentation. Levels have been reported to be higher among patients with an ischemic pattern of injury than in non-ischemic injury. The release of cTn has been seen in COVID-19 patients with acute coronary syndrome, tachyarrhythmias, cardiomyopathy, and myocarditis. In COVID-19, patients' cTn has been used as a marker of inflammation and myocardial injury. A large observational study from New York on patients hospitalized with SARS-CoV-2 showed a positive correlation between elevated cTnT and inflammatory markers[14].

Role of troponin as a prognostic indicator of cardiovascular outcomes in COVID-19: Sandoval *et al*[17] found higher levels of cTn in severe SARS-CoV-2 infection and opined that their serial measurement can aid in the risk stratification of COVID-19 patients. Based on the progression of the disease, they grouped COVID-19 patients in three phases; first - during admission where cTn elevation reflected the comorbidities; second - further rise in cTn with critical acute respiratory distress syndrome (ARDS) and; third - peak cTn with COVID-19 associated complications, including myocarditis and pulmonary embolism. Studies have shown that a high level of cTn and serial up-trending of cTn have been predictive of worse prognosis[18-20]. Troponin levels between 0.03 and 0.09 ng/mL were considered to be predictive of cardiac damage, with levels above 0.09 ng/mL conferring an even higher risk. A few studies utilising high sensitivity troponin have shown that troponin levels above 4 ng/L, 13 ng/L and 37 ng/L to be predictive of mild, severe and critical illness respectively[19]. Similarly, lower levels of cTn at presentation and a downward trend have been consistently reported among the survivors. Importantly COVID-19 patients with prior cardiovascular comorbidities have been at risk of further cardiovascular injury. Among these patients with cardiovascular comorbidities, cTn has been associated with further adverse prognosis.

Role of troponin on outcomes and mortality in COVID-19: Among patients with COVID-19, cTn was higher in deceased patients compared to survivors. Multiple studies have shown a significant correlation between cTn and in-hospital adverse events and mortality even in patients without comorbidities[14,21-28] (Table 1). Multiple studies show that cTnT and cTnI are independent predictors of mortality even after adjusting for confounding factors[29,30]. Scarl *et al*[21] reported that, in hospitalized patients with pre-existing comorbidities and SARS-CoV-2, there was a significant correlation between serum cTnI level and mortality. Salvatici *et al*[27] in their study utilising high sensitivity troponin, showed that in hospital survival rates was about 90% when cTnI was normal. The survival rate decreased to 87% when cTnI was above normal but less than 40 ng/L, and further reduced to 59%

Table 1 Summary of studies characterizing the role of cardiac troponin

Study	Type of study	Location	Number of participants	Recommendation
Diagnostic and prognostic utility of troponin				
Lala *et al*[14], 2020	Single center, Observational	New York	2736	cTn elevated in patients with primary cardiac etiology including MI. Other etiologies included arrythmias, HF, myocarditis and Takotsubu cardiomyopathy
Khaloo *et al* [15], 2022	Multicenter, Retrospective	Massachusetts	2450	
Sandoval *et al* [17], 2020	Review			Serial cTn measurement aids in risk stratification
Almeida *et al* [18], 2020	Single center, Retrospective	Brazil	183	Elevated cTn measured within first 24 h is associated with worst prognosis. Increased need for MV
Maino *et al* [19], 2021	Single center, Retrospective	Italy	189	
Arcari *et al* [20], 2020	Multicenter, Observational	Italy	111	cTn elevation correlated with poor prognosis and need for MV
Role in outcome and mortality				
Scarl *et al*[21], 2021	Single center, Retrospective	Ohio	81	In patients with pre-existing comorbidities, CTnI elevation is associated with mortality
Lala *et al*[14], 2020	Single center, Observational	New York	2,736	Threefold increase in mortality in patients with cTnI three times the upper limit of normal
Mueller *et al* [22], 2021	Review			cTn elevation is associated with significant in hospital adverse events
Henein *et al* [23], 2021	Multicenter, Retrospective	International, mainly European	748	
Kermali *et al* [24], 2020	Systematic review	China	607	
Arcari *et al* [25], 2021	Multicenter, Retrospective	Italy	252	cTn significantly elevated in patients with pre-existing comorbidities, and is associated with increased mortality
Lombardi *et al*[26], 2020	Multicenter,Cross sectional	Italy	614	Elevation in cTn associated with mortality. 45.3% patients had elevated cTn and correlated with 71% increase in mortality, and a 2-fold increase in additional complications inlcuding sepsis, PE, AKI
Salvatici *et al* [27], 2020	Single center, Retrospective	Italy	523	cTnT and cTnI remain independent predictors of mortality even after adjusting for potential confounders
Al Abbasi *et al*[28], 2020	Single center, Retrospective	Florida	257	Elevated cTnI in the first 24 h of admission had a significantly higher in hospital mortality, with 89.7% negative predictive value

cTn: Cardiac troponin; cTnT: Troponin T; cTnI: Troponin I; HF: Heart failure; MV: Mechanical ventilation; PE: Pulmonary embolism; AKI: Acute kidney injury.

with cTnI above 40 ng/L. These studies have shown that cTn drawn at admission had a high positive predictive value for serious illness and a high negative predictive value for death. An up-trending cTn among COVID-19 patients is shown to correlate with a twofold increase in complications including sepsis, pulmonary embolism, and acute kidney injury and a threefold increase in mortality. The level of cTn has been shown to correlate with the outcome within 24 h of hospital admission. A study from Florida showed that COVID-19 patients with elevated cTnI levels in the first 24 h of admission had a significantly higher in-hospital mortality as compared to those with a normal cTnI level[28]. Patients with a normal cTnI level at admission had a low risk of worse outcome demonstrating an 89.7% negative predictive value. Similar results were reported by two other studies showing an increased need for invasive mechanical ventilation and risk of death among patients with elevated cTn levels within the first 24 h of admission[18,19]. Therefore, measurement of cTnI after hospitalization for COVID-19, followed by longitudinal monitoring, can help clinicians intercept dynamic changes in the levels of cTnI as a surrogate marker of myocardial injury.

Troponin as a surrogate marker of cardiovascular dysfunction post-discharge in COVID-19: Elevated cTn has been associated with impaired left ventricular relaxation and decline in right ventricular function resulting in long-term sequelae. As a component of Long COVID-19, the persistence of cardiac injury has been reported in young patients following an acute COVID-19 episode until six months. A

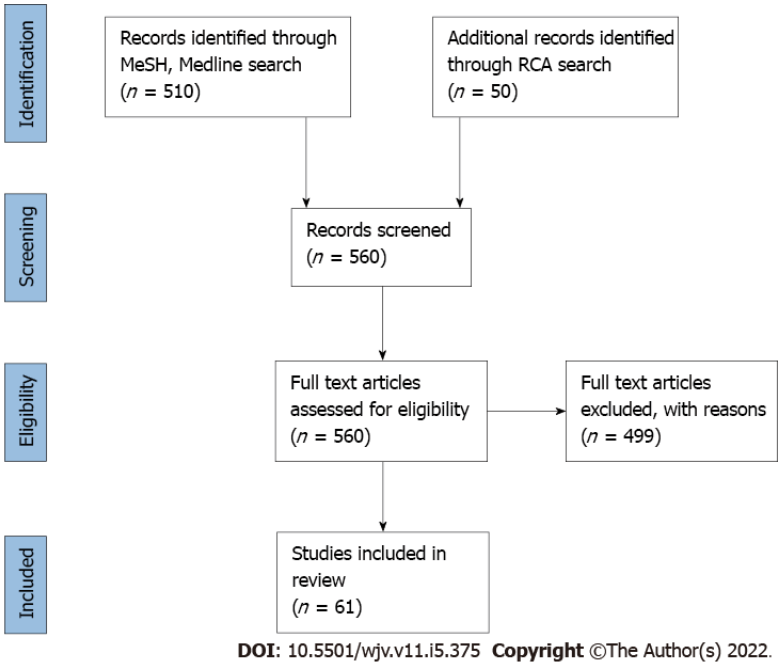

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Figure 1 PRISMA diagram of literature search and selection.

cross-sectional study of 144 patients who were followed up for 85 d after their recovery from SARS-CoV-2 showed that patients with baseline elevations in cTn had a higher incidence of dyspnea after discharge. These patients also had impaired diastolic dysfunction and elevated pulmonary artery (PA) pressures, as noted by echocardiography. They also had persistence of cTn until mid-follow-up[31]. A rise in the incidence of HF has also been seen in COVID-19 patients with elevated cTn in two large multicenter studies[15,26]. These studies signify that cTn can be used as diagnostic and prognostic tools for long-term cardiac outcomes related to SARS-CoV-2 infection in select subgroup of patients. Despite these observations, clinical judgment should be used to avoid any unnecessary diagnostic and therapeutic interventions triggered by the isolated cTn elevation.

Natriuretic peptides

Pathophysiology: Natriuretic peptides (NPs), including BNP and NT-proBNP, are quantitative biomarkers of hemodynamic myocardial stress and heart failure[32]. Brain natriuretic peptide is a preprohormone which is split into a single peptide and a propeptide (pro-BNP). Natriuretic peptides mediate their biological effects through guanylyl cyclase receptors [natriuretic peptide receptor (NPR)] A, B and C. Stress of the ventricular wall due to volume or pressure overload is the primary inducer of BNP synthesis, which acts on the kidney to induce natriuresis and diuresis[33] Natriuretic peptides are considered one of the initial diagnostic tools in acute HF patients. Historically, studies like TOPCAT[34] have supported its value, and over the past years, NT-proBNP has had a growing role in the standardization of the definition of HF.

Natriuretic peptides as a diagnostic marker of cardiovascular injury in COVID-19: Prior to the advent of SARS-CoV-2, multiple viral infections have been reported to induce HF due to direct viral invasion and pro-inflammatory cytokines leading to sympathetic activation. In SARS-CoV-2, elevation in NPs is a result of inflammatory overdrive, specifically interleukin (IL)-1β, IL-6, and monocyte chemoattractant protein-1 (MCP-1), which can lead to fulminant myocarditis. The rise in NPs is believed to be secondary to hypoxia and cardiac injury. In addition, widespread inflammation and decreased nitric oxide levels result in endothelial dysfunction, which causes heart failure symptoms. This can be a combination of pre-existing cardiac disease and the acute hemodynamic and hypoxemic stress related to COVID-19[32,35]. The use of vasopressor therapy, hypoxia-induced pulmonary vasoconstriction, inflammatory involvement of the myocardium, oxidative stress, and fibrin microthrombi in the vasculature contributes to the release of NPs[36-38]. Across multiple studies, NPs level were high among COVID-19 patients with and without HF. Higher levels of NPs have not been consistently shown to correlate with severe COVID-19 disease. Still, they have been shown to correlate with developing or worsening of heart failure in these patients (Table 2).

Role of natriuretic peptides as a prognostic indicator of cardiovascular complications in HF and COVID-19: In patients with COVID-19 and myocardial injury, the elevation of NPs has been reported consistently[7,36]. Mehra *et al*[39] suggested that in patients with COVID-19 and cardiac comorbidities,

Table 2 Summary of studies characterizing the role of natriuretic peptides

Study	Type of study	Location	Number of participants	Recommendation
Diagnostic and prognostic utility of natriuretic peptides				
Arcari *et al*[20], 2020	Multicenter, Observational	Italy	111	Positive correlation between the rise in NPs and COVID-19 disease severity. Half of these patients had their NP level above the upper limit of normal
Caro-Codón *et al*[40], 2021	Population	Spain	396	In patients with history of HF, elevation in NT-proBNP above the cut-off for normal suggested development of acute HF
Gao *et al*[41], 2020	Multicenter, Prospective	China	402	This study proposed a triple cut point strategy of NT-proBNP (HF unlikely if NT-proBNP < 300pg/L, grey zone 300-900 pg/L and HF likely if > 900 pg/L) for its role in developing acute HF and in determining prognosis. Thirty day mortality in HF group was 40.8%.
Sorrentino *et al* [42], 2020	Meta-analysis of 13 observational studies		2248	Natriuretic peptides have significant prognostic importance in predicting severity of COVID-19
Yoo *et al*[43], 2021	Single center, Retrospective cohort	New York	679	In patients without a history of HF, elevated admission NT-proBNP correlated with fewer hospital free, ICU free and ventilator free days compared to those with low NT-proBNP levels
Alvarez-Garcia *et al*[44], 2020	Single center, Retrospective	New York	6439	No difference identified in the level of NP and COVID-19 disease severity
Dawson *et al* [45], 2020	Meta-analysis	China	12 studies included	
Abdeen *et al* [46], 2021	Single center, Retrospective	New Jersey	230	
Role in outcome and mortality				
Gao *et al*[48], 2020	Single center, Retrospective	China	102	Natriuretic peptides independently associated with in-hospital mortality in severe COVID-19 patients. The cut off value predicting in hospital death was 88.64 pg/mL with a 100% sensitivity and 66.7% specificity.
Caro-Codón *et al*[40], 2021	Population	Spain	396	Elevations in NP correlated with in-hospital mortality, even after adjusting for relevant confounders
Calvo-Fernández A *et al*[49], 2021	Single center, Retrospective	Spain	872	Natriuretic peptide elevation is independently related to death or mechanical ventilation in COVID-19 patients
Selcuk *et al*[50], 2021	Single center, Retrospective	Istanbul	137	Among patients who did not have a baseline diagnosis of HF, NPs were independent predictors of mortality. This study used a cut off threshold of 260pg/ml predicting an in-hospital mortality with 82% sensitivity and 93% specificity
Iorio *et al*[51], 2022	Multicenter, Retrospective observational	Italy	341	The level of NP elevation correlated with mortality. Cut off threshold used in this study is 2598 pg/L predicting a 30-d mortality with 91.7% sensitivity and an 80% specificity
Belarte-Tornero *et al*[52], 2021	Single center, Retrospective	Spain	129	
Dalia *et al*[53], 2021	Systematic review	India	5967	Patients with fulminant COVID-19 and elevated NPs had an eight-fold increased risk of acute cardiac injury and death when compared to their counterparts
Pranata *et al* [54], 2020	Meta analysis		967	In patients with HF, natriuretic peptide elevation is associated with disease progression and mortality. This effect was seen even after adjustment for troponin and CKMB
Iorio *et al*[51], 2022	Multicenter, Retrospective observational	Italy	341	The combined effect of cTn and NT-proBNP was studied in COVID-19 patients. Irrespective of prior HF history, increased mortality was seen in patients with both biomarker elevation. In patients with only one biomarker elevation, case fatality higher in patients with NP elevation
Stefanini *et al* [55], 2020	Single center, Retrospective	Italy	397	

NP: Natriuretic peptide; NT-proBNP: N terminal pro-brain natriuretic peptide; HF: Heart failure; cTn: Cardiac troponin; COVID-19: Corona virus disease 2019.

the earliest manifestation of cardiac decompensation is due to diastolic dysfunction. This is secondary to hemodynamic instability and pulmonary complications in the early course of the disease. Subsequently, because of cytokine storm, systolic dysfunction ensues. A large multicenter study from Italy showed a

positive correlation between the rise in NPs and associated SARS-CoV-2 severity[20]. Half of the patients in this study had their NP level above the upper limit of normal. Similar results were reported from a large meta-analysis of 13 observational studies, including 2248 patients. The average NT-proBNP among COVID-19 patients with severe disease was 791 pg/mL, *vs* 160 pg/mL in non severe patients [42]. In patients with pre-existing HF and COVID-19, an elevation of NT-proBNP above the cut-off for normal[32] suggested an acute decompensation of HF, leading to a prolonged hospital stay[40]. Interestingly, in a different study from New York that included 679 patients without a history of HF, elevations in NT-proBNP correlated with longer ICU stay, hospital stay, and the increased need for mechanical ventilation[43]. Negative results were also seen in a few studies which did not identify any difference in the NP levels and COVID-19 severity[44-46]. These were however small studies, and given the lack of a diverse population, the results cannot be generalized.

Role of natriuretic peptide on outcomes and mortality in COVID-19: Heart failure per se is a significant risk factor for developing severe COVID-19[1,2,12]. In a series of 113 patients who died from SARS-CoV-2, HF was the most frequent cause of death after ARDS and sepsis[47]. In a large population study from Spain that enrolled patients with HF, elevation in NT-proBNP above the cut-off for normal was independently associated with mortality, even after adjusting for confounders[40]. Gao *et al*[48] reported an increased mortality in COVID-19 patients who had an elevated BNP above 88.64 pg/mL, with a 100% sensitivity and a 66.7% specificity. The significance of NPs in predicting mortality among SARS-CoV-2 patients is independent of their HF status. A single-center study with 137 patients without a prior diagnosis of HF showed that elevation of NPs is an independent predictor of mortality[50]. This study used a cut-off value of 260 pg/mL, predicting in-hospital mortality with 82% sensitivity and 93% specificity. It must be noted that the threshold used for NT-pro BNP in this study is lower than the cut-off used in the clinic and clinical trials for the diagnosis of HF. This implies that elevated NT-pro BNP levels even within the upper limit of the normal reference range could indicate an occult cardiac injury in COVID-19 patients. In patients with chronic HF, an elevated pro-BNP above suggested cut off of 2598 pg/mL was associated with an increased odds of 30 d mortality[52]. An extensive systematic review from India, including 5967 patients, found that non-survivors and patients with fulminant SARS-CoV-2 with elevated NPs, had an 8-fold increased risk of acute cardiac injury and death compared to their counterparts[53]. The average NT-proBNP across patients with severe COVID-19 was 1142 pg/mL. Two large center studies from Italy studied the combined role of troponins and NPs in COVID-19 associated disease progression and mortality. They found that patients with dual biomarker elevation had increased mortality, irrespective of their prior HF status[51,55].

Natriuretic peptides as a surrogate marker for new-onset heart failure post-discharge: Elevated NT-proBNP in COVID-19 patients without cardiac comorbidities indicates SARS-CoV-2 mediated cardiac complications. New-onset HF was seen in 23% of hospitalized patients with COVID-19 and was the most frequent cause of death after sepsis and ARDS[47]. A large prospective study in COVID-19 patients[56] used HFA-PEFF score (Heart Failure Association Pre-test assessment, Echocardiography & natriuretic peptide, Functional testing, Final etiology) with a specificity of 93% and a positive predictive value of 98% to rule in HFpEF. These patients had higher NT-proBNP levels when compared to their counterparts. Cardiac biomarkers are known to decline after the resolution of acute infection, as seen in ECHOVID-19 study[57]. On the contrary, persistent biomarker elevation despite infection resolution has been noted in two different studies[58,59]. They also had echocardiographic parameters of ventricular dysfunction. The exact cause of reduced ventricular myocardial function is unknown; however, it is presumed to be secondary to systemic inflammation and ventricular remodeling[60-62]. If the recovery is good, the prognosis is better, else, it predisposes them to the development of HF[63].

Additional biomarkers

Other biomarkers have also been implicated in determining prognosis and predicting mortality in patients with SARS-CoV-2. Significant elevations in creatine kinase MB (CK-MB) and NT-proBNP above the upper limit of normal are seen in critically ill patients with COVID-19, helping in risk stratification [64,65]. An increase in the level of myoglobin (MYO), NT-proBNP, and cTnI correlated with disease severity in patients with SARS-CoV-2[66]. Similar results were seen in two other studies identifying the prognostic significance of myoglobin, procalcitonin, and d-dimer in COVID-19[67,68]. Alongside troponin and natriuretic peptides, elevations in CK-MB and LDH (lactate dehydrogenase) have been shown to predict in-hospital mortality in patients with COVID-19[69]. Similarly, a rise in IL-6 and INR predicted an increased odds of 7-d mortality in patients admitted with SARS-CoV-2[64]. In addition, there is now data on novel emerging biomarkers and their role in predicting the disease severity in COVID-19. Among them, presepsin, growth differentiation factor 15 (GDF-15), soluble ST2, galectin 3, and copeptin have been studied.

Presepsin

Presepsin is a CD14 biomarker released into circulation by pro-inflammatory signals during infection. Through its interaction with T and B cells, it acts as an immunomodulator and has diagnostic and

prognostic significance in sepsis[70]. Its role has been implicated alongside natriuretic peptides in the diagnosis of HF. A single-center study with 506 patients showed that presepsin was elevated in patients with acute HF decompensation and correlated with their 6-month mortality[71]. Similar results were seen in another study, with higher presepsin levels correlating with longer ICU stay and increased mortality[72].

Role of presepsin in prognosis and outcomes in COVID-19: Presepsin elevation has been noted in patients with COVID-19, thus serving as a reliable biomarker[73]. Studies have shown a four-to-five-fold increase in serum presepsin, which correlates with disease severity when compared to their counterparts[74-76]. Fukada *et al*[77] in a small series of patients with COVID-19-related respiratory failure, found that presepsin is more expressed in severe cases than in mild cases. Similar results have been seen in other studies identifying the prognostic importance of presepsin with COVID-19 related disease severity[73,78]. Patients with presepsin values higher than 250 ng/L had a longer ICU stay when compared to the patients with lower values[78]. Park *et al*[74] suggested that an elevated presepsin level at 717 pg/mL is a significant predictor of 30-d mortality. A threefold rise in presepsin has been identified as a very specific indicator of 30-d mortality[75,79]. Thus, routine assessment of presepsin in COVID-19 may provide valuable clinical information for predicting adverse outcomes, as well as for guiding the clinical and therapeutic decision-making.

Soluble ST2

Soluble ST2 (sST2) is among the most important novel biomarkers for prognosis in HF. Upregulated in states of mechanical strain, it plays an essential role in myocardial hypertrophy and fibrosis. Studies have shown an increase in sST2 gene expression in the presence of cardiac injury. High circulating levels of sST2 are involved in the aberrant inflammatory process of ARDS and have also been linked to acute and chronic HF, myocardial infarction, sepsis, and fibrosis[80]. Among patients with ARDS, sST2 elevations up to ten times the normal expected for HF has been seen, and this correlated with an increase in their mortality[81,82]. As evident in PRIDE study, among the 593 patients admitted with acute dyspnea, sST2 concentrations were higher among those with acute HF[79]. NT-proBNP however outperformed sST2 for acute HF diagnosis (AUC = 0.94 *vs* 0.80; $P < 0.001$). In patients with HFpEF, Manzano-Fernández *et al*[83] showed sST2 to be superior to NT-proBNP for prognosis. In addition, it also strongly correlated to the 30-d, one-year, and four-year mortality. Rehman *et al*[84] found that values of sST2 correlated with the severity of HF, making it a powerful predictor of mortality. Lassus *et al*[85] showed that in patients with pre-existing HF, sST2, relative to other biomarkers, is a powerful variable for one-year mortality. Similarly, Breidthardt *et al*[86] reported that a dynamic change in sST2 value from admission to discharge was a stronger predictor of mortality than baseline values alone.

Role of sST2 in prognosis and outcomes in COVID-19: Soluble ST2 is linked to SARS-CoV-2 viremia and indicators of inflammation, cardiovascular disease, and thrombosis. Omland *et al*[87] found an association between sST2 and disease severity among patients hospitalized for COVID-19 and was independent of established risk factors. Elevated ST2 concentrations above 37.9 ng/mL correlated with severe disease, with non-survivors having concentration as high as 107 ng/mL. Similar results were seen by Huang *et al*[88] and Ragusa *et al*[89], who concluded that sST2 is an important COVID-19 prognostic marker and correlated with disease severity. This association was deemed secondary to pulmonary fibrosis, seen as a complication in COVID-19. Elevations in sST2 Levels strongly correlated with mortality in ICU patients with sepsis secondary to COVID-19[87,90]. Omland *et al*[87] also noted that elevations in sST2 correlated with poor outcomes on days 3 and 9 of hospitalization among patients with COVID-19.

Galectin-3

Galectin-3 (GAL-3) is a mineralocorticoid receptor-regulated pro-inflammatory molecule. It exhibits a pleiotropic role in mediating infection and inflammation. Gal-3 is a biomarker of fibrosis and inflammation and has been implicated in the development and progression of HF[91]. ARDS is chiefly mediated by releasing IL-1, IL-6, and TNF-α from macrophages, monocytes, and dendritic cells[92]. Gal-3 inhibition has been shown to reduce the release of these cytokines from immune cells[93]. The PRIDE study showed that higher galectin-3 concentration was a strong independent predictor of 60-d mortality and recurrent HF admissions[94]. Shah *et al*[95] showed that galectin-3 above a median value of 15.0 had a strong prognostic significance in HF and was a significant predictor of 4-year mortality.

Role of galectin-3 in prognosis and outcomes in COVID-19: Multiple studies have shown Gal-3 to be upregulated in patients suffering from severe COVID-19. Among patients with COVID-19, Gal-3 was shown to be considerably higher in bronchoalveolar immune cells in patients with severe disease when compared to those with mild disease[96]. Higher galectin-3 levels were found to be a major predictor of 60-d mortality and recurrent HF hospitalizations. In a study of SARS-CoV-2 associated ARDS patients, high Gal-3 above 35.3 ng/mL was linked to worse outcomes and shorter survival[97].

Copeptin

Copeptin is a surrogate marker for vasopressin release. Copeptin is an arginine-vasopressin (AVP) glycopeptide composed of 39 amino acids. It is released from the neurohypophysis by osmotic or hemodynamic stimulation with AVP, and its plasma levels correlate well. AVP is an antidiuretic and vasoconstrictive hormone. It shows the endogenous stress response and is released by stimuli including hypotension, hypoxia, and infections. However, its circadian rhythm, short half-life, and unstable molecule make it impossible to use it as a biomarker[98]. Copeptin is a more stable peptide, and its level in the blood can be easily detected. The role of copeptin has been implicated in chronic HF. Elevated copeptin levels, especially in HF patients with hyponatremia, has been linked to poor outcomes. Maisel *et al*[99] noted that patients with elevated copeptin levels had a greater risk of 90-d mortality and HF readmission.

Role of copeptin in prognosis and outcomes in COVID-19: The importance of copeptin as a biomarker in COVID-19 patients has not been very well studied. Gregoriano *et al*[100] found that the rise in copeptin levels correlated with the disease severity in COVID-19 patients. Copeptin level of 20 pmol/L had an 88.2% sensitivity and a 64.9% specificity for identifying severe disease. Similar results were seen by Hammad *et al*[101] by using a cut off level of 18.5 pmol/L, yielding a sensitivity of 93.3% and a specificity of 100% for severe COVID-19 disease. In these studies, patients with severe COVID-19 disease were also noted to have increased mortality.

Growth differentiation factor 15

Growth differentiation factor 15 (GDF-15), also known as macrophage inhibitory cytokine (MIC-1), is a member of the transforming growth factor-beta (TGF-β) superfamily that helps tissues survive inflammatory stress. GDF-15 expression outside the reproductive organs is low to absent; it is upregulated in pathological conditions that involve inflammation or oxidative stress, including cancer, cardiovascular, pulmonary, and renal disease[102].

Role of GDF-15 in prognosis and outcomes in COVID-19: In a study of 84 patients with COVID-19, Apfel *et al*[103] determined that higher circulating levels of GDF-15 correlated with the disease severity. Patients with COVID-19 had an average GDF-15 level of 2051 pg/mL when compared to 582 pg/mL in non COVID patients. GDF-15 levels were higher in patients requiring mechanical ventilation and correlated with increasing oxygen requirements. In a different study by Verhamme *et al*[102], higher GDF-15 Levels were associated with increased mortality risk. Figure 2 illustrates the variation of different cardiac bioenzymes across different etiologies for cardiovascular dysfunction.

RESULTS

A total of 560 papers were identified after extensive literature review, as depicted in the PRISMA diagram (Figure 1). Among them, 61 papers were eligible to be included in the review. Cardiac troponin and natriuretic peptides were the most extensively studied of the bioenzymes. The evidence of cardiac troponin as a diagnostic marker for cardiovascular injury in COVID-19 is robust and has been shown on thousands (n = 11290) of patients worldwide, in both prospective and retrospective studies (Table 1). A consistently elevated level of cTn has been reported in COVID-19 patients with mild myocarditis to severe cardiogenic shock. Multiple studies have shown that troponin levels above the 99th percentile of upper limit of normal, to be associated with worse prognosis. Elevated cTn has been shown to correlate with severe disease, higher oxygen requirement, ARDS, the need for respiratory support including noninvasive and invasive mechanical ventilation, the requirement of intensive care unit admission, acute kidney injury, multiorgan failure, sepsis, pulmonary embolism, major bleeding and in-hospital mortality (Table 1). Troponin levels elevated five times the upper limit of normal have shown a 2.5% increase in in-hospital mortality. NPs are the second most studied cardiac biomarker in studies reporting cardiac injury in patients with COVID-19. Multiple studies have echoed a significant positive correlation between the rise in natriuretic peptides and disease severity in SARS-CoV-2[20,40-43] (summary in Table 2). Many of these studies have utilised the cutoff points for NT-proBNP based off the triple cut point strategy from European society guidelines[32] . In patients with pre-existing HF, natriuretic peptides have been independently associated with increased odds of the need for mechanical ventilation and death across studies[40,48-55] (Table 2). Novel biomarkers including presepsin, copeptin, soluble ST2 and galectin have also been implicated as prognostic markers in COVID-19, as detailed in Table 3.

DISCUSSION

SARS-CoV-2 associated COVID-19 infection is a global disease with multiple clinical manifestations. Cardiovascular complications are a dreaded outcome, and assessment of cardiac bio enzymes is crucial

Table 3 Summary of studies characterizing the role of novel biomarkers in prognosis and outcomes in COVID-19

Biomarker in COVID	Study	Recommendation
Presepsin	Favaloro *et al*[73]	Presepsin elevation is a reliable biomarker in COVID-19
	Park *et al*[74]	A four-to-five-fold increase in presepsin correlates with disease severity in COVID-19
	Lippi *et al*[75]	
	Koyjit *et al*[73]	
	Fukada *et al*[77]	Presepsin is elevated in severe cases of SARS-CoV-2 associated respiratory complications
	Park *et al*[74]	Presepsin level at 717pg/ml is a significant predictor of 30-day mortality
	Dell'Aquila *et al*[79]	A threefold rise in presepsin has been identified as a very specific indicator of 30-day mortality
	Lippi *et al*[75]	
Soluble ST2 (sST2)	Omland *et al*[87]	Robust association between baseline sST2 level and disease severity along with poor outcome
	Huang *et al*[88]	Baseline sST2 is associated with a worse prognosis
	Ragusa *et al*[89]	Circulating level of sST2 can be used as a discharge prognosticator
Galectin-3	Caniglia *et al*[96]	Gal-3 is considerably higher in bronchoalveolar immune cells in patients with severe COVID-19 disease
	Portacci *et al*[97]	Higher galectin-3 is associated with worse outcomes and shorter survival
Copeptin	Gregoriano *et al* [100]	Serum copeptin level above 20 Pmol/L had sensitivity of > 88% to predict severe COVID-19
	Hammad *et al*[101]	Serum copeptin level above 18.5 Pmol/L had sensitivity of > 93% and specificity of 100% to predict severe COVID-19
GDF 15	Apfel *et al*[103]	Higher levels of GDF-15 correlated with severity of COVID-19

Gal-3: Galectin-3; GDF-15: Growth differentiation factor 15; sST2: Soluble ST2.

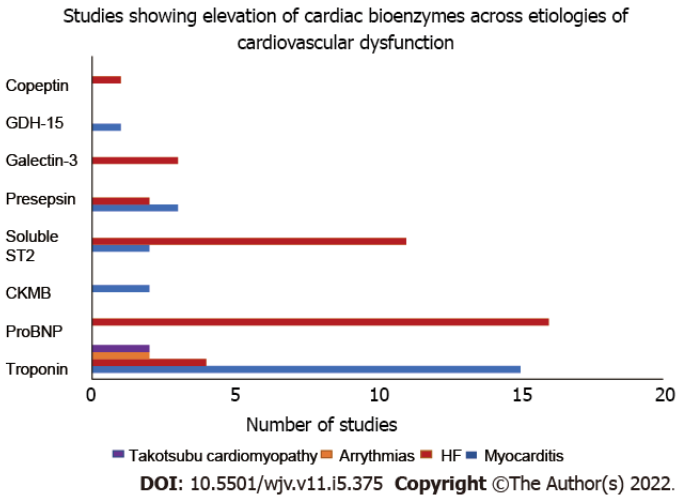

Figure 2 Studies showing elevation of cardiac bioenzymes across different etiologies of cardiovascular dysfunction.

in gauging the disease severity. Our review aims at highlighting the variation in these bio enzymes through the disease process and their role in predicting outcomes.

Troponin has been seen as a robust indicator of cardiovascular injury across aetiologies including myocarditis, coronary syndromes, and cardiomyopathy. Serum cTn above 0.09 ng/mL have been shown to confer a higher risk of cardiovascular injury. Generally, studies have shown that troponin levels above the 99th percentile of upper limit of normal are associated with a worse prognosis. Elevated levels on admission, and serial up-trending carry a high positive predictive value for worse prognosis. Furthermore, long term sequelae with impaired ventricular function and subsequent development of heart failure is seen in a select subset of patients with cTn elevation[103]. Alongside cTn, natriuretic peptides help in prognostication mainly in patients with HF. Elevations in levels above cut off for

normal[32] have been associated with worse outcomes. Multiple different studies citing the utility of NPs have been included in this review, and each of them had a unique cut off for HF. Irrespective of the cut-off used, elevated NT-proBNP was independently associated with poor outcomes regardless of the HF status[104]. This finding was common across studies.

The role of a few of these cardiac biomarkers has been studied before. However, our review is unique in its discussion about the role of novel biomarkers including presepsin, soluble ST2, galectin-3 which have not been studied extensively yet. Prior studies have highlighted their importance in HF, but not so much in COVID-19. Our review has consolidated these studies, to mention that these biomarkers, similar to troponin and NPs are elevated in patients with severe COVID-19 and can aid in prognosis [105,106].

Our study has a few limitations too. Majority of the studies that have been included are from China and European countries. This is partly because many studies were originally from Wuhan China, where the pandemic began, opening a possibility that many patients would have been repeated across studies. Another limitation is the nature of these studies, majority were retrospective or observational in nature. The trend of these bio enzymes could not be followed in patients who recovered from the illness. Small sample size of a few of these studies also precludes the generalisability. Hence future large prospective studies with follow up will be beneficial, especially for novel biomarkers.

CONCLUSION

SARS-CoV-2 associated COVID-19 infection undeniably has respiratory complications, however, extensive cardiovascular implications are also seen. Multiple cardiac biomarkers can help predict the severity of the disease and serve as prognostic indicators for outcomes and mortality. Assessment of cardiac bioenzymes at admission and their serial monitoring can help assess the severity of disease and predict mortality in patients with SARS-CoV-2 infection. A more liberal determination of cardiac biomarkers may improve early diagnosis and management of AHF, and other cardiovascular complications. COVID-19 associated myocarditis and HF have sequential effects even after the resolution of primary illness, and hence long-term correlation needs to be studied. In addition, there is emerging data on novel biomarkers, including growth GDF-15, soluble ST2, galectin 3, presepsin, and copeptin, which can aid in evaluation alongside natriuretic peptides and troponins. Further studies are needed to elude the critical importance of these novel markers.

ARTICLE HIGHLIGHTS

Research background

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is prevalent worldwide. Though lung injury is the most common presentation, cardiovascular dysfunction is seen on account of the widespread inflammation.

Research motivation

Cardiac biomarkers are released secondary to cardiovascular injury, and can be used as surrogate markers to gauge the disease severity.

Research objectives

To identify the role of individual biomarkers in diagnosing cardiac injury, and implications in determining prognosis and mortality.

Research methods

An extensive literature search was conducted for all studies on patients with COVID-19 associated cardiovascular injury and cardiac bioenzymes. Articles were screened using PubMed/Medline database, additionally reference citation analysis tool was also used. Eligible articles were then included in the study.

Research results

Cardiac troponin was seen as a robust diagnostic marker of cardiovascular injury across studies. Elevated troponin levels correlated with the level of disease severity. Similar results were seen alongside elevations in natriuretic peptides, irrespective of their prior diagnosis of heart failure.

Research conclusions

Multiple cardiac biomarkers can help predict the severity of disease and serve for prognostication purposes. Assessment of bioenzymes at admission and their serial monitoring can help predict

mortality in patients with COVID-19.

Research perspectives

New data is emerging on novel biomarkers including soluble ST2, galectin-3, presepsin and copeptin which can further aid in diagnostic evaluation alongside troponins and natriuretic peptides.

FOOTNOTES

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LETTER TO THE EDITOR

Possible agent for COVID-19 treatment: Rifampicin

Ozlem Celik Aydin, Sonay Aydın, Sureyya Barun

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Abstract

Rifampicin is a promising drug for the treatment of coronavirus disease 2019 based on its antiviral properties and recent *in silico* studies. *In silico* studies can serve as a foundation for further studies.

Key Words: Rifampicin; COVID-19; Treatment; *In silico*; Drug-drug interaction; Therapeutic potential

Core Tip: Rifampicin may be used as a treatment for coronavirus disease 2019 (COVID-19). Although it has a variety of drug-drug interactions, none of the important ones for the currently utilised COVID-19 medicines, favipiravir, enoxaparin, and aspirin, have been defined.

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TO THE EDITOR

We read the review written by Panayiotakopoulos and Papadimitriou[1] with interest.

The impacts of the coronavirus disease 2019 (COVID-19) pandemic are still being felt, and research into this topic continues due to the lack of a precise therapy. It is feasible to repurpose medications already used for other reasons for the treatment of COVID-19. The authors discussed rifampicin's antiviral capabilities, its potential effects in computer simulations, its safety, and its role in clinical practice. Rifampicin is an antibacterial drug that inhibits DNA-dependent RNA polymerase in *Mycobacterium tuberculosis*, and its antiviral effect has been shown on some viruses[2]. On this basis, the potential efficacy of rifampicin as a COVID-19 treatment drug has been demonstrated in *in silico* research[3]. We concur with the authors' suggestion for more research into the potential use of rifampicin for COVID-19.

In a study in which 20 United States Food and Drug Administration (FDA)-approved drugs were screened by molecular docking method in a possible drug design for COVID-19, rifampicin showed *in silico* binding to more than one target protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). Other macrocyclic antibiotics showing binding are polymyxin B and bafilomycin A[4]. In another *in silico* study of FDA-approved drugs to treat COVID-19 infection, rifampicin has stronger binding affinity for the COVID-19 main protease Mpro[5]. However, additional studies are needed for validation.

Due to the properties of rifampicin, various drug-drug interactions (DDIs) may occur during its possible use. Rifampicin promotes the expression of cytochrome p450 3A4 (CYP3A4) in the small intestine and liver, as noted in the review. Additionally, according to the work by Panayiotakopoulos and Papadimitriou[1], an essential feature of rifampicin is that it activates proteins such as the P glycoprotein (P-gp) drug transporter and CYP2C-mediated metabolism[6]. There are possible DDIs with drugs used for the treatment of COVID-19 and for additional diseases. Favipiravir is one of the antiviral medications used for the treatment of COVID-19. It is metabolized mostly *via* aldehyde oxidase and xanthine oxidase[7], and the probability of a pharmacological interaction between rifampicin and favipiravir is low. Lopinavir and ritonavir are two additional widely used antivirals; coadministration of these drugs with rifampin may result in a decrease in the plasma concentrations of ritonavir and lopinavir due to rifampin's induction of CYP450 3A4, the isoenzyme responsible for the metabolic clearance of ritonavir and lopinavir[8]. Remdesivir is widely used for COVID-19 treatment, which is metabolized through hydrolysis reaction to its triphosphate active form *via* by carboxylesterase 1 (80%), cathepsin A (10%), and CYP3A (10%). Since rifampicin is a potential inductor of CYP3A4, concomitant administration might increase the metabolism of remdesivir[9]. Dexamethasone has a strong anti-inflammatory impact and is typically used as an adjunctive treatment for COVID-19 pneumonia. Rifampin may increase corticosteroid hepatic metabolism, hence diminishing their therapeutic impact. Corticosteroids' half-life of elimination is shortened by up to 45% when co-administered with rifampin [10,11].

It has been suggested that prophylaxis of thrombosis in COVID-19 should include both anticoagulant and antiplatelet medications. Enoxaparin and aspirin are the two most often used anticoagulant and antiplatelet medications[12]. Fortunately, no significant medication interactions between these drugs and rifampicin have been identified. Apixaban and other direct oral anticoagulants can also be utilised. Rifampicin coadministration significantly increased apixaban plasma concentrations. When used orally, approximately 15% of apixaban is metabolised by CYP3A and roughly 6% by CYP1A2 and CYP2J2. The balance (50%) is eliminated unaltered in the form of faeces and urine. A single dose of rifampicin decreased apixaban clearance by 25%. Rifampicin largely influences apixaban absorption (and/or distribution), which could be attributed to an impairment of intestinal P-gp[13].

The authors said that rifampicin has been shown to be quite effective in treating COVID-19 in *in silico* tests. Additionally, multiple medication classes have been examined *in silico* for the treatment of COVID-19. Melatonin, ramelteon, and agomelatine, for example, have been demonstrated to significantly limit virus entry into cells in investigations. Ramelteon was proven to be the most effective antiviral against SARS-CoV-2[14].

FOOTNOTES

Author contributions: Aydın S, Aydin OC and Barun S conceived the study; Aydın S, Aydin OC and Barun S were responsible for designing, materials and supervision; Aydın S, Aydin OC and Barun S did the literature search, wrote the manuscript, and reviewed the manuscript critically; All authors have read and approved the final manuscript.

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