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Review

Prognosis and treatment of complications associated with COVID-19: a systematic review and meta-analysis

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ABSTRACT

The Coronavirus Disease 2019 (COVID-19) pandemic has been estimated to have claimed more than 6 million lives, and most deaths have been attributed to complications non-specific to the virus. Therefore, understanding and treating these complications are imperative. In this meta-analysis, we reviewed 181 studies published in early stages of the COVID-19 pandemic. We presented that the complications with high incidence among all COVID-19 cases were acute respiratory distress syndrome (ARDS, 18.52%), respiratory failure (16.54%), liver injury (14.13%) and multiple-organ dysfunction syndrome (MODS, 13.62%). Among patients who died, the most common complications were ARDS (84.10%), respiratory failure (78.75%) and respiratory injury (75.72%). Subsequently, we analyzed the risk factors for complications, and reviewed the currently available therapies according to complications and prognosis. To decrease the prevalence of COVID-19 complications and mortality, healthcare workers and patients should pay greater attention to the complications identified herein, particularly those occurring preclinically.

Keywords: COVID-19, SARS-CoV-2, complications, prognosis, treatment

1. INTRODUCTION

In December 2019, the city of Wuhan, China, provided numerous reports of an outbreak of pneumonia cases due to unexplained causes. These cases garnered substantial attention in China and other countries. Subsequently, the virus was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the related disease was named COVID-19. The World Health Organization declared the outbreak a global health emergency, which became a matter of worldwide concern by January 2020.

With the increasing number of confirmed cases each day, the economic and societal effects of COVID-19 have been immense, and the lack of specific tools to combat the SARS-CoV-2 virus has become apparent. Currently, overall COVID-19 diagnosis requires a combination of medical history, medical examination, potential extrapulmonary manifestations, and laboratory and radiologic data [1], because a sole examination can identify carriers but not symptomatic individuals; consequently the definition of asymptomatic individuals was doubted that they were just found before and after expressing the already known symptoms, and it is idealistic for a rational asymptomatic COVID-19 patient to exist in reality [2]. Some countries, such as America and Greece, have introduced rapid testing for autodiagnosis purposes to avoid cross-infection during the COVID-19 pandemic [3]. Beyond self-diagnosis, massive rapid-antigen-testing strategies have been used in the general population in several countries, and have certain advantages including shorter turnaround times and lower costs [4, 5]. However, every available assay targeting SARS-CoV-2 potentially yields both false-positive and false-negative results, thus placing patients, the general public and healthcare workers, particularly emergency physicians, at risk of infection [6]. Emergency departments have made great efforts in well-timed triage and risk stratification during this novel and unexpected pandemic [7]. Nonetheless, the worldwide death rate, as reported in late March 2022, has reached 6,050,018, and most deaths have been attributed to complications associated with COVID-19. Therefore, understanding and treating these complications are of utmost importance.

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus belonging to the B beta coronavirus lineage and the sarbecovirus subgenus [8, 9]. To date, SARS-CoV-2 is the seventh coronavirus known to be pathogenic to humans. The first four coronaviruses, 229E, OC43, NL63 and HKU1, caused simple common-cold symptoms [10]. The severe acute respiratory syndrome coronavirus (SARS-CoV) was identified in 2002–2003 in China, and the Middle East respiratory syndrome coronavirus (MERS-CoV) was identified in 2012–2013 in Saudi Arabia. Both showed strong infectivity and caused high mortality, thus substantially affecting human health and life. Several similarities have been described among SARS-CoV, MERS-CoV and SARS-CoV-2, particularly regarding their complications.

Although only 2 years have passed since the initial outbreak of COVID-19, numerous studies have been published in medical journals. These immense scientific efforts have been aimed at understanding SARS-CoV-2 by elucidating its evolution, epidemiology and genome. Clinically, healthcare workers have aimed to present laboratory and imaging findings, as well as available treatments for COVID-19. To our knowledge, this study is the first meta-analysis attempting to summarize the complications, including their prognosis and treatment, arising from COVID-19. We aim to present the incidence rates of the main complications in adult patients, and summarize the therapies that have been used to prevent and treat these complications. This review is intended to provide a single source compiling the vast currently available information, to offer a useful tool for researchers and healthcare workers battling against COVID-19.

2. METHODS

We performed this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.1. Search strategy

References were identified through searching of the PubMed, Embase, Cochrane Library, Web of science, medRxiv, bioRxiv and SSRN electronic databases without language restrictions. The search was performed by using various combinations of the keywords coronavirus, COVID-19, SARS-CoV-2, 2019-nCoV and Wuhan coronavirus.

2.2. Inclusion

All original studies reporting clinical complications between December 1, 2019 and May 21, 2021 were included in our meta-analysis. All included studies were screened independently by three reviewers.

2.3. Exclusion

Case reports and series with sample sizes below five were excluded. Studies reporting isolated complications or those in which patients with COVID-19 underwent surgical intervention during COVID-19 diagnosis or treatment were also excluded.

2.4. Data analysis

A single-arm meta-analysis was performed in Stata software. The original data from the included studies were first subjected to double-arcsine transformation to conform more closely to a normal distribution, then analyzed in Stata. The initial data from the meta-analysis were transformed with the formula (P = (sin(tp/2))2) to attain the final data. To objectively analyze the publication bias in the included studies, we performed the Egger test. $P < 0.05$ was considered to indicate the existence of publication bias.

3. COMPLICATIONS

3.1. Complications and their distribution

The first identified complication of COVID-19 was pneumonia. As the virus spread globally, it was reported to damage multiple organs, including the heart, liver and kidneys (**Figure 1**). These complications have resulted in severe morbidity and high mortality. Notably, some complications, such as hospital-acquired infections (hospital-acquired pneumonia and urinary-tract infections), pressure ulcers and deep vein thrombosis, can occur in any COVID-19 inpatients, and standard-practice preventive measures and treatment are recommended.

Several severe complications are commonly seen in COVID-19, including breathing difficulty in patients with ARDS or acute respiratory injury; chest tightness or pain in patients with acute cardiac injury; high creatinine, urea nitrogen or proteinuria levels in patients with acute kidney injury (AKI); and elevated AST or ALT in patients with liver injury [11, 12]. Guillain-Barré syndrome may also occur, but the incidence is very low [13]. Complications specific to pregnant women with COVID-19 include fetal distress, premature rupture of the membrane and miscarriage [14, 15]. Furthermore, given that SARS-CoV-2 may be present in the semen of COVID-19 patients and recovering patients, it may cause complications associated with reproduction, such as infertility or poor fetal growth [16]. Additionally, psychological effects, including anxiety, depression and suicide, should also be considered.

According to our meta-analysis (supplemental materials), among the common complications in patients with COVID-19, the incidence of ARDS was 18.52%, that of respiratory failure was 16.54%, and that of liver injury was 14.13% in all patients (**Figure 2**). In the patients who died, the incidence of ARDS was 84.10%, that of respiratory injury was 78.75%, and that of respiratory failure was 75.72% (**Figure 2**), thus suggesting that most patients with COVID-19 may die because of respiratory

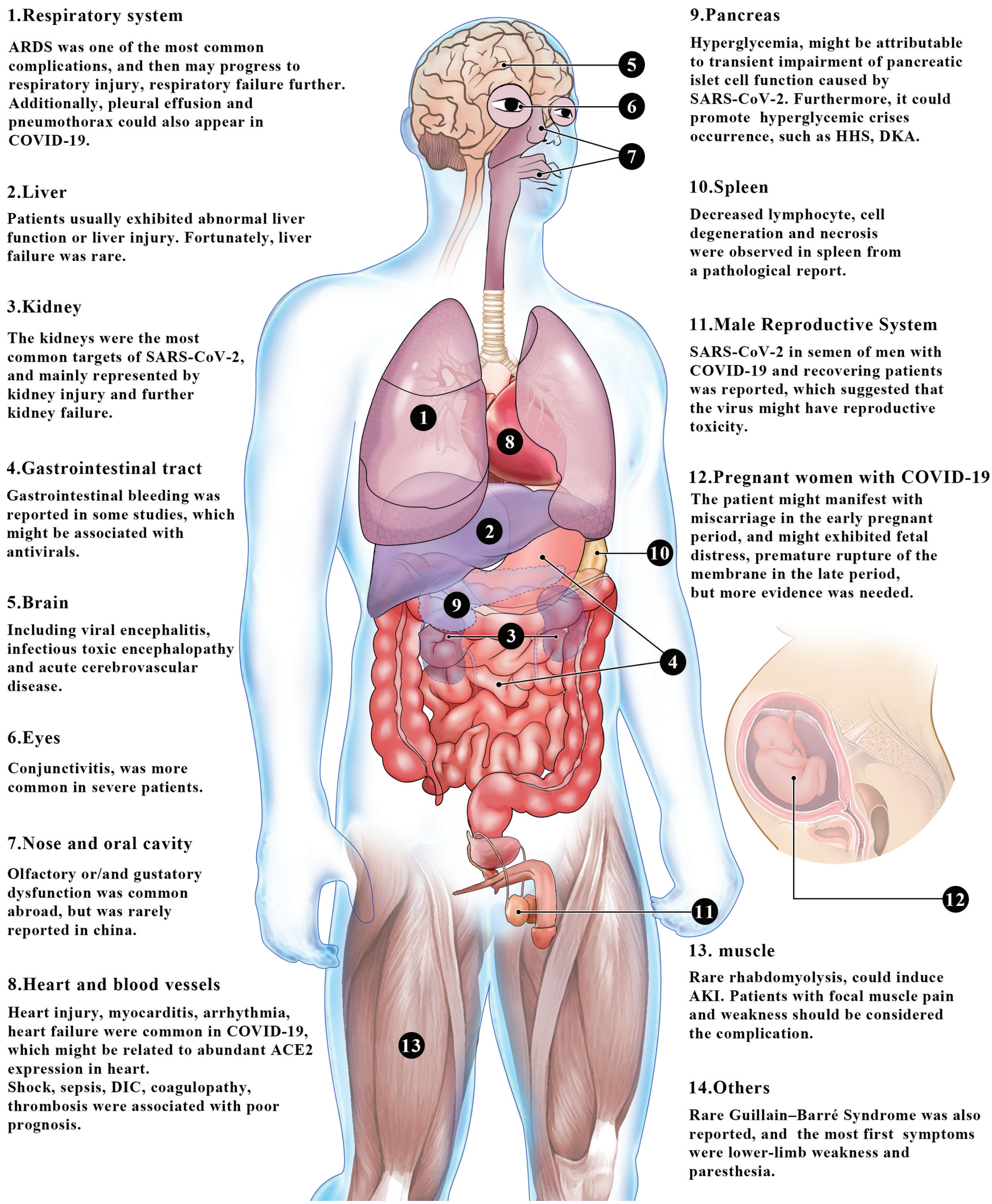

Figure 1 | Complications associated with COVID-19.
ACE2: angiotensin-converting enzyme, ARDS: acute respiratory distress syndrome, AKI: acute kidney injury, DIC: disseminated intravascular coagulation.

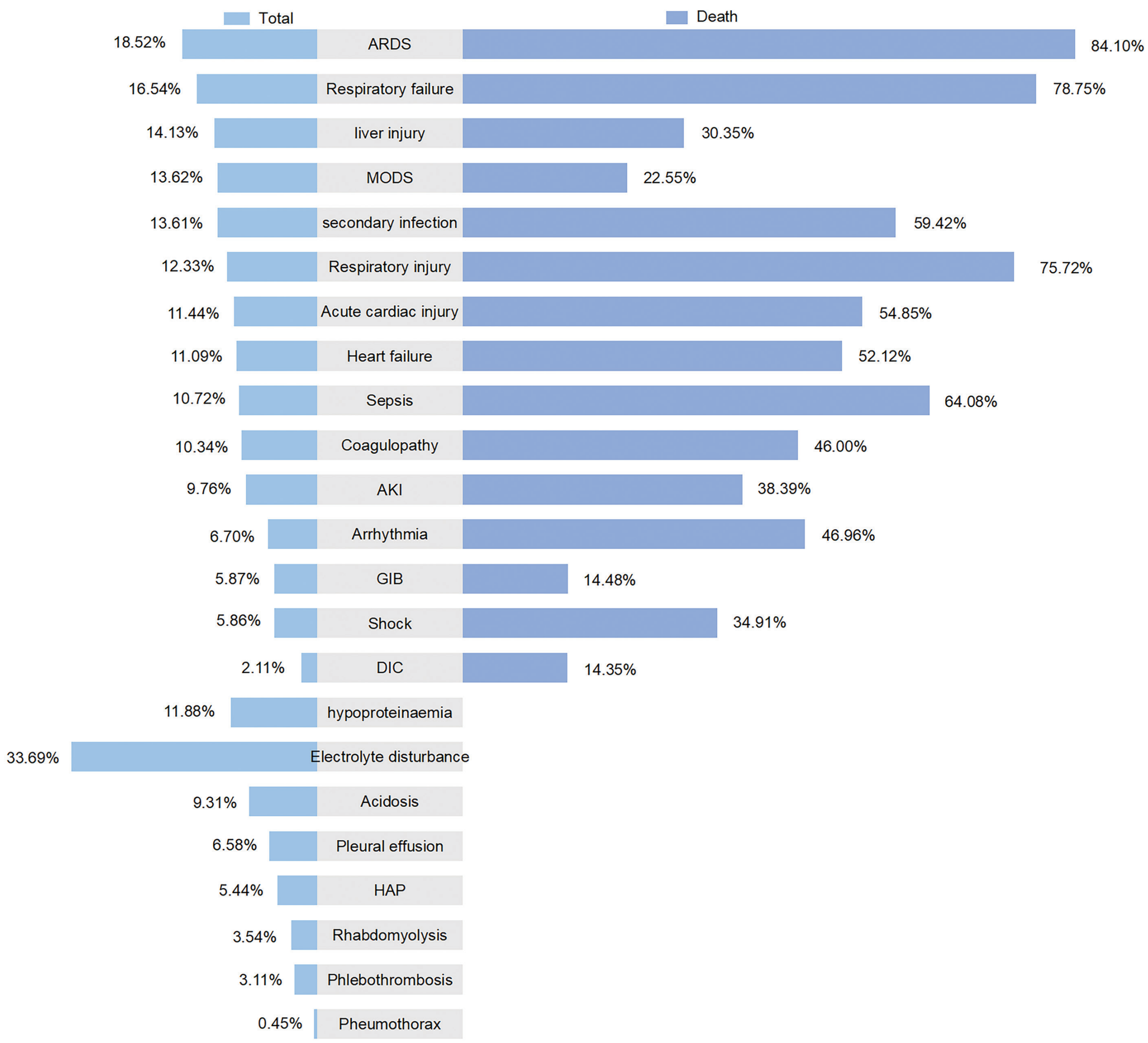

Figure 2 | Incidence of complications associated with COVID-19 in the entire patient cohort and in patients who died.
Blanks (i.e., hypoproteinemia and rhabdomyolysis) indicate few or no cases reported. GIB: gastrointestinal bleeding, MOD: multiple-organ damage.

compromise. A clear difference between severe cases and non-severe cases was observed for some complications (Figure 3).

3.2. Complications and pathogenesis

SARS-CoV-2 targets cells through the its receptor-binding domain in the S1 subunit of the spike protein of SARS-CoV-2, which binds the receptor angiotensin-converting enzyme 2 (ACE2) [17]. Subsequently, the viral particle enters the host cells through receptor-mediated endocytosis. In the target cells, the viral genome replicates. Several studies have identified that ACE2 is mainly expressed in lung type II alveolar epithelial cells (AT2); liver cholangiocytes; esophageal keratinocytes; ileal, rectal and stomach epithelial cells; kidney proximal tubules; and endothelial cells from small and large arteries and veins in many tissues (including the lung, stomach, small intestine, bone marrow, spleen, liver, kidney and brain) [16, 18]. These findings suggest that complications may be associated with the distribution of ACE2. Another study has indicated that ACE2 is expressed abundantly in endothelial cells, particularly in cardiac pericytes, and thus COVID-19 can be considered a vascular disease rather than a respiratory disease [19]. Overall, These evidence has demonstrated that SARS-CoV-2 has the potential to affect multiple organs and systems.

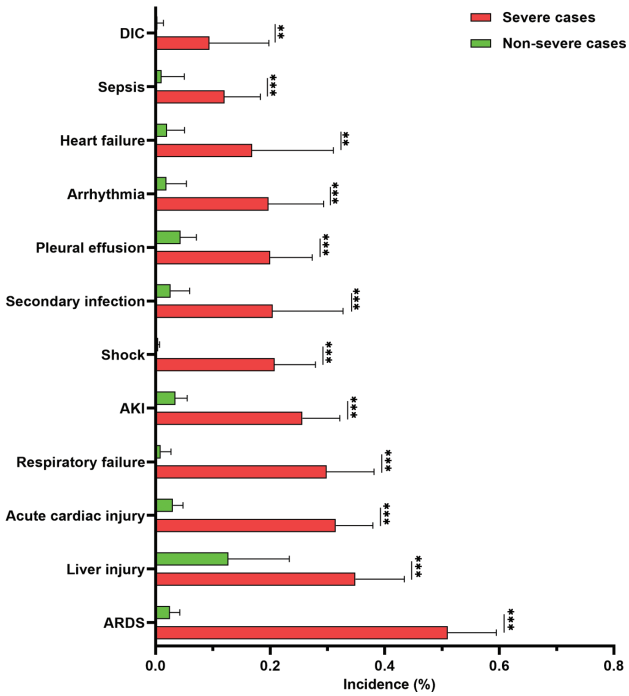

Figure 3 | Differences in a selection of complications between severe and non-severe cases.
Severe cases were defined as those in patients who were critically ill during hospitalization. *P < 0.05, **P < 0.001, ***P < 0.00001.

4. PREVENTION OF COMPLICATIONS

4.1. Prevention of infection

The first step in minimizing the effects of COVID-19 is limiting infection spread. COVID-19 is extremely transmissible, with a reported reproduction number (R_0) of approximately 3 [20, 21]. Because each person infected with COVID-19 has the potential to infect approximately three others, protection against SARS-CoV-2 infection plays a crucial role in decreasing the incidence of the disease.

Education campaigns should be conducted to promote precautions among the population at large, including frequent handwashing with soap and water for at least 20 seconds, or using an alcohol-based hand sanitizer; cough etiquette to cover coughs or sneezes with a tissue; and avoiding touching high-risk sites, specifically the eyes, nose and mouth, with unwashed hands. Additionally, the frequency of social gatherings must be decreased, and the use of personal protective equipment, such as masks, must be advocated when visiting public places. The general public should be encouraged to proactively report fever and other suspicious symptoms of SARS-CoV-2 infection, particularly if they had a travel history to epidemic areas, or close contact with people with confirmed or suspected cases [22].

Healthcare workers, particularly those at the frontlines, are at high risk of SARS-CoV-2 infection and hence must receive updated training on infection prevention and control. They must also be provided with adequate personal protective equipment, including surgical masks, disposable medical protective clothing and latex gloves [23]. Additionally, shift hours should be strictly controlled, and adequate rest, food and family support should be provided to avoid overwork. Moreover, studies during the COVID-19 pandemic have suggested that mental-health problems, including depression, anxiety and insomnia, are prevalent in a considerable proportion of healthcare workers, particularly nurses [24, 25]. Therefore, mental-health support is necessary for healthcare workers, particularly these exposed to COVID-19. Given that some reports have stated that the virus can persist on plastic and stainless-steel surfaces for as long as 72 hours [26], efficient disinfection of wards and medical waste is also key to infection prevention. Particular attention should be paid to bathrooms and soiled objects, because of possible transmission via the fecal route [27, 28].

At the governmental level, provision of information should be rapid and transparent, through the establishment of a daily press-release system. Medical institutions should follow integrated control measures, including patient isolation, contact tracing, quarantine and vaccination. Notably, some cases in the pre-symptomatic or post-symptomatic stages, or cases with paucisymptomatic COVID-19, are able to transmit the virus [29]. Thus, social distancing and mask-wearing were recommended or mandatory for the public during the COVID-19 pandemic. Social-distancing strategies, such as closing cinemas and restaurants, cancelling large public gatherings, and restricting and closely monitoring travel, have been demonstrated to be effective in China and other countries. Moreover, safe mask-wearing should also be recommended during the COVID-19 pandemic. Current studies have demonstrated that FFP/(K) N95 masks are an effective measure to prevent SARS-CoV-2 transmission and result in fewer respiratory adverse effects (such as cough, dyspnea and sputum production) than medical/surgical masks, whereas cotton cloth masks not only do not prevent infection but also are more likely to cause respiratory adverse effects [30]. A vaccine against SARS-CoV-2 is one of the most effective ways to prevent the spread of the virus, and thus vaccination of the public, particularly high-risk individuals, should be encouraged. However, the response to COVID-19 vaccination has varied among populations. For example, women and younger people are more likely to be vaccinated against COVID-19, whereas men with a basic education level and older people tend to be more hesitant to vaccinate against COVID-19 [31]. Furthermore, for both SARS and SARS-CoV-2, animal-to-human transmission is suspected to have caused the initial stage of the epidemic; therefore, all game-meat trading should be strictly regulated to terminate this route of transmission [32].

4.2. Screening causes of complications

In our review, we identified five main mechanisms leading to complications:

1. SARS-CoV-2 directly infects target organs or cells expressing the ACE2 receptor. Viral inclusions have been observed in lung cells [33], and viral particles have been found in bronchial and type II alveolar epithelial cells through electron microscopy.
2. An inflammatory cytokine storm produced by the immune response against the virus results in organ or systemic damage. Greater disease severity is associated with higher plasma levels of IL-2, IL-7, IL-10, GSCF, IP10, MCP1, MIP1A and TNF-α [12]. Another study has found that tocilizumab, an IL-6-receptor inhibitor, is efficient in treating severe COVID-19 [34].
3. Drug-induced complications (**Table 1**). Treatments such as lopinavir-ritonavir, an antiviral drug, may result in gastrointestinal adverse effects and hepatotoxicity [43, 44].
4. Complication chain reaction. COVID-19 patients with ARDS are predisposed to developing other complications, including AKI, acute cardiac injury or acute liver injury [54].
5. Deterioration of pre-existing comorbidities.
6. Simultaneous contribution of these mechanisms to the occurrence of clinical complications. This mechanism is the most likely scenario.

4.3. Recognizing preclinical complications

A retrospective cohort study has indicated that the median time from disease onset to death is 18.5 days, whereas the shortest survival duration from illness onset to death is 15 days, suggesting that COVID-19 progresses rapidly [61]. Given that COVID-19 complications are the leading cause of death, identifying the warning signs of these complications and taking proper measures might slow or halt the progression of COVID-19 and minimize the risk of mortality. Regular monitor of risk factors or signs (**Table 2**) associated with the pathogenesis and development of COVID-19 complications is recommended, particularly in people with pre-existing complications as well as in high-risk population groups, such as older people with comorbidities. The heavy burden of smoking and obesity, and the prevalence of cardiovascular diseases in modern society have placed people at risk of severe COVID-19 with complications [62]. In addition, close attention should be paid to pregnant women with COVID-19, although current evidence suggests that no serious complications occur in pregnant patients, and their outcomes are favorable [14, 63].

The effects of COVID-19 on mental health should not be discounted. Anxiety and depression have frequently been observed in patients with COVID-19, and some reports have indicated that suicidal risk may increase due to social isolation and separation from families [64]. Consequently, hospital staff should specifically ask whether patients are experiencing such symptoms, and should pay particular attention to patients with limited communication abilities and those in intensive care units (ICUs). Adequate recognition and treatment of psychological symptoms at early stages are crucial, because such symptoms can greatly influence patients' well-being.

5. TREATMENT OF COMPLICATIONS

5.1. Facility planning

Patient isolation is important to prevent nosocomial disease transmission, and protect the public and healthcare workers. For successful isolation, hospitals must be equipped with a suitable infrastructure. Patients with suspected or confirmed COVID-19 should be admitted to an airborne-infection isolation room with negative pressure relative to the surrounding areas, and equipped with accessible sinks, alcohol-hand-sanitizer dispensers and suite bathrooms. Patients with confirmed COVID-19 should be admitted to single rooms with negative pressure to prevent cross-infection within hospitals. However, rooms with negative pressure may place patients at risk of adverse effects because of the mental and psychological pressures of being in isolation; therefore, this aspect should also be considered. Furthermore, airborne-infection isolation rooms and hospital beds may be unavailable during outbreaks with high numbers of COVID-19 cases. To counteract this shortage, shelter hospitals in China, for example, have been created by modifying public venues [65], and might be a major reason for the successful control of COVID-19 in the early stages the pandemic in China.

According to many reports, shared wards accommodating only patients with COVID-19 can serve as an alternative. However, current evidence indicates that COVID-19 spreads mainly through airborne and direct-contact transmission; therefore, nosocomial transmission in shared wards may occur through aerosol generation, such as by coughing or sneezing. Thus, room ventilation, open space, sanitization of protective apparel, and proper use and disinfection of bathroom areas should be considered [66].

5.2. Triage of COVID-19 patients with complications

Although triage of COVID-19 patients with complications is an ethically complex issue, it has the potential to ensure optimal use of medical resources and maximize the number of lives saved per available resource. Difficult decisions regarding which patients should be admitted to ICU arise in situations in which medical resources are limited, and should be made according to the principles of equity and preservation of as many lives as possible [67]. For example, COVID-19 patients with ARDS or respiratory failure require mechanical ventilation; patients with shock (septic or cardiogenic), AKI or renal failure require continuous dialysis; and patients with multiple-organ failure require ICU admission [68]. When resources are scarce, the patients

Table 1 | Efficacy and risks of common drugs used to treat patients with COVID-19

Drugs	Efficacy	Risks
Remdesivir (nucleotide analog)	Superior antiviral activity to lopinavir-ritonavir in mice with MERS-CoV infection [35], and effective inhibition of SARS-CoV-2, MERS-CoV and SARS-CoV in vitro [36] have been reported. Adults with severe COVID-19 have not been found to benefit from remdesivir in a randomized trial [37], whereas adults with COVID-19 receiving intravenous remdesivir have shown shorter times to recovery in a double-blind trial [38].	No published safety data are available for SARS-CoV-2. One of 175 Ebola-infected patients after remdesivir administration experienced hypotension followed by cardiac arrest in a randomized trial [39].
Lopinavir-ritonavir (protease inhibitor)	No benefit was observed with lopinavir-ritonavir compared with standard care in hospitalized adult patients with severe COVID-19 in an open-label RCT [40]. However, efficacy has been observed in patients with SARS-CoV [41] but has been found to be unclear in patients with MERS-CoV [42].	Common gastrointestinal adverse effects include diarrhea, nausea and vomiting [40, 43]. Hepatotoxicity (elevated transaminases) and elevated odds of liver injury have been reported [44].
Chloroquine (antimalarial)	Effective antiviral activity against SARS-CoV and SARS-CoV-2 has been reported in vitro [36, 45]. Effective inhibition of the exacerbation of pneumonia and shorter disease course have been observed [46].	No published safety data are available for SARS-CoV-2, but some concerns include the possibility of QT prolongation, hypoglycemia, neuropsychiatric effects, retinopathy [47] and cardiovascular disorders (including ventricular hypertrophy, heart failure, pulmonary arterial hypertension and valvular dysfunction) [48, 49].
Hydroxychloroquine (antimalarial)	Enhanced viral clearance and decreased disease progression have been found in patients with COVID-19, particularly with administration of hydroxychloroquine in combination with azithromycin, in an open-label non-RCT [50]. This treatment is more effective than chloroquine in inhibiting SARS-CoV-2 in vitro [51]. For patients with COVID-19, hydroxychloroquine has not been associated with a decreased risk of death in an observational study [52].	No published safety data are available for SARS-CoV-2, but concerns include the possibility of QT prolongation, hypoglycemia, neuropsychiatric effects, retinopathy [47] and cardiovascular disorders (including ventricular hypertrophy, heart failure, pulmonary arterial hypertension and valvular dysfunction) [48, 49].
Corticosteroids (immunostimulators)	Proper use of corticosteroids has been found to decrease mortality and shorten the length of hospital stay for critically ill patients with SARS in a retrospective study of 401 patients [53]. In SARS-CoV-2-infected patients with ARDS, treatment with methylprednisolone has been found to decrease the risk of death in a prospective cohort study [54]. No clinical data for mild cases are available.	No published safety data are available for SARS-CoV-2, but diabetes and avascular necrosis in patients with SARS [55, 56], and secondary bacterial or fungal infection in influenza have been reported [57].
Ribavirin (RNA-dependent RNA polymerase inhibitor)	High concentrations inhibit SARS-CoV replication in vitro [58]. When used alone or in combination with interferons, no discernible effect on clinical outcomes or viral clearance has been observed in patients with MERS [59, 60]. No data are available on the efficacy of Ribavirin in the treatment of COVID-19.	No published safety data are available for SARS-CoV-2. High proportions of hemolytic anemia and liver toxicity have been reported in a SARS trial [58].

Table 2 | Common complications associated with COVID-19

Complications associated with COVID-19	When to be alert
ARDS	All COVID-19 patients
Acute respiratory injury	All COVID-19 patients
Respiratory failure	COVID-19 patients with respiratory injury
Acute cardiac injury	COVID-19 patients with chest discomfort and palpitations
Arrhythmia	All COVID-19 patients, particularly those treated with chloroquine or hydroxychloroquine
Heart failure	Severe COVID-19 patients or those treated with chloroquine or hydroxychloroquine
Shock	COVID-19 patients with cold extremities or weak peripheral pulses
Sepsis	COVID-19 patients with SARS-CoV-2 viremia
DIC	COVID-19 patients with elevated D-dimer levels
Coagulopathy	COVID-19 patients with abnormal coagulation parameters
Liver injury or liver-function abnormalities	All COVID-19 patients, particularly those treated with ribavirin or lopinavir-ritonavir
AKI	All COVID-19 patients, particularly those taking nephrotoxicity inducing drugs (e.g., NSAIDs or vancomycin)
Renal failure	COVID-19 patients with acute kidney injury
Multiple-organ failure	Severe COVID-19 patients, particularly those with DIC

Most of these complications can occur in any patient with COVID-19. However, the second column highlights when complications are most likely to occur and/or when healthcare professionals should be most alert.

benefiting most from ICU admission are considered a priority. To improve triage efficacy, policies should be implemented by trained clinicians, particularly experienced physicians [69].

Patients who require ICU care, compared with those who do not, tend to be older, to have comorbidities, and to show higher incidence of complications and more rapidly progressing trajectories [70]. In ARDS, old age is a significant risk factor for condition development and mortality [54], suggesting that older patients with ARDS would benefit more from ICU admission than younger patients. Triage should also be based on laboratory examinations, including D-dimer and C-reactive protein concentrations and lymphocyte counts.

5.3. Treatment of ARDS

ARDS is a clinical syndrome characterized by severe acute hypoxemia and inflammatory pulmonary edema, which finally leads to respiratory failure—a life-threatening complication in patients with COVID-19. In a report, 38 of 81 patients (approximately 47%) infected with SARS-CoV-2 died of respiratory failure, a leading cause of fatality [71]. Thus, effective treatment for ARDS might significantly improve the clinical outcomes of patients with severe COVID-19 (Table 3).

The initial recommended treatment for ARDS in the context of COVID-19 is supportive care, including high-flow nasal oxygen, lung-protective ventilation strategies, conservative intravenous fluid treatment for patients without shock, empirical early antibiotics for possible infection, periodic prone positioning and consideration of extracorporeal membrane oxygenation [78]. For early ARDS, termed type L with high compliance, larger tidal volumes (7–8 ml/kg of predicted body weight) are recommended to help prevent reabsorption atelectasis and hypercapnia with primary non-invasive options such as high-flow nasal cannulation (HFNC) [79]. HFNC effectively improves oxygenation and decreases or eliminates the need for tracheal intubation without affecting mortality [80]. Lower positive end-expiratory pressure (PEER; 8–10 cm H_2O) is considered appropriate, because higher PEER might accentuate the stress on highly permeable microvessels and compromise CO_2 exchange.

The condition of type L patients might remain unchanged, and then improve or worsen. If worsening occurs, heightened lung edema is observed, thereby decreasing the gas volume in the lung. Thus, patients might progressively undergo a transition from type L to type H with high elastance [79]. For patients with type H (severe ARDS) who may require endotracheal intubation, tidal volumes (4–8 ml/kg of predicted body weight), inspiratory pressures (plateau pressure <30 cm H_2O) and high PEER are the major lung-protective ventilation strategies [73, 78]. Adjusting PEER according to transpulmonary pressures measured with an esophageal balloon is considered to be good practice to protect lung injury. Conservative intravenous fluid strategies are crucial to alleviate pulmonary edema. A negative fluid balance of 0.5–1.0 L per day in patients

Table 3 | Therapeutic options and risks for ARDS associated with COVID-19

Therapy	Implementation	Risks
Decreased tidal volumes	4–8 ml/kg of PBW, initial tidal volume of 6 ml/kg PBW	High tidal volume might result in ventilator-induced lung injury [72].
Inspiratory pressures	Plateau pressure <30 cm H_2O	No clinical data are available.
HFNC or non-invasive ventilation	Might decrease or prevent the need for tracheal intubation without affecting mortality	No clinical data are available.
PEER	Moderate or high levels of PEEP for moderate or severe ARDS	Risks include barotrauma, hypotension and cardiac arrhythmias [73].
Neuromuscular blockade	decresing the work of breathing and patient-ventilator dyssynchrony, and improving oxygenation	Deep sedation is required and can cause residual paresis.
Inhaled pulmonary vasodilators	Prostaglandins and nitric oxide (NO) were commonly used, and NO at 5–20 parts per million was recommended	NO may be associated with heart failure and cardiopulmonary compromise [73].
Corticosteroids	Recommended for severe ARDS	Risks include hyperglycemia and neuromuscular weakness [74].
Renal replacement therapy	For oliguric renal failure, acid-base management and negative fluid balance	Risks include vascular-access complications, infection and electrolyte abnormalities.
High-frequency oscillatory ventilation	Not routinely recommended for moderate or severe ARDS	This treatment might increase mortality [75].
Recruitment maneuvers	Little value	Risks include hypotension, desaturation, decreased cardiac output, arrhythmias and pneumothorax.
Antibiotics	For possible concomitant bacterial infection	This treatment might result in dysbacteriosis.
Conservative intravenous fluid management	Negative fluid balance of 0.5–1.0 L per day	No clinical data are available.
ECMO	According to EOLIA trial criteria	Risks include thrombosis and hemorrhage, thrombocytopenia, altered medication pharmacokinetics, and infection and vascular-access complications [76, 77].

with ARDS without shock is recommended [81]. If shock is present in patients with ARDS, particularly those with coexisting AKI and oliguria, renal replacement therapy is recommended to maintain fluid balance. Risks, such as vascular-access complications, infection and electrolyte abnormalities, should be considered [73]. Given that the initial outbreak of COVID-19 occurred during influenza season [12, 61], empirical antibiotics should be used to prevent secondary infection. For patients with refractory hypoxemia and elevated plateau airway pressures or a need for ventilator synchrony, neuromuscular blockade with cisatracurium is an option. Inhaled 5–20 NO or inhaled prostaglandins in combination with prone positioning are the alternatives, particularly for patients with concomitant right heart failure [73]. Prone positioning is considered a first-line-treatment adjunct, and more than 12 hours per day for patients with severe ARDS in the absence of specific contraindications is recommended. In addition, a recent study has suggested that convalescent serum or plasma is a promising therapy for viral neutralization and immunomodulation in cases of severe ARDS [82]. Corticosteroids might be harmful in mild cases, but methylprednisolone has been demonstrated to be beneficial in COVID-19 patients with ARDS [54]. Some evidence suggests that high-frequency oscillatory ventilation and recruitment maneuvers have little value and are not routinely recommended. Finally, extracorporeal membrane oxygenation (ECMO) might serve as a last line of defense against severe ARDS or respiratory failure, and its use should follow the EOLIA trial findings [83].

5.4. Treatment of other major systemic complications

Patients with COVID-19 in addition to ARDS may exhibit acute liver injury, acute cardiac injury and AKI. These complications have high incidence after ARDS. Without intervention, these patients might develop multiple-organ failure, which is associated with high mortality.

Mild liver injury in patients with COVID-19 is usually transient, and liver laboratory-test levels and function could return to normal without any interventions beyond supportive care and regular monitor of liver biochemistry [84]. Reported cases of severe liver injury, acute liver failure or acute exacerbation of chronic liver failure are rare in patients with COVID-19 [12, 85]. Recognizing the etiology is key to treatment. First, the immune response to SARS-CoV-2 infection may mediate injury [86]. Second, SARS-CoV-2 replicating within hepatocytes may induce direct cytotoxicity, resulting in liver damage. Third, patients with pre-existing chronic liver disease are more likely to experience hepatic injury from SARS-CoV-2 infection. Finally, anoxia and drug-induced liver injury is frequently observed in patients with COVID-19, particularly in severe cases. Liver injury may result from a combination of the aforementioned factors.

COVID-19 patients with cardiac injury should first be examined for underlying cardiovascular disease (CVD) including hypertension, coronary heart disease and cardiomyopathy, because the mortality in COVID-19 patients with CVD is four times higher than that in all patients with COVID-19 [87]. The key to treating COVID-19 patients with cardiac injury or CVD is providing symptomatic management and supportive care. Some cases with refractory shock or ventricular arrhythmias due to cardiac injury may require mechanical support, because successful recovery has been observed with the use of ECMO [88]. Notably, increasing evidence indicates that disseminated intravascular coagulation (DIC) can escalate organ damage, particularly within the cardiovascular system; hence, anticoagulation should be considered. Furthermore, assessing pre-load responsiveness before fluid administration is essential. Particular attention must be paid to cardiac injury induced by certain drugs.

Advanced age, diabetes, hypertension, chronic kidney disease, shock or use of nephrotoxic drugs in COVID-19 patients with AKI are considered high-risk factors [89]. If possible, removing modifiable risk factors, such as improving shock, or decreasing or stopping the use of nephrotoxic drugs, is crucial. Symptomatic and supportive treatment could decrease the incidence of complications caused by AKI to some extent, including acid-base or electrolyte imbalances, and perturbed internal physiology. Additionally, continuous renal replacement therapy is recommended in patients with stage 2 or 3 AKI [90] as early as possible, particularly in patients with severe cytokine storm and multiple-organ failure [91].

6. PROGNOSIS

6.1. Risk stratification

Patients with COVID-19 are clustered into three groups according to mild (81%), severe (14%) and critical (5%) disease severity [92]. However, the distribution might change as the pandemic continues. Pregnant women generally tend to have milder illness and better prognosis [14, 63]. The factors influencing patient prognosis are numerous and complex, but age appears to be the most significant factor. For example, the current overall case-fatally rate (CFR) of COVID-19 in China has been reported to be 2.3%, but in people 70–79 years of age, the CFR is 8.0%, whereas people with 80 years of age or older have a CFR of 14.8% [93]. A higher CFR has been observed in some Western countries because of relatively larger aging populations: the US has a CFR of 5.8%, and Europe has a CFR of 8.5% [93].

COVID-19 complications are directly associated with patient prognosis. Older age and comorbidities may contribute to the progression of complications. For example, a cohort study has identified that ARDS is an independent risk factor for mortality, and older age additionally promotes the development of ARDS and the progression from ARDS to death [54]. AKI is corelated with higher mortality risk in patients with COVID-19, in a severity-dependent manner. Specifically, patients with stage 3 AKI show a quadrupled excess risk of death compared with patients without AKI [94]. Notably, soluble urokinase receptor levels, independently of biomarkers of kidney function and inflammation, are strongly correlated with incident AKI and are predictive of whether patients require dialysis [95]. Similarly, cardiac injury in patients with COVID-19 is associated with a higher risk of death, and patients with cardiac injury are more prone to experiencing other complications, including ARDS, AKI and liver injury [44]. Furthermore, patients with liver injury have a nine-fold greater risk of developing severe ARDS than those without liver injury [44]. Finally, coagulopathy, sepsis, respiratory failure and heart failure are also important contributors to high mortality.

6.2. Prognosis predictors

Patients with certain characteristics and medical history have poorer prognosis. Therefore, COVID-19 prognosis might viably be predicted by screening for such predictors. Predictors of poor prognosis are old age, male sex, smoking history, and comorbidities including hypertension, diabetes, chronic kidney disease, chronic pulmonary disease and cerebrovascular disease [96]. High CFR is observed in patients with cardiovascular disease (10.5%), diabetes (7.3%), chronic respiratory disease (6.3%), hypertension (6.0%) and cancer (5.6%) [87]. In terms of laboratory predictors, elevated LDH, CRP, D-dimer and lymphopenia are associated with higher death rates [61, 97]. In addition, the Sequential Organ Failure Assessment (SOFA) and quick Sequential Organ Failure Assessment (qSOFA) scoring systems are often used to assess the prognosis and severity of COVID-19. Higher SOFA or qSOFA scores correlate with higher mortality rates [61].

7. CONCLUSIONS

COVID-19 has become a major global public-health crisis, having already caused 6 million deaths worldwide, most resulting from well-understood complications. Screening and managing such complications, particularly in older male patients with comorbidities, are effective intervention tactic with the potential to decrease mortality. Currently, the primary goal should be to protect the population from SARS-CoV-2 infection. If infection does occur and complications ensue, the next-best step is optimal treatment of such complications. However, treatments are currently limited to non-specific antiviral agents and supportive care; therefore, effective drugs with powerful antiviral activity and low toxicity are urgently needed. On the basis of the Chinese experience, when novel infectious diseases occur in specific regions, the local government's public-health measures are crucial for controlling and limiting disease spread to other areas.

CONFLICTS OF INTEREST

All authors declare that there are no competing interests.

AUTHOR CONTRIBUTIONS

Xudong Xie, Liangcong Hu and Hang Xue proposed the research questions, developed the protocol and drafted the manuscript. Xudong Xie, Yuan Xiong and Lang Chen refined the search strategy. Xudong Xie, Ze Lin and Chenchen Yan searched for and collected the studies. Bobin Mi, Wu Zhou and Guohui Liu assessed the risk of bias in the eligible studies. Adriana C. Panayi, Bobin Mi, Wu Zhou and Guohui Liu critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript.

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