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Review Article

Coronavirus Disease 2019: A Review of Risk Factors, Severity, and Complications

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Abstract

The world is still facing the coronavirus disease 2019 (COVID-19) pandemic caused by coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), since it first appeared in Wuhan, China, in December 2019. The virus primarily affects the respiratory system, but increasing evidence indicates that SARS-CoV-2 can affect multiple organ systems and causes several complications. The risk factors for disease severity and complications of COVID-19 include cancer, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease (COPD), and other lung diseases, diabetes mellitus, down syndrome, heart conditions, human immunodeficiency virus (HIV) infection, neurologic conditions, obesity, pregnancy, smoking, sickle cell disease, solid organ or blood stem cell transplantation, substance use disorders, use of corticosteroids or other immunosuppressive medications. Since older people have one or more coexisting medical conditions, they are probably at the highest risk for fatal COVID-19 infections. COVID-19 disease severity can range from mild to critical, with the majority having only mild disease. The most common complication of this disease is acute respiratory distress syndrome (ARDS). Other complications include cardiovascular, renal, neurologic, thrombotic complications, liver injury, as well as bacterial, viral, and fungal coinfections. This review summarizes the current understanding of the risk factors, the severity of COVID-19 infection, and the most common complications of this disease.

Keywords: Coronavirus Disease 2019 (COVID-19); Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2); Risk Factors; Severity; Complications; Severe Acute Respiratory Distress Syndrome

Introduction

In late December 2019, several cases of pneumonia of unknown origin were noted in China, which were later determined to be caused by a novel coronavirus [1]. The virus was later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and it was identified as the causative agent of coronavirus disease 2019 (COVID-19) [2], which is currently causing a global pandemic.

SARS-CoV-2 has primarily affected the respiratory system, but increasing evidence indicates that SARS-CoV-2 can affect multiple organ systems with varying frequencies and degrees of severity, causing multiple complications [3].

The most common complications of this disease are respiratory failure and acute respiratory distress syndrome (ARDS) [4-6]. However, several other complications have been reported, including cardiovascular [7,8], renal [5,9,10], neurologic [11,12], thrombotic complications [13], liver injury [14,15], as well as bacterial, viral, and fungal coinfections [16,17].

This review provides insights into the current understanding of the risk factors, severity of COVID-19 infection, and the most common complications of this disease.

Risk factors and associated comorbidities for severe COVID-19 infection

Older age and coexisting comorbidities are risk factors for severe disease and death in COVID-19 patients [18] (Figure 1).

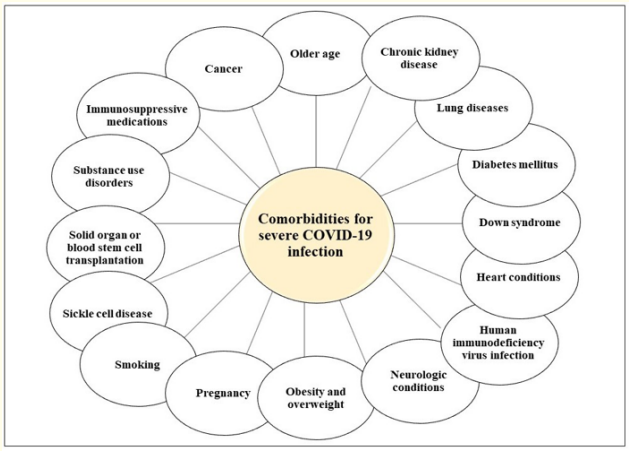

Figure 1: Comorbidities for severe COVID-19 infection [18-20]

Comorbidities such as cancer*, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease* (COPD), and other lung diseases (including interstitial lung disease, pulmonary fibrosis, pulmonary hypertension), diabetes mellitus, type 1* and type 2*, down syndrome, heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies), human immunodeficiency virus (HIV) infection, neurologic conditions, including dementia, obesity* (BMI ≥30 kg/m2) and overweight (BMI 25 to 29 kg/m2), pregnancy*, smoking* (current or former), sickle cell disease, solid organ or blood stem cell transplantation, substance use disorders, use of corticosteroids or other immunosuppressive medications have been considered as an established and probable risk factors for severe COVID-19 [19,20]. These comorbidities have been associated with severe COVID-19 in at least one meta-analysis or systematic review [starred conditions], or observational studies [20].

Because older people have one or more coexisting medical conditions, they are probably at the highest risk for fatal COVID-19 infections. The mortality rate in patients over the age of 65 is more than 80%, and it is more than 95% in patients over the age of 45 [19]. It has also been found that children and adolescents with preexisting conditions are more likely to have serious or fatal COVID-19 infections [19].

Comorbidities such as cystic fibrosis and thalassemia are two potential risk factors that have been supported by the majority of case series, case reports, or, if other study design, the sample size is small [20].

Comorbidities such as asthma, hypertension, immune deficiency, and liver disease are possible risk factors, but the evidence is mixed (comorbidities have been associated with severe COVID-19 in at least one meta-analysis or systematic review, but other studies have not reached the same conclusion [20].

In a systematic review and meta-analysis of 76 studies including 11,028 COVID-19 patients from multiple countries with approximately 57.5% were from mainland China, the most frequent comorbidities were hypertension (18.1%, 95% CI 15.4-20.8%), followed by cardiovascular disease (11.8%, 95% CI 9.4-14.2%) and diabetes (10.4%, 95% CI 8.7-12.1%) [21]. The pooled prevalence (95% CI) of COPD, chronic kidney disease, liver disease, and cancer were 2.0% (1.3-2.7%), 5.2% (1.7-8.8%), 2.5% (1.7-3.4%) and 2.1% (1.3-2.8%) respectively [21]. In another meta-analysis of seven studies, including 1,576 patients with COVID-19, the most prevalent comorbidities were hypertension (21.1%, 95% CI: 13.0-27.2%), diabetes (9.7%, 95% CI: 7.2-12.2%), cardiovascular disease (8.4%, 95% CI: 3.8-13.8%) and respiratory system disease (1.5%, 95% CI: 0.9-2.1%) [8]. Compared severe to non-severe patients, the pooled Odds Ratios (OR) of hypertension, respiratory system disease, and cardiovascular disease were 2.36 (95% CI: 1.46-3.83), 2.46 (95% CI: 1.76-3.44) and 3.42 (95% CI: 1.88-6.22) respectively [8].

Comorbidities may be risk factors for adverse outcomes [9]. Among the 138 patients with COVID-19, approximately half (46.4%) of them had comorbidities, in particular, patients requiring intensive care unit (ICU) had a higher number of comorbidities (72.2%) than those who did not require ICU care (37.3%) [9]. Patients with associated comorbidities including, but not limited to hypertension, diabetes mellitus, cardiovascular disease, chronic respiratory disease, cancer, chronic kidney disease, chronic liver disease, and cerebrovascular disease might be at higher risk for severe disease or death from COVID-19 [9]. In the Chinese data

of 44, 672 patients, 12.8% of patients had hypertension (39.7% of deaths; Case Fatality Rate [CFR] 6.0%), 5.3% had diabetes mellitus (19.7% of deaths; CFR 7.3%), 4.2% had cardiovascular disease (22.7% of deaths; CFR 10.5%), 2.4% had chronic respiratory disease (7.9 % of deaths; CFR 6.3%), and 0.5% had cancer (1.5% of deaths; CFR 5.6%) [22]. CFR was around 0.9% among patients with no comorbid conditions [22]. Similarly, in the data of 5,962 out of 63,573 deceased patients from Italy whose medical records were examined, 3.1% of patients presented with no comorbidities, 12.4% with single comorbidity, 18.4% with 2, and 66.2% with 3 or more [23]. The most common comorbidities were hypertension (66% of deaths), diabetes mellitus type 2 (29.1% of deaths), ischemic heart disease (27.9% of deaths), atrial fibrillation (24.3% of deaths), and chronic renal failure (201.0% of deaths) [23]. Based on preliminary data from the United States Center for Disease Control and Prevention (CDC) comprising 7,162 COVID-19 cases, 37.6% of patients had one or more comorbidities or risk factors, while 62.4% had no comorbidities, diabetes mellitus (10.9%), chronic lung disease (9.2%), and cardiovascular disease (9.0%) were the most commonly reported comorbidities [24]. Approximately 94% of COVID-19 related deaths have occurred in patients with at least one comorbidity or risk factor [24]. The proportion of COVID-19 patients with at least one comorbidity or risk factor was higher in those requiring ICU admission (78%) and those requiring hospitalization without ICU admission (71%) compared to non-hospitalized patients (27%) [24].

COVID-19 disease severity

The disease severity of COVID-19 can range from mild to critical. Among 44, 672 confirmed cases of COVID-19 from the China CDC, approximately 81% suffered only from mild disease and about 14% developed severe disease, while 5% were critical [22]. Mild disease included non-pneumonia and mild pneumonia cases [22]. Severe disease was characterized by dyspnea, respiratory rate ≥30/minute, blood oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO2/FiO2) ratio <300, and/or pulmonary infiltration >50% within 24-48 hours [22]. Critical was characterized by respiratory failure, shock, or multiorgan system dysfunction [22]. According to the Chinese CDC report, patients with mild COVID-19 course usually recover within 2 weeks, but it can take 3-6 weeks for those with severe or critical illnesses to recover [18].

The rate of ICU admission, mortality, length of hospitalization, and stay in the ICU for COVID-19 patients vary substantially between studies. These differences may relate to the characteristics of the study population, associated risk factors such as age and comorbidities, disease severity, as well as differences in hospital or ICU admission and discharge criteria. Studies suggest that about 14.2% to 39.7% of hospitalised patients with COVID-19 infection require ICU admission, mainly due to severe ARDS [25-27]. In a systematic review and meta-analysis of 656 patients, 20.3% required ICU admission, 32.8% presented with ARDS, and 6.2% with shock. CFR was 13.9% among hospitalized patients [25].

Patients with severe COVID-19 illness may develop dyspnea and hypoxemia within one week after the onset of symptoms, but progression to ARDS or end-organ failure can be rapid thereafter [5,6]. In a series of 463 confirmed COVID-19 patients from Metropolitan Detroit, United States, 76.7% of patients were hospitalized [26]. Among the hospitalized patients, 39.7% required ICU admission, of which 73.8% developed ARDS, 80.8 % required invasive mechanical ventilation (IMV), and 40.4% died within 30 days [26]. Dyspnea at presentation was associated with hospitalization and the need for ICU admission [26]. The Chinese CDC report showed that approximately 25% of severe and critical cases need IMV, whereas 75% require only oxygen supplementation [18].

In addition to respiratory support, patients with COVID-19 may require intensive care for supportive management of the most frequent complications of severe COVID-19. In a large study of 5,700 hospitalized patients with confirmed COVID-19 in New York City, United States, among patients who were discharged or died (n = 2,634), 14.2% required ICU admission, 12.2% received IMV, 3.2% were treated with kidney replacement therapy, and 21% died [27]. A systematic review and meta-analysis involving 16,561 patients with COVID-19 from 17 countries showed that among ICU patients, approximately three-quarters of cases experienced ARDS (76.1%) and one- quarter of cases experienced shock (25.3%) and/or acute kidney injury (27.1%) [28]. IMVS were required in 67.7% of patients and vasopressor supports were required in 65.9% of patients [28]. Renal replacement therapy was required in one-fifth (16.9%) of patients, and extracorporeal membrane oxygenation in 6.4% of patients [28].

Earlier studies from China showed that in patients with severe COVID-19 illness, the median time from illness onset to dyspnea was 5-8 days, the median time from illness onset to ARDS was 8-12 days, and the median time from illness onset to ICU admission was 9.5-12 days [6,9,10,29] According to a systematic review of 16,561 patients showed that the duration of ICU and hospital admissions was 10.8 days (95% CI, 9.3-18.4) and 19.1 days (95% CI, 16.3-21.9), respectively [28]. Another systematic review of 52 studies indicated that the length of hospital stay for COVID-19 patients

worldwide ranged from less than a week to almost 2 months, while the length of ICU stay was shorter and less variable, with studies reporting a median length of 1 to 3 weeks [30]. Of note is that patients who were discharged alive had a longer duration of stay than those who died during admission, but this variation was apparent for the overall stay and not for ICU stay [30]. Patients with COVID-19 appear to have stayed longer at the hospital in China than elsewhere. This can be explained by the variation in the criteria for admission and discharge between countries and by the different timing of the pandemic [30]. The estimated mortality rate among patients admitted to ICU ranged from 15% to 78% [6,9,10,26,28,29,31].

The Chinese CDC report showed that the time from symptom onset to death among patients who have died ranged from 2-8 weeks [18]. In a study of 52 critically ill patients from 710 with confirmed COVID-19 infection in China, 61·5% of patients had died at 28 days, and the median duration from ICU admission to death was 7 (IQR 3-11) days in non-survivors [10]. Compared with survivors, non-survivors were older (64·6 years [11·2] vs 51·9 years [12·9]), more likely to develop ARDS (81% vs 45%), and more likely to receive MV (94% vs 35%) [10]. Among 63,573 deceased patients from Italy, the median time from symptom onset to death was 12 days (7-20 days) [23].

Studies have shown that the in-hospital mortality rate of COVID-19 has been decreased during the pandemic [32,33]. A study of 5,121 patients with COVID-19 over 6 months from March through August 2020 at a single health system in New York City, showed that mortality decreased over time even after its adjustment for demographic and clinical factors, including comorbidities, admission vital signs, and laboratory results [32]. The standardized mortality ratio also decreased over time [32]. The potential explanation for this finding was to include improvement in hospital care of COVID-19, earlier interventions, and community awareness [32].

Complications of COVID-19

COVID- 2019 infection may be accompanied by several complications such as ARDS cardiovascular, renal, neurologic, thrombotic complications, gastrointestinal complications, bacterial, viral, and fungal coinfections as well as dermatologic complications (Figure 2). In a study of 138 COVID-19 patients from China, common complications included shock (12 [8.7%]), ARDS (27 [19.6%]), arrhythmia (23 [16.7%]), and acute cardiac injury (10 [7.2%]) [9]. Patients who received care in the ICU were more likely to have one of these complications than non-ICU patients [9]. In another study including data from 3,948 hospitalized patients with COVID-19 (March 1-May 31, 2020) and 5,453 hospitalized patients with influenza a (October 1, 2018-February 1, 2020) at the national Veterans Health Administration (VHA), the United States found that hospitalized patients with COVID-19 had a more than five-fold higher risk of in-hospital mortality and an increased risk of 17 respiratory and non-respiratory complications than hospitalized patients with influenza [16]. Respiratory complications were approximately 76.8% and included pneumonia (70.1%), respiratory failure (46.5%), and ARDS (9.3%). Non-respiratory complications included renal (39.6%), cardiovascular (13.1%), hematological (6.2%), neurological complications (4.1%), sepsis (24.9%) and bacteremia (4.7%) [16]. 24.1% of COVID-19 patients had compli-

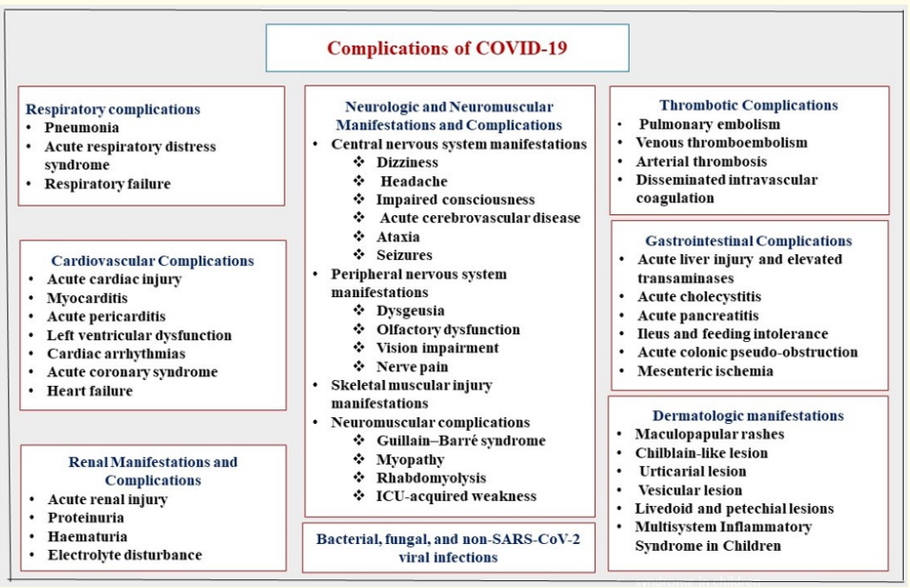

Figure 2: Complications of COVID-19 infection: Respiratory complications [4-6,16,22,28], cardiovascular complications [7,8], renal complications [5,9,10,27,28,39-45], neurologic and neuromuscular manifestations and complications [11,12, 56,57], thrombotic complications [13, 58-63], gastrointestinal complications [14,15, 66], bacterial, viral, and fungal coinfections [16,17] and dermatologic manifestations [67]

cations affecting three or more organ systems [16].

ARDS

ARDS is a major complication in patients with severe COVID-19 infection [4-6]. ARDS is defined by the Berlin Criteria as an acute hypoxaemic respiratory failure after an acute event (such as a respiratory viral infection) that presents as bilateral pulmonary infiltrates on lung imaging in the absence of solely cardiogenic or hydrostatic etiology [34]. Thus, the onset of ARDS is within one week of a known clinical insult or new or worsening respiratory symptoms [34].

The severity of ARDS is assessed by the degree of hypoxemia and has been categorized into three categories: mild (200 mm Hg < PaO_2/FIO_2 ≤ 300 mm Hg [with positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥ 5 cmH_2O, or non-ventilated], moderate (100 mm Hg < PaO_2/FIO_2 ≤ 200 mm Hg, [with PEEP ≥ 5 cmH_2O, or non-ventilated], and severe (PaO_2/FIO_2 ≤ 100 mm Hg [(with PEEP ≥ 5 cmH_2O, or non-ventilated] [34,35]. When PaO_2 is not available, SpO_2/FiO_2 ≤ 315 suggests ARDS (including in non-ventilated patients) [35]. Severe ARDS (invasively ventilated): Oxygenation Index (OI) ≥ 16 or Oxygenation Index using SpO_2 (OSI) ≥ 12.3 [35].

The typical initial symptom of ARDS is dyspnea. In a study of 201 patients with COVID-19 infection in China, 41.8% patients developed ARDS [4]. Among the patients with ARDS, many patients presented with dyspnea compared with those without ARDS (59.5% versus 15.6) [4]. The median duration from admission to development of ARDS was 2 days (IQR, 1-4 days) [4]. In a study of 138 COVID-19 patients from China, ARDS developed in 19.6% of patients [9]. The median durations from first symptoms to dyspnea, hospital admission, and ARDS were 5 days (IQR, 1-10), 7 days (IQR, 4-8), and 8 days (IQR, 6-12), respectively [9]. In another retrospective study of 659 COVID-19 patients in China, 11.5% patients developed ARDS [36]. The average time from onset to ARDS and admission to ARDS were 10 days and 3 days, respectively [36]. ARDS patients had a higher frequency of cough (80.3 % vs. 67.2 %), dyspnea (59.2% vs. 11.6%), fever (37.9°C vs. 37.4°C), and lung consolidation (53.9% VS 24.7%) than non-ARDS patients [36].

The greater risk factors associated with the development of ARDS and increased mortality in COVID-19 patients included older age, high fever (≥ 39°C), neutrophilia, organ and coagulation dysfunction (e.g. higher lactate dehydrogenase (LDH) and D-dimer), and comorbidities such as hypertension, diabetes [4]. Among patients with ARDS, treatment with methylprednisolone decreased the risk of death (HR, 0.38; 95% CI, 0.20-0.72) [4]. In another study, the risk factors that predicted the aggravation of ARDS included abnormal biochemical indicators such as lymphocyte count, creatine Kinase (CK), neutrophils to lymphocyte ratio (NLR), alanine aminotransferase (ALT), glutamate aminotransferase (AST), LDH, and C-reactive protein (CRP), presence of secondary bacterial infection as well as the presence of comorbidities such as hypertension and diabetes [36].

In a study of 138 COVID-19 patients from China, among the 36 patients in the ICU, 11.1% received high-flow oxygen therapy, 41.7% received non-invasive ventilation, and 47.2% received invasive ventilation, of whom 2.9% received extracorporeal membrane oxygenation as rescue therapy (ECMO) [9]. Of the 463 confirmed COVID-19 patients from Metropolitan Detroit, United States, the median time from symptom onset to the need for IMV was 8 days (IQR, 6-10 days), and the median time to IMV after admission was 1 day (IQR, 0-3 days) [26].

The incidence of ARDS in COVID-19 setting varies among studies. A global literature survey of 17 clinical studies, including 2,486 hospitalized patients with COVID-19 showed that the incidence of ARDS was 33% in hospitalized patients with COVID-19 and was 75% in ICU patients with COVID-19 but increased to 90% in non-survivors with COVID-196 [37]. The mortality rate for ICU COVID-19 patients was 40% and for those who received IMV was 59% and for COVID-19-associated ARDS was 45% [37].

Cardiovascular complications

Cardiovascular complications that may result from COVID-19 infection include acute cardiac injury, myocarditis, acute pericarditis, left ventricular dysfunction, cardiac arrhythmias, acute coronary syndrome and heart failure [7,8]. These cardiovascular complications may increase the mortality rate in patients with COVID-19 infection [38].

COVID-19 infection may lead to cardiovascular complications or exacerbation of preexisting cardiovascular disease [29,38]. Acute cardiac injury, characterized by elevations in cardiac troponin levels, is associated with a high mortality risk in patients with COVID-19 infection [39]. In a retrospective cohort study assessing

the association of cardiac injury with mortality in 416 hospitalized patients with COVID-19 in Wuhan, China, 19.7% of patients had cardiac injury [39]. Mortality was higher in patients with cardiac injury than in those without cardiac injury (42 of 82 [51.2%] vs 15 of 334 [4.5%]) [39].

The incidence of cardiac injury in COVID-19 infection still has not been identified. A meta-analysis of four studies in China of 341 total patients with COVID-19 infection, of whom 123 (36 %) patients had severe illnesses, revealed that troponin levels were significantly higher compared to those with mild disease in patients with severe COVID-19 infection [40].

The mechanisms of cardiac injury can include cardiac ischemic or non-ischaemic cardiac mechanisms, such as myocarditis [29,38]. Cardiac ischemic mechanism represents the coronary artery ischemia associated with underlying obstructive coronary heart disease and represents cardiac ischemia associated with increased coronary artery thrombosis, which can occur in the absence of coronary artery disease [41]. Cardiac injury can also occur due to severe cytokine storms with accompanying hemodynamic disturbances, systemic inflammation, and multiorgan failure [42]. The clinical features of the cytokine storm are related to the role of proinflammatory cytokines such as Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-18 (IL-18), Interferon gamma (IFN-γ), and Tumour necrosis factor α (TNF-α) [43]. These inflammatory cytokines have a role in atherosclerotic plaque rupture [29]. Non-cardiac ischemic mechanism includes myocarditis, which may lead to cardiac injury either through direct infection of cardiac myocytes or through infection of non-myocytes such as fibroblasts, endothelial cells or pericytes [41]. In addition, myocarditis can occur as a consequence of virus-specific inflammation or a general increase in inflammation affecting the heart due to systemic infection with the virus [41].

Renal complications

The kidneys are among the most commonly affected extrapulmonary organs, especially in critically ill patients with COVID-19 infection [5,9,10]. Frequent renal involvement in COVID-19 settings involves the occurrence of proteinuria [44], haematuria [44], electrolyte disturbance, especially hyperkalaemia [45], and the development of acute renal injury (AKI) [10,27,39,45].

A systematic review and meta-analysis of 22 observational cohort studies involving 17,391 COVID-19 patients, found that the most common renal complication was electrolyte disorders, especially hyperkalaemia, with an incidence of 12.5% (10.1-15.0) followed by AKI and renal replacement therapy at 11.0 % and 6.8% respectively [45].

AKI is a serious complication that may lead to increased mortality, prolonged hospital stay, and increased health costs [46-48]. Early detection and treatment of AKI can reduce related complications such as long-term CKD or end-stage kidney disease [49]. The mechanism of AKI in COVID-19 cases has not been fully elucidated. A wide variety of glomerular, vascular, and tubular diseases result from the interaction of COVID-19 with its cellular receptor angiotensin-converting enzyme 2 (ACE2), viral immune response, cytokine storm, hypoxemia, hemodynamic instability, thromboembolic events, and multiorgan failure [48]. Due to the close temporal association between AKI and respiratory failure occurrence, acute tubular necrosis is often associated with systemic collapse, may be a common cause of AKI in COVID-19 patients [44]. In addition, thrombotic microangiopathy leading to acute tubular necrosis is also likely since patients with COVID-19 are at risk of developing thromboembolic events [50].

Rhabdomyolysis can also be associated with AKI pathogenesis [48]. Pigmented castings with elevated levels of creatine phosphokinase due to rhabdomyolysis have been shown in a study of autopsy renal samples [48].

The direct SARS-CoV-2 viral cytopathic effect on the kidney as the major pathomechanism for COVID-19-related kidney injury is a point of debate [51,52]. While some studies have showing no evidence of direct renal SARS-CoV-2 viral invasion [53,54], the opposite has been reported [55]. Acute tubular Injury/necrosis has been identified as the predominant finding in the COVID-19 autopsy and biopsy series [48,51-54].

The autopsy series of 42 patients dying with COVID-19 reported that of 33 patients, 31 (94%) had AKI, including 6 with AKI stage 1 (18%), 9 with AKI stage 2 (27%) and 16 with AKI stage 3 (48%) [54]. Histological results of renal biopsies showed the presence of acute tubular injury but was generally mild compared to the degree of AKI [54]. These findings suggest a role for hemodynamic factors, such as aggressive fluid management [54]. One patient had collapsed focal segmental glomerulosclerosis (FSGS) and most had implications for their comorbidities (e.g., hypertensive arterio-

nephrosclerosis and diabetic glomerulosclerosis) [54].

In the biopsy series, a histopathologic evaluation of renal biopsies in 10 patients with COVID-19 and AKI showed different degrees of acute tubular necrosis and one patient had associated with extensive myoglobin casts. Additionally, two patients had signs of thrombotic microangiopathy, one with pauci-immune crescentic GN and one with global and segmental glomerulosclerosis with characteristics of healed collapsing glomerulopathy [52]. Another histopathologic evaluation of the biopsy series of 14 native and 3 allograft kidneys from patients with COVID-19 and AKI found that four patients had isolated acute tubular injury while five patients had acute tubular injury in association with collapsing glomerulopathy [51]. FSGS also identified as collapsing glomerulopathy, which could account for heavy proteinuria, has also been reported in some patients with COVID-19 in both biopsy and autopsy series [47].

The incidence of AKI in COVID-19 varies widely among studies. Of note, the incidence rates of AKI increased significantly in patients with severe COVID-19 infection requiring care in the ICU [10,27,29,31,44]. AKI is likely to affect 19.1% to > 50% of critically ill patients [31,44].

The AKI mortality in patients with COVID-19 also varies across studies but is higher among patients in need of renal replacement therapy [44]. A study of 5,449 hospitalized patients with COVID-19 in New York, United States, found that 36.6% patients developed AKI [44]. The proportions for stages1, 2, and 3 AKI were 46.5%, 22.4%, and 31.1%, respectively [44]. Among these patients with AKI, 14.3% required renal replacement therapy and 35% of them died [44]. AKI was mainly seen in COVID-19 patients with respiratory failure, particularly those on mechanical ventilation, with an incidence of 89.7% compared to 21.7% of non-ventilated patients. Approximately 96.8% of patients needing renal replacement therapy were on ventilators [44]. A systematic review and meta-analysis of 20 studies, including 13,137 mostly hospitalized patients from Asia, Europe, and United States with confirmed COVID-19, found that the incidence of AKI was 17%, ranging from 0.5% to 80.3% [46]. About 77% of AKI patients developed severe COVID-19 infection, and 52% died [46]. AKI was associated with substantially higher mortality among COVID-19 patients, with a pooled odds ratio of 15.27 (95 % CI, 4.82-48.36) compared with non-AKI patients [46]. Approximately 5% of all patients were in need of renal replacement therapy [46]. Geographical location and heterogeneity across studies may explain these wide variations in the incidence range [46].

Neurologic and Neuromuscular Manifestations and Complications

The neurologic manifestations caused by COVID-19 infection can be categorized into three main categorizes; central nervous system (CNS) manifestations, peripheral nervous system (PNS) manifestations and skeletal muscular injury manifestations. CNS manifestations include dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizures, while PNS manifestations include dysgeusia (taste impairment), olfactory dysfunction (smell impairment), vision impairment, and nerve pain. Impaired consciousness includes the change of consciousness level (somnolence, stupor, and coma) and consciousness content (confusion and delirium) [11].

In a retrospective study of 214 patients with COVID-19 infection, approximately 36.4% patients developed various neurological manifestations that included CNS manifestations (24.8%), PNS manifestations (8.9%), and skeletal muscle injury (10.7%) [11]. Most neurologic manifestations occur early during illness (median time 1-2 days) [11]. Patients with COVID-19 may also have a higher risk for encephalopathy and altered mental status. In a study of 4,491 hospitalized COVID-19 patients in New York City, United States, 13.5% developed a new neurologic disorder in a median of 2 days from symptom onset [56]. The most common diagnoses were: toxic/metabolic encephalopathy (6.8%), seizure (1.6%), stroke (1.9%), and hypoxic/ischemic injury (1.4%) [56].

Neurologic manifestations were more likely to develop in patients with severe infection, particularly acute cerebrovascular disease, conscious disturbance, and skeletal muscle injury [11]. Acute necrotizing hemorrhagic encephalopathy, seizures, and stroke have also been reported in patients with severe COVID-19 infection [12].

The mortality rate was high among COVID-19 patients with neurologic disorders (Hazard Ratio[HR] 1.38, 95% CI 1.17-1.62, P < 0.001) [56].

Neuromuscular complications such as Guillain-Barré syndrome (GBS), myopathy, rhabdomyolysis, and ICU-acquired weakness (ICUAW), have been reported in patients with COVID-19 [57]. Neu-

romuscular symptoms may be linked to direct viral action or indirectly due to cytokine release syndrome, para- or postinfectious dysimmune processes, critical illness, or as side effects of pharmacologic therapy, despite the absence of definitive evidence [57].

Thrombotic complications

Patients with COVID-19, in particular those who are critically ill or those with cardiovascular risk factors such as diabetes mellitus, obesity, and old age, have a high incidence of venous thromboembolism, arterial thrombosis and thrombotic microangiopathy, which could potentially increase the risk of death [13].

In a study of 184 patients with COVID-19 admitted to the ICU, the incidence of thrombotic complications was 31% [13]. Venous thromboembolism and arterial thrombotic events were reported in 27% and 3.7%, respectively. Pulmonary embolism was the most common thrombotic complication (81%) [13].

In meta-analysis of 42 studies involving 8271 COVID-19 patients, the venous thromboembolism rate was 21%, with a deep vein thrombosis rate of 20% and pulmonary embolism rate of 13% while the arterial thromboembolism rate was 2% [58]. Among ICU patients, the venous thromboembolism rate was 31%, deep vein thrombosis rate was 28%, pulmonary embolism rate was 19%, and arterial thromboembolism rate was 5% [58]. Thromboembolism significantly increased the mortality rate by 74% (OR, 1.74; 95%CI, 1.01-2.98; P = 0.04) [58].

Microclots (microvascular COVID-19 lung vessels, obstructive thromboinflammatory syndrome) have been used to describe the severe pulmonary manifestations of the disease [59]. Autopsies in patients with COVID-19 have shown that micro-thrombosis in the lungs has been reported in approximately 80% [60], but almost no organ is spared from thrombosis [61].

Some patients with severe infection with COVID-19 and multiorgan failure can progress to coagulopathy that meets the criteria for overt disseminated intravascular coagulation (DIC) according to the International Society of Thrombosis and Hemostasis criteria (ISTH) criteria [62]. These criteria included moderate to severe thrombocytopenia (platelet count <50 x109/L), Prothrombin Time (PT), and activated partial thromboplastin time (aPTT) prolongation, extreme D-dimer elevation, and reduced fibrinogen (< 1.0 g/L) [62]. A study of 183 patients with confirmed COVID-19 pneumonia in China found that non-survivors had significantly abnormal coagulation results including higher admission D-dimer and fibrinogen degradation product levels, and more prolonged prothrombin and partial thromboplastin times compared to survivors [63]. In addition, 71.4% of non-survivors had overt DIC (> 5 points, the ISTH criteria for overt DIC [62,63].

Elevated fibrinogen and D-dimer values, as well as mild PT/aPTT prolongation, are the most common coagulopathy patterns shown in patients hospitalized with COVID-19 [64]. This is accompanied by an increase in inflammatory markers (e.g., CRP) [64]. Unlike in classic DIC caused by bacterial sepsis or trauma, aPTT and/or PT are rarely prolonged, thrombocytopenia is mild (platelet count~ 100 $x10^9$/L), and lab findings suggesting microangiopathy are uncommon [64].

Gastrointestinal Complications

Liver injury

Liver injury as evidenced by increased levels of liver enzymes, in particular AST, ALT, has been shown in patients with COVID-19 infection. The cause of the liver injury is not clearly established, but might be caused by the direct viral infection of liver cells, or due to other causes such as drug hepatotoxicity, pneumonia-associated hypoxia, ICU-related infections and immune-mediated inflammation such as cytokine storm [14]. A Systematic Review of 7 studies showed that many patients with COVID-19 infection had a varying degree of deranged liver enzymes [14]. Liver injury was mild in most cases and correlated with the severity of COVID-19 infection [14]. Severe liver injury causing significant liver damage, liver failure, or death is uncommon [14]. In the majority of patients, the liver injury was self-limiting and not associated with acute liver failure [14]. A large cohort from New York, United States assessing acute liver injury in 2,273 patients with confirmed COVID-19, showed that 45% had mild and 21% had moderate acute liver injury, while 6.4% had severe liver injury [15]. Mild liver injury was defined as a level of ALT above the upper limit of normal (ULN) and below 2 times ULN, moderate liver injury was defined as ALT between 2-5 times ULN while severe liver injury was defined as ALT peak >5 times the ULN [15]. In multivariable analysis, severe liver injury was significantly associated with elevated inflammatory markers, such as ferritin and interleukin-6 and peak ALT was significantly associated with death or discharge to hospice (OR, 1.14; P = 0.044), adjusting for age, body mass index, diabetes, hypertension, intubation, and renal replacement therapy [15]. Patients with liver injury had a more severe clinical course, including higher rates of ICU admission (69%), intubation (65%), (renal

replacement therapy; 33%), and mortality (42%) [15].

Elevated GGT has also been reported in COVID-19 infection. A study of 515 patients with confirmed COVID-19 infection from Italy found that AST, ALT, and GGT were increased in 20.4%, 19%, and 13.6% of patients, respectively [65].

An abnormal baseline liver enzyme levels were correlated with severity of disease and higher ICU admission. Alkaline phosphatase (ALP) peak values associated with increased mortality rate [65]. other gastrointestinal complications such as acute cholecystitis, acute pancreatitis, ileus and feeding intolerance, acute colonic pseudo-obstruction, and mesenteric ischemia were also reported in COVID-19 patients (Figure 2).

Bacterial, viral, and fungal coinfections in COVID-19 patients

Bacterial, fungal, and non-SARS-CoV-2 viral infections have been reported in COVID-19 patients and may be associated with severe disease and worse outcomes [16,17]. Both upper and lower respiratory tract specimens can be tested for other respiratory viruses, such as influenza A and B (including zoonotic influenza A), respiratory syncytial virus, parainfluenza viruses, rhinoviruses, adenoviruses, enteroviruses, human metapneumovirus and endemic human coronaviruses. Lower respiratory tract specimens can also be tested for bacterial pathogens, including Legionella pneumophila [35]. In a meta-analysis and systematic review of 30 studies, including 3,834 patients with COVID-19, bacterial coinfections were reported in 7% (95% CI 3-12%, n=2183, I 2=92·2%) of hospitalised patients and 14% (95% CI 5-26, I2=74·7%) of critically ill patients [17]. The most common bacteria were Mycoplasma pneumoniae (42% of 27 confirmed bacterial pathogen detections), followed by Pseudomonas aeruginosa (12%, including one patient with bacteraemia) and Haemophilus influenzae (12%) [17]. Viral coinfection was reported in 3% of COVID-19 patients (95 % CI 1-6, n=1014, I2=623%), with Respiratory Syncytial Virus and influenza A being the most common viral pathogens identified. Only three of the studies included in this review reported fungal coinfections such as Candida albicans (isolated from the respiratory tract in five patients and the urinary tract of a sixth) [17]. Fungi in addition. Other fungal coinfections in respiratory samples were Aspergillus flavus (2 patients), Aspergillus fumigatus, and Candida glabrata (one patient each) [17].

Dermatologic Manifestations

Dermatologic manifestations such as maculopapular rashes, chilblain-like lesion, urticarial lesion, vesicular lesion, livedoid and petechial lesions as well as multisystem Inflammatory Syndrome in Children were also reported in COVID-19 patients [67].

Conclusion

Since the outbreak of COVID-19 more than a year ago, the world has been experiencing the worst pandemic crisis ever.

The virus mainly affects the respiratory system, but it can affect multiple organ systems and causes several complications. Higher risk for severe disease and mortality has been reported among older patients and those with comorbidities such as cancer, cerebrovascular disease, chronic kidney disease, COPD, and other lung diseases, diabetes mellitus, down syndrome, heart conditions, HIV infection, neurologic conditions, obesity, pregnancy, smoking, sickle cell disease, solid organ or blood stem cell transplantation, substance use disorders, use of corticosteroids or other immunosuppressive medications.

Because older people have one or more coexisting medical conditions, they are probably at the highest risk for fatal COVID-19 infections. The disease severity of COVID-19 can range from mild to critical.

The most common complication is ARDS. Other complications include cardiovascular, renal, neurologic, thrombotic complications, gastrointestinal complications, as well as bacterial, viral, and fungal coinfections.

Further studies are required to better understand of COVID-19 related complications and factors that account for the variability in the severity of the disease.

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