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REVIEW ARTICLE

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Risk factors for severe and critically ill COVID-19 patients: A review

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Abstract

The pandemic of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused an unprecedented global social and economic impact, and high numbers of deaths. Many risk factors have been identified in the progression of COVID-19 into a severe and critical stage, including old age, male gender, underlying comorbidities such as hypertension, diabetes, obesity, chronic lung diseases, heart, liver and kidney diseases, tumors, clinically apparent immunodeficiencies, local immunodeficiencies, such as early type I interferon secretion capacity, and pregnancy. Possible complications include acute kidney injury, coagulation disorders, thoromboembolism. The development of lymphopenia and eosinopenia are laboratory indicators of COVID-19. Laboratory parameters to monitor disease progression include lactate dehydrogenase, procalcitonin, high-sensitivity C-reactive protein, proinflammatory cytokines such as interleukin (IL)-6, IL-1β, Krebs von den Lungen-6 (KL-6), and ferritin. The development of a cytokine storm and extensive chest computed tomography imaging patterns are indicators of a severe disease. In addition, socioeconomic status, diet, lifestyle, geographical differences, ethnicity, exposed viral load, day of initiation of treatment, and quality of health care have been reported to influence individual outcomes. In this review, we highlight the scientific evidence on the risk factors of severity of COVID-19.

KEYWORDS

COVID-19, critical illness, risk factors, SARS-CoV-2, severity

1 | INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) pandemic reached over 45 million confirmed infections and claimed the lives of more than 1.2 million people worldwide.[1] The clinical features of COVID-19 are diverse and range from asymptomatic to critical illness and death.[2] Severe and critical cases represented 14% and 5% of laboratory-confirmed COVID-19 patients,[2] respectively. This posed a high burden to the healthcare system as it consumed most of its medical resources and contributed to the majority of deaths. Severe

patients present signs of dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation ≤ 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 mmHg, and/or lung infiltrates > 50% within 24 to 48 hours.[2] Critically ill cases may experience respiratory failure that requires mechanical ventilation, shock, disseminated coagulopathy, and other organs failure requiring admission to the intensive care unit (ICU).[3] A good understanding of the possible risk factors in combination to disease immunopathology associated with COVID-19 severity is helpful for clinicians in identifying patients who are at high risk and require prioritized treatment to prevent disease progression and adverse outcome.[4] Risk factors range from demographic factors, such as age,[3,5–7] sex and ethnicity,[8,9] diet and lifestyle habits[10,11] to underlying diseases[12–22] and complications,[23–26] and laboratory indications.[27–39] Many studies have reported predictive models using various risk factors to identify high-risk patients that may develop severe and critical illness.[40] It is worth noting that some studies address the risk factors of COVID-19 development in general, without any focus on disease severity, while others specifically focus on risk factors for disease progression to a critical stage. In this review, we present the current data on a comprehensive list of possible risk factors associated with COVID-19 severity.

2 | DEMOGRAPHIC FACTORS

2.1 | Older age and male gender

In a series of multivariable-adjusted analyses based on COVID-19 patient cohorts, higher disease severity was found to be associated with demographic factors, such as older age and male gender[3,6,8,9,41] (Figure 1). The median age of patients receiving intensive care was higher than those not admitted to the ICU (66 years vs 51 years). In hospitalized patients, the percentage of severe and critically ill cases ranged from 19.8% to 49.0% in adult cohorts,[3,42,43] and only 2.2% in a pediatric cohort.[12] In a US single-center study, 83.8% of patients who received invasive mechanical ventilation were male and significantly younger age was observed among patients who had been weaned successfully from mechanical ventilation.[44] Compared to patients aged 30–59 years, those aged below 30 and above 59 years were 0.6 (0.3–1.1) and 5.1 (4.2 – 6.1) times more likely to die after developing symptoms, respectively, according to data from 79 394 confirmed cases in China.[45]

Intriguingly, Kuo et al reported that biological aging was an optimal predictor of disease severity after performing biological age evaluations comprised of chronological age and nine PhenoAge

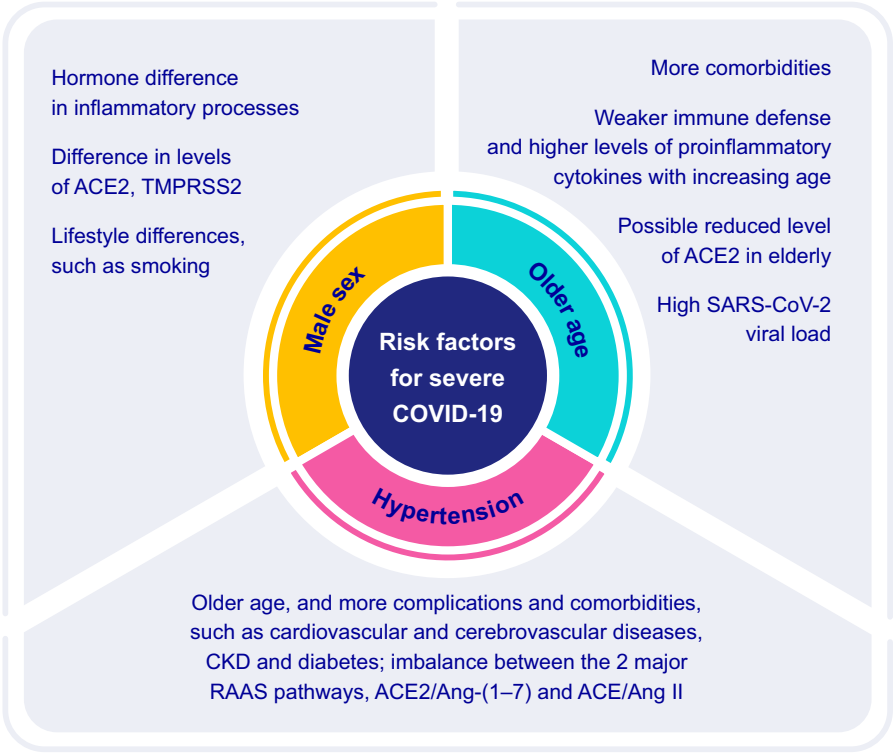

FIGURE 1 Mechanisms of age, sex, and hypertension on the severity of COVID-19. Old age and male gender are associated with more severe illness of COVID-19. Older age is associated with more comorbidities, weaker immune defense, and higher levels of proinflammatory cytokines. ACE2, which may offer protection against acute lung injuries caused by virus infection, is reduced in elderly and may contribute to higher risk of severity and mortality of COVID-19. The discrepancy of COVID-19 severity between male and female patients can be attributed to the differences in sex hormones involved in inflammatory processes, expression levels of ACE2 and TMPRSS2, and lifestyle. Hypertension is associated with a higher risk of severity and mortality of COVID-19. It is postulated that older age, and more comorbidities and complications, uncontrolled blood pressure, and imbalance between two major RASS, that is, downregulated ACE2/angiotensin-(1-7) and upregulated ACE/angiotensin II, contributed to elevated severity and mortality in hypertension patients with COVID-19

biomarkers (albumin, alkaline phosphatase, creatinine, log C-reactive protein (CRP), glucose, lymphocyte percentage, mean corpuscular volume, red blood cell distribution width, white blood cell count). COVID-19 test-positivity and all-cause mortality were positively associated with accelerated aging 10-14 years prior to the COVID-19 pandemic (odds ratio [OR]: 1.15 and 1.25, respectively, per 5-year acceleration).[46]

2.2 | Ethnicity

In a study of 10,926 COVID-19-related deaths, Black patients and South Asians were found to have a higher mortality risk compared with subjects of White ethnicity (adjusted hazard ratio [aHR] 1.48, 95%CI: 1.29–1.69; and 1.45, 95%CI: 1.32–1.58, respectively).[47,48] In cancer patients, non-White race was identified as an independent risk factor for hospitalization (HR: 1.62, 95% CI: 1.05-2.51), but not risk factor for severe respiratory illness of COVID-19.[49] In New York City, Hispanic race was associated with a higher risk of hospitalization (adjusted OR [aOR]: 1.63; 95%CI: 1.35–1.97) but not of critical illness and mortality.[50] A study of COVID-19 patients in South California (USA) also found that African Americans were predisposed to increased disease severity (OR: 2.1).[9] Ethnicities other than White were associated with higher COVID-19-related mortality in both type 1 and type 2 diabetes.[51] Interestingly, Black ethnicity was associated with a lower risk of death in patients with end-stage kidney disease hospitalized with COVID-19.[21] In UK Biobank cohort of over 400,000 individuals, ethnic minority groups such as Black ethnicity and Asian individuals in England had a higher risk of COVID-19 hospitalization. The observed associations were attenuated but remained marked after adjustment for socioeconomic, lifestyle and health-related factors.[52] However, another study from US found that race was not identified as a risk factor for death in COVID-19 after adjusting for sociodemographic and clinical factors.[53] Another case-control and cohort study found that comorbidities and socioeconomic status only partly contributed to greater admission risk of COVID-19 in Black and mixed ethnicity.[54] In summary, Black and other minority races were disproportionally affected with an elevated risk of hospitalization as well as severity and mortality. The possible associations between socioeconomic status and/or comorbidities with severity of COVID-19 in different ethnicity need to be clarified further.

3 | SYMPTOMS

3.1 | Fever

Fever was more frequently reported in hospitalized than in non-hospitalized COVID-19 patients.[55] Patients with fever had a higher risk of mechanical ventilation (aHR: 2.31; 95%CI: 1.95–2.75) and mortality (aHR: 1.51, 95% CI: 1.32–1.72) than those without fever.[56] Our previous study also showed that fever was more frequently reported in severe patients than in nonsevere patients.[3] Another study involving 52 critically ill COVID-19 patients showed that 98% presented fever.[57] Fever greater than 38.5°C on admission was positively correlated with the severity and mortality of COVID-19.[6] Fever was also associated with higher severity (OR: 6.21; 95%CI: 1.76–21.99) in cancer patients with COVID-19.[58] In pediatric COVID-19 patients, fever was also more frequently observed in patients with pneumonia than those without pneumonia (50% vs 27.8%).[12] A recent study found that serum IL-6 levels were higher in COVID-19 patients with fever compared to those without fever,[59] suggesting that fever may be caused by elevated IL-6, the major cytokine contributed to cytokine storm. Collectively, these findings suggest that fever is an important risk factor for severity and high fever might be a risk factor for mortality of COVID-19.

3.2 | Shortness of breath/dyspnea

In a cohort of 10 131 elderly COVID-19 patients, those with dyspnea had a higher risk of hospitalization (aHR: 2.18; 95%CI: 2.02–2.36), mechanical ventilation (aHR: 2.95; 95%CI: 2.49–3.49), and mortality (aHR: 1.78; 95%CI: 1.53–2.07).[56] Dyspnea was more common in COVID-19 patients with ≥ 2 comorbidities than in those with one comorbidity (55.4% vs 34.1%).[15] Our group has previously reported that chest tightness and dyspnea were more frequently presented in severe patients than in nonsevere patients.[3] Prevalence of dyspnea in critically ill COVID-19 patients was 63.5% (33/52),[57] and 76.2% were admitted to the ICU.[60] COVID-19 patients in the ICU were more likely to present dyspnea than non-ICU patients (63.9% vs 19.6%).[7] In cancer patients diagnosed with COVID-19, dyspnea was associated with a higher risk of severity (OR: 2.60; 95% CI: 1.00–6.76) and mortality (OR: 4.94; 95% CI: 1.99–12.25).[58] These findings suggest that the presence of dyspnea is an important risk factor for hospitalization and severity and may be associated with mortality of COVID-19.

3.3 | Gastrointestinal symptoms

Gastrointestinal symptoms such as nausea, vomiting, diarrhea, and emesis were more frequently reported in hospitalized COVID-19 patients.[55] Nausea (aHR: 1.56; 95%CI: 1.11–2.19) and diarrhea (aHR: 1.57; 95%CI: 1.21-2.02) were associated with a higher risk of mechanical ventilation.[56] We have previously reported that loss of appetite was significantly different between severe and nonsevere COVID-19 patients.[3] In cancer patients with COVID-19, gastrointestinal symptoms were associated with higher severity (OR: 7.38; 95%CI: 2.71–20.16).[58] In summary, currently available data indicate that the presence of gastrointestinal symptoms is associated with increased severity of COVID-19.

4 | COMORBIDITIES

4.1 | Arterial hypertension

Arterial hypertension (hypertension) was more frequently observed in severe COVID-19 patients compared to nonsevere patients.[13,61] Wang et al reported that the prevalence of hypertension was significantly higher among COVID-19 patients requiring ICU care than among those not admitted to ICU (58.3% vs. 21.6%; $P < .001$).[7] However, the prevalence of hypertension is high in the elderly and so this confounding factor should be excluded.

Li et al found that hypertension was an independent risk factor for severe COVID-19 (OR: 2.01; $P = .003$).[61] Huang et al showed that the OR of hypertension was 1.562 ($P = .092$) and 1.262 ($P = .458$) in the multivariate analysis of severity and mortality, respectively.[14] There was significant heterogeneity on the association between hypertension comorbidity and COVID-19 severity. The Center for Disease Control and Prevention (CDC) states that individuals with hypertension might be at increased risk for severe illness from COVID-19.[62] In a retrospective study including 803 COVID-19 patients with coexisting hypertension, high average systolic blood pressure and high systolic/diastolic blood pressure variability during hospitalization were independently associated with in-hospital mortality, ICU admission, and heart failure, suggesting that lower and stable blood pressure is predictive of a better prognosis for these patients.[63] The imbalance between the two major renin-angiotensin-aldosterone system pathways, that is, downregulated angiotensin-converting enzyme (ACE) 2/angiotensin-(1-7) and upregulated ACE/Angiotensin II,[64] may contribute to the increased risk of severity of COVID-19 patients with comorbidities and advanced age, as depicted in Figure 1. Poor control of blood pressure is a major risk for all cardiovascular deaths and becomes a confounding factor for COVID-19 deaths.[65,66]

Moreover, the use of angiotensin II receptor blockers (ARB)/ACE inhibitor (ACEI) for the treatment of COVID-19 patients with hypertension was associated with lower mortality when compared to those without ARB/ACEI therapy.[67] Another study showed that patients prescribed with at least 6 months of ARB/ACEI prior to SARS-CoV-2 infection were not associated with a higher susceptibility and mortality of COVID-19.[68] Other anti-hypertension medications were also not associated with susceptibility and mortality of COVID-19 patients with preexisting hypertension.[68]

4.2 | Diabetes

Diabetes is a common comorbidity in COVID-19 patients[5] and was suggested to be a risk factor of severe and fatal COVID-19 cases.[12] A meta-analysis showed that COVID-19 patients with diabetes had a higher risk (risk ratio [RR]: 2.96; 95% CI: 2.31–3.79) of severe disease or death,[69] and higher rate of ICU admissions.[70] In a cohort study of COVID-19 patients from New York City (USA), those with diabetes had an increased risk of hospital admission (OR: 2.24; 95%CI: 1.84–2.73) and critical illness (OR: 1.24; 95%CI: 1.03-1.50).[50] Another meta-analysis demonstrated that the ORs of diabetes for ICU admission and mortality were 2.79 (95%CI: 1.85–4.22) and 3.21 (95%CI: 1.82–5.64), respectively.[71] In addition, diabetic patients infected with SARS-CoV-2 had a higher risk of death in those with poor blood sugar control (higher HbA1c) before hospital admission.[47,51] Another study showed patients with hyperglycemia at admission had a higher risk of composite outcomes (ICU admission, mechanical ventilation and death), with OR 5.47 (95%CI 1.56-19.82).[72] Hyperglycemia during treatment in hospital was a risk factor for death in patients with severe COVID-19 (HR 1.8, 95% CI 1.1-2.8)[58]; moreover, individuals with new-onset diabetes during hospitalization had a higher mortality (HR: 9.42; 95%CI: 2.18-40.7) compared to those with hyperglycemia (HR:3.29; 95%CI: 0.65-16.6) or diabetes (HR: 4.63; 95%CI: 1.02-21.0).[73]

Mechanistically, the expression of ACE2, the entry receptor of SARS-CoV-2, is increased in type 2 diabetes mellitus patients in the lungs and other tissues.[74] This upregulation is associated with chronic inflammation, endothelial cell activation and insulin resistance which aggravates the inflammatory response and leads to dysfunction of the alveolar-capillary barrier[75] (Figure 2). In summary, the clinical course and prognosis of COVID-19 in diabetic patients was significantly more severe.

4.3 | Obesity

In a large cohort study of 433 995 COVID-19 patients, obese patients were at increased risk of hospitalization (adjusted relative risk [aRR]: 2.20) and severity (aRR: 2.30). This was not observed in patients aged 65-79 years but was notable in the population younger than 50 years (aRR: 5.02 and 13.80, respectively).[76] Similarly, Gao et al reported a higher severity and longer hospital stay in obese COVID-19 patients, which has positively correlated with BMI (aOR: 3.00 for obesity, aOR: 1.13 for BMI).[77] Obese patients with BMI ≥ 35 kg/m^2 had an increased risk of admission to the ICU (OR: 3.6) in COVID-19 patients < 60 years.[16] Male obese COVID-19 patients were at higher risk of severe outcome (OR5.66).[78] Moreover, BMI above 40 kg/m^2 was evaluated as an independent risk factor associated with mortality, more pronounced in patients younger than 50 years (aOR: 5.1).[79] Interestingly, obese COVID-19 patients with metabolic-associated fatty liver disease were at higher risk of severe outcome (aOR: 6.32) after adjustment for age, sex, smoking, diabetes, hypertension, and dyslipidemia.[80]

Impaired chest-wall elastance and reduced respiratory system compliance leading to damaged lung function,[81] higher levels of proinflammatory status and interleukin (IL)-6 levels, and a higher risk of thrombosis all contribute to increased risk of severe COVID-19 in obese patients,[82] as shown in Figure 2. In addition, endothelial cell activation and insulin resistance may also contribute to blood-gas barrier dysfunction.

ACE2 was overexpressed in the adipocytes of obese individuals. The involvement of ACE2 in pulmonary lipofibroblasts and

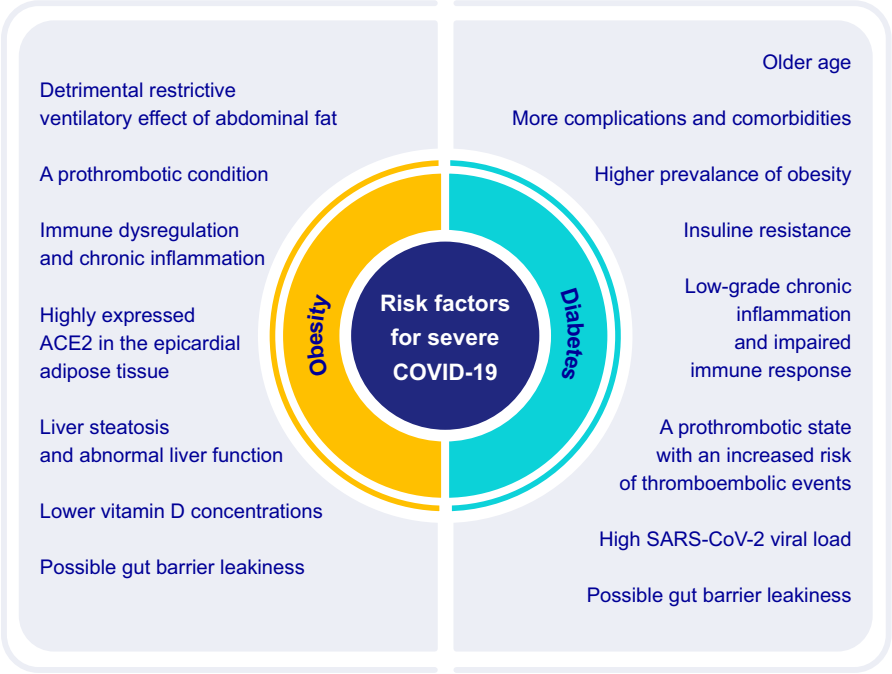

FIGURE 2 Mechanisms of diabetes and obesity on severity of COVID-19. Diabetes and obesity are risk factors of severity and worse prognosis of COVID-19. Diabetes is more prevalent with older age and associated with more complications and comorbidities. Diabetes and obesity are paralleled by low-grade chronic inflammation, compromised immune response, and a prothrombotic state. Moreover, adverse factors, including the detrimental restrictive ventilatory effect of abdominal fat, highly expressed ACE2 in the epicardial adipose tissue, liver steatosis, abnormal liver function, and inadequate vitamin D level, have been indicated in obese individuals

other adipose-like cells during SARS-CoV-2 infection remains largely unknown.[83] Obese subjects had higher expression of SARS-CoV-2-related molecules SLC16A3 (MCT4), integrin α (ITGA)3, nuclear factor of activated T cells 1 (NFATC1) in bronchial alveolar lavage samples and basigin (BSG) (CD147), peptidylpeptidyl-prolyl cis/trans isomerase a (PPIA, cyclophilin A), galectin-3 (LGALS3), and nucleotide-binding oligomerization domain (NOD) 2 in blood samples as compared to nonobese individuals.[84] In addition, MCT4, ITGA3, LGALS3, and CD44 positively correlated with BMI in the BAL, whereas BSG, PPIA, S100A9, CD44, LGALS3, and SLC16A3 positively correlated with BMI in the blood.[84] Furthermore, plasma soluble ACE2 levels were associated with BMI and leptin, a biomarker for obesity, HbA1C and homeostatic model assessment of insulin resistance (HOMA-IR), the biomarker for insulin resistance and hyperglycemia, suggesting a possible role of insulin resistance in COVID-19 severity.[85] All these aspects might play a role in the higher severity of COVID-19 in obese patients.

4.4 | Allergy and asthma

Current studies on the association between the severity of COVID-19 and allergic diseases and asthma are controversial. A study on adult and pediatric patients in Wuhan[5,12,61] and a large case series from China[2] showed no or low prevalence of asthma or allergic history in COVID-19 patients. Similarly, a study from New York City did not identify asthma in COVID-19 patients as a predisposing factor for receiving invasive mechanical ventilation.[86] Only 1.8% (24/1307) of COVID-19 patients admitted to the ICU had a history of asthma, as reported in a Russian cohort.[87] In a recent study, atopic status was associated with lower incidence of severe complications of COVID-19.[88] In contrast, other epidemiological data indicate that asthma and/or allergy comorbidities are positively correlated with the severity of COVID-19.[17,89,90] For example, data analysis of a population-based prospective cohort from 492 768 participants in the UK Biobank indicated that patients with asthma had a significantly higher risk of disease progression to a severe outcome (aOR: 1.39; $P = .002$) compared to healthy individuals.[17] In another large-scale Korean nationwide cohort of COVID-19 patients (n = 7340),[90] severe clinical outcomes were observed in 6.9% and 4.5% of patients with and without asthma (aOR: 1.62), respectively, and 4.7% and 3.7% of patients with and without allergic rhinitis, respectively (aOR: 1.27, $P < .05$). Interestingly, the results from both studies indicate that individuals with nonallergic asthma have a higher risk for severe outcome of COVID-19 than those with allergic asthma.[17,90] Poor asthma control is a risk factor for greater severity of virus-induced exacerbation,[91] therefore, maintaining optimal asthma control (with inhaled steroids, combination inhaled steroid plus long acting bronchodilator, or monoclonal antibody therapies) should be able to reduce risk of severe outcomes in COVID-19.[92] However, studies in Italy showed that severe asthma did not increase the risk of severe outcome of COVID-19.[93,94] In conjunction with asthma and COVID-19 severity, it was suggested that those with more severe asthma who require a high dose of inhaled corticosteroids (ICS) to maintain asthma control may be at risk of a worse prognosis from COVID-19,[95] although currently there is no evidence to support the withdrawal of ICS in patients treated with these drugs.[96] The inconsistent findings between asthma and the severity of COVID-19 may be due to the different scale of study in case series, criteria for hospitalization of COVID-19 patients, racial disparities, patient age, severity of asthma and the condition of asthma control in the patients. However, only few studies have reported adequate clinical information of asthma in the COVID-19 patients, including lung function, control status, asthma phenotypes, or treatment regimen of the patients, which leads to the

difficulty in comparison. The nasal and airway epithelial cells of patients with respiratory allergy are characterized by a reduced ACE2 expression[97,98] and upregulation of transmembrane protease serine 2 (TMPRSS2),[84] two essential molecules for entry of SARS-CoV-2 into the cell.[98] This may result in a lower risk of infection but a higher risk of severity. A recent large cohort study aiming to understanding the association between atopy and COVID-19 severity found that AR was associated with a lower rate and duration of hospitalization and lower duration of intubation for COVID-19 infections.[99] In summary, there is controversial findings for the association between asthma and severity of COVID-19, whereas allergic rhinitis has a protective effect against severe COVID-19. Further research is warranted to improve our current understanding of the type 2 immune response in COVID-19 as it is targeted by biologicals in the treatment of asthma and atopic dermatitis.[100,101] In addition, deeper insight into phenotypes and endotypes of asthma might provide more understanding of the pathophysiology of COVID-19 in asthma.[102]

4.5 | Chronic obstructive pulmonary disease (COPD)

A recent report demonstrated that COPD is not a predisposing factor for SARS-CoV-2 infection, but once the patient develops the disease they have an elevated risk of hospitalization (aOR: 1.36), ICU admission (aOR: 1.20) and receiving invasive mechanical ventilation (aOR: 1.49).[18] In a multicenter study including 476 COVID-19 patients, the prevalence of COPD was found to be significantly different according to disease severity: lowest in the moderate group (2.3%), intermediate in the severe group (5.6%) and highest in the critically ill group (15.7%).[103] Similarly, in a cohort of 289 hospitalized COVID-19 patients, 6.1% of nonsurvived patients were observed with COPD comorbidity, remarkably higher than the COPD prevalence of 0.6% of nonsevere patients.[3] There are significant differences in the prevalence of COVID-19 patients with coexisting COPD between countries. A higher prevalence of COPD was noted in ICU patients in Wuhan (8.3%),[104] Spain (38%), and Seattle (33%).[60,105,106] In a multicenter cohort of 191 COVID-19 patients, nonsurvivors had higher COPD prevalence (7%) compared to survivors (1%).[41] Guan et al demonstrated that COPD (hazard ratio [HR]: 2.681) was a risk factor for ICU admission, invasive ventilation, and death after adjustment for age and smoking in a Chinese nationwide COVID-19 analysis.[15]

Restricted pulmonary function is an important confounding factor and several molecular mechanisms have been proposed (Figure 3). The higher ACE2 expression in the airways in COPD subjects is negatively correlated with forced expiratory volume in the first second (FEV1)%.[107] Other molecules related to SARS-CoV-2 infection were also noted with increased expression in COPD subjects, such as SLC2A1 (GLUT1) in human bronchial epithelial cells, SLC7A5(CD98), ITGA3, and ITGA6 in bronchial biopsies.[84] A cohort of 961 COVID-19 patients in Wuhan showed a poorer clinical course among patients with coexisting COPD compared to asthmatics, with OR 23.433 for severe illness and OR 19.762 for acute respiratory distress syndrome (ARDS).[43] Consistently, ACE2 expression in the lower airways was elevated in COPD patients and reduced in asthma patients. Moreover, compared to asthmatics, patients with coexisting COPD were characterized by a reduction in $CD4^+$ T and $CD8^+$ T cells and B cells and elevated levels of the cytokines including tumor necrosis factor-α (TNF-α), IL-10, IL-8, and IL-6.[43]

4.6 | Interstitial lung disease (ILD)

COVID-19 patients with preexisting ILD are more susceptible to progressing to a severe or critical case due to restrictive ventilatory dysfunction and a limited pulmonary reserve (Figure 3). In addition, SARS-CoV-2 infection may trigger an exacerbation of underlying ILD and result in critical illness and poor outcome.[108] In 28 COVID-19 patients with preexisting ILD, 19 (67.9%) were severe or critical cases.[109] Continuation of immunosuppressive therapy in ILD patients was recommended as it would not have an adverse effect of COVID-19 and might even be beneficial given the hyperinflammation state in these patients.[108] COVID-19 patients with preexisting ILD had a poorer prognosis with fatalities ranging from 30.0% to 60.0% with OR from 3.2 to 5.5.[19,109,110]

4.7 | Chronic liver diseases (CLD)

2%-11% of patients with COVID-19 had underlying CLD and 14%-53% of patients with COVID-19 developed hepatic dysfunction.[7,111–114] Patients with CLD (cirrhosis, chronic hepatitis B, alcoholic liver disease, and other types of chronic hepatitis) are at increased risk of infection due to their altered immune function and are more susceptible to decompensation or development of acute-on-chronic liver failure with bacterial, fungal or viral infection. Patients with autoimmune liver diseases or post-transplant patients under immunosuppressive therapy are at an even higher risk.[115] A study in the US found that preexisting CLD was associated with higher fatalities (RR: 2.8; 95% CI 1.9–4.0, $P < .001$) as compared to patients without liver disease and the relative risk was significantly higher in patients with cirrhosis (RR: 4.6; 95% CI: 2.6–8.3, $P < .001$).[20]

4.8 | Chronic kidney diseases (CKD)

To date, there have been limited studies on the association between preexisting CKD and COVID-19 severity. This could be due to the lack of patient data on kidney function prior to infection or failing to state the definition of CKD in the study. It was reported that patients with coexisting CKD are at higher risk of death than those without CKD,[47] and becomes more prominent at a severe stage of CKD. In 10 482 patients with COVID-19, 419 presented end-stage kidney disease and had a higher rate of in-hospital death than those without COVID-19 (31.7% vs 25.4%).[21] Patients with CKD had a high prevalence of comorbidities, such as hypertension,

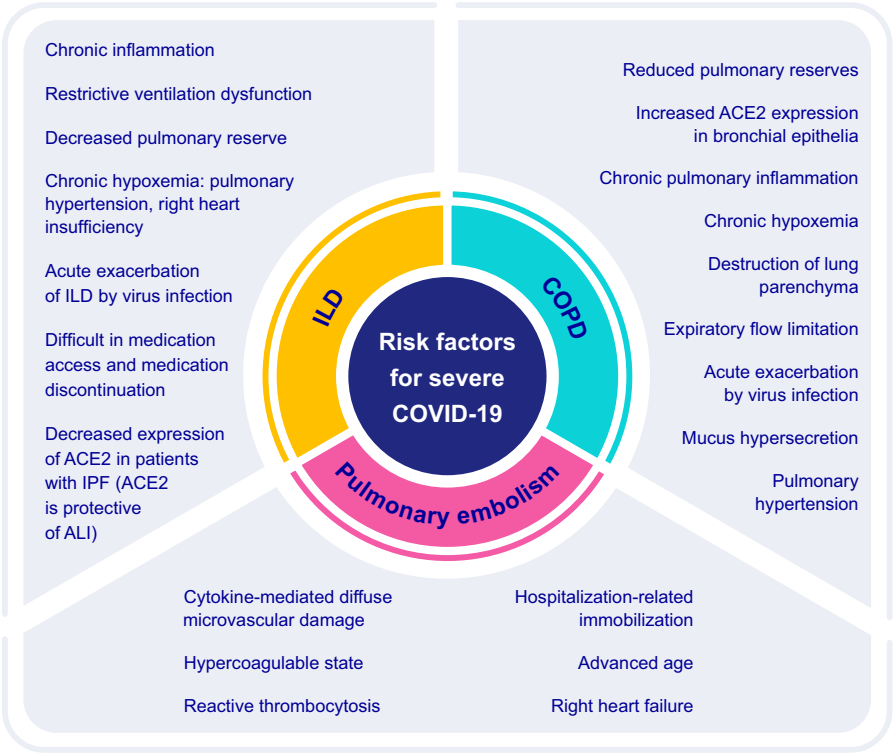

FIGURE 3 Possible mechanisms contributing to increased severity by chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), and pulmonary embolisms comorbidities. The increased risk of severity and adverse outcome in COVID-19 patients with coexisting COPD may be attributed to a reduced pulmonary reserve, increased ACE2 expression in bronchial epithelia, chronic pulmonary inflammation, chronic hypoxemia, destruction of lung parenchyma, expiratory flow limitation, acute exacerbation by virus infection, mucus hypersecretion, and pulmonary hypertension. Patients with ILD comorbidity are characterized by chronic inflammation, restrictive ventilation dysfunction, decreased pulmonary reserve, chronic hypoxemia resulting in pulmonary hypertension and right heart insufficiency, acute exacerbation of ILD by virus infection, difficulties in medication access and medication discontinuation, and decreased expression of ACE2 in patients with IPF (ACE2 is protective of ALI). These factors might all contribute to a higher risk of severe outcomes in ILD patients with COVID-19. Pulmonary embolism (PE) is a common and fatal complication in hospitalized COVID-19 patients, which aggravates the disease. Different mechanisms underly PE: cytokine-mediated diffuse microvascular damage, hypercoagulable state, reactive thrombocytosis, hospitalization-related immobilization, advanced age, and right heart failure

cardiovascular disease, and diabetes mellitus, which might contribute to the poorer outcomes among these COVID-19 patients.

4.9 | Cancer and chemotherapy

Patients with cancers and hematologic malignancies are vulnerable to SARS-CoV-2 infection due to compromised immunity.[116] Patients with cancer were at higher risk of severe cases than those without any comorbidities (OR: 3.61; 95% CI: 2.59–5.04, $P < .001$), as demonstrated in a study in Wuhan involving 13 077 COVID-19 patients.[22] In a matched cohort study involving 585 COVID-19 patients, 117 were active cancer patients. The results showed that active cancer was not associated with increased risk of ICU admission, intubation or death.[117] Older age, elevated IL-6, procalcitonin (PCT), D-dimer, reduced lymphocytes, advanced tumor stage, elevated TNF-α, N-terminal pro-B-type natriuretic peptide, reduced $CD4^+$ T cells, and reduced albumin-globulin ratio were all identified as risk factors of COVID-19 severity in patients with cancer.[22] Another study identified age > 65 years and treatment with immune checkpoint inhibitors (ICIs) as predictors for hospitalization and severe disease of COVID-19, independent of chemotherapy treatment and major surgery.[49] This is not consistent with the findings reported by Luo et al, which showed that programmed death 1 (PD-1) blockade therapy is not associated with the severity of COVID-19 patients with lung cancer.[118] Interestingly, having an initial cancer diagnosis > 24 months prior to infection was associated with increased severity (OR: 1.74; 95%CI: 0.71-4.26).[58] The conflicting conclusions for the impact of cancer on COVID-19 severity may be derived from confounding factors such as more comorbidities and older age in cancer patients. In summary, cancer comorbidity might be associated with a higher risk of prevalence and severity of COVID-19. Tumor type, duration and therapy may be determining factors correlated with COVID-19 severity.

4.10 | Pregnancy

Physiological changes in the immune and respiratory system may make pregnant women more susceptible to COVID-19 infection.[119] Associated with placental immaturity, the early ACE2 expression can

make the first trimester the most susceptible period for SARS-CoV-2 infection.[120] A report by the US CDC demonstrated that the prevalence of COVID-19 in pregnant women was 9.0% (8207/91412).[121] Pregnant COVID-19 women had a higher ICU admission rate than nonpregnant COVID-19 women (1.5% vs 0.9%); 0.5% of pregnant women required mechanical ventilation compared with 0.3% of nonpregnant women, with comparable mortality rates.[121] In Sweden, the risk of being admitted to ICU was also higher in pregnant and immediately postpartum women with laboratory-confirmed SARS-CoV-2, compared to nonpregnant women of similar age (relative risk: 5.39; 95% CI: 2089–10.08).[122] Taken together, currently available data showed a higher risk of ICU admission in pregnant women affected with COVID-19.

4.11 | Immunodeficiency

Studies of severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) suggest that patients with HIV often have a reduced risk of both virus infection and severe disease course.[123] This might be attributed to the suppression of coronavirus replication by antiretroviral therapy. However, these patients have a longer duration of the disease, which might be due to their immune-suppressed status.[123] In a Spanish cohort, 51 people living with HIV were coinfected with COVID-19 (incidence 1.8%) and all received antiretroviral therapy, and 13 of them (25.5%) progressed to severe case.[124] Inciarte et al recently reported a 0.9% incidence (53/5683) of COVID-19 in people living with HIV, which is lower than in the general population. Of these 53 patients, 6 (14%) were severe, 4 (8%) required ICU admission, and 2 (4%) died. Antiretroviral therapy was not associated with COVID-19 diagnosis and severity.[125] A meta-analysis involving 25 studies and 252 HIV patients coinfected with SARS-CoV-2 showed that 21.2% were at a severe and critical stage.[126] In summary, HIV is not associated with increased susceptibility of SARS-CoV-2 infection; however, there is some association as a risk factor of severe disease and mortality.

Meyts et al reported the course of COVID-19 in 94 patients with an underlying inborn error of immunity (IEI) that the patients with primary antibody deficiencies (n = 53, 56%) were the predominant group, and there were only 3 (3%) patients with innate immune defect. Among these 94 IEI patients with COVID-19, 34 (36%) were asymptomatic and mild COVID-19, 13 (14%) needed oxygen supplementation with noninvasive ventilation at admission, and 15 (16%) were admitted into ICU. Risk factors predisposing to severe disease and mortality in the general population were also found to affect IEI patients, including more younger patients. These data indicate that IEI may be a risk factor for severe COVID-19. A recent study has found a strong association between low type I interferon (IFN) production capacity and severity of COVID-19[127–129](Figure 4 and Figure 5). Nuclear factor-κB (NFKB) pathways activation in plasmacytoid dendritic cells is essential to produce large amounts of type I IFNs. All 4 patients with NFKB1 or NFKB2 mutations required hospitalization, with both NFKB2-deficient individuals being admitted to ICU,[130] also suggesting a protective role of Type I IFNs against severe COVID-19. Subcutaneous injection of IFN β-1a has been reported as an effective and safe treatment of severe COVID-19, significantly increasing discharge rate on day 14 and decreasing fatalities on day 28.[131] However, these results are preliminary and need to be investigated further with well-designed large sample-sized randomized double-blinded clinical trials before injected or inhaled IFN-β is recommended for the treatment of COVID-19. An ongoing clinical trial with SNG001, an inhaled IFN-β, showed promising results in reducing the odds of hospitalized COVID-19 patients progressing to severe disease (https://www.uhs.nhs.uk/ClinicalResearchinSouthampton/Research/News-and-updates/Articles/Inhaled-drug-prevents-COVID-19-patients-getting-worse-in-Southampton-trial.aspx).

4.12 | Viral Load

A high SARS-CoV-2 load can be detected at symptom onset, showing high levels in the first 24 h and peaking on day 5–6 of illness. It has been demonstrated that asymptomatic and postinfection individuals can be SARS-CoV-2 positive, especially in children. Viral genome can be detected in asymptomatic individuals. Viral load has been shown to be higher in symptomatic children (1.3×10^7 copies/mL [IQR 5.6×10^4 to 3.8×10^8]) than in asymptomatic children (2.0×10^3 copies/mL [IQR 162 to 1.7×10^5]).[132] These results stress the need for early detection of infection to minimize potential transmission.[133–136]

Exposure to high numbers of infective SARS-CoV-2 and kinetics of viral load were highly predictive markers of severe course and outcome in older patients.[137,138] SARS-CoV-2 can be detected in sputum, bronchoalveolar lavage fluid, pharyngeal swabs, and stool.[133,139] There is controversy on the association between viral load and disease severity in patients with COVID-19.[140] One study claimed that viral load appears to be a poor predictor of disease outcome and it is not age-dependent.[141] A positive correlation was found between age (compared to > 60 age) and peak viral load in the patients with COVID-19. The viral load in the samples was highest during the first week of symptom onset, then progressively decreased until 20 days except for one patient which SARS-CoV-2 PCR positivity persisted for up to 25 days.[142] Wang et al reported that most of the severely ill patients had viral shedding in various tissues for 20-40 days after the onset of disease and detectable viral RNA in the blood was strongly correlated with clinical severity.[143] Another study showed that variability of antiviral response in males and the elderly patients with COVID-19 are dependent on viral load and infection time. Viral load was related to ACE2 expression and may impact the prognosis of COVID-19.[144] Liu et al reported that cycle threshold (Ct) values of severe patients with COVID-19 were significantly lower compared to mild patients at the time of admission and the mean viral load of severe patients was around 60 times higher than that of mild patients.[145]

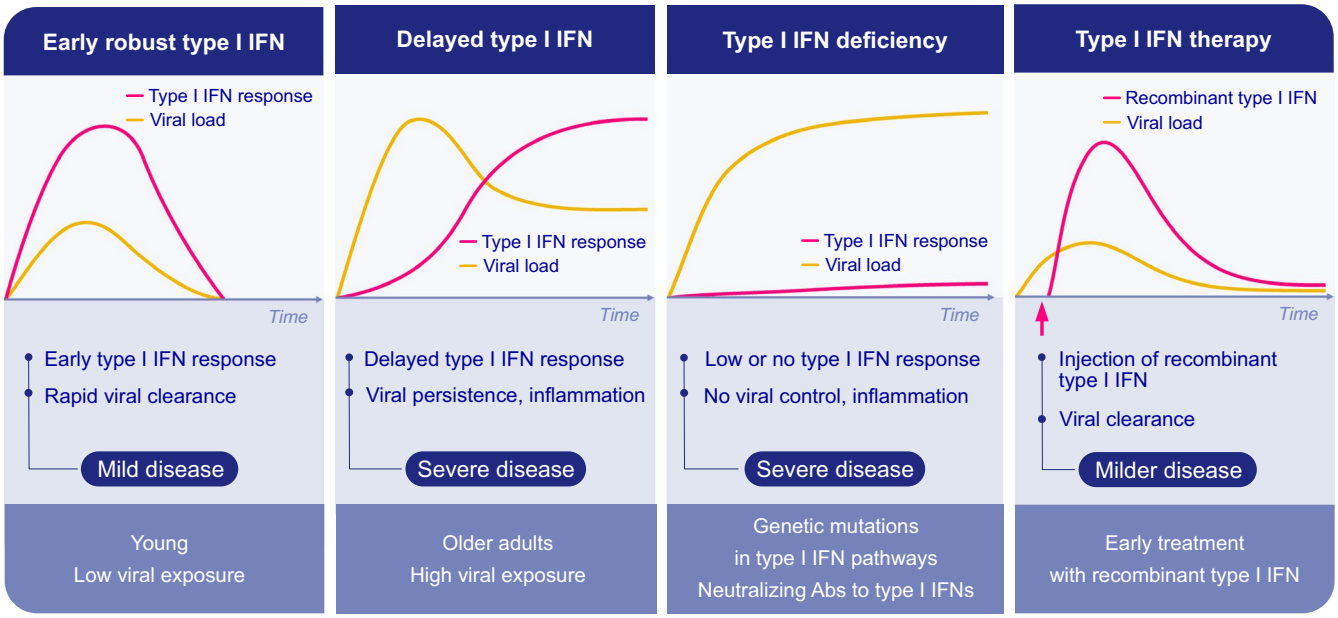

FIGURE 4 Type 1 interferon (IFN-I) immunity in patients with life-threatening COVID-19. IFN-I is vital in the immunity against virus infection, and a robust IFN-I response was suggested to contribute to severe disease due to hyperinflammation. In young people with low viral exposure, early robust IFN-I response results in rapid viral clearance and mild disease; in older adults with high viral exposure, delayed IFN-I response will lead to viral persistence, inflammation, and severe disease; in patients with genetic mutations in IFN-I pathways or neutralizing auto-Abs to type I IFNs, there is only low or no IFN-I response, which results in no viral clearance, persistent inflammation and severe disease; in those patients receiving early treatment with injected or inhaled recombinant type I IFNs, rapid viral clearance will result in mild disease

Other studies suggested that SARS-CoV-2 is considered a high viral load when Ct value < 25–27, medium viral load, Ct value 25-32 and low viral load, Ct value > 30-32. Risk factors associated with high viral load include older age, congestive heart failure, diabetes, chronic kidney disease, and the use of inhaled/nasal and oral steroids before admission.[142,146–148] Blot et al reported that the alveolar viral load at the onset of ARDS is closely correlated with disease progression, especially leading to hypoxemia.[149] Linder et al observed that fulminant myocarditis was not associated with SARS-CoV-2 infection in cardiac tissue from 39 consecutive autopsy cases even though SARS-CoV-2 was found in heart tissues.[150] Antiviral therapy such as convalescent plasma, remdesivir or early IFN treatment can reduce viral load and severity of diseases.[151–154] However, although inhales corticosteroid (ICS) such as ciclesonide has been shown to have potential antiviral activities against SARS-CoV-2, a recent study found that regular use of ICS was associated with neither increased nor decreased risk of COVID-19-related death in COPD and asthma patients,[155] and this discrepancy may be due to that ICSs other than ciclesonide were used in these patients.

5 | COMPLICATIONS

5.1 | Acute kidney injury (AKI)

Kidney disease is frequently observed in COVID-19 hospitalized patients. Early reports from China found the occurrence of AKI ranged from 0.5% to 29% in hospitalized COVID-19 patients.[41,114,156] Recent data from New York City found a 46% incidence of AKI among 3993 hospitalized patients with COVID-19.[157] Out of the patients with urine study results (435 from 1835 AKI patients), the majority presented proteinuria (84%) and hematuria (81%).[157] In 5449 hospitalized COVID-19 patients from New York City, 36.6% developed AKI and 14.3% of these patients progressed to necessitating renal replacement therapy (RRT). The majority of patients under mechanical ventilation developed AKI (86.9%), and 23.2% of intubated patients required RRT.[23] AKI is common among critically ill patients with COVID-19, 76% of patients admitted to ICU presented AKI, and it is considered a marker of disease severity and a negative prognostic factor for clinical outcomes.[41,157] In addition, proportion of COVID-19 patients with AKI stage 3 was higher in those admitted to ICU than those not in ICU (56% vs 32%).[157] After adjustment for demographics, comorbidities, and laboratory values, the risk for death of COVID-19 was higher for ICU patients with AKI than those without AKI (aOR: 11.4; 95% CI: 7.2 to 18), and the aOR for death was 9.2 (95% CI: 7.5 to 11.3) for all patients with AKI versus no AKI.[157] Similarly, increased risk of mortality in COVID-19 patients with increased baseline BUN (HR 7.15; 95% CI: 4.92 - 10.39), baseline serum creatine (HR 2.99; 95% CI: 2.00 - 4.47), and peak serum creatine > 133 μmol/L (HR 5.88; 95%CI: HR 3.90 - 8.87) was shown.[156] Increase in AKI stage was also associated with increased risk of death, with HR 3.51, 6.24, and 9.81 for AKI stage 1, 2, and 3 respectively.[156] Soluble urokinase plasminogen activator receptor (suPAR) has been identified

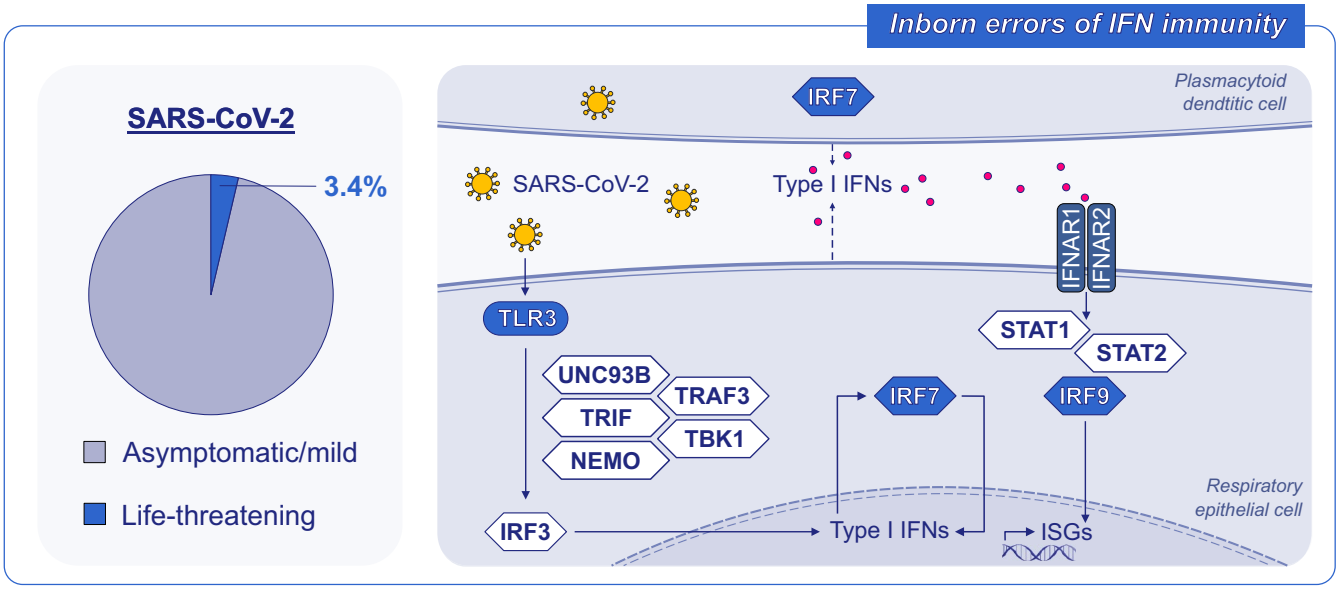

FIGURE 5 Inborn errors of type 1 interferon (IFN) immunity. Inborn errors of toll-like receptor 3 (TLR3) and interferon regulating factor 7 (IRF7)-dependent type I IFN immunity underly life-threatening COVID-19 pneumonia in patients with no prior severe infection. Loss of function (LOF) variants at 13 loci known to govern TLR3 and IRF7-dependent type I IFN immunity against influenza were also identified in 3.4% (23/659) patients with life-threatening COVID-19 pneumonia, compared to only 1 heterogeneous predicted to be LOF variation at the 13 loci (IRF7p. Leu99fs). SARS-CoV-2 infection stimulates type I IFNs production in plasmacytoid dendritic cells (pDC) in IRF7-dependent pathway; in respiratory epithelial cells, SARS-CoV-2 infection activates TLR3, which induces the production of Type I IFNs production in IRF3- and IRF7-dependent pathway; Type I IFNs secreted by pDCs bind to IFN-α receptors (IFNAR)1/2 and activate interferon-stimulated genes (ISGs), which have potent antiviral activity. (Zhang Q et al, *Science*. 2020 Sep 24)

as an immunologic risk factor for AKI. In a multinational observational study of adult patients hospitalized for COVID-19, AKI incidence rose with increasing suPAR tertials, from a 6.0% incidence in patients with suPAR < 4.60 ng/ml to a 45.8% incidence of AKI in patients with suPAR levels > 6.86 ng/ml. None of the patients with suPAR < 4.60 ng/ml required dialysis. The highest suPAR tertial was strongly associated with incident AKI (aOR: 9.15; 95%CI: 3.64–22.93).[158] In view of these results, suPAR might be used as a potential biomarker for AKI and COVID-19 severity.

5.2 | Coagulation disorders

COVID-19-associated coagulopathy is characterized by elevated D-dimer levels (increased thrombosis), lower platelet count, prolongation of prothrombin time (PT), activated partial-thromboplastin time (APTT), and elevated levels of fibrinogen, coagulation factor VIII, and von Willebrand factor.[159,160] Severe and critically ill patients had prolonged PT and levels of fibrinogen at admission compared with mild and moderate patients.[161] Fibrinogen levels were significantly higher in severe patients than in nonsevere patients (4.23 g/L vs 3.07 g/L, $P = .002$).[162] A meta-analysis involving nine studies and 1105 patients confirmed elevated levels of PT and D-dimer, but not APTT and PLT in severe patients.[163] A study with 1207 COVID-19 patients demonstrated that APTT > 37 s was associated with a higher risk (OR: 3.07; 95% CI: 1.37–6.86) of cardiovascular complications, which is an indicator of severity and mortality of COVID-19.[164] Bleedings associated with prophylactic or therapeutic anticoagulant therapy were more common in critically ill patients than in noncritically ill patients (7.6% vs 3.1%), and major bleeding almost only occurred in critically ill patients.[165] This suggests that bleeding may be an important determinant of critical illness. Interestingly, patients with congenital coagulation disorders had a lower COVID-19 prevalence, milder symptoms and better prognosis when compared to the general population in an Iran cohort study.[166]

5.3 | Thromboembolism

There is recent clinical evidence that COVID-19 patients are at higher risk of thromboembolism than other viral pneumonia,[26] which may be due to endothelial injury by the virus and disrupted cell membranes[24] and immobile state. The prevalence of thromboembolism in COVID-19 patients is most likely to be underestimated.[167] Bilaloglu et al reported a 16% incidence of thrombotic events diagnosed based on routine clinical care (pulmonary embolism [PE], deep vein thrombosis, myocardial infarction, ischemic stroke, and other thromboembolisms) in 3334 COVID-19 patients in New York City.[168] The prevalence of PE in this study was 3.2%, but computed tomography pulmonary angiography images indicated a significantly higher incidence of 24%.[26] Not surprisingly, thromboembolism complications are associated with severe and critical illness of COVID-19, as a stronger cytokine storm and inflammation develops in these patients. Moreover, thromboembolism in mild cases, especially PE

and microthrombi in small vessels and microvasculature[169] will inevitably progress to hypoxemia and poorer clinical outcomes. Other thromboembolisms, such as myocardial infarction, ischemia stroke, or thrombosis in other organs, including the liver, spleen, kidney, and intestine arteries, will also deteriorate the disease and develop into severe and critical illness and increase the mortality. Indeed, patients with PE were more frequently admitted in ICU and required mechanical ventilation[26] and longer hospital stays.[170] In a retrospective study involving 127 COVID-19 patients, D-dimer and CRP were biomarkers associated with the risk of venous thromboembolism (VTE). The receiver operating characteristic (ROC) curve of both variables combined had an area under the ROC curve (AUC) of 0.83 ($P < .05$). The predictive value of D-dimer > 15 μg/ml in combination with a CRP > 280 mg/dl was 98% for VTE.[171] A large cohort study of 1275 COVID-19 patients showed that high CRP and D-dimer levels at admission (≥150 mg/L and ≥ 1000 ng/ml, respectively) and a peak D-dimer ≥ 6000 ng/ml during hospital stay were independent factors associated with PE.[170] Therefore, D-dimer and CRP levels may be potential predictive biomarkers of developing VTE and PE. Possible mechanisms involved in PE formation are illustrated in Figure 3.

5.4 | Anticoagulants

Prophylactic and therapeutic anticoagulant therapy regimes have been used in COVID-19 patients with a higher risk of thromboembolism. Few reports have evaluated the effect of anticoagulant therapy on the severity of COVID-19. It has been recently reported that both therapeutic (aHR: 0.53; 95%CI: 0.45–0.62, $P < .001$) and prophylactic (aHR: 0.50; 95%CI: 0.45–0.57, $P < .001$) coagulants could reduce in-hospital mortality and intubation rates, with no significant difference between the prophylactic and therapeutic group.[25] In patients under mechanical ventilation, administration of therapeutic anticoagulants mitigated in-hospital mortality when compared to those not receiving anticoagulants (29.1% vs 62.7%).[172] Therapeutic enoxaparin could improve gas exchange and decrease the need for mechanical ventilation in severe COVID-19.[173] Even though there are a few studies with conflicting results, in general, most studies support a beneficial effect of anticoagulant therapy on reducing the mortality of COVID-19.[169] Further studies with a larger sample size are warranted to elucidate the association between anticoagulant therapy with the severity and mortality of COVID-19.

6 | LABORATORY INDICATORS

Diverse laboratory findings and biomarkers have been demonstrated to be associated with the severity and mortality of COVID-19, as depicted in Figure 6.

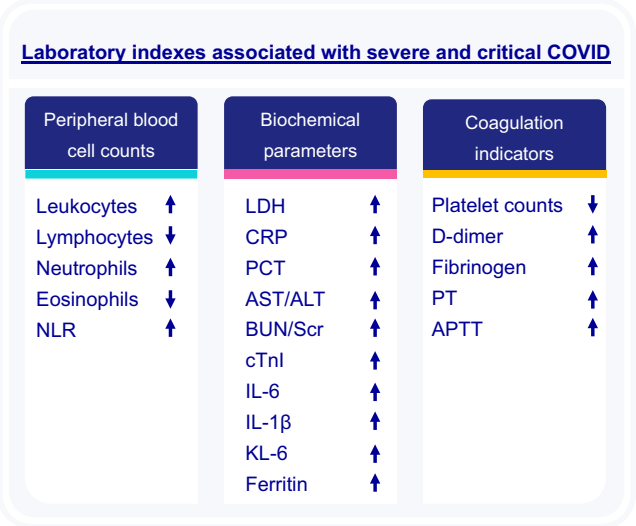

FIGURE 6 Laboratory indexes associated with severe and critical COVID-19. Changes in blood cell counts and differentiation: increased leukocytes, neutrophils and neutrophil-to-lymphocyte ratio (NLR), decreased lymphocytes and eosinophils counts. Changes in coagulation indicators: decreased platelet counts, increased D-dimer, fibrinogen, prothrombin time (PT) and activated partial-thromboplastin time (APTT). Increase in the level of biochemical parameters: lactate dehydrogenase (LDH), C-reactive protein (CRP), procalcitonin (PCT), AST/ALT, blood urea nitrogen (BUN)/Scr, cTnI, IL-6, IL-1β, and KL-6. All these changes may be aggravating factors for the disease course of COVID-19

6.1 | Leukocyte counts

Viral infection leads to dynamic changes in peripheral blood leukocyte counts and its subsets. Leukocytosis, elevated leukocyte counts (≥9.5×10^9/L), was associated with COVID-19 disease course,[3,5] and the increase was more pronounced in severe and critically ill patients compared to nonsevere patients,[3,5,61,174–176] which may be indicative of more prominent inflammation developed in severe patients. A meta-analysis also showed that COVID-19 patients in the severe group tended to have higher leukocyte counts (pooled mean difference: 1.32; 95%CI: 0.62–2.02; $P < .00001$) compared to the mild group.[28]

A higher neutrophil count at admission was found in severe or critically ill patients compared to mild and moderate patients.[27,177] The progressive increase in leukocyte count and sustained lymphopenia and eosinopenia in severe COVID-19 patients may be associated with the progression of inflammatory status, which might progress to a fatal clinical outcome.[3,61] The increased neutrophil-to-lymphocyte ratio (NLR) has been reported as an independent predictor of disease severity in COVID-19 patients.[12,177] Collectively, these results are indicative of neutrophilic leukocytosis, and the increased number of leukocytes and neutrophils may be an aggravating factor for the disease course of COVID-19.

6.2 | Lymphocyte counts

A sustained decrease in the peripheral blood lymphocyte count is an early indicator of severe/critically ill COVID-19 patients. There is a plethora of literature presenting lymphopenia in a significant proportion of patients with COVID-19.[3,5,12,27,28,61,174–177] The decreased lymphocyte counts might be caused by viral attachment, immune injuries from inflammatory mediators, or exudation of circulating lymphocytes into inflammatory lung tissues.[178] Several studies have also reported severe illness to be significantly associated with a more pronounced decline in the absolute number of lymphocytes, compared to mild cases.[104,114,179] For example, in a study of the first 41 laboratory-confirmed cases with COVID-19,[179] 63% of patients presented lymphopenia (lymphocyte count $< 1.0 \times 10^9$/L). The proportion of patients with lymphopenia in the ICU and non-ICU were 85% and 54%, respectively ($P = .045$). Yang et al reported that among 52 critically ill adult patients, lymphocytopenia occurred in 85% of patients and no significant difference was observed between survivors and nonsurvivors.[57]

Wang et al examined the peripheral lymphocyte subset alteration in COVID-19.[178] The results showed that compared to patients with mild illness, severe cases had significantly lower total lymphocytes ($P = .0007$), $CD4^+$ T cells ($P = .024$), $CD8^+$ T cells ($P = .005$), and B cells ($P = .018$).[178] Among the lymphocyte subsets, $CD8^+$ T cells tended to be a potential predictor for COVID-19 severity.[178] Similarly, Chen et al reported that decreased $CD4^+$ and $CD8^+$ T-cell counts and suppressed IFN-γ production by $CD4^+$ T cells are correlated with disease severity.[180] Interestingly, higher lymphocyte count ($\geq 1.1 \times 10^9$/L) was identified as a risk factor for patients with recurrence of SARS-CoV-2 RNA positivity.[181] A better understanding of the factors that affect lymphocytes, particularly T lymphocyte counts and their association with disease severity in COVID-19 patients is of importance for clinical management of COVID-19.

6.3 | Eosinophil counts

In the first preliminary study reporting eosinopenia in COVID-19 patients, decreased eosinophil counts ($< 0.02 \times 10^9$/L) was observed in 52.9% (73/138) patients.[5] However, there was no significant difference in the ratio of patients with decreased eosinophil counts between severe and nonsevere patients ($P = .06$). Many studies have demonstrated that eosinopenia was more prominent in severe COVID-19 patients than in mild patients.[29,175,182–184] Chen et al showed a reduction in eosinophil counts in most of the severe/critical and fatal COVID-19 patients compared to mild/moderate and survived subjects on admission (0.01×10^9/L vs 0×10^9/L, $P < .001$).[177] However, the difference in eosinophil counts between severe and mild COVID-19 patients was marginal and the technical limitations of measuring eosinophils make it clinically difficult to use eosinophil counts as a marker of severity of COVID-19.[185] It has to be considered specially for patients in ICU, who might be under systemic glucocorticoids treatment and eosinophil counts thus dampened. On the other hand, glucocorticoid-unresponsive massive eosinophilia has been reported in severely affected COVID-19 patients in association with drug rash with eosinophilia and systemic symptoms,[186] raising the question whether eosinophilia might be resistant to glucocorticoids. Immunophenotyping of whole blood leukocytes in COVID-19 patients revealed that eosinophil CRTH2 (Chemoattractant receptor-homologous molecule expressed on T(H)2 cells, CD294) expression was significantly decreased in the severe group compared to the mild group. Moreover, the expression of checkpoint inhibitor programmed death ligand-1 (PDL1), a functional marker of eosinophil, was significantly higher in the severe group compared to the mild group. Clinical severity scores such as sepsis-related organ failure assessment (SOFA) and WHO progression scale were correlated positively with PDL1 expression and negatively with CRTH2 expression in eosinophils.[187] These data suggested that decreased CRTH2 and/or increased PDL1 expression on eosinophils, but not eosinophil counts, represent risk factors for severe COVID-19.

The antiviral effect of eosinophils[183] may be reduced in COVID-19 patients with eosinopenia. Different mechanisms potentially contribute to eosinopenia in COVID-19 patients: a diminished release of eosinophils from the bone marrow, the block in eosinophilopoiesis, and direct eosinophil apoptosis induced by dysfunctional type I IFNs response during virus infection.[184]

These results collectively suggest that the degree of eosinopenia, especially before the start of systemic steroids, may serve as a potential predicting factor for the severity of COVID-19. Further studies are needed to explore a potential protective role of eosinophils in SARS-CoV-2 infection and the potential influence of allergy-elicited eosinophilic inflammation on COVID-19 disease course.

6.4 | D-dimer

Elevated D-dimer is common in COVID-19 patients and may be attributed to sepsis-induced coagulopathy and reflect the higher thromboembolic risk in severe COVID-19 cases.[26,188] D-dimer levels were significantly higher in severe than in nonsevere COVID-19 patients,[42] and higher in patients with PE than those without PE[26]; and D-dimer > 0.5 mg/L is associated with severe disease of COVID-19.[30] A meta-analysis including 5872 COVID-19 patients also found higher D-dimer concentrations were associated with severity and mortality in these patients.[189] In addition, D-dimer > 2.0 mg/L at admission was an independent risk factor for increased mortality (OR 10.7, 95%CI: 1.10–94.38) in 248 COVID-19 cases.[190] In 123 COVID-19 patients with VTE during hospitalization, D-dimer was associated with the risk of VTE, with OR 1.09 (95%CI: 1.06–1.11) for every 1 μg/ml increase of D-dimer. The OR for D-dimer > 7.5 μg/ml was 4.1 (95%CI: 2.94–5.71).[191] However, our previous study involving 127 severe COVID-19 patients did not identify D-dimer as a risk factor for mortality after adjusting according to age for each patient.[3]

Dynamic changes of serum D-dimer may be more closely associated with disease severity and outcome of COVID-19. A reduction

in D-dimer levels was observed in recovered patients, independent of anticoagulating therapy, whereas a continuous increase in the levels of D-dimer was predictive of a higher risk of thromboembolism and adverse outcomes.[41,174] Monitoring the dynamic variations of D-dimer is a useful diagnostic tool in predicting the prognosis of COVID-19 patients, and peak D-dimer levels were strongly associated with mortality in COVID-19 patients.[104]

6.5 | Platelet counts

Low platelet counts were frequently observed in COVID-19 patients, especially in severe and critically ill patients.[31,192] As in other viral infections, reduced platelet production, increased platelet destruction and consumption might contribute to thrombocytopenia, as proposed by Xu et al.[193] In severely ill patients, COVID-19- induced liver damage could additionally contribute indirectly to exacerbated thrombopenia.

Decreased platelet counts were also associated with higher fatalities.[27,31,41] In addition, a progressive reduction in platelets was associated with mortality in severe COVID-19 patients.[3] On the other hand, the increased platelet counts in the first 7 days after admission were associated with improved prognosis when compared to those with sustained or progressive reduction in platelet counts.[27]

Conflicting data have emerged on the association between platelet counts and severity of COVID-19. Some studies have found no significant difference in platelet counts between ICU and non-ICU patients,[179] pediatric patients with and without pneumonia,[12] and among nonsurvived, survived severe and nonsevere patients, although more patients with decreased platelet counts were found in survived severe patients than in nonsevere patients (35.9% vs 13.6%).[3] Taken together, these findings suggest that lower platelet counts at admission and decreasing platelet counts during the disease course may predict severe cases and poor outcome.

6.6 | Lactate dehydrogenase (LDH)

Elevated serum LDH levels have been widely reported in COVID-19 cases and were predominantly higher in severe patients.[194] According to a meta-analysis including 3117 hospitalized COVID-19 patients,[195] the mean value of LDH in severe patients was 1.54 times higher than in nonsevere cases (344.48U/L vs 224.20U/L; 95%CI: 307.08–381.88U/L and 205.33–243.07U/L, respectively). The positive correlation between increasing levels of LDH and IL-6 and disease severity ($r = 0.749$, $P < .001$) makes it a valuable candidate biomarker for monitoring severe COVID-19 patients.[33] Additionally, elevated baseline LDH levels were significantly associated with risk of ARDS (HR: 1.61; 95%CI: 1.44–1.79) and mortality (HR: 1.30; 95%CI: 1.11–1.52).[196] Using a mathematical modeling approach, LDH was identified to have the highest weight in both training and evaluation sets based on the area under the curve (AUC) score (94.27 ± 0.82 and 92.29 ± 2.62, respectively), when compared to other biomarkers (low lymphocyte counts and hs-CRP), which stressed that high level of LDH was the most valuable predictive factor for mortality.[180] Notably, gradually decline of LDH occured within 10 days after admission in noncritical cases but not in critical or deceased cases throughout the course of illness. Both IL-6 and LDH were considered as independent predictive laboratory parameters for assessing the severity of COVID-19, in which an early decline may be related to better outcomes.[197] Since higher levels of LDH had been observed in nonsurvivors at the early stage of the illness,[198] measuring it on admission will be of greater predictive value for patients' risk rather than during ICU. Therefore, LDH is reasonably regarded as a valuable biomarker for severe and critical COVID-19 patients, especially those suffering from cardiac comorbidities.

6.7 | Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)

Biochemical abnormalities of the liver were commonly observed in hospitalized patients with COVID-19,[199] and those with hypoxemia or severe inflammation were more likely to present abnormal biochemical parameters on admission, which may be attributed to cell membrane physiology changes and the development of a cytokine storm. The cause and role of liver damage in COVID-19 however is unclear and, by some authors, has been considered to be collateral damage of a cytotoxic response during viral infection.[200] The prevalence of increased levels of AST and ALT in severe patients (39.4% and 28.1%, respectively) was much higher than that of nonsevere cases. In a multicenter retrospective cohort study including 5771 adult COVID-19 patients, the median value of AST and ALT was higher in severe patients (n = 1,186, 20.6%) compared to nonsevere patients (n = 4585, 79.4%), with 31.0 U/L vs 22.0 U/L in AST and 26.0 U/L vs 23.0 U/L in ALT.[34] In contrast, other studies have not identified any differences in liver function test results between severe and nonsevere cases.[201] While an early elevation of AST and its correlation with COVID-19 severity stresses the critical role of immune-mediated inflammation in liver damage, the underlying mechanisms are not fully understood. Viral RNA at high titers has been detected in liver in concentrations exceeding viremia, as founded in an autopsy,[202] suggesting that liver infection with SARS-CoV-2 may contribute to elevated serum AST and ALT in severe COVID-19 patients. Liver biochemical parameters should be closely monitored, and to date, no specific therapy has been recommended in the clinical management of liver disease comorbidity.[115] Elevated AST was also associated with a high risk of mortality, as shown in a cohort of 10 131 US veterans, those with AST > 89 U/L had an aHR of 1.86 (95% CI: 1.35–2.57) when compared to those with AST ≤ 25 U/L.[56]

6.8 | Blood urea nitrogen (BUN) and creatinine

Severe and critical COVID-19 cases are predisposed to renal damage or AKI, mainly indicated by elevated BUN and serum creatinine

(Scr) levels. A prominent relevance between the development of AKI, mortality and kidney-related diseases was reported in hospitalized COVID-19 patients.[156] Notably, the prevalence rates of patients with increased BUN and Scr levels among severe cases were 13.1% and 14.4%, respectively, which were significantly higher than those in mild cases.[156] In a meta-analysis involving 25 278 patients with COVID-19, higher levels of Scr and BUN were associated with severe cases (Scr: MD: 7.78 μmol/L; 95% CI: 4.43 - 11.14, $P < .00001$; BUN: MD: 2.12 mmol/L; 95% CI: 1.74 - 2.50, $P < .00001$).[203] In addition, the development of AKI in patients with elevated baseline Scr level was much more rapid than in most COVID-19 cases (2 days vs 6 days).[35] Thus, high levels of BUN and Scr should be regarded as an important index in the risk stratification of disease severity in COVID-19 patients.

6.9 | Cardiac troponin I (cTNI)

Cardiac injury is manifested in patients with COVID-19. Cardiac troponin I (cTnI) has been identified as a biomarker of cardiac injury. In a study of 416 cases of COVID-19 (35 ICU patients and 381 non-ICU patients), the level of cTnI was significantly higher in the ICU group ($P < .05$).[36] Nonsurvivors had significantly higher levels of cTnI than survivors ($P < .001$).[204] In a multivariate logistic regression analysis, Chen et al reported that elevated cTnI was an independent risk factor of critical disease (OR 26.9, $P = .001$).[205] Lala et al showed that the degree of cardiac injury, small (cTnI: 0.03–0.09 ng/ml) and large (cTnI > 0.09 ng/ml), was significantly associated with COVID-19 fatality (aHR: 1.75 and 3.03, respectively).[189] Based on a mixed-effects Cox model analysis, a recent study concluded that the aHR of 28-day mortality for elevated high-sensitivity cTnI was 7.12 ($P = .001$), suggesting that the cutoff threshold of biomarkers to assess cardiac injury in COVID-19 patients should be lower.[206] Collectively, these findings suggest that increased cTnI levels are associated with COVID-19 severity and mortality.

6.10 | C-reactive protein (CRP)

High levels of serum CRP are key markers of disease progression and a risk factor for mortality of severe COVID-19 patients and is indicative of a developing cytokine storm in COVID-19 patients.[3,137] 375 patients with COVID-19 presented elevated levels of high-sensitivity (hs)-CRP (26.3 mg/L [2.0 mg/L–99.10 mg/L]).[180] In a study of 989 patients in Wuhan, higher hs-CRP levels (reference 4 mg/L) were observed in COVID-19 patients, compared to the controls (27.4 [8.9–66.8] mg/L vs 3.1 [3.1–14.8] mg/L).[37] A CRP cutoff value of 34.67 mg/L (sensitivity 82.3%, specificity 73%) discriminates severe and nonsevere COVID-19 pneumonia relative to D-dimer.[207] Out of 32 studies, 20 have shown a nearly four-fold higher risk of poor outcomes in COVID-19 patients with elevated CRP.[208] Laboratory analysis of patients admitted to the ICU showed an overall increase of CRP levels in the first seven days, peaking between days two and three.[48]

6.11 | Procalcitonin (PCT)

Increased PCT (normal range 0–0.1 ng/mL) levels were more commonly observed in severe COVID-19 patients (mean 0.1 ng/mL, range [0.06–0.3] ng/mL) compared to nonsevere patients (mean 0.05 ng/mL, range [0.03–0.1] ng/mL).[5,42] These results are in accordance with recent studies where elevated levels of PCT were found in 85 out of 290 patients[209] and are associated with mortality in patients with COVID-19.[3,137] Increased PCT values were associated with a nearly 5-fold higher risk of severe SARS-CoV-2 infection.[32] COVID-19 patients with eosinopenia had higher hs-CRP (50.5 vs 24.6 mg/L) and PCT (0.085 vs 0.05 ng/dL) concentrations than those without eosinopenia .[29] Increased levels of PCT were also detected in COVID-19 pediatric patients even with mild pneumonia, and were more prevalent in pediatric patients with pneumonia compared to the asymptomatic ones.[12] The PCT levels of discharged patients with COVID-19 were restored to normal levels during recovery. These findings suggest that PCT may be a useful biomarker for monitoring disease course.[179,210]

6.12 | Type I interferons (IFN-I)

IFN-I is vital in the immunity against virus infection and a robust IFN-I response was suggested to contribute to severe disease due to hyperinflammation.[211] In COVID-19, severe and critically ill COVID-19 patients had impaired IFN-I activity and robust inflammatory gene expression in blood cells[38] or bronchial lavage fluid macrophages.[128] A recent study found that 101 of 987 patients with life-threatening COVID-19 pneumonia had neutralizing IgG autoantibodies (auto-Abs) against IFN-ω (13 patients), the 13 types of IFN-α (36 patients), or both (52 patients), at the onset of critical disease. These auto-Abs neutralized the ability of the corresponding IFN-I to block SARS-CoV-2 infection in vitro. Auto-Abs were not present in mild symptomatic and asymptomatic COVID-19 patients and only in 4/1277 healthy controls. Moreover, most of these patients with auto-Abs against IFN-I were male and in older age[127](Figure 7). Another report found at least 23 of 659 patients with life-threatening COVID-19 pneumonia have known or new genetic defects at eight loci involved in the TLR3- and IRF7-dependent induction and amplification of IFN-I[129](Figure 5). These data collectively suggest that deficiency in IFN-I response could cause severe and critically ill COVID-19. Tests screening for serum type I IFNs levels or rapid production capacity will be of great clinical importance t to identify high-risk patients.

6.13 | IL-6

SARS-CoV-2 can trigger signaling of the NOD-like receptor family, pyrin domain containing 3 inflammasome activation in monocytes/macrophages, production of high levels of proinflammatory mediators such as IL-6, IL-1β, enhanced cell death and lead to a cytokine

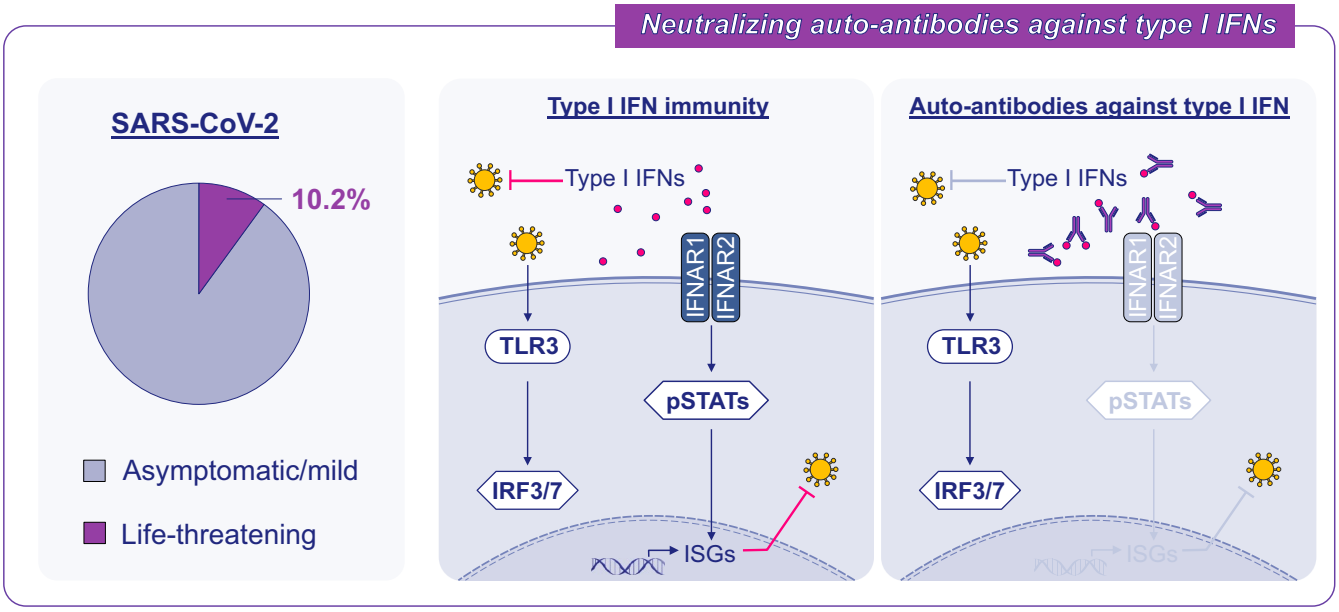

FIGURE 7 Neutralizing autoantibodies against type I IFNs. In 101 of 987 (10.2%) life-threatening COVID-19 patients, neutralizing IgG autoantibodies (auto-Abs) against IFN-ω (in 13 patients), the 13 types of IFN-α (in 36 patients), or both (in 52 patients), were found at the onset of critical disease; a few also had auto-Abs against the other three type I IFNs. By contrast, these auto-Abs were not found in 663 individuals with asymptomatic or mild SARS-CoV-2 infection and were present in only 4 of 1227 healthy individuals. These auto-Abs neutralized the ability of the corresponding type I IFNs to block SARS-CoV-2 infection in vitro. The underlying mechanisms of these neutralizing auto-Abs impairing type I IFN immunity are depicted in this figure. ISGs: interferon-stimulated genes; IFNAR: IFN-α receptors. (Bastard P et al, *Science* 2020 Sep 24)

storm.[212] Synthesis of CRP can be induced by elevated IL-6 levels, a key inflammatory marker involved in the cytokine storm.[3,137,213] The presence of a systemic inflammatory response has been underlined in a meta-analysis showing that COVID-19 patients had higher levels of IL-6 in nonsurvivors vs survivors cases (weighted mean difference: 4.6 pg/mL; 95%CI: [3.4−5.8] pg/mL) and severe vs nonsevere (weighted mean difference: 1.7 pg/mL; 95%CI: [0.8−2.6] pg/mL).[214] When identifying patients at high risk for severe COVID-19, a cutoff value greater than 55 pg/mL was recommended for serum IL-6.[215] Critically ill patients (64.0 pg/mL) were characterized by significantly higher IL-6 levels compared with moderate and severe patients. Mortality was found to be associated with an IL-6 value of ≥ 100 pg/mL. SARS-CoV-2 RNAemia was closely associated with elevated IL-6 levels and poor prognosis in COVID-19.[213] IL-6 levels were higher among patients with immune dysregulation than patients in an intermediate state of immune activation. Tocilizumab, an anti-IL-6 mAb, has been suggested as a potential biological to partially restore the immune dysregulation associated with SARS-CoV-2[216] and the efficacy of Tocilizumab is still being investigated with ongoing clinical trials.

6.14 | IL-1β

Increased IL-1β concentrations, a sign of inflammatory storm in COVID-19 patients,[217,218] were positively correlated with disease severity.[219,220] A statistical difference was found between patients with nonsevere COVID-19 (13.7 ± 5.8 pg/ml) and those admitted to the ICU (40.8 ± 10.4 pg/ml).[221] A critical threshold value for IL-1β higher than 0.5 pg/mL was suggested as predictive of poor COVID-19 prognosis. IL-1β remained significant even after adjustment for demographics and comorbidities.[59,222] Several biologicals have been investigated targeting the IL-1β inflammatory pathway. Anakinra, a recombinant human IL-1 receptor antagonist, was reported to reduce the need for invasive mechanical ventilation and mortality in patients with severe forms of COVID-19.[223] Similarly, canakinumab, an anti-IL-1β mAb, may inhibit the dysregulated immune response in COVID-19 patients and dampen myocardial injury or other immunopathological diseases.[222,224]

6.15 | Krebs von den Lungen-6 (KL-6)

KL-6 is mainly produced by damaged or regenerating alveolar type II pneumocytes.[39] Both baseline or peak serum KL-6 levels were higher in critical and severe COVID-19 cases than in nonsevere cases.[225] Consistently, another study also demonstrated higher serum concentrations of KL-6 in severe patients than in nonsevere patients, with a cutoff value of 406.5 U/ml.[39] Xue et al found similar results and showed that KL-6 levels correlated with pulmonary lesion area in digital radiography and computed tomography images, oxygen index and oxygen partial pressure difference of alveolar artery (PAaDO2).[226] These findings suggest that serum KL-6 can be used as a novel biomarker for severe COVID-19.

6.16 | Chest computed tomography (CT) imaging patterns

Chest CT scans have been routinely used as a diagnostic tool at the early stage of COVID-19, although with a relatively low specificity.[227] Pulmonary manifestations and their correlated chest CT imaging in COVID-19 are diverse and subpleural ground-glass opacity and consolidation are the most common signs.[43]

Chest CT images can also be used to assess the severity and prognosis of COVID-19. Li et al found that a high lung lesion score was associated with severity. CT findings associated with severe/critical COVID-19 pneumonia included consolidation, linear opacities, crazy-paving patterns, bronchial wall thickening, high CT scores, and extrapulmonary lesions.[41] We previously showed that the numbers of affected pulmonary lobes were higher in severe patients than in nonsevere patients, and were correlated with age, CRP, D-dimer and BUN.[3] Similarly, Xiong et al demonstrated that CRP, erythrocyte sedimentation rate and LDH significantly correlated with the severity of pneumonia on initial CT and follow-up CT images indicated disease progression during the early stage from illness onset.[228] Artificial intelligence (AI)-assisted CT quantification of pneumonia lesions is based on three features: percentages of ground-glass opacity volume (PGV), semi-consolidation volume (PSV), and consolidation volume (PCV). These measurements taken at day 0 and day 4 provide an early and noninvasive indication of progression of disease to a severe course.[229] In addition, the semi-quantitative CT pneumonia score is a valuable tool to help clinicians identify patients at higher risk of complications and mortality.[113,230] AI algorithms can identify important clinical markers correlated with COVID-19 pneumonia lesions and also provide accurate clinical prognosis that can aid clinicians to provide risk-stratified treatment.[42]

In summary, different chest CT imaging features correlate with severity of COVID-19 and CT scans can be used as a diagnostic tool to monitor the outcome of COVID-19 patients.

6.17 | Ferritin

Elevated levels of serum ferritin were associated with mortality and the development of severe outcomes in COVID-19. Cytokine storm syndrome can cause multiorgan failure and hyperferritinemia.[137,151,231,232] A study including 141 patients with COVID-19 reported that hyperferritinemia (Serum ferritin > 500 μg/L) was observed in all severe patients on admission, and the mild cases had a normal mean serum ferritin level of (303 ± 224 μg/ml); moreover, severe and ICU patients had higher ferritin levels than the mild patients (2.6 times and 5.8 times, respectively).[233] Another study found higher mean serum ferritin levels in moderate and severe patients than in mild patients (mild 327.27; moderate 1555; severe 2817.6; ng/ml).[234] ROC curve analysis confirmed the excellent prognostic accuracies of serum ferritin (cutoff value 500 μg/L) in discriminate patients with severe clinical conditions (AUC 0.939, CI: 0.894–0.985; $P < .001$).[233] A meta-analysis of 189 observational studies with data from 57 563 COVID-19 patients reported that a significant difference in mean ferritin levels of 606.37 ng/mL (95%CI: 461.86–750.88) was detected between survivors and nonsurvivors.[235] Another meta-analysis involving 25 studies and 5350 patients showed that high ferritin was associated with a poor outcome in COVID-19 and development of ARDS.[179] Wu et al reported that patients with ARDS had significantly higher serum ferritin levels than patients without comorbidities (1029.28 ng/ml vs 457.66 ng/ml, $P < .01$).[196] Plasma exchange, high-volume hemofiltration, and desferrioxamine might be used to lower ferritin levels in patients with COVID-19. These therapies are already used for the treatment of sepsis and macrophage activation syndrome.[236,237]

7 | DIET AND LIFESTYLE

There is substantial scientific evidence that foods and nutrients affect immune system functions, and many metabolic or chronic diseases have been implicated with poor diet and lifestyle.[238] The discrepancy in mortality rates of COVID-19 between European countries suggests that diet may play a vital role in maintaining homeostasis essential for fighting infections.[11] Although there is a scarcity of data, diet and lifestyle may be potential risk factors of COVID-19 (Figure 8).

7.1 | Vitamin C and vitamin D

Vitamin C acts as an antioxidant and cofactor for regulatory enzymes and acts on both the innate and adaptive immune system.[239] It has been recently demonstrated that vitamin C might attenuate proinflammatory and procoagulant mechanisms, ameliorating vascular and lung injury in sepsis and ARDS.[240] A recent randomized trial evaluating patients with sepsis and ARDS suggested a beneficial effect of high-dose intravenous vitamin C on mortality.[241] A pilot study in 21 critically ill COVID-19 patients found low serum levels of vitamin C and vitamin D. Older age and low vitamin C levels appeared to be co-dependent risk factors for mortality in COVID-19 patients.[242] Currently, a new clinical trial has been initiated to investigate the beneficial effects of high-dose vitamin C on the treatment of severe COVID-19.[243]

Vitamin D is well-known to regulate gene transcription and immune response. The active metabolite of vitamin D, 1,25-dihydroxyvitamin D (1,25-$(OH)_2D_3$) modulates nuclear factor (NF)-κB activity and then induces the production of many molecules amplifying the inflammatory response, such as IL-6, IL-1β, TNF-α and IFN-α, stimulates the production, mobilization, and adhesion of inflammatory cells, and influences the production of enzymes such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2, phospholipase A2 and free radicals.[244,245] A recent review indicated that vitamin D ameliorates the inflammatory response through multiple pathways and protects against respiratory infections and reduces the risk of

FIGURE 8 Potential benefits of diet on COVID-19. An appropriate and healthy diet is thought to be a protective factor against COVID-19. Micronutrients (vitamins C and D, and minerals), proteins, diet fiber, short-chain fatty acids (SCFAs), cabbage and fermented vegetables, omega-3 polyunsaturated fatty acids (PUFAs), Mediterranean diet, intermittent fasting, and ketogenic diet may potentially improve the prognosis of COVID-19

influenza and COVID-19.[246] In summary, vitamin C and D may play a role against COVID-19 infection through multiple pathways of the immune system and inflammatory response. Further research is warranted to assess vitamin D deficiency as a risk factor for the severity of COVID-19.

7.2 | Proteins

There are limited reports on high- or low-protein diets in the context of COVID-19. Mice with protein-calorie malnutrition had a diminished expression of IFN-γ, TNF-α, and iNOS in lung tissues, comprising their ability to fight infection.[247] Thereby, an appropriate intake of proteins to maintain physiological requirements is essential in maintaining a healthy immune response to protect against SARS-CoV-2.

7.3 | Carbohydrates

There is a scarcity of data on the association between carbohydrates and COVID-19. High-carbohydrate diet contributes to the prevalence of obesity, insulin resistance and type 2 diabetes, which are all risk factors of severe COVID-19.[248] In view of these results, a high-carbohydrate diet may increase the risk of severe COVID-19.

7.4 | Mediterranean diet

The Mediterranean diet (MD) is typically high in vegetables, fruits, whole grains, beans, nuts, seeds, and olive oil, weekly intake of fish, poultry, eggs, and moderate dairy products, but limits intake of red meat. It is regarded as a healthy and sustainable dietary pattern and is associated with reduced risk factors for cardiovascular disease,[249] and may have protective effects against COVID-19. As shown in several surveys on changes in eating habits during the pandemic, the adherence to MD increased in some individuals.[250–252] However, there are limited data on the association between MD and COVID-19 severity and further studies are warranted.

7.5 | Ketogenic diet and intermittent fasting

The ketogenic diet (KD) is a low-carbohydrate diet resulting in a metabolic state called ketosis. KD leads to weight loss, decreases in blood sugar and favorable changes in serum triglycerides and may be beneficial in managing certain medical conditions, such as epilepsy.[253] KD was proposed as a prophylactic diet regimen that might limit viral loads.[254] Moreover, eucaloric ketogenic diet (EKD) had a putative benefit for anti-inflammation through modulation of immune metabolism and prevention of cytokine storm syndrome, which involves in inhibiting M1 macrophages, activating M2 macrophages, stimulating IFN-α synthesis and hindering viral replication.[255] Thus, a multicenter randomized controlled trial has been developed to evaluate the effects of EKD with natural Mediterranean food as a supplementary strategy to treat moderate COVID-19 patients and is currently pending governmental approval.[255] The main endpoint is to prevent disease progression to critical illness and reduce mortality. In addition, intermittent fasting, a commonly used dietary practice, should be considered as a potential therapeutic strategy for COVID-19, as it has been previously demonstrated as an effective method to treat obesity and insulin resistance.[256]

7.6 | Minerals

Certain macro-minerals and trace elements are essential and have key roles in the immune response toward infection. For example, magnesium was found to be inversely correlated with the levels of hs-CRP, IL-6, and TNF-α.[257] Common trace elements such as zinc, iron, copper, and selenium also act as co-factors for various enzymes involved in antioxidant reactions and have key immunomodulatory roles.[258] However, the roles of these micronutrients on the severity of COVID-19 infection is not fully understood.

7.7 | Short-chain fatty acids

Short-chain fatty acids (SCFAs) are metabolic compounds fermented from dietary fiber by the gut microbiota. Increased SCFAs were

TABLE 1 Categories of possible risk and protective factors for severe and critically ill COVID-19 according to the strength of current available evidence

Risk and protective factors for severe COVID-19			
Strong and consistent associations	**Weak or limited associations**	**Preliminary and/or conflicting evidence for associations**	**More research needed to assess associations**
Severe disease in old age	Severe disease in those with preexisting hypertension	Severe disease with asthma	Protective effect of vitamin C
Severe disease in male gender	Severe disease in those with CKD	Severe disease and high viral load during exposure	Protective effect of vitamin D
Severe disease in obesity	Severe disease in those with active cancers	Severe disease with coagulation disorders during hospitalization	Less severe disease with intermittent fasting
Severe disease with fever at admission	Protective effect of allergic rhinitis	Less severe disease with anticoagulant usage	Less severe disease with Mediterranean diet
Severe disease with dyspnea/ shortness of breath at admission	Severe disease in heavy smokers	Severe disease with elevated D-dimer levels	Less severe disease with ketogenic diet
Severe disease with gastrointestinal symptoms at admission	Less severe disease in those with HIV	Severe disease with high serum levels of AST and ALT	Severe disease with mineral deficiency (zinc)
Severe disease with diabetes	Severe disease in those with deficiency in type I IFNs	Severe disease with high serum levels of IL-1β	Protective effect of short-chain fatty acids
Severe with COPD	Severe disease in healthcare workers	Severe disease with high levels of serum ferritin	Protective effect of omega-3 fatty acids
Severe disease with preexisting ILD	Severe disease in those with IEIs	Protective effect of fermented vegetables	Protective effect of high-fiber diet
Severe disease in CLD		Immune suppressive receiving patients	
Severe disease in pregnant women			
Severe disease in patients who developed AKI during hospitalization			
Severe disease in thromboembolism during hospitalization			
Severe disease with high leukocyte counts			
Severe disease with lymphopenia			
Severe disease with eosinopenia			
Severe disease with thrombocytopenia			
Severe disease with high serum LDH levels			
Severe disease with high BUN and serum creatine levels			
Severe disease with high serum cTNI levels			
Severe disease with high serum CRP levels			
Severe disease with high serum PCT levels			
Severe disease with high serum IL-6 levels			

(Continues)

TABLE 1 (Continued)

Risk and protective factors for severe COVID-19			
Strong and consistent associations	**Weak or limited associations**	**Preliminary and/or conflicting evidence for associations**	**More research needed to assess associations**
Severe disease with high serum KL-6 levels			
Severe disease with high chest CT pneumonia score and numbers of affected pulmonary lobes			

Abbreviations: AKI, Acute kidney injury; ALT, alanine aminotransferase; AST, Aspartate aminotransferase; BUN, Blood urea nitrogen; CKD, Chronic kidney disease; CLD, Chronic liver disease; COPD, Chronic obstructive pulmonary disease; CRP, C-reactive protein; CT, Computed tomography; cTNI, Cardiac troponin I; HIV, human immunodeficiency virus; IEI, inborn error of immunity; IFN, Interferon; IL-1β, Interleukin-1β; IL-6, interleukin-6; ILD, Interstitial lung disease; KL-6, Krebs von Lungen-6; LDH, Lactate dehydrogenase; PCT, Procalcitonin.

associated with higher whole-grain intake and exert anti-inflammatory effects through SCFA-related G-protein-coupled receptor[259] by modulating cytokine secretion in monocytes,[260] and by regulating the migration of immune cells.[261] Taken together, SCFAs may play a key role in modulating the inflammatory process associated with COVID-19.

7.8 | Omega-3 fatty acids

Omega-3 polyunsaturated fatty acids (PUFAs), especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been demonstrated to exhibit anti-inflammatory effects in various diseases.[262] Arachidonic acid (AA)-derived lipid autacoids, including prostaglandins (PGs), thromboxane and leukotrienes, are collectively termed eicosanoids and are critical mediators of inflammation, resolution and tissue homeostasis. Infectious processes can activate inflammasome formation leading to an eicosanoids storm consisting of both proinflammatory and anti-inflammatory mediators. SARS-CoV-2 infection leads to tissue damage, cell debris release, endoplasmic reticulum stress, inflammatory enzyme induction and thus triggering an eicosanoids storm, which then stimulates a cytokine storm.[263] The development of an eicosanoid storm is well-documented as a key pathogenic event in COVID-19. EPA/DHA can shift the endogenous eicosanoid profile from arachidonic acid (AA) to EPA-/DHA-derived metabolites, diminishing the synthesis of inflammatory eicosanoids and cytokines, and stimulates the production of specialized pro-resolving lipid mediators (SPMs) to restore immune homeostasis and limit the critical inflammatory period.[263,264] These results suggest that omega-3 PUFAs could ameliorate the inflammatory state caused by viral infections, including COVID-19, and two clinical trials have been initiated to assess the benefits of dietary supplementation with omega-3 PUFA for the treatment of severe COVID-19 patients.[264]

7.9 | High-fiber diet

A high-fiber diet has beneficial effects on glucose metabolism, leading to lower glycemia and higher plasma levels of insulin-sensitizing adipocytokine. It might also reduce the levels of proinflammatory cytokines such as IL-6, IL-18, and TNF-α.[265,266] A high-fiber diet promotes gut microbiota diversity leading to favorable mucosal inflammation.[267]

7.10 | Other diet-related factors

Diet might, at least partially, explain the discrepancies in mortality rates observed between and within countries. Notably, the consumption of fermented vegetables was identified to mitigate COVID-19 severity. For each g/day increase of consumption of fermented vegetables, the mortality risk for COVID-19 was found to decrease by 35.4%.[10]

7.11 | Occupation-related factors: healthcare workers

Healthcare workers are considered at high risk of exposure to and infection with SARS-CoV-2, due to higher viral load exposure and increased exposure time.[268] Data from China CDC showed that healthcare workers accounted for 3.8% of COVID-19 cases, 14.8% of them were classified as severe or critical, and the mortality rate was 0.3%, neither exceeding the overall rate (19% and 2.3%, respectively).[2] Another survey of COVID-19 infection among 9684 healthcare workers in a Wuhan hospital showed that the infection rate was 1.1%, and 15.5% of cases were severe or critical illness and one (0.9%) died.[269] In Germany and Malaysia, the mortality rate was 0.2%–0.5% and severe illness was more common in doctors than in other occupational groups (8.1% vs 4.1%).[270] In both two studies, most healthcare workers were infected in the early outbreak when personal protective equipment was inadequate. Healthcare workers in Italy were also disproportionally affected with an approximate 20% infection rate, which is significantly higher than that of the general population.[271] Certain activities in contact with patients such as clinical lung function test, due to the emission of small droplets containing viral particles, may convey an additional risk of SARS-CoV-2 infection for health workers

facing asymptomatic individuals during COVID-19 due to the emission of small droplets containing viral particles.[272] The relationship between COVID-19 severity and specific activities in the clinics or other settings that considerably increase the risk of infection warrants further and detailed investigations. Overall, health care workers represent a risk group for his possibility of exposure and high prevalence of infection. Because of high dose and repeated exposure, they are also under the risk of severity; however, alertness and early intervention possibility may be a factor that balances the development of sever disease.

7.12 | Smoking

Smoking is associated with a higher expression of ACE2 in airway epithelial cells, predisposing an individual to SARS-CoV-2 infection.[84] There is increasing evidence demonstrating that smoking is also associated with severity and mortality of COVID-19, as suggested by the World Health Organization.[273] A recent meta-analysis found that 25.6% (8417/32849) of hospitalized COVID-19 patients had a smoking history. Current smokers had a significant increased risk of severe COVID-19 (RR: 1.80; 95%CI: 1.14–2.85), and severe or critical COVID-19 (RR: 1.98; 95%CI: 1.16–3.38). Former smokers also had a significant increased risk of severe COVID-19 (RR: 1.31; 95%CI: 1.12–1.54) and severe or critical COVID-19 (RR: 1.35; 95%CI: 1.19–1.53). Both current and former smoking patients had an elevated risk of in-hospital mortality, disease progression, and need for mechanical ventilation.[274,275] However, above-mentioned studies did not clarify whether the risk of smoking on severe COVID-19 is caused by smoking-related diseases such as COPD and coronary heart disease, and also lower socioeconomic status in smoking individuals. There is no cohort study addressing the contributing factors associated with risk of smoking in COVID-19. In any case, appropriate measures should be taken to support and maintain smoking cessation and thus protect the vulnerable population and diminish the risk of developing severe/critical illness.[274]

8 | DISCUSSION AND FUTURE PROSPECTS

Identifying risk factors for the progression to severe and critical ill COVID-19 is of great importance for clinician and public health strategies to deal with this disease. We reviewed all possible risk factors contributing to severe and critically ill COVID-19 and summarized in Table 1. However, some of these factors are predictive of severe and critical illness with strong evidence, some are speculative, and others are still preliminary and need to be studied further with larger cohort. Not all of listed risk factors are identified as independent risk factors for severity of COVID-19 by multivariate analyses. Old age and obesity are appearing with many comorbidities, which are all mentioned as risk factors for severe COVID-19. In addition, most of these risk factors were derived from COVID-19 patients admitted into hospital, those COVID-19 patients with severe chronic underlying disease may be reluctant to SARS-CoV-2 testing or admission, which will result in underestimation of the prevalence of chronic illness in COVID-19 and make it difficult to precisely assess the impact of chronic illness on the severity of COVID-19. On the other hand, those people with chronic illness may modify their behavior, such as rigorously self-quarantine to avoid infection of SARS-CoV-2, which will result in apparently low susceptibility and prevalence of COVID-19 in these patients.

Although different factors potentially contribute to the disease severity, many of these factors are clinical manifestations during the course of COVID-19 and the direction of their change within the first days of hospitalization is indicative of development of a severe disease. In addition, the respective importance of these risk factors may differ individually. A predicting model integrating all possible risk factors stratified with different weight will be helpful to clinical practice. Respective risk factors for hospital admission, severe disease, critical illness, intubation and mechanical ventilation, ICU admission or patients needing other advanced life support system need to be investigated further. In addition, the impact of socioeconomic status, lifestyle, geodemographic factors, availability of good quality medical resources on the severity of COVID-19 are required to be focused in further research.

9 | CONCLUSION

The major risk factors of severe clinical course and outcomes of COVID-19 patients have been identified as elderly age, male gender, ethnicity, fever, dyspnea, gastrointestinal symptoms, preexisting hypertension, diabetes, obesity, COPD, ILD, tumor, immunodeficiencies, pregnancy, thromboembolism, coagulation disorders, leukocytosis, lymphopenia, eosinopenia, elevated serum levels of D-dimer, LDH, AST and ALT, BUN and creatine, cTnI, CRP, PCT, IL-6, IL-1β, KL-6, ferritin, higher CT pneumonia score, high number of affected pulmonary lobes, and smoking. The link between allergy, asthma, and COVID-19 severity is unclear and needs to be investigated further. Chronic liver disease, chronic kidney disease, cancer, and occupation of healthcare workers were identified as risk factors of severity. Deficiency in production of or presence of autoantibodies against type I IFNs is associated with severe COVID-19. Living with HIV has not been identifeid as a risk factor for severity. Anticoagulant therapy was demonstrated to improve disease prognosis of severe patients. Nutrition plays a key role in maintaining an efficient immune response. Diet supplementation with high-dose vitamin C, vitamin D, minerals, short-chain fatty acid and omega-3 fatty acid, adequate protein and carbohydrate content, Mediterranean diet, and high-fiber diet might be beneficial in mounting an adequate immune response to fight against SARS-CoV-2 infection and diminish the inflammation leading to a severe clinical course and poor outcomes.

CONFLICTS OF INTEREST

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