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Predictors of COVID-19 severity: A literature review

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Summary

The coronavirus disease 2019 (COVID-19) pandemic is a rapidly evolving global emergency that continues to strain healthcare systems. Emerging research describes a plethora of patient factors—including demographic, clinical, immunologic, hematological, biochemical, and radiographic findings—that may be of utility to clinicians to predict COVID-19 severity and mortality. We present a synthesis of the current literature pertaining to factors predictive of COVID-19 clinical course and outcomes. Findings associated with increased disease severity and/or mortality include age > 55 years, multiple pre-existing comorbidities, hypoxia, specific computed tomography findings indicative of extensive lung involvement, diverse laboratory test abnormalities, and biomarkers of end-organ dysfunction. Hypothesis-driven research is critical to identify the key evidence-based prognostic factors that will inform the design of intervention studies to improve the outcomes of patients with COVID-19 and to appropriately allocate scarce resources.

Keywords

COVID-19; predictors; SARS-CoV-2; severity

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AUTHOR CONTRIBUTIONS

Benjamin Gallo Marin contributed to the conception of the manuscript, drafted the manuscript, circulated for review, and revised the final manuscript. Ghazal Aghagoli contributed to the conception of the manuscript, drafted the manuscript, circulated for review, and revised and approved the final manuscript. Katya Lavine contributed to drafting, revising, and approving the final manuscript. Lanbo Yang contributed to drafting the manuscript and approved the final manuscript. Emily J. Siff, Silvia S. Chiang, Thais P. Salazar-Mather, Luba Dumenco, Michael C Savaria, Su N. Aung, Timothy Flanigan contributed to drafting the manuscript and revising and approving the final manuscript. Ian C. Michelow conceptualized, reviewed, and revised and approved the manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

1 INTRODUCTION

The newly described coronavirus disease (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has strained healthcare systems around the world. The viral spread has been amplified not only by the occurrence of asymptomatic infections but also by limited widespread testing and personal protective equipment (PPE) for healthcare providers across the world.[1] The overwhelming influx of COVID19-infected patients to many hospitals presents a need to thoroughly understand the clinical, radiological, and laboratory findings associated with greater disease severity and mortality. Here, we synthesize the current literature to describe early demographic, clinical, virologic, immunologic, hematological, biochemical, and radiographic factors that may correlate with COVID-19 disease severity. In this paper, we will use the World Health Organization's (WHO) definition of severe pneumonia to categorize severe disease. As of 27 May 2020, the WHO's most recent clinical guidelines define "severe disease" as adults with clinical signs of pneumonia (fever, dyspnea, cough, and fast breathing) accompanied by one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or oxygen saturation (SpO_2) ≤ 90% on room air.[2] The precise determinants of severe disease are not known, but it appears that primarily host factors rather than viral genetic mutations drive the pathogenesis.[3] However, emerging data from a non-peer-reviewed paper suggest that a D614G mutation in the viral spike (S) protein of strains from Europe and the United States, but not China, is associated with more efficient transmission.[4] Identification of potential risk factors that predict the disease course may be of great utility for healthcare professionals to efficiently triage patients, personalize treatment, monitor clinical progress, and allocate proper resources at all levels of care to mitigate morbidity and mortality. Here, we present a review of the current literature on patient factors that have been proposed as predictors for COVID-19 severity and mortality.

2 METHODS

The primary databases utilized to retrieve the salient medical literature presented in this review were PubMed, ScienceDirect, and Google Scholar. The search terms, used both separately and in combination, included: "transmission," "COVID-19," "coronavirus," "SARS-CoV-2," "Severity," "Critical," "Predictor," "Prognostic," "Markers," and "Children." Only articles in English were included.

3 COMMON SYMPTOMS OF COVID-19

Common clinical symptoms of COVID-19 include fever, dry cough, and fatigue. Less common symptoms include headache, dizziness, abdominal pain, nausea, and vomiting.[5] Patients may present with anosmia (loss of smell), dysgeusia (distortion or loss of taste), nausea, and diarrhea a few days prior to the fever. Although fever is an important clue, it may be absent. However, of the 191 patients hospitalized in Wuhan, China, in January 2020, 94% of patients had fever on admission.[6] Notably, this statistic is representative only of symptomatic, hospitalized patients. A small proportion of hospitalized patients complain of dyspnea, headache, sore throat, congestion, and hemoptysis while others can remain

relatively asymptomatic.[6–8] These symptoms are not specific to COVID-19 and overlap with other viral and bacterial infections.

4 CLINICAL PREDICTORS OF DISEASE SEVERITY

4.1 Demographics

Certain demographic factors reported in the literature are associated with a higher rate of a severe clinical course of COVID-19.[9–14] Among these, older age is a major predictor of mortality and it is thus considered a key factor in the proposed clinical severity risk scores.[10,14–22] As of 16 March 2020, 62% of patients hospitalized with COVID-19 in the United States were older than age 55. Conversely, less than 1% of hospitalized patients were 19 years old or younger.[23] In a retrospective cohort study of 1591 patients in Italy critically ill with COVID-19, the median age was 63 years.[22] Data also suggest that male sex is a variable that is independently associated with COVID-19 severity.[24,25]

4.2 Comorbidities

Pre-existing conditions, such as cardiovascular disease, chronic kidney disease, chronic lung diseases (particularly COPD), diabetes mellitus, hypertension, immunosuppression, obesity, and sickle cell disease, predispose patients to an unfavorable clinical course and increased risk of intubation and death.[6,8,10,26–31]

The Center for Disease Control and Prevention (CDC) has issued an updated list of risk factors for severe disease.[31] Body-mass index (BMI) > 30, which is a proxy for obesity, is considered a strong predictor. A study in Mexico found that among 32 583 patients (12 304 cases and 20 279 controls) who had at least one comorbid disorder, obesity, followed by diabetes, and hypertension were substantial risk factors for both acquiring infection as well as for developing severe disease.[32] The CDC also included sickle cell anemia, moderate-to-severe asthma, and pregnancy as risk factors for severe illness.[31] Elevated levels of glycosylated hemoglobin (HbA1c), which is a surrogate marker for long-term blood glucose control in diabetes mellitus, has been linked to inflammation, hypercoagulation, and high mortality (27.7%).[33]

The American College of Cardiology released a clinical bulletin in March 2020, that reported increased case fatality rates for patients with pre-existing conditions than those without pre-existing conditions. Fatality rates were highest for cardiovascular disease (10.5%) compared with diabetes (7.3%), COPD (6.3%), hypertension (6.0%), and cancer (5.6%). In contrast, patients without pre-existing conditions had a fatality rate of <1%.[34]

Cancer is thought to be a major comorbidity that is associated with poor COVID-19 outcomes. A nationwide analysis in China showed that patients with various types of cancer, particularly hematological and pulmonary malignancies, have a higher probability of developing severe COVID-19 complications compared with patients without cancer.[35] This trend has been reported by others as well.[36–39] Unsurprisingly, advanced tumor stage is linked to worse outcomes.[37] However, it is possible that COVID-19 mortality in cancer patients is more strongly associated with male sex, comorbidities, and advanced age than

chemotherapy or cytotoxic interventions.[40] Solid organ transplant recipients also appear to be at a higher risk for COVID-19 complications.[41]

Investigators have attempted to create prediction models that incorporate several clinical and laboratory parameters. In order to account for comorbidities in such models, a multicenter study in China developed and internally validated a prediction nomogram based on symptoms, vital signs, and comorbidities in 366 laboratory-confirmed COVID-19 emergency department (ED) patients.[42] This model had a Harrel's concordance-index (C-Index) of 0.863 (95% CI, 0.801–0.925), which suggests it showed good discrimination and calibration.[42]

4.3 Hypoxia

A strong association between hypoxemia and worse clinical outcomes has been reported.[19,43] A study of 140 patients with COVID-19-associated pneumonia found that oxygen saturation (SpO_2) > 90.5% predicted survival with a sensitivity of 84.6% and specificity of 97.2%, whereas dyspnea was independently associated with mortality in multivariable analyses.[43] Within a retrospective group of critically ill patients in Italy, the median partial pressure of oxygen to fraction of inspired oxygen ratio (PaO_2/FiO_2) was 160 mmHg with a median positive end-expiratory pressure (PEEP) of 14 mmHg; the PaO_2/FiO_2 was found to be higher in younger patients (163.5) and lower in older patients (156).[22] In this study, older patients (n = 786, ≥64 years old), when compared to younger patients (n = 796, <64 years old), were more likely to die (36% vs 15%, respectively; difference 21%; 95% CI 17%–26%; $P < .001$).[22]

4.4 Radiographic features of severe disease

Imaging modalities are clinically useful in revealing important findings linked to the development of the severe disease. As of 7 April 2020, a multidisciplinary panel of pulmonologists and radiologists from 10 countries established recommendations regarding the use of chest x-ray (CXR) and computed tomography (CT) in COVID-19 patients. The panel recommended that chest imaging is indicated for patients with poor or worsening respiratory function, or if they are determined to be at risk for disease progression.[44]

In addition, the multidisciplinary panel highlighted that, while CXR can be useful in detecting disease progression, CT is more sensitive early in the disease course.[44] The most common CT findings are ground-glass opacities or bilateral consolidation in the peripheral lower lung fields.[45,46] However, early in the disease course or in those with mild symptoms, chest imaging may be normal. The presence of pulmonary fibrosis was associated with older age and higher rate of intensive care unit (ICU) admission.[47] In a recent report of a small cohort, a significant portion of deceased patients with confirmed COVID-19-associated pneumonia had consolidation and air bronchograms on chest imaging and a minority of survivors had consolidation with or without air bronchograms. The median CT score, which is defined by degree of attenuation and consolidation in specific lung regions, was higher in patients who died.[48] Specific CT findings, such as traction bronchiectasis (a subtype of bronchiectasis with bronchial dilation within abnormal lung parenchyma), extensive distribution of abnormalities, and lymph node involvement, have also been reported in

critically ill patients. In addition, architectural distortion has been described, which refers to disruption of the normal architecture as defined by the American College of Radiology. The abnormalities include "spiculations radiating from a point and focal retraction or distortion of the edge of the parenchyma."[49] In a retrospective cohort of 81 patients in Wuhan, China, pleural effusions and lymphadenopathy were infrequent CT findings.[50] An Italian study that examined CT images of 627 suspected COVID-19 cases suggested that an enlarged pulmonary artery diameter, which may indicate pulmonary arterial hypertension, is associated with COVID-19 mortality.[51] In another study of 302 Italian patients, a new CXR scoring system (*Brixia* 18-point severity scale) together with older age and immunocompromised status could predict the risk of in-hospital mortality in patients with COVID-19.[52]

5 LABORATORY TESTS AND OTHER MARKERS OF END-ORGAN DYSFUNCTION AND DISEASE SEVERITY

Certain laboratory markers may predict COVID-19 prognosis.[53] Findings commonly associated with worse outcomes include elevated D-dimer levels, C-reactive protein (CRP), LDH, and high-sensitivity cardiac troponin I.[5,6,8,10,11,54–57] However, it remains to be proven that these and other biomarkers are in the causative pathway of SARS-CoV-2-related pathobiology.

5.1 Coagulation defects

Coagulation abnormalities and large-vessel stroke in SARS-CoV-2 patients have been described, suggesting that markers of thrombosis may be of great prognostic importance, even in younger patients.[58,59] Elevated D-dimer levels suggest extensive thrombin generation and fibrinolysis, and is associated with poor prognosis in COVID-19,[20,55,57,60] which has prompted clinicians to hypothesize that increased D-dimer concentrations are indicative of co-existing venous thromboembolisms that may lead to ventilation-perfusion mismatch.[54] Some investigators have proposed the use of D-dimer blood levels for patient triage.[61] A study of 343 COVID-19 patients revealed that 12/67 patients with D-dimer levels ≥2.0 μg/mL on admission died compared with only 1/267 patients who had levels <2.0 μg/mL ($P < .001$; hazard ratio, 51.5; 95% CI, 12.9–206.7).[62] In another study, D-dimer levels ≥1.0 μg/mL on admission were associated with higher in-hospital mortality.[6] Alterations in other markers of coagulation (thrombocytopenia and prolonged prothrombin time) have been shown to be associated with increased risk of death in COVID-19.[53,63,64] Furthermore, restored platelet counts during hospitalization have been shown to predict survival.[65] Studies suggest that patients with severe COVID-19 develop hypercoagulability rather than consumptive coagulopathy, resulting in excessive fibrin polymerization and elevated risk of thrombosis.[66–69] Similarly, high levels of Factor VIII, a procoagulant acute phase reactant and low Protein C activity, an endogenous anticoagulant, have been described in some critically ill patients, suggesting that these biomarkers may be useful to predict COVID-19 severity.[70] A case of COVID-19 complicated by ARDS, altered mental status, and acute renal failure had a massive elevation in von Willebrand factor concentration and activity, each >500%, indicating severe endothelial injury.[71] These observations may lead to targeted therapeutic interventions to improve outcomes. Therefore, the notion that SARS-

CoV-2 can infect vascular endothelium, a major regulator of thrombosis and hemostasis, might account for the thrombotic burden seen in severely affected patients.[71,72]

5.2 Cardiac dysfunction

Blood chemistry markers of cardiac dysfunction are hypothesized to be associated with COVID-19 severity.[73] Emerging evidence that COVID-19 is linked to cardiac complications is mounting, with reports of severe systolic dysfunction[74] and fulminant myocarditis.[75–77] Furthermore, ST-segment elevation in COVID-19 is linked to poor prognosis, despite variabilities in patient presentation.[78] Similarly, impaired left-ventricular and right-ventricular function and tricuspid regurgitation (> grade 1) were all found to be significantly linked to COVID-19 mortality.[79] A retrospective cohort study of 138 patients reported that patients who received ICU level of care were more likely to have acute cardiac injury than non-ICU patients, although the precipitating event was not defined.[5] Similarly, underlying cardiovascular disease predisposes to severe COVID-19-related complications,[6] and elevated troponin (as defined by serum levels >99th percentile; > 28 pg/mL) may also be (a) independent risk factors for in-hospital mortality[80] and (b) more predictive of poor prognosis than underlying cardiovascular disease alone.[81] Thus, routine electrocardiography and transthoracic echocardiography may be important when assessing the course of COVID-19 patients.

COVID-19-related cardiac complications are associated with elevations in both troponin and brain natriuretic peptides (BNP).[79,82–85] A meta-analysis that included 17 794 patients demonstrated that patients with high troponin I levels were more likely to have an unfavorable prognosis (OR = 5.22, 95% CI = 2.73–7.31, $P < .001$) and that high troponin I levels (>13.75 ng/L), in combination with either elevated AST levels (>28 U/L) or older age, (>60 years) were strong predictors of poor outcomes.[86]

5.3 Alterations in white blood cell (WBC) counts

The WBC repertoire in COVID-19 patients may have some utility in predicting disease severity. Evidence from multiple studies suggests that, compared to patients with mild COVID-19, patients with severe disease have lower granulocyte counts.[7,8,87,88] Further evidence also links the severity of COVID-19 to the degree of lymphopenia, in which blood lymphocyte percentage is inversely associated with severity and prognosis.[89,90] A recent meta-analysis of 20 peer-reviewed publications identified statistically significant reductions in total lymphocytes, CD4+ and CD8+ T cells, B cells, and NK cells in patients with severe COVID-19 disease compared with moderate or mild cases, and T cell subsets exhibited the largest standardized reduction.[91] Other reports have also shown that reduced CD4+ and CD8+ T cell counts and decreased functional diversity amongst these cell populations correlate with worse outcomes.[87,92–94] On the other hand, increased numbers of basophils and neutrophils appear to predict severity.[65] In a study of 81 patients, those with an elevated neutrophil-to-lymphocyte ratio (>9.8) had a higher incidence of acute respiratory distress syndrome (ARDS) ($P = .005$) and higher rates of both non-mechanical and mechanical ventilation ($P = .002$ and $P = .048$, respectively).[88] Although it has been suggested that COVID-19 patients with peripheral blood eosinophil counts below the normal range (<0.02 $\times 10^9$/L) are more likely to exhibit chest CT lesions, respiratory complications, and longer

hospital stays than patients with a normal eosinophil count—the use of steroids may confound this association.[95]

5.4 Liver injury

Elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are more likely to occur in patients with critical COVID-19 and end-organ damage.[8,96] A study of 329 SARS-CoV-2 infected patients with abnormal liver enzyme tests at the time of admission, than those with normal results, had a higher rate of transfer to the ICU (20% vs 8%; $P < .001$), need for mechanical ventilation (14% vs 6%; $P = .005$), acute kidney injury (22% vs 13%, $P = .009$), and mortality (21% vs 11%; $P = .009$).[97] Hypoalbuminemia,[75,96] which has been suggested as a predictor of mortality in the general patient population,[98] has been implicated as an independent predictive factor for COVID-19 mortality.[99,100] Thus, some clinicians have speculated that infusion of albumin in COVID-19 may be potentially protective against mortality, but this has not been proven.[101] A reduced albumin-globulin ratio (0.12; 95% CI, 0.02–0.77; $P = .024$) has also been linked to poor prognosis in COVID-19 cancer patients.[37] A recent multicenter, retrospective study of 160 patients of ages between 35 and 65 years suggested that an elevated Liver Fibrosis Index (FIB-4) (≥2.67) is an independent risk factor for severe COVID-19.[102] FIB-4 was calculated as follows: (age × AST [IU/L])/(platelets [$\times 10^9$] × √ALT [IU/L]). Elevated FIB-4 was specifically associated with a significantly higher risk of ICU admission and more frequent mechanical ventilation (37.8% vs 18.3%, $P = .009$).[102]

5.5 Non-specific biomarkers of cellular injury

Abnormalities in markers of cellular injury, particularly elevated lactate dehydrogenase (LDH), have been linked to greater disease severity.[6,9,10,20,75,81,103] Recent data suggest that LDH may be related to respiratory function and be an important predictor of respiratory failure in COVID-19 patients.[104] A prediction model using age, LDH, and CD4+ ([$age \times LDH$]/$CD4$) showed that the area under the receiver operating characteristic (ROC) curve was significantly higher than the areas for each of these variables alone.[42] A value ≥82 was found to have a sensitivity of 81% and a specificity of 93% for early prediction of a complicated disease course in SARS-CoV-2-infected patients.[42] Elevation of α-hydroxybutyrate dehydrogenase, another marker of cellular injury that is suggestive of kidney, cardiac, and red blood cell damage, is also thought to be linked with COVID-19 severity.[12,105] In a study with a relatively small sample size, α-hydroxybutyrate dehydrogenase was found to be elevated in critically ill patients.[103]

5.6 Renal dysfunction

Kidney dysfunction and failure have been reported in patients with severe disease.[6,13,75,80,106] Certain urine biomarkers, such as urine glucose and protein, have been proposed to offer insight into the degree of COVID-19 severity.[107] While renal dysfunction may be indicative of systemic vascular and inflammatory complications, histopathologic analyses have suggested the possibility that SARS-CoV-2 has the capacity to directly infect the renal tubular epithelium,[106] suggesting that these and other biomarkers related to renal structure and function may offer prognostic information.

6 CLINICAL APPLICATION OF PREDICTION TOOLS TO RISK STRATIFY PATIENTS

Various prediction models are emerging to risk stratify patients. A lymphocyte percentage-time model has been proposed, in which the changes in patients' lymphocyte levels were categorized as follows: (a) if the patient's lymphocyte percentage was >20% within 10 to 20 days after symptom onset, a moderate disease could be predicted, (b) if the patient's lymphocyte percentage decreased to 5% to 20% within 10 to 20 days after symptom onset, a severe disease progression could be predicted, and (c) if the patient's lymphocyte percentage decreased to <5% within 17 to 19 days, a high risk of mortality could be predicted.[89] In addition, a non-peer-reviewed study of 375 COVID-19 patients identified three key biomarker thresholds (LDH < 365 U/L, lymphocytes >14.7%, high-sensitivity [hs] CRP < 41.2 mg/L) that reliably predicted a favorable prognosis. This study constructed a machine learning-based prognostic prediction model that was able to accurately predict survival rates of severe COVID-19 patients with an accuracy >90%.[108] Elevated CRP, alone or in conjunction with other biomarkers, has been proposed as a predictor of COVID-19 severity in other studies as well,[20,26,55,107,109–111] and a positive correlation between elevated CRP levels and severely abnormal CT findings has been described.[90]

Because COVID-19 may lead to a cytokine release syndrome and cytokines are important mediators of the inflammatory response, it has been proposed that detecting elevated levels of pro- and anti-inflammatory cytokines (such as interleukin-6 [IL-6][26,53,57,64,94,109,112] and interleukin-10 [IL-10][53,112,113]) may be of great importance for early recognition of severe complications. In this context, a meta-analysis found that a high IL-6/IFN-γ ratio was significantly increased in patients with severe COVID-19,[114] although a causative role was not proven. Of note, elevated IL-6 and D-dimer concentrations in patients with cancer have been proposed as risk factors for unfavorable COVID-19 outcomes.[37] While a statistically significant elevation of the chemokine, RANTES (CCL5), has been reported in the early stages of mild-to-moderate COVID-19,[113] one study has indicated that this marker is linked with severe disease.[94] Furthermore, increases in IL-10 and IL-1RA early in the course of disease were significantly associated with severe disease.[113] Persistent high levels of plasma IP-10 and monocyte chemotactic protein-3 (MCP-3) may also be particularly strong predictors for COVID-19 severity, even though at least 14 cytokines have been shown to be increased in critically ill patients.[115]

7 PREDICTORS OF SEVERITY IN PEDIATRIC PATIENTS

Pediatric patients account for a small percentage of COVID-19 cases. Of the 149 082 cases reported in the United States from 12 February to 2 April 2020, only 1.7% of cases were under the age of 18.[116] For children 0 to 17 years of age, data from studies suggest that pre-existing conditions and young age (<1 year) are associated with more severe disease.[116,117] The comorbidities included chronic lung disease and asthma, cardiovascular disease, immunosuppression, malignancy, thrombocytopenia, severe anemia, epileptic encephalopathy, autism, CHARGE syndrome, and DiGeorge Syndrome.[116,117] On the other hand, a retrospective cohort study in the United Kingdom determined that among children

with COVID-19 admitted to the ICU for mechanical ventilation, the proportion with complex underlying medical conditions did not differ significantly from those without comorbidities.[118,119] Further studies are required to delineate specific risk factors for severe outcomes in children. Nevertheless, it is likely that the lower prevalence of underlying chronic medical disorders in children accounts to some extent for the lower rates of COVID-19 complications in the pediatric population.[120]

Radiographic studies in children have been described in a retrospective study of 20 COVID-positive hospitalized children in China. Computerized tomography frequently detected consolidation with a surrounding halo sign as well as ground-glass opacities on CT. Although these signs are not pathognomonic of COVID-19, they may support that diagnosis.[121]

Children with pneumonia are frequently coinfected with viruses and bacteria.[122] However, it is not yet known if this phenomenon holds true for SARS-CoV-2-related pneumonia. A small study from China described coinfections with other common respiratory viruses and *Mycoplasma pneumoniae* in some children with COVID-19.[121] Further studies will be needed to define whether coinfections predispose to more severe disease.

Multisystem inflammatory syndrome in children (MIS-C) temporally related to COVID-19, is a newly described, rare, and potentially life-threatening hyperinflammatory syndrome with overlapping features of typical or incomplete Kawasaki disease, toxic shock syndrome, or macrophage activation syndrome.[123–128] It appears that MIS-C represents a post-infectious inflammatory process that follows a few weeks or more after infection with SARS-CoV-2 when the PCR assay is typically negative and antibody test is frequently positive.[129] In a case series of eight pediatric patients in the United Kingdom with COVID-19 and MIS-C, all individuals presented with dramatic gastrointestinal symptoms including abdominal pain, non-bloody diarrhea, and vomiting.[124] Imaging in five patients revealed gastrointestinal abnormalities including ascites, ileitis, dilation of the biliary tree, and gallbladder edema.[124] Decreased WBC and platelet counts, as well as lymphopenia, and elevated ferritin and triglycerides were commonly observed in patients with MIS-C.[126]

An attractive hypothesis to account for less severe disease in children compared with adults is that children express less cell surface enzyme angiotensin-converting enzyme 2 (ACE2) receptors in their nasal epithelia.[130] Because ACE2 is a functional receptor of SARS-CoV-2,[131,132] it is possible that lower expression of ACE2 in nasal epithelia could account for reduced viral entry in children and, thus, a milder infection. If this is proven, then targeting ACE2 expression in the nasal epithelium may be a potential therapeutic approach to reduce transmission of COVID-19.

8 LIMITATIONS

The information presented in this review must be considered along with several important limitations. The data presented here were obtained largely from reports that emerged early during the pandemic. In addition, the wide diversity of study methodologies, statistical approaches, sample sizes, population characteristics, geographic sites, and quality of

publications may have confounded our interpretation of the data. Finally, many of the apparent associations described in this review have yet to be repeated by other investigators and validated using robust statistical methods. Nevertheless, in the context of a severe pandemic caused by a novel virus, it is vital to address knowledge gaps in the field and identify factors that are potentially predictive of COVID-19 complications that warrant further investigation.

9 CONCLUSION

In order to improve health outcomes, the identification and validation of factors that predict COVID-19 disease progression is vital. Factors including age, comorbidities, immune response, radiographic findings, laboratory markers, and indicators of organ dysfunction may individually or collectively predict worse outcomes. However, the difficulty of predicting COVID-19 disease severity is underscored by the fact that SARS-CoV-2 appears to have tropism for diverse tissues including primarily the respiratory tract but also the brain, endothelium, heart, kidney, and liver.[7] Identification of factors that predict complications of COVID-19 is pivotal for guiding clinical care, improving patient outcomes, and allocating scarce resources.

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Abbreviations:

ALT	alanine aminotransferase
ACE2	angiotensin-converting enzyme 2
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC	area under the curve
AUROC	area under the receiver operating characteristic curve
BMI	body-mass index
CDC	Center for Disease Control and Prevention
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CT	computed tomography
CXR	chest x-ray
ED	emergency department

HbA1c	glycosylated hemoglobin
ICU	Intensive Care Unit
IFN-γ	interferon gamma
IL-6	Interleukin-6
IL-10	Interleukin-10
LDH	lactate dehydrogenase
MIS-C	multisystemic inflammatory syndrome in children and adolescents temporally related to COVID-19
NHS	National Health Service
OR	odds ratio
PaO_2/FiO_2	partial pressure of oxygen to fraction of inspired oxygen ratio
PEEP	positive end-expiratory pressure
PPE	personal protective equipment
SpO2	oxygen saturation
WHO	World Health Organization

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