Abstract

Since the first report on it in December 2019 in Wuhan, China, the novel coronavirus disease 2019 (COVID-19) has rapidly spread throughout the world. Due to the lack of effective therapy available for COVID-19 patients, the identification of risk factors for the severe course of the disease is a matter of urgency. Therefore, the aim of this review was to report on evidence-based risk factors affecting the severity and prognosis of COVID-19. We searched the PubMed database for current literature to identify relevant publications concerning risk factors for COVID-19 severity. Demographic and social factors (age, gender, race, in-center communities/nursing homes), clinical factors (smoking, hypertension, obesity, diabetes, chronic lung diseases, cardiovascular diseases — CVD, chronic kidney disease — CKD, malignancies, dementia, cardiomyopathies, immunocompromised state), laboratory markers (C-reactive protein — CRP, leukocytosis, ferritin, interleukin (IL)-6, D-dimer, lactate dehydrogenase — LDH, aspartate aminotransferase — AST, procalcitonin, creatinine, lymphopenia, IL-2, IL-7, IL-10, granulocyte colony-stimulating factor — G-CSF, also known as colony-stimulating factor 3 — CSF 3, interferon gamma-inducible protein-10 — IFN-10, monocyte chemoattractant protein-1 — MCP-1, macrophage inflammatory protein—1 alpha — MIP1A, tumor necrosis factor alpha — TNF-α), and genetic factors related to both the virus and the host were discussed. The identification of the potential risk factors affecting the severity and prognosis of COVID-19 may provide a chance for earlier and more effective management of COVID-19.

Key words: risk factors, severity, demographics, COVID-19, SARS-CoV-2
Introduction

Coronavirus disease 2019 (COVID-19) is a viral disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Currently, the outbreak of the COVID-19 pandemic has become a major clinical threat all over the world. The World Health Organization (WHO) declared the outbreak of COVID-19 as a worldwide pandemic in March 2020. Globally, as of November 19, 2020, there have been 55,928,327 confirmed cases of COVID-19, including 1,344,003 deaths, reported to WHO. Based on genomic and phylogenetic studies, SARS-CoV-2 might originate from bat coronaviruses, although its exact origin remains unknown.

The novel coronavirus is believed to be contagious during its incubation period, commonly observed as 3–7 days and being reported as up to 14 days. The transmission of SARS-CoV-2 from patients who have not yet developed symptoms has been reported in numerous studies. Coronavirus disease 2019 presents a wide variety of clinical manifestations. The most common symptoms of the disease which have been reported repeatedly include fever, cough, fatigue, muscle pain, headache, and dyspnea. Some other symptoms, such as diarrhea, expectoration, loss of taste and/or smell, hemoptysis, nasal obstruction, or runny nose, have been reported less frequently. Recently, the immune system has been recognized to play a critical role in providing preexisting immunity to SARS-CoV-2. Lymphopenia has been commonly observed in COVID-19, with levels more profound in more severe cases, while peripheral bilateral ground-glass opacity or consolidation in chest computed tomography (CT) scans have been reported as the most common radiological finding.

The spectrum of COVID-19 symptoms ranges from asymptomatic and mild symptomatic cases to a severe hyperinflammatory state, followed by acute respiratory distress syndrome (ARDS) and death. The severity of the disease has been categorized as mild, moderate, severe, and critical condition. Fortunately, up to 40% of SARS-CoV-2 infections may be asymptomatic, suggesting that some people could be protected from the disease. More than 80% of the infected patients present no more than mild symptoms, resembling a common cold with a dry cough, fatigue and fever. In mild cases, dyspnea, the clinical evidence of pneumonia and respiratory insufficiency have not been observed, while resting blood oxygen saturation (SpO2) remained usually above 93%. Patients with moderate disease suffer from fever, respiratory symptoms or pneumonia. In severe disease, dyspnea and hypoxemia occur, with the respiratory rate reaching 30 breaths/min or more and SpO2 ≤ 93% under resting conditions. In the most severe COVID-19 cases, ARDS, multiple organ dysfunction syndrome (MODS), shock, and coagulation abnormalities have been observed. Severe cases of COVID-19 presenting with respiratory failure require early and prolonged support with mechanical ventilation.

Risk factors for COVID-19 severity are complex and comprise demographic, clinical, laboratory, and genetic factors, concerning both the host and the virus variability. Until now, apart from symptomatic treatment, there is no evidence known for the effective causative therapy of COVID-19. Therefore, identifying the main risk factors affecting the severity and prognosis of COVID-19 seems to be of particular importance. Hence, the aim of this narrative review was to report on evidence-based risk factors affecting the severity and prognosis of COVID-19.

Methods

The authors searched the PubMed database to identify relevant publications published between January 2020 and November 2020, and presenting demographic, clinical, laboratory, and genetic COVID-19 risk factors. The following inclusion criteria were used: original and review articles that discussed risk factors for the severity and outcome of COVID-19; the availability of the full text of the article; and papers published in the English language.

Demographic, social and clinical factors

Numerous studies have demonstrated that elderly patients are more likely to experience severe COVID-19 manifestation than their younger counterparts. Older age (>65 years), male gender and obesity have been stated as the most common risk factors, with age reported so far as the strongest determinant of the severity of the disease. Also, social risk factors, typically conducive to social distancing, have been reported to be of great importance. Thus, the COVID-19 pandemic has affected a large proportion of nursing home residents, with higher prevalence in the in-center dialysis community. The Epidemiology Working Group for NCIP Epidemic Response has demonstrated comorbidities to be an important risk factor as well. Cardiovascular diseases (CVD), arterial hypertension (HTA), diabetes, chronic lung diseases, severe asthma, neoplasms, and chronic kidney disease (CKD), especially under dialysis treatment, have been reported to increase the risk of COVID-19 severity and morbidity. It has been recently reported that even a younger age of ≥60 years is associated with a major risk. Presumably, the age-related diminishing of the physiological activity of both respiratory and cardiovascular systems
provides a good explanation for the impaired clearance of pathogens.\textsuperscript{50,51} Taking into account the dysfunction of arterial endothelium, nitric oxide (NO) availability – the main intracellular antiviral defense – decreases significantly in the elderly.\textsuperscript{52} Zhou et al. showed that older age, the initial Sequential Organ Failure Assessment (SOFA) score >2, D-dimer >1 µg/1 mL, and the respiratory rate >24 breaths/min were independent risk factors for COVID-19 mortality in the Chinese population.\textsuperscript{53} Also dementia was described as associated with a higher mortality rate in a study of 16,749 patients hospitalized for COVID-19.\textsuperscript{54} Among symptoms, dyspnea has been recognized as an independent risk factor for the severity of the disease. Furthermore, a significant association between COVID-19 severity and the smoking status has been demonstrated.\textsuperscript{48,55}

Another significant risk factor for COVID-19 severity which has been noted is race. Black, South Asian and minority ethnic groups have been reported to be at higher risk of the poor outcome of COVID-19 as compared to Caucasians, even after the adjustment for other factors.\textsuperscript{43,56,57}

In an observation of 1,289 oncological patients with solid tumors, age and the use of corticosteroids before COVID-19 diagnosis, together with thoracic primary tumor site, were independently associated with COVID-19 severity.\textsuperscript{58} Except cytotoxic chemotherapy, associated with a slight increase in the risk of death, none of the anticancer drug protocols administered during the 3 months preceding COVID-19 had a significant effect on its mortality or severity. It is worth emphasizing that 39% of patients had their systemic anticancer treatment interrupted or stopped following COVID-19 diagnosis.\textsuperscript{59} According to the Center for Disease Control and Prevention (CDC), the most important risk factors for COVID-19 severity are cancer, CKD, chronic obstructive pulmonary disease (COPD), heart failure, coronary artery disease, cardiomyopathies, immunocompromised state from solid-organ transplant, obesity, Down syndrome, pregnancy, sickle-cell disease, smoking, and type 2 diabetes.\textsuperscript{59} Regarding the pathophysiological importance of endocrine-immune-vascular interactions for the clinical course of COVID-19, metabolic syndrome has also been suspected to increase the risk of the severe course of COVID-19.\textsuperscript{60} However, some data is inconsistent, which might be caused by the limited samples size or the presence of multiple confounding factors.\textsuperscript{61–63} In the Chinese population, hypertension, diabetes and CVD were independently associated with COVID-19 severity, which was confirmed in a recent meta-analysis.\textsuperscript{64} Despite initial controversies at the early stage of the pandemic, the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II type 1 receptor blockers (ARBs) could contribute to the improvement of COVID-19 outcome in hypertensive patients.\textsuperscript{65} Recently, a prospective observational cohort study based on the data collected in the Risk stratification in COVID-19 patients in the ICU (RISC-19-ICU) registry showed that the main mortality predictors in critically ill COVID-19 patients were oxygenation deficit, and renal and microvascular dysfunction, together with coagulatory activation.\textsuperscript{56}

The severity of COVID-19 might also be related to the amount of viral load, which has been observed to be higher in patients with severe COVID-19 than those with mild COVID-19.\textsuperscript{57}

### Laboratory risk factors

The monitoring of laboratory markers serves as a sensitive indicator of the severity of the disease, important for clinicians. Elevated levels of C-reactive protein (CRP), ferritin, interleukin (IL)-6, and plasma D-dimer are usually observed during infection. Hypercoagulability marked as elevated D-dimer concentration has been described to be indicative of poor COVID-19 prognosis.\textsuperscript{58,69} Recently, IL-6 has been identified as the key predictor of mortality in COVID-19.\textsuperscript{63} As SARS-CoV-2 originates from China, most of former studies regarding COVID-19 severity refer to the Chinese population. Huang et al. showed higher plasma levels of IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), interferon gamma-inducible protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1alpha (MIP1A), and tumor necrosis factor alpha (TNF-α) in COVID-19 intensive care units (ICU) patients.\textsuperscript{10} It has also been demonstrated that leukocytosis, high scores on the modified quick SOFA, an elevated serum level of aspartate aminotransferase (AST) (more than 3 times), and a serum level of creatinine of 2 mg/dL or more are markers of a significantly higher risk of ICU admission and mortality in COVID-19 patients.\textsuperscript{70} The neutrophil-to-lymphocyte ratio has also been reported to be one of the major predictors of COVID-19 severity.\textsuperscript{71}

A recent meta-analysis confirmed that reduced levels of lymphocytes and hemoglobin, elevated leukocytosis, AST, alanine aminotransferase (ALT), blood creatinine, blood urea nitrogen, high-sensitivity troponin, creatine kinase, high-sensitivity CRP, IL-6, D-dimer, ferritin, lactate dehydrogenase (LDH), and procalcitonin, and a high erythrocyte sedimentation rate were risk factors for severe COVID-19.\textsuperscript{72} In the Chinese population, total protein and albumin concentrations have also been identified as independent risk factors for severe disease.\textsuperscript{48} Lactate dehydrogenase and prealbumin have been demonstrated to be associated with the severity of the disease. The mortality risk is associated with age, LDH, CRP, D-dimer, and lymphopenia in patients with comorbidities.\textsuperscript{73,74} An independent association between glycated hemoglobin (HbA\textsubscript{1c}) and COVID-19 death rate has been also revealed.\textsuperscript{75–77}

Based on the secure health analytics platform which covers 40% of all patients in England (OpenSAFELY),
it has been shown that a HbA1c level of at least 58 mmol/mol is associated with a higher risk of COVID-19-related death. Recently, IP-10 and MCP-1 have been demonstrated to be novel biomarkers of COVID-19 severity, which may be related to the risk of patients’ death from COVID-19.

Genetic factors

SARS-CoV-2 genetic diversity

Coronaviruses are RNA viruses that belong to order Nidovirales, family Coronaviridae and subfamily Coronavirinae. The genome of one strain of SARS-CoV-2 is 29.9 kilo-bases (kb) in size, with 29,891 nucleotides encoding 9,860 amino acids. There are 2 types of SARS-CoV-2 (L and S), which are defined by means of 2 different single nucleotide polymorphisms (SNPs). In a study comparing SARS-CoV-2 genetic diversity in mild and severe cases, it was demonstrated that the consensus sequences of all viruses were very similar, showing more than 99.8% sequence identity, regardless of the severity of the disease. However, patients with severe symptoms exhibited a significantly higher number of variants in coding and non-coding regions as compared to mild cases, and it was concluded that within-host diversity might play a role in the development of severe disease outcomes in COVID-19 patients, particularly among the older ones. Shikov et al. demonstrated that several rare ACE2 variants, including rs146598386, rs73195521, rs755766792, and others, were likely to affect the outcome of COVID-19. Among the accessory SARS-CoV-2 proteins, ORF3a is the largest one, containing 274 amino acids. The potential role of ORF3a mutations in an elevated mortality rate for the SARS-CoV-2 infection through host immune evasion and immoderate cytokine storm has been recently shown. Majumdar and Niyogi revealed a decent association between SARS-CoV-2 ORF3a mutations and a higher mortality rate.

Human genetic diversity

Recently, ABO blood groups have been implicated in susceptibility to the SARS-CoV-2 infection. Blood group A has been found to be associated with a minimally increased risk of acquiring COVID-19 in comparison with non-A groups; moreover, blood group O has been associated with a minimally decreased risk of acquiring COVID-19 in comparison with non-O groups. The Rh(D) positive blood type was associated with the SARS-CoV-2 infection and death.

The renin-angiotensin-aldosterone system (RAAS) is of great importance in COVID-19, having considered the fact that angiotensin-converting enzyme 2 (ACE2) is the major receptor for SARS-CoV-2 on alveolar epithelial cells. Transmembrane protease serine 2 (TMPRSS2) – a molecule that is necessary for spike protein (S protein) priming – and ACE2 are expressed, except alveoli, also in blood vessels, olfactory epithelium, the brain, the heart, the kidneys, the bladder, and the intestine, thus explaining the varied symptoms observed in COVID-19 patients. Together with ACE2, TMPRSS2 and dipeptidyl peptidase-4 (DPP4) have been reported to play an important role in the severity of the disease. It has been established that SARS-CoV-2 uses the receptor ACE2 for entry and TMPRSS2 for S protein priming. The ACE2 or TMPRSS2 DNA polymorphisms are likely associated with genetic susceptibility to COVID-19.

The gene ApoE, located on 19q13.32, is one of the highly co-expressed genes in type II alveolar cells in the lungs, which has been investigated in regard to COVID-19 prognosis. Kuo et al. showed that the ApoE e4 genotype predicted severe COVID-19 in the UK Biobank cohort, independently of the pre-existing CVD, dementia and type 2 diabetes. Variations in human leukocyte antigen (HLA) have also been determined concerning the identification of individuals at higher risk of the disease. HLA-B*46:01 had the fewest predicted binding peptides for SARS-CoV-2, suggesting that individuals with this allele could be particularly vulnerable to COVID-19. Conversely, HLA-B*15:03 showed the greatest capacity to present highly conserved SARS-CoV-2 peptides, which are shared among common human coronaviruses. The 3p21.31 gene cluster has been identified as a genetic susceptibility locus in patients with COVID-19-dependent respiratory failure. The potential involvement of the ABO blood group system was confirmed in a study involving 1,980 patients with COVID-19 and a severe disease course, defined as respiratory failure.

Recently, there has been much interest in interferon (IFN) research in regard to the SARS-CoV-2 infection. Available data implicates the importance of type 1 IFN (IFN-1) signaling, including defects in IFN-1 gene expression in defense against the SARS-CoV-2 infection, and suggests that the inherited deleterious variants may explain the subset of severe COVID-19. Zhang et al. and Bastard et al. revealed mutations in genes that belong to the Toll-like receptor 3 (TLR3) and IFN-1 signaling pathways, leading to undetectable levels of interferon alpha (IFN-α) in blood plasma during coronavirus infection, thus linking the mutations to defective IFN-α production and COVID-19 severity. It has been shown that the degree of an increase of uracil in SARS-CoV-2 variants correlates with the enhanced production of TNF-α and IL-6 when compared with stimulation with the single-stranded RNA (ssRNA) sequence of the virus isolated in Wuhan. Thus, RNA editing has been stated a factor for mutation bias in SARS-CoV-2 variants, which could affect the production of host inflammatory cytokines and influence SARS-CoV-2 overreactivity.

The COVID-19 risk factors discussed in this paper are presented comprehensively in Table 1.
Conclusions
Coronaviruses, including SARS-CoV-2, are characterized by fewer gene mutations than other RNA viruses. Although differences in within-host diversity between mild and severe COVID-19 cases have been revealed, direct factors determining COVID-19 severity are not yet fully described. Therefore, the accurate evaluation of the role of SARS-CoV-2 variant-dependent and host-dependent risk factors for COVID-19 severity and fatality may help to identify potential drug target candidates for further study and bring hope for a breakthrough in COVID-19 treatment.

Table 1. Risk factors associated with coronavirus disease 2019 (COVID-19)

| Risk factors associated with coronavirus disease 2019 (COVID-19) |
|---------------------------------------------------------------|
| **Demographic and social**                                    |
| – older age                                                   |
| – male gender                                                 |
| – race (Black, South Asian, minority ethnic groups)           |
| – nursing home residents                                      |
| – in-center communities (dialysis)                            |
| **Clinical**                                                  |
| – obesity                                                     |
| – comorbidities (CVD, HTA, DM, COPD, asthma, CKD/dialysis, neoplasms, sickle-cell disease) |
| – immunocompromised state from solid-organ transplant         |
| – dementia                                                    |
| – smoking                                                     |
| – pregnancy                                                   |
| – initial SPOA score >2                                        |
| – dyspnea, respiratory rate >24 breaths/min                   |
| – high amount of viral load                                   |
| **Laboratory**                                                |
| – elevated classical markers (CRP, ferritin, IL-6, D-dimer, IL-2, IL-7, IL-10, G-CSF, TNF-α, creatinine, AST, ALT, blood urea nitrogen, troponin, creatine kinase, HB₄₋₄) |
| – elevated new markers (IP-10, MCP-1, MIP1A)                  |
| – leukocytosis                                                |
| – lymphopenia                                                 |
| – high neutrophil-to-lymphocyte ratio                        |
| **Human genetic**                                             |
| – ABO blood group                                             |
| – RH positive blood type                                      |
| – ACE, TMPRSS2, DPP4, APOE e4 gene polymorphisms              |
| – HLA variations                                              |
| – defects in IFN-I gene expression                            |
| **SARS-CoV-2 genetic**                                        |
| – within-host SARS-CoV-2 diversity                            |
| – RNA editing                                                 |
| – ACE2 variants (including rs146598386, rs73195521, rs755766792, etc.) |
| – ORF3a protein mutations                                     |

SARS-CoV-2 – severe acute respiratory syndrome coronavirus-2; CVD – cardiovascular diseases; HTA – arterial hypertension; DM – diabetes mellitus; COPD – chronic obstructive pulmonary disease; CKD – chronic kidney disease; SOFA – Sequential Organ Failure Assessment; CRP – C-reactive protein; IL – interleukin; G-CSF – granulocyte colony-stimulating factor; TNF-α – tumor necrosis factor alpha; AST – aspartate aminotransferase; ALT – alanine aminotransferase; HB₄₋₄ – glycated hemoglobin; IP-10 – interferon gamma-inducible protein-10; MCP-1 – monocyte chemoattractant protein-1; MIP1A – macrophage inflammatory protein-1alpha; ACE – angiotensin-converting enzyme; TMPRSS2 – transmembrane protease serine 2; DPP4 – dipeptidyl peptidase-4; HLA – human leukocyte antigen; IFN-I – type I interferon; ACE2 – angiotensin-converting enzyme 2.

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