Chapter 5
Prognosis in COVID-19 Patients: Statistics, Risk Factors

Bozena Sosnowska, Agata Bielecka-Dabrowa, and Maciej Banach

Introduction

In April 2022, the number of death due to COVID-19 is almost 6 million (despite it is predicted that it may be even 13–16 million excess deaths due to COVID-19) and fatality rate is 2%. Fatality rate of COVID-19 continues to change as the pandemic progress [1]. The disease course of COVID-19 varies greatly from asymptomatic infection to severe condition resulting in death [2]. The prognosis of most patients is good but approximately 20% of all COVID-19 patients develop severe or life-threatening complications [3]. The average time from SARS-CoV-2 exposure to symptom onset is 5 days [4–6]. According to data from China, an estimated 10–15% of mild cases progress to severe, and 15–20% of severe cases go on to become critical [3].

Identification of prognostic factors is important for reducing morbidity and mortality caused by the disease [2]. Due to limited antiviral treatment options for COVID-19, the severity of disease is closely related to the prognosis [7]. There is a significant difference between severe and non-severe patients with COVID-19 in

B. Sosnowska (✉) · M. Banach
Department of Preventive Cardiology and Lipidology, Medical University of Lodz (MUL), Łódź, Poland
e-mail: bozena.sosnowska@umed.lodz.pl; maciej.banach@umed.lodz.pl; maciej.banach@iczmp.edu.pl

A. Bielecka-Dabrowa
Department of Preventive Cardiology and Lipidology, Medical University of Lodz (MUL), Łódź, Poland

Department of Cardiology and Adult Congenital Heart Diseases, Polish Mother's Memorial Hospital Research Institute (PMMHRI), Łódź, Poland

M. Banach (ed.), *Cardiovascular Complications of COVID-19*, Contemporary Cardiology, https://doi.org/10.1007/978-3-031-15478-2_5

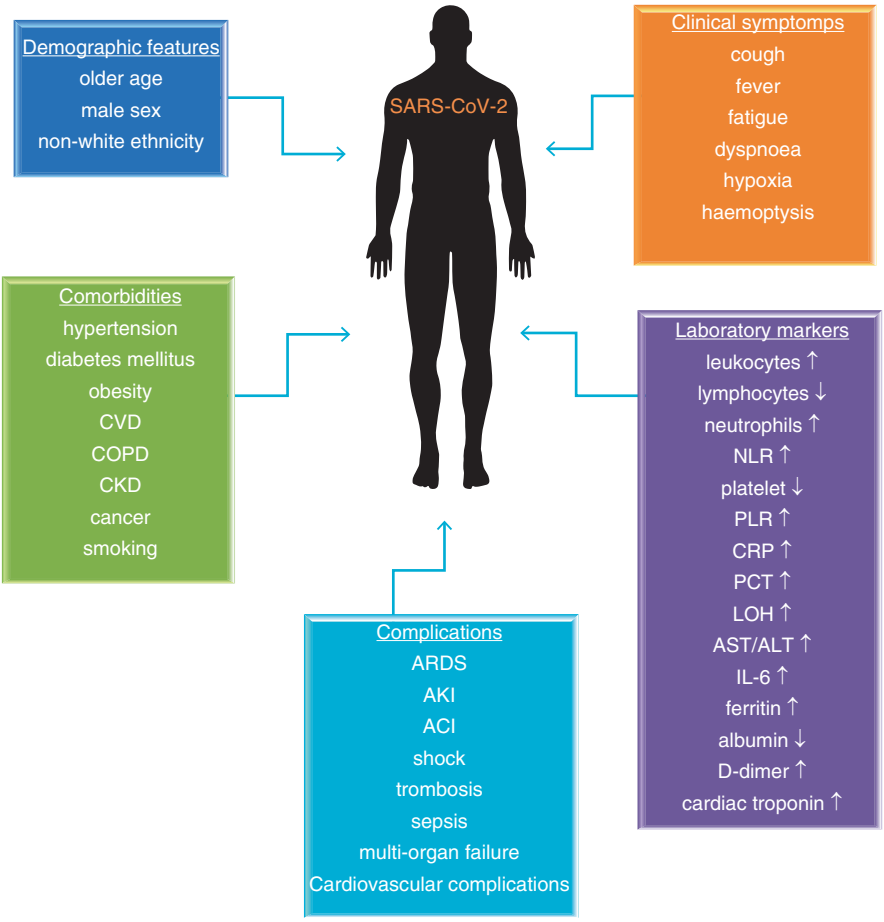

Fig. 5.1 Risk factors associated with the prognosis in COVID-19 patients. *CVD* cardiovascular disease, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *ARDS* acute respiratory distress syndrome, *AKI* acute kidney injury, *ACI* acute cardiac injury, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *CRP* C-reactive protein, *PCT* procalcitonin, *LDH* lactate dehydrogenase, *AST* Aminotransferase, *ALT* alanine aminotransferase, *IL-6* Interleukin 6

terms of demographic features, clinical symptoms, comorbidities, laboratory parameters, complications, and outcomes [8–10]. The most important factors influencing the prognosis of patients with COVID-19 are discussed below and summarized in Fig. 5.1.

Demographic Features

Age and Sex

COVID-19 causes infection in all age groups, although severe disease is more common in older adults [9]. Older age (>65) is closely associated with the worse prognosis of COVID-19 [7, 11]. The median age of hospitalized patients varies between 49 and 70 years and from 66 to 77 for fatal cases [12–18]. COVID-19 associated hospitalization by age is shown in Fig. 5.2.

It was found that older age is significantly associated with the disease severity and endpoints including death, admission to intensive care unit (ICU), acute respiratory distress syndrome (ARDS), invasive ventilation, and cardiac abnormality [7, 19]. Increased age in patients with COVID-19 is the strongest predictor of death [20]. Elderly patients were more than twice as likely to have severe or critical illness when compared with middle-aged patients [21].

Moreover, it was indicated that ARDS, multiple organ failure, and death are more often in older subjects with pre-existing diseases including diabetes, hypertension, and cardiovascular disease. Reason for poor prognosis for elderly patients is probably associated with a higher frequency of comorbidities or/and age-related immune dysfunction resulting from low-grade chronic inflammation [8].

At advanced age, there is an increased risk of death for both sexes, but at all ages above 30 years males have a significantly higher risk of death than females [22]. The Global Health 50/50 research initiative, which presents an overview of sex-disaggregated data from countries worldwide, indicated that despite similar numbers of COVID-19 cases in men and women there is an increased case fatality rate in men [23]. Some studies indicated that up to 90% of severe cases were men [24].

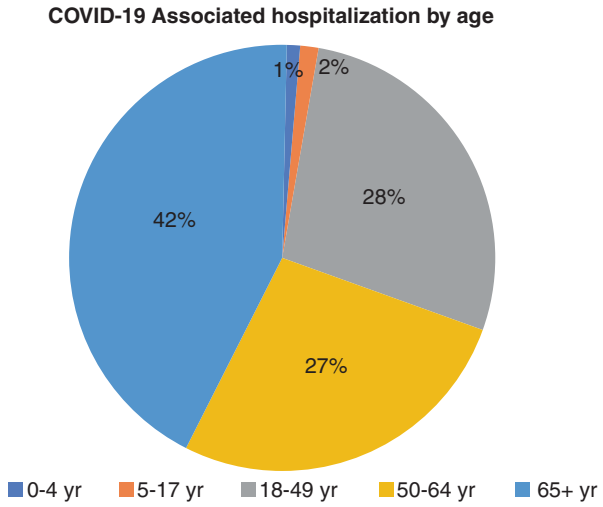

Fig. 5.2 COVID-19 associated hospitalization by age, preliminary data as of 02 APR 2022 (COVID-NET). (Based on the data from [64])

Large-scale meta-analysis of more than 3 million global cases showed that male patients have almost three times the odds of requiring intensive care unit admission and higher odds of death compared to females [25]. ICU mortality in female COVID-19 patients was lower than in male patients (27% vs. 39% respectively), independent of age, disease severity, smoking, obesity, comorbidities, anti-infection/inflammatory therapy, and country [26]. Males had higher risk of reaching severe disease and adverse prognostic endpoints including death, ARDS, admission to ICU, invasive ventilation, and cardiac abnormality [19].

The cause of worse prognosis and death in males compared to females is probably associated with the protection of the X chromosome and sex hormones, which play an essential role in innate and acquired immunity [27, 28]. The greater predisposition of men to become infected with COVID-19 may result from differences in the levels of cell receptors (angiotensin converting enzyme) and molecules that assist the entry of SARS-CoV-2 through the fusion of the virus with the cell membrane (transmembrane serine protease 2) [29].

Ethnicity

Ethnic and race differences among COVID-19 patients' hospitalizations and mortality have been widely reported. African-Caribbean (Black), Latin, and South Asian origin experience grater hospitalization and mortality from COVID-19 than white individuals [30, 31]. Single-site studies revealed that Black people were 1.7 to 2. times more likely to be hospitalized due to COVID-19 than White or other racial and ethnic minority groups [32, 33].

Meta-analysis of 45 articles indicated that race may be associated with COVID-19 outcomes because of the increased occurrence of comorbidities in racial and ethnic minority groups but did not confirmed ethnicity as an independent poor prognostic factor for COVID-19 [34]. However, this study did not analyze the role of socioeconomic determinants, which disproportionately affect racial and ethnic minority populations [35].

Ethnicities other than White were associated with higher COVID-19-related mortality in type 1 and type 2 diabetes [36]. It was found that comorbidities and socioeconomic status only partly contributed to greater admission risk of COVID-19 in Black and mixed ethnicity [37]. Asian patients had a higher risk of experiencing greater COVID-19 cardiorespiratory disease severity than non-Hispanic White patients [38]. Retrospective cohort study of more than one million of individuals, representing diverse racial and ethnic minority groups indicated that an increase incidence of severe COVID-19 among Black/African American and Hispanic individuals is due to higher infection rates, not increased susceptibility to the severe course of disease [39]. The authors concluded that the differences associated with COVID-19 among patients of different races are most likely due to social, not biological, factors [39].

Clinical Symptoms

COVID-19 infection is now recognized as a multisystem disease, causing a wide range of clinical manifestations [40]. Approximately 80% of all SARS-CoV-2 infected patients are asymptomatic or develop symptoms characteristic of mild or moderate pneumonia [41]. Approximately 15% of COVID-19 patients develop severe condition with viral pneumonia with the need of hospitalization. Only about 5% of cases develop critical illness, presenting acute respiratory distress syndrome, all types of shock or multiple organ failure, and require mechanical ventilation or admission to ICU; approximately 2% of cases are fatal [3, 42].

The most common clinical symptoms are fever, cough, dyspnea, fatigue, malaise, and sputum production [8, 43, 44]. Meta-analysis of 45 studies with 4203 patients indicated that the most common clinical symptoms are fever, cough, and dyspnea (80.5%, 58.3%, and 23.8%, respectively) [45]. Early recognition of severe infection may allow early medical intervention and improve outcomes in patients with COVID-19 [7].

Another meta-analysis of 20 studies and in 3326 patients with COVID-19 indicated that some initial symptoms including abdominal pain, dyspnea, hemoptysis, anorexia, diarrhea, fatigue, expectoration, fever, and cough occurred more frequently in severe COVID-19 patients than in mild COVID-19 patients [46]. Recent study indicated that clinical symptoms associated with critical illness were dyspnea, hypoxia, and hemoptysis [47]. Meta-analysis of 26 studies involving 7274 COVID-19 patients indicated that non-survivors in compering to survivors were more likely to present with dyspnea (66% vs. 34%), hemoptysis (4% vs. 3%), chest tightness (46% vs. 30%), expectoration (42% vs. 32%), and fatigue (50% vs. 44%). Moreover, dyspnea, hemoptysis, expectoration, chest tightness, fatigue, and sputum production were found to be significant risk factors of mortality [10, 48].

Patients with dyspnea were six times more likely to have an ICU admission and were more likely to die compared to those without dyspnea [43] what might relate to the fact that dyspnea is more common in COVID-19 patients with ≥2 comorbidities than in those with one comorbidity [49]. Dyspnea and hypoxemia may be developed in severe ill patients within 1 week after onset of the disease and may quickly progress to acute respiratory distress syndrome or end-organ failure [14].

Hypoxemia is an independent prognostic factor for the severe course of COVID-19 [50] and is associated with in-hospital mortality [51]. The study of Huang et al. indicated that 32% of COVID-19 patients showed varying degrees of hypoxemia [12]. The most serious manifestation is worsening arterial hypoxemia, eventually leading to acute respiratory distress syndrome promptly needing mechanical ventilation [3, 49]. Patients with fever had a higher risk of the worse course of COVID-19, mechanical ventilation, and mortality than those without fever [52–54]. Fever greater than 38.5 °C on admission was positively correlated with the severity and mortality of COVID-19 [55].

It was reported that the duration of fever was associated with the prognosis. The time from admission to a normal temperature was 7 days for patients with severe

disease and 2 days for patients with mild disease [56]. Although respiratory manifestations are the most common, studies have reported that gastrointestinal symptoms including diarrhea, nausea/vomiting, and abdominal pain, are also frequent in patients with COVID-19, with a prevalence of up to 30% [57, 58]. It was indicated that gastrointestinal symptoms were strongly associated with severe COVID-19 disease and might be associated with the prognosis with COVID-19 [59–61]. Meta-analysis of 35 studies, including 6686 patients found that gastrointestinal symptoms were a significant risk factor for disease severity [61]. However, last meta-analysis including 53 studies and 55,245 COVID-19 patients found that gastrointestinal symptoms were not associated with higher mortality so the prognostic value of these symptoms in COVID-19 requires further investigation [62]. The prognostic value of gastrointestinal symptoms in COVID-19 might not be as significant as other factors such as age, concomitant diseases, and respiratory manifestations.

Comorbidities and the Course of COVID-19

The presence of comorbidities influences the prognosis and prolongs the recovery time. Individuals with underlying chronic disease have greater risk for severe course of COVID-19 and death [63]. Underlying comorbidities in COVID-19 patients were shown in Fig. 5.3 [64]. The most prevalent affecting the course of the COVID-19 disease and prognosis are hypertension, cardiovascular disease (CVD), diabetes mellitus, and respiratory diseases [8–10, 45, 65]. Recent systemic review including ten studies and 3912 participants indicated hypertension as the most common disease linked with the severe COVID-19 (59.3%), followed by obesity (48.7%),

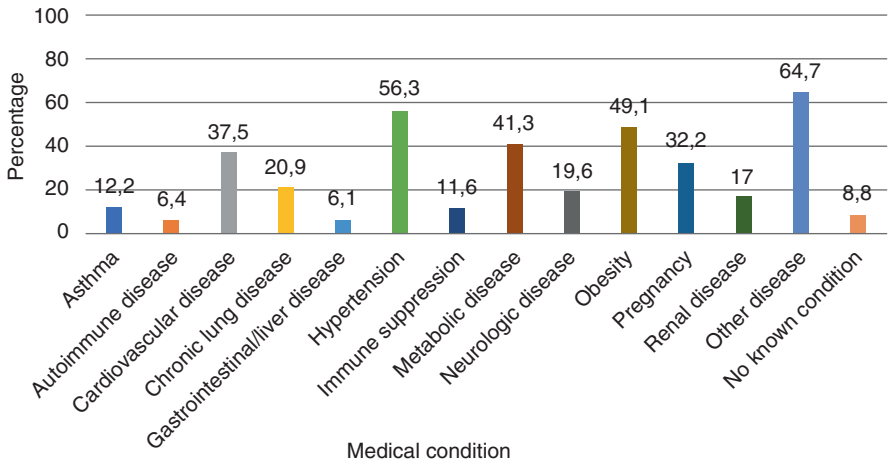

Fig. 5.3 Underlying comorbidities in COVID-19 patients (COVID-NET). Hospitalization data (March 2020–July 2021). (Based on the data from [64])

chronic lung disease (19.8%), metabolic disease (43.6%), and CVD (35.6%) [66]. Study by Hatmi et al. suggested that among comorbidities in COVID-19 patients the most powerful prognostic factors for mortality rate were pre-existing CVD, diabetes mellitus, respiratory disease, and hypertension. Whereas the most important prognostic factors for severity of COVID-19 were CVD and hypertension [3, 65, 67].

COVID-19 itself also may induced cardiovascular complications such as myocardial injury, myocarditis, arrhythmias, acute coronary syndrome, and venous thromboembolism [66–71]. It was indicated that even small amounts of myocardial injury were associated with an increased risk of patient mortality [68]. Meta-analysis of 17 studies with a total of 5815 patients revealed that the most common cardiovascular complications in COVID-19 patients were heart failure, myocardial injury, cardiac arrhythmia, and acute coronary syndrome [69].

Evaluation of the early development of persistent myocardial injury is a useful prognostic tool in patients with severe COVID-19 [72]. Cardiovascular risk factors such as hypertension, diabetes mellitus, and obesity were associated with ICU admission and poor prognosis [66]. Interestingly that lipid disorders are not associated with the severe course of the disease, in opposite in patients in acute phase reduced cholesterol level is observed.

Hypertension

Hypertension is thought to be an independent risk factor for severe COVID-19 and a strong predictor of poor prognosis including ARDS, ICU admission and mortality [73, 74]. Hypertension is found to be the most common comorbidity in COVID-19 patient. Individual studies have shown that the prevalence of hypertension in fatal cases is from 39% to 65% [16–18, 75]. A systematic review indicated that COVID-19 patients with hypertension were two times more likely to require ICU admission and 1.7 times more likely to have more severe disease [74]. In a retrospective study of 803 COVID-19 patients with hypertension, high mean systolic blood pressure, and high variability of systolic / diastolic blood pressure during hospitalization were independently associated with mortality, ICU admission, and heart failure [76]. The prognosis for patients with hypertension is markedly worse when SARS-Cov-2 infection was complicated by myocardial injury and in the presence of CVD [77].

Diabetes Mellitus

Diabetes as a common underlying disease in COVID-19 patients is associated with worse prognosis [12, 78–88]. Diabetes in hospitalized patients with COVID-19 was reported in 3–25% of non-critical [80, 81] and in 15–31% of critical cases [7, 80, 81]. COVID-19 patients with diabetes mellitus have high risk of severe disease, ARDS, shock, multi-organ failure, death, and ICU admissions [80–83]. Recent

meta-analysis with 344,431 COVID-19 patients indicated that the proportion of patients with diabetes was dramatically higher in the severe or non-survival group then in controls. Patients with diabetes had a 3.55-fold higher risk of progression of COVID-19 and 3.83-fold higher risk of mortality compared with those without diabetes [10]. Newly diagnosed diabetes was associated with higher mortality than known diabetes in hospitalized COVID-19 patients [84, 85]. Well-controlled diabetes correlated with a reduced risk of detrimental complications and all-cause mortality in subjects with COVID-19 and pre-existing diabetes [88].

Obesity

Obesity may also be a prognostic factor for severity of COVID-19 and fatal outcomes [89–91]. A meta-analysis of 208 studies and total of more than three million participants from over 32 countries revealed that overweight increased the risk of COVID-19-related hospitalizations but not death while obesity and extreme obesity increase the risk of both hospitalizations and death [92]. In the recent meta-analysis of ten observational studies with 10,233 COVID-19 patients the prevalence of obesity in persons with poor outcomes was 34% [93]. Patients with body mass index (BMI) >35 kg/m^2 need seven times more often the use of mechanical ventilation compared [94]. Moreover, BMI >40 kg/m^2 was found as an independent risk factor associated with mortality, more prominent in patients younger than 50 years [95].

Chronic Obstructive Pulmonary Disease (COPD)

Nationwide population study with 4610 patients indicated that COPD patients had higher risk of ICU care and mechanical ventilation than patients without COPD and the risk for all-cause mortality was approximately two times higher in patients with COPD than in those without [96]. The prevalence of COPD among COVID-19 patients ranges from 0 to 10% worldwide, but most reports are from China [49, 97, 98]. In Europe, the prevalence of COPD is 5.6–11% [99–102]. Progression to severe course of COVID-19 in COPD patients has ranged from 20 to 50% [49, 103, 104]. Mortality with COVID-19 and COPD is also lower compering to other major comorbidities (CVD, diabetes); whereas risk severity seems to be comparable (3–4 folds) [105, 106].

Chronic Kidney Disease

Chronic kidney disease (CKD) is one of the factors that significantly impact COVID-19 patients' prognosis, and influence on the disease severity [106, 107]. Prevalence of CKD in patients with COVID-19 ranged from 0.4 to 49% [108]. Data

on mortality in patients with COVID-19 and CKD are limited and varying from 16% to 53% [109, 110]. Recent review indicated that patients with CKD are more likely to have worse outcomes from COVID-19 compared to individuals without CKD [108]. More advanced CKD relates to higher risk of COVID-19 severity, hospitalization, and mortality [108].

Cancer

The prevalence of cancer among COVID-19 patients range from 0.29% to 2.6% [106, 111–113] and, mortality is estimated from 5% to 8.3% [106, 111] and research results regarding the prognostic significance of cancers in COVID 19 patients are inconclusive. Some studies have found comparable mortality rates between patients with cancer and those without cancer after adjusting for age and comorbidities [114, 115]. Recent large electronic health record based on US study reported higher rates of death among patients with COVID-19 and cancer compared to those without (14.9% vs. 5.26%) [112]. Studies regarding influence of cancer treatment for outcomes in COVID-19 patients are inconsistent [111, 116–118].

Recently published large cohort study indicated that patients with recent cancer treatment and COVID-19 had a significantly higher risk of adverse outcomes, and subjects with no recent chemotherapy and chemoimmunotherapy had similar risk of mortality and ICU stay and a lower risk of mechanical ventilation and hospitalization compared with COVID-19 patients without cancer [119]. It was also found that patients with metastatic solid tumors and hematologic malignant neoplasms had worse outcomes compared with patients with nonmetastatic solid tumors [119].

Special Conditions and Populations of Patients and the COVID-19 Course

Smoking

Smoking history is a high-risk factor for severe course and mortality among patients hospitalized for COVID-19 [65, 120]. Recent meta-analysis of 47 studies with a total of 32,849 hospitalized COVID-19 patients indicated that current smokers have an increased risk of admitting to hospital with severe COVID-19 and are approximately twice as likely to develop severe or critical COVID-19 as former or never-smokers [121]. Authors suspected that smokers are exposed to higher SARS-CoV-2 loads due to elevated expression of angiotensin converting enzyme 2 (ACE2), which may provide a mechanistic explanation for the higher risk of severe disease and mortality in smoking patients with COVID-19 [121, 122].

Mendelian randomization analyses of 281,105 White British subjects showed that genetically predicted propensity to initiate smoking was associated with 45% higher risks of SARS-CoV-2 infection (OR 1.45, 95% CI: 1.10 to 1.91) and 60% higher risk of hospitalization (OR 1.60, 95% CI: 1.13 to 2.27). Genetically predicted increase in number of cigarettes smoked per day was associated with higher risks of infection, hospitalization, and death [120].

Pregnancy

Physiological changes in the immune and respiratory systems during pregnancy may make pregnant women more susceptible to COVID-19 infection. Especially the first trimester of pregnancy may be the period most susceptible to SARS-CoV-2 infection due to early ACE2 expression associated with placental immaturity [123, 124]. Pregnant women with SARS-CoV-2 infection are at increased risk of ICU admission, mechanical ventilation, and death compared with both pregnant women without COVID-19 and nonpregnant individuals with COVID-19 [125–128]. Retrospective cohort study with 14,104 patients indicated that a composite outcome of maternal death or serious morbidity associated with hypertension in pregnancy, postpartum hemorrhage, or infection other than SARS-CoV-2 occurred significantly more common in women with COVID-19 compared with individuals without COVID-19 [129].

Children

Children can be infected as easily as adults but are more often asymptomatic and have milder course of disease due to their immature immune systems [130]. A small percentage (<7%) of children admitted to the hospital for COVID-19 develop severe disease requiring mechanical ventilation [131]. The risks factors for the infection of SARS-CoV-2 and the severity of disease are children age and comorbidities [131]. Young infants and older adolescents had higher risk of developing severe disease [131, 132]. Additionally, older children may develop multisystem inflammatory syndrome (MIS-C) with severe disease [133]. This multisystem inflammatory syndrome in children is uncommon (2 in 100,000 persons aged <21 years) [134].

Selected Laboratory Parameters Values and the COVID-19 Course

Leukocyte Counts

Elevated leukocyte count ($\geq 9.5 \times 10^9$/L) is associated with course of COVID-19 disease [14, 49]. Leukocytosis was observed in 28.1% to 68.1% of patients, depending on the severity of the disease and comorbidities [135–138]. Patients with severe and

fatal COVID-19 had significantly increased leukocyte count compared to non-severe disease and survivors [49, 139, 140]. Leukocyte counts were found to be a prognostic marker in diagnosis of progression to serious or severe disease in COVID-19 patients [141]. A meta-analysis of 45 studies identified that elevated leukocyte predicted ICU admission and mortality [45]. Another meta-analysis on 21 studies including 3377 patients indicated that patients with severe disease had a mild increased in leukocyte level (WMD: 0.41×10^9/L), while patients who died had higher level of this parameter (WMD: 4.15×10^9/L) [139]. Meat-analysis of 13 studies with 3027 participants indicated that white blood cells (WBC) $< 4 \times 10^9$/L predicted better clinical status in COVID-19 patients [9]. Myari et al. assessed that WBC belong to one of the most efficient indicators of critical disease [142]. Current evidence suggests that although leukocyte counts can be used as a predictor factor for severe COVID-19 condition, however, other factors should be also taken into account [143].

Lymphocyte Counts

Decreased level of lymphocytes is one of the typical characteristics of SARS-CoV-2 infection, which is associated with poor outcomes [144]. Lymphopenia was observed in up to 96.1% of severe COVID-19 patients, and its degrees correlate with the intensity of proinflammatory cytokine storm, disease severity, and outcome [7, 145–147]. A meta-analysis of 28 studies involving 6449 COVID-19 patients demonstrated that lymphopenia (<1500 lymphocytes/μL) had nearly threefold higher risk of poor outcomes compared with better outcomes [148]. Study on peripheral lymphocyte subset alteration in COVID-19 indicated that severe ill patients had lower total lymphocytes CD4+ T cells, CD8+ T cells, and B cells in compering to patients with mild illness. CD8+ T cells were found to be a potential predictor of COVID-19 severity [149].

Decrease of T-lymphocyte subsets was associated with in-hospital death and severe course of COVID-19. Lower counts of T lymphocyte subsets; lymphocyte (<500/μL), CD3 +T-cell (<200/μL), CD4+ T-cell (<100/μL), CD8+ T-cell (<100/μL), and B-cell (<50/μL) were linked to higher risk of in-hospital death. The alarming values that can predict in-hospital death of lymphocyte, CD3+ T-cell, CD4+ T-cell, CD8+ T-cell, and B-cell were 559/μL, 235/μL, 104/μL, 85/μL, and 82/μL, respectively [150].

Neutrophil Counts

Neutrophil count was found to be a prognostic marker in diagnosis of progression to severe and critical disease in COVID-19 patients [141, 142]. Meta-analysis of 34 studies and 344,431 participants revealed that increased neutrophil count is significantly higher in the severe group than in the non-severe [10]. Neutrophilia was found to be associated with both ARDS development and progression to death [54].

A meta-analysis of 6320 patients found that neutrophil counts identified severe patients with 100% sensitivity and 81% specificity at a cut-off value of $>3.74 \times 10^9$/L [141]. It was found that neutrophil-to-lymphocyte ratio (NLR) is one of the powerful prognostic factors of an early identification of severe COVID-19 [152]. Increase in NLR is commonly observed in COVID-19 patients and is associated with poor clinical outcomes [146, 153].

A scoping review of 529 studies involving 165,020 patients from 28 different countries investigating the correlation between initial laboratory values with mortality and disease severity in COVID-19 indicated that among many reported laboratory values, NLR was the most frequent statistically significant laboratory parameter in predicting disease severity [154].

Study of Liu et al. reported that NLR could be an independent predictor of mortality and the risk of in-hospital mortality was higher by 8% for each unit increase in NLR. This risk was independent of other risk factors of death such as older age, comorbidities, and high level of D-dimer [140, 152]. The cut-off value of NLR (7.4) allowed predicting mortality with high accuracy [155]. Another study revealed that high NLR (≥10) and D-dimer (≥2.0 μg/mL), especially when combined, are strong predictors of death risk for patients with severe COVID-19 [156]. NLR is not only important to stratify the severity of the disease, but also to predict mortality in severe cases [156].

Platelet Counts

Low platelet counts were commonly observed in SARS-CoV-2 infections, it can be detected in almost half of the COVID-19 patients and in almost 95% of those critically ill [10, 157]. Thrombocytopenia usually occurs more than 10 days after the onset of symptoms [150]. The meta-analysis of Zong et al. revealed the association between thrombocytopenia and three-fold enhanced risk of a composite outcome of ICU admission, progression to ARDS, and mortality [158]. Several other studies confirmed that low platelets counts may be predictive markers of the severity of COVID-19 [159, 160]. It was found that platelet count is an independent risk factor of mortality among COVID-19 patients, where a 50×10^9/L increase is associated with 40% decreased mortality [148, 161]. Some authors suggested the value of 150×10^9/L as a cut-off level for platelet count to predict poor prognosis [151]. Among the most common hematologic parameters with evidenced prognostic value in diagnosis of progression to serious or severe disease in COVID-19 patients belongs also platelet-to-lymphocyte ratio (PLR) [162, 163]. Systematic review reported that an elevated PLR is associated with severe illness in COVID-19 patients compering to those with mild disease however cut-off levels for this parameter differ significantly in studies [162, 164–166]. Recent systemic review and meta-analysis revealed that elevated level of PLR on admission in COVID-19 patients is associated with higher morbidity and mortality but further studies regarding the cut-off value of PLR are needed [167].

C-Reactive Protein (CRP)

C-reactive protein after lymphopenia is the most frequently described prognostic biomarker in COVID-19 [148, 168–170]. Meta-analysis of 20 studies including 4843 COVID-19 patients, indicated that elevated CRP (>10 mg/L) is associated with nearly fourfold higher risk of poor outcomes [148]. Another study found that median concentration of CRP was nearly ten-fold higher in critically ill patients compering to mildly ill patients [171]. A study of 1834 COVID-19 patients from Italy and the United Kingdom showed that CRP levels ≥40.0 mg/L were associated with 31.9% mortality, whereas mortality in patients with CRP levels <40.0 mg/L was 15% [172]. High levels of CRP are prognostic markers of disease progression and a risk factor for mortality of severe COVID-19 patients and are indicators of a developing cytokine storm [168–175].

Procalcitonin (PCT)

Procalcitonin is a promising prognostic biomarker of COVID-19 progression [176]. Patients with increased procalcitonin levels are at high risk of progression to critical illness [9]. Increased PCT values are associated with a nearly five-fold higher risk of severe COVID-19 and may have been a marker of bacterial coinfection, thereby resulting in complications of COVID-19 and hence a higher rate of ICU admission in these patients [171, 177]. Single study of Hu et al. indicated that serial PCT measurements may be helpful in predicting the prognosis [178]. The cut-off value of 0.16 ng/mL for PCT predicted mortality with high accuracy [155].

Lactate Dehydrogenase (LDH)

Meta-analysis of 18 studies with 5394 patients showed that elevated LDH values are associated with approximately fivefold more risk of poor outcomes in COVID 19 patients [148]. Similarly study of Henry et al. indicated that elevated LDH levels were associated with six-fold increase odds of severe disease and a 16-fold increase in odds of mortality in COVID-19 patients [139]. A meta-analysis of 45 studies identified that elevated LDH predicted mortality and was the only laboratory parameter which predicted both ARDS and ICU admission [45]. Another meta-analysis of 10,399 patients from 21 studies indicated that the association between LDH elevation and poor prognosis was not affected by age, gender, hypertension, or diabetes [179]. The value of 280 U/L is suggested as a cut-off level for LDH to predict poor prognosis [151]. Moreover, LDH levels >400 U/L on admission to the hospital were independently associated with the severity of the disease, so measuring the LDH value at the beginning of the infection may be a biomarker of severe and critical course of COVID-19 [180].

Interleukin 6 (IL-6)

Interleukin 6 may be increased in COVID-19 patients, and it was indicated as an important marker of disease severity and predictor of mortality [181], and its expression time is longer than other cytokines (TNF and IL-1) [182]. Increased IL-6 was recorded in 87% of severe cases [50]. When identifying patients at high risk for severe COVID-19, a cut-off value for IL-6 greater than 55 pg/mL was indicated. Critically ill patients have significantly higher IL-6 levels compared with moderate and severe patients. IL-6 > 80 pg/mL predicts respiratory failure and need for mechanical ventilation [175] and value of ≥100 pg/mL was associated with mortality in COVID-19 [183, 184]. The concentration of IL-6 > 24 pg/mL at initial assessment predicted the development of hypoxemia requiring hospitalization [185]. The currently accepted theory is that overexpression of IL-6 has a crucial role in the induction and propagation of cytokine storm leading to lung injury and ARDS [186–189].

D-Dimer

D-dimer levels are associated with COVID-19 severity and in-hospital mortality [190]. Elevated D-dimer levels are common in patients with COVID-19, suggest extensive thrombin generation and fibrinolysis and are revealed almost three-fold higher risk of poor outcomes [148, 191, 192]. Meta-analysis of six studies indicated that COVID-19 patients with elevated D-dimers have worse clinical outcomes including all-cause mortality, ICU admission, and acute respiratory distress syndrome [193]. D-dimer level that could predict worse prognosis in COIVD-19 patients varies in literatures between >1 mg/L and >2.14 mg/L [7, 194]. It was proposed that a level of >2.0 mg/L on admission could predict death [194, 195]. COVID-19 patients with high D-dimer levels have longer hospitalizations in ICU and lengths of hospital stay [7]. Monitoring the dynamic changes of D-dimer is a useful marker in predicting the prognosis of COVID-19 patients, and peak D-dimer levels were strongly associated with mortality [196].

Ferritin

Elevated levels of serum ferritin were associated with the development of severe outcomes and mortality in COVID-19. Serum ferritin was proposed as one of the markers for potential progression to critical illness [139]. A single study of 141 patients with COVID-19 indicated that elevated ferritin (>500 μg/L) was observed in all severe patients on admission, and the mild patients had a normal mean serum ferritin level; moreover, severe patients and patients who needed admission to the

ICU had higher ferritin levels than the mild patients (2.6 times and 5.8 times, respectively) [197]. It was showed that each 0.1 mg/L increase of ferritin was associated with 3% shortened ICU survival time [198]. Serum ferritin levels were reported to be significantly increased in non-survivors vs. survivors (WMD: 760.2 ng/mL) and as compared to severe vs. non-severe disease (WMD: 408.3 ng/mL) and were suggested as a parameter to be used for monitoring prognosis in COVID-19 patients over the course of hospitalization [193]. Non-survivors showed ferritin levels on admission around 1400 ng/mL, which is between 3 and 4 times higher than that observed in survivors [199]. Meta-analyses revealed that high ferritin levels were associated with severe COVID-19 mortality and development of ARDS as well as with thrombotic complications [200, 201].

Albumin

Albumin levels were found to be a predictive biomarker for outcomes in COVID-19 patients [202–204]. Decreased levels of albumin are among the most common abnormal laboratory findings in COVID-19 patients [151]. Low serum albumin concentrations in critical illness have been associated with poor outcomes. Hypoalbuminemia (<3.5 g/dL) is present in 74% of patients with severe COVID-19 [205]. It was found that hypoalbuminemia was an independent predictor for mortality in COVID-19 patients [206, 207]. Similarly, a multicenter retrospective cohort study of 1555 COVID-19 patients indicated that low serum albumin levels on admission were associated with a higher risk of all-cause mortality within 30 days of hospitalization. Albumin levels below 2.5 g/dL were associated with an almost 60% higher <30 days in-hospital all-cause mortality [208]. Patients with higher albumin levels on admission had a 72% decreased risk of developing venous thromboembolism for every 1 g/dL increase of albumin. Moreover, higher albumin levels on admission were associated with a lower risk of developing ARDS, admission to the ICU and fewer total adverse events [209].

Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT)

Meta-analysis of 18 studies with 6,383 patients reported that elevated AST (>40 IU/L) values are associated with nearly threefold higher risk of poor outcomes in COVID-19 patients [148]. Similarly, elevated ALT (>40 IU/L) were associated with twofold increased likelihood of poor outcomes [148]. Patients with abnormal liver enzyme tests at the time of admission had a higher rate of transfer to the ICU (20% vs. 8%), need for mechanical ventilation (14% vs. 6%), acute kidney injury (22% vs. 13%), and mortality (21% vs. 11%) compared to patients with normal

results [210]. In contrary, Huang et al. did not find any difference in AST and ALT values between severe and no severe cases [12]. Similarly, studies of Aloiso et al. did not confirm prognostic values of ALT in COVID-19 patients [202, 211]. Thus, the role of liver enzymes as prognostic biomarkers is debatable and probably have minimal clinical significance [212].

Cardiac Troponin

Troponin is one of the biomarkers of cardiac injury. In the study of Shi et al. elevation of cardiac troponin I (cTnI) > 28 pg/mL was an independent risk factor for COVID-19 severity and mortality [213]. Elevated troponin levels were rare in COVID-19 patients with a mild course (1–20%), common in severe patients (46–100%), and frequent in the critically ill and fatal outcomes [213–215]. Patients with underlying CVD and increased troponin levels had the higher mortality almost 70% compared to patients with only one of these two risk factors [82].

Elevated levels of cTnI remain an independent predictor of death compering to other elevated acute phase proteins and inflammatory markers in patients with CVD [68]. In the study of Peiró et al. cardiac troponin I was a significantly better predictor for 30-day all-cause death compared to other inflammatory biomarkers such as CRP, D-dimer, and lactate dehydrogenase, and the level as low as 21 ng/L was able to provide excellent prediction capacity [216].

Complications

Complications (early, not associated with the long COVID) are another risk factors associated with death among critically ill patients. Common complication in COVID-19 patients include acute respiratory distress syndrome, acute kidney injury (AKI), acute cardiac injury (ACI), thrombosis, gastrointestinal complications, neurologic complications, sepsis, shock, multi-organ failure, and secondary infections [47, 217, 218]. Experiencing adverse complications has a high risk of COVID-19 mortality. Study of Yang et al. indicated that 67%, 29%, 29%, and 23% of hospitalized COVID-19 patients, experienced adverse complications such as ARDS, AKI, liver dysfunction, and ACI, respectively. Of patients developing ARDS, AKI, ACI, and liver dysfunction adverse complications, 74%, 80%, 75%, and 60% of them died, respectively [15].

Meta-analysis of 12 studies with a total of 3064 COVID-19 patients indicated that the most common complications were acute respiratory distress syndrome (30.93%) followed by acute liver injury (22.8%), shock (10.9%), acute kidney injury (7%), and acute cardiac injury (6.4%). Older populations were a high-risk group of developing adverse complications. It was revealed that as the mean age increased by 1 year, the ARDS, AKI, ACI, and shock increased by a factor of 2.9

[219]. Development of ARDS and progression from ARDS to death is associated with risk factors such as older age, neutrophilia, organ, and coagulation dysfunction [220]. Cardiovascular complications in COVID-19 patients may include myocardial injury, heart failure, arrhythmias, acute coronary syndrome, and venous thromboembolism [66, 221, 222]. Meta-analysis of 3044 confirmed COVID-19 cases from 12 studies indicated that the most common cardiovascular complications were myocardial injury (21.2%) and arrhythmia (15.3%), then heart failure (14.4%) and acute coronary syndrome (1.0%). Myocardial injury and heart failure were more frequent in non-survivors, regardless of a history of CVD [221]. Cardiac complications, which are becoming more prevalent with the progress in the study of COVID-19, influence the development and prognosis of disease.

Reinfection

It was thought that individuals who recovered from COVID-19 generate a robust immune response and develop protective immunity; however, since August 2020, numerous cases with reinfection have been documented [223–225]. Positive COVID-19 antibodies after infection can provide protection against reinfection in most studied patients [226]. Cases of reinfection in patients are relatively rare [227], however, in the time of omicron there were many new cases of reinfection.

A systematic review indicated 17 cases of individuals infected with different genetic strains of SARS-CoV-2 confirmed by PCR. The results indicated that reinfection with different strains is possible, and the second episode of the infection might be more severe in nearly 20% of patients and result in serious complications in elderly and immunocompromised [86]. At present it is unclear how long serum antibodies and virus-specific T cells persist after infection, how common reinfection with SARS-CoV-2 can be and whether it occur in individuals with detectable immune memory [228, 229].

Conclusions and Take-Home Message

Prognosis in COVID-19 patients is closely related to the severity of disease. Between patients with severe and none-severe course of the disease significant difference exists in terms of demographic features, clinical symptoms, comorbidities, laboratory parameters, and complications. Laboratory biomarkers are fast and easy to obtain and preferred modality to monitor and predict prognosis of disease. Continuous controlling of laboratory parameters is essential to identify those patients who may progress to severe status and allow timely preventative efforts and optimization of high-risk patients. Knowledge on COVID-19 prognostic factors is constantly changing (however, hypertension, obesity, diabetes, COPD, seems to be the ones that occur the most often in the available analyses); new biomarkers are

analyzing which could be useful in COVID-19 prognosis [230–236]. Available data also suggest that the optimalization of the underlaying conditions and risk factors may significantly decrease the risk of severe COVID-19 course [230–236]. The creation of a machine learning system to fully analyze the profile of a patient with COVID 19, both in terms of demography, comorbidities, previous infections, and the concentration of laboratory biomarkers, may be an option for early detection of patients at risk of severe COVID-19 requiring hospitalization.

References

1. Global COVID-19 statistics. Available at: https://www.worldometers.info/coronavirus/#countries (Access 05 FEB 2022).
2. Lake MA. What we know so far: COVID-19 current clinical knowledge and research. Clin Med (Lond). 2020;20:124–7.
3. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323:1239–42.
4. Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med. 2020;172:577–82.
5. Singhal T. Review of coronavirus Disease-2019 (COVID-19). Indian J Pediatr. 2020;87:281–6.
6. McCue C, Cowan R, Quasim T, Puxty K, McPeake J. Long term outcomes of critically ill COVID-19 pneumonia patients: early learning. Intensive Care Med. 2021;47:240–1.
7. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–62.
8. Wang Z, Deng H, Ou C, Liang J, Wang Y, Jiang M, Li S. Clinical symptoms, comorbidities and complications in severe and non-severe patients with COVID-19: a systematic review and meta-analysis without cases duplication. Medicine (Baltimore). 2020;99:e23327.
9. Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. J Infect. 2020;81:e16–25.
10. Zhang L, Hou J, Ma FZ, Li J, Xue S, Xu ZG. The common risk factors for progression and mortality in COVID-19 patients: a meta-analysis. Arch Virol. 2021;166:2071–87.
11. Imam Z, Odish F, Gill I, et al. Older age and comorbidity are independent mortality predictors in a large cohort of 1305 COVID-19 patients in Michigan, United States. J Intern Med. 2020;288:469–76.
12. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.
13. Zhou B, She J, Wang Y, Ma X. The clinical characteristics of myocardial injury in severe and very severe patients with 2019 novel coronavirus disease. J Infect. 2020b;81:147–78.
14. Chen L, Zhang B, Ti MN, Yang K, Zou Y, Zhang S. Clinical course of severe and critically ill patients with coronavirus disease 2019 (COVID-19): a comparative study. J Infect. 2020;81:e82–4.
15. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020b;8:475–81.
16. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:m1295.
17. Cao J, Tu W-J, Cheng W, et al. Clinical features and shortterm outcomes of 102 patients with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis. 2020;71:748–55.

18. Tomlins J, Hamilton F, Gunning S, Sheehy C, Moran E, MacGowan A. Clinical features of 95 sequential hospitalised patients with novel coronavirus 2019 disease (COVID-19), the first UK cohort. J Infect. 2020;81:e59–61.
19. Fang X, Li S, Hy Y, et al. Epidemiological, comorbidity factors with severity and prognosis of COVID-19: a systematic review and meta-analysis. Aging. 2020;12:12493–503.
20. Figliozzi S, Masci PG, Ahmadi N, Tondi L, Koutli E, Aimo A, Stamatelopoulos K, Dimopoulos MA, Caforio ALP, Georgiopoulos G. Predictors of adverse prognosis in COVID-19: a systematic review and meta-analysis. Eur J Clin Investig. 2020;50:e13362.
21. Luo H, Liu S, Wang Y, et al. Age differences in clinical features and outcomes in patients with COVID-19, Jiangsu, China: a retrospective, multicentre cohort study. BMJ Open. 2020;10:e039887.
22. Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL. Considering how biological sex impacts immune responses and COVID-19 outcomes. Nat Rev Immunol. 2020;20:442–7.
23. Global Health 50/50. Sex, gender and COVID-19: overview and resources. 2020. https://globalhealth5050.org/covid19. Accessed February 2022.
24. Inciardi RM, Adamo M, Lupi L, et al. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in northern Italy. Eur Heart J. 2020a;41:1821–9.
25. Peckham H, de Gruijter NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, Rosser EC, Webb K, Deakin CT. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nat Commun. 2020;11:6317.
26. Meijs DAM, van Bussel BCT, Stessel B, et al. Better COVID-19 intensive care unit survival in females, independent of age, disease severity, comorbidities, and treatment. Sci Rep. 2022;12:734.
27. Ghosh S, Klein RS. Sex drives dimorphic immune responses to viral infections. J Immunol. 2017;198:1782–90.
28. Schurz H, Salie M, Tromp G, Hoal EG, Kinnear CJ, Möller M. The X chromosome and sex-specific effects in infectious disease susceptibility. Hum Genomics. 2019;13:2.
29. Gao YD, Ding M, Dong X, et al. Risk factors for severe and critically ill COVID-19 patients: a review. Allergy. 2021;76:428–55.
30. Sze S, Pan D, Nevill CR, et al. Ethnicity and clinical outcomes in COVID-19: a systematic review and meta-analysis. EClinicalMedicine. 2020;29:100630.
31. Mackey K, Ayers CK, Kondo KK, et al. Racial and ethnic disparities in COVID-19-related infections, hospitalizations, and deaths: a systematic review. Ann Intern Med. 2021;174:362–73.
32. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and mortality among black patients and white patients with COVID-19. N Engl J Med. 2020;382:2534–43.
33. Muñoz-Price LS, Nattinger AB, Rivera F, et al. Racial disparities in incidence and outcomes among patients with COVID-19. JAMA Netw Open. 2020;3:e2021892.
34. Raharja A, Tamara A, Kok LT. Association between ethnicity and severe COVID-19 disease: a systematic review and meta-analysis. J Racial Ethn Health Disparities. 2021;8:1563–72.
35. Magesh S, John D, Li WT, et al. Disparities in COVID-19 Outcomes by Race, Ethnicity, and Socioeconomic Status: A Systematic-Review and Meta-analysis. JAMA Netw Open. 2021;4:e2134147.
36. Holman N, Knighton P, Kar P, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. Lancet Diabetes Endocrinol. 2020;8:823–33.
37. Zakeri R, Bendayan R, Ashworth M, et al. A case-control and cohort study to determine the relationship between ethnic background and severe COVID-19. EClinicalMedicine. 2020;28:100574.
38. Rodriguez F, Solomon N, de Lemos JA, et al. Racial and ethnic differences in presentation and outcomes for patients hospitalized with COVID-19: findings from the American Heart Association's COVID-19 cardiovascular disease registry. Circulation. 2021;143:2332–42.

39. Shortreed SM, Gray R, Akosile MA, et al. Increased COVID-19 infection risk drives racial and ethnic disparities in severe COVID-19 outcomes. J Racial Ethn Health Disparities. 2022:1–11.
40. White-Dzuro G, Gibson LE, Zazzeron L, White-Dzuro C, Sullivan Z, Diiorio DA, Low SA, Chang MG, Bittner EA. Multisystem effects of COVID-19: a concise review for practitioners. Postgrad Med. 2021;133:20–7.
41. Yanes-Lane M, Winters N, Fregonese F, Bastos M, Perlman-Arrow S, Campbell JR, Menzies D. Proportion of asymptomatic infection among COVID-19 positive persons and their transmission potential: a systematic review and meta-analysis. PLoS One. 2020;15:e024153.
42. Jiang F, Deng L, Zhang L, Cai Y, Cheung CW, Xia Z. Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). J Gen Intern Med. 2020;35:1545–9.
43. Jain V, Yuan JM. Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis. Int J Public Health. 2020;65:533–46.
44. da Rosa MR, Francelino Silva Junior LC, Santos Santana FM, et al. Clinical manifestations of COVID-19 in the general population: systematic review. Wien Klin Wochenschr. 2021;133:377–82.
45. Zhang JJY, Lee KS, Ang LW, Leo YS, Young BE. Risk factors for severe disease and efficacy of treatment in patients infected with COVID-19: a systematic review, meta-analysis, and meta-regression analysis. Clin Infect Dis. 2020;71:2199–206.
46. He X, Cheng X, Feng X, Wan H, Chen S, Xiong M. Clinical symptom differences between mild and severe COVID-19 patients in China: a meta-analysis. Front Public Health. 2021;14:561264.
47. Huang C, Soleimani J, Herasevich S, et al. Clinical characteristics, treatment, and outcomes of critically ill patients with COVID-19: a scoping review. Mayo Clin Proc. 2021;96:183–202.
48. Yang L, Jin J, Luo W, Gan Y, Chen B, Li W. Risk factors for predicting mortality of COVID-19 patients: a systematic review and meta-analysis. PLoS One. 2020;30(15):e0243124.
49. Guan WJ, Liang WH, Zhao Y, et al. China medical treatment expert group for COVID-19. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020;55:2000547.
50. Wei YY, Wang RR, Zhang DW, et al. Risk factors for severe COVID-19: evidence from 167 hospitalized patients in Anhui. China J Infect. 2020;81:e89–92.
51. Xie J, Covassin N, Fan Z, et al. Association between hypoxemia and mortality in patients with COVID-19. Mayo Clin Proc. 2020;95:1138–47.
52. Ioannou GN, Locke E, Green P, et al. Risk factors for hospitalization, mechanical ventilation, or death among 10131 US veterans with SARS-CoV-2 infection. JAMA Netw Open. 2020;3:e2022310.
53. Lechien JR, Chiesa-Estomba CM, Place S, et al. COVID-19 task force of YO-IFOS. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. J Intern Med. 2020;288:335–44.
54. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan. China JAMA Intern Med. 2020;180:934.
55. Wolff D, Nee S, Hickey NS, Marschollek M. Risk factors for Covid-19 severity and fatality: a structured literature review. Infection. 2021;49:15–28.
56. Han J, Shi LX, Xie Y, Zhang YJ, Huang SP, Li JG, Wang HR, Shao SF. Analysis of factors affecting the prognosis of COVID-19 patients and viral shedding duration. Epidemiol Infect. 2020;148:e125.
57. Remes-Troche JM, Ramos-de-la-Medina A, Manriquez-Reyes M, Martinez-Perez-Maldonado L, Lara EL, Solis-Gonzalez MA. Initial gastrointestinal manifestations in patients with severe acute respiratory syndrome coronavirus 2 infection in 112 patients from Veracruz in southeastern Mexico. Gastroenterology. 2020;159:1179–81.

58. Cholankeril G, Podboy A, Aivaliotis VI, et al. High prevalence of concurrent gastrointestinal manifestations in patients with severe acute respiratory syndrome coronavirus 2: early experience from California. Gastroenterology. 2020;159:775–7.
59. Li X, Li T, Wang H. Treatment and prognosis of COVID-19: current scenario and prospects (review). Exp Ther Med. 2021;21:3.
60. Zheng T, Yang C, Wang HY, et al. Clinical characteristics and outcomes of COVID-19 patients with gastrointestinal symptoms admitted to Jianghan Fangcang shelter Hospital in Wuhan. China J Med Virol. 2020;92:2735–41.
61. Mao R, Qiu Y, He JS, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2020;5:667–78.
62. Wang Y, Li Y, Zhang Y, Liu Y, Liu Y. Are gastrointestinal symptoms associated with higher risk of mortality in COVID-19 patients? A systematic review and meta-analysis. BMC Gastroenterol. 2022;22:106.
63. Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, Hosein Z, Padda I, Mangat J, Altaf M. Comorbidity and its impact on patients with COVID-19. SN Compr Clin Med. 2020;2:1069–76.
64. COVIDNet. Centers for Disease Control and Prevention. Available at: https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html#medicalConditionsColumnDiv. Accessed 10 April 2022.
65. Hatmi ZN. A systematic review of systematic reviews on the COVID-19 pandemic. SN Compr Clin Med. 2021;3:419–36.
66. Pepera G, Tribali MS, Batalik L, Petrov I, Papathanasiou J. Epidemiology, risk factors and prognosis of cardiovascular disease in the coronavirus disease 2019 (COVID-19) pandemic era: a systematic review. Rev Cardiovasc Med. 2022;23:28.
67. Murthy S, Archambault PM, Atique A, et al. Characteristics and outcomes of patients with COVID-19 admitted to hospital and intensive care in the first phase of the pandemic in Canada: a national cohort study. CMAJ Open. 2021;9:E181–8.
68. Majure DT, Gruberg L, Saba SG, Kvasnovsky C, Hirsch JS, Jauhar R. Northwell health COVID-19 research consortium. Usefulness of elevated troponin to predict death in patients with COVID-19 and myocardial injury. Am J Cardiol. 2021;138:100–6.
69. Kunutsor SK, Laukkanen JA. Cardiovascular complications in COVID-19: a systematic review and meta-analysis. J Infect. 2020;81:e139–41.
70. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5:819–24.
71. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. JAMA Cardiol. 2020;5:831.
72. Nuzzi V, Merlo M, Specchia C, et al. The prognostic value of serial troponin measurements in patients admitted for COVID-19. ESC Heart Failure. 2021;8:3504–11.
73. Chen J, Liu Y, Qin J, Ruan C, Zeng X, Xu A, Yang R, Li J, Cai H, Zhang Z. Hypertension as an independent risk factor for severity and mortality in patients with COVID-19: a retrospective study. Postgrad Med J. 2021;5:postgradmedj-2021-140674.
74. Pranata R, Lim MA, Huang I, Raharjo SB, Lukito AA. Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: a systematic review, meta-analysis and meta-regression. J Renin-Angiotensin-Aldosterone Syst. 2020;21:1470320320926899.
75. Deng G, Yin M, Chen X, Zeng F. Clinical determinants for fatality of 44,672 patients with COVID-19. Crit Care. 2020;24:179.
76. Ran J, Song Y, Zhuang Z, et al. Blood pressure control and adverse outcomes of COVID-19 infection in patients with concomitant hypertension in Wuhan. China Hypertens Res. 2020;43:1267–76.
77. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5:811–8.

78. Hussain A, Bhowmik B. Do Vale Moreira NC COVID-19 and diabetes: knowledge in progress. Diabetes Res Clin Pract. 2020;162:108142.
79. Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020;36:e3319.
80. Pugliese G, Vitale M, Resi V, Orsi E. Is diabetes mellitus a risk factor for Corona virus disease 19 (COVID-19)? Acta Diabetol. 2020;57:1275–85.
81. Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: prevalence, pathophysiology, prognosis and practical considerations. Diabetes Metab Syndr. 2020;14:303–10.
82. Guo L, Shi Z, Zhang Y, et al. Comorbid diabetes and the risk of disease severity or death among 8807 COVID-19 patients in China: a meta-analysis. Diabetes Res Clin Pract. 2020;166:108346.
83. Shi Q, Zhang X, Jiang F, et al. Clinical characteristics and risk factors for mortality of COVID-19 patients with diabetes in Wuhan, China: a two-center. Retrospective Study Diabetes Care. 2020;43:1382–91.
84. Li H, Tian S, Chen T, et al. Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19. Diabetes Obes Metab. 2020;22:1897–906.
85. Fadini GP, Morieri ML, Boscari F, et al. Newly-diagnosed diabetes and admission hyperglycemia predict COVID-19 severity by aggravating respiratory deterioration. Diabetes Res Clin Pract. 2020;168:108374.
86. Wang W, Shen M, Tao Y, et al. Elevated glucose level leads to rapid COVID-19 progression and high fatalit. BMC Pulm Med. 2021;21:64.
87. Logette E, Lorin C, Favreau C, et al. A machine-generated view of the role of blood glucose levels in the severity of COVID-19. Front Public Health. 2021;9:695139.
88. Zhu L, She ZG, Cheng X, et al. Association of Blood Glucose Control and Outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab. 2020;31:1068–1077.e3.
89. Földi M, Farkas N, Kiss S, et al. Obesity is a risk factor for developing critical condition in COVID-19 patients: a systematic review and meta-analysis. Obes Rev. 2020;21:e13095.
90. Foo O, Hiu S, Teare D, Syed AA, Razvi S. A global country-level analysis of the relationship between obesity and COVID-19 cases and mortality. Diabetes Obes Metab. 2021;23:2697–706.
91. Simonnet A, Chetboun M, Poissy J, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obesity (Silver Spring). 2020;28:1195–9.
92. Sawadogo W, Tsegaye M, Gizaw A, et al. Overweight and obesity as risk factors for COVID-19-associated hospitalisations and death: systematic review and meta-analysis. BMJ Nutr Prev Health. 2022;5(1):10–8.
93. Malik P, Patel U, Patel K, Martin M, Shah C, Mehta D, Malik FA, Sharma A. Obesity a predictor of outcomes of COVID-19 hospitalized patients-a systematic review and meta-analysis. J Med Virol. 2021;93:1188–93.
94. Tamara A, Tahapary DL. Obesity as a predictor for a poor prognosis of COVID-19: a systematic review. Diabetes Metab Syndr. 2020;14:655–9.
95. Klang E, Kassim G, Soffer S, Freeman R, Levin MA, Reich DL. Severe obesity as an independent risk factor for COVID-19 mortality in hospitalized patients younger than 50. Obesity (Silver Spring). 2020;28:1595–9.
96. Lee SC, Son KJ, Han CH, Park SC, Jung JY. Impact of COPD on COVID-19 prognosis: a nationwide population-based study in South Korea. Sci Rep. 2021;11:3735.
97. Leung JM, Niikura M, Yang CWT, Sin DD. COVID-19 and COPD. Eur Respir J. 2020;56:2002108.
98. Guan WJ, Ni ZY, Hu Y, et al. China medical treatment expert Group for Covid-19 clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–20.
99. Lagi F, Piccica M, Graziani L, et al. Early experience of an infectious and tropical diseases unit during the coronavirus disease (COVID-19) pandemic, Florence, Italy, February to march 2020. Euro Surveill. 2020;25:2000556.

100. Cecconi M, Piovani D, Brunetta E, et al. Early predictors of clinical deterioration in a cohort of 239 patients hospitalized for Covid-19 infection in lombardy. Italy J Clin Med. 2020;9:1548.
101. Israelsen SB, Kristiansen KT, Hindsberger B, et al. Characteristics of patients with COVID-19 pneumonia at Hvidovre hospital, march-April 2020. Dan Med J. 2020;67:A05200313.
102. de Abajo FJ, Rodríguez-Martín S, Lerma V, et al. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. Lancet. 2020;395:1705–14.
103. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;146:110–8.
104. Feng Y, Ling Y, Bai T, et al. COVID-19 with different severities: a multicenter study of clinical features. Am J Respir Crit Care Med. 2020;201:1380–8.
105. Hong L, Shiyan C, Min L, Hao N, Hongyun L. Comorbid chronic diseases are strongly correlated with disease severity among COVID-19 patients: a systematic review and meta-analysis. Aging Dis. 2020;11:668–78.
106. Bajgain KT, Badal S, Bajgain BB, Santana MJ. Prevalence of comorbidities among individuals with COVID-19: a rapid review of current literature. Am J Infect Control. 2021;49:238–46.
107. Alyammahi SK, Abdin SM, Alhamad DW, Elgendy SM, Altell AT, Omar HA. The dynamic association between COVID-19 and chronic disorders: an updated insight into prevalence, mechanisms and therapeutic modalities. Infect Genet Evol. 2021;87:104647.
108. Jdiaa SS, Mansour R, El Alayli A, Gautam A, Thomas P, Mustafa RA. COVID-19 and chronic kidney disease: an updated overview of reviews. J Nephrol. 2022;35:69–85.
109. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020;97:829–38.
110. Oyelade T, Alqahtani J, Canciani G. Prognosis of COVID-19 in patients with liver and kidney diseases: an early systematic review and meta-analysis. Trop Med Infect Dis. 2020;5:80.
111. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21:335–7.
112. Wang Q, Berger NA, Xu R. Analyses of risk, racial disparity, and outcomes among US patients with cancer and COVID-19 infection. JAMA Oncol. 2021;7:220–7.
113. Desai A, Sachdeva S, Parekh T, Desai R. Covid-19 and cancer: lessons from a pooled meta-analysis. JCO Glob Oncol. 2020;6:557–9.
114. Rüthrich MM, Giessen-Jung C, Borgmann S, et al. LEOSS study group. COVID-19 in cancer patients: clinical characteristics and outcome-an analysis of the LEOSS registry. Ann Hematol. 2021;100:383–93.
115. Miyashita H, Mikami T, Chopra N, et al. Do patients with cancer have a poorer prognosis of COVID-19? An experience in new York City. Ann Oncol. 2020;31:1088–9.
116. Liang J, Jin G, Liu T, et al. Clinical characteristics and risk factors for mortality in cancer patients with COVID-19. Front Med. 2021;15:264–74.
117. Zhang H, Han H, He T, et al. Clinical characteristics and outcomes of COVID-19-infected cancer patients: a systematic review and meta-analysis. J Natl Cancer Inst. 2021;113:371–80.
118. Liu H, Yang D, Chen X, et al. The effect of anticancer treatment on cancer patients with COVID-19: a systematic review and meta-analysis. Cancer Med. 2021;10:1043–56.
119. Chavez-MacGregor M, Lei X, Zhao H, Scheet P, Giordano SH. Evaluation of COVID-19 mortality and adverse outcomes in US patients with or without cancer. JAMA Oncol. 2022;8:69–78.
120. Clift AK, von Ende A, Tan PS, et al. Smoking and COVID-19 outcomes: an observational and mendelian randomisation study using the UK biobank cohort. Thorax. 2022;77:65–73.
121. Reddy RK, Charles WN, Sklavounos A, Dutt A, Seed PT, Khajuria A. The effect of smoking on COVID-19 severity: a systematic review and meta-analysis. J Med Virol. 2021;93:1045–56.
122. Smith JC, Sausville EL, Girish V, et al. Cigarette smoke exposure and inflammatory signaling increase the expression of the SARS-CoV-2 receptor ACE2 in the respiratory tract. Dev Cell. 2020;53:514–29.
123. Dashraath P, Wong JLJ, Lim MXK, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol. 2020;222:521–31.

124. Pringle KG, Tadros MA, Callister RJ, Lumbers ER. The expression and localization of the human placental prorenin/renin-angiotensin system throughout pregnancy: roles in trophoblast invasion and angiogenesis? Placenta. 2011;32:956–62.
125. Zambrano LD, Ellington S, Strid P, et al. Characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status: United States. MMWR Morb Mortal Wkly Rep. 2020;69:1641–7.
126. Jering KS, Claggett BL, Cunningham JW, et al. Clinical characteristics and outcomes of hospitalized women giving birth with and without COVID-19. JAMA Intern Med. 2021;181:714–7.
127. Allotey J, Stallings E, Bonet M, et al. PregCOV-19 living systematic review consortium. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020;370:m3320.
128. DeBolt CA, Bianco A, Limaye MA, et al. Pregnant women with severe or critical coronavirus disease 2019 have increased composite morbidity compared with nonpregnant matched controls. Am J Obstet Gynecol. 2021;224:510.e1–510.e12.
129. Metz TD, Clifton RG, Hughes BL, et al. Association of SARS-CoV-2 infection with serious maternal morbidity and mortality from obstetric complications. JAMA. 2022;327:748–59.
130. Frenkel LD, Gomez F, Bellanti JA. COVID-19 in children: pathogenesis and current status. Allergy Asthma Proc. 2021;42:8–15.
131. Götzinger F, Santiago-García B, Noguera-Julián A, Lanaspa M, Lancella L, Carducci FIC. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health. 2020;4:653–61.
132. Swann OV, Holden KA, Turtle L, et al. Clinical characteristics of children and young people admitted to hospital with COVID-19 in United Kingdom: prospective multicentre observational cohort study. BMJ. 2020;370:m3249.
133. Yasuhara J, Kuno T, Takagi H, Sumitomo N. Clinical characteristics of COVID-19 in children: a systematic review. Pediatr Pulmonol. 2020;55:2565–75.
134. Levin M. Childhood multisystem inflammatory syndrome: a new challenge in the pandemic. N Engl J Med. 2020;383:393–5.
135. Wang LS, Wang YR, Ye DW, Liu QQ. A review of the 2019 novel coronavirus (COVID-19) based on current evidence. Int J Antimicrob Agents. 2020;19:105948.
136. Abdo-Cuza A, Castellanos-Gutiérrez R, Treto-Ramirez J, et al. Safety and efficacy of intranasal recombinant human interferon alfa 2b as prophylaxis for COVID-19 in patients on a hemodialysis program. J Ren Endocrinol. 2020;7:e05.
137. Khaled SA, Hafez AA. Aplastic anemia and COVID-19: how to break the vicious circuit? Am J Blood Res. 2020;10:60.
138. Radisic MV, Piro MA, Mori I, Rotryng F, Santamarina JF. SARS-CoV-2 and dengue virus co-infection. A case report. Hemoglobin. 2020;16:15.
139. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med. 2020;58:1021–8.
140. Liu Y, Du X, Chen J, Jin Y, Peng L, Wang HHX, Luo M, Chen L, Zhao Y. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect. 2020;81:e6–e12.
141. Elshazli RM, Toraih EA, Elgaml A, et al. Diagnostic and prognostic value of hematological and immunological markers in COVID-19 infection: a meta-analysis of 6320 patients. PLoS One. 2020;15:e0238160.
142. Myari A, Papapetrou E, Tsaousi C. Diagnostic value of white blood cell parameters for COVID-19: is there a role for HFLC and IG? Int J Lab Hematol. 2022;44:104–11.
143. Karimi Shahri M, Niazkar HR, Rad F. COVID-19 and hematology findings based on the current evidences: a puzzle with many missing pieces. Int J Lab Hematol. 2021;43:160–8.
144. Lee J, Park SS, Kim TY, Lee DG, Kim DW. Lymphopenia as a biological predictor of outcomes in COVID-19 patients: a Nationwide cohort study. Cancers (Basel). 2021;13:471.

145. Yang AP, Li HM, Tao WQ, et al. Infection with SARS-CoV-2 causes abnormal laboratory results of multiple organs in patients. Aging. 2020;12:10059–69.
146. Liu J, Li S, Liu J, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine. 2020;55:102763.
147. Song CY, Xu J, He JQ, Lu YQ. COVID-19 early warning score: a multi-parameter screening tool to identify highly suspected patients. MedRxiv. 2020;
148. Malik P, Patel U, Mehta D, Patel N, Kelkar R, Akrmah M, Gabrilove JL, Sacks H. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis a. BMJ Evid Based Med. 2021;26:107–8.
149. Wang F, Nie J, Wang H, et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. J Infect Dis. 2020;221:1762–9.
150. Xu XW, Wu XX, Jiang XG, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ. 2020;368:m606.
151. Pourbagheri-Sigaroodi A, Bashash D, Fateh F, Abolghasemi H. Laboratory findings in COVID-19 diagnosis and prognosis. Clin Chim Acta. 2020;510:475–82.
152. Simadibrata DM, Calvin J, Wijaya AD, Ibrahim NAA. Neutrophil-to-lymphocyte ratio on admission to predict the severity and mortality of COVID-19 patients: a meta-analysis. Am J Emerg Med. 2021;42:60–9.
153. Yan X, Li F, Wang X, et al. Neutrophil to lymphocyte ratio as prognostic and predictive factor in patients with coronavirus disease 2019: a retrospective cross-sectional study. J Med Virol. 2020;92:2573–81.
154. Zhu A, Zakusilo G, Lee MS, Kim J, Kim H, Ying X, Chen YH, Jedlicka C, Mages K, Choi JJ. Laboratory parameters and outcomes in hospitalized adults with COVID-19: a scoping review. Infection. 2022;50:1–9.
155. Sayah W, Berkane I, Guermache I, et al. Interleukin-6, procalcitonin and neutrophil-to-lymphocyte ratio: potential immune-inflammatory parameters to identify severe and fatal forms of COVID-19. Cytokine. 2021;141:155428.
156. Terra POC, Donadel CD, Oliveira LC, Menegueti MG, Auxiliadora-Martins M, Calado RT, De Santis GC. Neutrophil-to-lymphocyte ratio and D-dimer are biomarkers of death risk in severe COVID-19: a retrospective observational study. Health Sci Rep. 2022;9(5):e514.
157. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. Clin Chim Acta. 2020t;506:145–8.
158. Zong X, Gu Y, Yu H, Li Z, Wang Y. Thrombocytopenia is associated with COVID-19 severity and outcome: an updated meta-analysis of 5637 patients with multiple outcomes. Lab Med. 2021;52:10–5.
159. Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19 - a systematic review. Life Sci. 2020;254:117788.
160. Xiao LN, Ran X, Zhong YX, Li SS. Clinical value of blood markers to assess the severity of coronavirus disease 2019. BMC Infect Dis. 2021;21:921.
161. Liu Y, Sun W, Guo Y, Chen L, Zhang L, Zhao S. Association between platelet parameters and mortality in coronavirus disease 2019: retrospective cohort study. Platelets. 2020;31:490–6.
162. Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol. 2020n;84:106504.
163. Qu R, Ling Y, Zhang YH, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. J Med Virol. 2020;92:1533–41.
164. Simadibrata DM, Pandhita BAW, Ananta ME, Tango T. Platelet-to-lymphocyte ratio, a novel biomarker to predict the severity of COVID-19 patients: a systematic review and meta-analysis. J Intensive Care Soc. 2020;5:371.
165. Sun S, Cai X, Wang H, et al. Abnormalities of peripheral blood system in patients with COVID-19 in Wenzhou. China Clin Chim Acta. 2020;507:174–80.

166. Zhao Y, Yu C, Ni W, Shen H, Qiu M, Zhao Y. Peripheral blood inflammatory markers in predicting prognosis in patients with COVID-19. Some differences with influenza a. J Clin Lab Anal. 2021;35:e23657.
167. Sarkar S, Kannan S, Khanna P, Singh AK. Role of platelet-to-lymphocyte count ratio (PLR), as a prognostic indicator in COVID-19: a systematic review and meta-analysis. J Med Virol. 2022;94:211–21.
168. Zhang JJ, Cao YY, Tan G, et al. Clinical, radiological, and laboratory characteristics and risk factors for severity and mortality of 289 hospitalized COVID-19 patients. Allergy. 2021;76:533–50.
169. Azkur AK, Akdis M, Azkur D, et al. Immune response to SARSCoV-2 and mechanisms of immunopathological changes in COVID-19. Allergy. 2020;75:1564–81.
170. Lentner J, Adams T, Knutson V, et al. C-reactive protein levels associated with COVID-19 outcomes in the United States. J Osteopath Med. 2021;121:869–73.
171. Xu B, Fan CY, Wang AL, et al. Suppressed T cell-mediated immunity in patients with COVID-19: a clinical retrospective study in Wuhan. China J Infect. 2020;81:e51–60.
172. Stringer D, Braude P, Myint PK, et al. The role of C-reactive protein as a prognostic marker in COVID-19. Int J Epidemiol. 2021;50:420–9.
173. Rizzi M, Costanzo M, Tonello S, et al. Prognostic markers in hospitalized COVID-19 patients: the role of IP-10 and C-reactive protein. Dis Markers. 2022;2022:3528312.
174. Chen W, Zheng KI, Liu S, Yan Z, Xu C, Qiao Z. Plasma CRP level is positively associated with the severity of COVID-19. Ann Clin Microbiol Antimicrob. 2020;19:18.
175. Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol. 2020;146:128–136.e4.
176. Ahmed S, Jafri L, Hoodbhoy Z, Siddiqui I. Prognostic value of serum procalcitonin in COVID-19 patients: a systematic review. Indian J Crit Care Med. 2021;25:77–84.
177. Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chim Acta. 2020;505:190–1.
178. Hu R, Han C, Pei S, Yin M, Chen X. Procalcitonin levels in COVID-19 patients. Int J Antimicrob Agents. 2020;56:106051.
179. Martha JW, Wibowo A, Pranata R. Prognostic value of elevated lactate dehydrogenase in patients with COVID-19: a systematic review and meta-analysis. Postgrad Med J. 2021:postgradmedj-2020-139542.
180. Zeng Z, Yu H, Chen H, et al. Longitudinal changes of inflammatory parameters and their correlation with disease severity and outcomes in patients with COVID-19 from Wuhan. China Crit Care. 2020;24:525.
181. Liu T, Zhang J, Yang Y, et al. The role of interleukin-6 in monitoring severe case of coronavirus disease 2019. EMBO Mol Med. 2020;12:e12421.
182. Tanaka T, Narazaki M, Kishimoto T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. Immunotherapy. 2016;8:959–70.
183. Chen X, Zhao B, Qu Y, et al. Detectable serum severe acute respiratory syndrome coronavirus 2 viral load (RNAemia) is closely correlated with drastically elevated interleukin 6 level in critically ill patients with coronavirus disease 2019. Clin Infect Dis. 2020;71:1937–42.
184. Aziz M, Fatima R, Assaly R. Elevated interleukin-6 and severe COVID-19: a meta-analysis. J Med Virol. 2020;92:2283–5.
185. Sabaka P, Koščálová A, Straka I, Hodosy J, Lipták R, Kmotorková B, Kachlíková M, Kušnírová A. Role of interleukin 6 as a predictive factor for a severe course of Covid-19: retrospective data analysis of patients from a long-term care facility during Covid-19 outbreak. BMC Infect Dis. 2021;21:308.
186. Magro G. SARS-CoV-2 and COVID-19: is interleukin-6 (IL-6) the 'culprit lesion' of ARDS onset? What is there besides tocilizumab? SGP130Fc. Cytokine X. 2020;2:100029.
187. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe. 2020;27:992–1000.e3.

188. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395:1033–4.
189. Song P, Li W, Xie J, Hou Y, You C. Cytokine storm induced by SARS-CoV-2. Clin Chim Acta. 2020;509:280–7.
190. Samprathi M, Jayashree M. Biomarkers in COVID-19: an up-to-date review. Front Pediatr. 2021;8:607647.
191. Shang W, Dong J, Ren Y, et al. The value of clinical parameters in predicting the severity of COVID-19. J Med Virol. 2020;92:2188–92.
192. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in new York City: a prospective cohort study. Lancet. 2020;395:1763–70.
193. Bansal A, Singh AD, Jain V, et al. The association of D-dimers with mortality, intensive care unit admission or acute respiratory distress syndrome in patients hospitalized with coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. Heart Lung. 2021;50:9–12.
194. Yao Y, Cao J, Wang Q, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. J Intensive Care. 2020;8:49.
195. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, Zhang Z. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost. 2020;18:1324–9.
196. Ye W, Chen G, Li X, et al. Dynamic changes of D-dimer and neutrophil-lymphocyte count ratio as prognostic biomarkers in COVID-19. Respir Res. 2020;21:169.
197. Gandini O, Criniti A, Ballesio L, Giglio S, Galardo G, Gianni W, Santoro L, Angeloni A, Lubrano C. Serum ferritin is an independent risk factor for acute respiratory distress syndrome in COVID-19. J Infect. 2020;81:979–97.
198. Kukoč A, Mihelčić A, Miko I. Clinical and laboratory predictors at ICU admission affecting course of illness and mortality rates in a tertiary COVID-19 center. Heart Lung. 2022;53:1–10.
199. Gómez-Pastora J, Weigand M, Kim J, Wu X, Strayer J, Palmer AF, Zborowski M, Yazer M, Chalmers JJ. Hyperferritinemia in critically ill COVID-19 patients - is ferritin the product of inflammation or a pathogenic mediator? Clin Chim Acta. 2020;509:249–51.
200. Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. Ther Adv Respir Dis. 2020;14:1753466620937175.
201. Kaushal K, Kaur H, Sarma P, et al. Serum ferritin as a predictive biomarker in COVID-19. A systematic review, meta-analysis and meta-regression analysis. J Crit Care. 2022;67:172–81.
202. Aloisio E, Chibireva M, Serafini L, et al. A comprehensive appraisal of laboratory biochemistry tests as major predictors of COVID-19 severity. Arch Pathol Lab Med. 2020;144:1457–64.
203. Chen S, Zhang D, Zheng T, Yu Y, Jiang J. DVT incidence and risk factors in critically ill patients with COVID-19. J Thromb Thrombolysis. 2021;51:33–9.
204. Aziz M, Fatima R, Lee-Smith W, Assaly R. The association of low serum albumin level with severe COVID-19: a systematic review and meta-analysis. Crit Care. 2020;24:255.
205. Violi F, Ceccarelli G, Cangemi R, et al. Hypoalbuminemia, coagulopathy, and vascular disease in COVID-19. Circ Res. 2020;127:400–1.
206. Huang J, Cheng A, Kumar R, et al. Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. J Med Virol. 2020;92:2152–8.
207. Salinas M, Blasco Á, Santo-Quiles A, et al. Laboratory parameters in patients with COVID-19 on first emergency admission is different in non-survivors: albumin and lactate dehydrogenase as risk factors. J Clin Pathol. 2021;74:673–5.
208. Zekri-Nechar K, Zamorano-León JJ, Segura-Fragoso A, et al. Albumin binds COVID-19 spike 1 subunit and predicts in-hospital survival of infected patients-possible alteration by glucose. J Clin Med. 2022;11:587.
209. Kheir M, Saleem F, Wang C, Mann A, Chua J. Higher albumin levels on admission predict better prognosis in patients with confirmed COVID-19. PLoS One. 2021;16:e0248358.

210. Piano S, Dalbeni A, Vettore E, et al. Abnormal liver function tests predict transfer to intensive care unit and death in COVID-19. Liver Int. 2020;40:2394–406.
211. Aloisio E, Colombo G, Arrigo C, Dolci A, Panteghini M. Sources and clinical significance of aspartate aminotransferase increases in COVID-19. Clin Chim Acta. 2021;522:88–95.
212. Aloisio E, Panteghini M. Aspartate aminotransferase in COVID-19: a probably overrated marker. Liver Int. 2021;41:2809–10.
213. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5:802–10.
214. Sandoval Y, Januzzi JL, Jaffe AS. Cardiac troponin for assessment of myocardial injury in COVID-19: JACC review topic of the week. J Am Coll Cardiol. 2020;76:1244–58.
215. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5:811–8.
216. Peiró ÓM, Carrasquer A, Sánchez-Gimenez R, et al. Biomarkers and short-term prognosis in COVID-19. Biomarkers. 2021;26:119–26.
217. Cao M, Zhang D, Wang Y, et al. Clinical features of patients infected with the 2019 novel coronavirus (COVID-19) in Shanghai, China. medRxiv [Preprint]. 2020:2020.03.04.20030395.
218. Fu L, Fei J, Xu S, et al. Acute liver injury and its association with death risk of patients with COVID-19: a hospital-based prospective case-cohort study. medRxiv [Preprint]. 2020:20050997.
219. Tiruneh SA, Tesema ZT, Azanaw MM, Angaw DA. The effect of age on the incidence of COVID-19 complications: a systematic review and meta-analysis. Syst Rev. 2021;10:80.
220. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180:934–43.
221. Zhao YH, Zhao L, Yang XC, Wang P. Cardiovascular complications of SARS-CoV-2 infection (COVID-19): a systematic review and meta-analysis. Rev Cardiovasc Med. 2021;22:159–65.
222. Bompard F, Monnier H, Saab I, et al. Pulmonary embolism in patients with COVID-19 pneumonia. Eur Respir J. 2020;56:2001365.
223. Selvaraj V, Herman K, Dapaah-Afriyie K. Severe, symptomatic reinfection in a patient with COVID-19. R I Med J. 2013;2020(103):24–6.
224. Wang J, Kaperak C, Sato T, Sakuraba A. COVID-19 reinfection: a rapid systematic review of case reports and case series. J Investig Med. 2021;69:1253–5.
225. West J, Everden S, Nikitas N. A case of COVID-19 reinfection in the UK. Clin Med (Lond). 2021;21:e52–3.
226. Lumley SF, O'Donnell D, Stoesser NE, Matthews PC, Howarth A, Hatch SB, Marsden BD, Cox S, James T, Warren F. Antibodies to SARS-CoV-2 are associated with protection against reinfection. N Engl J Med. 2021;384:533–40.
227. SFV H, Charlett A, et al. SIREN Study Group. Do antibody positive healthcare workers have lower SARS-CoV-2 infection rates than antibody negative healthcare workers? Large multi-Centre prospective cohort study (the SIREN study), England: June to November 2020. medRxiv medRxiv [Preprint]. 2021;
228. Sette A, Crotty S. Adaptive immunity to SARS-CoV-2 and COVID-19. Cell. 2021;184:861–80.
229. Cohen JI, Burbelo PD. Reinfection With SARS-CoV-2: Implications for Vaccines. Clin Infect Dis. 2021;73:e4223–8.
230. Bianconi V, Mannarino MR, Figorilli F, et al. The detrimental impact of elevated ferritin to iron ratio on in-hospital prognosis of patients with COVID-19. Expert Rev Mol Diagn. 2022;15:1–10. https://doi.org/10.1080/14737159.2022.2052047.
231. Kouhpeikar H, Khosaravizade Tabasi H, et al. Statin use in COVID-19 hospitalized patients and outcomes: a retrospective study. Front Cardiovasc Med. 2022;9:820260.

232. Banach M, Burchardt P, Chlebus K, et al. PoLA/CFPiP/PCS/PSLD/PSD/PSH guidelines on diagnosis and therapy of lipid disorders in Poland 2021. Arch Med Sci. 2021;17(6): 1447–547.
233. Bradley SA, Banach M, Alvarado N, Smokovski I, Bhaskar SMM. Prevalence and impact of diabetes in hospitalized COVID-19 patients: a systematic review and meta-analysis. J Diabetes. 2022;14(2):144–57.
234. Vahedian-Azimi A, Mohammadi SM, Heidari Beni F, Banach M, Guest PC, Jamialahmadi T, Sahebkar A. Improved COVID-19 ICU admission and mortality outcomes following treatment with statins: a systematic review and meta-analysis. Arch Med Sci. 2021;17(3):579–95.
235. Rezabakhsh A, Sadat-Ebrahimi SR, Ala A, Nabavi SM, Banach M, Ghaffari S. A close-up view of dynamic biomarkers in the setting of COVID-19: striking focus on cardiovascular system. J Cell Mol Med. 2022;26(2):274–86.
236. Surma S, Banach M, Lewek J. COVID-19 and lipids. The role of lipid disorders and statin use in the prognosis of patients with SARS-CoV-2 infection. Lipids Health Dis. 2021;20(1):141.