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Parameters for severity and mortality in covid-19 patients

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Abstract: Background: The novel coronavirus disease 2019 COVID-19 pandemic reached over 528 million confirmed infections and claimed the lives of more than 6 million people worldwide. The clinical features of COVID-19 are diverse and range from asymptomatic to critical illness and death. Severe and critical cases represented 14% and 5% of laboratory-confirmed COVID-19 patients, respectively. Severe patients present signs of dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation ≤ 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 mmHg, and/or lung infiltrates > 50% within 24 to 48 hours. Critically ill cases may experience respiratory failure that requires mechanical ventilation, shock, disseminated coagulopathy, and other organs failure requiring admission to the intensive care unit (ICU). A good understanding of the possible risk factors in combination to disease immunopathology associated with COVID-19 severity is helpful for clinicians in identifying patients who are at high risk and require prioritized treatment to prevent disease progression and adverse outcome. Risk factors range from demographic factors, such as age, sex and ethnicity, diet and lifestyle habits to underlying diseases and complications, and laboratory indications. Many studies have reported predictive models using various risk factors to identify high-risk patients that may develop severe and critical illness. It is worth noting that some studies address the risk factors of COVID-19 development in general, without any focus on disease severity, while others specifically focus on risk factors for disease progression to a critical stage.

Keywords: *COVID-19 Patients*

Introduction

Coronavirus disease 2019 (COVID-19) is defined as an illness caused by a novel coronavirus, which now is called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; formerly called 2019-nCoV), and was first identified as an outbreak of respiratory illness cases in Wuhan City, Hubei Province, China. It was initially reported to the WHO on December 31, 2019. On January 30, 2020, the WHO declared the COVID-19 outbreak a global health emergency. On March 11, 2020, the WHO declared COVID-19 a pandemic, its first such designation since declaring H1N1 influenza a pandemic in 2009.The disease caused by SA RS-CoV-2 was termed COVID-19 by the WHO, the acronym derived from "coronavirus disease 2019." The name was chosen to avoid stigmatizing the virus's origins in terms of populations, geography, or animal associations. On February 11, 2020, the Coronavirus Study Group of the International Committee on Taxonomy of Viruses issued a statement announcing an official designation for the novel virus: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) **(1).**

On April 3, 2020, the CDC issued a recommendation that the general public, even those without symptoms, should begin wearing face coverings in public settings where social-distancing measures are difficult to maintain in order to abate the spread of COVID-19. The feasibility and implications of strategies for suppression and mitigation have been rigorously analyzed and are being encouraged or enforced by many governments in order to slow or halt viral transmission. Population-wide social distancing of the entire population plus other interventions (e.g., home self-isolation, school and business closures) was strongly advised. These policies may be required for long periods to avoid rebound viral transmission. As the United States is experiencing another surge of COVID-19 infections, the CDC has intensified their recommendations for transmission mitigation. They have recommended universal face mask use, physical distancing, avoiding nonessential indoor spaces, postponing travel, enhancing ventilation, and hand hygiene **(2).**

In the United States, over 25.4 million reported cases of COVID-19 have been confirmed as of January 28, 2021, resulting in over 427,000 deaths, making it the third leading cause of death after heart disease and cancer. Beginning in late March 2020, the United States had more confirmed infections than any other country in the world. The United States also has the most confirmed deaths in the world, followed by Brazil and India. The novel coronavirus disease 2019 COVID-19 pandemic reached over 528 million confirmed infections and claimed the lives of more than 6 million people worldwide. The clinical features of COVID-19 are diverse and range from asymptomatic to critical illness and death. Severe and critical cases represented 14% and 5% of laboratory-confirmed COVID-19 patients, respectively **(3).**

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

Diverse laboratory findings and biomarkers have been demonstrated to be associated with the severity and mortality of COVID-19,

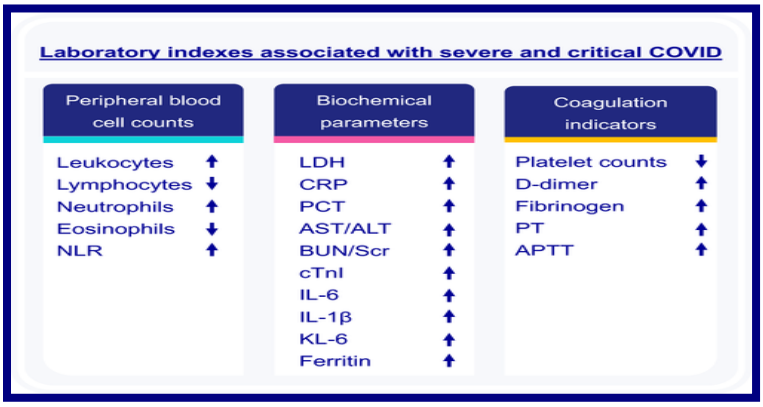

Fig. (1): Laboratory indexes associated with severe and critical COVID-19. Changes in blood cell counts and differentiation: increased leukocytes, neutrophils and neutrophil-to-lymphocyte ratio (NLR), decreased lymphocytes and eosinophils counts. Changes in coagulation indicators: decreased platelet counts, increased D-dimer, fibrinogen, prothrombin time (PT) and activated partial-thromboplastin time (APTT). Increase in the level of biochemical parameters: lactate dehydrogenase (LDH), C-reactive protein (CRP), procalcitonin (PCT),

AST/ALT, blood urea nitrogen (BUN)/Scr, cTnI, IL-6, IL-1β, and KL-6. All these changes may be aggravating factors for the disease course of COVID-19 **(5).**

Leukocyte counts:

Viral infection leads to dynamic changes in peripheral blood leukocyte counts and its subsets. Leukocytosis, elevated leukocyte counts (≥9.5 × 10^9/L), was associated with COVID-19 disease course, and the increase was more pronounced in severe and critically ill patients compared to mild illness patients, which may be indicative of more prominent inflammation developed in severe patients. A meta-analysis also showed that COVID-19 patients in the severe group tended to have higher leukocyte counts (pooled mean difference: 1.32; 95%CI: 0.62−2.02; P < .00001) compared to the mild group **(6).**

A higher neutrophil count at admission was found in severe or critically ill patients compared to mild and moderate patients. The progressive increase in leukocyte count and sustained lymphopenia and eosinopenia in severe COVID-19 patients may be associated with the progression of inflammatory status, which might progress to a fatal clinical outcome. The increased neutrophil-to-lymphocyte ratio (NLR) has been reported as an independent predictor of disease severity in COVID-19 patients. Collectively, these results are indicative of neutrophilic leukocytosis, and the increased number of leukocytes and neutrophils may be an aggravating factor for the disease course of COVID-19 **(7).**

Lymphocyte counts:

A sustained decrease in the peripheral blood lymphocyte count is an early indicator of severe/critically ill COVID-19 patients. There is a plethora of literature presenting lymphopenia in a significant proportion of patients with COVID-19. The decreased lymphocyte counts might be caused by viral attachment, immune injuries from inflammatory mediators, or exudation of circulating lymphocytes into inflammatory lung tissues. Several studies have also reported severe illness to be significantly associated with a more pronounced decline in the absolute number of lymphocytes, compared to mild cases. For example, in a study of the first 41 laboratory-confirmed cases with COVID-19, 63% of patients presented lymphopenia (lymphocyte count < 1.0 × 10^9/L). The proportion of patients with lymphopenia in the ICU and non-ICU were 85% and 54%, respectively (P = .045). **(8).**

Yang et al.,(9) reported that among 52 critically ill adult patients, lymphocytopenia occurred in 85% of patients and no significant difference was observed between survivors and non-survivors**.**

Wang et al., (10) examined the peripheral lymphocyte subset alteration in COVID-19. The results showed that compared to patients with mild illness, severe cases had significantly lower total lymphocytes (P = .0007), $CD4^+$ T cells (P = .024), $CD8^+$ T cells (P = .005), and B cells (P = .018). Among the lymphocyte subsets, $CD8^+$ T cells tended to be a potential predictor for COVID-19 severity.

Eosinophil counts:

In the first preliminary study reporting eosinopenia in COVID-19 patients, decreased eosinophil counts (< 0.02 × 109/L) was observed in 52.9% (73/138) patients. However, there was no significant difference in the ratio of patients with decreased eosinophil counts between severe and non-severe patients (P = .06). Many studies have demonstrated that eosinopenia was more prominent in severe COVID-19 patients than in mild patients. Chen et al showed a reduction in eosinophil counts in most of the severe/critical and fatal COVID-19 patients compared to mild/moderate and survived subjects on admission (0.01 × 109/L vs 0 × 109/L, P < .001) **(11).**

However, the difference in eosinophil counts between severe and mild COVID-19 patients was marginal and the technical limitations of measuring eosinophils make it clinically difficult to use eosinophil counts as a marker of severity of COVID-19. It has to be considered especially for patients in ICU, who might be under systemic glucocorticoids treatment and eosinophil counts thus dampened. On the other hand, glucocorticoid-unresponsive massive eosinophilia has been reported in severely affected COVID-19 patients in association with drug rash with eosinophilia and systemic symptoms, raising the question whether eosinophilia might be resistant to glucocorticoids. Immunophenotyping of whole blood leukocytes in COVID-19 patients revealed that eosinophil CRTH2 (Chemoattractant receptor-homologous molecule expressed on T(H)2 cells, CD294)

expression was significantly decreased in the severe group compared to the mild group. Moreover, the expression of checkpoint inhibitor programmed death ligand-1 (PDL1), a functional marker of eosinophil, was significantly higher in the severe group compared to the mild group. Clinical severity scores such as sepsis-related organ failure assessment (SOFA) and WHO progression scale were correlated positively with PDL1 expression and negatively with CRTH2 expression in eosinophils. These data suggested that decreased CRTH2 and/or increased PDL1 expression on eosinophils, but not eosinophil counts, represent risk factors for severe COVID-19 **(8).**

The antiviral effect of eosinophils may be reduced in COVID-19 patients with eosinopenia. Different mechanisms potentially contribute to eosinopenia in COVID-19 patients: a diminished release of eosinophils from the bone marrow, the block in eosinophilopoiesis, and direct eosinophil apoptosis induced by dysfunctional type I IFNs response during virus infection **(7).**

These results collectively suggest that the degree of eosinopenia, especially before the start of systemic steroids, may serve as a potential predicting factor for the severity of COVID-19. Further studies are needed to explore a potential protective role of eosinophils in SARS-CoV-2 infection and the potential influence of allergy-elicited eosinophilic inflammation on COVID-19 disease course **(8).**

D-dimer:

Elevated D-dimer is common in COVID-19 patients and may be attributed to sepsis-induced coagulopathy and reflect the higher thromboembolic risk in severe COVID-19 cases. D-dimer levels were significantly higher in severe than in nonsevere COVID-19 patients, and higher in patients with PE than those without PE; and D-dimer > 0.5 mg/L is associated with severe disease of COVID-19. A meta-analysis including 5872 COVID-19 patients also found higher D-dimer concentrations were associated with severity and mortality in these patients. In addition, D-dimer > 2.0 mg/L at admission was an independent risk factor for increased mortality (OR 10.7, 95%CI: 1.10−94.38) in 248 COVID-19 cases. In 123 COVID-19 patients with VTE during hospitalization, D-dimer was associated with the risk of VTE, with OR 1.09 (95%CI: 1.06−1.11) for every 1 μg/ml increase of D-dimer. The OR for D-dimer > 7.5 μg/ml was 4.1 (95%CI: 2.94−5.71). However, our previous study involving 127 severe COVID-19 patients did not identify D-dimer as a risk factor for mortality after adjusting according to age for each patient **(6).**

Dynamic changes of serum D-dimer may be more closely associated with disease severity and outcome of COVID-19. A reduction in D-dimer levels was observed in recovered patients, independent of anticoagulating therapy, whereas a continuous increase in the levels of D-dimer was predictive of a higher risk of thromboembolism and adverse outcomes. Monitoring the dynamic variations of D-dimer is a useful diagnostic tool in predicting the prognosis of COVID-19 patients, and peak D-dimer levels were strongly associated with mortality in COVID-19 patients **(11).**

Platelet counts:

Low platelet counts were frequently observed in COVID-19 patients, especially in severe and critically ill patients. As in other viral infections, reduced platelet production, increased platelet destruction and consumption might contribute to thrombocytopenia .In severely ill patients, COVID-19- induced liver damage could additionally contribute indirectly to exacerbated thrombopenia. Decreased platelet counts were also associated with higher fatalities. In addition, a progressive reduction in platelets was associated with mortality in severe COVID-19 patients. On the other hand, the increased platelet counts in the first 7 days after admission were associated with improved prognosis when compared to those with sustained or progressive reduction in platelet counts **(11).**

Conflicting data have emerged on the association between platelet counts and severity of COVID-19. Some studies have found no significant difference in platelet counts between ICU and non-ICU patients, pediatric patients with and without pneumonia, and among non-survived, survived severe and non-severe patients, although more patients with decreased platelet counts were found in survived severe patients than in non-severe patients (35.9% vs 13.6%). Taken together, these findings suggest that lower platelet counts at

admission and decreasing platelet counts during the disease course may predict severe cases and poor outcome **(12)**.

Lactate dehydrogenase (LDH):

Elevated serum LDH levels have been widely reported in COVID-19 cases and were predominantly higher in severe patients. According to a meta-analysis including 3117 hospitalized COVID-19 patients, the mean value of LDH in severe patients was 1.54 times higher than in non-severe cases (344.48U/L vs 224.20U/L; 95%CI: 307.08−381.88U/L and 205.33−243.07U/L, respectively). The positive correlation between increasing levels of LDH and IL-6 and disease severity (r = 0.749, $P < .001$) makes it a valuable candidate biomarker for monitoring severe COVID-19 patients **(6).**

Additionally, elevated baseline LDH levels were significantly associated with risk of ARDS (HR: 1.61; 95%CI: 1.44−1.79) and mortality (HR: 1.30; 95%CI: 1.11−1.52). Using a mathematical modeling approach, LDH was identified to have the highest weight in both training and evaluation sets based on the area under the curve (AUC) score (94.27 ± 0.82 and 92.29 ± 2.62, respectively), when compared to other biomarkers (low lymphocyte counts and hs-CRP), which stressed that high level of LDH was the most valuable predictive factor for mortality**(11).**

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT):

Biochemical abnormalities of the liver were commonly observed in hospitalized patients with COVID-19, and those with hypoxemia or severe inflammation were more likely to present abnormal biochemical parameters on admission, which may be attributed to cell membrane physiology changes and the development of a cytokine storm. The cause and role of liver damage in COVID-19 however is unclear and, by some authors, has been considered to be collateral damage of a cytotoxic response during viral infection. The prevalence of increased levels of AST and ALT in severe patients (39.4% and 28.1%, respectively) was much higher than that of non-severe cases. In a multicenter retrospective cohort study including 5771 adult COVID-19 patients, the median value of AST and ALT was higher in severe patients (n = 1,186, 20.6%) compared to non-severe patients (n = 4585, 79.4%), with 31.0 U/L vs 22.0 U/L in AST and 26.0 U/L vs 23.0 U/L in ALT. In contrast, other studies have not identified any differences in liver function test results between severe and non-severe cases **(6).**

While an early elevation of AST and its correlation with COVID-19 severity stresses the critical role of immune-mediated inflammation in liver damage, the underlying mechanisms are not fully understood. Viral RNA at high titers has been detected in liver in concentrations exceeding viremia, as founded in an autopsy, suggesting that liver infection with SARS-CoV-2 may contribute to elevated serum AST and ALT in severe COVID-19 patients. Liver biochemical parameters should be closely monitored, and to date, no specific therapy has been recommended in the clinical management of liver disease comorbidity. Elevated AST was also associated with a high risk of mortality, as shown in a cohort of 10 131 US veterans, those with AST > 89 U/L had an aHR of 1.86 (95% CI: 1.35−2.57) when compared to those with AST ≤ 25 U/L **(13).**

Blood urea nitrogen (BUN) and creatinine:

Severe and critical COVID-19 cases are predisposed to renal damage or AKI, mainly indicated by elevated BUN and serum creatinine (Scr) levels. A prominent relevance between the development of AKI, mortality and kidney-related diseases was reported in hospitalized COVID-19 patients. Notably, the prevalence rates of patients with increased BUN and Scr levels among severe cases were 13.1% and 14.4%, respectively, which were significantly higher than those in mild cases **(14).**

Cardiac troponin I (cTNI):

Cardiac injury is manifested in patients with COVID-19. Cardiac troponin I (cTnI) has been identified as a biomarker of cardiac injury. In a study of 416 cases of COVID-19 (35 ICU patients and 381 non-ICU patients), the level of cTnI was significantly higher in the ICU group ($P < .05$). Non-survivors had significantly higher levels of cTnI than survivors ($P < .001$). In a multivariate logistic regression analysis, Chen et al reported that elevated cTnI was an independent risk factor of critical disease (OR 26.9, $P = .001$) **(5). Lala et al (15)** showed that the degree of cardiac injury, small (cTnI: 0.03−0.09 ng/ml) and large (cTnI > 0.09 ng/ml), was significantly associated with COVID-19 fatality (aHR: 1.75 and 3.03, respectively). Based on a mixed-effects Cox model

analysis, a recent study concluded that the aHR of 28-day mortality for elevated high-sensitivity cTnI was 7.12 (*P* = .001), suggesting that the cutoff threshold of biomarkers to assess cardiac injury in COVID-19 patients should be lower. Collectively, these findings suggest that increased cTnI levels are associated with COVID-19 severity and mortality **(12)**.

C-reactive protein (CRP):

Recent studies showed that C-reactive protein (CRP) is positively correlated with the severity of different infections. CRP is a plasma protein produced by the liver cells, called hepatocytes, and its production can be induced by various inflammatory mediators like IL-6. In addition to being a biomarker of acute inflammation, it has recently shown to be associated with chronic inflammations, such as cardiovascular diseases and Type II diabetes mellitus. Also, the early expansion of plasma CRP level is shown to increase the likelihood of developing plasma leakage. Hence, CRP level could early predict COVID-19-associated severe pneumonia. In this regard, although there are blood markers that appear to be linked with the degree of severity and mortality, the level of CRP was sharply increased in severely SARS-CoV-2 infected patients **(15)**

Procalcitonin (PCT):

Increased PCT (normal range 0−0.1 ng/mL) levels were more commonly observed in severe COVID-19 patients (mean 0.1 ng/mL, range [0.06−0.3] ng/mL) compared to non-severe patients (mean 0.05 ng/mL, range [0.03−0.1] ng/mL). These results are in accordance with recent studies where elevated levels of PCT were found in 85 out of 290 patients and are associated with mortality in patients with COVID-19**.** Increased PCT values were associated with a nearly 5-fold higher risk of severe SARS-CoV-2 infection. COVID-19 patients with eosinopenia had higher hs-CRP (50.5 vs 24.6 mg/L) and PCT (0.085 vs 0.05 ng/dL) concentrations than those without eosinopenia **(16).** Increased levels of PCT were also detected in COVID-19 pediatric patients even with mild pneumonia, and were more prevalent in pediatric patients with pneumonia compared to the asymptomatic ones. The PCT levels of discharged patients with COVID-19 were restored to normal levels during recovery**.** These findings suggest that PCT may be a useful biomarker for monitoring disease course **(6).**

Type I interferons (IFN-I):

IFN-I is vital in the immunity against virus infection and a robust IFN-I response was suggested to contribute to severe disease due to hyper inflammation. In COVID-19, severe and critically ill COVID-19 patients had impaired IFN-I activity and robust inflammatory gene expression in blood cells or bronchial lavage fluid macrophages. A recent study found that 101 of 987 patients with life-threatening COVID-19 pneumonia had neutralizing IgG autoantibodies (auto-Abs) against IFN-ω (13 patients), the 13 types of IFN-α (36 patients), or both (52 patients), at the onset of critical disease. These auto-Abs neutralized the ability of the corresponding IFN-I to block SARS-CoV-2 infection in vitro. Auto-Abs were not present in mild symptomatic and asymptomatic COVID-19 patients and only in 4/1277 healthy controls. Moreover, most of these patients with auto-Abs against IFN-I were male and in older age. Another report found at least 23 of 659 patients with life-threatening COVID-19 pneumonia have known or new genetic defects at eight loci involved in the TLR3- and IRF7-dependent induction and amplification of IFN-I. These data collectively suggest that deficiency in IFN-I response could cause severe and critically ill COVID-19. Tests screening for serum type I IFNs levels or rapid production capacity will be of great clinical importance t to identify high-risk patients **(11).**

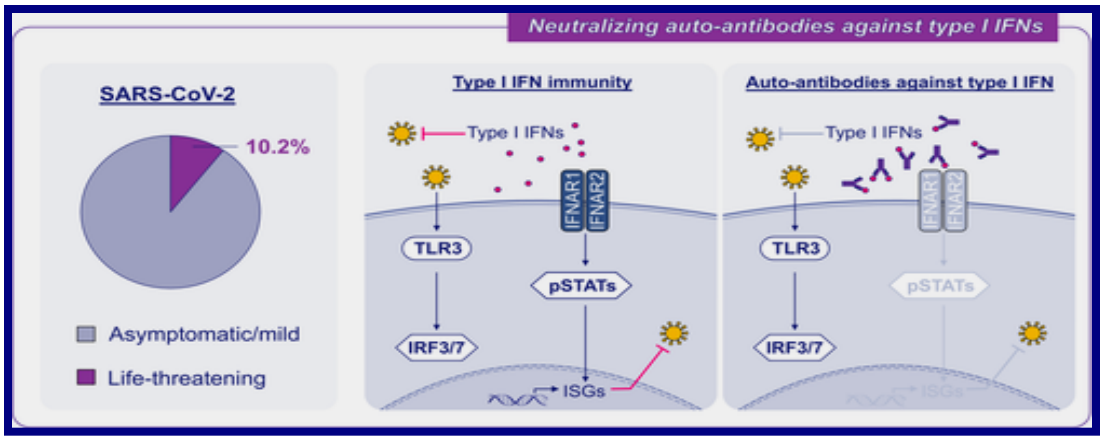

Fig.(2): Neutralizing autoantibodies against type I IFNs. In 101 of 987 (10.2%) life-threatening COVID-19 patients, neutralizing IgG autoantibodies (auto-Abs) against IFN-ω (in 13 patients), the 13 types of IFN-α (in 36 patients), or both (in 52 patients), were found at the onset of critical disease; a few also had auto-Abs against the other three type I IFNs. By contrast, these auto-Abs were not found in 663 individuals with asymptomatic or mild SARS-CoV-2 infection and were present in only 4 of 1227 healthy individuals. These auto-Abs neutralized the ability of the corresponding type I IFNs to block SARS-CoV-2 infection in vitro. The underlying mechanisms of these neutralizing auto-Abs impairing type I IFN immunity are depicted in this figure. ISGs: interferon-stimulated genes; IFNAR: IFN-α receptors. **(16).**

IL-6:

SARS-CoV-2 can trigger signaling of the NOD-like receptor family, pyrin domain containing 3 inflammasome activation in monocytes/macrophages, production of high levels of proinflammatory mediators such as IL-6, IL-1β, enhanced cell death and lead to a cytokine storm **(17)**

Synthesis of CRP can be induced by elevated IL-6 levels, a key inflammatory marker involved in the cytokine storm **(5).** The presence of a systemic inflammatory response has been underlined in a meta-analysis showing that COVID-19 patients had higher levels of IL-6 in non-survivors vs survivors cases (weighted mean difference: 4.6 pg/mL; 95%CI: [3.4−5.8] pg/mL) and severe vs non- severe (weighted mean difference: 1.7 pg/mL; 95%CI: [0.8−2.6] pg/mL)**.** When identifying patients at high risk for severe COVID-19, a cutoff value greater than 55 pg/mL was recommended for serum IL-6 **(18).**

Critically ill patients (64.0 pg/mL) were characterized by significantly higher IL-6 levels compared with moderate and severe patients. Mortality was found to be associated with an IL-6 value of ≥ 100 pg/mL. SARS-CoV-2 RNAemia was closely associated with elevated IL-6 levels and poor prognosis in COVID-19 **(5).** IL-6 levels were higher among patients with immune dysregulation than patients in an intermediate state of immune activation .Tocilizumab, an anti-IL-6 mAb, has been suggested as a potential biological to partially restore the immune dysregulation associated with SARS-CoV-2 and the efficacy of Tocilizumab is still being investigated with ongoing clinical trials **(19).**

Chest computed tomography (CT) imaging patterns:

Chest computed tomography (CT) can be positive in the early phase, several days after the onset of the opening symptom (0−4 days). Over time, the CT findings change characteristically. In the progressive stage (5−8 days), the affected areas usually grow and sometimes thickened interlobular and intralobular lines appear inside the ground glass opacity GGO. This combination pattern is called crazy paving. It is not characteristic for other viral pneumonias; hence, it can help the differential diagnosis, the peak stage (9−13 days) is at about the 10th day. Consolidation often appears mixed with or after GGO. It can be seen as an early sign in elderly patients. The most severe clinical status is acute respiratory distress syndrome, which is radiologically equivalent to diffuse alveolar damage, in the absorption phase, organizing pneumonia pattern appears, and fibrous stripes can be seen with reverse halo sign and mild architectural distortion **(19).**

Ferritin:

Elevated levels of serum ferritin were associated with mortality and the development of severe outcomes in COVID-19. Cytokine storm syndrome can cause multi organ failure and hyperferritinemia **(10).** A study including 141 patients with COVID-19 reported that hyperferritinemia (Serum ferritin > 500 μg/L) was observed in all severe patients on admission, and the mild cases had a normal mean serum ferritin level of (303 ± 224 μg/ml); moreover, severe and ICU patients had higher ferritin levels than the mild patients (2.6 times and 5.8 times, respectively) , ROC curve analysis confirmed the excellent prognostic accuracies of serum ferritin (cutoff value 500 μg/L) in discriminate patients with severe clinical conditions (AUC 0.939, CI: 0.894−0.985; $P < .001$) **(20).**

A meta-analysis of 189 observational studies with data from 57563 COVID-19 patients reported that a significant difference in mean ferritin levels of 606.37 ng/mL (95%CI: 461.86−750.88) was detected between survivors and non-survivors**(21).**

In December 2019, a novel Coronavirus causing the Coronavirus disease 2019 (COVID-19) emerged in Wuhan, China, leading to a global pandemic. The clinical symptoms of COVID-19 range from mild flu-like symptoms to acute respiratory distress syndrome**.** While children and healthy young adults are often less affected by the disease, vulnerable individuals such as the elderly and people with chronic lung disease or cardiovascular comorbidities are at high risk of experiencing complicated courses needing invasive ventilation or circulatory support **(22).**

Recent studies suggest that COVID-19 causes a relevant increase in risks of mortality and morbidity**.** Although the true impact of COVID-19 on mortality and morbidity has become more evident in recent studies, insights regarding psychological burden beyond the acute phase of the illness in these patients and their relatives who may be at high risk for adverse psychological outcomes is limited **(23).**

In fact, most countries have implemented orders to isolate at home or other quarantine measures to contain the spread of COVID-19. As a consequence, patients hospitalized for COVID-19 are often quarantined, and visits also by family members are limited to prevent further spread of the virus. Research during previous epidemics showed that these may be associated with adverse psychological effects on patients and relatives, including an increased risk of anxiety disorders, depression and post-traumatic stress disorder (PTSD). Research on the short-term psychological consequences of the COVID-19 pandemic has shown adverse psychological effects **(24)**.

For instance, a large Swiss survey including 10472 participants of the general public found the prevalence of moderately severe or severe depressive symptoms to increase from 9.1% during confinement at the time of the first pandemic wave to 11.7% during the following partial confinement, and 18% during the second wave. When asked about their symptom levels before the pandemic, i.e., during the first two weeks of February 2020, only 3.4% of participants reported moderately severe or severe depressive symptoms. A cross-sectional German study evaluating 15037 participants from the general population during the beginning of the pandemic reported rates of depressive and anxiety symptoms of 14.3% and 19.7%, respectively, retrospectively assessed rates of depressive and anxiety symptoms before the pandemic were significantly lower with rates of 7.6% and 9%, respectively. **(25)**

While including large samples, interpretation of findings of these studies is partially limited due to their naturalistic approach and lack of pre-COVID-19 data. Findings of prospective studies assessing probability samples of the general population yielded mixed results. Two prospective studies analyzing the prevalence of anxiety before and after the outbreak in two different samples of the general population each, found an increase in clinically relevant symptoms. Findings of a similar Dutch long-term study in older adults and a study comparing serious psychological distress in two samples of the US general population were in line with this **(26)**.

Relatives of patients hospitalized with COVID-19 might be equally affected but evidence is scarce. The study of **Dorman-Ilan et al. (27)** suggests that both isolated COVID-19 patients and relatives might suffer from similarly high levels of anxiety and depressive symptoms during the initial stage of hospitalization.

While heightened psychological distress during the acute phase of the illness in patients and their relatives can be expected, it might be additionally relevant to investigate how many experience clinically relevant symptoms persisting beyond that initial phase and which characteristics might be related to this. However, only few studies evaluated this, so far. Recent studies from Italy, Turkey and China investigating COVID-19 survivors about one to two months after hospital discharge found a prevalence of 10% to 42% for anxiety, 11% to 31% for depression, 12% to 28% for PTSD, and 40% for insomnia, suggesting persisting psychological distress in a considerable number of patients. Furthermore, a recent Chinese study revealed that 23% of patients still experienced anxiety or depression even 6 months after discharge **(6)**.

Factors associated with increased psychological distress might include sociodemographic, illness-related, psychosocial and hospital-related characteristics. A systematic review on the psychological impact of past viral respiratory epidemics indicated that female patients and those with lower education levels experience increased anxiety, depression and PTSD**.** Studies evaluating psychological distress in the context of COVID-19 found female gender, higher age and not being employed to be associated with anxiety. Further, female gender, lower education, not being employed, were potential risk factors for depression **(28).**

The healthcare providers, who are working as the frontliners during the pandemic, are perceived to be overwhelmed and experiencing burnout, even posttraumatic stress disorder (PTSD), from the deluge of COVID-19 cases they have been handling**.** Sixty percent of healthcare providers such as physicians, nurses, and pharmacists are reported to have experienced burnout. Their heavy workloads affect their ability to cope with the demands of their work and to derive a sense of fulfillment from ensuring patients' safety and providing people with high-quality care **(29)** .

The responsibility of healthcare providers is to directly provide and manage COVID-19 care processes, which, considering the overwhelming number of cases, may cause them to develop mental health issues and fail to perceive their own psychological distress symptoms such as anxiety or depression**.** The perspectives of healthcare providers experiencing burnout during the current pandemic should thus be obtained to gain a better understanding of how they are handling such situation and to help them resolve their issues. They experience challenges in dealing with the unpredictable pandemic due to their limited preparedness, the rapid changes occurring in the disease, and the difficulty of performing their duties due to the lack of protocol, accurate information, and proper equipment for preventing contamination. Limited preparedness may lead to physical and psychological problems such as high levels of stress, anxiety, fear, helplessness, hopelessness, anger, stigma and even death **(30).**

During the COVID-19 pandemic, severe shortage of medical resources such as hospital beds, ventilators and intensive care unit (ICU) beds, protective equipment, healthcare workers, were allocated to the prevention, control and treatment of coronavirus infection. This is the case, especially in the epicenters of the disease outbreak in different countries, which led to the insufficiency of healthcare resources and a great burden of healthcare systems. The widespread closing of stores and businesses in the United States and around the world due to the coronavirus is unprecedented. Stores, factories, and many other businesses have closed by policy mandate, downward demand shifts, health concerns, or other factors. For example, the number of active business owners in the United States plummeted from 15.0 million in February 2020 to 11.7 million in April 2020 and only partially rebounded by June, by June losses were at 1.2 million. The shutdowns and reductions in work activity are likely to have resulted in substantial lost income for business owners and may result in permanent closures **(31).**

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