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

Ya-dong Gao[1], Mei Ding[1,2], Xiang Dong[1], Jin-jin Zhang[1], Ahmet Kursat Azkur[3], Dilek Azkur[4], Hui Gan[1], Yuan-li Sun[1], Wei Fu[1], Wei Li[1], Hui-ling Liang[1], Yi-yuan Cao[5], Qi Yan[6], Can Cao[1], Hong-yu Gao[6], Marie-Charlotte Brüggen,[7] Willem van de Veen,[2] Milena Sokolowska,[2] Mübeccel Akdis[2], Cezmi A Akdis[2]¶

1. Department of Allergology, Zhongnan Hospital of Wuhan University, China

2. Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Switzerland

3. Department of Virology, Faculty of Veterinary Medicine, University of Kirikkale, Kirikkale, Turkey

4. Division of Pediatric Allergy and Immunology, Department of Pediatrics, Faculty of Medicine, University of Kirikkale, Kirikkale, Turkey

5. Department of Radiology, Zhongnan Hospital of Wuhan University, China

6. Department of Geriatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, China

7. Department of Dermatology, University Hospital Zurich, Zurich, Switzerland; Faculty of Medicine, University of Zurich, Zurich, Switzerland

Ya-dong Gao: ORCID ID: 0000-0003-1251-7608

Xiang Dong: ORCID ID: 0000-0002-5241-4307

Azkur Ahmet Kursat: ORCID ID: 0000-0002-5597-8917

Azkur Dilek: ORCID ID: 0000-0002-4396-9087

Hui Gan: ORCID ID: 0000-0002-4960-1507

Wei Fu: ORCID ID: 0000-0001-8353-9092

Willem van de Veen: ORCID ID: 0000-0001-9951-6688

Milena Sokolowska: ORCID ID: 0000-0001-9710-6685

Mübeccel Akdis: ORCID ID: 0000-0003-0554-9943

Cezmi A Akdis: ORCID ID: 0000-0001-8020-019X

¶To whom correspondence should be addressed:

Professor Cezmi A Akdis

Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich,

Herman-Burchard Strasse 9,

7265, Davos Wolfgang, Switzerland

Email: akdisac@siaf.uzh.ch

Key Words

SARS-CoV-2; COVID-19; severity; critical illness; mortality; risk factors; age; gender; ethnicity, comorbidities; complications; blood cell count; thromboembolisms; proinflammatory cytokines; chest CT imaging; treatment; diet; lifestyle

Abstract

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

INTRODUCTION

On 15 October 2020, the novel coronavirus disease 2019 (COVID-19) pandemic reached over 40 million confirmed infections and claimed the lives of more than 1 million people worldwide[1]. The clinical features of COVID-19 are diverse and range from lack of symptoms to critical illness and death[2]. Severe and critical cases represented 14% and 5% of laboratory-confirmed COVID-19 patients[2], respectively. This posed a high burden to the healthcare system as it consumed most of its medical resources and contributed to the majority of deaths. Severe patients present signs of dyspnea, respiratory frequency ≥30/ min, blood oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 mmHg, and/or lung infiltrates > 50% within 24 to 48 hours[2]. Critically ill cases may experience respiratory failure that requires mechanical ventilation, shock, disseminated coagulopathy, and other organs failure requiring admission to the intensive care unit (ICU)[3]. A good understanding of the possible risk factors in combination to disease immunopathology associated with COVID-19 severity is helpful for clinicians in identifying patients who are at high-risk and require prioritized treatment to prevent disease progression and adverse outcome[4]. Risk factors range from demographic factors, such as

age[3,5-7], sex and ethnicity[8,9], diet and lifestyle habits[10,11] to underlying diseases[12-22] and complications[23-26], and laboratory indications[27-39]. Many studies have reported predictive models using various risk factors to identify high-risk patients that may develop severe and critical illness[40]. It is worth noting that some studies address the risk factors of COVID-19 development in general, without any focus on disease severity, whilst others specifically focus on risk factors for disease progression to a critical stage. In this review, we present the current data on a comprehensive list of possible risk factors associated with COVID-19 severity.

Demographic factors

Older age and male gender

In a series of multivariable-adjusted analyses based on COVID-19 patient cohorts, higher disease severity was found to be associated with demographic factors, such as older age and male gender[3,6,8,9,41] (Fig. 1). The median age of patients receiving intensive care was higher than those not admitted to the ICU (66 years vs 51 years)[7]. In hospitalized patients, the percentage of severe and critically ill cases ranged from 19.8% to 49.0% in adult cohorts[3,42,43], and only 2.2% in a pediatric cohort[12]. In a US single-center study, 83.8% of patients who received invasive mechanical ventilation were male and significantly younger age was observed among patients who were weaned successfully from mechanical ventilation[44]. Compared to patients aged 30 − 59 years, those aged below 30 and above 59 years were 0.6 (0.3 − 1.1) and 5.1 (4.2 − 6.1) times more likely to die after developing symptoms, respectively, according to data from 79 394 confirmed cases in China[45]. The fatality risk of all cases showed a distinct age-related pattern with a high elderly mortality rate, particularly those aged 60 − 69 (30.2%), 70 − 79 (30.5%) and above 80 (20.3%)[45].

Intriguingly, Kuo et al. reported that biological aging was an optimal predictor of disease severity after performing biological age evaluations comprised of chronological age and nine clinical biomarkers. COVID-19 test-positivity and all-cause mortality were positively associated with accelerated aging 10-14 years prior to the COVID-19 pandemic (odds ratio [OR]: 1.15 and 1.25, respectively, per 5-year acceleration)[46].

Ethnicity

In a study of 10,926 COVID-19-related deaths, Black patients and South Asians were found to have a higher mortality risk compared with subjects of White ethnicity (adjusted hazard ratio [aHR] 1.48, 95%CI: 1.29 − 1.69; and 1.45, 95%CI: 1.32 − 1.58, respectively)[47,48]. In cancer patients, non-White race was identified as an independent risk factor for hospitalization[49]. In New York City, Hispanic race was associated with a higher risk of hospitalization (adjusted OR [aOR]: 1.63; 95%CI: 1.35 − 1.97) but not of

critical illness and mortality[50]. A study of COVID-19 patients in South California (USA) also found that African Americans were predisposed to increased disease severity (OR: 2.1)[9]. Ethnicities other than White were associated with higher COVID-19-related mortality in both type 1 and type 2 diabetes[51]. Interestingly, Black ethnicity was associated with a lower risk of death in patients with end-stage kidney disease hospitalized with COVID-19[21]. In summary, Black and Hispanic races were disproportionally affected with an elevated risk of hospitalization, severity and mortality; underlying diseases may be important confounding factors.

Symptoms

Fever

Fever was more frequently reported in hospitalized than in non-hospitalized COVID-19 patients[52]. Patients with fever had a higher risk of mechanical ventilation (aHR: 2.31; 95%CI: 1.95 − 2.75) and mortality (aHR: 1.51, 95% CI: 1.32 − 1.72) than those without fever[53]. Our previous study also showed that fever was more frequently reported in severe patients than in non-severe patients[3]. Another study involving 52 critically ill COVID-19 patients showed that 98% presented fever[54]. Fever greater than 38.5°C on admission was positively correlated with the severity and mortality of COVID-19[6]. Fever was also associated with higher severity (OR: 6.21; 95%CI: 1.76 − 21.99) in cancer patients with COVID-19[55]. In pediatric COVID-19 patients, fever was also more frequently observed in patients with pneumonia than those without pneumonia (50% vs 27.8%)[12]. Collectively, these findings suggest that fever is an important risk factor for severity and high fever might be a risk factor for mortality of COVID-19.

Shortness of breath/dyspnea

In a cohort of 10131 elderly COVID-19 patients, those with dyspnea had a higher risk of hospitalization (aHR: 2.18; 95%CI: 2.02 − 2.36), mechanical ventilation (aHR: 2.95; 95%CI: 2.49 − 3.49) and mortality (aHR: 1.78; 95%CI: 1.53 − 2.07)[53]. Dyspnea was more common in COVID-19 patients with ≥ 2 comorbidities than those with one comorbidity (55.4% vs 34.1%)[15]. Our group has previously reported that chest tightness and dyspnea were more frequently presented in severe patients than in non-severe patients[3]. Prevalence of dyspnea in critically ill COVID-19 patients was 63.5% (33/52)[54], and 76.2% were admitted to the ICU[56]. COVID-19 patients in the ICU were more likely to present dyspnea than non-ICU patients (63.9% vs 19.6%)[57]. In cancer patients diagnosed with COVID-19, dyspnea was associated with a higher risk of severity (OR: 2.60; 95% CI: 1.00 − 6.76) and mortality (OR: 4.94; 95% CI: 1.99 − 12.25)[55]. These findings suggest that the presence of dyspnea is an important risk factor for hospitalization and severity and may be associated with mortality of COVID-19.

Gastrointestinal symptoms

Gastrointestinal symptoms such as nausea, vomiting, diarrhea and emesis were more frequently reported in hospitalized COVID-19 patients[52]. Nausea (aHR: 1.56; 95%CI: 1.11 − 2.19) and diarrhea (aHR: 1.57; 95%CI: 1.21-2.02) were associated with a higher risk of mechanical ventilation[53]. We have previously reported that loss of appetite was significantly different between severe and non-severe COVID-19 patients[3]. In cancer patients with COVID-19, gastrointestinal symptoms were associates with higher severity (OR: 7.38; 95%CI: 2.71 − 20.16)[55]. In summary, currently available data indicates that the presence of gastrointestinal symptoms is associated with increased severity of COVID-19.

Comorbidities that increase severe outcomes

Hypertension

Hypertension was more frequent in severe COVID-19 patients compared to non-severe patients[13,58]. Wang et al. reported that the prevalence of hypertension was significantly higher among COVID-19 patients requiring ICU care than those not admitted to ICU (58.3% vs. 21.6%; $P < 0.001$)[7]. However, the prevalence of hypertension is high in the elderly and so this confounding factor should be excluded.

Li et al. found that hypertension was an independent risk factor for severe COVID-19 (OR: 2.01; $P = 0.003$)[58]. Huang et al. showed that the OR of hypertension was 1.562 ($P = 0.092$) and 1.262 ($P = 0.458$) in the multivariate analysis of severity and mortality, respectively[14]. There was significant heterogeneity on the association between hypertension comorbidity and COVID-19 severity. The Center for Disease Control and Prevention (CDC) states that individuals with hypertension are at increased risk for severe illness from COVID-19[12]. In a retrospective study including 803 COVID-19 patients with co-existing hypertension, high average systolic blood pressure (SBP) and high SBP/diastolic BP variability during hospitalization were independently associated with in-hospital mortality, ICU admission, and heart failure, suggesting that lower and stable BP is predictive of a better prognosis for these patients[59]. The imbalance between the two major renin-angiotensin-aldosterone system pathways, angiotensin-converting enzyme (ACE) 2/Angiotensin-(1–7) and ACE/Angiotensin II[60] may contribute to the increased risk of severity of COVID-19 patients with comorbidities and advanced age as depicted in Fig. 1.

Moreover, the use of angiotensin II receptor blockers (ARB)/ACE inhibitor (ACEI) for the treatment of COVID-19 patients with hypertension was associated with lower mortality when compared to those without ARB/ACEI therapy[61]. Another study showed that patients prescribed with at least 6 months of ARB/ACEI prior to SARS-CoV-2 infection were not associated with a higher susceptibility and mortality

of COVID-19[62]. Other anti-hypertension medications were also not associated with susceptibility and mortality[62].

Diabetes

Diabetes is a common comorbidity in COVID-19 patients[5], and was suggested to be a risk factor of severe and fatal COVID-19 cases[12]. A meta-analysis showed that COVID-19 patients with diabetes had a higher risk (risk ratio [RR]: 2.96; 95% CI: 2.31 − 3.79) of severity or death[63], and higher rate of ICU admissions[64]. In a cohort study of COVID-19 patients from New York City (USA), those with diabetes had an increased risk of hospital admission (OR: 2.24; 95%CI: 1.84 − 2.73) and critical illness (OR: 1.24; 95%CI: 1.03-1.50)[50]. Another meta-analysis demonstrated that the ORs of diabetes for ICU admission and mortality were 2.79 (95%CI: 1.85 − 4.22) and 3.21 (95%CI: 1.82 − 5.64), respectively[65]. In addition, diabetic patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had a higher risk of death, irrespective of the blood sugar levels[47]. Moreover, patients with poor blood sugar control were identified to be at higher risk of COVID-19-related death than those patients with well-controlled blood sugar level[51].

Mechanistically, ACE2 expression, the entry receptor of SARS-CoV-2, is elevated in type 2 diabetes mellitus patients in the lungs and other tissues[66]. This upregulation is associated with chronic inflammation, endothelial cell activation and insulin resistance which aggravates the inflammatory response and leads to dysfunction of the alveolar-capillary barrier[67] (Fig. 2). In summary, the clinical course and prognosis of COVID-19 in diabetic patients was significantly more severe.

Obesity

In a large cohort study of 433,995 COVID-19 patients, obese patients presented an increased risk of hospitalization (adjusted relative risk [aRR]: 2.20) and severity (aRR: 2.30). This was not observed in patients aged 65-79 years but was notable in the population with age younger than 50 years (aRR: 5.02 and 13.80, respectively)[68]. Similarly, Gao et al. reported a higher risk of severity and longer hospital stay in obese COVID-19 patients, which was positively correlated with BMI (aOR: 3.00 for obesity, aOR: 1.13 for BMI).[69] Obese patients with BMI ≥35 kg/m^2 had an increased risk of admission to the ICU (OR: 3.6) in COVID-19 patients < 60 years[16]. Male obese COVID-19 patients were at higher risk of severe outcome compared to healthy individuals with OR of 5.66[70]. Moreover, BMI above 40 kg/m^2 was evaluated as an independent risk factor associated with mortality, more pronounced in patients younger than 50 years (aOR: 5.1)[71]. Interestingly, obese COVID-19 patients with metabolic-associated fatty liver disease were at higher risk of severe outcome (aOR: 6.32) after adjustment for age, sex, smoking, diabetes, hypertension and dyslipidemia[72].

Impaired chest-wall elastance and reduced respiratory system compliance leading to damaged lung function[73], higher levels of pro-inflammatory status and interleukin (IL)-6 levels, and a higher risk of thrombosis all contribute to increased risk of severe COVID-19 in obese patients[74], as shown in Fig. 2. In addition, endothelial cell activation and insulin resistance may also contribute to blood-gas barrier dysfunction.

ACE2 was overexpressed in the adipocytes of obese individuals. The involvement of ACE2 in pulmonary lipofibroblasts and other adipose-like cells during SARS-CoV-2 infection remains largely unknown[75]. Obese subjects had higher expression of SARS-CoV-2-related molecules SLC16A3 (MCT4), integrin α (ITGA)3, nuclear factor of activated T cells 1 (NFATC1) in bronchial alveolar lavage samples and basigin (BSG) (CD147), peptidylpeptidyl−prolyl cis/trans isomerase a (PPIA, cyclophilin A), galectin-3 (LGALS3), and nucleotide-binding oligomerization domain (NOD) 2 in blood samples as compared to non-obese individuals[76]. In addition, MCT4, ITGA3, LGALS3 and CD44 positively correlated with BMI in the BAL, whereas BSG, PPIA, S100A9, CD44, LGALS3 and SLC16A3 positively correlated with BMI in the blood[76]. In addition, plasma soluble ACE2 levels were associated with BMI and leptin, a biomarker for obesity, HbA1C and homeostatic model assessment of insulin resistance (HOMA-IR), the biomarker for insulin resistance and hyperglycemia, suggesting a possible role of insulin resistance in COVID-19 severity[77]. All these aspects might play a role in the higher severity of COVID-19 in obese patients.

Allergy and asthma

Current studies on the association between the severity of COVID-19 and allergic diseases and asthma are controversial. A study on adult and pediatric patients in Wuhan[5,12,58] and a large case-series from China[2] showed no or low prevalence of asthma or allergic history in COVID-19 patients. Similarly, a study from New York City did not identify asthma in COVID-19 patients as a predisposing factor for receiving invasive mechanical ventilation[78]. Only 1.8% (24/1307) of COVID-19 patients admitted to the ICU had a history of asthma, as reported in a Russian cohort[79]. In a recent study, atopic status was associated with lower incidence of severe complications of COVID-19[80]. In contrast, other epidemiological data indicates that asthma and/or allergy comorbidities are positively correlated with the severity of COVID-19[17,81,82]. For example, data analysis of a population-based prospective cohort from 492,768 participants in the UK Biobank indicated that patients with asthma had a significantly higher risk of disease progression to a severe outcome (aOR: 1.39; $P = 0.002$) compared to healthy individuals[17]. In another large-scale Korean nationwide cohort of COVID-19 patients ($n = 7340$)[82], severe clinical outcomes were observed in 6.9% and 4.5% of patients with and without asthma (aOR: 1.62), respectively, and 4.7% and 3.7% of patients with and without allergic rhinitis, respectively (aOR: 1.27, $P < 0.05$). Interestingly, the results from both

studies indicate that individuals with non-allergic asthma have a higher risk for severe outcome of COVID-19 than those with allergic asthma[17,82]. Studies in Italy showed that severe asthma did not increase the risk of severe outcome of COVID-19[83,84]; however, another study demonstrated that those with more severe asthma who require a high dose of inhaled corticosteroids to maintain asthma control may be at risk of a worse prognosis from COVID-19[85]. The nasal and airway epithelial cells of patients with respiratory allergy is characterized by a reduced ACE2 expression[86,87] and upregulation of transmembrane protease serine 2 (TMPRSS2)[76], two essential molecules for entry of SARS-CoV-2 into the cell.[87] This may result in a lower risk of infection but a higher risk of severity. Further research is warranted to improve our current understanding of the type 2 immune response in COVID-19 as it is targeted by biologicals in the treatment of asthma and atopic dermatitis[88,89]. In addition, deeper inside into phenotypes and endotypes of asthma might provide more understanding of the pathophysiology of COVID-19 in asthma[90].

Chronic obstructive pulmonary disease (COPD)

A recent report demonstrated that COPD is not a predisposing factor for SARS-CoV-2 infection, but once the patient develops the disease they have an elevated risk of hospitalization (aOR: 1.36), ICU admission (aOR: 1.20) and receiving invasive mechanical ventilation (aOR: 1.49)[18]. In a multicenter study including 476 COVID-19 patients, the prevalence of COPD was found to be significantly different according to disease severity: lowest in the moderate group (2.3%), intermediate in the severe group (5.6%) and highest in the critically ill group (15.7%) [91]. Similarly, in a cohort of 289 hospitalized COVID-19 patients, 6.1% of non-survived patients were observed with COPD comorbidity, remarkably higher than the COPD prevalence of 0.6% of non-severe patients [3]. There are significant differences in the prevalence of patients with coexisting COPD between countries. A higher prevalence of COPD was noted in ICU patients in Wuhan (8.3%)[7], Spain (38%) and Seattle (33%)[56,92,93]. In a multicenter cohort of 191 COVID-19 patients, non-survivors had higher COPD prevalence (7%) compared to survivors (1%). [41] Guan et al. demonstrated that COPD (hazard ratio [HR]: 2.681) was a risk factor for ICU admission, invasive ventilation and death after adjustment for age and smoking in a Chinese nationwide COVID-19 analysis[15].

Restricted pulmonary function is an important confounding factor and several molecular mechanisms have been proposed (Fig. 3). The higher ACE2 expression in the airways in COPD subjects is negatively correlated with forced expiratory volume in the first second (FEV1)%[94]. Other molecules related to SARS-CoV-2 infection were also noted with increased expression in COPD subjects, such as SLC2A1 (GLUT1) in human bronchial epithelial cells, SLC7A5(CD98), ITGA3, and ITGA6 in bronchial biopsies[76]. A cohort of 961 COVID-19 patients in Wuhan showed a poorer clinical course among patients with coexisting COPD compared to asthmatics, with OR 23.433 for severe illness and OR 19.762 for

acute respiratory distress syndrome (ARDS)[43]. Consistently, ACE2 expression in the lower airways was elevated in COPD patients and reduced in asthma patients. Moreover, compared to asthmatics, patients with coexisting COPD were characterized by a reduction in $CD4^+$ T and $CD8^+$ T cells and B cells and elevated levels of the cytokines including tumor necrosis factor-α (TNF- α), IL-10, IL-8 and IL-6[43].

Interstitial lung disease (ILD)

COVID-19 patients with preexisting ILD are more susceptible to progressing to a severe or critical case due to restrictive ventilatory dysfunction and a limited pulmonary reserve (Fig. 3). In addition, SARS-CoV-2 infection may trigger an exacerbation of underlying ILD and result in critical illness and poor outcome[95]. In 28 COVID-19 patients with preexisting ILD, 19 (67.9%) were severe or critical cases[96]. Continuation of immunosuppressive therapy in ILD patients was recommended as it would not have an adverse effect of COVID-19 and might even be beneficial given the hyperinflammation state in these patients[95]. COVID-19 patients with preexisting ILD had a poorer prognosis with fatalities ranging from 30.0% to 60.0% with OR from 3.2 to 5.5[19,96,97].

Chronic liver diseases (CLD)

Approximately 2-11% of patients with COVID-19 had underlying CLD and 14-53% of patients with COVID-19 developed hepatic dysfunction[57,98-101]. Patients with CLD (cirrhosis, chronic hepatitis B, alcoholic liver disease, and other types of chronic hepatitis) are at increased risk of infection due to their altered immune function and are more susceptible to decompensation or development of acute-on-chronic liver failure with bacterial, fungal or viral infection. Patients with autoimmune liver diseases or post-transplant patients under immunosuppressive therapy are at an even higher risk[102]. None of these studies identified CLD as a risk factor for severe and critical illness. A study in the US found that preexisting CLD was associated with higher fatalities (RR: 2.8; 95% CI 1.9 − 4.0, $P < 0.001$) as compared to patients without liver disease and the relative risk was significantly higher in patients with cirrhosis (RR: 4.6; 95% CI: 2.6 − 8.3, $P < 0.001$)[20].

Chronic kidney diseases (CKD)

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

prevalence of comorbidities, such as hypertension, cardiovascular disease, and diabetes mellitus, which might contribute to the poorer outcomes among these COVID-19 patients.

Cancer and chemotherapy

Patients with cancerogenous tumors and hematologic malignancies are vulnerable to SARS-CoV-2 infection due to compromised immunity[103]. Patients with cancer were at higher risk of severe cases than those without any comorbidities (OR: 3.61; 95% CI: 2.59 − 5.04, P < 0.001), as demonstrated in a study in Wuhan involving 13077 COVID-19 patients[22]. This is in contrast to a cohort study involving 1044 active cancer patients with COVID-19 in the UK, which showed a lower ICU admission rate when compared to those cancer patients without COVID-19[104]. Older age, elevated IL-6, procalcitonin (PCT), D-dimer, reduced lymphocytes, advanced tumor stage, elevated TNF-α, N-terminal pro-B-type natriuretic peptide, reduced $CD4^+$ T cells and reduced albumin–globulin ratio were all identified as risk factors of COVID-19 severity in patients with cancer[22]. Another study identified age > 65 years and treatment with immune checkpoint inhibitors (ICIs) as predictors for hospitalization and severe disease, independent of chemotherapy treatment and major surgery[49]. This is not consistent with the findings reported by Luo et al., which showed that programmed death 1 (PD-1) blockade therapy is not associated with the severity of COVID-19 patients with lung cancer[105]. Interestingly, having an initial cancer diagnosis > 24 months prior to infection was associated with increased severity (OR: 1.74; 95%CI: 0.71-4.26)[55]. In summary, cancer comorbidity is associated with a higher risk of prevalence and severity of COVID-19. Tumor type, duration and therapy may be determining factors correlated with disease severity.

Pregnancy

Physiological changes in the immune and respiratory system may make pregnant women more susceptible to COVID-19 infection[106]. Associated with placental immaturity, the early ACE2 expression can make the first trimester the most susceptible period for SARS-CoV-2 infection[107]. A report by the US CDC demonstrated that the prevalence of COVID-19 in pregnant women was 9.0% (8207/91412)[108]. Pregnant COVID-19 women had a higher ICU admission rate than nonpregnant COVID-19 women (1.5% vs 0.9%); 0.5% of pregnant women required mechanical ventilation compared with 0.3% of nonpregnant women, with comparable mortality rates[108]. In Sweden, the risk of being admitted to ICU was also higher in pregnant and immediately postpartum women with laboratory-confirmed SARS-CoV-2, compared to nonpregnant women of similar age (relative risk: 5.39; 95% CI: 2089 − 10.08)[109]. Taken together, currently available data showed a higher risk of ICU admission in pregnant COVID-19 women.

Immunodeficiency

Studies of severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome-CoV suggest that patients with HIV often have a reduced risk of both virus infection and severe disease course[110]. This might be attributed to the suppression of coronavirus replication by antiretroviral therapy. However, these patients have a longer duration of the disease, which might be due to their immune-suppressed status[110]. In a Spanish cohort, 51 people living with HIV were coinfected with COVID-19 (incidence 1.8%) and all received antiretroviral therapy, and 13 of them (25.5%) progressed to severe case[111]. Inciarte et al. recently reported a 0.9% incidence (53/5683) of COVID-19 in people living with HIV, which is lower than in the general population. Of these 53 patients, 6 (14%) were severe, 4 (8%) required ICU admission, and 2 (4%) died. Antiretroviral therapy was not associated with COVID-19 diagnosis and severity[112]. A meta-analysis involving 25 studies and 252 HIV patients coinfected with SARS-CoV-2 showed that 21.2% were at a severe and critical stage[113]. In summary, HIV is not associated with increased susceptibility of SARS-CoV-2 infection and is not a risk factor of severe disease and mortality.

Meyts et al. reported the course of COVID-19 in 94 patients with an underlying inborn error of immunity (IEI) that the patients with primary antibody deficiencies were the predominant group (56%). A significant subgroup of IEI patients had mild COVID-19 and risk factors predisposing to severe disease and mortality in the general population were also found to affect IEI patients, including more younger patients[114]. A recent study has found a strong association between low type-I interferon (IFN) production capacity and severity of COVID-19[115-117](Fig. 4 and Fig. 5). Subcutaneous injection of IFN β-1a has been reported as an effective and safe treatment of severe COVID-19, significantly increasing discharge rate on day 14 and decreasing fatalities on day 28[118]. An ongoing clinical trial with SNG001, an inhaled IFN-β, showed promising results in reducing the odds of hospitalized COVID-19 patients progressing to severe disease (https://www.uhs.nhs.uk/ClinicalResearchinSouthampton/Research/News-and-updates/Articles/Inhaled-drug-prevents-COVID-19-patients-getting-worse-in-Southampton-trial.aspx).

Viral Load

Exposure to high concentrations of SARS-CoV-2 and kinetics of viral load were highly predictive markers of severe course and outcome in older patients[119,120]. There is controversy on the association between viral load and disease severity in patients with COVID-19[121]. For patients with COVID-19 viral load in week 1 or week 3, median viral load was 6.70 $\log_{10}$ copies per mL (range: 4.17 – 8.64)[122]. SARS-CoV-2 can be detected in the sputum, the bronchoalveolar lavage fluid, the pharyngeal swabs, and in the stool[123,124]. A high SARS-CoV-2 load can be detected at symptom onset, showing high levels in the first 24 h and peaking on day 5 − 6 of illness. It has been recently demonstrated that asymptomatic and post-symptomatic individuals can be SARS-CoV-2 positive, especially in children. Viral genome can be

detected in asymptomatic individuals. These results stress the need for early detection of infection to minimize potential transmission[123,125-127]. Assessment of cycle threshold (Ct) value patients is a valuable measurement for the care of hospitalized patients with COVID-19. Studies suggested that SARS-CoV-2 is considered a high viral load when Ct value < 25 − 27, medium viral load, Ct value 25 – 32 and low viral load, Ct value > 30 – 32. Risk factors associated with high viral load include older age, congestive heart failure, diabetes, chronic kidney disease, and the use of inhaled/nasal and oral steroids before admission[128-131]. Blot et al. reported that the alveolar viral load at the onset of ARDS is closely correlated with disease progression, especially leading to hypoxemia[132]. In contrast, a recent study showed an initial and median SARS-CoV-2 viral load ranging from 3 to 10 $\log_{10}$ copies/ml and 6.78 $\log_{10}$ copies/ml, respectively. According to this study, viral load appears to be a poor predictor of disease outcome and it is not age-dependent[133]. Linder et al. observed that fulminant myocarditis was not associated with SARS-CoV-2 infection in cardiac tissue from 39 consecutive autopsy cases even though SARS-CoV-2 was found in heart tissues[134]. Antiviral therapy such as convalescent plasma, remdesivir or early IFN treatment can reduce viral load and severity of diseases[135-138].

Complications

Acute kidney injury (AKI)

Kidney disease is frequently observed in COVID-19 hospitalized patients. Early reports from China found the occurrence of AKI ranged from 0.5% to 29%[41,101,139]. Cheng et al. reported an AKI rate of only 5.1% in 701 patients from Wuhan, China[139]. Recent data from New York City found a 46% incidence of AKI among 3993 hospitalized patients with COVID-19[140]. Out of the patients with urine study results (435 from 1835 AKI patients), the majority presented proteinuria (84%) and hematuria (81%)[140]. Another study from New York of 5449 hospitalized COVID-19 patients, 36.6% developed AKI and 14.3% of these patients progressed to necessitating renal replacement therapy (RRT). The majority of patients under mechanical ventilation developed AKI (86.9%), and 23.2% of intubated patients required RRT[23]. AKI is common among critically ill patients with COVID-19, 76% of patients admitted to ICU presented AKI, and it is considered a marker of disease severity and a negative prognostic factor for clinical outcomes[41,140]. Soluble urokinase plasminogen activator receptor (suPAR) has been identified as an immunologic risk factor for AKI. In a multinational observational study of adult patients hospitalized for COVID-19, AKI incidence rose with increasing suPAR tertials, from a 6.0% incidence in patients with suPAR < 4.60 ng/ml to a 45.8% incidence of AKI in patients with suPAR levels > 6.86 ng/ml. None of the patients with suPAR < 4.60 ng/ml required dialysis. The highest suPAR tertial was strongly associated

with incident AKI (aOR: 9.15; 95%CI: 3.64 − 22.93)[141]. In view of these results, suPAR might be used as a potential biomarker for AKI and COVID-19 severity.

Thromboembolism

There is recent clinical evidence that COVID-19 patients are at higher risk of thromboembolism than other viral pneumonia[26], which may be due to endothelial injury by the virus and disrupted cell membranes[24] and immobile state. The prevalence of thromboembolism in COVID-19 patients is most likely to be underestimated[142]. Bilaloglu et al. reported a 16% incidence of thrombotic events diagnosed based on routine clinical care (pulmonary embolism [PE], deep vein thrombosis, myocardial infarction, ischemic stroke and other thromboembolisms) in 3334 COVID-19 patients in New York City[143]. The prevalence of PE in this study was 3.2%, but computed tomography pulmonary angiography (CTPA) images indicated a significantly higher incidence of 24%[26]. Not surprisingly, thromboembolism complications are associated with severe and critical illness of COVID-19, as a stronger cytokine storm and inflammation develops in these patients. Moreover, thromboembolism in mild cases, especially PE and microthrombi in small vessels and microvasculature[144] will inevitably progress to hypoxemia and poorer clinical outcome. Other thromboembolisms, such as myocardial infarction, ischemia stroke, or thrombosis in other organs, including the liver, spleen, kidney and intestine arteries will also deteriorate the disease and develop into severe and critical illness and increase the mortality. Indeed, patients with PE were more frequently admitted to the ICU and required mechanical ventilation[26]. In a retrospective study involving 127 COVID-19 patients, D-dimer and CRP were biomarkers associated with the risk of venous thromboembolism (VTE). The receiver operating characteristic (ROC) curve of both variables combined had an area under the ROC curve (AUC) of 0.83, $p < 0.05$. The predictive value of D-dimer > 15 μg/ml in combination with a CRP > 280 mg/dl was 98% for VTE[145]. Therefore, D-dimer and CRP levels may be potential predictive biomarkers of developing VTE.

Coagulation disorders

COVID-19-associated coagulopathy is characterized by elevated D-dimer levels (increased thrombosis), lower platelet count, prolongation of prothrombin time (PT) and activated partial-thromboplastin time (APTT), elevated levels of fibrinogen, blood coagulation factor VIII, and von Willebrand factor[146,147]. Severe and critically ill patients had prolonged PT and levels of fibrinogen at admission compared with mild and moderate patients[148]. Fibrinogen levels were significantly higher in severe patients than in non-severe patients (4.23 g/L vs 3.07 g/L, $P = 0.002$)[149]. A meta-analysis involving nine studies and 1105 patients confirmed elevated levels of PT and D-dimer, but not APTT and PLT in severe patients[150]. A study with 1207 COVID-19 patients demonstrated that APTT > 37 s was associated with a high risk (OR:

3.07; 95% CI: 1.37 − 6.86) of cardiovascular complications, which is an indicator of severity and mortality of COVID-19[151]. Further studies with a larger sample size are needed to clarify the association of the above-mentioned clinical parameters with the severity of COVID-19. Bleedings associated with prophylactic or therapeutic anticoagulant therapy were more common in critically ill patients than in noncritically ill patients (7.6% vs 3.1%), and major bleeding almost only occurred in critically ill patients[152]. This suggests that bleeding may be an important determinant of critical illness. Interestingly, patients with congenital coagulation disorders had a lower COVID-19 prevalence, milder symptoms and better prognosis when compared to the general population in an Iran cohort study[153]. Possible mechanisms involved in PE formation are illustrated in Fig. 3.

Anticoagulants

Prophylactic and therapeutic anticoagulant therapy regimes have been used in COVID-19 patients with a higher risk of thromboembolism. Few reports have evaluated the effect of anticoagulant therapy on the severity of COVID-19. It has been recently reported that both therapeutic (aHR: 0.53; 95%CI: 0.45 − 0.62, P < 0.001) and prophylactic (aHR: 0.50; 95%CI: 0.45 − 0.57, P < 0.001) coagulants could reduce in-hospital mortality and intubation rates, with no significant difference between the prophylactic and therapeutic group[25]. In patients under mechanical ventilation, administration of therapeutic anticoagulants mitigates in-hospital mortality when compared to those not receiving anticoagulants (29.1% vs 62.7%)[154]. Therapeutic enoxaparin could improve gas exchange and decrease the need for mechanical ventilation in severe COVID-19[155]. Even though there are a few studies with conflicting results, in general, most studies support a beneficial effect of anticoagulant therapy on reducing the mortality of COVID-19[144]. Further studies with a larger sample size are warranted to elucidate the association between anticoagulant therapy with the severity and mortality of COVID-19.

Laboratory Indicators

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

Leukocyte counts

Viral infection leads to dynamic changes in peripheral blood leukocyte counts and its subsets. Leukocytosis, elevated leukocyte counts ($\geq 9.5\times10^9$/L), was associated with COVID-19 disease course[3,5] and the increase was more pronounced in severe and critical patients compared to non-severe patients[3,5,58,156-158], which may be indicative of the 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 < 0.00001) compared to the mild group[28].

A higher neutrophil count on admission was found in severe or critically ill patients compared to mild and moderate patients[27,159]. The progressive increase in leukocyte count and sustained lymphopenia and eosinopenia in severe COVID-19 patients may be associated with the progression of inflammatory status, which might progress to a fatal clinical outcome[3,58]. The neutrophil-to-lymphocyte ratio (NLR) has been reported as an independent predictor of disease severity in COVID-19 patients[12,159]. Collectively, these results are indicative of leukocytosis, and the altered number of leukocytes and neutrophils may be an aggravating factor for the disease course of COVID-19.

Lymphocyte counts

A sustained decrease in the peripheral blood lymphocyte count is an early indicator of severe/critically ill COVID-19 patients. There is a plethora of literature presenting lymphopenia in a significant proportion of patients with COVID-19[3,5,12,27,28,58,156-159]. The decreased lymphocyte counts might be caused by viral attachment, immune injuries from inflammatory mediators, or exudation of circulating lymphocytes into inflammatory lung tissues[160]. 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[7,101,161]. For example, in a study of the first 41 laboratory-confirmed cases with COVID-19[161], 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 = 0.045). Yang et al. reported that among 52 critically ill adult patients, lymphocytopenia occurred in 85% of patients and no significant difference was observed between survivors and non-survivors[54].

Wang et al. examined the peripheral lymphocyte subset alteration in COVID-19[160]. The results showed that compared to patients with mild illness, severe cases had significantly lower total lymphocytes (P = 0.0007), $CD4^+$ T cells (P = 0.024), $CD8^+$ T cells (P = 0.005), and B cells (P = 0.018)[160]. Among the lymphocyte subsets, $CD8^+$ T cells tended to be a potential predictor for COVID-19 severity[160]. Similarly, Chen et al. reported that decreased $CD4^+$ and $CD8^+$ T cell counts and suppressed IFN-γ production by $CD4^+$ T cells may be correlated with disease severity[162]. Interestingly, higher lymphocyte count (≥ 1.1×10^9/L) was identified as a risk factor for patients with recurrence of SARS-CoV-2 RNA positivity[163]. A better understanding of the factors that affect lymphocytes, particularly T lymphocyte counts and their association with disease severity in COVID-19 patients is of importance for clinical management of COVID-19.

Eosinophil counts

In the first preliminary study reporting eosinopenia in COVID-19 patients[5], decreased eosinophil counts (< 0.02×10^9/L) was commonly observed in these patients (73/138, 52.9%). However, there was no significant difference in the ratio of patients with decreased eosinophil counts between severe and non-severe patients (P = 0.06). Many studies have demonstrated that eosinopenia is more prominent in severe COVID-19 patients than in mild patients[29,157,164-166]. Chen et al. showed a reduction in eosinophil counts in most of the severe/critical and fatal COVID-19 patients compared to mild/moderate and survived subjects on admission (0.01×10^9/L vs 0×10^9/L, P < 0.001)[159]. 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[167]. Interestingly, immunophenotyping of whole blood leukocytes in COVID-19 patients revealed that eosinophil CRTH2 (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[168]. These data suggested that eosinophil surface marker expression, but not eosinophil counts, represents a risk factor for severe COVID-19.

The eosinopenia in COVID-19 patients may be due to the anti-viral effect of eosinophils[165]. The underlying pathophysiology may involve 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[166].

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

D-dimer

Elevated D-dimer is common in COVID-19 patients and may be attributed to sepsis-induced coagulopathy and reflect the higher thromboembolic risk in severe COVID-19 cases[26,169]. D-dimer levels were significantly higher in severe than in non-severe COVID-19 patients[42], and higher in patients with PE than those without PE[26]; and D-dimer > 0.5 mg/L is associated with severe disease of COVID-19[30]. A meta-analysis including 5872 COVID-19 patients also found higher D-dimer concentrations were associated with severity and mortality in these patients[170]. 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[171]. 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)[172]. However, our previous study involving 127 severe COVID-19 patients did not identify D-dimer as a risk factor for mortality after adjusting according to age for each patient[3].

Dynamic changes of serum D-dimer may be more closely associated with disease severity and outcome of COVID-19. A reduction in D-dimer levels was observed in recovered patients, independent of anticoagulating therapy, whereas a continuous increase in the levels of D-dimer was predictive of a higher risk of thromboembolism and adverse outcomes[41,156]. 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[7].

Platelet counts

Low platelet counts were frequently observed in COVID-19 patients, especially in severe and critically ill patients[31,173]. Reduced platelet production, increased platelet destruction and consumption might contribute to thrombocytopenia, as proposed by Xu et al.[174].

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

Conflicting data has emerged on the association between platelet count and severity of COVID-19. Some studies have found no significant difference in platelet count between ICU and non-ICU patients[161], pediatric patients with and without pneumonia[12], and among non-survived, survived severe and non-severe patients, although more patients with decreased platelet count were found in survived severe patients than in non-severe patients (35.9% vs 13.6%)[3]. Taken together, these findings suggest that a lower platelet count at admission and decreasing platelet count during the disease course may predict severe cases and poor outcome.

Lactate dehydrogenase (LDH)

Elevated serum LDH levels have been widely reported in COVID-19 cases and were predominantly higher in severe patients[175]. According to a meta-analysis including 3,117 hospitalized COVID-19 patients[176], 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 ($r = 0.749$, $P < 0.001$), makes it a valuable candidate biomarker for monitoring severe COVID-19 patients[33]. Additionally, elevated baseline LDH levels were significantly associated with risk of ARDS (HR: 1.61; 95%CI: 1.44 − 1.79) and mortality (HR: 1.30; 95%CI: 1.11 − 1.52)[177]. Another study revealed that high level of LDH alone was the most valuable predictive factor for mortality[162]. Therefore, LDH is reasonably regarded as a valuable biomarker for severe and critical COVID-19 patients, especially those suffering from cardiac comorbidities.

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)

Biochemical abnormalities in the liver were commonly observed in hospitalized patients with COVID-19[178], and those with hypoxia manifestations 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 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 5,771 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 = 4,585, 79.4%), with 31.0 U/L vs 22.0 U/L in AST and 26.0 U/L vs 23.0 U/L in ALT[34]. In contrast, other studies have not identified any differences in liver function test results between severe and non-severe cases[179]. Whilst 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. Liver biochemical parameters should be closely monitored, and to date, no specific therapy has been recommended in the clinical management of liver disease comorbidity[102]. Elevated AST was also associated with a high risk of mortality, as shown in a cohort of 10131 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[53].

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[139]. Notably, the prevalence 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[139]. In a meta-analysis involving 25,278 patients with COVID-19, higher levels of Scr and BUN were associated with severe cases (Scr: MD: 7.78 μmol/L; 95% CI: 4.43 – 11.14, $P < 0.00001$; BUN: MD: 2.12 mmol/L; 95% CI: 1.74 – 2.50, P

< 0.00001)[180]. In addition, the development of AKI in baseline Scr elevated patients was much more rapid than in most COVID-19 cases (2 days vs 6 days) [35]. Thus, high levels of BUN and Scr should be regarded as an important index in the risk stratification of disease severity in COVID-19 patients.

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 ($P < 0.05$)[36]. Non-survivors had significantly higher levels of cTnI than survivors ($P < 0.001$)[181]. In a multivariate logistic regression analysis, Chen et al. reported that elevated cTnI was an independent risk factor of critical disease (OR 26.9, $P = 0.001$)[182]. Lala et al. showed that the degree of cardiac injury, small (cTnI: 0.03 − 0.09 ng/ml) and large (cTnI > 0.09 ng/ml), was significantly associated with COVID-19 fatality (aHR: 1.75 and 3.03, respectively)[170]. 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 ($P = 0.001$), suggesting that the cut-off threshold of biomarkers to assess cardiac injury in COVID-19 patients should be lower[183]. Collectively, these findings suggest that increased cTnI levels are associated with COVID-19 severity and mortality.

C-reactive protein (CRP)

High levels of serum CRP is a key marker of disease progression and is a risk factor for mortality of severe COVID-19 patients and is indicative of a developing cytokine storm in COVID−19 patients[3,184]. 375 patients with COVID-19 presented elevated levels of high-sensitivity (hs)-CRP (26.3 mg/L [2.0 mg/L− 99.10 mg/L])[162]. In a study of 989 patients in Wuhan, elevated hs-CRP (reference 4 mg/L) were more frequently observed in COVID-19 patients than in 45.2% of the controls (27.4 [8.9 − 66.8] mg/L and 3.1 [3.1 − 14.8] mg/L, respectively)[37]. A CRP cutoff value of 34.67 mg/L (sensitivity 82.3%, specificity 73%) discriminates severe and non-severe COVID-19 pneumonia relative to D-dimer[185]. Out of 32 studies, 20 have shown a nearly four-fold higher risk of poor outcomes in COVID-19 patients with elevated CRP[186]. Laboratory analysis of patients admitted to the ICU showed an overall increase of CRP levels in the first seven days, peaking between days two and three[48].

Procalcitonin (PCT)

Increased PCT (normal range 0 − 0.1 ng/mL) levels were more commonly observed in severe patients (mean 0.1 ng/mL, range [0.06 − 0.3] ng/mL) with COVID-19 compared to non-severe (mean 0.05 ng/mL, range [0.03 − 0.1] ng/mL)[5,42]. These results are in accordance with recent studies where elevated levels of PCT were found in 85 out of 290 patients[187], and are associated with mortality in patients with COVID-

19[3,184]. Increased PCT values were associated with a nearly 5-fold higher risk of severe SARS-CoV-2 infection[32]. Patients with eosinopenia had higher hs-CRP (50.5 vs 24.6 mg/L) and PCT (0.085 vs 0.05 ng/dL) concentrations in COVID-19[29]. Increased levels of PCT were detected in COVID-19 pneumonia, though mild, and it was more prevalent in the pediatric population compared to asymptomatics[12]. The PCT levels of discharged patients with COVID-19 were restored to normal levels during recovery. These findings suggest that PCT may be a useful biomarker for monitoring disease course[161,188].

Type I interferons (IFN-I)

IFN-I is vital in the immunity against virus infection and a robust IFN-I response was suggested to contribute to severe disease due to hyperinflammation[189]. In COVID-19, severe and critically ill COVID-19 patients had impaired IFN-I activity and robust inflammatory gene expression in blood cells[38] or bronchial lavage fluid macrophages[116]. 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), or both (52), 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 older age[115](Fig. 7). Another report found at least 23 of the 659 patients with life-threatening COVID-19 pneumonia studied have known or new genetic defects at eight loci involved in the TLR3- and IRF7-dependent induction and amplification of IFN-I[117](Fig. 5). These data collectively suggest that deficiency in IFN-I response could cause severe and critically ill COVID-19. Tests screening for anti-IFN antibodies and a genetic deficiency of IFN-I production will be of great interest to identify high-risk patients.

IL-6

SARS-CoV-2 can trigger 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[190]. Synthesis of CRP can be induced by elevated IL-6 levels, a key inflammatory marker involved in the cytokine storm[3,184,191]. The systemic inflammatory response is evident in a meta-analysis of COVID-19 patients revealing elevated levels of IL-6 in non-survivors vs survivors (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)[192]. When identifying patients at high-risk for severe COVID-19 a cut-off value greater than 55 pg/mL was recommended for serum IL-6[193]. 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[191]. IL-6 levels were higher among patients with immune dysregulation than patients in an intermediate state of immune activation. Tocilizumab has been suggested as a potential biological to partially restore the immune dysregulation associated with SARS-CoV-2[194].

IL-1β

Increased IL-1β concentrations were positively correlated with disease severity[195,196], by aggravating the inflammatory storm in COVID-19 patients[197,198]. A statistical difference was found between patients with non-severe COVID-19 (13.7 ± 5.8 pg/ml) and those admitted to the ICU (40.8 ± 10.4 pg/ml)[199]. A critical threshold value for IL-1β of > 0.5 pg/mL was suggested as predictive of COVID-19 survival. IL-1β remained significant even after adjustment for demographics and comorbidities[200,201]. Several biologicals have been investigated targeting the IL-1β inflammatory pathway. Anakinra, a recombinant human IL-1 receptor antagonist, was reported to reduce the need for invasive mechanical ventilation and mortality in patients with severe forms of COVID-19[202]. Similarly, canakinumab may inhibit the dysregulated immune response in COVID−19 patients and dampen myocardial injury or other immunopathological diseases[201,203].

Krebs von den Lungen-6 (KL-6)

KL-6 is mainly produced by damaged or regenerating alveolar type II pneumocytes[39]. Both baseline or peak serum KL-6 levels were higher in critical and severe COVID-19 cases than in non-severe cases[204]. Consistently, another study also demonstrated higher serum concentrations of KL-6 in severe patients than in non-severe patients, with a cut-off value of 406.5 U/ml[39]. Xue et al. found similar results and showed that KL-6 levels correlated with pulmonary lesion area in digital radiography and computed tomography images, oxygen index and oxygen partial pressure difference of alveolar artery (PA-aDO2)[205]. These findings suggest that serum KL-6 can be used as a novel biomarker for severe COVID-19.

Chest computed tomography (CT) imaging patterns

Chest CT scans have been routinely used as a diagnostic tool at the early stage of COVID-19, although with a relatively low specificity[206]. Chest CT imaging manifestations of COVID-19 are diverse and subpleural ground-glass opacity and consolidation are the most common signs[43].

Chest CT images can also be used to assess the severity and prognosis of COVID-19. Li et al. found that a high lung lesion score was associated with severity. Clinical features associated with severe/critical COVID-19 pneumonia included CT findings of consolidation, linear opacities, crazy-paving patterns,

bronchial wall thickening, high CT scores, and extrapulmonary lesions[41]. We previously showed that the numbers of affected pulmonary lobes were higher in severe patients than in non-severe patients, and were correlated with age, CRP, D-dimer and BUN[3]. Similarly, Xiong et al. demonstrated that CRP, erythrocyte sedimentation rate and LDH significantly correlated with the severity of pneumonia on initial CT and follow-up CT images indicated disease progression during the early stage from illness onset[207]. Artificial intelligence (AI) assisted CT quantification of pneumonia lesions is based on three features: percentages of ground-glass opacity volume (PGV), semi-consolidation volume (PSV), and consolidation volume (PCV). These measurements taken at day 0 and day 4 provide an early and non-invasive indication of progression of disease to a severe course[208]. In addition, the semi-quantitative CT pneumonia score is a valuable tool to help clinicians identify patients at higher risk of complications and mortality[100,209]. AI algorithms can identify important clinical markers correlated with COVID-19 pneumonia lesions and also provide accurate clinical prognosis that can aid clinicians to provide risk-stratified treatment[42].

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

Ferritin

Elevated levels of serum ferritin were associated with mortality and the development of a severe outcomes in COVID-19. Cytokine storm syndrome can cause multiorgan failure and hyperferritinemia[119,135,210,211]. A study including 141 patients with COVID-19 reported that severe and ICU patients had higher ferritin levels than the mild patients (2.6 times and 5.8 times, respectively)[212]. A meta-analysis of 189 observational studies with data from 57,563 COVID-19 patients reported that a significant difference in mean ferritin levels of 606.37 ng/mL (95% CI: 461.86 − 750.88) was detected between survivors and non-survivors[213]. Another meta-analysis involving 25 studies and 5350 patients showed that high ferritin was associated with a poor outcome in COVID-19 and development of ARDS[161]. Wu et al. reported that patients with ARDS had significantly higher serum ferritin levels than patients without comorbidities (457.66 ng/ml vs 1029.28 ng/ml, $P < 0.01$)[177]. Plasma exchange, high-volume hemofiltration, and desferrioxamine might be used to lower ferritin levels in patients with COVID-19. These therapies are already used for the treatment of sepsis and macrophage activation syndrome[214,215].

Diet and lifestyle

There is substantial scientific evidence that foods and nutrients affect immune system functions, and many metabolic or chronic diseases have been implicated with poor diet and lifestyle. The discrepancy in mortality rates of COVID-19 between European countries suggests that diet may play a vital role in

maintaining homeostasis essential for fighting infection[11]. Although there is a scarcity of data, diet and lifestyle may be potential risk-factors of COVID-19 (Fig. 8).

Vitamin C and vitamin D

Vitamin C acts as an antioxidant and cofactor for regulatory enzymes and acts on both the innate and adaptive immune system[216]. It has been recently demonstrated that vitamin C might attenuate proinflammatory and procoagulant mechanisms, ameliorating vascular and lung injury in sepsis and ARDS[217]. A recent randomized trial evaluating patients with sepsis and ARDS suggested a beneficial effect of high-dose intravenous vitamin C on mortality[218]. A pilot study in 21 critically ill COVID-19 patients found low serum levels of vitamin C and vitamin D. Older age and low vitamin C levels appeared to be co-dependent risk factors for mortality in COVID-19 patients[219]. Currently, a new clinical trial has been initiated to investigate the beneficial effects of high-dose vitamin C on the treatment of severe COVID-19[220].

Vitamin D is well-known to regulate gene transcription and immune response. The active metabolite of vitamin D, 1,25-dihydroxyvitamin D ($1,25\text{-}(OH)_2D_3$) modulates nuclear factor (NF)-κB activity and then induces the production of many molecules amplifying the inflammatory response, such as IL-6, IL-1β, TNF-α, stimulates the production, mobilization, and adhesion of inflammatory cells, and influences the production of enzymes such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2, phospholipase A2 and free radicals[221,222]. A recent review indicated that vitamin D ameliorates the inflammatory response through multiple pathways and protects against respiratory infections and reduces the risk of influenza and COVID-19[223]. In summary, vitamin C and D may play a role against COVID-19 infection through multiple pathways of the immune system and inflammatory response. Further research is warranted to assess vitamin D deficiency as a risk factor for the severity of COVID-19.

Proteins

There are limited reports on high- or low-protein diets in the context of COVID-19. Mice with protein-calorie malnutrition had a diminished expression of IFN-γ, TNF-α, and iNOS in lung tissues, comprising their ability to fight infection[224]. Thereby, an appropriate intake of proteins to maintain physiological requirements is essential in maintaining a healthy immune response to protect against SARS-CoV-2.

Carbohydrates

There is a scarcity of data on the association between carbohydrates and COVID-19. A recent report has suggested that a high carbohydrate diet contributes to the prevalence of obesity, insulin resistance and

type 2 diabetes, which are all risk factors of severe COVID-19[225]. In view of these results, a high-carbohydrate diet may increase the risk of severe COVID-19.

Mediterranean diet and intermittent fasting

The Mediterranean diet (MD) is typically high in vegetables, fruits, whole grains, beans, nuts, seeds, and olive oil, weekly intake of fish, poultry, eggs, and moderate dairy products, but limits intake of red meat. It is regarded as a healthy and sustainable dietary pattern and is associated with reduced risk factors for cardiovascular disease[226], and may have protective effects against COVID-19. As shown in several surveys on changes in eating habits during the pandemic, the adherence to MD increased in some individuals[227-229]. However, there is limited data on the association between MD and COVID-19 severity and further studies are warranted.

Ketogenic diet

The ketogenic diet (KD) is a low-carbohydrate diet resulting in a metabolic state called ketosis. KD leads to weight loss, decreases in blood sugar and favorable changes in serum triglycerides, and may be beneficial in managing certain medical conditions, such as epilepsy[230]. KD was proposed as a prophylactic diet regimen that might limit viral loads[231]. Moreover, eucaloric ketogenic diet (EKD) had a putative benefit for anti-inflammation through modulation of immune metabolism and prevention of cytokine storm syndrome, which involves in inhibiting M1 macrophages, activating M2 macrophages, stimulating IFN-α synthesis and hindering viral replication[232]. Thus, a multi-center randomized controlled trial has been developed to evaluate the effects of EKD with natural Mediterranean food as a supplementary strategy to treat moderate COVID-19 patients and is currently pending governmental approval [232]. The main endpoint is to prevent disease progression to critical illness and reduce mortality. In addition, intermittent fasting, a commonly used dietary practice, should be considered as a potential therapeutic strategy for COVID-19, as it has been previously demonstrated as an effective method to treat obesity and insulin resistance[233].

Minerals

Certain macro-minerals and trace elements are essential and have key roles in the immune response towards infection. For example, magnesium was found to be inversely correlated with the levels of hs-CRP, IL-6, and TNF-α[234]. Common trace elements such as zinc, iron, copper and selenium also act as co-factors for various enzymes involved in antioxidant reactions and have key immunomodulatory roles[235]. However, the roles of these micronutrients on the severity of COVID-19 infection is not fully understood.

Short-chain fatty acids

Short-chain fatty acids (SCFAs) are metabolic compounds fermented from dietary fiber by the gut microbiota. Increased SCFAs were associated with higher whole-grain intake and exert anti-inflammatory effects through SCFA-related G-protein-coupled receptor[236] by modulating cytokine secretion in monocytes[237], and by regulating the migration of immune cells[238]. Taken together, SCFAs may play a key role in modulating the inflammatory process associated with COVID-19.

Omega-3 fatty acids

Omega-3 polyunsaturated fatty acids (PUFAs), especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been demonstrated to exhibit anti-inflammatory effects in various diseases[239]. Arachidonic acid (AA)-derived lipid autacoids, including prostaglandins (PGs), thromboxane and leukotrienes, are collectively termed eicosanoids and are critical mediators of inflammation, resolution and tissue homeostasis. Infectious processes can activate inflammasome formation leading to an eicosanoids storm consisting of both proinflammatory and anti-inflammatory mediators. SARS-CoV-2 infection leads to tissue damage, cell debris release, endoplasmic reticulum stress, inflammatory enzyme induction and thus triggering an eicosanoids storm, which then stimulates a cytokine storm[240]. The development of an eicosanoid storm is well-documented as a key pathogenic event in COVID-19. EPA/DHA can shift the endogenous eicosanoid profile from arachidonic acid (AA) to EPA-/DHA-derived metabolites, diminishing the synthesis of inflammatory eicosanoids and cytokines, and stimulates the production of specialized pro-resolving lipid mediators (SPMs) to restore immune homeostasis and limit the critical inflammatory period[240,241]. These results suggest that omega-3 PUFAs could ameliorate the inflammatory state caused by viral infections, including COVID-19, and two clinical trials have been initiated to assess the benefits of dietary supplementation with omega-3 PUFA for the treatment of severe COVID-19 patients[241].

High-fiber diet

A high-fiber diet has beneficial effects on glucose metabolism with lower glycemia and higher plasma levels of insulin-sensitizing adipocytokine. It might also reduce the levels of proinflammatory cytokines such as IL-6, IL-18 and TNF-α[242,243]. A high-fiber diet promotes gut microbiota diversity leading to favorable mucosal inflammation[244].

Other diet-related factors

Diet might explain the discrepancies in mortality rates observed between and within countries. Notably, the consumption of fermented vegetables was identified to mitigate COVID-19 severity. For each g/day

increase of consumption of fermented vegetables, the mortality risk for COVID-19 was found to decrease by 35.4%[10].

Occupation-related factors: healthcare workers

Healthcare workers are considered at high risk of exposure to and infection with SARS-CoV-2, due to higher viral load exposure and more exposure time[245]. Data from China CDC showed that healthcare workers accounted for 3.8% of COVID-19 cases, 14.8% of them were classified as severe or critical, and the mortality rate was 0.3%, neither exceeding the overall rate (19% and 2.3%, respectively)[2]. Another survey of COVID-19 infection among 9684 healthcare workers in a Wuhan hospital showed that the infection rate was 1.1%, and 15.5% of cases were severe or critical and one (0.9%) died[246]. In Germany and Malaysia, the mortality rate was 0.2% − 0.5% and severe illness was more common in doctors than in other occupational groups (8.1% vs 4.1%)[247]. Healthcare workers in Italy were also disproportionally affected with an approximate 20% infection rate, which is significantly higher than that of the general population, and some of them have died[248]. Clinical lung function test may convey risk of SARS-CoC-2 infection for health workers during COVID-19 due to the emission of small droplets containing viral particles[249]. The relationship between COVID-19 severity and specific occupations, such as healthcare workers, warrants further and detailed investigations.

Smoking

Smoking is associated with a higher expression of ACE2 in airway epithelial cells, predisposing an individual to SARS-CoV-2 infection[76]. There is increasing evidence demonstrating that smoking is associated with severity and mortality, as suggested by the World Health Organization[250]. A recent meta-analysis found that 25.6% (8417/32849) of hospitalized COVID-19 patients had a smoking history. Current smokers had a significant increased risk of severe COVID-19 (RR: 1.80; 95% CI: 1.14 − 2.85), and severe or critical COVID-19 (RR: 1.98; 95%CI: 1.16 − 3.38). Former smokers also had a significant increased risk of severe COVID-19 (RR: 1.31; 95%CI:1.12 − 1.54) and severe or critical COVID-19 (RR: 1.35; 95% CI: 1.19 − 1.53). Both current and former smoking patients had an elevated risk of in-hospital mortality, disease progression and need for mechanical ventilation[251,252]. Therefore, appropriate measures should be taken to support and maintain smoking cessation to protect the vulnerable population and diminish the risk of the disease progressing to a severe/critical illness[251].

Conclusion

The major risk factors of severe clinical course and outcomes of COVID-19 patients have been identified as elderly age, male gender, ethnicity, fever, dyspnea, gastrointestinal symptoms, preexisting

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

Legends

Figure 1 Mechanisms of age, sex and hypertension on the severity of COVID-19.

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

Figure 2 Mechanisms of diabetes and obesity on severity of COVID-19.

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

Figure 3: **Possible mechanisms contributing to increased severity by chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD) and pulmonary embolisms comorbidities.**

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

Figure 4 Type 1 interferon (IFN) immunity in patients with life-threatening COVID-19.

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

Figure 5. Inborn errors of type 1 interferon (IFN) immunity.

Inborn errors of toll-like receptor 3 (TLR3) and interferon regulating factor 7 (IRF7)-dependent type I IFN immunity underly life-threatening COVID-19 pneumonia in patients with no prior severe infection. Loss of function (LOF) variants at 13 loci known to govern TLR3 and IRF7-dependent type I IFN immunity against influenza were also identified in 3.4% (23/659) patients with life-threatening COVID-19 pneumonia, compared to only 1 heterogeneous predicted to be LOF variation at the 13 loci (IRF7p. Leu99fs). SARS-CoV-2 infection stimulates type I IFNs production in plasmacytoid dendritic cells (pDC)

in IRF7-dependent pathway; in respiratory epithelial cells, SARS-CoV-2 infection activates TLR3, which induces the production of Type I IFNs production in IRF3- and IRF7- dependent pathway; Type I IFNs secreted by pDCs bind to IFN-α receptors (IFNAR)1/2 and activate interferon stimulated genes (ISGs), which have potent antiviral activity. (Zhang Q et al., *Science.* 2020 Sep 24).

Figure 6. **Laboratory indexes associated with severe and critical COVID-19.**
Changes in blood cell counts and differentiation: increased leucocytes, 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.

Figure 7. Neutralizing autoantibodies against type I IFNs.
In 101 of 987 (10.2%) life-threatening COVID-19 patients, neutralizing IgG autoantibodies (auto-Abs) against IFN-ω (13 patients), the 13 types of IFN-α (36), or both (52), 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 1,227 healthy individuals. These auto-Abs neutralized the ability of the corresponding type I IFNs to block SARS-CoV-2 infection in vitro. The underlying mechanisms of these neutralizing auto-Abs impairing type I IFN immunity are depicted in this figure. ISGs: interferon-stimulated genes; IFNAR: IFN-α receptors. (Bastard P et al., *Science* 2020 Sep 24)

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

References

1. World Health Organizatio (WHO). Coronavirus disease (COVID2019) situation reports https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed Sept 22, 2020.
2. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020; 323(13): 1239-42.
3. 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* 2020.
4. Sokolowska M, Lukasik Z, Agache I, et al. Immunology of COVID-19: mechanisms, clinical outcome, diagnostics and perspectives – a report of the European Academy of Allergy and Clinical Immunology (EAACI). *Allergy* 2020: In Press.
5. Ou M, Zhu J, Ji P, et al. Risk factors of severe cases with COVID-19: a meta-analysis. *Epidemiol Infect* 2020; 148: e175.
6. Wolff D, Nee S, Hickey NS, Marschollek M. Risk factors for Covid-19 severity and fatality: a structured literature review. *Infection* 2020.
7. 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(1): 169.
8. Zhang J, Wang X, Jia X, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. *Clin Microbiol Infect* 2020; 26(6): 767-72.
9. Ebinger JE, Achamallah N, Ji H, et al. Pre-existing traits associated with Covid-19 illness severity. *PLoS One* 2020; 15(7): e0236240.
10. Bousquet J, Anto JM, Czarlewski W, et al. Cabbage and fermented vegetables: From death rate heterogeneity in countries to candidates for mitigation strategies of severe COVID-19. *Allergy* 2020.
11. Bousquet J, Anto JM, Iaccarino G, et al. Is diet partly responsible for differences in COVID-19 death rates between and within countries? *Clin Transl Allergy* 2020; 10: 16.
12. Du H, Dong X, Zhang JJ, et al. Clinical characteristics of 182 pediatric COVID-19 patients with different severities and allergic status. *Allergy* 2020.
13. Li R, Tian J, Yang F, et al. Clinical characteristics of 225 patients with COVID-19 in a tertiary Hospital near Wuhan, China. *J Clin Virol* 2020; 127: 104363.
14. Huang S, Wang J, Liu F, et al. COVID-19 patients with hypertension have more severe disease: a multicenter retrospective observational study. *Hypertens Res* 2020; 43(8): 824-31.
15. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J* 2020; 55(5).
16. Lighter J, Phillips M, Hochman S, et al. Obesity in Patients Younger Than 60 Years Is a Risk Factor for COVID-19 Hospital Admission. *Clin Infect Dis* 2020; 71(15): 896-7.
17. Zhu Z, Hasegawa K, Ma B, Fujiogi M, Camargo CA, Jr., Liang L. Association of asthma and its genetic predisposition with the risk of severe COVID-19. *J Allergy Clin Immunol* 2020; 146(2): 327-9 e4.
18. Attaway AA, Zein J, Hatipoglu US. SARS-CoV-2 infection in the COPD population is associated with increased healthcare utilization: An analysis of Cleveland clinic's COVID-19 registry. *EClinicalMedicine* 2020: 100515.
19. Esposito AJ, Menon AA, Ghosh AJ, et al. Increased Odds of Death for Patients with Interstitial Lung Disease and COVID-19: A Case-Control Study. *Am J Respir Crit Care Med* 2020.
20. Singh S, Khan A. Clinical Characteristics and Outcomes of Coronavirus Disease 2019 Among Patients With Preexisting Liver Disease in the United States: A Multicenter Research Network Study. *Gastroenterology* 2020; 159(2): 768-71 e3.
21. Ng JH, Hirsch JS, Wanchoo R, et al. Outcomes of patients with end-stage kidney disease hospitalized with COVID-19. *Kidney Int* 2020.

22. Tian J, Yuan X, Xiao J, et al. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. *Lancet Oncol* 2020; 21(7): 893-903.
23. Hirsch JS, Ng JH, Ross DW, et al. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int* 2020; 98(1): 209-18.
24. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med* 2020; 383(2): 120-8.
25. Nadkarni GN, Lala A, Bagiella E, et al. Anticoagulation, Mortality, Bleeding and Pathology Among Patients Hospitalized with COVID-19: A Single Health System Study. *J Am Coll Cardiol* 2020.
26. Bompard F, Monnier H, Saab I, et al. Pulmonary embolism in patients with COVID-19 pneumonia. *Eur Respir J* 2020; 56(1).
27. 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.
28. Huang G, Kovalic AJ, Graber CJ. Prognostic Value of Leukocytosis and Lymphopenia for Coronavirus Disease Severity. *Emerg Infect Dis* 2020; 26(8): 1839-41.
29. Zhao L, Zhang YP, Yang X, Liu X. Eosinopenia is associated with greater severity in patients with coronavirus disease 2019. *Allergy* 2020.
30. Yu HH, Qin C, Chen M, Wang W, Tian DS. D-dimer level is associated with the severity of COVID-19. *Thromb Res* 2020; 195: 219-25.
31. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. *Clin Chim Acta* 2020; 506: 145-8.
32. Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. *Clin Chim Acta* 2020; 505: 190-1.
33. 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(7): e12421.
34. Lei F, Liu YM, Zhou F, et al. Longitudinal Association Between Markers of Liver Injury and Mortality in COVID-19 in China. *Hepatology* 2020; 72(2): 389-98.
35. Yang X, Jin Y, Li R, Zhang Z, Sun R, Chen D. Prevalence and impact of acute renal impairment on COVID-19: a systematic review and meta-analysis. *Crit Care* 2020; 24(1): 356.
36. Zeng JH, Wu WB, Qu JX, et al. Cardiac manifestations of COVID-19 in Shenzhen, China. *Infection* 2020.
37. Yu Q, Wang Y, Huang S, et al. Multicenter cohort study demonstrates more consolidation in upper lungs on initial CT increases the risk of adverse clinical outcome in COVID-19 patients. *Theranostics* 2020; 10(12): 5641-8.
38. Hadjadj J, Yatim N, Barnabei L, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science* 2020; 369(6504): 718-24.
39. d'Alessandro M, Cameli P, Refini RM, et al. Serum KL-6 concentrations as a novel biomarker of severe COVID-19. *J Med Virol* 2020.
40. Sotgiu G, Gerli AG, Centanni S, et al. Advanced forecasting of SARS-CoV-2-related deaths in Italy, Germany, Spain, and New York State. *Allergy* 2020; 75(7): 1813-5.
41. 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(10229): 1054-62.
42. Zhang K, Liu X, Shen J, et al. Clinically Applicable AI System for Accurate Diagnosis, Quantitative Measurements, and Prognosis of COVID-19 Pneumonia Using Computed Tomography. *Cell* 2020; 181(6): 1423-33 e11.
43. Ye Z, Zhang Y, Wang Y, Huang Z, Song B. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. *Eur Radiol* 2020; 30(8): 4381-9.

44. Mughal MS, Kaur IP, Jaffery AR, et al. COVID-19 patients in a tertiary US hospital: Assessment of clinical course and predictors of the disease severity. *Respir Med* 2020; 172: 106130.
45. Wu JT, Leung K, Bushman M, et al. Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China. *Nat Med* 2020; 26(4): 506-10.
46. Kuo CL, Pilling LC, Atkins JC, et al. COVID-19 severity is predicted by earlier evidence of accelerated aging. *medRxiv* 2020.
47. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; 584(7821): 430-6.
48. Wendel Garcia PD, Fumeaux T, Guerci P, et al. Prognostic factors associated with mortality risk and disease progression in 639 critically ill patients with COVID-19 in Europe: Initial report of the international RISC-19-ICU prospective observational cohort. *EClinicalMedicine* 2020; 25: 100449.
49. Robilotti EV, Babady NE, Mead PA, et al. Determinants of COVID-19 disease severity in patients with cancer. *Nat Med* 2020; 26(8): 1218-23.
50. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ* 2020; 369: m1966.
51. 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(10): 823-33.
52. Burke RM, Killerby ME, Newton S, et al. Symptom Profiles of a Convenience Sample of Patients with COVID-19 - United States, January-April 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69(28): 904-8.
53. 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(9): e2022310.
54. 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* 2020; 8(5): 475-81.
55. Russell B, Moss C, Papa S, et al. Factors Affecting COVID-19 Outcomes in Cancer Patients: A First Report From Guy's Cancer Center in London. *Front Oncol* 2020; 10: 1279.
56. Arentz M, Yim E, Klaff L, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *JAMA* 2020; 323(16): 1612-4.
57. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; 323(11): 1061-9.
58. 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(1): 110-8.
59. 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.
60. South AM, Brady TM, Flynn JT. ACE2 (Angiotensin-Converting Enzyme 2), COVID-19, and ACE Inhibitor and Ang II (Angiotensin II) Receptor Blocker Use During the Pandemic: The Pediatric Perspective. *Hypertension* 2020; 76(1): 16-22.
61. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med* 2020; 382(19): 1787-99.
62. Fosbol EL, Butt JH, Ostergaard L, et al. Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With COVID-19 Diagnosis and Mortality. *JAMA* 2020; 324(2): 168-77.
63. 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.
64. 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(7): 1382-91.

65. Roncon L, Zuin M, Rigatelli G, Zuliani G. Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. *J Clin Virol* 2020; 127: 104354.
66. Rajpal A, Rahimi L, Ismail-Beigi F. Factors leading to high morbidity and mortality of COVID-19 in patients with type 2 diabetes. *J Diabetes* 2020.
67. Hayden MR. Endothelial activation and dysfunction in metabolic syndrome, type 2 diabetes and coronavirus disease 2019. *J Int Med Res* 2020; 48(7): 300060520939746.
68. Fresan U, Guevara M, Elia F, et al. Independent role of morbid obesity as a risk factor for COVID-19 hospitalization: a Spanish population-based cohort study. *Obesity (Silver Spring)* 2020.
69. Gao F, Zheng KI, Wang XB, et al. Obesity Is a Risk Factor for Greater COVID-19 Severity. *Diabetes Care* 2020; 43(7): e72-e4.
70. Cai Q, Chen F, Wang T, et al. Obesity and COVID-19 Severity in a Designated Hospital in Shenzhen, China. *Diabetes Care* 2020; 43(7): 1392-8.
71. 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(9): 1595-9.
72. Zheng KI, Gao F, Wang XB, et al. Letter to the Editor: Obesity as a risk factor for greater severity of COVID-19 in patients with metabolic associated fatty liver disease. *Metabolism* 2020; 108: 154244.
73. Jose RJ, Manuel A. Does Coronavirus Disease 2019 Disprove the Obesity Paradox in Acute Respiratory Distress Syndrome? *Obesity (Silver Spring)* 2020; 28(6): 1007.
74. Sattar N, McInnes IB, McMurray JJV. Obesity Is a Risk Factor for Severe COVID-19 Infection: Multiple Potential Mechanisms. *Circulation* 2020; 142(1): 4-6.
75. Kruglikov IL, Scherer PE. The Role of Adipocytes and Adipocyte-Like Cells in the Severity of COVID-19 Infections. *Obesity (Silver Spring)* 2020; 28(7): 1187-90.
76. Radzikowska U, Ding M, Tan G, et al. Distribution of ACE2, CD147, CD26, and other SARS-CoV-2 associated molecules in tissues and immune cells in health and in asthma, COPD, obesity, hypertension, and COVID-19 risk factors. *Allergy* 2020.
77. Kornilov SA, Lucas I, Jade K, Dai CL, Lovejoy JC, Magis AT. Plasma levels of soluble ACE2are associated with sex, Metabolic Syndrome, and its biomarkers in a large cohort, pointing to a possible mechanism for increased severity in COVID-19. *Crit Care* 2020; 24(1): 452.
78. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical Characteristics of Covid-19 in New York City. *N Engl J Med* 2020; 382(24): 2372-4.
79. Avdeev S, Moiseev S, Brovko M, et al. Low prevalence of bronchial asthma and chronic obstructive lung disease among intensive care unit patients with COVID-19. *Allergy* 2020.
80. Scala E, Abeni D, Tedeschi A, et al. Atopic status protects from severe complications of COVID-19. *Allergy* 2020.
81. Garg S, Kim L, Whitaker M, et al. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 - COVID-NET, 14 States, March 1-30, 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69(15): 458-64.
82. Yang JM, Koh HY, Moon SY, et al. Allergic disorders and susceptibility to and severity of COVID-19: A nationwide cohort study. *J Allergy Clin Immunol* 2020.
83. Antonicelli L, Tontini C, Manzotti G, et al. Severe asthma in adults does not significantly affect the outcome of COVID-19 disease: Results from the Italian Severe Asthma Registry. *Allergy* 2020.
84. Heffler E, Detoraki A, Contoli M, et al. COVID-19 in Severe Asthma Network in Italy (SANI) patients: Clinical features, impact of comorbidities and treatments. *Allergy* 2020.
85. Kow CS, Capstick T, Hasan SS. Are severe asthma patients at higher risk of developing severe outcomes from COVID-19? *Allergy* 2020.
86. Jackson DJ, Busse WW, Bacharier LB, et al. Association of respiratory allergy, asthma, and expression of the SARS-CoV-2 receptor ACE2. *J Allergy Clin Immunol* 2020; 146(1): 203-6 e3.

87. Kimura H, Francisco D, Conway M, et al. Type 2 inflammation modulates ACE2 and TMPRSS2 in airway epithelial cells. *J Allergy Clin Immunol* 2020; 146(1): 80-8 e8.
88. Vultaggio A, Agache I, Akdis CA, et al. Considerations on Biologicals for Patients with allergic disease in times of the COVID-19 pandemic: an EAACI Statement. *Allergy* 2020.
89. Matucci A, Caminati M, Vivarelli E, et al. COVID-19 in severe asthmatic patients during ongoing treatment with biologicals targeting type 2 inflammation: Results from a multicenter Italian survey. *Allergy* 2020.
90. Skevaki C, Karsonova A, Karaulov A, Xie M, Renz H. Asthma-associated risk for COVID-19 development. *J Allergy Clin Immunol* 2020.
91. 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(11): 1380-8.
92. Leung JM, Niikura M, Yang CWT, Sin DD. COVID-19 and COPD. *Eur Respir J* 2020; 56(2).
93. Barrasa H, Rello J, Tejada S, et al. SARS-CoV-2 in Spanish Intensive Care Units: Early experience with 15-day survival in Vitoria. *Anaesth Crit Care Pain Med* 2020.
94. Leung JM, Yang CX, Tam A, et al. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. *Eur Respir J* 2020; 55(5).
95. Southern BD. Patients with interstitial lung disease and pulmonary sarcoidosis are at high risk for severe illness related to COVID-19. *Cleve Clin J Med* 2020.
96. Huang H, Zhang M, Chen C, et al. Clinical characteristics of COVID-19 in patients with preexisting ILD: A retrospective study in a single center in Wuhan, China. *J Med Virol* 2020.
97. Santos CS, Morales CM, Alvarez ED, Castro CA, Robles AL, Sandoval TP. Determinants of COVID-19 disease severity in patients with underlying rheumatic disease. *Clin Rheumatol* 2020; 39(9): 2789-96.
98. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 2020; 5(5): 428-30.
99. Mantovani A, Beatrice G, Dalbeni A. Coronavirus disease 2019 and prevalence of chronic liver disease: A meta-analysis. *Liver Int* 2020; 40(6): 1316-20.
100. 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.
101. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; 382(18): 1708-20.
102. Garrido I, Liberal R, Macedo G. Review article: COVID-19 and liver disease-what we know on 1st May 2020. *Aliment Pharmacol Ther* 2020; 52(2): 267-75.
103. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020; 21(3): 335-7.
104. Lee LYW, Cazier JB, Starkey T, et al. COVID-19 prevalence and mortality in patients with cancer and the effect of primary tumour subtype and patient demographics: a prospective cohort study. *Lancet Oncol* 2020.
105. Luo J, Rizvi H, Egger JV, Preeshagul IR, Wolchok JD, Hellmann MD. Impact of PD-1 Blockade on Severity of COVID-19 in Patients with Lung Cancers. *Cancer Discov* 2020; 10(8): 1121-8.
106. Dashraath P, Wong JLJ, Lim MXK, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. *Am J Obstet Gynecol* 2020; 222(6): 521-31.
107. 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(12): 956-62.
108. Ellington S, Strid P, Tong VT, et al. Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-June 7, 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69(25): 769-75.

109. Collin J, Bystrom E, Carnahan A, Ahrne M. Public Health Agency of Sweden's Brief Report: Pregnant and postpartum women with severe acute respiratory syndrome coronavirus 2 infection in intensive care in Sweden. *Acta Obstet Gynecol Scand* 2020; 99(7): 819-22.
110. Xu Z, Zhang C, Wang FS. COVID-19 in people with HIV. *Lancet HIV* 2020; 7(8): e524-e6.
111. Vizcarra P, Perez-Elias MJ, Quereda C, et al. Description of COVID-19 in HIV-infected individuals: a single-centre, prospective cohort. *Lancet HIV* 2020; 7(8): e554-e64.
112. Inciarte A, Gonzalez-Cordon A, Rojas J, et al. Clinical characteristics, risk factors, and incidence of symptomatic coronavirus disease 2019 in a large cohort of adults living with HIV: a single-center, prospective observational study. *AIDS* 2020; 34(12): 1775-80.
113. Mirzaei H, McFarland W, Karamouzian M, Sharifi H. COVID-19 Among People Living with HIV: A Systematic Review. *AIDS Behav* 2020.
114. Meyts I, Bucciol G, Quinti I, et al. Coronavirus Disease 2019 in patients with inborn errors of immunity: an international study. *J Allergy Clin Immunol* 2020.
115. Bastard P, Rosen LB, Zhang Q, et al. Auto-antibodies against type I IFNs in patients with life-threatening COVID-19. *Science* 2020.
116. Bost P, Giladi A, Liu Y, et al. Host-Viral Infection Maps Reveal Signatures of Severe COVID-19 Patients. *Cell* 2020; 181(7): 1475-88 e12.
117. Zhang Q, Bastard P, Liu Z, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science* 2020.
118. Davoudi-Monfared E, Rahmani H, Khalili H, et al. A Randomized Clinical Trial of the Efficacy and Safety of Interferon beta-1a in Treatment of Severe COVID-19. *Antimicrob Agents Chemother* 2020; 64(9).
119. Azkur AK, Akdis M, Azkur D, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. *Allergy* 2020; 75(7): 1564-81.
120. Hagman K, Hedenstierna M, Gille-Johnson P, et al. SARS-CoV-2 RNA in serum as predictor of severe outcome in COVID-19: a retrospective cohort study. *Clin Infect Dis* 2020.
121. Walsh KA, Jordan K, Clyne B, et al. SARS-CoV-2 detection, viral load and infectivity over the course of an infection. *J Infect* 2020; 81(3): 357-71.
122. To KK, Tsang OT, Leung WS, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis* 2020; 20(5): 565-74.
123. Zhurakivska K, Troiano G, Pannone G, Caponio VCA, Lo Muzio L. An Overview of the Temporal Shedding of SARS-CoV-2 RNA in Clinical Specimens. *Frontiers in public health* 2020; 8: 487.
124. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N Engl J Med* 2020; 382(12): 1177-9.
125. Arons MM, Hatfield KM, Reddy SC, et al. Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. *N Engl J Med* 2020; 382(22): 2081-90.
126. Yokota I, Shane PY, Okada K, et al. Mass screening of asymptomatic persons for SARS-CoV-2 using saliva. *Clin Infect Dis* 2020.
127. Salvatore PP, Dawson P, Wadhwa A, et al. Epidemiological Correlates of PCR Cycle Threshold Values in the Detection of SARS-CoV-2. *Clin Infect Dis* 2020.
128. Westblade LF, Brar G, Pinheiro LC, et al. SARS-CoV-2 Viral Load Predicts Mortality in Patients with and without Cancer Who Are Hospitalized with COVID-19. *Cancer cell* 2020.
129. Magleby R, Westblade LF, Trzebucki A, et al. Impact of SARS-CoV-2 Viral Load on Risk of Intubation and Mortality Among Hospitalized Patients with Coronavirus Disease 2019. *Clin Infect Dis* 2020.
130. Smithgall MC, Scherberkova I, Whittier S, Green DA. Comparison of Cepheid Xpert Xpress and Abbott ID Now to Roche cobas for the Rapid Detection of SARS-CoV-2. *J Clin Virol* 2020; 128: 104428.

131. Pujadas E, Chaudhry F, McBride R, et al. SARS-CoV-2 viral load predicts COVID-19 mortality. *Lancet Respir Med* 2020; 8(9): e70.
132. Blot M, Jacquier M, Manoha C, Piroth L, Charles PE. Alveolar SARS-CoV-2 viral load is tightly correlated with severity in COVID-19 ARDS. *Clin Infect Dis* 2020.
133. Jacot D, Greub G, Jaton K, Opota O. Viral load of SARS-CoV-2 across patients and compared to other respiratory viruses. *Microbes and infection* 2020.
134. Lindner D, Fitzek A, Bräuninger H, et al. Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases. *JAMA cardiology* 2020.
135. Riggioni C, Comberiati P, Giovannini M, et al. A compendium answering 150 questions on COVID-19 and SARS-CoV-2. *Allergy* 2020.
136. Wu Y, Hong K, Ruan L, et al. Patients with Prolonged Positivity of SARS-CoV-2 RNA Benefit from Convalescent Plasma Therapy: A Retrospective Study. *Virologica Sinica* 2020: 1-8.
137. Frediansyah A, Nainu F, Dhama K, Mudatsir M, Harapan H. Remdesivir and its antiviral activity against COVID-19: A systematic review. *Clinical epidemiology and global health* 2020.
138. Wang S, Pan Y, Wang Q, Miao H, Brown AN, Rong L. Modeling the viral dynamics of SARS-CoV-2 infection. *Mathematical biosciences* 2020; 328: 108438.
139. 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(5): 829-38.
140. Chan L, Chaudhary K, Saha A, et al. AKI in Hospitalized Patients with COVID-19. *J Am Soc Nephrol* 2020.
141. Azam TU, Shadid HR, Blakely P, et al. Soluble Urokinase Receptor (SuPAR) in COVID-19-Related AKI. *J Am Soc Nephrol* 2020.
142. Price LC, McCabe C, Garfield B, Wort SJ. Thrombosis and COVID-19 pneumonia: the clot thickens! *Eur Respir J* 2020; 56(1).
143. Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. *JAMA* 2020.
144. Sivaloganathan H, Ladikou EE, Chevassut T. COVID-19 mortality in patients on anticoagulants and antiplatelet agents. *Br J Haematol* 2020.
145. Dujardin RWG, Hilderink BN, Haksteen WE, et al. Biomarkers for the prediction of venous thromboembolism in critically ill COVID-19 patients. *Thromb Res* 2020; 196: 308-12.
146. Chan NC, Weitz JI. COVID-19 coagulopathy, thrombosis, and bleeding. *Blood* 2020; 136(4): 381-3.
147. Bowles L, Platton S, Yartey N, et al. Lupus Anticoagulant and Abnormal Coagulation Tests in Patients with Covid-19. *N Engl J Med* 2020; 383(3): 288-90.
148. Long H, Nie L, Xiang X, et al. D-Dimer and Prothrombin Time Are the Significant Indicators of Severe COVID-19 and Poor Prognosis. *Biomed Res Int* 2020; 2020: 6159720.
149. Bi X, Su Z, Yan H, et al. Prediction of severe illness due to COVID-19 based on an analysis of initial Fibrinogen to Albumin Ratio and Platelet count. *Platelets* 2020; 31(5): 674-9.
150. Xiong M, Liang X, Wei YD. Changes in blood coagulation in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. *Br J Haematol* 2020; 189(6): 1050-2.
151. Huang D, Yang H, Yu H, Wang T, Yao R, Liang Z. A novel risk score to predict cardiovascular complications in patients with coronavirus disease 2019 (COVID-19): A retrospective, multicenter, observational study. *Immun Inflamm Dis* 2020.
152. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood* 2020; 136(4): 489-500.
153. Karimi M, Haghpanah S, Shahsavani A. Prevalence and clinical features of COVID-19 in Iranian patients with congenital coagulation disorders. *Blood Transfus* 2020; 18(5): 413-4.

154. Paranjpe I, Fuster V, Lala A, et al. Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19. *J Am Coll Cardiol* 2020; 76(1): 122-4.
155. Lemos ACB, do Espirito Santo DA, Salvetti MC, et al. Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID). *Thromb Res* 2020; 196: 359-66.
156. Liu Y, Du X, Chen J, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. *J Infect* 2020; 81(1): e6-e12.
157. Qin C, Zhou L, Hu Z, et al. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. *Clin Infect Dis* 2020; 71(15): 762-8.
158. Mo P, Xing Y, Xiao Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clin Infect Dis* 2020.
159. Chen R, Sang L, Jiang M, et al. Longitudinal hematologic and immunologic variations associated with the progression of COVID-19 patients in China. *J Allergy Clin Immunol* 2020; 146(1): 89-100.
160. Wang F, Nie J, Wang H, et al. Characteristics of Peripheral Lymphocyte Subset Alteration in COVID-19 Pneumonia. *J Infect Dis* 2020; 221(11): 1762-9.
161. 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.
162. Yan L, Zhang H-T, Goncalves J, et al. An interpretable mortality prediction model for COVID-19 patients. *Nature Machine Intelligence* 2020; 2(5): 283-8.
163. Chen J, Xu X, Hu J, et al. Clinical course and risk factors for recurrence of positive SARS-CoV-2 RNA: a retrospective cohort study from Wuhan, China. *Aging (Albany NY)* 2020; 12(17): 16675-89.
164. Xie G, Ding F, Han L, Yin D, Lu H, Zhang M. The role of peripheral blood eosinophil counts in COVID-19 patients. *Allergy* 2020.
165. Rosenberg HF, Dyer KD, Domachowske JB. Eosinophils and their interactions with respiratory virus pathogens. *Immunol Res* 2009; 43(1-3): 128-37.
166. Lindsley AW, Schwartz JT, Rothenberg ME. Eosinophil responses during COVID-19 infections and coronavirus vaccination. *J Allergy Clin Immunol* 2020; 146(1): 1-7.
167. Lippi G, Sanchis-Gomar F, Henry BM. Eosinophil count in coronavirus disease 2019: more doubts than answers. *QJM* 2020.
168. Vitte J, Diallo AB, Boumaza A, et al. A granulocytic signature identifies COVID-19 and its severity. *J Infect Dis* 2020.
169. Danwang C, Endomba FT, Nkeck JR, Wouna DLA, Robert A, Noubiap JJ. A meta-analysis of potential biomarkers associated with severity of coronavirus disease 2019 (COVID-19). *Biomark Res* 2020; 8: 37.
170. Lala A, Johnson KW, Januzzi JL, et al. Prevalence and Impact of Myocardial Injury in Patients Hospitalized With COVID-19 Infection. *J Am Coll Cardiol* 2020; 76(5): 533-46.
171. 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.
172. Choi JJ, Wehmeyer GT, Li HA, et al. D-dimer cut-off points and risk of venous thromboembolism in adult hospitalized patients with COVID-19. *Thromb Res* 2020; 196: 318-21.
173. Amgalan A, Othman M. Hemostatic laboratory derangements in COVID-19 with a focus on platelet count. *Platelets* 2020; 31(6): 740-5.
174. Xu P, Zhou Q, Xu J. Mechanism of thrombocytopenia in COVID-19 patients. *Ann Hematol* 2020; 99(6): 1205-8.
175. Mori S, Ai T, Otomo Y. Characteristics, laboratories, and prognosis of severe COVID-19 in the Tokyo metropolitan area: A retrospective case series. *PLoS One* 2020; 15(9): e0239644.

176. Bao J, Li C, Zhang K, Kang H, Chen W, Gu B. Comparative analysis of laboratory indexes of severe and non-severe patients infected with COVID-19. *Clin Chim Acta* 2020; 509: 180-94.
177. 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(7): 934-43.
178. Fu Y, Zhu R, Bai T, et al. Clinical Features of COVID-19-Infected Patients With Elevated Liver Biochemistries: A Multicenter, Retrospective Study. *Hepatology* 2020.
179. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395(10223): 497-506.
180. Shao M, Li X, Liu F, Tian T, Luo J, Yang Y. Acute kidney injury is associated with severe infection and fatality in patients with COVID-19: A systematic review and meta-analysis of 40 studies and 24,527 patients. *Pharmacol Res* 2020; 161: 105107.
181. Shi S, Qin M, Cai Y, et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *Eur Heart J* 2020; 41(22): 2070-9.
182. Chen C, Chen C, Yan JT, Zhou N, Zhao JP, Wang DW. [Analysis of myocardial injury in patients with COVID-19 and association between concomitant cardiovascular diseases and severity of COVID-19]. *Zhonghua Xin Xue Guan Bing Za Zhi* 2020; 48(7): 567-71.
183. Qin JJ, Cheng X, Zhou F, et al. Redefining Cardiac Biomarkers in Predicting Mortality of Inpatients With COVID-19. *Hypertension* 2020; 76(4): 1104-12.
184. Azkur AK, Akdis M, Azkur D, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. *Allergy* 2020; 75(7): 1564-81.
185. Soraya GV, Ulhaq ZS. Crucial laboratory parameters in COVID-19 diagnosis and prognosis: An updated meta-analysis. *Med Clin (Engl Ed)* 2020; 155(4): 143-51.
186. Malik P, Patel U, Mehta D, et al. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. *BMJ Evid Based Med* 2020.
187. Zhang JJ, Cao YY, Dong X, et al. Distinct characteristics of COVID-19 patients with initial rRT-PCR-positive and rRT-PCR-negative results for SARS-CoV-2. *Allergy* 2020; 75(7): 1809-12.
188. Hu R, Han C, Pei S, Yin M, Chen X. Procalcitonin levels in COVID-19 patients. *Int J Antimicrob Agents* 2020; 56(2): 106051.
189. Carli G, Cecchi L, Stebbing J, Parronchi P, Farsi A. Is asthma protective against COVID-19? *Allergy* 2020.
190. Sokolowska M, Lukasik Z, Agache I, et al. Immunology of COVID-19: mechanisms, clinical outcome, diagnostics and perspectives - a report of the European Academy of Allergy and Clinical Immunology (EAACI). *Allergy* 2020.
191. Chen X, Zhao B, Qu Y, et al. Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely correlated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. *Clin Infect Dis* 2020.
192. 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(7): 1021-8.
193. Aziz M, Fatima R, Assaly R. Elevated interleukin-6 and severe COVID-19: A meta-analysis. *J Med Virol* 2020.
194. 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(6): 992-1000 e3.
195. Lucas C, Wong P, Klein J, et al. Longitudinal analyses reveal immunological misfiring in severe COVID-19. *Nature* 2020; 584(7821): 463-9.

196. Wang J, Jiang M, Chen X, Montaner LJ. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: Review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. *J Leukoc Biol* 2020; 108(1): 17-41.
197. Wen W, Su W, Tang H, et al. Immune cell profiling of COVID-19 patients in the recovery stage by single-cell sequencing. *Cell Discov* 2020; 6: 31.
198. Jesenak M, Banovcin P, Diamant Z. COVID-19, chronic inflammatory respiratory diseases and eosinophils-Observations from reported clinical case series. *Allergy* 2020; 75(7): 1819-22.
199. McElvaney OJ, McEvoy NL, McElvaney OF, et al. Characterization of the Inflammatory Response to Severe COVID-19 Illness. *Am J Respir Crit Care Med* 2020; 202(6): 812-21.
200. Del Valle DM, Kim-Schulze S, Huang HH, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med* 2020.
201. Bonini S, Maltese G. COVID-19 Clinical trials: Quality matters more than quantity. *Allergy* 2020.
202. Huet T, Beaussier H, Voisin O, et al. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol* 2020; 2(7): e393-e400.
203. Sheng CC, Sahoo D, Dugar S, et al. Canakinumab to reduce deterioration of cardiac and respiratory function in SARS-CoV-2 associated myocardial injury with heightened inflammation (canakinumab in Covid-19 cardiac injury: The three C study). *Clin Cardiol* 2020.
204. Awano N, Inomata M, Kuse N, et al. Serum KL-6 level is a useful biomarker for evaluating the severity of coronavirus disease 2019. *Respir Investig* 2020.
205. Xue M, Zheng P, Bian X, et al. Exploration and correlation analysis of changes in Krebs von den Lungen-6 levels in COVID-19 patients with different types in China. *Biosci Trends* 2020.
206. Hope MD, Raptis CA, Henry TS. Chest Computed Tomography for Detection of Coronavirus Disease 2019 (COVID-19): Don't Rush the Science. *Ann Intern Med* 2020; 173(2): 147-8.
207. Xiong Y, Sun D, Liu Y, et al. Clinical and High-Resolution CT Features of the COVID-19 Infection: Comparison of the Initial and Follow-up Changes. *Invest Radiol* 2020; 55(6): 332-9.
208. Liu F, Zhang Q, Huang C, et al. CT quantification of pneumonia lesions in early days predicts progression to severe illness in a cohort of COVID-19 patients. *Theranostics* 2020; 10(12): 5613-22.
209. Li Y, Han X, Alwalid O, et al. Baseline characteristics and risk factors for short-term outcomes in 132 COVID-19 patients with diabetes in Wuhan China: A retrospective study. *Diabetes Res Clin Pract* 2020; 166: 108299.
210. Tural Onur S, Altın S, Nedime Sokucu S, et al. Could ferritin level be an indicator of COVID-19 disease mortality? *J Med Virol* 2020.
211. Wang F, Yao Y, Hou H, et al. Delayed virus-specific antibody responses associate with COVID-19 mortality. *Allergy* 2020.
212. Gandini O, Criniti A, Ballesio L, et al. Serum Ferritin is an independent risk factor for Acute Respiratory Distress Syndrome in COVID-19. *J Infect* 2020.
213. Taneri PE, Gómez-Ochoa SA, Llanaj E, et al. Anemia and iron metabolism in COVID-19: a systematic review and meta-analysis. *European journal of epidemiology* 2020; 35(8): 763-73.
214. Ruscitti P, Giacomelli R. Ferritin and Severe COVID-19, from Clinical Observations to Pathogenic Implications and Therapeutic Perspectives. *The Israel Medical Association journal : IMAJ* 2020; 8(22): 450-2.
215. Perricone C, Bartoloni E, Bursi R, et al. COVID-19 as part of the hyperferritinemic syndromes: the role of iron depletion therapy. *Immunol Res* 2020; 68(4): 213-24.
216. Carr AC, Maggini S. Vitamin C and Immune Function. *Nutrients* 2017; 9(11).
217. Fisher BJ, Kraskauskas D, Martin EJ, et al. Mechanisms of attenuation of abdominal sepsis induced acute lung injury by ascorbic acid. *Am J Physiol Lung Cell Mol Physiol* 2012; 303(1): L20-32.

218. Fowler AA, 3rd, Truwit JD, Hite RD, et al. Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial. *JAMA* 2019; 322(13): 1261-70.
219. Arvinte C, Singh M, Marik PE. Serum levels of vitamin C and vitamin D in a cohort of critically ill COVID-19 patients of a north American community hospital intensive care unit in may 2020. A pilot study. *Med Drug Discov* 2020: 100064.
220. Carr AC. A new clinical trial to test high-dose vitamin C in patients with COVID-19. *Crit Care* 2020; 24(1): 133.
221. Chen Y, Zhang J, Ge X, Du J, Deb DK, Li YC. Vitamin D receptor inhibits nuclear factor kappaB activation by interacting with IkappaB kinase beta protein. *J Biol Chem* 2013; 288(27): 19450-8.
222. Bonizzi G, Karin M. The two NF-kappaB activation pathways and their role in innate and adaptive immunity. *Trends Immunol* 2004; 25(6): 280-8.
223. Grant WB, Lahore H, McDonnell SL, et al. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. *Nutrients* 2020; 12(4).
224. Chan J, Tian Y, Tanaka KE, et al. Effects of protein calorie malnutrition on tuberculosis in mice. *Proc Natl Acad Sci U S A* 1996; 93(25): 14857-61.
225. Bornstein SR, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol* 2020; 8(6): 546-50.
226. Rees K, Takeda A, Martin N, et al. Mediterranean-Style Diet for the Primary and Secondary Prevention of Cardiovascular Disease: A Cochrane Review. *Glob Heart* 2020; 15(1): 56.
227. Rodriguez-Perez C, Molina-Montes E, Verardo V, et al. Changes in Dietary Behaviours during the COVID-19 Outbreak Confinement in the Spanish COVIDiet Study. *Nutrients* 2020; 12(6).
228. Sanchez-Sanchez E, Ramirez-Vargas G, Avellaneda-Lopez Y, Orellana-Pecino JI, Garcia-Marin E, Diaz-Jimenez J. Eating Habits and Physical Activity of the Spanish Population during the COVID-19 Pandemic Period. *Nutrients* 2020; 12(9).
229. Di Renzo L, Gualtieri P, Pivari F, et al. Eating habits and lifestyle changes during COVID-19 lockdown: an Italian survey. *J Transl Med* 2020; 18(1): 229.
230. Westman EC, Mavropoulos J, Yancy WS, Volek JS. A review of low-carbohydrate ketogenic diets. *Curr Atheroscler Rep* 2003; 5(6): 476-83.
231. Soliman S, Faris ME, Ratemi Z, Halwani R. Switching Host Metabolism as an Approach to Dampen SARS-CoV-2 Infection. *Ann Nutr Metab* 2020: 1-7.
232. Sukkar SG, Bassetti M. Induction of ketosis as a potential therapeutic option to limit hyperglycemia and prevent cytokine storm in COVID-19. *Nutrition* 2020; 79-80: 110967.
233. Hannan MA, Rahman MA, Rahman MS, et al. Intermittent fasting, a possible priming tool for host defense against SARS-CoV-2 infection: Crosstalk among calorie restriction, autophagy and immune response. *Immunol Lett* 2020; 226: 38-45.
234. Chacko SA, Song Y, Nathan L, et al. Relations of dietary magnesium intake to biomarkers of inflammation and endothelial dysfunction in an ethnically diverse cohort of postmenopausal women. *Diabetes Care* 2010; 33(2): 304-10.
235. Maggini S, Pierre A, Calder PC. Immune Function and Micronutrient Requirements Change over the Life Course. *Nutrients* 2018; 10(10).
236. Le Poul E, Loison C, Struyf S, et al. Functional characterization of human receptors for short chain fatty acids and their role in polymorphonuclear cell activation. *J Biol Chem* 2003; 278(28): 25481-9.
237. Saemann MD, Bohmig GA, Osterreicher CH, et al. Anti-inflammatory effects of sodium butyrate on human monocytes: potent inhibition of IL-12 and up-regulation of IL-10 production. *FASEB J* 2000; 14(15): 2380-2.

238. Parada Venegas D, De la Fuente MK, Landskron G, et al. Short Chain Fatty Acids (SCFAs)-Mediated Gut Epithelial and Immune Regulation and Its Relevance for Inflammatory Bowel Diseases. *Front Immunol* 2019; 10: 277.
239. Rogero MM, Leao MC, Santana TM, et al. Potential benefits and risks of omega-3 fatty acids supplementation to patients with COVID-19. *Free Radic Biol Med* 2020; 156: 190-9.
240. Hammock BD, Wang W, Gilligan MM, Panigrahy D. Eicosanoids: The Overlooked Storm in Coronavirus Disease 2019 (COVID-19)? *Am J Pathol* 2020; 190(9): 1782-8.
241. Weill P, Plissonneau C, Legrand P, Rioux V, Thibault R. May omega-3 fatty acid dietary supplementation help reduce severe complications in Covid-19 patients? *Biochimie* 2020.
242. Conte L, Toraldo DM. Targeting the gut-lung microbiota axis by means of a high-fibre diet and probiotics may have anti-inflammatory effects in COVID-19 infection. *Ther Adv Respir Dis* 2020; 14: 1753466620937170.
243. Iddir M, Brito A, Dingeo G, et al. Strengthening the Immune System and Reducing Inflammation and Oxidative Stress through Diet and Nutrition: Considerations during the COVID-19 Crisis. *Nutrients* 2020; 12(6).
244. Carlson JL, Erickson JM, Lloyd BB, Slavin JL. Health Effects and Sources of Prebiotic Dietary Fiber. *Curr Dev Nutr* 2018; 2(3): nzy005.
245. Escribese MM, Nistal-Villan E, Fernandez P, et al. Cross-sectional pilot study exploring the feasibility of a rapid SARS-CoV-2 immunization test in health and nonhealthcare workers. *Allergy* 2020.
246. Lai X, Wang M, Qin C, et al. Coronavirus Disease 2019 (COVID-2019) Infection Among Health Care Workers and Implications for Prevention Measures in a Tertiary Hospital in Wuhan, China. *JAMA Netw Open* 2020; 3(5): e209666.
247. Nienhaus A, Hod R. COVID-19 among Health Workers in Germany and Malaysia. *Int J Environ Res Public Health* 2020; 17(13).
248. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? *Lancet* 2020; 395(10231): 1225-8.
249. Greening NJ, Larsson P, Ljungstrom E, Siddiqui S, Olin AC. Small droplet emission in exhaled breath during different breathing manoeuvres: Implications for clinical lung function testing during COVID-19. *Allergy* 2020.
250. WHO. Smoking and COVID-19. *WHO scientific brief* 2020.
251. 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* 2020.
252. Gulsen A, Arpinar Yigitbas B, Uslu B, Droemann D, Kilinc O. The effect of smoking on COVID-19 symptom severity: Systematic review and meta-analysis. *MedRxiv* 2020: 2020.08.15.20102699.