Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Immunology 224 (2021) 108651

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Review Article

Interrelations between COVID-19 and other disorders

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ARTICLE INFO

Keywords:
COVID-19
Comorbidities
Novel coronavirus
Preexisting condition
Severe outcome
SARS-CoV-2 outcome
Diabetes
Hypertension
Asthma
Cardiovascular diseases

ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a respiratory tract virus that causes Coronavirus disease (COVID-19). The virus originated in Wuhan, China, in December 2019 and has spread across the globe to-date. The disease ranges from asymptomatic carriers to symptoms such as fever, sore throat, cough, lung infections, and in severe cases, acute respiratory distress syndrome, sepsis, and death. As many as 50% of patients reported having at least one comorbidities with COVID-19 upon hospital admission. Hypertension, diabetes, chronic obstructive pulmonary disease, obesity, and cardiovascular diseases are among the most commonly reported. Comorbidities are contributing to acute disease prognosis and increased risk of severe symptoms. Around 70% of patients who require ICU care have been observed to have comorbidities. This review intends to understand how some of these comorbidities affect the disease's prognosis and how severe the outcome can be expected.

1. Introduction

Today, the world is in the grips of the novel virus belonging to the coronavirus family named SARS-CoV-2, and the infection it causes is named COVID-19 [1]. The beginning of the virus can be traced back to December 2019 and is known to have originated from the Wuhan region of the Hubei province in China [2,3]. This highly contagious virus has spread across 220 countries and territories worldwide, and by the mid of March was deemed a pandemic by the World Health Organization. Although Pfizer and BioNTech announced on 9 November that their COVID-19 vaccine candidate was 90% effective in clinical trials, it will only be available to the general public in 2021. Therefore there is still an urgent need to contain the virus's spread, particularly for high-risk people.

The infection spreads from person to person in close contact, from predominantly symptomatic individuals and asymptomatic carriers [3]. Initially, the reproductive number (R_0) was estimated to be in the range of 1.4-5.7, with an average value of 2.2, which means an infected individual has the potential to pass on the infection to at least two more people [4]. The virus's incubation period is assessed to be between 2 to 14 days, with 5.2 days on average (95% confidence interval, 4.1 to 7.0) [5,6]. SARS-CoV-2 belongs to the coronavirus family of viruses, which are single-stranded, encapsulated, RNA viruses. Members of the coronavirus family have been known to cause respiratory, hepatic, and neurological diseases [2]. Genetically, the SARS-CoV-2 virus showed 89% similarity to the batSARS-like-CoVZXC21 virus and 82% similarity

Abbreviations: ACE2, angiotensin-converting enzyme 2; AMI, acute myocardial infarction; ARBs, angiotensin II receptor blockers; ARDS, acute respiratory distress syndrome; CRS, cytokine activation or release syndrome; COPD, chronic obstructive pulmonary disease; HCT, hematopoietic cell transplant; IMV, invasive mechanical ventilation; OR, odd ratio; RR, relative risk, risk ratio; SOT, solid organ transplant; T1D, type 1 diabetes; T2D, type 2 diabetes.

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https://doi.org/10.1016/j.clim.2020.108651
Received 1 November 2020; Received in revised form 11 December 2020; Accepted 12 December 2020
Available online 14 December 2020

to human SARS-CoV [7]. Hence the name SARS-CoV-2. The CoV is a single-stranded positive 30 kb RNA viruses (+ssRNA) with a spike glycoprotein outer layer that gives them a crown-like appearance. Past research indicated that the CoV family's virulence comes from their non-structural proteins, which hinder the innate immune response, thus producing an excessive inflammatory response and impaired adaptive host immune defense. This can cause damage to the tissues affected by the virus's invasion and on a systemic level. Spike glycoproteins promote replication (viral assembly and release), thereby increasing pathogenicity [2,8].

Patients with COVID-19 can be symptomatic or asymptomatic. According to early reports, most commonly reported mild symptoms, in about 81 % of patients, include cough, sore throat, fever, myalgia, and moderate pneumonia. Patients with serious disease showed symptoms of severe pneumonia, dyspnea, and very low blood oxygen saturation ($\leq$ 93%), which was observed in about 14% of cases. Critical symptoms occurred in about 5% of cases and included respiratory failure, multi-organ failure, and septic shock. Mild infections were observed to clear-up in a week, whereas severe cases experienced acute respiratory failure, even leading to sepsis and death. Most fatalities were reported in middle-aged/elderly populations with preexisting conditions, including diabetes, heart and kidney diseases, chronic obstructive pulmonary disease, cancer, and immune diseases [2,5]. Fig. 1 reports the percentage of hospitalization and death by age among COVID-19 patients, according to data from the Centers for Disease Control and Prevention [9].

Waiting for the vaccine distribution, the need of the moment is to consolidate as much information as possible on COVID-19 in order to establish a plan to fight the virus through an antiviral strategy based on rational immunomodulatory tools centered on healthy diet and lifestyle and with a proper prevention protocol (physical distancing, avoiding crowds, wearing a mask, keeping rooms well ventilated, cleaning your hands, and coughing into a bent elbow or tissue), especially for the most susceptible and weak people [10–13]. In this light, the present review collects the available literature on the effects of viral infection on pre-existing medical conditions such as hypertension, diabetes, cardiovascular diseases, obesity, chronic obstructive pulmonary disease, kidney disease, cancer, asthma, immunodeficiency, pregnancy, and lifestyle choice like smoking habit. We also reviewed the existing studies and literature on SARS-CoV and MERS-CoV infections, which are closely related to the SARS-CoV-2 virus, and collected the current data and statistics related to the interrelations between COVID-19 and other preexisting disorders (Fig. 2).

2. Interrelation between Covid-19 and disorders with strongest and most consistent evidence

2.1. Diabetes mellitus

Observations made so far with COVID-19 patients worldwide have to lead to a probable conclusion that patients with diabetes as comorbidity are at higher risk of experiencing severe adverse effects due to infection [14,15]. This has also been established in the analysis of SARS-CoV and MERS-CoV infections [16]. The prevalence of diabetes among hospitalized patients with COVID-19 fluctuates in the range of 10 to 34% but even more, according to several studies [17–21]. A number of studies conducted in China and Italy have shown a more severe course of SARS-CoV-2 infection, requiring transfer to the intensive care unit (ICU) and mechanical ventilation in patients with diabetes [22–24]. An analysis of 168 fatal pneumonia cases due to COVID-19 in Wuhan showed that 75% of the deceased patients were men at an average age of 75 years, and a quarter of these patients had diabetes [24]. A case series study in the New York City area showed a diabetes incidence of about 34% among 5700 patients hospitalized with COVID-19 [20].

Diabetes is characterized by reduced insulin production, classified as Type 1 diabetes (T1D), caused by an attack on pancreatic β cells due to an autoimmune condition, and Type 2 diabetes (T2D), where the body is unable to respond to insulin effectively. T2D is the most commonly occurring diabetes type and is reported as the major comorbidity of COVID-19 [25,26]. In a longitudinal Chinese study of 7300 patients, subjects with T2D showed significantly higher mortality (about three times higher) from COVID-19 than non-diabetic individuals [26]. Studies conducted in T2D affected humans and mice have shown a change in the immune profile from regulatory T-cells to proinflammatory Th1 and Th17 $CD4^+$ T cells [25,27]. This mechanism and its consequences are thought to make diabetic patients more susceptible to infections [28]. It is known that any respiratory infections are

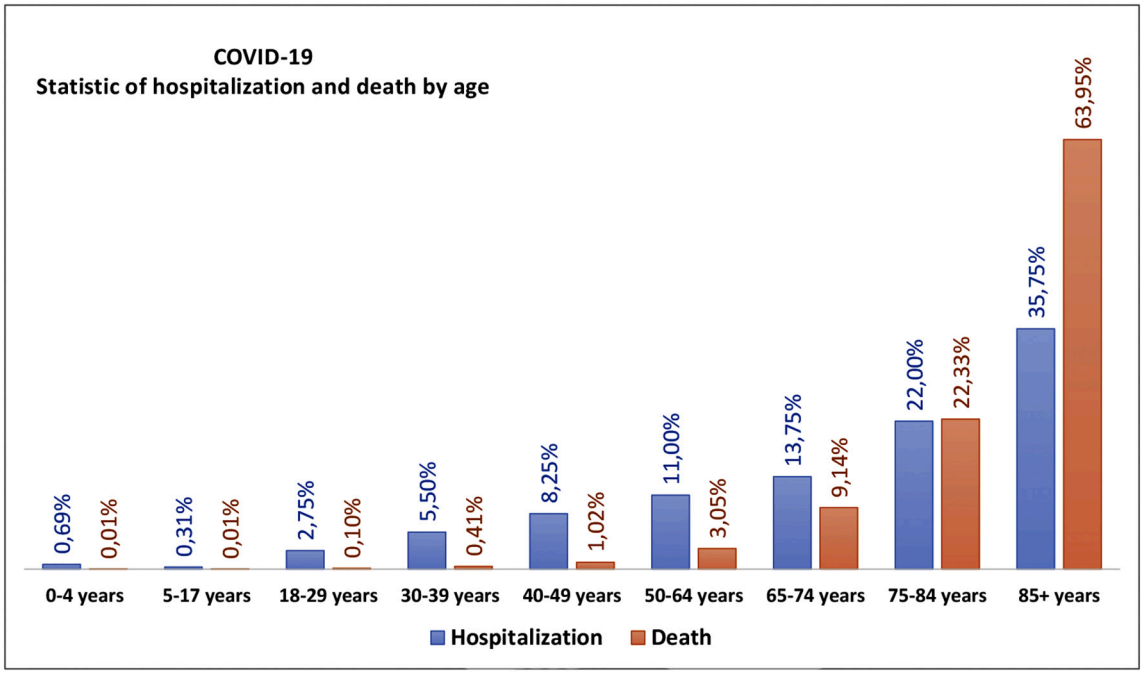

Fig. 1. Percentage of hospitalization and mortality by age among COVID-19 patients, according to data from Centers for Disease Control and Prevention [9].

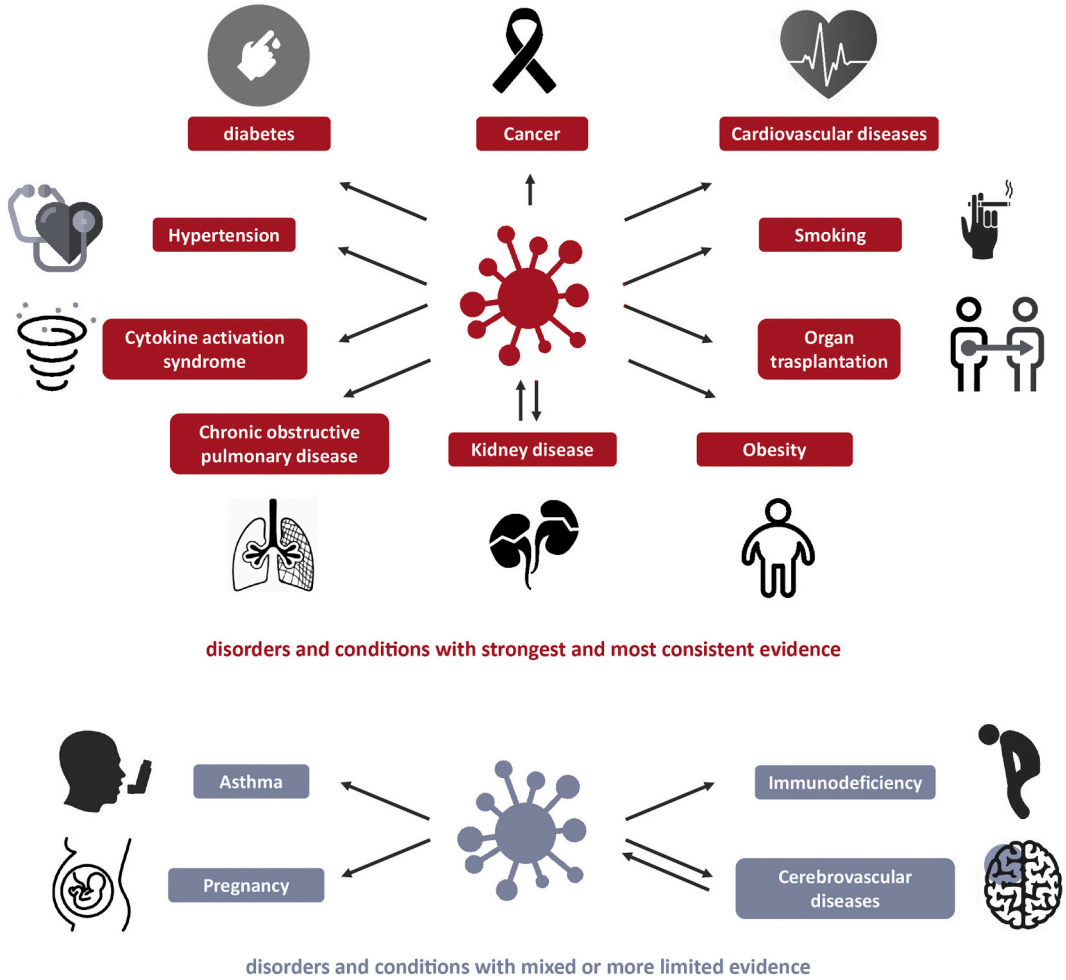

Fig. 2. Interrelation between severe Covid-19 and comorbidities/conditions

accompanied by temporary insulin resistance development, especially in overweight people. The situation is complicated by the need to use glucocorticoids, which leads to an increase in the dose of hypoglycemic drugs. Diabetes is associated with a maladaptive inflammatory response leading to a worsening of the viral infection course and the possibility of bacterial complications [28,29].

To better understand how diabetes affects COVID-19 disease prognosis, we could look at a MERS-CoV study conducted on mice engineered to be susceptible to MERS-CoV and had T2D (using a high-fat diet). These mice exhibited symptoms that were highly severe as compared to non-diabetic mice. The main characteristics included delayed initiation of inflammation, slower inflammatory response, and more significant pulmonary inflammation. A reduced CD4+ T-cells response was observed, with lower cytokine and chemokine production [25]. Similar physiology can likely be expected with SARS-CoV-2 infection due to the high genetic similarity between SARS-CoV-2 and MERS-CoV [8,25].

In another study conducted by Yang *et al.*, the relationship between SARS-CoV receptor Angiotensin-converting enzyme 2 (ACE2) and multiorgan infection was researched. Data were obtained from autopsies and ACE2 receptor staining of infected lethal cases. SARS-CoV was found to have damaged the lungs, kidney, heart, and the endocrine part of the pancreas. This was directly related to fatality. Pancreatic exocrine and endocrine tissue was affected, leading to damage to islets, resulting in acute insulin-dependent diabetes [22]. Thus the SARS-CoV-2 has the potential to be lethal to patients who have diabetes or borderline diabetes.

2.2. *Hypertension*

As per some studies, approximately 15% to 30% of patients with COVID-19 have a history of hypertension [18,30,31]. Nearly 75% of patients who died from a pandemic in Italy suffered from hypertension [32]. There is increasing evidence showing that patients with hypertension are more susceptible to COVID-19 as compared to a healthy individual. A systematic review based on a meta-analysis evaluating the association of hypertension and COVID-19 showed an almost 2.5-fold increase in the risk of severe forms of COVID-19 in patients with hypertension (Odd Ratio, OR 2.49). The same trend was characteristic of mortality risk (OR 2.42) [33]. ACE2 and ACE enzymes exhibit vasodilator and vasoconstrictor abilities, thanks to which they regulate blood homeostasis. ACE2 uses Angiotensin 1 (Ang 1) as it is a substrate and hydrolyzes it to form Ang 1-9, which is further used as a substrate by ACE to produce Ang 1-7. These products show anti-inflammatory, protective, and vasodilatory properties. ACE2 acts as a receptor for the SARS-CoV virus. ACE2 is expressed mainly by the epithelia of the human airway, causing the onset of infection in the respiratory tract [8,34]. Kidneys, cardiovascular system, and gastrointestinal system also produce ACE2 [35]. It has been determined that the SARS-CoV-2 virus binds to ACE2 receptors with the help of the spike protein [36,37]. *In vitro* tests with SARS-CoV have demonstrated that as the production of ACE2 increases, the susceptibility to infection also increases [38].

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers are common medications used to treat hypertension. Their primary function is to inhibit the expression of Angiotensin-converting enzyme 1 (ACE1), but these medications have also been

shown to promote the expression of ACE2 [31]. Considering that, just like the SARS-CoV, the SARS-CoV-2 virus shows more susceptibility to the presence of excess ACE2, the chances of infection and contracting the disease increases too. Chances of severe and fatal infection are, consequently, higher too [31,36].

While treatment with ACEIs may increase susceptibility to infections, renin-angiotensin system (RAS) inhibitors do not show any increased susceptibility. A study conducted on animals [39] showed an increase in ACE2 mRNA expression using lisinopril while keeping ACE2 levels the same. The other experimental studies have shown that ACE2 has a protective effect on lung tissue damage by stimulating the formation of Ang 1-7 from Ang 2. This reduces the inflammatory process in the lungs. Angiotensin 1 receptor blockers can also reduce the inflammatory response in the lungs, heart, and kidneys, reducing the risk of ARDS, myocarditis, or acute kidney damage [40–42]. Calcium antagonists can be a good alternative to ACE2 in the treatment of hypertension; no evidence has been found of their effect on the inflammatory response in lungs at COVID-19 patients [36].

Confirmation of these data resulted from a multicenter study involving 1128 Chinese hypertensive patients suffering from COVID-19, of which 188 took ACEI / ARB. In these groups, the risk of mortality from all causes was statistically significantly lower than those who did not take these antihypertensive drugs (3.7% versus 9.8%, P = 0.01) [17]. Further investigation and studies are needed to identify how COVID-19 and hypertension affect each other.

2.3. Cardiovascular diseases

Approximately 2.5% to 16% of patients with COVID-19 have cardiovascular disease [18,24,43,44]. RAS is involved in the regulation of blood pressure and cardiovascular activities. While angiotensin 2 possesses properties such as vasoconstriction and pro-inflammation effects, angiotensin1-7 displays favorable qualities to the cardiovascular system (such as anti-thrombotic and anti-arrhythmic effects) [31]. The balance between ACE1 and ACE2 is crucial to maintain good cardiovascular health. As discussed in the earlier sections, SARS-CoV-2 most likely infects by attaching to receptors on ACE2. Hence, any comorbidities with cardiovascular conditions need to be closely monitored [31]. The cardiovascular system's complications include acute myocardial damage, myocarditis, myocardial infarction, heart failure, rhythm disorders, and thromboembolism. Also, in the treatment of COVID-19, interaction with cardiovascular drugs must be considered [45]. A study, which included more than 44,000 COVID-19 patients with diseases of the cardiovascular system, showed a five-fold increase in mortality compared to initially healthy patients (10.5% and 2.3%, respectively) [46].

As with MERS-CoV and SARS-CoV, heart failure chances are high with SARS-CoV-2, although only limited conditions were observed [47,48]. In the study conducted by Chen *et al.*, among 99 patients with confirmed COVID-19 infection, 13 were observed with elevated creatinine kinase, and 75 showed an increase in lactate dehydrogenase [49]. In a bigger study conducted by Guan *et al.*, 13.7% of patients with confirmed COVID-19 infections showed increased creatinine kinase levels, and 37.2% showed an increase in lactate dehydrogenase [50]. At a d-dimer level in patients with COVID-19 greater than 1 μg/ml, the risk of mortality increases significantly (18.42 CI [2.64–128.55]; p = 0.0033) [18]. There is still no clear evidence that these effects are caused by the SARS-CoV-2 virus or other factors, including low oxygen in the blood. From the 41 cases of COVID-19 reported initially in Wuhan, 5 of them experience myocardial injury with troponin I level >28 pg/mL [17]. The acute cardiac injury was observed in a patient with severe symptoms needing ICU care [18]. It is noteworthy that some of the initial patients visited the doctor with symptoms of heart palpitations and chest tightness rather than respiratory distress [43]. These injuries can be attributed to the ACE2 pathways.

The clinical manifestations of myocarditis in cases of COVID-19 are similar to the symptoms of an acute coronary syndrome; ECG signs include ST elevation or depression, T inversion; ultrasound examination reveals hypokinesis zones [51]. Systemic inflammation typical of COVID-19 is one of the leading risk factors for rupture of atherosclerotic plaques and acute myocardial infarction (AMI). The processes of increased blood coagulation also contribute to the development of coronary complications [52]. It was found that influenza and other viral infections increase the risk of developing AMI by 2.8-6.1 times during the first week of illness [53,54].

Heart rhythm disturbances occur in 7-17% of patients with COVID-19 [55], depending on the severity. The cause of arrhythmias can be hypoxia, inflammatory stress, and metabolic disorders. With a simultaneous increase in troponin level in the patient's blood, it is necessary to consider acute coronary syndromes or acute myocardial damage [51]. Patients with underlying cardiovascular conditions are more susceptible to the infection, and they have a higher chance of experiencing aggravated pneumonia and severe symptoms [5]. The use of ACEIs and angiotensin II receptor blockers (ARBs) is a conventional treatment for cardiovascular conditions. Both these drugs upregulate ACE2 and can play a dual role in either making the patient more susceptible to SARS-CoV-2 or reducing the severity of lung infection. ACEIs and ARBs can also potentially help in reducing the risk of heart injury [31]. Discontinuing the use of these drugs in COVID-19 patients is not currently recommended. Further research is required to establish a plan of treatment.

2.4. Chronic obstructive pulmonary disease

Emami *et al.* studied comorbidities of various diseases with COVID-19 using meta-analysis from different early studies and found COPD reported in only five articles. The prevalence of COVID-19 patients with COPD was only 0.95%, a considerably small number in comparison to other preexisting conditions [56]. Surprisingly, comorbidities with COPD appeared underreported in the literature. One possible reason could be the difficulty in diagnosing COPD, unlike diabetes, especially in China. However, more recent data from countries like Italy and the United States, COPD has been associated with a significant severe COVID-19 infection with a more than fivefold increased risk [57,58]. In the meta-analysis of Wang *et al.,* COPD has been identified as an independent risk factor associated with COVID-19 patients with OR of 5.97 (P<0.001) [59].

There has been some insight into how the SARS-CoV-2 virus possibly binds to the ACE2 receptors from a study conducted by Ji H-L *et al.* The SARS-CoV-2 virus has two regions, S1 and S2, in their spike proteins. S1 helps bind to the ACE2 of the host, and S2 helps integrate the viral RNA with the cell membrane. Plasmin, produced by the host, cleaves the virus's S protein and increases its ability to bind to ACE2 [60]. The primary production of plasmin or plasminogen happens through the plasminogen activator system. This system is responsible for fibrinolysis. Plasminogen activator inhibitor-1 (PAI-1) is a serine protease inhibitor that inhibits the activation of plasmin. The PAI-1 levels have been higher in COPD patients in a study conducted by Waschki *et al.* This may inhibit plasmin, which further provides a lower number of receptors for viral binding. Further investigation is needed to check the validity of this theory [61].

2.5. Smoking

Smoking has always been associated with respiratory diseases' severe progression, including COPD and asthma [62]. It has also been associated with weak immune system response to infections, even in so-called healthy smokers with no preexisting conditions [63]. The risk of infections like influenza has been known to increase with smoking considerably and has led to more severe symptoms [64]. Some of the significant effects of smoking on influenza include higher incidences of other bacterial infections, a rapid decrease of influenza antibodies, and damage to the host's antiviral metabolism [18]. Also, a higher mortality

rate was observed in smokers with MERS-CoV viral infection [62].

In a study conducted by Guan *et al.*, among 1099 patients with COVID-19 from China, 16.9% of patients with severe symptoms were smokers, 5.2% were former smokers. Among the non-severe cases, 11.8% were current smokers, and 1.3% of them were former smokers. Among patients that needed ICU care or were fatal, 25.5% were smokers [50]. Liu *et al.* performed an analysis on a group of 78 people infected with SARS-CoV-2, where the percentage of smokers in the severe outcome group was higher (27.3%) as compared to the group with a better prognosis (3%) (p=0.019) [65].

RAS pathway and ACE2 production, again, play a crucial role in identifying the effect of smoking on COVID-19. ACE2 expression was studied in a group of smokers and non-smokers. Results revealed that the ACE2 expression levels were significantly higher in smokers than in the never-smokers. As this upregulation of ACE2 is associated with increased susceptibility to viral infections, especially of the SARS-CoV infection, it can be deduced that smokers have a higher chance of getting infected and exhibiting severe symptoms [18]. A more recent series of meta-analysis studies agree with the statistically significant conclusion that smoking enhances the risk of progressing and severe disease in COVID-19 [66–69].

2.6. Kidney disease

There are some data on associations between kidney disease and CoV-induced respiratory disease, and it is impossible to explain considering the influence of any single factor. On the one hand, high doses of broad-spectrum antibiotics that are sometimes administered to infected patients may cause interstitial nephritis [70]. On the other hand, CoVs may have kidney tropism as viral RNA was detected in urine from 21% to 50% of SARS cases [71]. Besides, patients with multiorgan failures frequently develop refractory hypotension, which often is supported by infusion of adrenaline/noradrenaline. Therefore, the hypotension-induced reduction of glomerular filtration with vasoconstriction and secondary bacterial sepsis might lead to acute renal failure that is occasionally observed in patients with CoV-induced respiratory disease [72].

During the SARS-CoV outbreak, a study was conducted on 536 patients to observe comorbidities with kidney diseases. At the time of initial presentation, patients showed a normal creatinine level, but in the later stage of the disease, 6.7% of the patients had a raised plasma creatinine level. A creatinine level of more than 274 μmol/L was considered to indicate renal dysfunction. It was found that patients who developed acute respiratory distress syndrome (ARDS) were of higher risk to acquire a kidney dysfunction. Out of 72 patients that developed ARDS, 45.8% demonstrated manifestations of acute renal failure. All patients with renal failure were treated in critical care, and the fatality was high in these cases [73]. A meta-analysis of four reports, which in total considered 1389 patients, supports the observation that patients with chronic kidney disease have an increased risk of severe SARS-CoV-2 infection [72].

A study covering 701 COVID-19-positive patients showed that 44% had, and 26.9% developed hematuria, with about 3.2% of cases showing acute renal failure. The prognosis for such patients was very grim and had a high risk of mortality [74]. The renal system is possibly affected due to high fever and sore throat, which leads to lower intake of fluids, causing dehydration that reduces the kidneys' filtration rate. If this is not reversed and the ischemic shock continues, it may lead to necrosis. The progression of COVID-19 may lead to sepsis, creating a cytokine shock syndrome. In some studies on SARS-CoV, the direct viral effect on the renal cells has been detected. The renal cells express ACE2 100-times more than the lungs, thus making it a direct target. Some renal injury has also been associated with inappropriate use of non-steroidal anti-inflammatory medicines [75].

Considering how the virus and the disease progression has a high chance of detrimental effect on the renal system, patients with preexisting chronic renal diseases need to be treated with the utmost caution if they are infected, as their risk of mortality is higher. Chronic renal diseases usually exist with other comorbidities such as diabetes, a cardiovascular illness, which are, as already stated, further risk factors for critical COVID-19 [72,76]. In general, patients with existing renal conditions need to be advised to take extra precautions to avoid any exposure to infection. Healthcare practitioners should add extra caution to protocols for patients requiring regular dialysis.

2.7. Cancer

Older people have higher rates of all-sites cancers, and they are also more susceptible to severe COVID-19. Still, some categories of cancer patients are particularly at risk due to their immune suppression. These categories include patients on chemotherapy or who have received it within the last three months, patients on extensive radiotherapy, and recently undergone bone marrow or stem cell transplantation or are still immunosuppressants. Besides, patients with cancers of lymphatic and hemopoietic systems (for example, chronic leukemia, lymphoma, or myeloma) are also at increased risk [77]. If cancer patients develop COVID-19, they will be more likely to have a more negative prognosis [65]. Cancer patients need to visit health care facilities more often, as they need continuous treatment and status monitoring. Furthermore, because intensive care units in many hospitals are concentrated on managing severe COVID-19 cases, their beds may be unavailable for cancer patients in need of emergency care. Finally, if the infection spreads among oncology professionals, the distraction effect will be even more profound [78]. In the study conducted by D Wang *et al.*, 7.2% of patients in a 138 infected cohort were found to have malignancies [79]. In another study by Guan *et al.*, among 1099 patients, 0.9% were found to have any form of cancer, and 30% of those developed severe outcomes [50]. Among the fatalities, the most common demographic was the older and middle-aged population having a history of existing conditions such as tumor surgery [5]. Overall, there is growing evidence pointing to remarkable hospitalization rates and severe COVID-19 outcomes in cancer patients. [80–82].

Haematopoietic Cell Transplant (HCT) is widely used to treat various malignancies and requires a course of immunosuppressants post-transplant [83]. Some past studies conducted on pediatric patients who had a HCT and were infected with a coronavirus needed a significantly high rate of respiratory support and showed a higher mortality rate. There was prolonged shedding of the virus when tested 100 days after HCT. Respiratory support was needed for a high rate of patients who had undergone HCT. The fatality rate was high, too, in immunocompromised individuals [84,85]. High viral load and prolonged steroid use before HCT were associated with more prolonged virus shedding in patients [86].

It is noteworthy that some types of cancer patients, like blood cancer, have a profoundly weakened immune system and are at high risk for infection. Other cancer types, including breast and lung cancers, do not automatically cause immunosuppression. One crucial guideline for healthcare workers in cancer treatment is to weigh the benefits of treatment over the risk of infection, and further research is needed for this [87].

Generally, although the outcome for cancer patients infected with SARS-CoV-2 is grim, the rate of age-related severe outcome outnumbers the risk of cancer. One of the most worrisome risks for cancer patients now is the unavailability of continued treatment due to workers' workload and the saturation of the health system. [88]. Patients are faced with the dilemma of whether to expose themselves to infection by opting to go out for a treatment or forgo the treatment and risk a flare-up of the disease.

2.8. Cytokine activation syndrome

Cytokine activation or release syndrome (CRS) is an inflammatory

response to an infection or a drug and usually develops after a treatment like chemotherapy. CRS occurs due to the activation of bystander immune cells and endothelial cells by binding the CAR T-cell receptor to its antigen. Activation of bystander immune cells results in the mass production of cytokines. Patients with CRS are highly susceptible to infections as they are under immunosuppressive treatment. Usually, symptoms develop very late and lead to a grim prognosis. Viral infections, primarily targeting the respiratory system, are commonly seen. The massive cytokine release probably causes a type of immune paralysis and makes the patient susceptible to infections [89,90].

Many times, virus infections cause an uncontrolled release of cytokines leading to inflammation and a cytokine storm. In the case of coronavirus infections, rapid viral replication, and inflammatory cell infiltrations lead to lung injury and ARDS. In one study conducted on 41 in-patients in China, high levels of interleukins, granulocyte-colony stimulating factor (G-CSF), interferon-γ-inducible protein (IP10), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein 1 alpha (MIP1A), tumor necrosis factor (TNFα) were recorded in ICU patients with severe outcomes [91]. In the same cohort of patients, Zhou *et al.* found all fatal cases to have a high level of IL-6 [43,63]. In another study, lymphocytopenia was observed in all 123 patients with severe COVID-19. CD8+ count reduced by 61.9%, and NK cells reduced 47.62% in ICU cases, which was higher than the reduction in non-ICU cases. In most fatal cases, the NK levels and CD8+ levels had fallen low, leading to sepsis, multiorgan failure, and death [92].

Initial anti-inflammation therapy is essential to prevent cytokine storm. There is a range of pharmaceutical agents that possess anti-inflammatory activity, including non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs), immunosuppressants (ISs), and chloroquine/hydroxychloroquine. Besides, such inflammatory cytokines antagonists as TNF inhibitors, IL-6R monoclonal antibodies, Janus kinase inhibitor (JAK) inhibitors, IL-1 antagonists can produce anti-inflammatory effects [93]. When COVID-19 reaches the stage of CRS, the use of immunomodulatory agents may be justified in an attempt to reduce systemic inflammation before it transforms into multiorgan failure. It was proposed to combine corticosteroids (CSs) with such cytokine inhibitors as tocilizumab or anakinra. Also, intravenous infusions of immune globulin may be used to modulate the immune response. Because the prognosis for this category of patients is generally poor, it is important to recognize CRS early to provide anti-inflammatory therapy [94].

However, several questions related to anti-inflammatory therapy provision remain unanswered as it is of great importance to balance potential benefits with potential harms. Firstly, CSs may increase the risk of secondary infection and reduce virus elimination. Inflammatory cytokines antagonists can only block specific inflammatory factors and might not be effective against CRS as other cytokines may play an important role. Also, JAK inhibitors inhibit the production of INF-α and thus, may not be a good treatment option for this category of patients [95]. However, the most important issue is identifying an optimal time window, which is likely to be an early period of abrupt deterioration of the patient's state that is commonly observed at 1 or 2 weeks after disease onset [96].

2.9. Obesity

Obesity is a risk factor for adverse outcomes in critically ill patients with COVID-19. Increasing evidence showed that subjects with obesity showed a longer hospital stay and a five-fold higher risk of death [97]. Initially, this association was not clearly identified, probably because obesity is not so common in China and Italy, the first countries affected by the infection, and in which the earliest statistics between comorbidity and exacerbation of the disease were highlighted. However, subsequent evidence in the USA, which is the country with the highest obesity rate globally, has converged on this additional, prominent risk factor [98]. However, the hypothesis that obesity could have an important impact on the severity of COVID-19 was undoubted to be considered. It is known that SARS-Cov-2 infection involves damage to lung tissue and that obese people have reduced lung function and, also, compared to normal-weight patients, it is more difficult to compensate for the lack of oxygen through invasive mechanical ventilation (IMV). Moreover, the release of inflammatory cytokines TNF-α and IL-6 from infected pneumocytes and lung cells of infected patients could exacerbate the proinflammatory condition already associated with obesity. A retrospective cohort study involving 124 patients indicated that obese people with body mass index (BMI) > 30 kg/m^2 and severely obese subjects with BMI > 35 kg/m^2 constituted 47.6% and 28.2% of the total hospitalized cases, respectively. The patients that required IMV reached 68.6%, and the disease severity was associated with the increase of BMI [99]. The OR for IMV in patients with BMI > 35 respect patients with BMI < 25 was 7.36. In another study enrolling 103 infected people, 47 % were admitted to ICU. Between this group, severe obesity has been associated with five times higher probability of ICU admission (adjusted OR 5.39). Obesity and severe obesity were associated with a seven and ten times higher probability to require IMV (aOR: 6.85 and 9.99, respectively) [100].

In a cross-sectional study involving 5416 adults, hospitalization rates were higher among obesity and severe obesity with an adjusted rate ratio (aRR) = 2.9 and 4.4, respectively [101].

A multivariable Poisson regression model, also stratified by sex and age, has been applied in a retrospective cohort study to estimate BMI's adjusted effect and other factors on risk for death at 21 days, among 6916 SARS-CoV2 infected. Male aged 60 years or younger patients with a high BMI were particularly at risk [102]. In summary, obesity is a risk factor for the severity of COVID-19. Therefore, it is urgent to pay more attention to this category of predisposed subjects for targeted preventive and therapeutic interventions.

2.10. Solid-organ transplantation

Solid-organ transplant (SOT) recipients are at higher risk of developing critical COVID-19, mainly because of their chronic immunosuppression and related comorbidities. Several case series highlighted this association. In particular, hospitalized kidney transplant recipients with COVID-19 often require intensive care admission and have a very high early fatality rate [103–105]. In a case series, the association between COVID-19 infection and the case mortality rate of 25% has been highlighted in recipients of heart and liver transplants [106,107]. The SARS-CoV-2 infection has a severe course, generally in all SOT recipients [107]. Some reports do not confirm this association, but this has been attributed to the small cohort evaluated in the Italian study from Travi *et al.* [108]. In a large multicenter cohort study involving more than 50 transplant centers, the mortality among SOT recipients hospitalized for COVID-19 has been estimated to reach 20.5%. The study involved 482 SOT recipients, of which 66% underwent kidney or kidney-pancreas transplantation, 15.1% liver, 11.8% heart, and 6.2% lung, respectively [109]. However, the main mortality factors were associated with age and comorbidities rather than with measures related to immunosuppression intensity.

3. Interrelation between Covid-19 and disorders with mixed or more limited evidence

3.1. Asthma

Initially, the limited research data did not verify the potential relationship between asthma and COVID-19. The numerous subsequent studies in different countries to evaluate an increasing number of cases allowed us to draw some conclusions. A follow-up of patients with COVID-19 at Tongji Hospital (Wuhan) showed that the prevalence of asthma was 0.9%, significantly lower than the overall rate in the city's adult population. Mortality in severe cases of COVID-19 in patients with

asthma has also been reported to reach 32.5% [65]. Some reports highlighted the association of asthma with the prolonged duration of intubation in COVID-19 [110]. Asthma exacerbations have been commonly known to be caused by infections, mostly respiratory viruses like the rhinovirus, coronavirus, and influenza. Such infections and worsening of asthma are particularly common in the pediatric population. In a study of 108 children with asthma for 13 months, respiratory samples were collected when asthma worsened, showing that 85% of cases tested positive for a respiratory virus [111]. This exacerbation of asthma with viral infection has also been recorded in adults. In general, it was observed that asthma patients do not have a higher risk of infection; rather, only the severity of infection is altered. They tend to take a longer time to recover and sometimes require intensive care. Viral infection symptoms with asthma comorbidities included upper and lower respiratory tract infections that were more severe and lasted longer in healthy individuals. Allergic asthma patients are at higher risk of developing a more severe disease upon viral infection [112]. Immunologically, asthma patients tend to have a slower response to viral infections as they show reduced and slow production of Type 1 interferons; the production of neutrophils increases in asthmatic patients, which indicates the presence of viral infections [113].

In the United States, a nasal epithelial transcript was analyzed in a large sample of patients with asthma compared with a group of healthy people to assess the effect of their immunity on susceptibility to COVID-19. It was found that the transmembrane Serine Protease 2 (TMPRSS) 2 and ACE2 genes, which play a significant role in the development of SARS-CoV-2, are associated with type 2 cytokine inflammation and the corresponding transmission of interferon signals. These data may indicate a high susceptibility of asthma patients to COVID-19 and the possible severe disease course in such patients [114]. Other authors suggest using the indicator TMPRSS2 and ACE2 gene expression to predict the outcome of COVID-19 in patients with asthma, especially with concomitant diabetes, and in African Americans [115–117].

A different opinion is shared by Jackson *et al.,* who argue that respiratory allergies and experimental exposure to the allergen can reduce the expression of the SARS-CoV-2, ACE2 receptor, leading to a decrease in susceptibility to COVID-19 [118]. The protective role of asthma against the severity of viral infection has also been postulated by an Italian immunology group [119]. The protective effect could be due to type 2 asthma (Th2) - skewed immunity, interferon-mediated immune responses, and increased eosinophils in the airways. However, additional studies are needed in this regard. One study conducted in Singapore during the SARS-CoV outbreak noted that children with asthma did not have any higher risk of infection. SARS-CoV was generally very mild or asymptomatic in children and hardly led to ARDS. Hence, having asthma did not pose a new threat to infections. This data was not conclusive since the sample size was small, and also, the evaluation was done when schools were shut and the city was under lockdown, which would have reduced exposure to the virus [120]. In an observational retrospective cohort study that included 177 children and young adults with clinical confirmed COVID-19, the most frequent overall underlying medical condition was asthma (20%). However, asthmatics were not more common in the hospitalized or critically ill cohort than in the noncritically ill cohort [121].

Lower COVID-19 susceptibility in patients with preexisting asthma has been reported in a retrospective cross-sectional study using data from a large nationwide health maintenance organization in Israel [122].

It would therefore appear that exacerbation of asthma is not the primary determinant of a severe disease requiring hospitalization but rather suggests that asthmatics may experience asthma exacerbations following the SARS-CoV-2 infection. More recently, different risks associated with SARS-CoV-2 infection and the disease development, progression, and severity have been connected differently across Th2 vs. non-Th2 asthma endotypes [123].

3.2. Pregnancy

The potential adverse effects on pregnancy during the COVID-19 pandemic have often shown varying results. Some reports indicate that no increased risk of spontaneous abortion and spontaneous preterm birth has been found and that severe maternal and neonatal complications were not observed in pregnant women with COVID-19 pneumonia who had vaginal or cesarean delivery [124–127]. From these results appears that COVID-19 disease severity in pregnant women is similar to that in non-pregnant subjects [127,128]. Other results show an association between pregnancy (pregnant and postpartum women) and a greater risk of admission to intensive care and the need for mechanical ventilation compared to non-pregnant women. However, the risk of death was found similarities between the two groups [129–131]. With this conflicting evidence, pregnant women should be especially aware of the risks associated with their health and that of their newborns concerning severe COVID-19. Consequently, they and their family members should pay particular attention to the indicated measures to prevent SARS-CoV-2 infection and follow proper prevention counseling.

3.3. Immunodeficiency

Not only immunodeficient people who have undergone cancer therapy or who have undergone organ transplants have a higher risk of developing critical COVID-19. Among immunocompromised individuals, people who have undergone a blood or bone marrow transplant, poorly controlled HIV people, those who use corticosteroids or medicines that weaken the immune system, and those with some immunodeficiency conditions, in general, should be taken into account [132]. The immunosuppressive medication affects cell-mediated and humoral immunity, resulting in more severe or higher infection risk in such patients. This has been evident in rhinovirus and influenza infections but has not been proved with coronaviruses to date [133,134]. It is important to note that coronavirus uses the host's innate immunity to mount a dysregulated and excessive immune response, which is usually the cause for the severity of the disease. This is probably one reason why the bats are a healthy reservoir for the virus, as their immune response is weaker [135]. There is a possibility that an immunocompromised individual maybe just a carrier or show very little severity with infection and possibly at a lower risk. This needs to be corroborated with further studies [134]. HIV and COVID-19 are characterized by elevated inflammatory states that could cause complications. However, it appears that well-controlled HIV individuals are not at greater of severe COVID-19 respect poorly controlled HIV individuals, which may have worse outcomes. In a large population-based study in the UK (from the Open SAFELY platform), it has been reported that individuals with HIV have more than twice the probability of dying from COVID-19 than people without HIV [136]. This conclusion was reached after adjustment for a range of potential confounders such as demographic characteristics, the factors related to the personal lifestyle, and considering any comorbidities. Confirmation of these results also come from multicentre research (from the TriNETX network) [137]. However, clearer evidence is needed to support a causal association between HIV infection and COVID-19 outcomes. Moreover, future prospective controlled studies are necessary to determine the attributable risk of immunosuppression on COVID-19 severity and the proper therapeutic strategy to be adopted in relation to different immunocompromised patients.

3.4. Cerebrovascular disease and neurological manifestations

A quantitative evidence synthesis of clinical data between non-survivors and survivors pose cerebrovascular disease with a RR = 3.3, which means that people suffering from such diseases will have more than three times the risk of developing critical COVID-19 and related death [138]. This result has been based on considering 852 patients (603 survivors and 249 non-survivors) with confirmed SARS-CoV-2 infection

from four retrospective Chinese studies. Several meta-analyses confirmed such association [139–141]. Particular precautions should be taken in the management of COVID-19 patients with preexisting cerebrovascular disease. Moreover, patients with COVID-19 can develop cerebrovascular disease [142]. A single-center study showed that cerebrovascular disease had an incidence of 1.4% (23 in 1683 cases) in patients with COVID-19 with high morbidity and fatality. Death was due to hemorrhagic predisposition leading to thrombotic microangiopathy caused by epitheliopathy [143]. In a prospective study of 4491 COVID-19 patients hospitalized in New York City, 606 (13.5%) developed a new neurologic disorder [144]. After adjusting for a range of confounder factors, infected patients with neurologic disorders showed an increased risk of in-hospital mortality and decreased possibility of discharge home. Neurophatogenesis can result from direct effects of the virus. However, most usually reflect the systemic response to infection and could be multifactorial, including neurologic injury from systemic dysfunction, renin-angiotensin system dysfunction, immune dysfunction, proinflammatory state, parainfectious and postinfectious triggers, and direct viral invasion of the nervous system [145].

The most common neurological manifestations (occurring in about half of COVID-19 hospitalized patients) are myalgia, headache, and encephalopathy, followed by other less common disorders such as dizziness, dysgeusia, or anosmia [146]. Also, neuromuscular diseases have been reported (Guillain-Barré syndrome) and other less common neurologic manifestations, including meningoencephalitis, acute disseminated encephalomyelitis, acute hemorrhagic necrotizing encephalopathy, posterior reversible encephalopathy syndrome, and generalized myoclonus [147]. Further studies are needed to ascertain whether the viral infection is an etiological factor of neurological damage or simply coincidental and depends on causes such as secondary systemic complications or side effects of drug treatment.

4. Conclusion

We have some evidence based on the SARS and MERS epidemics that comorbidities such as diabetes, hypertension, and cardiovascular diseases predispose risk factors for severe infections, leading to critical care and fatality. The same trend has been observed with SARS-CoV-2 and COVID-19 disease. The fatality rate has been considerably high for patients who suffer from one or more comorbidities, with these three conditions mentioned topping the list. Just like in the case of SARS and MERS, the ACE2 receptors play a crucial role in determining the severity of the disease, and the upregulation of ACE2 is probably to blame for the severity of disease in diabetic and hypertensive patients.

As this is an ongoing pandemic, the understanding of COVID-19 is evolving, and much more research is needed to establish a clear relationship between the preexisting conditions discussed and the severity of the disease. It appears that the highest contributors to severity are hypertension, diabetes, obesity, smoking, severe immunodeficiency, and cardiovascular conditions, and COPD. Other conditions, such as asthma, pregnancy, and slight immunosuppressant conditions, are affected by mixed or more limited evidence. Conditions like chronic renal diseases and cytokine activation syndrome may be exacerbated due to COVID-19, and extra care is required for such patients. A treatment plan for patients with comorbidities needs extra care to ensure that there are no drug cross-interactions.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare they have no actual or potential competing financial interests.

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