



# SARS, MERS, COVID-19: Identification of Patients at a Higher Risk: A Narrative Review

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## Abstract

The different presentations, comorbidities, and outcomes of COVID-19 highlight the importance of early identification and proper triage of patients. High-risk patients can be divided into patients with common comorbidities and patients with special categories. Common comorbidities include, but are not limited to, Cardiovascular Disease (CVD), Diabetes Mellitus (DM), immunosuppression, underlying respiratory disease, and obesity. Certain categories of COVID-19 patients are also at increased risk, including neonates and pregnant women. In the present article, we delineate the reported risk factors for acquisition of infection, and for increased severity of the clinical disease. We also comparatively analyze those risk factors associated with COVID-19 and with the antecedent human acute respiratory syndrome-causing viruses, SARS-CoV-1 and MERS-CoV. We hypothesize that the structural similarities of the three viruses predict a similarity in the profile of high-risk patients. Several pathophysiological patterns have been detected to support this theory.

**Keywords:** SARS-CoV; MERS-CoV; SARS-CoV-2; COVID-19; Cardiovascular disease; Hypertension; Immune suppression; High-risk; Pregnancy; Risk factors.

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### Key Summary Points

The severity of SARS, MERS, and COVID-19 is associated with common risk factors.

- Screening for late-onset metabolic and cardiac disorders is advised in high-risk patients who have recovered from any of the three respiratory coronavirus infections. This is because a significant association has been observed between such late complications and previous SARS infection, and SARS, MERS, and COVID-19 share similar disease mechanisms and comorbidities.
- SARS, MERS, and COVID-19 have a worse prognosis in pregnancy, and pregnant women are advised to take extra precautions in the current pandemic.
- Immunocompromised and cancer patients must exercise caution during this pandemic, but more importantly, they should receive the necessary care for their underlying illness.

### Introduction

A century has passed since the dramatic Spanish Influenza pandemic, which resulted in a global crisis and nearly 50 million deaths. The coronavirus outbreak of December 2019 may be on a trajectory to rival, in human cost, the influenza crisis of 1918, with estimates of almost 135 million confirmed cases worldwide and three million deaths at the time of this writing [1].

In the last 20 years, three viruses of the Coronaviridae family have struck human communities in three separate outbreaks, the most recent being the most severe. The first epidemic was caused by the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1) in 2003. It was followed by the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012 (ongoing), and finally, the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which began in December 2019 (the first case reported on December 12) and was declared a pandemic by March 11, 2020 [1-3]. Coronaviruses have become the main pathogens of emerging respiratory disease outbreaks.

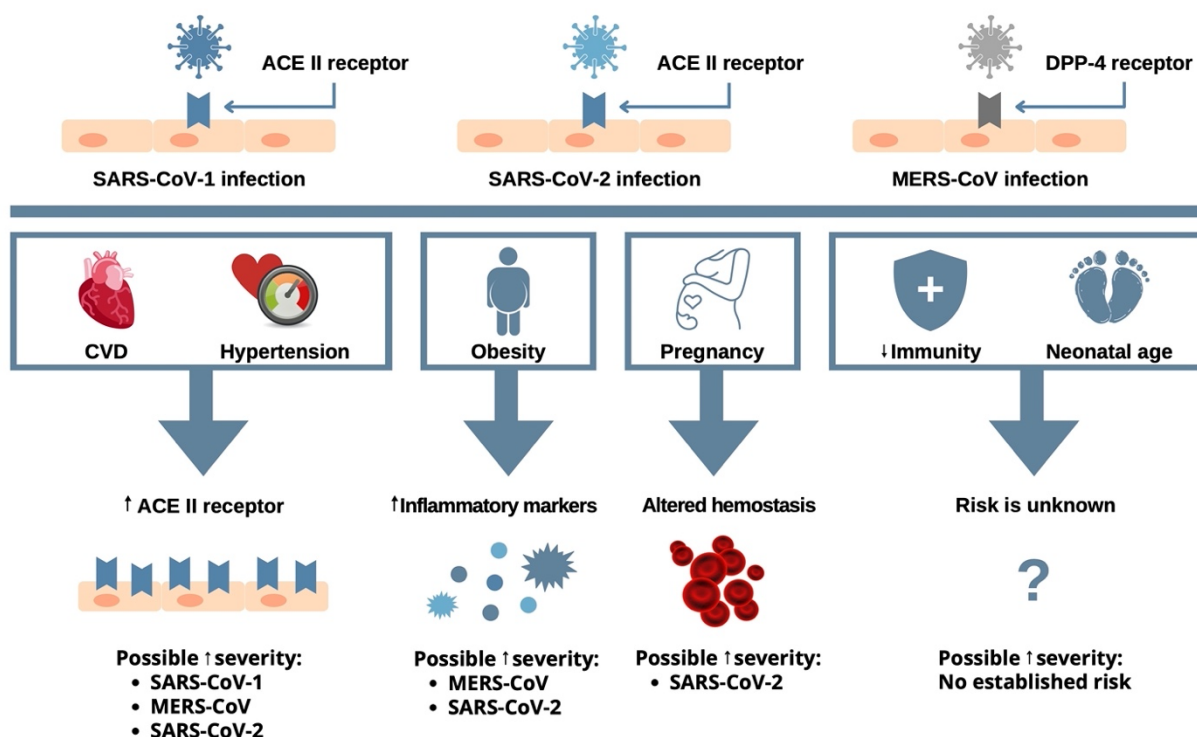
The clinical presentations of the three viral infections are similar despite some variations. Since the three viruses belong to the same family and share a similar structure [4-6], we hypothesize that the risk factors for severity are also similar.

In addition to the classical risk factors such as chronic lung diseases and immune dysfunction, other more common comorbidities also play a role. Hypertension, cardiovascular diseases, diabetes mellitus, older age, and pregnancy are under investigation for their possible association with disease severity (Figure 1) [7, 8]. Most patients with one or more of these conditions are at increased risk of mortality and morbidity (Table 1) [9-12].

### Methods

The authors conducted a PubMed literature search to identify publications with no date of publication restrictions that addressed the risk factors for severity of infection by the three coronaviruses (SARS-CoV-1, SARS-CoV-2, MERS-CoV). The authors used the following keywords: "SARS-CoV", "MERS-CoV", "SARS-CoV-2", "COVID-19", "Cardiovascular disease", "Hypertension", "Immune Suppression", "Pregnancy", "Neonates", "Malignancy", "Diabetes Mellitus", "Respiratory disease", and "Obesity".

Then, the authors scanned selected publications and their reference list for other relevant references that were not identified by the initial search. The selection of the most relevant papers according to the authors' opinion was included in this review.



**Figure 1:** Proposed model of interaction between host factors and viral agents: SARS-CoV-1, MERS-CoV, and SARS-CoV-2: SARS-CoV-1 and SARS-CoV-2 establish infectivity by binding to angiotensin II converting enzyme receptor while MERS-CoV binds to dipeptidyl peptidase-4 receptor. Hypertension and cardiovascular diseases have been linked to increased disease severity in the setting of SARS and COVID-19 which maybe attributed to the increased expression of angiotensin-converting enzyme II receptor expression on endothelial cells. In addition, obesity seems to be an established risk factor for disease severity in the setting of MERS and COVID-19. This is possibly secondary to the increased inflammatory markers at baseline in the obese population. Another proposed risk is pregnancy which has shown to correlate with severity of COVID-19 which is marked by thrombotic events fascilitated by the alteration of hemostasis during pregnancy. On the other hand, immunodeficiency and neonatal age have not demonstrated to be risk factors for increased severity of the infection in the setting of SARS, MERS, or COVID-19.

*Abbreviations:* CVD, Cardiovascular disease; ACE II, angiotensin converting enzyme II; DPP-4, dipeptidyl peptidase-4; SARS-CoV-1, severe acute respiratory syndrome coronavirus 1; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MERS-CoV, Middle East respiratory syndrome coronavirus; ↑, increased; ↓, decreased.

## Discussion

### I. Patients with Common Comorbidities

#### 1. Cardiovascular Disease and Diabetes

The relationship between the cardiovascular system and the recent coronavirus infections can be traced to processes at the molecular level. Both SARS-CoV-1 and SARS-CoV-2 infect host cells by the binding of their viral spike protein to angiotensin-converting enzyme 2 (ACE2) receptors which are highly

expressed in the lungs and the heart [4]. Although MERS-CoV does not enter the target cells by binding to ACE2 receptors, it does bind to Dipeptidyl-peptidase 4 (DPP-4) [5, 6]. DPP-4 is expressed on different tissue types that also express ACE 2 receptors [13, 14]. This suggests that the three coronaviruses have overlapping ranges of tropism.

Cardiovascular disease (CVD) is a term that encompasses a variety of diseases involving the heart and blood vessels. Although different etiologies,

pathophysiologies, and risk factors are associated with the variants of CVD in coronavirus infection, ACE plays a role in most of these variants. This occurs either through the underlying disease process or due to increased receptor expression as a result of the administration of renin-angiotensin-aldosterone system inhibitors [15]. Increased ACE2 expression in affected patients might explain their associated increased risk. New evidence suggests that the use of ACEIs or ARBs is associated with a lower risk of mortality among COVID-19 patients with hypertension [16]. However, the relationship between COVID-19 and CVD requires further investigation.

Following the outbreak of COVID-19, 12% of the first 41 cases reported in China were described as having acute cardiac injury [17]. The blood pressure of patients admitted to the intensive care unit (ICU) was significantly higher than in those not admitted to the ICU (mean systolic blood pressure 145 mm Hg and 122 mm Hg respectively; with a p-value < 0.05) [17]. In another single-center, retrospective study that included 52 critically ill patients of whom 20 survived, 12 of the original 52 patients (23%) had a cardiac injury, and only three of those patients survived. The diagnosis of cardiac injury was based on serum concentration of hypersensitive cardiac troponin I (hsTNI) above 28 pg/mL [11]. Moreover, the mean systolic blood pressure of non-survivors was 140 mm Hg, [11] which suggests poor prognosis associated with cardiac injury and increased blood pressure.

Other reports have shown similar results supporting the correlation between disease severity and cardiac involvement. hsTNI was significantly higher in non-survivors in comparison with survivors in a retrospective cohort study (22.2 pg/mL (5.6–83.1) and 3.0 pg/mL (1.1–5.5) respectively with a p-value < 0.0001) [12]. hsTNI was also noted to be higher in ICU patients than in non-ICU patients (11.0 pg/mL (5.6–26.4) and 5.1 pg/mL (2.1–9.8) respectively with p-value < 0.004) [9]. Likewise, ICU patients, in comparison with

non-ICU patients, demonstrated significantly higher levels of serum creatine kinase-MB in one report (18 U/L (12–35) vs. 13 U/L (10–14) (normal range is <25) with p-value <0.001) [9]. Other studies, however, have not supported this finding: Levels of serum creatine kinase–MB were not found to differ significantly among groups of patients with or without severe disease, respectively. (83.0 U/L (56.0–112.0) and 66.0 U/L (38.5–144.0) (normal range is between 40 and 200) with p-value= 0.192) [10].

As of this writing, many studies have strongly hinted at a positive correlation between cardiac involvement and severity of SARS-CoV-2 infection [7, 18], and this potential correlation merits careful investigation. However, the use of intensive-care admission as a marker for disease severity in SARS-CoV-2 can be problematic, especially since acute cardiac syndromes may necessitate a stay in the ICU regardless of their etiology – whether COVID-19-related or not. In addition, the potential confounding effects of the stressful ICU environment on criteria such as blood pressure should be considered.

Drug-induced cardiac injury has been proposed as a mechanism in COVID-19 cardiac manifestations. Antiviral agents, among other medications, carry a risk of cardiac toxicity [8]. Many of the patients in the above-noted retrospective or cohort studies had received antiviral medications at some point during their disease [9–12]. While the overall role of these medications in COVID-19 cardiac manifestations still needs to be clarified, it seems prudent at this time to recommend that healthcare professionals monitor high-risk patients for drug-induced cardiotoxicity [8].

Heart Failure (HF) is another comorbidity and risk factor for severity linked to COVID-19. Observational studies on COVID-19 inpatients have reported a significant increase in mortality in HF compared to patients without HF [19]. Several pathophysiological processes seem to play a role. Some reports



hypothesize that HF predisposes the patient to more severe infections including COVID-19 due to reduced immunity, general frailty, and reduced hemodynamic ability of the patient. Cytokine dysregulation in HF patients is suspected to play a role in increasing the risk of infection and the severity of disease [20]. Conversely, COVID-19 could be the inciting factor of HF. Several articles, discussed previously, described the association between COVID-19 and myocarditis [7, 8, 18, 21, 22]. Cardiac injury secondary to myocarditis could predispose the patient to congestive HF [23]. COVID-19 might also present as an exacerbation of chronic HF. The pathophysiology follows the pattern of other viral infections such as the previous SARS-CoV and influenza. We hypothesize that COVID-19 directly infects the myocardium initiating this spiral of events. The interplay between HF and COVID-19 spurs further investigation.

Limited data exist on cardiovascular involvement in the MERS-CoV and SARS-CoV-1 epidemics; this can probably be explained by the relatively low number of cases associated with these epidemics compared to SARS-CoV-2. The two earlier outbreaks combined have thus far resulted in fewer than 11,000 cases overall, and fewer than 2,000 deaths [2, 3]. Studies concerned with MERS-CoV did describe cardiovascular morbidities such as acute myocarditis and heart failure related to infection [24]. However, no cases of severe cardiac events were reported for SARS-CoV-1 infections. In a case series of MERS patients from three separate ICUs in Saudi Arabia, a non-significant increase in median systolic blood pressure was documented during the illness of 12 patients, [25] but the correlation was not further explored.

Hypertension and diabetes have been implicated as risk factors in SARS and COVID-19, possibly based on the previously noted mechanisms involving ACE receptors. Besides, most of the severe cases of MERS-CoV reported in the literature were in adults with underlying

conditions, including the common comorbidities of diabetes and hypertension [26, 27]. The results of a meta-analysis by Badawi et al. suggest that the prevalence of hypertension and diabetes in MERS-CoV patients is approximately 50% for each [28]. Regarding COVID-19, nearly all published cohort studies have described patients with baseline diabetes and hypertension [9-12]. The incidence of infection is probably randomly distributed among these patients, but the increased severity of disease among those with cardiovascular disease and diabetes is quite alarming in these groups [11]. Of note, ACE2 genetic polymorphisms have been linked to diabetes, stroke, and hypertension in Asian populations; emerging data suggest that ACE2 expression levels correlate with organ damage and that ACE2 levels and polymorphisms may translate to clinical outcomes that vary across ethnicities [29]. Finally, based on previous studies of other coronaviruses, long-term cardiovascular morbidity may be a valid concern for patients who have recovered from COVID-19 infection. A 12-year follow-up study of 25 SARS-CoV-1 survivors demonstrated that 68% had hyperlipidemia, 44% had cardiovascular system abnormalities, and 60% had glucose metabolism disorders [30].

## 2. Cancer and Immune Suppression

The overall risk of infection is high in immunocompromised patients including those on antineoplastic therapy, those with Acquired Immunodeficiency Syndrome (AIDS), those on immunosuppressive therapy, and patients with altered immune responses due to other disorders [31-34]. The pathogenicity of infecting organisms may range from opportunistic to highly transmissible. Since coronaviruses (SARS-CoV-1 and MERS-CoV) in general and SARS-CoV-2, in particular, are highly contagious, the most significant risk factor for getting the infection is exposure to the pathogen [35, 36]. In principle, then, all the members of a population would be

expected to be at high risk for infection, so it might be hard to assess whether immunocompromised patients as a group are more likely than others to test positive for these viruses.

Regarding the severity of infection in patients with weakened immune responses, different studies have reported conflicting risk assessments [37-39]. A study of 1,590 confirmed COVID-19 cases from 575 hospitals in China found that the percentage of patients with a history of cancer was higher than the incidence of cancer in the overall Chinese population (1% and 0.29% respectively with  $p$ -value $<0.001$ ) [39, 40]. The study also showed that these patients were at increased risk of developing severe symptoms in comparison to patients without a history of cancer (39% and 8% respectively with  $p$ -value $<0.0003$ ) [39]. However, age was also cited as a significant risk factor in this study (OR 1.43, 95% CI 0.97–2.12;  $p=0.072$ ); and the median age of cancer patients was 63.1 years, versus a median age of 48.7 years for those without cancer [39]. Therefore, the suggested increased risk of severity in cancer patients might be attributable to the more established risk factor of older age.

Other reports have shown no association between increased risk of severity and immune suppression [37]. In a study of 200 children who had received a liver transplant, only three patients tested positive for SARS-CoV-2 despite being in a severely affected geographic region (Bergamo, Italy), and none developed pulmonary symptoms [37]. However, the low incidence of infection could be attributed to limited exposure to the virus, which in turn might be attributable to the lifestyle and behaviors of this selected patient population (e.g. relative isolation related to underlying disease or post-transplant immunosuppression). The results of the study, and the suggestion that transplant patients were not at an increased risk for severe infection, should also be considered in the light of the small number of cases of infection (three), and the fact that all patients were children –

since age is considered an important risk factor for severity [39]. The fatality rate for COVID-19 among cancer patients is considerably higher than the fatality rate among all COVID-19 patients; it seems that these cancer patients, particularly when lymphopenic, cannot mount an effective response against SARS-CoV-2 [41]. Disease progression in children in the first SARS outbreak was self-limiting and followed the course of other common respiratory viral illnesses [42]. In addition, there were no reported cases of SARS-CoV-1 infection in immunosuppressed patients. A 2018 study on MERS found no increase in risk for the infection among patients with immune suppression or cancer [38]. Thus, based on the existing literature, immune suppression does not seem to play a role in coronavirus disease severity and might even be protective. More evidence is urgently needed to support or refute this theory. One proposed explanation for this phenomenon is that the damage caused by a coronavirus infection might be induced via an exaggerated immune response rather than by the virus itself. This concept has been supported by the finding that bats, the natural reservoir of the coronaviruses, do not become ill from the virus and probably have a tolerance to it [43, 44].

Of note, one significant risk factor for cancer patients and immunosuppressed patients in the recent COVID-19 outbreak was believed to be their inability to access healthcare services that were overwhelmed with COVID-19 cases. Either because of a lack of medical supplies or personnel or due to a fear of infection, cancer patients might experience cancellation or delays in follow-up, treatment, clinical trials, or misdiagnosis of common complications that could accompany their disease [45]. These issues were not evident in the previous coronavirus outbreaks, probably because of the limited number of cases in each outbreak compared with the current one.

**Table 1:** The percentage of patients with underlying chronic diseases in the different reports on clinical characteristics of patients with COVID-19.

Study	Location	Number of patients	Median Age (Years)	% diabetes (%)	% hypertension (%)	% Respiratory diseases (%)	% Cancer and immune suppressed (%)
Huang et al <sup>17</sup>	Wuhan	41	49 (IQR 41–58)	20	15	2	2
Wang et al <sup>19</sup>	Wuhan	138	56 (IQR 42-68)	10.1	31.2	2.9	7.2
Yang et al <sup>11</sup>	Wuhan	52*	59.7 <sup>‡</sup> (SD=13.3)	17	-	8	4
Young et al <sup>79</sup>	Singapore	18	47 (IQR 31-73)	28 <sup>‡</sup>	28 <sup>‡</sup>	-	-
Zhang et al <sup>10</sup>	Wuhan	140	57 (IQR 25-87)	12.1	30	2.8	-
Zhou et al <sup>12</sup>	Wuhan	191	56 (IQR 46–67)	19	30	3	1
Liu et al <sup>80</sup>	Wuhan	137	57 (IQR 20–83)	10.2	9.5	1.5	1.5
Liu et al <sup>81</sup>	Shenzhen	12	53.7 (IQR 43.5-65)	16.6	25	8.3	0
Guan et al <sup>82</sup>	Mainland China	1,099	47 (IQR 35- 58)	7.4	15	1.1	1.1

% diabetes, percentage of patients with underlying diabetes; % hypertension, percentage of patients with underlying hypertension; % Respiratory diseases, percentage of patients with underlying respiratory disease such chronic obstructive lung disease; % Cancer and immune suppressed, percentage of patients with underlying Cancer or are immune suppressed because of variable causes; -, no data available; IQR, interquartile range; \*All patients were admitted to the ICU;<sup>‡</sup> reported as mean; <sup>‡</sup> reported in combination as comorbidities.

### 3. Underlying Respiratory Disease and Obesity

The Centers for Disease Control (CDC) has listed chronic lung disease and severe obesity (body mass index >40) among the risk factors for severity in COVID-19 infection [46]. A higher prevalence of obesity may account for increased mortality from COVID-19 [47].

Obesity furnishes a sinister background for COVID-19 infection. First: obesity represents a basal inflammatory state; interleukin-6, C-reactive protein, tumor necrosis factor- $\alpha$ , and adipokines are often high, inflammatory macrophages supplant regulatory M2 cells, and pancreatic  $\beta$ -cell function is hindered, thus impairing the metabolic and immune response to infection at baseline [48, 49]. Second: SARS-CoV-2 may act directly on the  $\beta$ -cells, perhaps through an angiotensin-

converting enzyme 2-mediated interaction, further exacerbating this dysregulated immunity [48]. Third: obesity

not only causes reduced lung volume and restrictive-pattern lung impairment but may also promote type 2 inflammation, which impacts the bronchi and lung parenchyma [48].

The interplay between obesity and viral infection has been studied in influenza, and these findings may apply to SARS-CoV-2, too. Compared to lean mice, obese mice infected with influenza show decreased levels of interferon- $\gamma$  (which plays an important role in clearing viruses), B-cells, and virus-specific antibodies [50]. Also, influenza-infected cells from obese adult humans show lower expression of activation markers (CD28, CD40 ligand, CD69, IL-12R, IFN- $\gamma$ , granzyme B) [50]. Similar studies on SARS-CoV-2 would significantly enhance the current

understanding of COVID-19 pathophysiology in obese patients.

A growing body of data suggests that COVID-19 patients with COPD are more likely to experience a severe disease course (ICU admission, mechanical ventilation, death) than non-COPD patients [51]. A meta-analysis that included eight different studies cited respiratory-system disease as one of the most prevalent comorbidities among very ill patients (Odds ratio (OR) =  $2 \pm 0$ , 95% confidence interval (CI) 1-3%) [52]. Similarly, obesity and underlying lung diseases were reported as risk factors for increased severity in MERS-CoV infection [25, 27, 53-55]. Reports on clinical outcomes of the SARS-CoV-1 outbreak of 2003 included patients with severe obesity and pre-existing respiratory conditions such as chronic obstructive pulmonary disease, [56] but the evidence was not sufficient to establish a clear association with severity. Hence, it is suggested that patients with chronic lung diseases and obesity receive close monitoring and follow-up, pending the results of further studies to clarify the relationship of these comorbidities with severe coronavirus infection.

## II. Special Categories of Patients

### 1. Neonates and Pregnant Women

Pregnant women are more likely to contract a respiratory pathogen due to decreased immunity during the time of pregnancy [57]. They are also at higher risk for developing lower respiratory tract infections (LRTIs) with worse outcomes because of the physiological changes of pregnancy (decreased functional residual capacity secondary to increased edema in the airways and lungs). Besides, pregnant women's increased need for oxygen makes them more susceptible to hypoxia [58]. Moreover, in pregnant patients in their third trimester who are positive for SARS-CoV-1 infection and experiencing severe respiratory illness, hypoxia affects placental oxygen delivery to the fetus as evidenced by increased intervillous and

subchorionic fibrin on histopathological examination [59].

#### A. Neonates

Adverse neonatal outcomes have been documented in cases of pregnant women diagnosed with MERS-CoV, SARS-CoV-1, and SARS-CoV-2 infections [60-62]. Although data on the neonatal outcome of pregnant women diagnosed with MERS-CoV infection is limited to 13 cases at this time, a series of five cases of children born to MERS-CoV-positive mothers reported by Assiri et al. showed that of these five deliveries one was a stillbirth and another was premature and not viable [60]. Concerning fetal development in mothers with SARS-CoV-2 and SARS-CoV-1 infections, restricted growth, fetal distress, polyhydramnios, respiratory distress, thrombocytopenia with abnormal liver function, preterm labor, and even death of the fetus have been described [61, 62].

Children born via Cesarean section to mothers positive for either SARS-CoV-2 or SARS-CoV-1 have tested negative for the virus, which makes the possibility of vertical transmission in case of SARS-CoV-2 and SARS-CoV-1 very unlikely [63, 64]; however, this may not be true for all strains of coronavirus causing disease in humans. Human Coronavirus 229E (HCoV-229 E) has shown ambiguous evidence of vertical transmission either via viremia or through the ascending pathway. Therefore, evidence concerning the vertical transmission of MERS-CoV, SARS-CoV-1, and SARS-CoV-2 is still inconclusive [65].

#### B. Pregnant Women

Not only can MERS, SARS, and COVID-19 affect fetal well-being, but they might also impact the mother's health and prognosis. According to Lam et al., in a case-control group of matched pregnant and non-pregnant women positive for SARS-CoV-1, pregnant and non-pregnant women had a similar presentation at the time of diagnosis. However, pregnant women had a worse clinical course compared to non-pregnant women, marked by an increased risk for intubation, renal failure, and diffuse



intravascular coagulopathy (DIC) [66]. Twelve other cases of pregnant women positive for SARS-CoV-1 documented in the Princess Margaret Hospital in Hong Kong showed that this viral infection may have a detrimental effect on pregnant women's health and clinical outcome. Among the 12 women in this study, three of them died, leading to a case fatality rate of 25%. Furthermore, pregnant women infected with SARS-CoV-1 had three times the risk of requiring mechanically assisted ventilation, when compared with non-pregnant women suffering from the same viral infection [61]. Data on pregnancy and COVID-19 is still being studied. A study published in the American Journal of Obstetrics & Gynecology in April 2020 recommended universal screening for SARS-CoV-2 in pregnant women admitted to labor units, due to the high proportion of asymptomatic patients; in the authors' retrospective case series of 43 pregnant women with COVID-19, 14 (32.6%) were asymptomatic [67]. It appears that complications from COVID-19 are common in both pregnant women (caesarian section and others) and neonates (most commonly pneumonia and respiratory distress syndrome), although the risk of neonatal infection appears low [68]. Newer data provided by a study by Jering et al., whereby they analyzed the Premier Healthcare database (encompassing around 20% of the hospitalizations in the United States of America) between April 1 and November 23, 2020, provided more input on the mortality and morbidity of COVID-19 in pregnancy [69]. COVID-19 increased mortality among pregnant women with an odds ratio (OR) of 28.26 (CI=12.68-62.08). In addition, through their retrospective analysis, Jering et al. demonstrated that pregnant women who test positive for SARS-CoV-2 are more likely to develop venous thromboembolism (OR= 3.52 [CI=2.09-5.92]), preeclampsia (OR=1.36[CI=1.11-1.33]) and undergo preterm labor (OR=1.26 [CI=1.14-1.38]) [69]. Furthermore, a major limitation to understanding the interaction between the physiology of pregnancy and COVID-19

infection and the clinical outcome of pregnant women who test positive for the viral infection is the exclusion of pregnant women from clinical trials and vaccines, which may lead to limiting data output on the prognosis of this population with the current proposed treatments.

Data related to pregnant women with MERS infection is sparse and contradictory. In one report from Saudi Arabia, two out of five pregnant women positive for MERS-CoV succumbed to their illness. Of the two patients who died, one allegedly had no comorbidities before presentation to healthcare, but the second patient had a previous medical history of asthma, pulmonary fibrosis, and spontaneous pneumothorax which made her more susceptible to hypoxia.<sup>60</sup> However, other reported cases of pregnant women positive for a MERS-CoV infection showed less dramatic clinical outcomes [70, 71].

Most of the published data on neonates born to pregnant women positive for either SARS-CoV-1 or MERS-CoV infection is anecdotal in origin and should be interpreted with caution.

## 2. Infants, Children and Adolescent

### A. Infectivity

Children's infectivity rates for SARS-CoV-1 are lower than those of adults [72]. A similar pattern is seen in children suspected to be potential carriers of MERS-CoV. Their milder symptoms (and sometimes the absence of symptoms) and shorter disease duration, limiting the development of positive serologies, may present obstacles to the accurate assessment of infectivity [73]. A cohort study was carried out on 2,235 children under 13 years of age in Saudi Arabia, where subjects were tested for the presence of nucleic acid specific for MERS-CoV. No subject tested positive for the virus, which makes the population of children a very unlikely reservoir [74]. For SARS-CoV-2, children have a similar risk of contraction as adults but are less likely to develop severe symptoms [74]. It is

possible that children play a significant but inadvertent role in spreading the disease, especially since their symptoms are often relatively mild [75].

### B. Route of Transmission

Contact with camels and having an infected household member have been cited as the most important risk factors for MERS-CoV transmission to children [73]. Having an infected household member was also found to be the most significant risk factor in a case series of nine infants under one year of age diagnosed with COVID-19, where family clustering occurred in all nine subjects [76]. No studies describing the route of transmission of SARS-CoV-1 in infants were found in the literature.

### C. Clinical Presentation

In a case series of 47 children and teenagers who tested positive for SARS-CoV-1, the major symptoms were cough, malaise, chills, rhinorrhea, and myalgia. Abnormal radiological studies were reported in 31 subjects with a mean age of 14.4 years, while children with normal findings on imaging had a mean age of 12.5 years. In one of the cases, abnormal radiological findings persisted for six months after the resolution of symptoms. Interestingly, lymphopenia may have been a risk factor for having radiological abnormalities in this group of children and teenagers [77]. The fact that the group demonstrating radiological abnormalities had a higher mean age suggests that teenagers may have a presentation similar to that of adults and less like that of children, which is typically milder [72]. However, radiological findings may not always correlate with clinical presentation in a child positive for SARS-CoV-2 – for example, in the reported case of an asymptomatic child whose computed tomography (CT) scan showed a ground-glass appearance of the lungs [78].

### Conclusion

Efforts to manage the previous outbreaks of SARS-CoV-1 and MERS-CoV were

directed at containment, and they seem to have been successful. By contrast, the SARS-CoV-2 pandemic is shattering constraints, devastating global health and the economy, and exhausting healthcare resources. Under these extraordinary circumstances, it is vital that we continue to define patient risk factors and shed light on evidence that has thus far been inconclusive. A more intensive focus should be placed on the investigation of at-risk groups and individuals, which will not only advance the care of patients and the allocation of resources but may also help elucidate mechanisms of disease, as shown in this review. Along with immediate behavioral changes such as social distancing, and the eventual introduction of effective medications and vaccines, there is an urgent need for identification of patients at high risk for coronavirus infection or exacerbation of the disease, so that they may be provided with appropriate management. At the present time, comparative analyses such as this one are limited by their subjects: while available data on SARS and MERS pertain mostly to their nature as pandemics of viral and respiratory disease, data on COVID-19 is readily available and ever-evolving as this current crisis continues to rage.

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