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.

Literature Review of COVID-19, Pulmonary and Extrapulmonary Disease

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ABSTRACT

In December 2019 novel coronavirus-Severe Acute Respiratory Syndrome-Corona Virus2 (SARS-CoV2)-originated from Wuhan, China, and spread rapidly around the world. This literature review highlights the dynamic nature of COVID-19 transmission and presentation. Analyzing 59 relevant articles up to May 1st, 2020 reflects that the main reported clinical manifestation of COVID-19 pandemic is fever and respiratory involvement. Also, current literature demonstrates a wide spectrum of different and atypical presentation(s) of COVID-19. The definite route of SARS-CoV2 transmission is respiratory droplets, however, virus nucleic acid has been detected in the stool and urine specimens as well. The severity of symptoms and outcomes of COVID-19 vary based on the patient's medical background, age, sex, and concurrent medical conditions (e.g. pregnancy). This is the first review that classifies all essential points regarding COVID-19 manifestations at a glance to improve the outcome of the patients by a better insight into diagnosis and management.

Keywords: COVID-19; Manifestations; Novel corona virus (2019-ncov); Presentations; Severe acute respiratory syndrome-corona virus2 (sars-cov2); Transmission. **[Am J Med Sci 2021;361(5):567–574.]**

INTRODUCTION

Coronaviruses (CoVs) are a large family of Coronavirinae affecting both humans and animals. The first human CoV (HCoV) was identified in the mid-1960s in human embryonic tracheal organ cultures and until 2003 only two HCoV species, HCoV-229E, and HCoV-OC43, were recognized. To date, six HCoVs have been identified, Severe Acute Respiratory Syndrome-Corona Virus2 (SARS-CoV2) is classified into the beta-CoVs group (Figure 1). Before the last two lethal outbreaks of HCoVs by Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) these viruses were considered relatively benign.[1,2] Table 1 compares some of the specifications of three lethal human coronaviruses (HCoVs).

Coronavirus family is spherical, enveloped, non-segmented, single-strand, positive-sense RNA with a large known genome, of 30–32 kb. The "crown-like" spikes on the outer edge of its surface give the coronaviruses its name -the virus wears a crown.[6]

Infection by SARS-CoV2 (the initial name was 2019-nCOV) causes Coronavirus Disease 2019 (COVID-19) which is transmitted through large droplets generated during coughing and sneezing by either symptomatic patients or asymptomatic people. The incubation period of COVID-19 varies from 2–14 days. Virus sneaks into respiratory cells (type 2 pneumonocytes and ciliated bronchial epithelial cells) via attachment between Angiotensin-Converting Enzyme 2 (ACE2) receptors and Spike Glycoprotein (S Glycoprotein).[7]

The most common initial clinical manifestations of COVID-19 include fever (82%), cough (61%), myalgia and/or fatigue (36%), shortness of breath (26%), headache (12%), sore throat (10%) and gastrointestinal symptoms (9%). Laboratory findings are different from normal findings to lymphopenia (0.93×10^9/L) and abnormal C - reactive protein (33.72 mg/dL).[8] According to a retrospective review on 25 death cases of COVID-19, an elevated level of neutrophils, Serum Amyloid A (SAA), Procalcitonin (PCT), C-Reactive Protein (CRP), Troponin I (cTnI), D-Dimer and Lactate Dehydrogenase (LDH) can be considered as factors of disease progression.[9] Also, a case report study mentioned that decreased plasma level of albumin (Hypoalbuminemia) is another identified marker of critical illness in COVID-19 patients.[10] The most described radiological findings in COVID-19 pneumonia are consolidation and bilateral multilobar ground-glass opacification (GGO) with a peripheral or posterior distribution, mainly in the lower lobes and less frequently within the right middle lobe.[11]

For the diagnosis in patients with suspected infection, the following procedures are recommended: Real-

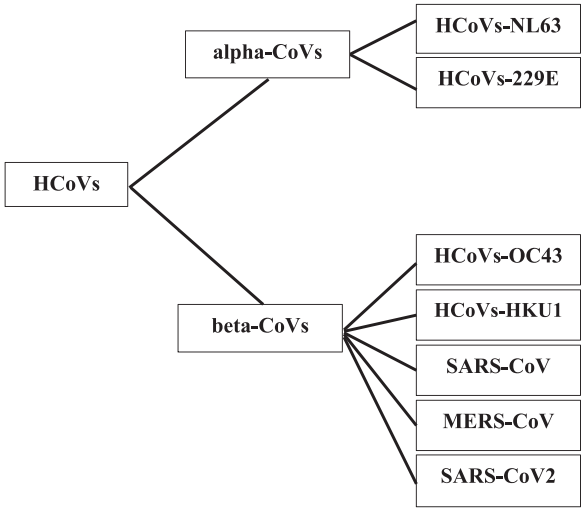

FIGURE 1. Different types of Human Coronaviruses (HCoVs).

Time Polymerase Chain Reaction (RT-PCR) to detect the positive nucleic acid of SARS-CoV2 in sputum, nasopharyngeal swab, and secretions of the lower respiratory tract samples, while viral nucleic acids are detectable in blood and digestive tract (fecal/anal swabs) as well. Multi-sample nucleic acid detection is preferable to a single sample method and could improve accuracy, reduces the false-negative rate, provides a better guide for clinical treatment, and evaluating the therapeutic effect.[12,13]

Given the clinical feature of SARS-CoV2 infection varies from an asymptomatic state to a wide spectrum of clinical presentations this review article conducted to integrate and summarize the novel and rare information about COVID-19 manifestations which have been reported up to May 1st, 2020. Also, this review contains different clinical situations that might be affected by SARS-CoV2 infection such as pregnancy and breast-feeding. We also focused on clinical differences at both ends of the age in this review. SARS-COV2 represents the causal agent of a potentially fatal disease (COVID-19) that is actually of great global public health concern.

METHODS

To comprise this review article our team assessed 59 accessible articles about COVID-19 in the current literature. We leaned on qualitative, non-statistical tools for consolidating, evaluating, and interpreting the results of the conducted papers. In the following, we explain what strategy we used in our methodology. First, by focusing on various reports about COVID-19 manifestations and engaging in relevant current articles we formulated the research scope before beginning the review process. For selecting studies we conducted a systematic search via Google engine and PubMed database which is a widely used search engine, founded and maintained by the United States National Center for Biotechnology Information (NCBI) at the US National Library of Medicine (NLM).[14] The following keywords have been used: "COVID-19" OR "2019 novel coronavirus" OR "2019-nCoV" OR "SARS-CoV-2″ OR "Wuhan coronavirus" AND "presentation" OR "characteristic" OR "manifestations". After finding relevant studies to our literature review, we carefully screened studies that met the formulated inclusion criteria including **1)** case reports, case series, cohort studies and reviews (literature review, systematic review, and meta-analysis) that considered COVID-19 manifestations, **2)** current and retrospective studies about SARS-CoV2's impact on specific organ systems, **3)** clinical differences of COVID-19 in particular groups including children, senile people, pregnant women, and breastfeeding mothers.

Finally, 61 papers were screened for eligibility according to their title and text. A total of 59 papers out of 61 focused on COVID-19. Thirty five of the conducted papers were an original article, 20 of them were review and/or meta-analysis and 4 of the surveyed studies were case reports. Research letters and supplemental articles have been used based on their content. We only reviewed articles in English and collected clinical data by specifying relevant study components including the country of the study, date of the study, type of the study, patient age range, patient medical status, and symptoms category (respiratory, GI, cardiovascular, etc.). Review of the articles and data collection performed by two researchers of our team separately but the possibility of publication bias cannot be ruled out.

RESULTS AND DISCUSSION

As of April 5th, 2020, 1,218,090 confirmed cases of COVID-19 with 65,836 deaths (Case Fatality Rate: 5.4%)

TABLE 1. Coronavirinae subfamily specifications.

Virus	Virus reservoir[3]	Incubation Period[4]	First involved city, country	MM/Yr	Receptor	Diarrhea%[5]	Ocular involvement[48]	Average CFR[a]%[1,16]
SARS-CoV	Bat	2–7 days	Guangdong, China	Nov/2002	ACE2[b]	20–25	Negative	10
MERS-CoV	Bat	5 days	Saudi Arabia	June/2012	DPP4[c]	20–25	Negative	30
COVID-19/ SARS-CoV2	Bat, ±Mink	2–14 days	Wuhan, China	Dec/2019	ACE2	Rare	Positive	0.08 –10.8 (Varies per location and time)

[a] Case Fatality Rate.
[b] Angiotensin-Converting Enzyme 2.
[c] Di-Peptidyl Peptidase 4.

has been reported.[15] Given a study on April 16th, 2020, the case fatality rate (CFR) varied between 0.08 −10.8% for 65 countries.[16] Based on the "*worldmeters.info*" website, on May 1st, 2020, confirmed cases of COVID-19 were 3,329,453 with 234,725 deaths (CFR: 18.2%).

To date, in different parts of the world, a wide spectrum of different and atypical manifestations of SARS-CoV2 infection have been described. Yet the dominant clinical manifestation of COVID-19 is a respiratory illness. The virus infects alveolar cells by binding to the ACE2 receptors. These functional cellular receptors are also expressed on other species of cells such as intestinal enterocytes, nephrocytes, arterial, and venous endothelial cells. Therefore, the extrapulmonary manifestations of SARS-CoV2 in the course of the disease are also possible. This section sheds light on documented different presentations and various outcomes of COVID-19 along with close attention to SARS-CoV2's impact on different population groups including pregnant women, breastfeeding mothers, children, and senile people.

SARS-CoV2/COVID-19 and lower respiratory system

The involvement of the lower respiratory tract by SARS-CoV2 is varied, ranging from asymptomatic carriers to pneumonia and acute respiratory distress syndrome (ARDS). According to different studies, the median time from onset of symptoms to dyspnea is 5 days, hospitalization 7 days, and acute respiratory distress syndrome (ARDS) 3−8 days.[10,17] A pooled analysis of 468 patients with pneumonia reported 70.9% of patients required oxygen therapy, 28.8% needed mechanical ventilation, 3.1% of patients required extracorporeal membrane oxygenation (ECMO), and the overall mortality was 8.2%.[18]

Although there is no clear risk factor for COVID-19, several factors have an impact on the prognosis of respiratory illness including male sex, age (>50 yo), positive smoking history, and coexisting underlying disease(s). Numerous studies reported that a significant proportion of patients had at least one underlying disease. Based on *Chih-Cheng Lai* et al. hypertension (HTN) is the most underlying disease (14.9%) followed by diabetes mellitus (7.4%) and cardiovascular disease (4.2%)[18]; in another literature review by *Pramath Kakodkar* et al. these proportions are slightly different; they considered 1458 COVID-19 cases; 28% of the patients had comorbidity (s), the most underlying disorders were HTN (55.3%), CAD/CVA (Coronary artery disease/Cerebrovascular accident) (31.5%) and diabetes mellitus (30.6%) respectively. According to *Guan* et al. "in patients with severe COVID-19, any underlying conditions were significantly more common as compared with non-severe COVID-19 cases" (38.2% vs. 22.5%, $P<0.001$).[4,19]

SARS-CoV2/COVID-19 and gastrointestinal (GI) tract

Along with the respiratory system, the GI tract is another system that frequently involves in the COVID-19 course; however, some patients can present with digestive symptoms in the absence of respiratory symptoms. Mostly incidence of digestive manifestations is higher in the later than in the early stage of the disease. Also, in patients with higher disease severity liver injury is more common, so monitoring of liver function in the course of the disease is recommended. Another important point about GI tract involvement is the shedding of SARS-CoV2 into feces which implicates the possibility of fecal-oral transmission.[20,21]

A systematic review and meta-analysis on 60 studies by *Cheung KS* et al. showed 17.6% of patients diagnosed with SARS-CoV2 had gastrointestinal symptoms; of the pooled data prevalence of anorexia was 26.8%, diarrhea 12.5%, nausea/vomiting 10.2%, and abdominal pain/discomfort 10.2%. Virus RNA has been detected in fecal samples of 48.1% of patients which is higher among those with diarrhea than those without diarrhea (38.5% vs 8.7%; $p = 0.019$). Furthermore, when SARS-CoV2 nucleic acid turns to negative in throat swabs can still be positive in the feces and could persist in stool ≥33 days from illness onset. Therefore, healthcare workers need to follow hygienic instructions and appropriate protective measures carefully during collecting fecal samples or performing endoscopic procedures in patients with SARS-CoV2 even after patient recovery.[22]

Besides the GI symptoms mentioned above, SARS-CoV2 affects the liver as well. Liver damage can occur during disease progression and/or treatment of COVID-19 in patients with or without pre-existing liver diseases. In a case report by *Zhe Xu* et al. the pathology report of liver biopsy specimens of a deceased patient showed moderate microvascular steatosis and mild lobular and portal activity which indicates that the cause of the injury may be SARS-CoV2 infection or drug-induced liver injury.[23] Possible mechanisms of liver damage by COVID-19 including *i)* Immune-mediated *ii)* Direct toxicity due to active viral replication in hepatic cells *iii)* Anoxia and hypoxic hepatitis as a result of respiratory failure *iv)* Drug Inducer Liver Injury (DILI) such as lopinavir/Ritonavir, Remdesivir, Chloroquine, Tocilizumab, Uminefovir, and Chinese traditional medicine *v)* Reactivation of pre-existing liver disease.[24-26]

Liver damage presents with elevated serum liver biochemistries in hospitalized patients with SARS-CoV2 infection. The incidence of rising serum levels of AST, ALT, and Bilirubin ranges from 14−53%. Men and more severe cases of COVID-19 are more predisposed to increased liver enzymes. Also, a low albumin level is associated with severe infection and poor prognosis; therefore regular monitoring of liver biochemistries should be performed in all COVID-19 patients.[15]

SARS-CoV2/COVID-19 and cardiovascular (CV) system

SARS-CoV2 has significant implications for the cardiovascular care of patients. First, the virus has a direct

and indirect effect on the CV system that could cause complications such as Acute Cardiac Injury (ACI), vascular inflammation, myocarditis, cardiac arrhythmias, heart failure, and venous thromboembolism. Second, underlying cardiovascular disease (CVD) increases the incidence and severity of infectious disease. Third, medications under investigation for COVID-19 could have cardiovascular side-effects. Fourth, patients with SARS-CoV2 have an impact on the rapid triage of Non-SARS-CoV2 cardiovascular patients.[27-29]

The reported prevalence of underlying cardiovascular disease (HTN, CAD, cardiomyopathy) in COVID-19 patients is 4.2% overall, and up to 40% in hospitalized patients.[1] Furthermore, *Dhainaut* et al. study revealed: "the presence of pre-existing CVD increases the incidence and severity of infectious disease."[27]

Fang et al. suggested that in patients with comorbidities like HTN and diabetes mellitus (DM) which are treating with angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin II type-I receptor blockers (ARBs), ACE2 receptors are upregulating. Given the fact that the virus is using the ACE2 receptor to infect the cells, increased expression of ACE2 receptors would facilitate the infection process by SARS-CoV2 in patients who are on ACEIs/ARBs.[30] Moreover, the most reported comorbidities in patients with SARS-CoV2 are HTN and DM which is interpretable by vast taking ACEIs /ARBs in these two groups and can describe the reason why these patient populations tend to have more severe SARS-CoV2 phenotypes.[4,18]

The most commonly reported cardiac sequel in patients with SARS-CoV2 infection is Acute Cardiac Injury (12% −27.8%). ACI is determined by elevated cardiac troponins (cTnI and cTnT). The most likely mechanism for ACI by SARS-CoV2 is direct viral involvement of cardiomyocytes and the effect of inflammatory biomarkers especially interleukin-6 (IL-6) and serum ferritin levels which have been higher in nonsurvivor patients. Besides ARDS, ACI and myocarditis are other strong and independent factors associated with a higher mortality rate in COVID-19 patients.[1,28,31]

The level of cardiac troponin T (cTnT) is another important predictive factor in patients with SARS-CoV2. Higher levels of cTnT are associated with a higher level of N-terminal pro-brain natriuretic peptide (NT-proBNP) and also higher incidence of complications such as ARDS, malignant cardiac arrhythmias, acute kidney injury (AKI), acute coagulopathy as well as higher mortality rates. The mortality during hospitalization for patients without underlying CVD and normal cTnT was significantly lower than patients with underlying CVD and elevated cTnT (7.62% vs. 69.44%).[31]

SARS-CoV2/COVID-19 and neurological presentations

Neurological manifestations of SARS-CoV2 have not been widely reported. However, available studies show different neurological presentions of COVID-19, including dizziness, headache, acute cerebrovascular disease, encephalitis, neuralgia, and muscle injury with elevated creatine kinase levels.[32-34] *Liu* et al. study conducted the first case of encephalitis due to COVID-19 in Beijing. The patient presented with convulsions and persistent hiccups. The neurology examination disclosed slow pupillary response, bilateral ankle clonus, bilateral positive Babinski sign, and meningeal irritation. Brain CT Scan was normal. The lumbar puncture (LP) revealed an increased opening pressure of 330mmH2O, positive PCR for SARS-CoV2 along with normal biochemical and cytological parameters.[32]

An atypical neurological manifestation of SARS-CoV2 has been highlighted by *Dugue* et al. In this case report, they documented the acute neurology event of COVID-19 in a 6-week-old term male infant in the form of brief episodes of sustained upward gaze associated with dystonic bilateral leg extension and altered responsiveness. CSF profile was unremarkable but the respiratory RT-PCR panel was positive for rhinovirus and SARS-CoV2 as a co-infection. This case highlights the possibility of rare but important neurological presentations in children.[35] Another important point about the interaction between SARS-CoV2 and neurology system is the outcome of COVID-19 in patients with pre-existing neurology disorders. According to available reviews, cerebrovascular disease is one of the underlying conditions with a negative impact on the clinical course of SARS-CoV2 infection and could increase the mortality rate.[1,4,19]

SARS-CoV2/COVID-19 and renal presentations - Urology considerations

There is not much data available about the involvement of the renal system in the course of SARS-CoV2 infection. The most common renal manifestation of COVID-19 is Acute Kidney Injury (AKI)- based on the highest serum creatinine level or urine output criteria. The prevalence of AKI varies in different studies from 0.5−7%. The interconnected mechanisms in AKI consist of *1)* cytokine damage (especially IL-6), *2)* organ cross-talk-the close relationship between alveolar and tubular damage in ARDS patients, and *3)* systemic effect-positive fluid balance in critically ill patients could result in renal compartment syndrome. AKI like ARDS and myocardial injury can increase the mortality ratio in COVID-19 patients.[5,19,36,37]

Interestingly, *Ling* et al. study is one of the reports in the literature that demonstrates the presence of SARS-CoV2 nucleic acid in the urine sample of 4 patients out of 58 cases (6.9%). Furthermore, viral RNA in the urine sample like stool specimens can remain positive even after the throat swab turns to negative. On the contrary, other available studies have not found the SARS-CoV2 nucleic acid in the urine and semen samples of the patients.[38-40]

Previous studies reported the presence of Hepatitis B Virus (HBV), Papillomavirus as well as HIV in the surgical smoke during laparoscopic/robotic surgeries, laser/electrocoagulation treatment, and electrocautery, which all raise the concerns of passible aerosol transmission of SARS-CoV2 in the same procedures as well. Although there is no evidence of urine transmission for SARS-CoV2, maintaining appropriate protective measures during endoscopic procedures and urethral catheterization is highly recommended. Moreover, based on *van Doremalen* et al. investigation, SARS-CoV2 remains viable and infectious in aerosols for hours (in their experiment for three hours) and on surfaces up to days (depending on the inoculum shed). Therefore the transmission of the SARS-CoV2 via aerosols shouldn't be ignored. To minimize the risk of infection in the surgeons, different guidelines suggest to *i)* wear goggles or shield visor mask in procedures *ii)* use the devices that are capable of filtering the aerosolized particles during laparoscopic procedures iii) consider the lowest allowed intra-abdominal pressure for the pneumoperitoneum in robotic or laparoscopic surgeries along with adequate and complete deflation of the pneumoperitoneum.[41,42]

SARS-CoV2/COVID-19 and ENTpresentations-Dentistry considerations

Very limited studies worked on otolaryngology presentations of SARS-CoV2. According to a study in Italy, loss of the sense of taste (*ageusia)* and smell (*anosmia*) can represent the first or the only manifestation of SARS-CoV2 infection. In another study on 214 hospitalized patients with confirmed SARS-CoV2 infection in Wuhan China, taste impairment (12 patients [5.6%]) and smell impairment (11 patients [5.1%]) were the most common peripheral nervous system (PNS) presentations. Ageusia and anosmia in COVID-19 are not associated with nasal obstruction or any other forms of rhinitis; therefore, the possible mechanism would be sensorineural dysfunction which is caused by direct damage to the olfactory and gustatory receptors by SARS-CoV2.[34,43]

In dental care setting, due to the specificity of the procedures which involve face-to-face communication with patients, frequent exposure to saliva and blood, and the handling of sharp instruments, the risk of infection is very high. The New York Times published an article on March 15th, 2020, entitled "The Workers Who Face the Greatest Coronavirus Risk". This article with an impressive schematic figure explains "dentists" as healthcare workers who are most exposed to the risk of being affected by SARS-CoV2, even much more than nurses and general physicians. The most recommended guidelines by some organizations, such as The National Health Surveillance Agency in Brazil is indicated only emergency and urgent dental care should be performed during the COVID-19 pandemic. Also, universal precautions and the management practice for the staffs are quite similar to what takes place in other highly contagious circumstances such as careful sterilization and disinfection of patient-care items, safe injection practice, using personal protective equipment (PPE), working at an acceptable distance from the patients - as often as possible - and equipping handpieces with anti-reflux devices to avoid contaminations. Finally, the dentists should also prefer to choose methods of surgery that are associated with less aerosol production in the environment.[44, 45]

SARS-CoV2/COVID-19 and ocular involvement

Transmission of SARS-CoV2 through mucous membranes like conjunctival epithelium is an important source of infection. The fact that Infectious droplets and body fluid can easily contaminate the exposed and unprotected mucous membranes (eyes, mouth, and nose) suggests that eye contact with SARS-CoV2 can cause acute respiratory infection. Different ocular manifestations of CoVs have been documented in animals including conjunctivitis, anterior uveitis, retinitis, and optic neuritis but the information about eye involvement by CoVs in humans is limited. According to *Li* et al. study, 17% of children showed conjunctivitis with HCoV-NL63 infection. No ocular presentation has been described in SARS-CoV and MERS-CoV infections.[46-48]

Wu et al. in a case series study documented the effect of the SARS-CoV2 on the eye in humans. This study was done on 38 patients with confirmed SARS-CoV2 and reported 12 patients (31.6%) presented ocular symptoms which all were compatible with *Conjunctivitis* including conjunctival hyperemia, chemosis, epiphora, and increased secretions. Eleven of these 12 patients (91.7%) had positive results for SARS-CoV2 on RT-PCR from nasopharyngeal swabs. Of these, 2 patients (16.7%) had positive results for SARS-CoV2 on RT-PCR from both conjunctival and nasopharyngeal swabs. Although the information about ocular involvement and/or ocular transmission is limited, healthcare professionals should consider viral conjunctivitis as a possible presentation of SARS-CoV2 and take the full recommended measures including strict hand hygiene and protecting the exposed mucous membranes by wearing goggles or face masks.[48, 49]

SARS-CoV2/COVID-19 in dermatology

Dermatologists are at risk for SARS-CoV2 infection due to the close contact with the skin and the mucosa. According to the literature knowledge, 20% of COVID-19 patients showed non-specific skin lesions such as erythematous rash, petechia, urticaria, and vesicles. Also, different skin conditions have emerged mainly as a result of prolonged contact with PPE and excessive personal hygiene including pressure injury, contact dermatitis, facial inflammatory papules, itch, pressure urticaria, and exacerbation of pre-existing skin disease such as seborrheic dermatitis, rosacea, and acne. Besides all skin

lesions listed above, hyperhidrosis has been reported in 75% of Chinese health care workers involved in care for COVID-19 patients; this may result in a higher risk for non-diphtheroid corynebacterial disorders, other bacterial infections, and tinea. On the other hand, exaggerated hand washing with detergents/disinfectants can destroy the hydro-lipid cover of the skin surface and may cause irritation and even the development of contact dermatitis. Therefore, the use of preventive measures such as emollients, barrier creams, and moisturizers, is essential to prevent skin lesions during the COVID-19 pandemic.[50-52]

SARS-CoV2/COVID-19 in pregnancy and breastfeeding

Given the previous epidemics (SARS-CoV and MERS-CoV), as well as physiological changes during pregnancy, pregnant women are a vulnerable group to be affected by the virus. The findings of current studies do not report convincing evidence related to vertical transmission of SARS-CoV2 during delivery and breast milk from mother to fetus. The type of delivery, whether a cesarean section or normal vaginal delivery (NVD) in infected mothers with SARS-CoV2, does not show any impact on fetus involvement. However, according to some studies, a mother's infection with SARS-CoV2 during pregnancy can cause complications for both the mother and the fetus, including miscarriage, fetal distress, preterm delivery, respiratory distress, coagulopathy accompanied by liver dysfunction, and death of the mother but does not infect the newborn; thus monitoring suspected pregnant women is essential. Based on reported cases, all neonates with confirmed COVID-19 had been infected after birth via cough of the mother or other relatives, or through the infected environment. The average time of symptoms presentation in infants was between 5 and 17 days after birth. The most common sign and symptoms of SARS-CoV2 in infected infants were reported as tachypnea, milk regurgitation, vomiting, cough, fever, pneumothorax, liver disorders, thrombocytopenia, and pulmonary changes in chest CT scan. In terms of mother-newborn bonding and breastfeeding, different protocols have provided different recommendations for mothers with positive SARS-CoV2. *World Health Organization (WHO 2020)* and *United Nations Children's Fund (UNICEF 2020)* suggest skin to skin contact in the delivery room and exclusively breastfeeding with the concurrent adoption of hygiene measures, while the CDC's recommendation is contrary. According to *Centers for Disease Control and Prevention (CDC 2020)* "If the mother is under investigation or test is positive for COVID-19, the option of ensuring mothers and neonates cared for in separate rooms should be considered as the first choice". CDC's recommendation results formula feeding for newborns and the consequences of not starting and continuing breastfeeding, all of which need to be shared with the family and with healthcare professionals for final decision.[53-55]

SARS-CoV2/COVID-19 in children

The data show that the prevalence of SARS-CoV2 infection in children $\leq$ 18 years of age is relatively low, accounting for approximately 2.4% of all reported cases. *Jiatong* et al. investigation revealed that 56% of children with COVID-19 had clear evidence of transmission through family gatherings. Since most of the studies originated from China and children were unlikely to visit the *Huanan Seafood Wholesale Market* [as a possible point of origin of the 2019-nCoV pandemic], human-to-human transmission is considered to be the strongest dynamic of transmission. Children of all ages appeared susceptible to COVID-19, the youngest of the confirmed child cases up to the end of March 2020 was merely 30-hour of age and the oldest was 18-year-old. According to different review studies, no significant gender difference has been documented among infected children; only in a small study about COVID-19 involving children less than one year of age, seven out of total nine cases were girls; however, due to the small sample size, it is not possible to determine whether gender could be taken as a predictor of susceptibility to SARS-CoV2 infection.[56-58]

Compared to adult patients of COVID-19, most children diagnosed with milder symptoms, faster recovery, shorter detoxification time, and good prognosis with very rare deaths. The most common initial manifestations of COVID-19 in children have been cough, pharyngeal erythema, and fever. A few children did not exhibit fever but only presented a cough or diarrhea. Although studies generally report the milder course of the disease in children, based on the *Dugue* et al. case report in a 6-week infant, healthcare providers should always bear in mind the possibility of a rare and atypical presentation(s) of COVID-19.[35,57,59]

SARS-CoV2/COVID-19 in the elderly

Senile men with chronic comorbidities are more likely to get infected with SARS-CoV2. They also have a higher risk of developing complications of COVID-19, including ARDS, ACI, AKI, and liver injury. Different studies demonstrated identical initial presentations of SARS-CoV2 infection in both the elderly and younger ages. The most common symptoms in the elderly were fever followed by cough, dyspnea, and fatigue; but the *Pneumonia Severity Index (PSI)* score of the elderly group was higher compared to the young and middle-aged group. In terms of laboratory findings in the elderly, lymphocytopenia was a common laboratory finding, and also the proportion of lymphocytes in the investigated elderly group was significantly lower than the younger age. The C - reactive protein (CRP) level was significantly higher than younger and middle-aged patients. A study by *Liu* et al. reported no significant differences in neutrophil ratio, procalcitonin, hemoglobin level, platelet count, and serum creatinine level in elderly vs. young patients.[3,60,61]

In terms of Imaging findings of SARS-CoV2 in the elderly, patients older than 60 years old showed more

extensive ground-glass opacification (GGO), a higher proportion of multiple lobes involvement, and also more atypical findings in the chest CT workup.[11,60]

Regarding the predictors of COVID-19 outcome in elderly, an investigation on 339 patients with a mean age of 71 years in Renmin Hospital of Wuhan University declares that the symptom of dyspnea, presence of comorbidities (CVD, Chronic Obstructive Pulmonary Disease), and occurrence of complications such as ARDS in the course of the disease, are strong predictors of death in senile patients. On the other hand, a high level of lymphocytes was predictive of a better outcome of SARS-CoV2 in this group. Regardless of the determinants listed above, the current literature reflects "age" itself can complicate the course of the disease, so that the mortality rate in patients ≥60 years old reaches 8.8% compared to 0.46% for patients <60 years old. Therefore, "age" is one of the key factors in predicting the outcome of COVID-19 and should be considered as an independent variable in COVID-19 mortality.[4,61]

CONCLUSIONS

To our knowledge, this is the first literature review that summarized and classified a variety of symptoms of COVID-19 at a glance. Current evidence is mostly documented from Chinese studies where COVID-19 originated. Our research demonstrates that SARS-CoV2 infection has a dynamic nature of the presentation and disease severity varies based on the patient's medical background, age, sex, and concurrent medical conditions (e.g. pregnancy). We believe this study provides essential and recent clinical information on different aspects of COVID-19 manifestation to help healthcare professionals raise awareness about the disease course in order to improve outcomes by a better insight into diagnosis and management and consequently prevention of higher health and economic costs. However, because of the rapid spread of the virus globally and the dynamic nature of the disease, the reported evidence might be subject to change in the future when further knowledge will be acquired about the COVID-19 pandemic.

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