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Systematic Review: The effect of Infection Severe AcuteRespiratory Syndrome Coronavirus (SARS)-CoV-2 in Pediatric Patient

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Background: The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus-2(SARS-CoV-2), originated in Wuhan, China in December 2019 and has spread globally.Signand other symptoms include fever, cough, fatigue, myalgia, dyspnea, and diarrhea. Although, few patients had conjunctivitis as the initial symptom.The first confirmed pediatric case of Severe AcuteRespiratory Syndrome (SARS)-CoV-2 infection wasreported in Shenzhen on January 20 , and by January31, more than 20 pediatric cases were reported in China.**Objective:**To identify the effect of infection Severe AcuteRespiratory Syndrome Coronavirus (SARS)-CoV-2 in pediatric patient .**Methods:**The data was collected by searching the literature on article search sites, namely Google and Pubmed. The data search was carried out systematically using keywords *coronavirus, coronavirus infection.***Result:**There are 214 articles found. After eliminating duplicated articles, the titles and abstracts of each article were analyzed across 87 articles excluding 127 articles. The full-text articles in the remaining 7 articles were analyzed again and 80 articles were excluded. **Conclusion:**Recent literature shows that the infection SARS-CoV-2 there are symptoms, suggesting the involvement of the gastrointestinal tract, heart, cardiovascular system, kidneys, and other organs.

Keywords:*Infection, SARS-COV-2, Pediatric*

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Introduction

Coronavirus disease 2019 (COVID-19) hasspread rapidly and caused a pandemicglobally, according to an announcement from World HealthOrganization (WHO) on March 10, 2020.[1,2] Corona virusnew which is also known as severe acute respiratorycoronavirus syndrome 2 (SARS-CoV-2) is included in βcoronavirus, which can cause system infectionsmultiple, especially respiratory infectionsresembles a severe acute respiratory syndrome. Signand other symptoms include fever, cough, fatigue, myalgia,dyspnea, and diarrhea. Although, few patientshad conjunctivitis as the initial symptom.[3,4,5]

The transmission of SARS-CoV-2 occurs predominantlyvia respiratory droplets released during coughing and sneezing,as well as during normal speech and respiration.[6,7,8,9] Due totheir relatively large size, droplets do not remain suspended inthe air for long periods of time, nor are they able to traversedistances of more than 1–2m.[10] However, these dropletsrapidly settle onto surfaces, which poses its own threat oftransmission, as viable virus remains detectable for up to 72hours on stainless steel or plastic surfaces, and for up to 24hours on cardboard.[11,12,13,14] Critically, droplet generation is dramaticallyreduced via the use of face masks.[15,16] Even normalspeech generates thousands of droplets per second, which under stagnant air conditions, may remain suspended forseveral minutes.[17] Indoor environments appear to be a particularlyhigh-risk setting for transmissionone outbreak wasdirectly linked to air-conditioning causing spread from asingle infected individual to nine others due to airflow patternswithin a restaurant.[18]Transmission does not generallyoccur via aerosolization or airborne spread, which (due totheir small size) would facilitate both a longer distance ofdissemination and prolonged time suspended in the airhowever, certain medical procedures (e.g., nebulizer or CPAPuse, or intubation) may result in aerosolization, with potentiallyinfectious aerosols then lingering in the environment formore than 3 hours.[19,20]

The first confirmed pediatric case of Severe AcuteRespiratory Syndrome (SARS)-CoV-2 infection wasreported in Shenzhen on January 20 , and by January31, more than 20 pediatric cases were reported in China. Thereafter, many pediatric case reports and caseseries were reported. But the epidemiological and

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clinicalpatterns of the COVID-19 in pediatric patients still remainlargely unclear despite the worldwide spread. Thisreport aims to identify the effect of Infection Severe Acute Respiratory Syndrome Coronavirus (SARS)-CoV-2 in pediatric patient

Methods

Outcome

The primary outcome of this study was the systematic evaluationand characterization of currently reported pediatric cases of SARSCoV-2 infection. In particular, the primary analysis focused on effect of infection Severe Acute Respiratory Syndrome Coronavirus (SARS)-CoV-2 in pediatric patient

Search Strategy

Search strategywasdesigned to retrieve all articles published from December 1, 2019, to March 3, 2020, combining the generic terms *coronavirus* and *coronavirus infection* in key electronic bibliographic databases (PubMed and Google search) following the Preferred Reporting Items for Systematic review (PRISMA) reporting guideline. The same investigators independently assessed full texts of records deemed eligible for inclusion. Any discrepancies were resolved by discussion and consensus. Authors of publications reporting unclear data were contacted by email for clarification.

Inclusion criteria

1. Population: children withconfirmed severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) infection
2. Study design: retrospective studies (cross-sectional studies,case-control studies, case series, and case reports), bulletins,and national reports
3. Outcome: to identify the effect of Infection Severe Acute Respiratory Syndrome Coronavirus (SARS)-CoV-2 in pediatric patient
4. Articles in English
5. Scientific articles that have been published and are available online

Exclusion criteria

1. Clinical guidelines, consensus documents, clinical trials,and conference proceedings

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2. Studies about other serotypes of severe acute respiratorysyndrome coronavirus and Middle East respiratory syndromecoronavirus infection

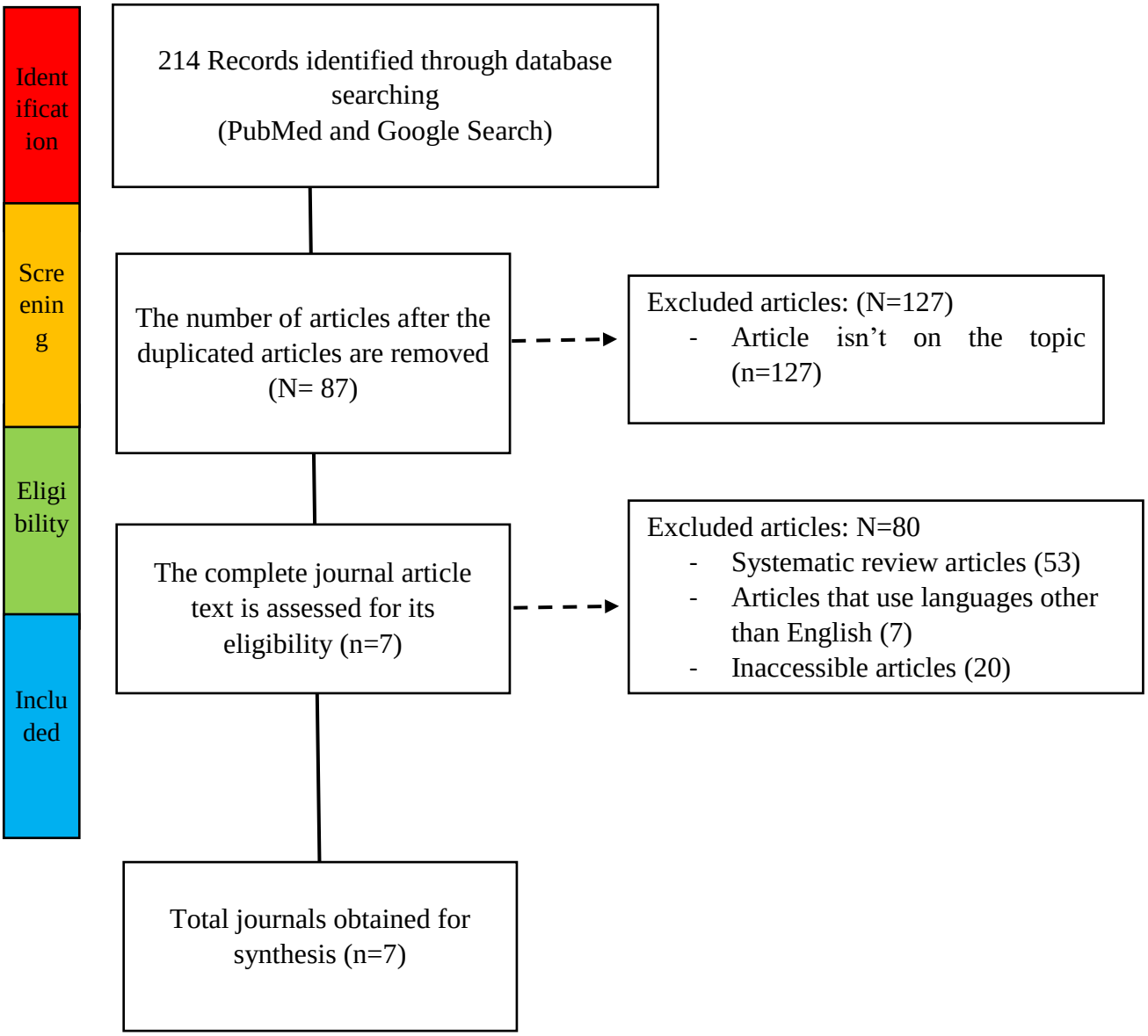

Figure 1. A diagram showing the selection of articles for review

Literature searches were conducted on online databases, namely Pubmed and Google Search using keywords namelyterms *coronavirus* and *coronavirus infection*, there are 214 articles found. After eliminating duplicated articles, the titles and abstracts of each article were analyzed across 87 articles excluding 127 articles. The full-text articles in the remaining 7 articles were analyzed again and 80 articles were excluded.

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Table 1. Research ofPediatric Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2):

No.	Author	Year	Title	Conclusion
1.	Yonker, et al[18]	2020	Pediatric Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): Clinical Presentation, Infectivity, and Immune Responses	This study reveals that children may be a potential source of contagion in the SARS-CoV-2 pandemic despite having milder disease or a lack of symptoms; immune dysregulation is implicated in severe postinfectious MIS-C.
2	Castagnoli, et.al[19]	2020	Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents	Clinical features and management of children with SARS-CoV-2 infection. The rapid spread of COVID-19 across the globe and the lack of European and US data on pediatric patients require further epidemiologic and clinical studies to identify possible preventive and therapeutic strategies.
3	Jiehao, et.al[20]	2020	A Case Series of Children With 2019 Novel Coronavirus Infection: Clinical AndEpidemiologic al Features	Allpediatric patients had an epidemiological link directly or indirectly to Wuhan or other endemic area of Hubei, where theoutbreak of COVID originated and is ongoing. Most of the pediatric cases occurring outside of Wuhan were secondary casesafter exposure to adult cases through household contact or travel contact. However, we cannot neglect the potential risk oftransmission from the infected child to adult contacts, as shownin patient
4	Zhang, et.al[21]	2020	Clinical and epidemiological characteristics of pediatric SARS-CoV-2 infections in China: A multicenter case series	This case series described the clinical and epidemiological characteristics of pediatric patientswith COVID-19. Our data presented the clinical features of pediatric patients to facilitate early identification and intervention in suspected patients. Notwithstanding the relatively limitednumber of samples, our findings offer valuable insight into the early diagnosis and epidemicncontrol of COVID-19 in

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				children.
5	Synowiec, et al[22]	2021	Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): a Systemic Infection	The clinical presentation ranges from asymptomatic to mild respiratory tract infections and influenza-like illness to severe disease with accompanying lung injury, multiorgan failure, and death. Although the lungs are believed tobe the site at which SARS-CoV-2 replicates, infected patients often report othersymptoms, suggesting the involvement of the gastrointestinal tract, heart, cardiovascular system, kidneys, and other organs;
6	Deville, et.al[23]	2021	COVID-19: Clinical manifestations and diagnosis in children	COVID-19 in children is usually mild, although severe cases have been reported, including cases with hypotension and multisystem involvement. In case series of children with COVID-19, the most common symptoms are fever and cough. Other symptoms include shortness of breath, myalgia, rhinorrhea, headache, nausea/vomiting, abdominal pain, diarrhea, sore throat, fatigue, and loss of smell or taste. Additional symptoms that have been reported in adults include chills or shaking chills
7	Roberta et al[24]	2021	Symptomatic and Asymptomatic Viral Shedding in Pediatric Patients Infected With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Under the Surface	A large percentage of infected children may be asymptomatic or presymptomatic despite infection with SARS CoV-2 and that both asymptomatic and symptomatic individuals may shed virus for prolonged periods of time (2 to 3 weeks) regardless of symptoms. These findings are highly relevant to the development of public health strategies to mitigate and contain spread within communities, particularly as affected communities begin their recovery phases

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DISCUSSION

Since the global emergence and spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initial attention appropriately focused on severely affected adults,who represent the highest proportion of symptomatic infections.[1] However, as the pandemic has evolved, a significant effect on children has also become evident.[2]Data frommultiple affected countries have corroborated that children are clearly susceptible to infection and may develop severe primary and unique secondary inflammatory complications of infection, including multisystem inflammatory syndrome of children.[3-5]However, the vast majority of infected children have mild or unrecognized disease, and this populationmay play important epidemiologic roles by potentiating spread of infection through communities6 and/or boosting herd immunity. Only small numbers of children have been included in prior studies focused on kinetics of viral shedding in the setting of symptomatic or asymptomatic SARSCoV-2 infection.[7-12]To our knowledge, no prior studies have systematically focused on the frequency of asymptomatic infection in children or the duration of symptoms and viral shedding in both asymptomatic and symptomatic children.

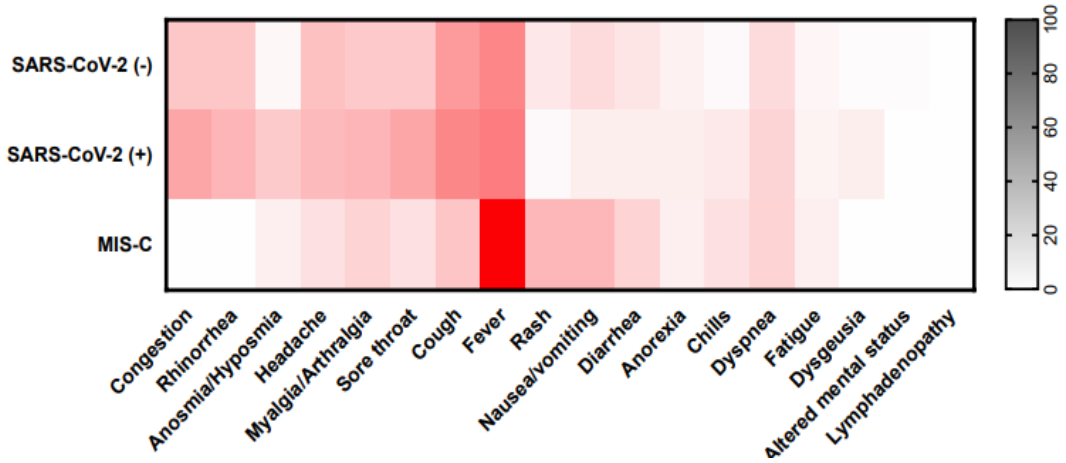

Figure 2. Presenting symptoms of enrolled patients. Darker color intensity depicts increased prevalence of a symptom within each cohort. Patients were grouped by SARS-CoV-2 qPCR results (positive or negative) or diagnosis of MIS-C.[20]

The novel human coronavirus mainly affects the respiratory system, causing a respiratory disease characterized by cough (mostly dry), dyspnea, fatigue, and, in severe cases, pneumonia or

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respiratory failure (corroborated by radiographic bilateral ground glass opacity).[25-28]Damage to the airway tract and lungs was evident during biopsy and autopsy studies.[29-32]Diffuse alveolar damage (DAD) and airway inflammation have been reported both in humans and in nonhuman primates.[33]The leading cause of mortality for SARS-CoV-2 is respiratory failure from acute respiratory distress syndrome (ARDS).[34] ARDS can be related to airway remodeling caused by pulmonary fibrosis and systemic inflammation.[35] The exact molecular mechanism of airway remodeling during the COVID-19 remains unknown and is associated with both viral replication in the tissue and dysregulation of natural pathways such as cytokine production or oxidative stress. Finally, the identification of viral cellular targets may shed some light on potential therapeutic and preventive strategies that may be used in COVID-19 patients with ARDS in the future.

Although coronaviral infections in humans are associated mainly with respiratory tract disease, accompanying symptoms in the gastrointestinal (GI) tract have been reported. According to one study, during a SARS-CoV outbreak in March 2003 in Hong Kong, 19.6% of infected patients developed nausea, diarrhea, and/or vomiting. Another study reported that 38% of patients experienced diarrhea during their illness. Interestingly, some patients (5.8%) with fever and diarrhea did not develop a respiratory disease. Consequently, viral replication in the small and large intestine of patients with SARS-CoV was confirmed. Infection by the second highly pathogenic coronavirus, MERS-CoV, was also associated with GI symptoms. Descriptive studies from 2012 to 2013 reported that a quarter of MERS-positive patients had accompanying GI symptoms, including diarrhea and vomiting. Importantly, not only highly pathogenic coronaviruses but also seasonal human coronaviruses are associated with GI infections. As an example, 33% of HCoV-NL63-positive patients and 57% of HCoV-OC43-positive patients in France developed digestive problems such as abdominal pain, diarrhea, and vomiting. These data clearly show that the fecal-oral route of coronavirus transmission is an important research area that needs further investigation during the COVID-19 pandemic.[36]

The cardiovascular system was also thought to be a target for SARS-CoV-2 infection. Cardiovascular sequelae have been reported for other highly pathogenic human coronaviruses. In SARS-CoV patients, these are usually mild and self-limitingbut MERS-CoV is associated with acute myocarditis and heart failure. It is well recognized that patients with preexisting

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cardiovascular diseases are more likely to suffer COVID-19 complications and to require admission to an intensive care unit (ICU). Furthermore, myocardial injury and heart failure are considered to be sequelae of COVID-19. Nevertheless, one may say that cardiovascular clinical manifestations may be solely the result of thrombosis.[37]

Endothelial cells are another cell population in the lungs but also in the cardiovascular system; importantly, they express ACE2 receptors and TMPRSS2 protease, as well as some other molecules that may mediate infection (e.g., CD147). The presence of SARS-CoV-2 virions was confirmed within endothelial cells; moreover, endotheliitis and elevated levels of circulating endothelial cells were observed.[38,39]The infection results in the production of virulent progeny viruses, which was confirmed using human capillary organoids.

There are several hypotheses about the mechanism of underlying cardiac injury during the course of COVID-19; these include direct injury mediated by SARS-CoV-2 virus invasion, pulmonary infection, induced severe cases of hypoxia resulting in damage to myocardial cells, cardiotoxicity of antiviral drugs, and indirect damage mediated by excessive inflammatory responses. Such indirect damage is especially relevant in patients with preexisting conditions, as inflammation may be associated with rupture of the coronary atherosclerotic plaques.[40]

At the moment, not much data concerning the effects of SARS-CoV-2 on the immune system are available. Palatine tonsils are among the first lines of defense, and SARS-CoV-2 was reported to infect and replicate in 3D tonsil organoids, reflecting the in vivo tonsil epithelium. Further, other organs responsible for the immune responses were investigated, and cell degeneration or necrosis was also observed in the spleen. Additionally, Diao et al. showed that lymphocytopenia is common among COVID-19 patients, and that finding was confirmed by other studies. It was suggested that components of the immune system might be infected by SARS-CoV-2 and that poor prognoses might be related to loss of specific T-cell subsets. It was also demonstrated that the virus infects alveolar macrophages, as well as ACE2-positive and CD68-positive macrophages, and induces interleukin-6 (IL-6) secretion, which is in some cases associated with a fatal outcome. A similar effect was observed for SARS-CoV and MERS-CoV, and while most laboratories report poor, incomplete, or abortive replication, these viruses seem to prime macrophages and dendritic cells to release proinflammatory cytokines, leading to systemic

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hyperinflammation ("cytokine storm"). What is more, SARSCoV-2 was frequently detected in monocytes and B cells and, to a lesser extent, in T cells of COVID-19 patients.[41]

Acute renal injury was first considered to be an extrapulmonary clinical presentation of SARS-CoV-2 infection. Renal involvement was first suggested in reports describing the isolation of infectious viral particles from patients' urine. Chu et al. demonstrated that SARS-CoV-2 replicates in multiple kidney cell. Among these, the virus productively replicates in CRFK (feline), PK-15 (porcine), RK-13 (rabbit), and LLCMK2 (monkey) cells. They also observed SARS-CoV-2 replication in 293T human embryonic kidney cells. However, they observed CPE formation only in nonhuman primate kidney cell lines Vero E6 and FRhK-4, where infected cells visibly rounded together and detached from the monolayer. Another recent study by Monteil et al. demonstrated robust SARS-CoV-2 replication in a human kidney organoid model. Several RNA-seq studies identified multiple cell types in the kidney that showed extensive ACE2 expression.[42,43]

Liver injury has been reported in some patients with severe SARS-CoV-2; the available data show that 2% to 11% of COVID-19 patients had liver comorbidities. This suggests that this organ is a potential secondary infection site for SARS-CoV-2. Importantly, liver impairment has been previously reported in patients infected with SARS-CoV or MERS-CoV. Indicatively, significant elevation of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) levels has been reported in patients with severe SARS-CoV-2 cases, as well as abnormal bilirubin levels

The pancreas is also a potential target for SARS-CoV-2. Pancreatitis was reported in ferrets infected with a feline coronavirus. In the case of SARS-CoV-2, clinical reports have described acute hyperglycemia and transient diabetes in COVID-19 patients without a history of type 2 diabetes, which may indicate pancreatic injury. Of note, Liu et al. observed increased levels of amylase and lipase in the sera of patients with severe SARS-CoV-2, and some of those patients also presented focal pancreatic enlargement and dilatation of the pancreatic duct under computed tomography scanning.[43,44]

The involvement of human coronaviruses in a neurological disease was suggested a long time ago. For example, an immunocompromised child with OC43 coronavirus developed fatal progressive encephalitis. The neurotropic potential of OC43 and 229E coronaviruses was

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demonstrated through experimental infection of several microglial, oligodendrocytic, and astrocytic cell lines. Neurological symptoms, including headache, confusion, and impaired consciousness, have also been reported in some patients with COVID-19. Modest SARS-CoV-2 replication was observed in U251 human glioblastoma cells, which may indicate the neurotropic potential of this virus. Very recently, some groups utilized a human brain organoid model to study the pathophysiology of SARS-CoV-2. Although they observed inefficient SARS-CoV-2 replication in this model, they showed that SARS-CoV-2 targets the soma of cortical neurons and is associated with Tau missortment in the axons and soma.[45,46]

Eyes were suggested to be potential entry points for SARS-CoV-2 and secondary infection sites. Clinical signs of SARS-CoV-2 infection in the eyes ranged from mild (e.g., chemosis, epiphora, and conjunctival hyperemia) to visual impairment, ophthalmoparesis, and retinitis. In multiple cases, viral RNA was detected in ocular discharges of SARS-CoV-2 patients both with and without conjunctivitis. The onset of conjunctivitis in some cases precluded the respiratory symptoms and it is hypothesized that SARS-CoV-2 may be transferred from the eyes to the respiratory system through the nasolacrimal duct connecting the eyes and the nasal cavity.[47]

From an infection control perspective, it is critical to identify infected children early for quarantine purposes. Onethird of school-aged children presenting with illness during the height of the local pandemic were found to have SARSCoV-2 infection.[48,49] However, children display relatively mild or no symptoms. Although ACE2 expression was increased in SARS-CoV-2-infected children, ACE2 expression did not impact viral load within the upper airway. Similarly, although younger children had a decreased ACE2 expression, age also did not impact viral load. This finding suggests that, regardless of disease susceptibility, children can carry high viral loads, which is a key consideration when opening up schools and daycare centers.[50,51,52,53,54,55]

Conclusion

SARS-CoV-2 is a virus that has just emerged and caused a pandemic that paralyzed the world. Our understanding of the threat is still limited, and apart from the mortality rate, the long-term consequences of infection should be discussed extensively, especially when different epidemic management strategies are considered. While the main outcome of COVID-19 involves the lungs, other organs have also been reported to be affected. During the COVID-19 pandemic, we have seen a tremendous increase in research on the coronavirus. Influence of SARS-COV-2

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infection in these pediatric patients infected patients often report other symptoms, suggesting the involvement of the gastrointestinal tract, heart, cardiovascular system, kidneys, and other organs.

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