Possible reasons for the disparities in COVID-19 symptoms between adults and children

Liqiang Zhou1, Shuxing Xing1

Abstract

A new coronavirus, currently known as SARS-CoV-2, was the source of several acute atypical respiratory illnesses in Wuhan, Hubei Province, China, in December 2019. The virus that caused this illness was known as COVID-19. The virus can spread from person to person and has produced a global pandemic. The death toll keeps rising, and many nations have been compelled to implement lockdowns and social separation. The issue of focused therapy's lack persists. According to epidemiological research, youngsters typically have lesser symptoms, but older individuals are more likely to have severe conditions. Here, we examined the state of our understanding of this illness and thought about possible reasons for the disparities in symptoms between adults and children.

Keywords: COVID-19, adult, children, vaccine, social distancing

Introduction

A cluster of acute atypical respiratory diseases was reported in Wuhan, China, in December 2019. From Wuhan, this quickly spread to other places. It was quickly determined that a brand-new coronavirus was to blame. Because of its strong similarity (~80%) to SARS-CoV, which caused acute respiratory distress syndrome (ARDS) and high mortality during 2002–2003, the novel coronavirus was called the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, 2019-nCoV). It was formerly believed that a zoonotic transmission connected to the seafood market in Wuhan, China, was the source of the SARS-CoV-2 outbreak. Subsequently, it was established that the ensuing outbreak was primarily caused by human-to-human transmission.2 Coronavirus disease 19 (COVID-19) was the name of the virus-caused illness, and the World Health Organization (WHO) proclaimed a pandemic. COVID-19 has been recorded in almost 200 nations and territories, affecting a significant number of people globally.3, 4 As of April 7, 2020, the Center for Systems Science and Engineering (CSSE) at John Hopkins University 5 reports that some 1,400,000 cases had been documented globally. The respiratory system is the primary organ system affected by the SARS-CoV-2 virus, while other organ systems are also affected. The original case series from Wuhan, China 6 described fever, dry cough, and dyspnea as symptoms associated with lower respiratory tract infections. Furthermore, there were reports of headache, vertigo, widespread weakness, vomiting, and diarrhea.7 The respiratory symptoms of COVID-19 are now well known to be highly variable, ranging from minor symptoms to severe hypoxia with ARDS. The Wuhan case already mentioned indicates that there was a mere 9 days between the commencement of symptoms and the development of ARDS, indicating a rapid progression of respiratory symptoms.8 This illness may also be lethal. Globally, the death toll from severe illnesses has continued to rise. According to epidemiological research, the incidence of mortality is significantly lower in children, 8,9 and greater in the elderly population.10 With no effective targeted therapy, current medical management is primarily supportive. Clinical trials have evaluated a number of medications, such as azithromycin, lopinavir-ritonavir, remdesivir, and hydroxychloroquine10,11,12, but none of these has yet been shown to be a surefire treatment. Clinical trials are testing more treatments. Many nations have imposed lockdowns and social distance in an effort to slow the virus's spread. In this section, we will summarize what we now know about COVID-19 and explore the underlying mechanism that accounts for the disease's varied symptomatology, paying special attention to the differences between patients...
who are children and adults.

**COVID-19 epidemiological data**

To date, many studies have been reports on experiences in China. The majority of COVID-19 cases at the start of the outbreak were reported to be in the elderly.\(^\text{13}\) As the outbreak persisted, there was a little increase in cases among children under the age of 18, but the number of cases among those 65 and older rose as well. At first, there were more male patients; but, as the number of cases rose, no discernible gender difference was seen. Five days was the average incubation period. 2.3% was the total case-fatality rate.\(^\text{14, 15}\) Using information from two Wuhan hospitals, the risk factors for in-hospital mortality were investigated. The multi-variable analysis revealed that admission d-dimer > 1 μg/mL, greater sequential organ failure assessment (SOFA) score, and older age were risk factors.\(^\text{10}\) Diabetes, hypertension, and coronary artery disease were also regarded as risk factors in the univariable analysis. An analysis of 85 COVID-19 fatal patients in Wuhan, with a median age of 65, revealed that multi-organ failure was the primary cause of death for most patients, with respiratory failure, shock, and ARDS being observed in 94%, 81%, and 74% of cases, respectively.\(^\text{16}\) Severe illnesses were associated with high D-dimer levels, fibrinogen, and delayed thrombin time, which is consistent with the high occurrence of multiorgan failure.\(^\text{17}\) Since the China outbreak, SARS-CoV-2 has spread around the world. The United States has the highest reported number of COVID-19 patients as of early April 2020, followed by China, Germany, France, Spain, and Italy. Italy was severely impacted by the China pandemic. In the Chinese series, the mortality rate was likewise greater in the elderly population. The case-fatality rate in Italy was reported to be 7.2% \(^\text{15, 18}\), which was three times higher than the rate in China. While the case fatality rate for patients 70 years of age or above was higher in Italy, it was relatively comparable in both nations for patients 0 to 69 years of age. Given that 23% of Italians were 65 years of age or older, the country's high case-fatality rate could be somewhat explained by its demographic makeup.

There are numerous resources that contain statistics from the US and other nations.\(^\text{5, 19}\) In the near future, we anticipate learning more about certain countries' experiences. The proportion of kids among all COVID-19 cases was low right from the start of this outbreak. Based on data from February 2020, the Chinese Center for Disease Control and Prevention (China CDC) reported that children under 10 and those between the ages of 11 and 19 accounted for 1% of all cases.\(^\text{14}\) Given that 20% of the population is in this age bracket, there may be a lower prevalence of COVID-19 in the pediatric population. If fewer tests were performed on children because they had less symptoms, this could represent an underestimating of the true incidence in the pediatric population. One complicating issue is that the Chinese New Year holidays caused schools to be closed for the most of the outbreak, which may have reduced child exposure. 4.4%, 50.9%, 38.8%, and 5.9% of patients were classified as asymptomatic, mild, moderate, or severe, respectively, in the China CDC report on 2134 pediatric COVID-19 patients.\(^\text{20}\) On the other hand, serious illnesses affected 18.5% of adult patients.\(^\text{20}\) The proportion of severe and critical cases was 10.6%, 7.3%, 4.2%, 4.1%, and 3.0% for the age group of <1, 1–5, 6–10, 11–15, and ≥16 years, respectively. Infants were the most susceptible to severe types of infections. For the age groups of 0–9 and 10–19, there was no case-fatality rate. Just 1.2% of COVID-19 patients in Italy were between the ages of 8 and 18.\(^\text{18}\) Age groups 0–9 and 10–19 had case–fatality rates of 0% and 0.2%, respectively, which was comparable to Chinese data. Children under the age of 19 accounted for 6.3% of all cases that tested positive for COVID-19, according to data released by the Korean CDC in late March.\(^\text{21}\) The US CDC published a research on April 6, 2020, that included 2572 COVID-19 cases among children under the age of 18.\(^\text{22}\) Despite accounting for 22% of all cases in the US, this age group accounted for only 1.7% of all cases that were recorded. Overall, the findings indicated that, contrary to Chinese stories, youngsters exhibited fewer symptoms than adults. Just 73% of the kids whose full medical records were accessible experienced fever, coughing, or dyspnea. In contrast, 93% of adults between the ages of 18 and 64 who were surveyed during the same period stated. Children from 1 to 17 years old were expected to be hospitalized at a rate of no more than 14%.\(^\text{22}\) A number of deaths have been reported in the US and other countries, and more information is required. In contrast, infants accounted for the highest percentage of hospitalization (15–62%), which was again similar to the data from the Chinese CDC. Overall, the pediatric population had a favorable outcome. Concerning COVID-19 severity, there is an increasing amount of interest in the correlation between disease severity and gender. The findings indicated that more men than women died from severe disease, despite the Chinese dataset showing an equal number of cases for males and females.\(^\text{23, 24}\) Similar findings were shown by data from other nations.\(^\text{25}\) COVID-19 adverse outcomes have been linked to concomitant conditions such as pulmonary disease, cardiovascular disease, and hypertension. These disorders are associated with alcohol consumption and smoking and are more common in men.\(^\text{25}\) Another possible explanation was immunological variations based on sex.\(^\text{13}\) Furthermore, women were found to be roughly 50% more likely than men to engage in non-pharmaceutical behaviors, such as hand washing, wearing face masks, and avoiding crowds,\(^\text{26}\) which may contribute to the adoption of protective behaviors in the context of pandemics.

**The way that SARS-CoV-2 enters host cells**

Coronaviruses are ~30 kb, positive-sense, enclosed, single-stranded RNA viruses. Numerous host species are infected by them.\(^\text{27}\) Based on their genetic structure, they can be broadly classified into four genera: α, β, γ, and δ. Only mammals are infected by coronaviruses α and β.\(^\text{28}\) A member of the α coronavirus family, human coronaviruses like 229E and NL63 cause croup and the common cold. SARS-CoV, SARS-CoV-2, and Middle East
respiratory syndrome coronavirus (MERS-CoV) fall under the Beta coronavirus category. The five stages of a virus's life cycle within its host are attachment, penetration, biosynthesis, maturity, and release. Viruses penetrate host cells by endocytosis or membrane fusion once they adhere to host receptors (penetration). Viral RNA reaches the nucleus for replication as soon as the virus's contents are released into the host cells. Viral proteins are produced (biosynthesised) from viral mRNA. After maturation, fresh virus particles are produced and released. The four structural proteins that make up coronaviruses are the nucleocapsid (N), membrane (M), envelope (E), and spike (S). A transmembrane trimeric glycoprotein that protrudes from the viral surface makes up the spike, which controls host tropism and coronavirus variety. The two functional subunits of spike are the S1 subunit, which binds to the host cell receptor, and the S2 subunit, which fuses the viral and cellular membranes. It was discovered that ACE2 (angiotensin converting enzyme 2) functions as a SARS-CoV receptor. The spike for SARS-CoV-2 also linked to ACE2, according to structural and functional studies. The lung, heart, ileum, kidney, and bladder have significant levels of ACE2 expression. On lung epithelial cells, ACE2 was abundantly expressed in the lung. It is need to conduct additional research to determine whether SARS-CoV-2 binds to another target. After SARS-CoV-2 attaches itself to the host protein, the spike protein is broken down by proteases. As a model, a two-step sequential protease cleavage was suggested to activate the spike protein of SARS-CoV and MERS-CoV. This cleavage comprised of priming at the S1/S2 cleavage site and activation at the S′2 site, which is located next to a fusion peptide inside the S2 subunit. S1 and S2 subunits stay non-covalently linked following the cleavage at the S1/S2 cleavage site, and the distal S1 subunit helps stabilize the membrane-anchored S2 subunit at the prefusion state. The spike for membrane fusion is thought to be activated by subsequent cleavage at the S′2 location through irreversible conformational changes. The coronavirus spike is distinct from other viruses in that it can be cleaved and activated by a variety of proteases. Among coronaviruses, SARS-CoV-2 is distinct due to its furin cleavage site (also known as the "RPPA" sequence) located at the S1/S2 site. In stark contrast to SARS-CoV spike, which was integrated into assembly without cleavage, the S1/S2 site of SARS-CoV-2 underwent complete cleavage during biosynthesis. Furin is widely expressed, which probably makes this virus extremely deadly even though other proteases including cathepsin L and transmembrane protease serine 2 (TMPRSS2) have also been known to cleave the S1/S2 site. Reaction of hosts to SARS-CoV-2
Patients infected with SARS-CoV-2 might have anything from mild symptoms to multiple organ failure and severe respiratory failure. Even in patients who are asymptomatic, the distinctive pulmonary ground glass opacification can be observed on a CT scan. This virus can probably infiltrate and kill lung epithelial cells because ACE2 is strongly expressed on their apical side in the alveolar area. This is consistent with the observation that the distal airway was frequently the site of the early lung injury. The three primary elements of innate immunity in the airway are dendritic cells (DCs), alveolar macrophages, and epithelial cells. Underneath the epithelium are DCs. On the apical side of the epithelium are macrophages. As innate immune cells, DCs and macrophages combat viruses before adaptive immunity gets involved. A overview of T cell-mediated defenses against coronaviruses has been published. Antigen presentation by DCs and macrophages triggers T cell responses. SARS-CoV-2 enters APCs in what way? Apoptotic virus-infected cells can be phagocytized by DCs and macrophages. For instance, DCs and macrophages can phagocytize virus-infected apoptotic epithelial cells, presenting antigen to T cells. Or may the virus primarily infect DCs and macrophages? The Immunological Genome database indicates that there is some, but not much, ACE2 expression on alveolar macrophages and (splenic) dendritic cells. This question can be addressed by identifying whether or not SARS-CoV-2 binds to APCs using a different protein. In addition to ACE2, SARS-CoV can also bind to DC-SIGN-grabbing nonintegrin (DC-SIGN) and DC-SIGN-related protein (DC-SIGNR, L-SIGN), which are unique intercellular adhesion molecules for dendritic cells. DC-SIGN is highly expressed on macrophages and dendritic cells. If SARS-CoV-2 has another target, it may be able to infect DCs and alveolar macrophages directly. Further research is required on this. To give T cells viral antigens, these antigen-presenting cells migrate to the draining lymph nodes. T lymphocytes with CD4+ and CD8+ functions are essential. While CD8+ T cells are able to eradicate virally infected cells, CD4+ T cells stimulate B cells to encourage the development of virus-specific antibodies. The majority of immunological research involving severe COVID-19 patients were published. Individuals with severe illnesses displayed lymphopenia, specifically a decrease in T lymphocytes in the peripheral blood. Proinflammatory cytokines, such as interleukin (IL)-6, IL-10, granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein (MIP)1α, and tumor necrosis factor (TNF)-α, have been found to be more abundant in the plasma of patients with severe illnesses. Patients’ IL-6 levels increased with the severity of their diseases. Higher expression of CD69, CD38, and CD44 in those patients revealed that CD4+ and CD8+ T cells were activated. T cell exhaustion was indicated by a higher number of checkpoint receptor Tm3+PD-1+ subgroups in CD4+ and CD8+ T cells. On CD8+ T cells, NK group 2 member A (NKG2A), another indicator of fatigue, was raised. It’s possible that T cell exhaustion contributed to the disease’s advancement. An additional intriguing discovery revealed that patients with severe COVID-19 disease had abnormal pathogenic CD4+ T cells that coexpressed granulocyte-macrophage colony-stimulating factor (GM-CSF) and interferon (IFN)-γ. It has previously been documented that T cells produce GM-CSF in response to viral infection. Although GM-CSF can promote T cell function and aid in the differentiation of innate immunity cells, excessive doses of the substance can cause tissue damage. In earlier studies using robust T cell receptor
(TCR) responses, GM-CSF+IFN-γ+ CD4+ T cells were observed in a larger percentage of CD8+ T cells expressing GM-CSF and secreting IL-6 in experimental autoimmune encephalomyelitis (EAE) models. It is important to note that only adult patients’ reports were included in these immunological research. It is necessary to investigate immunological responses in the pediatric population. Research on SARS-CoV revealed that in addition to IL-6, lung epithelial cells infected with the virus also produced IL-8. One well-known chemoattractant for T cells and neutrophils is IL-8. Severe COVID-19 patients’ lungs were shown to have a significant infiltration of inflammatory cells. These cells are most likely a mixture of innate and adaptive immune cells. We anticipate that neutrophils will make up the majority of innate immune cells. Since neutrophils can cause lung damage, they can be a double-edged sword. Given the reported considerable drop in circulating T cells, the majority of the observed infiltrating adaptive immune cells were probably T cells. The main cytotoxic T cells are CD8+ T cells. Pathological cytotoxic T cells generated from CD4+ T cells were also present in severe individuals. Although these cytotoxic T cells can eliminate viruses, they also aggravate lung tissue. These diseased T cells secrete GM-CSF, which is then recognized by circulating monocytes. Subsets of inflammatory monocytes, known as CD14+CD16+ subsets, were shown to be considerably more prevalent in COVID-19 patients than in healthy controls, despite their rarity. The increased expression of IL-6 by these inflammatory CD14+CD16+ monocytes probably speeds up the development of the systemic inflammatory response. It's interesting to notice that innate lymphoid cells (ILC2) and ILC3 showed considerable expression of ACE2. NK cells belong to ILC1, which makes up around 95% of the ILCs in the lung. The function of ILC2 and ILC3 is mucous homeostasis. Very little research has been done on ILC2 and ILC3 in coronavirus infection to far. Severe illnesses have also been linked to thrombosis and pulmonary embolism in addition to respiratory symptoms. This is consistent with the observation that severe illnesses were associated with elevated levels of fibrinogen and d-dimer. The endothelium is responsible for promoting fibrinolysis, anti-aggregation, and vasodilation. Given that endothelium is crucial for the regulation of thrombosis, hypercoagulable profiles observed in severe illnesses probably represent substantial endothelial damage. ACE2 is also expressed by endothelial cells. Notably, one-third of lung cells are endothelial cells. Viral invasion may be facilitated by endothelium damage-induced microvascular permeability.

Possible reason for the COVID-19 variation between children and adults

When viruses like the influenza and respiratory syncytial viruses infect the respiratory system, infants and young children are usually at a high risk of being admitted to hospitals. On the other hand, when compared to older individuals, juvenile COVID-19 patients generally have lesser symptoms. It's still unclear why children and adults differ from one another. Children may have lower viral loads even if they contract COVID-19 since a recent study revealed a link between the severity of the virus and the quantity of viral loads (or the length of the virus-shedding period). A few theories can be thought of in this line. The first possibility is that adults and children may express ACE2 at different levels. Well-differentiated ciliated epithelial cells were found to express ACE2 more frequently, according to a prior study. After birth, human lung and epithelial cells continue to develop. Pediatric populations may have lower levels of ACE2 expression. ACE2 expression in mice increased approximately after birth, according to data from the lung gene expression analysis portal. Its expressiveness dropped until about P10, at which point it rose. This trend might be consistent with the clinical picture of the patient, as newborns were vulnerable to serious disease in children. Gender may potentially have an impact on ACE2 expression. The X chromosome is home to the ACE2 gene. Men have larger circulating levels of ACE2 than women do. The disparity in severity and mortality between the sexes in both the adult and pediatric populations may have some bearing on this. The second theory is that youngsters react to the SARS-CoV-2 virus in a way that differs from adults' responses. As people age, the distribution of T cell subsets changes from naïve T cells to effector T cells, central memory T cells, and effector memory T cells due to thymic involution and ongoing antigen stimulation. Co-stimulatory molecules like CD27 and CD28 stop expressing during this phase, which makes the body more vulnerable to infections. It is unknown if the development of pathogenic T cells in adult patients with severe COVID-19 illnesses is a result of this underlying aging process or not. Early on after birth, CD4+ T cells are biased toward Th2 and have reduced ability to produce proinflammatory cytokines linked with Th1. Inflammatory and cytotoxic mediator expression was decreased by CD8+ T cells. Infants' sensitivity to SARS-CoV-2 may be explained by a decreased T cell's capacity to kill the virus early on after birth. According to a study comparing young and old macaques infected with SARS-CoV, older macaques exhibited worse lung pathology and stronger proinflammatory responses. A comparable outcome was documented utilizing both young and old mice infected with SARS-CoV. A cytokine storm or huge proinflammatory response that causes multi-organ dysfunction (MODS) and ARDS is a hallmark of a severe COVID-19 infection. Additionally, it has been proposed that children's and adults' inflammatory responses differ greatly. Proinflammatory cytokines, which control neutrophil activity and have been linked to the severity of ARDS, are known to increase with age. Although there isn't yet an animal model for SARS-CoV-2, a preclinical model is anticipated in the near future. The third theory is that the coexistence of other viruses, which is typical in young children's mucosa lungs and airways, may allow the SARS-CoV-2 virus to compete with others and suppress its growth. We don't currently have any research evaluating different viruses in addition to SARS-CoV-2 to ascertain this possibility. Instead, a mix of these theories could account for the differences in COVID-19 phenotypes between adults and children. Designing immunotherapy to eradicate COVID-19 might benefit from an understanding of why children are generally less vulnerable to severe cases of the virus.
Conclusions
The COVID-19 pandemic is a current problem that affects individuals all around the world. The goal of current management, in the absence of basic therapeutic breakthroughs, is to slow the virus's transmission while giving sick patients supportive care. The development of targeted medicines is desperately needed. Immune-based treatments may be more effectively targeted if the differences between the reactions of children and adults to this virus are understood.

References


34. X. Zou, K. Chen, J. Zou, P. Han, J. Hao, Z. Han, Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection, Journal. (2020).


