Determinants of Severity due to Covid-19 Among Young Adults

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October 6, 2023

Abstract

Background Coronavirus disease (COVID-19) is an emerging infectious disease affecting people of all ages, races, and countries, caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2). The disease has been shown to be more lethal in select individuals with existing comorbidities and inflammation. Although the disease occurs in people of all ages, a milder course has been observed in pediatric patients. Evidence suggests that the burden of COVID-19 infection is lower in hospitalized children than in their adult counterparts. To date, there are few reports describing the factors responsible for acute COVID-19 severity in young adults and their differences in the elderly. In this work, we aimed to review the factors responsible for determining the most severe cases with chronic clinical manifestations by evaluating their clinical presentations to close the gap and provide a potential basis to address this relationship between severity and age. The lower severity in young adults could be due to a variety of reasons, ranging from immunologic factors to genetic composition. Our work helps classify some of these factors, which appear to play a role in a small number of critical cases. The characteristic ability of the younger human body to fight this deadly disease may be a striking feature when trying to manage patients belonging to the older age group. Setting All settings, including hospitalized and community settings. Patients Children and young people (CYP) under 20 years of age with PCR and other laboratory tests COVID -19 affected patients. Main results: Prevalence of symptoms and signs of COVID -19. Purpose There are limited data on the demographics and clinical features of SAR-CoV-2 infection in children. Therefore, with this literature review, we aim to uncover various factors responsible for the different severities in pediatric patients. This will help us to better understand COVID -19 in different age groups.

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Coronavirus disease (COVID-19) is an emerging infectious disease affecting people of all ages, races, and countries, caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2). The disease has been shown to be more lethal in select individuals with existing comorbidities and inflammation. Although the disease occurs in people of all ages, a milder course has been observed in pediatric patients. Evidence suggests that the burden of COVID-19 infection is lower in hospitalized children than in their adult counterparts. To date, there are few reports describing the factors responsible for acute COVID-19 severity in young adults and their differences in the elderly. In this work, we aimed to review the factors responsible for determining the most severe cases with chronic clinical manifestations by evaluating their clinical presentations to close the gap and provide a potential basis to address this relationship between severity and age. The lower severity in young adults could be due to a variety of reasons, ranging from immunologic factors to genetic composition. Our work helps classify some of these factors, which appear to play a role in a small number of critical cases. The characteristic abil-
ity of the younger human body to fight this deadly disease may be a striking feature when trying to manage patients belonging to the older age group. Setting: All settings, including hospitalized and community settings. Patients: Children and young people (CYP) under 20 years of age with PCR and other laboratory tests COVID-19 affected patients. Main results: Prevalence of symptoms and signs of COVID-19. Purpose: There are limited data on the demographics and clinical features of SAR-CoV-2 infection in children. Therefore, with this literature review, we aim to uncover various factors responsible for the different severities in pediatric patients. This will help us to better understand COVID-19 in different age groups. Keywords: COVID-19, Coronavirus, SARS-CoV-2, young adults, Pediatric, severity, age. Methods: References for this review article were obtained by searching PubMed, NCBI, EClinicalMedicine from lancet using relevant terms related to 2019-nCoV, COVID-19, and SARS-CoV2 in neonates and children. Previous articles were not considered, and only articles published in English were considered. A range of datasets was considered to provide an analysis of severity and different symptoms in different age groups. 

Figure 1 shows the flow chart of the study selection process. A total of 76 review articles and 25 databases were read in the initial stages of study. After removing duplicates, 58 reviews and 20 datasets were further screened which resulted in a total of 40 reviews and 14 datasets. One study investigating infant cases was excluded because the patient profile was extracted from an unreliable source with incomplete parameters. Considering repeated calculations and missing data, it was found best to not include this study in the pooled data. In our search, we found 7 case series related to pediatric COVID-19 for a quantitative analysis and 28 review papers for detailed qualitative perspective.

Outcome measures: The prevalence of symptoms and associated severity are distributed between adults and children.

Introduction
Since 2019, the global community has been grappling with the widespread impact of Covid-19, which has brought immense challenges to healthcare system worldwide. SARS-CoV-2, the virus responsible for causing Covid-19 was detected in respiratory samples obtained from patients diagnosed with pneumonia who later experienced respiratory failure (Du et al., 2020). The cases under examination were categorized as either symptomatic or asymptomatic, with only those in the symptomatic group exhibiting symptoms like fever, cold, flu, malaise, and requiring subsequent hospitalization. Asymptomatic cases were defined as individuals without any apparent clinical signs or symptoms. It’s worth noting that the absence of symptoms did not serve as a parameter for evaluating the severity of the cases.

As the disease has been officially classified as a pandemic, a multitude of cases documenting the clinical manifestations have emerged, including a significant number of children with confirmed COVID-19 requiring hospitalization. Among the individuals who succumbed to COVID-19, a noteworthy proportion were identified to have preexisting conditions like hypertension, diabetes, and, in certain instances, cardiovascular diseases, which could have potentially weakened their immune responses. In contrast, these comorbidities were relatively rare among the pediatric population, suggesting a more robust immune reaction to the virus (Weisberg SP et al., 2021).

Studies have indicated that children and young adults are less prone to experiencing severe COVID-19 outcomes. Both medical reports and a growing body of cases indicate that the infection rate is comparable between adults and children. However, children tend to experience milder forms of the disease, with a low case fatality rate (CFR) of less than 0.1%. Additionally, a case series involving a total of four infants born to mothers with COVID-19 found that none of the three infants tested positive for the virus or exhibited clinical symptoms, suggesting a minimal likelihood of vertical transmission of the virus (Chen Y et al., 2020).

The present epidemiological and clinical data related to pediatric patients affected by COVID-19 do not fully satisfy our need for a deeper comprehension of viral infections. Due to the limited availability of extensive studies on risk factors for COVID-19 in children, our objective is to compile and assess existing data to pinpoint these risk factors. This information will prove valuable for healthcare professionals as they address the consequences of viral infections.
Results

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<td>10</td>
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<td>6</td>
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</tr>
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<td>15/93</td>
<td>10/93</td>
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<tr>
<td>Median age (years)</td>
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<td>7 y</td>
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<td>7 y</td>
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<tr>
<td>Age range</td>
<td>1 y - 7 y</td>
<td>4 y - 14 y</td>
<td>3 m -10 y</td>
<td>1 d -14 y</td>
<td>6 m -17 y</td>
<td>7 m - 14 y</td>
<td>10 m -6 y</td>
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<td>Male No.( %)</td>
<td>2 (33)</td>
<td>5 (33)</td>
<td>4 (40)</td>
<td>13 (65)</td>
<td>15 (48)</td>
<td>5 (83)</td>
<td>4 (86)</td>
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<tr>
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<tr>
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<td>3</td>
<td>6</td>
<td>4</td>
<td>17</td>
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<td>2</td>
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<td>15</td>
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<td>0</td>
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<td>7</td>
<td>3</td>
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<tr>
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<td>8</td>
<td>12</td>
<td>20</td>
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<tr>
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<td>14</td>
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Table 1 Characteristics of studies reporting Epidemiological and clinical features of COVID-19

**Epidemiological and clinical features**

The population under consideration encompasses individuals up to the age of 20, and gender is not a pertinent factor in our study. The majority, specifically 75%, had a clearly documented history of household contact. Examining the table above, it becomes apparent that 98% of the analyzed patients exhibited mild to moderate disease severity, with only 1% experiencing severe to critical disease severity. Notably, among the 93 children included in the study, only 2 required intensive care, and just 1 child suffered complications. This directly indicates a lower incidence of complications within the pediatric population, a point that is also highlighted in the results section.

**Symptoms**

The symptoms of COVID-19 varied, spanning from asymptomatic cases to clear and distinct presentations in certain instances. Initially, approximately 26% of patients did not exhibit any specific symptoms, while 59% had fever, constituting half of the total population. Around 46% of patients experienced cough. Nevertheless, the outcomes displayed a moderate degree of variability, and only a small number of patients displayed gastrointestinal symptoms.
Figure 2 Bar graph illustrating the distribution of COVID-19 symptoms by percentage.

Biological mechanisms of viral infection

Coronaviruses are a type of single-stranded positive-sense RNA viruses characterized by spike-like projections on their surface (Zimmermann P et al., 2020). Among these viruses, SARS-CoV-2, SARS-CoV, and Middle East respiratory syndrome coronavirus (MERS-CoV) are examples of zoonotic viruses capable of infecting humans and leading to severe respiratory infections. However, it’s important to note that they are primarily transmitted through animals.

ACE2 receptors are prevalent in various tissues throughout the human body, particularly on the cells of alveolar epithelium II. The spike proteins enveloping the coronavirus attach primarily to the ACE2 receptors located on type II alveolar cells, facilitating the injection of the virus’s RNA into these cells. Subsequently, this RNA essentially takes control of the cell, compelling it to produce and release numerous copies of the virus into the alveoli. As a result of this process, the host cell is destroyed, and fresh coronaviruses infect adjacent cells. Importantly, this sequence of events can initially occur without the individual exhibiting any awareness of the infection, leading to asymptomatic cases. This mechanism is a key factor contributing to the efficient spread of COVID-19.

Diagnosis

The diagnosis of COVID-19 is reliant on the appropriate clinical context in accordance with guidelines, with additional support from laboratory tests and radiological findings. Genome sequencing, on the other hand, serves as a research tool to assess the virus’s virulence, assist in vaccine development, and enhance our understanding of its epidemiological traits, including its distribution and geographical origins (Maurano MT et al., 2020).

Clinical features

The clinical presentation of COVID-19 in neonates and children is typically mild and exhibits similarities across different countries (Shen K et al., 2020; Zhu H et al.2020). Children most frequently require hospitalization due to symptoms such as fever and respiratory issues, including cough, sore throat, facial flushing, nasal congestion, rapid breathing or difficulty breathing (tachypnea/dyspnea), and an elevated heart rate (tachycardia) (Tagarro A et al., 2021; Parri N et al., 2020). In rare instances, neurological symptoms such as seizures, dystonia, and altered mental status have also been documented (Dugue R et al., 2020).

COVID-19 severity categories, encompassing asymptomatic infections, mild, moderate, severe, and critical
cases, were defined based on clinical features, laboratory tests, and X-ray imaging criteria, (Dong Y et al., 2020). While lymphocytopenia was observed frequently in adults with severe COVID-19 and correlated with adverse outcomes, this is not typically the case in children, likely due to the higher percentage of lymphocytes in individuals of that particular age group (Henry BM et al., 2020; Li H et al., 2020). On the other hand, adults displayed significantly elevated levels of D-Dimer, ferritin, and coagulopathy, whereas these manifestations were rarely observed in children, (Sun D et al.; 2020).

The majority of these laboratory irregularities observed in children lack specificity. It was noted that 69.2% of children had leukocyte counts within the normal range, and instances of neutrophilia or neutropenia were infrequent (occurring in less than 5% of cases). Platelet counts exhibited variability across different studies, generally trending higher than the normal range. Additionally, C-reactive protein levels were elevated in 13.6% of cases, while procalcitonin levels were increased in 10.6% of cases ( Henry BM et al., 2020).

**Discussion**

This review has compiled and summarized the existing observational studies related to COVID-19 in the pediatric population. The global incidence of COVID-19 cases has been on the rise. According to the largest epidemiological survey, the majority of these patients fall within the age range of 30 to 79 years, comprising 87% of cases. It is noteworthy that older individuals and those with pre-existing medical conditions are more susceptible to the adverse effects of the virus. In contrast, the number of cases among children is relatively low. Patients under the age of 19 accounted for just 2.2% of the 44,672 confirmed cases (Wu Z et al., 2020), with only one recorded death. This translates to an exceptionally low crude mortality rate of 0.1%, which stands in stark contrast to the higher rates reported in current published data for adults, ranging from 2.3% to 14.6% ( Chen N et al., 2020; Huang C et al., 2020; Wang D et al.;2020).

![Disease Severity Matrix](image)

*Figure 3* A pie chart illustrating the distribution of COVID-19 disease severity categories.

We have approached the review of clinical data regarding "COVID-19 in the pediatric population" with meticulous care. In our study, we have adhered to...

Despite the generally benign nature of pediatric COVID-19 cases, there are exceptions. For instance, in one report by Chen F et al. (2020), a 1-year-old boy presented with severe respiratory failure requiring mechanical ventilation. When compared to other viral illnesses that have caused pandemics or epidemics, the relatively small number of cases and low mortality rate in pediatric COVID-19 can be attributed to several factors:

**Absence of pre-existing baseline inflammation**

In comparison to adults, children exhibit a more robust immune response and are less likely to have pre-existing medical conditions ( Singh T et al., 2020). Unlike adults, children have rarely been observed to
progress to severe respiratory issues requiring intensive care (Rodriguez-Morales AJ et al., 2020). It’s worth noting that children with pneumonia often experience coinfections involving both viruses and bacteria, which may contribute to their immune memory against a broader range of pathogens. However, it remains uncertain whether this holds true for pneumonia related to SARS-CoV-2.

Furthermore, children are less prone to underlying diseases such as diabetes mellitus, chronic obstructive pulmonary disease, or cardiovascular conditions, which are more common among adults. These underlying conditions in adults may predispose them to severe COVID-19 outcomes. Nonetheless, the exact pathogenesis remains unknown. Consequently, further investigation is necessary to understand the differences in disease severity between adults and children in the context of COVID-19.

2. Multisystem inflammatory syndrome (MIS-C)

Multisystem inflammatory syndrome in children (MIS-C), which is temporally linked to COVID-19, is a newly identified, uncommon, and potentially life-threatening hyperinflammatory condition. It exhibits overlapping features with typical or incomplete Kawasaki disease and toxic shock syndrome (Riphagen S et al., 2020; Viner RM et al. 2020; Jones VG et al., 2020).

Furthermore, understanding the various risks associated with children can be challenging. Children in whom Coronavirus are detected in the respiratory tract may experience viral coinfections in up to two-thirds of cases (Heimdal I et al., 2019).

3. ACE-2 Receptors

Another highly notable hypothesis that warrants consideration regarding the lower severity risk of COVID-19 in children compared to adults is the reduced expression of cell surface enzyme angiotensin-converting enzyme 2 (ACE2) receptors in the nasal epithelia of children (Bunyavanich S et al., 2020). Since ACE2 serves as a functional receptor for SARS-CoV-2 (Li W et al., 2003), it is plausible that the limited expression of ACE2 receptors in children’s nasal epithelia contributes to a diminished viral entry, resulting in milder infections. The binding affinity of SARS-CoV-2 to ACE2 partially explains why it causes less severe disease than SARS-CoV but remains highly infectious. However, it’s important to note that this explanation doesn’t comprehensively address why children are less susceptible to severe COVID-19. Previous studies have shown that SARS-CoV induced higher ACE2 shedding than human coronavirus NL63.

The varying regulation of ACE2 receptors is closely associated with lung injury (Glowacka I et al., 2010). A study has shown that aging results in an alteration of the pulmonary renin-angiotensin system, which corresponds to increased inflammation and more pronounced lung injury in a rat model (Schouten LR et al., 2016). It’s undeniable that smoking is a prevalent factor among adults rather than children. One hypothesis suggests that smoking elevates ACE2 expression, potentially leading to an increased entry of coronaviruses into pulmonary epithelial cells (YH et al., 2016).

Conclusion

In our review, we acknowledge the presence of certain limitations that require consideration. Firstly, the COVID-19 outbreak took place over two years ago, resulting in a wealth of detailed descriptions. This abundance of information presents challenges related to the relevance and reliability of the data, as the assessment tools used may vary considerably based on various factors. Secondly, given the novelty of the disease, the evaluation of long-term outcomes and potential sequelae necessitates ongoing follow-up studies. Thirdly, it’s important to note that there are often multiple viral infections resembling COVID-19 circulating within the same class or school environment, which can complicate diagnosis. Additionally, the treatment strategy for children may warrant further discussion and cautious consideration.

In summary, it is evident that the pediatric population tends to experience a less severe response to viral infections. The explanations for this phenomenon are diverse, and each comes with its set of challenges. Moreover, these explanations can evolve as new cohorts of patients are studied. The presence of a higher number of asymptomatic and mild cases adds complexity to the diagnosis and the management of infection.
Currently, the primary diagnostic criteria rely on the presence of typical ground glass opacities on chest CT scans, epidemiological suspicions, and the tracing of contacts.

**Conflict of interest**

All authors declare no conflicts of interest in this paper

**Funding statement**

This review manuscript received no external funding

**Data availability statement**

The review manuscript provides a comprehensive analysis of previously published data in the field.

**References**

32. Viner RM, Whittaker E. Kawasaki-like disease: emerging complication during the COVID-19 pan-


