Review Article

Risk factors for death among children and young people hospitalized with COVID-19: a literature review

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Background and Objective: Coronavirus disease 2019 (COVID-19) has been a most important global issue since December 2019. Although for children, the clinical course of COVID-19 is milder, it may still cause a multi-system inflammatory syndrome and has rendered 22,000 deaths among children and young people. The objective of this review is to provide an up-to-date information about COVID-19 related mortality and relevant risk factors in children and young people.

Methods: This study provides a narrative review of COVID-19 related mortality and relevant risk factors in children and young people. Electronic searches for studies were conducted using PubMed and Web of Science, with a date time up to April 22, 2022. Only publications in English were included.

Key Content and Findings: With the Omicron being the dominant circulating variant, the absolute risk of death from COVID-19 is extremely low in children and young people. We found that those who are with multiple co-morbidities, from non-white ethnic groups, and in low- and middle-income countries might have increased risk of intensive care unit admission and death. And vaccination is always critical to reduce the incidence of severe COVID-19 cases.

Conclusions: This review provides an overview of the COVID-19 related mortality and relevant risk factors. Since this disorder continues to evolve, a prompt diagnosis and treatment strategy will allow for the best possible care and outcome for patients with COVID-19.

Keywords: Risk factor; mortality; pediatric; SARS-CoV-2; coronavirus disease 2019 (COVID-19)

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Introduction

On 11 March 2020, the World Health Organization (WHO) classified coronavirus disease 2019 (COVID-19) as a global pandemic (1). So far, there have been five variants of concern (VOCs) (2): Alpha (B.1.1.7, U.K. variant), Beta (B.1.351, South Africa), Gamma (P.1, Brazil), Delta (B.1.617.2, India), and Omicron (B.1.1.529, Africa). The Omicron variant, first identified in Botswana in November 2021, has become the dominant circulating variant (3), and decreasing deaths from infections was also observed (4).

Globally, there had been more than 505 million confirmed cases of COVID-19, including 6.2 million deaths, until April 22, 2022 (5). Previous studies have reported that the disease severity for children is

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Table 1 The search strategy summary

Items	Specification
Date of Search	From April 13, 2022 to April 22, 2022
Databases and other sources searched	PubMed, Web of Science
Search terms used	"sever*", "multisystem inflammatory syndrome", "died", "death", "mortality", "risk factor*", "predict*", "COVID-19", "Novel Corona Virus", "SARS-Cov-2", "coronavirus disease 2019", child*, infant*, neonat*, newborn*, adolescent*
Timeframe	Literature published up to April 22, 2022
Inclusion and exclusion criteria	Included study type: Review, Systematic Review, Cohort Study, Observational Study, case series, Clinical Trial and The World Health Organization COVID-19 online dashboard Language restrictions: English
Selection process	All the authors conducted the selection after discussion

COVID-19 coronavirus disease 2019.

significantly lower than adults (6,7). However, there were still 22,000 deaths among children and adolescents, aged 0 to 19, due to COVID-19 (5). So, it is important to identify the children and young people (CYP) at a greatest risk of severe diseases or even death caused by SARS-CoV-2 infection. The objective of this review is to provide an up-to-date information about COVID-19 related mortality rate and relevant risk factors in CYP. We present the following article in accordance with the Narrative Review reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-22-19/rc).

Methods

Electronic searches for studies were conducted using PubMed and Web of Science (*Table 1*), specifically for studies related to the COVID-19 mortality of the children and young people. The key search terms included "sever*", "multisystem inflammatory syndrome", "death", "mortality", "COVID-19", "Novel Corona Virus", "SARS-Cov-2", and "coronavirus disease 2019", and a date time up to April 22, 2022. Only publications in English were included. The final reference list was based on the relevance to the broad scope of this narrative review.

Discussion

Overview of COVID-19 related mortality in children

The majority of COVID-19 related death occurred within 7 days after getting a positive SARS-CoV-2 test result, and the maximum time between death and the positive result was reported as 45 days (8). Previous studies have revealed that children account for 1% to 5% of COVID-19 cases (6,9), with a varying mortality rate between less than 1% to 8% in hospitalized children (10-22). Since the varying mortality rate can be partially explained by the difficulty in distinguishing whether SARS-CoV-2 infection was the direct cause of death or a comorbidity, Smith *et al.* undertook a more strict evaluation criteria, it was reported that some CYP died with a positive SARS-CoV-2 test as a coincidental finding and the mortality rate of COVID-19 in CYP was two per million with wild-type and Alpha being the predominant variants (8). The Omicron variant seems to be more transmissible and less virulent than previously circulating variants (10), and there were almost no recorded or excess deaths attributable to it per 100,000 population (4). We briefly presented the COVID-19 related death among children and young people with different predominating variants based on a national/regional level database or multicenter studies in the Supplementary file (Table S1).

Risk factors for death among children and young people hospitalized with COVID-19

Co-morbidity

It is widely accepted that, underlying comorbidities render CYP more vulnerable to illnesses and infections, thus they are the main risk factors for COVID-19 related death (8,23). For children with underlying medical conditions, immunocompromised children or those with respiratory/cardiac disease took the largest part (152, 65.2%) (24). The

odds of severe disease increased in children hospitalized with multiple co-morbidities, with an OR ratios of 2.58 (2.41–2.75) for 2 comorbidities; 2.97 (2.04–4.32) for ≥3 comorbidities (7), especially for those with combined neuro-disabilities and respiratory conditions (8). And it remains an argument whether asthma, diabetes and trisomy 21 will increase the risk of pediatric intensive care unit (PICU) admission or death for CYP with COVID-19 (8,11,25).

Clinical manifestation

Several variables, including older age, lower lymphocyte count, higher lactate dehydrogenase and co-morbidity were considered to be independent high-risk factors for the exacerbation of COVID-19 (26). And it has been reported that extrapulmonary systemic hyperinflammation plays a key role in exacerbation of COVID-19 (27). For example, IL-1ra and IL-6 levels were elevated significantly in severe COVID-19 patients versus mild ones during the first wave of the pandemic. However, compared with the first wave, the cytokine storm profile is at a lower level during the second wave, with only IP-10 concentration significantly elevating in severe patients but IL-1ra and IL-6 keeping steady (28). Among pediatric patients, blood coagulation indicators including ferritin, D-Dimer and INR, immune and inflammation indicators such as IL6, LDH, neutrophil lymphocyte ratio, neutrophil, and platelet count are commonly used for both risk and mortality prediction (29,30).

Sociodemographic factors

Among the CYP population, Odds of PICU admission for COVID-19 were higher among neonates than others (13). But teenagers were more likely to die of SARS-CoV-2 than younger children (8). The overall case fatality rate was negatively correlated with socioeconomic status (8,10,11,31,32). Comparing to white ethnic groups, the mortality rate of SARS-Cov-2 infection was higher in CYP from non-white ethnic groups, but the absolute risk of death from SARS-CoV-2 is still extremely low (8,11). Since previous studies have shown that differences persist when deprivation factor was controlled, biological pre-disposition might contribute to the ethnic differences (8,33,34).

Multisystem inflammatory syndrome in children

There are studies describing SARS-CoV-2 infected children who become critically sick because of multi-system involvement. WHO uses the term multisystem inflammatory syndrome in children and adolescents temporarily related to covid-19 (MIS-C) (35), while the Royal College of Pediatrics and Child Health (RCPCH) describes this as pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) (36). MIS-C usually presents a series of symptoms including fever, evidence of systemic inflammation, and involvement of more than two organs or systems (37). Among children with MIS-C, older age and higher initial ferritin level are associated with an increased risk of ICU admission, and the severity of MIS-C seems greater when Delta variants have replaced the wild-type variant (38,39). Despite that almost one-third of patients with MIS-C need transferring to ICU (40), 85% of hospitalized patients discharged within 10 days.

Immunology

Differences in immune responses could reflect the severity of COVID-19 disease. Studies have shown that the immune responses of both children and adults to mild SARS-CoV-2 infection are similar (41-43), but diverge after progressing into a severe stage, such as children having higher IFN response (43), higher absolute lymphocyte counts (44,45). The prevalence of severe COVID-19 was higher in immunodeficient pediatric patients with T cell development and/or function (46,47), which indicated that IFN signaling and T cell function might contribute to an increasing susceptibility to severe COVID-19. Some comorbidities, like cerebrovascular disease, obesity, and diabetes, can cause a dysfunctional immune response to infection by epigenetic and metabolic reprogramming of immune cells (48).

Vaccination

The prognosis of COVID-19 among adult population was improved significantly by application of vaccine against SARS-CoV-2 (20,49). The mass vaccination programs were initiated during the summer of 2021 in adolescents aged 12 or older, and the BNT162b2 (Pfizer-BioNTech) covid-19 vaccine was further authorized for emergency use in children aged 5 to 11 on October 29, 2021 (50). Studies have shown that vaccination of eligible persons, along with other prevention strategies such as masking, is critical to reduce the incidence of severe COVID-19 among CYP population regardless of the prominent variants (20,51,52), though one study does claim that the vaccine- or infection-induced immunity is less effective against the Omicron than the Delta variant (53) and its effect on preventing immune mediated complications including MIS-C, remains to be verified (32).

Genetic perspective

Genomic surveillance plays the key role in monitoring

SARS-CoV-2 mutation and spread of variants in a timely manner, even weeks before the onset of an infection wave, which can raise public health awareness and detect mutations that may reduce the efficacy of treatment (54). Multiple studies of adults have confirmed that loss-of-function variants of TLR7, a sensor for SARS-CoV-2 single-stranded RNA137–140, were associated with severe COVID-19. TLR7 signaling promotes the secretion of IL-6, IL-1β, and IL-23, IFN signaling, and generation of the TH17 subset of helper T cells in response to viral infections (55).

Limitation

In this review, the mortality rate and relevant risk factors among children and young people during the pandemic were explored through data supported by national-level evidence. Since it is difficult to determine whether SARS-CoV-2 infection severs as the direct cause of death because of the different study design and the mild or asymptomatic phenotype of COVID-19 among CYP, mortality rate might be overestimated in many studies. And relevant data when Omicron being the predominant variants are still accumulating and more evidence is needed.

Summary

With the Omicron being the dominant circulating variant, the absolute risk of death from SARS-CoV-2 is still extremely low, though those who are with multiple co-morbidities, from non-white ethnic groups, and in low- and middle-income countries might be in increased risk of PICU admission and death. And vaccination is always critical to reduce the incidence of severe COVID-19 cases. Since the clinical and demographic characteristics vary when different variants circulate, understanding of this disorder continues to evolve, and prompt diagnosis and treatment allow for the best possible outcome for patients with COVID-19.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://pm.amegroups.com/article/view/10.21037/pm-22-19/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://pm.amegroups.com/article/view/10.21037/pm-22-19/coif). WZ serves as an unpaid Executive Editor-in-Chief of *Pediatric Medicine*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Detailed search strategy of one database as an example:
PubMed:
((("risk factor"[Title/Abstract]) OR (predict*[Title/Abstract])) AND ((((sever*[Title/Abstract]) OR (multisystem inflammatory syndrome[Title/Abstract])) OR (death[Title/Abstract])) OR (mortality[Title/Abstract]))) AND (("COVID-19"[Title/Abstract] OR "Novel Corona Virus"[Title/Abstract] OR "SARS-Cov-2"[Title/Abstract] OR "coronavirus disease 2019"[Title/Abstract] OR "COVID-19"[MeSH Terms]))

Table S1 Brief summarization of COVID-19 related mortality among children and young people

First author	Country	Data sources	Population		Cut-off date	Variants of concern	Mortality
			Number	Age			
Yuanyuan Dong (21)	China	Nationwide case series reported to the Chinese Center for Disease Control and Prevention	731 confirmed COVID-19 patients and 1,412 suspected patients	Younger than 18 years old	Jan - Feb, 2020	Wild-type	a 14-year-old boy from Hubei province died
Stefania Bellino (19)	Italy	The national case-based surveillance system	3,836 Confirmed COVID-19 patients, 511 were hospitalized	Younger than 18 years old	- May, 2020	Wild-type	0.1% (4/511)
Aline de Siqueira Alves Lopes (22)	Brazil	The health surveillance and mortality information systems of Sergipe's Health Secretary and hospital records	37 COVID-19 related deaths	Younger than 19 years old	-Sep, 2020	Wild-type	4.87 deaths for 100000 population <19 years old; most deaths occurred among infants (44.1/100,000)
Leora R. Feldstein (12)	USA	COVID-19 network including 66 hospitals in 31 states	Case series of 1116 patients, 539 were diagnosed with MIS-C and 577 with COVID-19	Younger than 21 years old	Mar - Dec, 2020	Wild-type	10 (1.9%) with MIS-C and 8 (1.4%) with COVID-19
Olivia V Swann (14)	United Kingdom	260 hospitals in England, Wales, and Scotland	627 hospitalized COVID -19 patients	Younger than 19 years old	Jan - July, 2020	Wild-type	1% (6/627)
A. Danielle Iuliano (13)[†]	USA	CDC examined data from three surveillance systems and a large health care database. Data on in-hospital deaths were available from a subset of 148 hospitals.	147 hospitalized COVID -19 patients	Younger than 17 years old	Jan 1-21, 2021	Wild-type	1.1% (1/87)
			272 hospitalized COVID -19 patients	Younger than 17 years old	Aug - Sep, 2021	Delta	0
			405 hospitalized COVID -19 patients	Younger than 17 years old	Dec, 2021 -Jan, 2022	Omicron	0
Judith Ju Ming Wong (15)	Seven countries (China, Japan, Singapore, Malaysia, Indonesia, India, and Pakistan)	Eight hospitals across seven countries contributed data to the Pediatric Acute and Critical Care COVID-19 Registry of Asia (PACCOVRA)	849 patients suspected of COVID-19, of whom 260 (30.6%) were laboratory-confirmed COVID-19 cases.	Younger than 21 years old	Jan - Nov, 2020	Wild-type	2.3% (6/256, all of which occurred in India and Pakistan)
Jean B. Nachega (10)	Six Sub-Saharan African Countries	Data from 25 hospitals Democratic Republic of the Congo (7 facilities), Ghana (2 facilities), Kenya (1 facility), Nigeria (2 facilities), South Africa (10 facilities), and Uganda (3 facilities)	469 hospitalized COVID-19 patients	Younger than 19 years old	Mar - Dec, 2020	Wild-type	8.3% (39/469)
Joseph L. Ward (11)	England	Data for all hospitalizations	6,338 hospitalizations with COVID-19 patients	Younger than 17 years old	Feb, 2019 - Jan, 2021	Wild-type	0.13% (8/6,338)
Eduardo A Oliveira (16,17)	Brazil	the Influenza Epidemiological Surveillance Information System (a nationwide surveillance database of patients admitted to hospital with severe acute respiratory disease)	11,613 hospitalized with COVID-19 patients	Younger than 20 years	Feb, 2020 -Jan, 2021	Wild-type	7.6% (886/11,613)
			10,017 Hospitalized with COVID-19 patients	Younger than 20 years	Jan - May, 2021	Gamma variant	7.6% (765/10,017)
Clare Smith (8)	England	The National Child Mortality Database (NCMD)	61 COVID-19 patients died with a positive SARS-CoV-2 test	Younger than 18 years	Mar, 2020 -Feb, 2021	Wild-type	<0.01% 25/12,023,568 CYP living in England
Chanapai Chaiyakulsil (18)	Thailand	Thammasat University Hospital care system, Thailand	698 hospitalized with COVID-19 patients	Younger than 15 years old	Apr - Aug, 2021	Delta and Alpha	0.1% (1/698)
Dallas J. Smith (20)[†]	China	Death counts were obtained from the Hong Kong Department of Health, China	Total number of deaths related to COVID-19	Younger than 19 years old	Jan - Mar, 2022	Omicron	11 death

[†], the study contains adult population, but only the information of children and young people was presented in this table. COVID-19 Coronavirus disease 2019; CDC center of disease control; MIS-C multisystem inflammatory syndrome in children and adolescents temporarily related to covid-19; CYP children and young people.

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