Adegboro et al. *Afr. J. Clin. Exper. Microbiol.* 2022; 23 (4): 335 - 344 https://www.afrjcem.org

African Journal of Clinical and Experimental Microbiology. ISSN 1595-689X Oct 2022; Vol.23 No.4
AJCEM/2162. https://www.ajol.info/index.php/ajcem

Review Article **Open Access**

A systematic review of clinical characteristics, co-morbidities and outcomes of COVID-19 in children and adolescents

*[1]Adegboro, B., [2]Musa-Booth, T. O., [3]Mba, I. N., [4]Ibrahim, R. R., [1]Medugu, N., [5]Abayomi, S. A., and [6]Babazhitsu, M.

Departments of [1]Medical Microbiology/Immunology and [3]Chemical Pathology, Nile University of Nigeria, Abuja, Nigeria
[2]1928, Woodlawn Drive, Woodlawn, Maryland 21207, USA
[4]Department of Statistics, Faculty of Science, University of Abuja, Abuja, Nigeria
[5]Department of Medical Microbiology, LAUTECH Teaching Hospital, Ogbomoso, Nigeria
[6]Department of Medical Microbiology and Parasitology, Faculty of Basic Clinical Sciences, College of Health Sciences, Usmanu Danfodiyo University, Sokoto, Sokoto State, Nigeria
*Correspondence to: boazadegboro@gmail.com; boaz.adegboro@nileuniverity.edu.ng

Abstract:

Background: COVID-19 is a major global health challenge that has affected all age groups and gender, with over 5 million deaths reported worldwide to date. The objective of this study is to assess available information on COVID-19 in children and adolescents with respect to clinical characteristics, co-morbidities, and outcomes, and identify gaps in the literatures for appropriate actions.
Methodology: Electronic databases including Web of Science, PubMed, Scopus, and Google Scholar were searched for observational studies such as case series, cross-sectional and cohort studies published from December 2019 to September 2021, using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guide. Data extracted included (i) patient demography (age and gender), (ii) clinical characteristics including vaccination status and presence of co-morbidities, (iii) clinical management including the use of sequential organ failure assessment (SOFA) scores, oxygen requirement, use of mechanical ventilation, and (iv) disease outcomes including length of hospital and intensive care unit (ICU) admission, recovery, complications with sequelae, or death. Data were analyzed using descriptive statistics.
Results: A total of 11 eligible studies were included with a total of 266 children and adolescents; 137 (51.5%) females and 129 (48.5%) males. The mean age of the children was 9.8 years (range of 0 - 19 years), and children ≥ 6 years were more affected (40.7%) than age groups 1 - 5 years (31.9%) and < 1 year (27.4%). The major co-morbidities were respiratory diseases including pre-existing asthma (3.4%), neurologic conditions (3.4%) and cardiac pathology (2.3%). Majority (74.8%, 199/266) of the patients were discharged without sequelae, 0.8% (2/266) were discharged with sequalae from one study, and mortality of 1.9% (5/266) was reported, also from one study. SOFA scores of patients at admission were not stated in any of the study, while only one study reported patient vaccination status.
Conclusion: It is recommended that safe vaccines for children < 1 year of age should be developed in addition to other preventive measures currently in place. SOFA scores should be used to assess risk of COVID-19 severity and monitor prognosis of the disease, and vaccination status of children should be documented as this may impact the management and prognosis of the disease.

Keywords: COVID-19; children; co-morbidity; hospital admission; ICU admission; disease outcome

Received Dec 1, 2021; Revised Jul 18, 2022; Accepted Jul 19, 2022

Une revue systématique des caractéristiques cliniques, des comorbidités et des résultats du COVID-19 chez les enfants et les adolescents

*[1]Adegboro, B., [2]Musa-Booth, T. O., [3]Mba, I. N., [4]Ibrahim, R. R., [1]Medugu, N., [5]Abayomi, S. A., et [6]Babazhitsu, M.

Départements de [1]Microbiologie Médicale/Immunologie et [3]Pathologie Chimique, Nile University of Nigeria, Abuja, Nigeria
[3]1928, Promenade Woodlawn, Woodlawn, Maryland 21207, Etats-Unis
[4]Département de Statistique, Faculté des Sciences, Université d'Abuja, Abuja, Nigeria
[5]Département de Microbiologie Médicale, LAUTECH Hôpital Universitaire, Ogbomoso, Nigéria
[6]Département de Microbiologie Médicale et de Parasitologie, Faculté des Sciences Cliniques Fondamentales, Collège des Sciences de la Santé, Université Usmanu Danfodiyo, Sokoto, État de Sokoto, Nigéria
*Correspondance à: boazadegboro@gmail.com; boaz.adegboro@nileuniverity.edu.ng

Résumé:

Contexte: Le COVID-19 est un défi sanitaire mondial majeur qui a touché tous les groupes d'âge et tous les sexes, avec plus de 5 millions de décès signalés dans le monde à ce jour. L'objectif de cette étude est d'évaluer les informations disponibles sur le COVID-19 chez les enfants et les adolescents en ce qui concerne les caractéristiques cliniques, les comorbidités et les résultats, et d'identifier les lacunes dans la littérature pour des actions appropriées.
Méthodologie: Des bases de données électroniques, notamment Web of Science, PubMed, Scopus et Google Scholar, ont été recherchées pour des études d'observation telles que des séries de cas, des études transversales et de cohorte publiées de décembre 2019 à septembre 2021, en utilisant les éléments de rapport préférés pour les revues systématiques et les méta -Guide des analyses (PRISMA). Les données extraites comprenaient (i) la démographie des patients (âge et sexe), (ii) les caractéristiques cliniques, y compris le statut vaccinal et la présence de comorbidités, (iii) la prise en charge clinique, y compris l'utilisation des scores d'évaluation séquentielle des défaillances d'organes (SOFA), les besoins en oxygène, l'utilisation de la ventilation mécanique et (iv) les résultats de la maladie, y compris la durée de l'admission à l'hôpital et en unité de soins intensifs (USI), la récupération, les complications avec séquelles ou le décès. Les données ont été analysées à l'aide de statistiques descriptives.
Résultats: Un total de 11 études éligibles ont été incluses avec un total de 266 enfants et adolescents ; 137 (51,5%) femmes et 129 (48,5%) hommes. L'âge moyen des enfants était de 9,8 ans (intervalle de 0 à 19 ans), et les enfants ≥ 6 ans étaient plus touchés (40,7%) que les tranches d'âge 1-5 ans (31,9%) et < 1 an (27,4%). Les principales comorbidités étaient les maladies respiratoires, y compris l'asthme préexistant (3,4%), les troubles neurologiques (3,4 %) et la pathologie cardiaque (2,3%). La majorité (74,8%, 199/266) des patients sont sortis sans séquelles, 0,8% (2/266) sont sortis avec des séquelles d'une étude et une mortalité de 1,9% (5/266) a été rapportée, également d'une étude. Les scores SOFA des patients à l'admission n'ont été indiqués dans aucune des études, tandis qu'une seule étude a rapporté le statut vaccinal des patients.
Conclusion: Il est recommandé que des vaccins sûrs pour les enfants de < 1 an soient développés en plus des autres mesures préventives actuellement en place. Les scores SOFA doivent être utilisés pour évaluer le risque de gravité du COVID-19 et surveiller le pronostic de la maladie, et le statut vaccinal des enfants doit être documenté car cela peut avoir un impact sur la gestion et le pronostic de la maladie.

Mots clés: COVID-19; enfants; comorbidité; admission à l'hôpital; admission aux soins intensifs; issue de la maladie

Introduction:

Coronavirus disease-2019 (COVID-19) is a disease caused by severe acute respiratory syndrome-coronavirus-2 (SARS-COV-2), a newly discovered respiratory virus, which has caused over 5 million deaths globally from respiratory tract, cardiac and renal complications, and from an overwhelming cytokine storm (1). It belongs to the kingdom Orthornavirae, phylum Pisuviricota, order Nidovirales, family Coronaviridae, subfamily Orthocoronavirinae and genus Betacoronavirus (1). The highest risk has been found in elderly people, especially the ones with other co-morbidities (2). However, recent data has suggested that children are also affected but present with much milder symptoms (3). Although children do not appear to be at high risk of severe disease, they can spread the virus to others. Therefore, preventive measures should be taken (4,5).

A study by Cui et al., (5) reported a 55-day old female infant in China who was admitted after she tested positive to COVID-19 because she was severely sick with decreased arterial oxygen and elevated lactic acid. A one-year-old boy with COVID-19 was also reported from Wuhan's children's hospital with clinical presentations of diarrhoea, vomiting and shortness of breath (6). Vertical transmission of COVID-19 is yet to be confirmed from available data. However, perinatal SARS-COV-2 infection has been shown to lead to fetal distress, thrombocytopaenia accompanied by abnormal liver function and even death (7). The aim of this systematic review is to assess available information in the literature on the clinical characteristics, co-morbidities, and outcomes of COVID-19 in children and adolescents, and identify gaps in clinical case management of the disease.

Materials and method:

Literature search strategy

A two-step strategy was employed in conducting this systematic review. First, electronic (online) databases including Web of Science, PubMed, Scopus, and Google Scholar were searched by three of the authors (RRI, NM and TOM) for observational studies such as case series and cohort design, published between December 2019 and September 2021. Secondary sources were subsequently searched, including references of articles previously identified during the initial search. The keywords used for the search were; 'COVID-19' OR 'SARS-CoV-2' OR 'coronavirus' AND 'childhood' OR 'paediatric' OR 'child', 'SARS-CoV-2 infections in children' OR 'childhood SARS-CoV-2 infections', 'COVID-19 OR 'SARS-CoV-2' AND 'children'.

Identification of eligible publications

The PRISMA guide was used for the identification of eligible publications (Fig. 1). The inclusion criteria for selecting publications for the systematic review were; (i) articles on observational study design such as case series, cross-sectional and cohort studies; and (ii) articles with a study population of children <19 years of age containing information on patient demography such as age and gender, clinical characteristics including vaccination status and presence of co-morbidities, clinical management including the use of SOFA score, oxygen and/or mechanical ventilation requirement, and disease outcome including length of hospital and ICU admission, recovery, complications, or death. Articles that did not contain data on these characteristics, and single case reports, articles containing secondary data such as consensus documents, clinical trials, clinical guidelines, letters, editorials, reviews, systematic reviews and/or meta-analysis were excluded.

A total 1136 articles were retrieved from all the databases searched and after removing duplicate publications, a total of 194 articles were screened. Screening of abstracts and titles of 92 of these articles resulted in selection of 47 eligible articles for which full text assessments were subsequently conducted. Quality scores were awarded to each article using the Joanna Briggs Institute (JBI) critical appraisal list for prevalence studies (8). Article with scores of 7-9 was considered high quality, 4-6 moderate quality, and < 3 low quality. Only moderate and high-quality articles were included in the systematic review, and this yielded a total of 11 articles (Table 1). Resolution of any disagreement on eligibility of any article was achieved through discussions and consensus by third author (BA).

Data extraction and analysis

Information extracted from the 11 eligible articles includes; corresponding authors surname, publication year, number of children in the study, age at diagnosis of COVID-19, SOFA score, vaccination status, co-morbidities, length of hospital and ICU admission, requirement for oxygen and/or artificial ventilation, and treatment outcomes (Table 1). The data were entered into Excel spreadsheet and analysed using descriptive statistics.

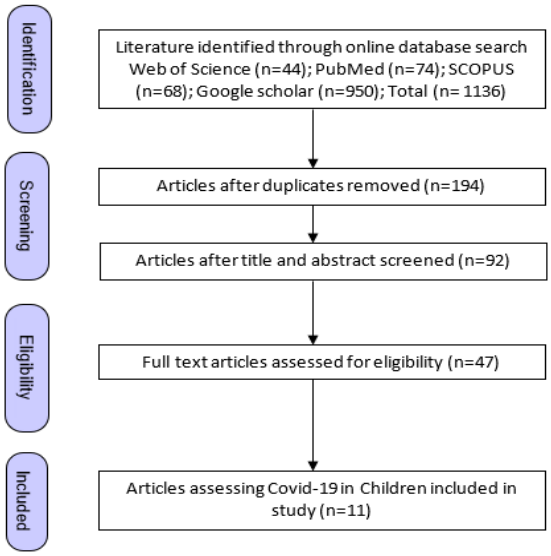

Fig. 1: Process for selection of publications (PRISMA guide) for the systematic review

Table 1: Characteristics of included studies on COVID-19 in children used for systematic review

S/N	Authors	Article type	Country of origin	Publication setting	Year of publication	Sample size	No of males	No of females	Age range (median age of onset)	Reference
1	Abdel-Mannan et al	Case series	London, UK	Hospital	2020	4	2	2	8 – 15 years (12 years)	(9)
2	Posfay-Barbe et al	Case series	Switzerland	Outpatient clinic and hospital	2020	40	18	22	0 - 16 years (11.1 years)	(10)
3	Ma et al	Single center retrospective study	Wuhan, China	Children's Hospital	2020	50	28	22	0 - 16 years (2.5 years)	(11)
4	Tang et al	Retrospective study	Shenzhen, China	Hospital	2020	26	9	17	1 – 13 years (7 years)	(13)
5	Oualha et al	Single center retrospective study	Paris, France	Hospital	2020	27	10	17	1 month - 18 years (6 years)	(14)
6	Qui et al	Observational retrospective cohort study	Zhejiang, China	Hospitals	2020	36	23	13	1 – 16 years (8.3±3.5 years)	(15)
7	Cai et al	Case series	Anhui & Quigdon, China	Hospitals	2020	10	4	6	3 months – 10 years (5.6 years)	(16)
8	Xia et al	Case series	Wuhan, China	Hospitals	2020	20	13	7	1day - 14years 7months (2 years 1.5 months)	(17)
9	Wei et al	Retrospective study	China	Hospitals	2020	9	2	7	1 – 11 months (6 months)	(18)
10	Xu et al	Observational	China	Hospital	2020	10	6	4	2 months - 15 years (7.9 years)	(19)
11	Zhang et al	Retrospective observational case series	China	Hospitals	2020	34	14	20	1 month - 12 years (2.8 years)	(11)
Total						**266**	**129**	**137**		

Results:

Characteristics of included studies on COVID-19 in children

A total of 11 studies on COVID-19 in children (9-19) met our eligibility criteria and were used for the systematic review, with 266 children; 137 (51.5%) females and 129 (48.5%) males. The mean age of the children was 9.8 years (range of 0-19 years) (Table 1).

Age of children with COVID-19 at diagnosis.

The specific age of children with COVID-19 at diagnosis were available for 113 patients (some studies had a mixture of specific ages, age ranges, and mean age). Of these 113 children, age group ≥ 6 years were more affected with COVID-19 (40.7%) than age group 1-5 years (31.9%) and children < 1 year of age (27.4 %). The mean age reported across studies where specific ages were not reported or partially reported ranged from 6-11.1 years (10, 13–15). Table 2 shows the age group distribution of the children with COVID-19 from the selected studies.

Co-morbidity in children with COVID-19

Table 3 shows the specific types of co-morbidities reported in the studies used for the review. While 60.2% (160/266) of children with COVID-19 in the review had no co-morbidity (reported in two studies), pre-existing asthma/respiratory diseases (3.4%), neurological diseases (3.4%) and cardiac pathology (2.3%) were the most frequent co-morbidities reported. The study by Oualha et al., (14) reported positive correlation between existence of co-morbidities and increased mortality.

Table 2: Age of children and adolescents with COVID-19 at diagnosis

Age at diagnosis	No of studies	No of patients	Percentage (reference)
< 1 year	5	31	27.4 (11,16–19)
1-5 years	7	36	31.9 (11,13–17,19)
≥6	8	46	40.7 (9,11,13–17,19)
Total		**113**	

Table 3: Prevalence of co-morbidity in children with COVID-19

Co-morbidity	No of studies	No of patients	Percentage (reference)
Pre-existing asthma/other respiratory condition	1	9	3.4 (10,11,14)
Cardiac pathology	2	6	2.3 (11,17)
Neurological	3	9	3.4 (11,14,17)
Obesity	2	3	1.1 (9,10)
Sickle cell disease	1	4	1.5 (14)
Diabetes mellitus	1	3	1.1 (10)
Hypertension	1	1	0.4 (10)
Malignancy	1	1	0.4 (11)
Premature birth	1	2	0.8 (10)
No co-morbidity	2	160	60.2 (9–11,13,15,17–19)
Co-morbidity not mentioned	1	68	25.6 (12,14,16)
Total		**266**	

SOFA score and vaccination status of children with COVID-19 at diagnosis

None of the studies recorded SOFA score of the patients at first diagnosis and none except one reported the vaccination status of the children.

Maximum length of hospital admission for children with COVID-19

Most studies reported the maximum duration of admission of the children with variable information about the specific days each patient stayed on admission. The range of hospital stay among those admitted and discharged in hospital was < 1 day - 6 weeks. Four studies reported that children were admitted in hospital without stating the actual number of days spent. In these four studies, some sub-sets of the patients were still on admission at the time of preparing this paper for publication. In one study, it was unclear if any of the patients were admitted into hospital (Table 4). Abdel-Manna et al., (9) reported admission days of 2-3 weeks for patients with two other patients still on admission at three and six weeks respectively at the time of this preparation.

Shorter admission durations were reported by Klara et al., (10) with median of three days and all patients discharged by seven days. Qui et al., (15) reported mean admission duration of two weeks for children with COVID-19 and all of them recovered completely by six weeks. Five studies (11,12,14,18,19) did not specify lengths of admission (Table 4).

Length of ICU admission of children with COVID-19

All except three studies (12,13,17) reported that a proportion of the children were admitted in hospital but most children (52.3%) were not managed in the ICU (Table 5). One child was in the ICU for less than two weeks and another for more than two weeks (9). The duration of ICU admission was not specified in 29 patients. (Table 5).

Requirement for artificial ventilation

Mechanical ventilation was not used for 157 (59.0%) of patients as reported in seven studies (10,11,14–16,18,19). A total of 13 children received mechanical ventilation for duration between 1-18 days in total (9,14). There was no report for 36.1% of children in the studies selected (Table 6).

Treatment outcome of children with COVID-19

A total of 74.8% of the children with COVID-19 recovered fully (9-13,15,16,18,19) and were discharged from hospital (Table 7). Mortality was reported in 1.9% of the children (14) and two children were reported to have sequelae at the time of this manuscript preparation (9).

Table 4: Length of hospital admission of children with COVID-19

Length of hospital admission (weeks)	No of studies	No of patients	Percentage (reference)
< 1	1	7	4.3 (10)
1 - < 2	1	26	16.0 (13)
< 3	1	18	11.1 (17)
2-3 - < 4	1	10	6.2 (16)
< 5	1	27	(13)
< 6	1	36	22.2 (15)
Not available	1	4	2.5 (9)
Not specified	5	61	37.7 (11,12,17,18,19)
Total		**162**	

Table 5: Length of ICU admission of children with COVID-19

Length of ICU admission (weeks)	No of studies	No of patients	Percentage (reference)
< 2	1	1	0.4 (9)
> 2	1	1	0.4 (9)
No admission	6	139	52.3 (10,11,15,16,18,19)
Not specified	2	29	10.9 (9,14)
Not available	3	96	36.1 (12,13,17)
Total		**266**	

Table 6: Requirement for and length of artificial ventilation

Requirement/length of artificial ventilation (days)	No of studies	No of patients	Percentage (reference)
1 - 7	1	4	1.5 (9)
1 - 18	1	9	3.4 (14)
No admission	6	157	59.0 (10,11,14–16,18,19)
Not reported	3	96	36.1 (12,13,17)
Total		**266**	

Table 7: Treatment outcomes of children with COVID-19

Treatment outcome	No of studies	No of patients	Percentage (reference)
Full recovery and discharged	9	199	74.8 (9–13,15,16,18,19)
Recovered with sequelae (morbidity)	1	2	0.8 (9)
Death (mortality)	1	5	1.9 (14)
Discharged with unreported sequelae	3	52	19.5 (12,14,17)
Unreported	2	8	3.0 (17,19)
Total		**266**	

Discussion:

In this systematic review, we aimed to assess current literature on COVID-19 in children. We identified 11 papers for final inclusion in the review and obtained information on age of children at diagnosis, presence of co-morbidities, duration of hospital and ICU admission, requirement for oxygen and/or mechanical ventilation, SOFA scoring, and vaccination status. A total of 266 children with COVID-19 were reviewed and the mean age of the children was 9.8 years (age range 0-19 years) with

129 males and 137 females (M:F ratio of 1:1.1). SARS-COV-2 has been reported to infect children of all ages and gender, including newborns, infants, and young children (18). When mainland China confirmed 11,791 COVID-19 cases at the onset of COVID-19, 74 (0.6%) of them were between the ages of 1.5 months and 18 years (20). In a study of 474 paediatric patients on admission in a facility at the peak of the pandemic in 2020, about 5.2% of them were found to be positive with a mean age of 5.83 years, and significantly higher than those that tested negative (21).

In a retrospective analysis of 366 hospitalized children aged ≤16 years with respiratory infections in three branches of Tongji hospital all located in central Wuhan, 6 (1.6%) patients had SARS-COV-2 infection, with median age of 3 years (age range 1-7 years) (20). The Centers for Disease Control and Prevention reported that children constituted 2% of 44,672 cases in China as at early 2020, and 4.5% of 1,663,519 cases in the US by the middle of year 2020 (22). In South Korea, about 6.4% of confirmed cases were reported to be children with no record of death (23). In a meta-analysis of 14 studies by Yudan et al., (24), the age range of children with COVID-19 was 0-17 years and mean age was 5.5± 2.2 years (95% CI 4.2–6.8).

Currently, the median age of patients with COVID-19 in the US is 11 years (age range 0-17 years) and in China, it is 7 years (age range 1-18 years)(25,26). Children under 10 years of age have been shown by the Chinese CDC to account for 1% of confirmed COVID-19 cases while the United States CDC reported that children < 18 years of age accounted for 4.5% of 2,336,615 confirmed cases (27–29). Our current systematic review showed that COVID-19 was less frequent among children < 1 year of age (27.4%) than among children ≥ 6 years of age (40.7%), who also had more severe disease. Therefore, it is advisable to develop safe vaccines for this age group in addition to other preventive measures.

The SOFA score is a validated prognostic scoring protocol with scores ranging from 0-24, where scores of 0-4 could be assigned for each of the 6 organ systems of the body (neurologic, pulmonary, cardiovascular, renal, hepatic, haematologic) depending on the evidence of organ failure. Higher scores have been found to correlate with higher likelihood of in-hospital mortality (30,31). COVID-19 patients with higher SOFA scores are at increased mortality risk (32,33). In our review, none of the study reported on the use of SOFA scores to assess the risks of COVID-19 at admission or monitor the progress of the disease on admission. It would be advantageous for paediatric physicians to assess COVID-19 progression and monitor prognosis in hospitalized patients using SOFA scoring system and clearly document these in the case files of hospitalized patients, from which the importance of the scoring system can be assessed in future studies.

Mass vaccination has been reported from recent studies to decrease population transmission of SARS-COV-2 (34). Children appear to be less susceptible to SARS-CoV-2 infection and transmission, compared to adults (35,36) however, they generally have higher rates of social contact than adults (37). Therefore, vaccinating children will help to protect the more vulnerable adults from the virus (34,38–41). The proportion of children COVID-vaccinated has been shown to vary from country to country due to differences in vaccine availability, vaccine hesitancy and efficiency of vaccination programmes (39). The vaccination status of the children with COVID-19 in our review was not reported in any the studies except one. The knowledge of childhood vaccination status might be necessary to assess whether fully vaccinated children mount a stronger immune response to the SARS-CoV-2 than those not vaccinated.

Children with COVID-19 and underlying diseases are at increased risk of developing a severe or critical illness. Respiratory neurological and cardiac co-morbidities were the most frequent underlying diseases in this systematic review. Co-morbidities commonly reported to be associated with poorer COVID-19 outcomes are developmental delays, immune suppression, obesity, diabetes, seizure disorders, congenital heart diseases, chronic pulmonary disease (including asthma), chronic kidney disease, chronic liver disease, malnutrition, and hematologic conditions such as sickle cell disease (42,43). Reassuringly, the mortality rate of children with COVID-19 remains low accounting for <1% of all deaths due to COVID-19 in the United States (44,45).

The median length of admission in children hospitalized with COVID-19 has been reported to be 7.5 days (range 5-13 days) (46). The admission length for the children with record of hospitalization in our systematic review was < 1 day - 6 weeks. Majority of children with COVID-19 reportedly have mild clinical disease, with faster recovery and therefore most did not require hospital admissions (47). In the United States, fewer children were admitted to hospital and ICU with 5.7-20.0% and 0.58%-2.0% respectively, compared to adults aged 18-64 years with 10.0-33.0% and 1.4-4.5% respectively.

With regards to requirement for artificial ventilation, a study of 220 children with COVID-19 on admission in Turkey by Yayla et al., (48) reported that only three (1.4%) children required respiratory support, and all of them had underlying co-morbidities including fulminant myocarditis, Stevens-Johnson syndrome and osteopetrosis. On the other

hand, Prata-Barbosa et al., (49) studied 79 children admitted into the ICU of a hospital in Brazil with COVID-19 and observed that 51 of them (65%) required some form of ventilatory support. This is far higher than 4.9% (13/266) of children we found requiring mechanical ventilation in our review. Hypoxic respiratory failure was the most common reason for requiring ventilatory support (50). Concerning COVID-19 mortality in children, the overall mortality has been reported to be about 0.1% compared to 2.27% in adults (37), but the mortality reported in one study (14) from our review was 1.9%.

Conclusion:

Data from our systematic review and the literature indicate that prognosis of COVID-19 in children is good, as many infected children tend to have mild disease and recovered without sequelae, and mortality is low. However, we recommend that SOFA scores should be used to assess risk of COVID-19 severity and monitor prognosis in children requiring hospitalization to reduce adverse outcomes, and vaccination status of children should be documented, as this may impact the management and prognosis of the disease.

As a result of the emergence of SARS-CoV-2 variants and children being possible source of virus transmission, it is recommended that children should be fully vaccinated and comply with other preventive measures such as wearing of face masks, observing social distancing, and avoiding crowded areas. Development of effective vaccines for children < 1 year of age is desirable for additional protection since these infants are susceptible to severe COVID-19.

Contributions of authors:

AB designed the outline of the systematic review, served as the consensus reviewer, and edited the manuscript. MTO screened and reviewed journal for articles, analyzed the data, prepared the tables and wrote portions of the manuscript. IRR screened and reviewed the articles, analyzed the results and prepared the tables. MIN wrote the literature review. ASA and BM reviewed the articles and wrote portions of the manuscript. NM screened the articles, extracted data and edited the manuscript.

Source of funding:

No funding was received for the study

Conflict of interest:

No conflict of interest is declared

References:

1. Coronavirus disease (COVID-19). https://www.who.int/emergencies/diseases/novel-coronavirus-2019
2. Coronavirus. https://www.who.int/health-topics/coronavirus#tab=tab_1
3. Wang, D., Ju, X. L., Xie, F., et al. clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous regions) of Northern China. Zhonghua Er Ke Za Zhi. Chinese J Paediatr. 2020; 58: 269, 274
4. Coronavirus in Kids and Babies: Risks, Symptoms, and Prevention. https://www.webmd.com/lung/coronavirus-covid-19- babies-children#1
5. Cui Y., Tian, M., Huang, D., et al. A 55-day old female infant infected with 2019 novel coronavirus disease: presenting with pneumonia, liver injury, heart damage. J Infect Dis. 2020; 221: 1775-1781
6. Chen, F., Liu, Z. S., Zhang, F. R., et al. First case of severe childhood novel coronavirus pneumonia in China. Zhonghua Er Ke Za Zhi. Chinese J Paediatr. 2020; 58: E005
7. Zhu, H., Wang, L., Fang, C., et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Paediatr. 2020; 9: 51-60
8. The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews Checklist for Systematic Reviews and Research Syntheses. https://jbi.global/sites/default/files/2019-05/JBI_Critical_Appraisal-Checklist_for_Systematic_Reviews2017_0.pdf
9. Abdel-Manna, O., Eyre, M., Löbel, U., et al. Neurologic and Radiographic Findings Associated With COVID-19 Infection in Children. JAMA Neurol. 2020; 77; 1440–1445. doi: 10.1001/jamaneurol.2020.2687.
10. Posfay-Barbe, K. M., Wagner, N., Gauthey, M., et al. COVID-19 in Children and the Dynamics of Infection in Families. Pediatrics. 2020; 146 (2): e20201576. doi: 10.1542/peds.2020-1576.
11. Zhang, C., Gu, J., Chen, Q., et al. Clinical and epidemiological characteristics of pediatric SARS-CoV-2 infections in China: A multicenter case series. PLoS Med. 2020; 17 (6): e1003130. doi:https://doi.org/10.1371/journal.pmed.1003130
12. Ma, H., Hu, J., Tian, J., et al. A single-center, retrospective study of COVID-19 features in children: a descriptive investigation. BMC Med. 2020; 18 (1): 123. doi: 10.1186/s12916-020-01596-9.
13. Tang, A., Xu, W., Shen, M., et al. A retrospective study of the clinical characteristics of COVID-19 infection in 26 children. medRxiv. 2020.03.08.20029710; doi:https://doi.org/10.1101/2020.03.08.20029710.
14. Oualha, M., Bendavid, M., Berteloot, L., et al. Severe and fatal forms of COVID-19 in children. Arch Paediatr. 2020; 27 (5): 235-238. doi: 10.1016/j.arcped.2020.05.010.
15. Qiu, H., Wu, J., Hong, L., Luo, Y., Song, Q., and Chen, D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis.2020;20(6):689-696 https://doi.org/10.1016/S1473-3099(20)30198-5
16. Cai, J., Xu, J., Lin, D., et al. A Case Series of Children With 2019 Novel Coronavirus Infection: Clinical and Epidemiological Features. Clin Infect Dis. 2020; 71 (6): 1547-1551. doi: 10.1093/cid/ciaa198.
17. Xia, W., Shao, J., Guo, Y., Peng, X., Li, Z., and Hu, D. Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. Paediatr Pulmonol. 2020; 55 (5): 1169-1174. doi: 10.1002/ppul.24718.
18. Wei, M., Yuan, J., Liu, Y., Fu, T., Yu, X., and Zhang, Z. J. Novel Coronavirus Infection in Hospitalized Infants Under 1 Year of Age in China. JAMA. 2020; 323 (13): 1313-1314. doi: 10.1001/jama.2020.2131.
19. Xu, Y., Li, X., Zhu, B., et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persis-

tent fecal viral shedding. Nat Med. 2020; 26 (4): 502- 505. doi: 10.1038/s41591-020-0817-4 20.
Fang, F., and Luo, X. P. Facing the pandemic of 2019 novel coronavirus infections: the pediatric perspectives. Zhonghua er Ke Za Zhi. Chinese J Paediatr. 2020; 58: E001.
21. Balasubramanian, S., Rao, N. M., Goenka, A., Roderick, M., and Ramanan, A. V. Coronavirus Disease 2019 (COVID-19) in Children - What We Know So Far and What We Do Not. Indian Paediatr. 2020; 57: 435.
22. Feng, Z., Li, Q., Zhang, Y, et al. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) - China, 2020. China CDC Weekly. 2020; 2 (8): 113 - 122. doi: 10.46234/ccdcw2020.032
23. Ludvigsson, J. F. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr. 2020; 109: 1088.
24. Ding, Y., Yan, H., and Guo, W. Clinical Characteristics of Children With COVID-19: A Meta-Analysis. Front Paediatr. 2020; 8: 431.
25. Bialek, S., Gierke, R., Hughes, M., McNamara, L. A., Pilishvili, T., and Skoff, T. CDC COVID-19 Response Team. Coronavirus Disease 2019 in Children-United States, February 12–April 2, 2020. MMWR Morb Mortal WklyRep.2020;69:422–426. doi: 10.15585/mmwr.mm6914e4
26. Dong, Y., Mo, X., Hu, Y., et al. Epidemiology of COVID-19 Among Children in China. Pediatrics. 2020; 145 (6): e20200702. doi: 10.1542/peds.2020-0702.
27. Wu, Z., and McGoogan, J. M. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020; 323: 1239–1242.
28. Sahu, K., and Kumar, R. Current perspective on pandemic of COVID-19 in the United States. J Fam Med Prim Care. 2020; 9: 1784.
29. Han, D., Li, R., Han, Y., Zhang, R., and Li, J. Covid-19: Insight into the asymptomatic SARS-CoV-2 infection and transmission. Int J Biol Sci. 2020; 16: 2803–2811.
30. Lopes Ferreira, F., Peres Bota, D., Bross, A., Mélot, C., and Vincent, J. L. Serial Evaluation of the SOFA Score to Predict Outcome in Critically Ill Patients. JAMA. 2001; 286: 1754–1758.
31. Raith, E. P., Udy, A. A., Bailey, M., et al. Prognostic Accuracy of the SOFA Score, SIRS Criteria, and qSOFA Score for In-Hospital Mortality Among Adults with Suspected Infection Admitted to the Intensive Care Unit. JAMA. 2017; 317 (3): 290 – 300. doi:10.1001/jama.2016.20328
32. Zhou, F., Yu, T., Du, R., et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395 (10229): 1054 – 1062.
33. Yang, Z., Hu, Q., Huang, F., Xiong, S., and Sun, Y. The prognostic value of the SOFA score in patients with COVID-19: A retrospective, observational study. Medicine (Baltimore). 2021; 100: e26900.
34. Milman, O., Yelin, I., Aharony, N., et al. Community -level evidence for SARS-CoV-2 vaccine protection of unvaccinated individuals. Nat Med. 2021; 27: 1367–1369.https://doi.org/10.1038/s41591-021-01407-5
35. Ismail, S. A., Saliba, V., Lopez Bernal, J., Ramsay, M. E., and Ladhani, S. N. SARS-CoV-2 infection and transmission in educational settings: a prospective cross-sectional analysis of infection clusters and outbreaks in England. Lancet Infect Dis. 2021; 21: 344.
36. Guan, W., Ni, Z., Hu, Y., et al. COVID-19 Disease 2019 in China. N Engl J Med. 2020; 382(18):1708-1720. doi: 10.1056/NEJMoa2002032.
37. Mossong, J., Hens, N., Jit, M., et al. Social Contacts and Mixing Patterns Relevant to the Spread of Infectious Diseases. PLoS Med. 2008; 5: 0381–0391. https://doi.org/10.1371/journal.pmed.0050074
38. Hilton, J., and Keeling, M. J. Incorporating household structure and demography into models of endemic disease. J Roy Soc Interface.2019;16: 2019031720190317 http://doi.org/10.1098/rsif.2019.0317
39. Maldonado, Y. A., O'Leary, C. S. T., Banerjee, R., et al. COVID-19 vaccines in children and adolescents. Paediatr. 2021; 148: 2021052336.
40. Sahu, K. K., Siddiqui, A. D., and Cerny, J. Managing sickle cell patients with COVID-19 infection: the need to pool our collective experience. Br J Haematol. 2020; 190: e86.
41. Shekerdemian, L. S., Mahmood, N. R., Wolfe, K. K., et al. Characteristics and Outcomes of Children with Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. JAMA Paediatr. 2020; 174: 868–873.
42. Hoang, A., Chorath, K., Moreira, A., et al. COVID-19 in 7780 pediatric patients: a systematic review. E-Clinical Medicine. 2020; 24: 100433.
43. Leeb, R. T., Price, S., Sliwa, S., et al. COVID-19 Trends Among School-Aged Children — United States, March 1–September 19, 2020. MMWR Morb Mortal Wkly Rep. 2020; 69: 1410–1415.
44. Castagnoli, R., Votto, M., Licari, A., et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. JAMA Paediatr. 2020; 174 (9): 882 – 889.
45. Chen, J., Qi, T., Liu, L., et al. Clinical progression of patients with COVID-19 in Shanghai, China. J Infect. 2020; 80: e1–e6.
46. Riphagen, S., Gomez, X., Gonzalez-Martinez, C., Wilkinson, N., and Theocharis, P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020; 395: 1607–1608.
47. de Souza, T. H., Nadal, J. A., Nogueira, R. J. N., Pereira, R. M., and Brandão, M. B. Clinical manifestations of children with COVID-19: A systematic review. Paediatr Pulmonol. 2020; 55 (8): 1892-1899. doi: 10.1002/ppul.24885.
48. Yayla, B. C. C., Ozsurekci, Y., Aykac, K., et al. Characteristics and Management of Children with COVID-19 in Turkey. Balkan Med J. 2020; 37: 341.
49. Prata-Barbosa, A., Lima-Setta, F., Santos G. R., et al. Pediatric patients with COVID-19 admitted to intensive care units in Brazil: a prospective multicenter study. J Paediatr. 2020; 96: 582-592. doi: 10.1016/j.jped.2020.07.002.
50. Alfraij, A., Bin Alamir, A. A., Al-Otaibi, A. M., et al. Characteristics and outcomes of coronavirus disease 2019 (COVID-19) in critically ill pediatric patients admitted to the intensive care unit: A multicenter retrospective cohort study. J Infect Publ Hlth. 2021; 14 (2): 193-200.