Title: Epidemiological, Clinical and Biomarker Profile of Pediatric Patients Infected with COVID-19

Komal Shah[1*], Mudita Upadhyaya[2], Yogini Kandre[3], Apurvakumar Pandya[4], Vishakh Saraf[5], Deepak Saxena[6], Dileep Mavalankar[7]

[1*]Assistant Professor, Indian Institute of Public Health Gandhinagar - 382042, Gujarat, India

[2]Independent Researcher, 9138 Harbor Hills Drive, Houston Texas, 77054, USA

[3]Programe Associate, Indian Institute of Public Health Gandhinagar - 382042, Gujarat, India

[4]Economic Evaluation Specialist, Indian Institute of Public Health Gandhinagar-382042, Gujarat, India

[5]MPH Student, Indian Institute of Public Health Gandhinagar-382042, Gujarat, India

[6]Professor, Indian Institute of Public Health Gandhinagar-382042, Gujarat, India

[7]Director, Indian Institute of Public Health Gandhinagar - 382042, Gujarat, India

Dr. Komal Shah (*Corresponding Author)
Assistant Professor,
Indian Institute of Public Health - Gandhinagar
Opp. Air Force Head Quarters, Nr. Lekawada Bus Stop,
Gandhinagar-Chiloda Road, Gandhinagar - 382042
Mob: 9924264500
Email: kshah@iiphg.org

ABSTRACT

Background: Given the limited and diverse nature of published literature related to COVID-19 in pediatrics, it is imperative to provide evidence-based summary of disease characteristics for guiding policy decisions. We aim to provide comprehensive overview of epidemiological, clinical and biomarker profile of COVID-19 infection in pediatric population.

Methods: For this umbrella review, published systematic reviews from PubMed and pre-print databases were screened. Literature search was conducted from December 2019 to April 2021. Details of clinical, radiological, laboratory features were collected from each review. Qualitative observations were synthesized and pooled prevalence of mortality and asymptomatic cases were assessed using meta-analysis.

Results: Evidence synthesis of 38 systematic reviews included total 1145 studies and 3,34,398 children and adolescents. Review revealed that COVID-19 is relatively milder with better prognosis in pediatrics. However, patients with comorbidity are at higher risk. Meta-analysis of reviews showed that 21.17% (95% CI: 17.818 to 24.729) of the patients were asymptomatic and mortality rate was 0.12% (95% CI:0.0356-0.246). Though there was no publication bias, significant heterogeneity was observed. Fever (48-64%) and cough (35-55.9%) were common symptoms, affecting almost every alternate patient. Ground glass opacities (prevalence range:27.4-61.5%) was most frequent radiographic observation. Rise in C-reactive protein, lactate dehydrogenase and D-dimer ranged from 14-54%, 12.2-50% and 0.3-67% respectively. Some of the included reviews (44.7%-AMSTAR; 13.2%-GRADE) were of lower quality.

Conclusion: Current umbrella review provides most updated information regarding characteristics of COVID-19 infection in pediatrics and can be used to guide policy decision regarding vaccination prioritization, early screening and identification of at-risk population.

Keywords: COVID-19, Pediatrics, Mortality, Asymptomatic, Biomarkers, Radiology

INTRODUCTION

Since March 2020, SARS-CoV-2 virus has been declared as a global pandemic, accounting for over 16 crore cases and 34 million deaths worldwide.[1] The disease is mainly manifested as infectious pneumonia and is transmitted in the community through cough, sneeze and exhales of an infected person.[2,3] While children may not be as susceptible as adults, they can become carrier of the disease and can subsequently infect older age groups.[4,5] During earlier phase of the pandemic, pediatric population as compared to their adult counterparts had received lesser attention from scientific fraternity and policy makers. This was principally due to presumed lower prevalence and severity of COVID-19 in this subset of population.

However, across the globe a gradual increase in pediatric cases is observed since April 2020. At first Europe and America started witnessing greater infectivity in this population and very recently during second wave similar patterns were observed in India also. These cases are expected to increase many folds during upcoming waves. A steep rise of 3% in cumulative child cases was reported in first two weeks of May, 2021 by American Academy of Pediatrics.[6] With present vaccination strategies targeting only adults, pediatric population remains to be vulnerable to COVID-19 infection in near future. Henceforth preparedness for upcoming waves with respect to protection of children and adolescent appears to be an important aspect. This can be facilitated through careful study of available evidences reporting disease transmission trends, characteristic and consistent features of the infection in terms of clinical symptoms, biomarkers and radiographic images.

Our goal, therefore, was to conduct an umbrella review of published systematic reviews and meta-analysis for studying COVID-19 transmission and provide summary evidence of symptoms and

characteristic features of COVID -19 in the children and adolescents. We also aimed to provide quantitative estimate of the mortality and asymptomatic disease burden in this subset of the population.

METHODS

Search Strategy

To identify relevant systematic reviews and meta-analyses, we searched PubMed and pre-print databases (MedRxiv) from December 2019 to April 2021. The search was conducted using index terms (e.g., MeSH terms): COVID-19, SARS-CoV-2, COVID-2019, 2019-nCOV, 2019 novel coronavirus infection, coronavirus disease-19, coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2, novel coronavirus, children, infant, neonate, young, newborn, baby, babies, adolescent, adolescence, pediatric, pediatric, juvenile, teenager, review, systematic review, meta-analysis. These search terms were combined as search sets, using Boolean operators (AND, OR, NOT). Additionally, we used the reference lists of the searched articles and previous reviews to identify and included additional relevant articles. We excluded duplicate studies from the final search.

Inclusion criteria

We included systematic reviews and meta-analyses published in English that were conducted in children and adolescents and those reported modes of transmission and details of symptoms (or asymptomatic prevalence), mortality, radiographic and biomarker profile of COVID-19 infection.

Exclusion Criteria

Studies on adult patients, published in languages other than English and studies which were not systematic reviews or meta-analyses were excluded from the review. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Moher, Liberati, Tetzlaff, & Altman, 2009) was used to conduct this umbrella review (Figure 1).

Data Extraction

Three independent reviewers (K.S., M.U. and A.P.) screened the title and abstracts and assigned unique identification numbers to all included articles. Key information was abstracted from the articles by three independent coders (K.S., M.U. and A.P.) and categorized in an evidence table using the following codes: author(s), title, country, population, study period, number of studies included in the review, total cases, general findings, symptoms, radiographic findings, laboratory findings, other findings and limitations. Any discrepancy in the coding was resolved by consensus. In addition, two senior researchers (D.S. and D.M.) with expertise in epidemiology and disease prevention reviewed the methodology and coding results.

Quality assessment

Two independent researchers (V.S. and Y.K.) categorized the reviews into high quality, moderate, low and critically low-quality using AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews to assess the methodological quality of review and meta-analysis).[7] AMSTAR 2 is designed to evaluate the risk of bias and its interpretation by the authors of the included systematic reviews (of randomized control trials as well as non-randomized control studies). GRADE (Grading of Recommendations Assessment, Development, and Evaluation) was used to assess quality of evidence for the outcome.[8]

Data Synthesis

Data from the systematic reviews was abstracted into evidence tables. Consensus or variations related to relevant variables were reported and presented as descriptive summaries in the result section. A meta-analysis was performed for mortality and asymptomatic disease prevalence using quantitative data provided by individual studies. We used a random-effect/fixed-effect model (based on heterogeneity) to calculate pooled weighted proportions with the 95% confidence interval. Heterogeneity or between-study variance was assessed using Cochran's Q test ($p < 0.10$), and quantified using the I^2 statistics. $I^2 > 50\%$ and a $p < 0.05$ were considered substantial heterogeneity. All statistics were performed using Review Manager (RevMan) Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014 was used to conduct the meta-analysis. Publication bias was assessed using Begg's test and Egger's test.

RESULTS

Scope of the systematic reviews included in the study was to cover various aspects of COVID-19 infection that included transmission trends, characteristic laboratory and clinical features and morbidity-mortality burden in pediatric population. Total of 930 records were screened, and 38 records[9-46] were finally selected for the review (figure 1). Out of 38 systematic reviews, 19 studies had qualitative components and had presented findings of meta-analysis for various aspects (table 1). Evidence synthesis of 38 systematic reviews included total 1145 studies and 3,34,398 children and adolescents. The review included studies those were conducted right from very initial phase of pandemic (December 2019) to recent time (latest in April 2021), that essentially reflected and captured condition of infection during various waves and seasons. Nineteen (50%) studies provided details of asymptomatic disease burden and it was found that 13-43% of the patients had asymptomatic course of the disease. Quantitative data of mortality was provided by 47.4% of the studies (n=18) and the proportion of patient died ranged from 0-1%. Smallest review included 9

studies, whereas Hoang et al., (2020) presented largest review with 131 individual studies addressing varied dimensions of COVID-19 in pediatric patients. Not all studies reported details of comorbid conditions.

Quality of evidence

The quality assessment characteristics are shown in **Supplementary table 1.** According to the AMSTAR scores, 17 (44.7%studies were of low quality, 16 (42.1%) studies of medium quality, and 5 (13.2%) studies of high quality. About 19 (50%) studies did not assess methodological quality of selected studies. The quality of evidence for the primary outcomes of each included review was assessed using the GRADE method **(Supplementary table 2).** GRADE approach showed 5 (13.2%) of the 38 primary outcomes studies were based on very low-quality evidence, and 11 (28.9%) on high-quality evidence.

Clinical symptom profile of children and adolescents with COVID-19

Details regarding entire spectrum of symptoms and their pooled prevalence is presented in table 2. Quantitative analysis of the asymptomatic population's proportion was assessed through combining the data of nineteen systematic reviews and are presented as meta-analysis (figure 2A). Cumulative pooled prevalence showed that 21.17% (95% C.I.: 17.818-24.729; random effect model) were asymptomatic. Though there was no publication bias (as indicated by Begg's and Egger's tests), significant heterogeneity was observed. Other symptoms included fever, headache, cough, sneezing, rhinorrhea, myalgia, sore throat, tachycardia, tachypnea, diarrhea, constipation in some cases Shortness of breath and dizziness. Majority of the studies reported fever (prevalence range: 48–64%) and cough (prevalence range: 35-55.9%) as most commonly symptoms with affecting almost every alternate patient. Few systematic review studies (n=9) reported nasal

symptoms (running nose –11-11.2%; nasal congestion –2-20%, rhinorrhea –7.6-16%); however, none of these studies described symptoms of loss of smell.

Radiological features of children and adolescents with COVID-19

The most common radiographic features were ground glass opacities (prevalence ranged from 27.4% to 61.5%), followed by patchy consolidation and pneumonia, unilateral pneumonia and bilateral pneumonia. Details of each radiological finding are reported in table 2. All the studies have provided features from computer tomographic images; however, one systematic review had presented findings from chest X-ray as well where patchy lesions, ground glass opacities and consolidation appeared as distinct features. Considerable proportion of patients (35.7% - Nino et al., 2020; 23% - Hoang et al., 2020) appeared normal on chest x-ray examination Imaging techniques in some cases proved to be an effective diagnostic too even in absence of clinical signs and symptoms.

Laboratory findings of children and adolescents with COVID-19

Current evidence synthesis showed that similar to adults, in pediatric patients also numerous biochemical markers were found altered. Commonly reported abnormal laboratory findings included leucopenia, leukocytosis, thrombocytosis, thrombocytopenia, elevated- lactate dehydrogenase, creatine-kinase MB, C-reactive protein and D-dimer. Rise in C-reactive protein, lactate dehydrogenase and D-dimer levels were ranging from 14-54%, 12.2-50% and 0.3-67% respectively. Comprehensive list of laboratory associates of COVID-19 in pediatrics are presented in table 2. However, limited reviews (44%; 17 out of 38) provided details of laboratory markers and there was significant heterogeneity in terms of type of marker used for assessment.

Transmission, treatment and outcomes

Disease transmission in this population was majorly through household contacts with relatively low severity index. Children and adolescent patients with COVID-19 had a good prognosis with recovery within 1 to 2 weeks of disease onset. Commonly, cases were treated with interferon-alpha, oxygen therapy, and antibiotics such as Azithromycin.[11,12,22] Steroid treatment using Methyl prednisone was also noted in some studies in the review conducted by Bhuiyan and colleagues.[11] Critical illness in children manifests with severe pneumonia characterized by oxygen concentrations (<92%), autoinflammatory shock, and respiratory distress which were treated with mechanical ventilation, anti-viral (Interferon and Oseltamivir) and immunomodulating regimens. Meta-analysis of the quantitative data presented by 18 studies showed cumulative pooled proportion of mortality as 0.12% (95% CI: 0.0356 to 0.246; random effect model) (figure 2B). This meta-analysis showed higher heterogeneity but lack of significant publication bias.

Key findings from each review were documented and summary observations are presented in table 3. Reviews reported lack of data and heterogeneity as major limitations.

DISCUSSION

Current umbrella review was planned to assist some critical policy decisions: 1) preparedness of countries expecting next waves of the diseases for protecting pediatric population 2) vaccine prioritization strategies for pediatric population.

To the best of our knowledge this is one of the first and most updated umbrella review providing comprehensive view of all the aspects of COVID-19 infections in pediatric patients. Brief overview of gaps in current knowledge, key insights provided by present umbrella review,

strength, limitation and potential policy implications of the same are summarize as figure 3. Review findings postulated that COVID-19 in children and adolescents is an uncomplicated febrile disease of the upper or lower respiratory tract. Transmission trend analysis showed that majority of the pediatric patients developed the infection after close contact with the adult infected family member. Our previous study (Shah et al) presented secondary attack rate (SAR) in household contacts of pediatric index cases as 1.7% (95% CI: 0.74–4%), which was considerably lower than SAR in adults.[47] Shah et al also showed that as compared to children, adolescents (12-18 years of age) are more susceptible to the infection, comprising of 74% of the total pediatric cases. However, this needs to be interpreted with caution as 1) significant proportion of pediatric patients are asymptomatic and hence might be escaped from testing in spite of being an index case in the family,[11] 2) majority of the screening program did not included children and adolescents, so milder cases recovering without any medical attention might also be missed, and 3) mean incubation period in children was longer than adult contributing in difficult identification of index case. The review findings also suggested that the possibility of intrauterine vertical transmission is low and hence infection from positive mother to infant is rare.[9] Similarly, there was no report of disease transmission from new born to mothers. We found that though children are also susceptible to COVID-19 infection, serious complications or death is sporadical with cumulative mortality of 0.12% (range 0-0.99%). Similar to mortality statistics, requirement of intensive care unit and ventilation was lower in this group.[39] That resulted in faster recovery with shorter hospital stay and lesser severity of the disease in pediatrics.

Meta-analysis found that significant proportion of pediatric patients were asymptomatic with prevalence ranging from 14 – 43% (Cumulative prevalence – 21.17%). Most common symptoms are fever and coughing which needs to be monitored. Furthermore, children and adolescents are

potential carriers, like adults, and can transmit the infection among the population.[12] Therefore, early identification and intervention in pediatric patients with COVID-19 are essential in order to control the pandemic. One study conducted by Rodriguez-Gonzalez et al., showed that cardiovascular complications are very common in pediatric COVID patients and can be fatal in case of pre-existing cardiac disease.[18] Authors recommended to keep a strict monitoring of the early symptoms in this subgroup of population in order to avoid preventable complications such as pediatric multisystem inflammatory syndrome, arrhythmia, pulmonary hypertension, heart failure, and even fulminant myocarditis. Similar to Rodriguez-Gonzalez et al other recent research also demonstrated that these underlying co-morbidities predispose patients to critical conditions during COVID-19.[18,40]

Nearly half of the included systematic reviews provided radiographic features of the COVID-19 positive children and adults and it was found that though relatively milder majority of the imaging features are similar to adults. Hoang et al[20] and Nino et al[33] – authors reported substantial number of normal chest X-rays and CT in COVID infected pediatric patients and hence suggested to interpret the radiological characteristics with caution due to overlapping with co-infection. Nimo et al also emphasized on the need of lung imaging framework for a novel scoring system using computer-assisted methods for early and accurate diagnosis of the disease. Absence of conventional imaging features of viral respiratory features such as increased perihilar markings and hyperinflation was also noted by the authors. However, in contrast to Hoang et al, Nino et al suggested that in pediatric cases with COVID-19, the CT abnormalities are distinct than other viral respiratory infections and can be used for early diagnosis of the disease. Studies pointed that information regarding true sensitivity and specificity of CT or X-ray for COVID-19 might be lower

than adult population due to 1) lack of strong features on imaging and 2) lack of studies comparing the images in RT-PCR negative patients.

Profile of laboratory biomarkers was assessed and found to be relatively milder especially in case of inflammatory markers. Though found to alter, a lot of heterogeneity was observed in the case of D-dimer, lactate dehydrogenase and C-reactive protein which are hallmark of COVID-19 infection in adults. Some studies have also indicated myocardial damage in pediatric patients as reflected through elevated CK-MB and lactate dehydrogenase.[18] Albeit, unlike other characteristic features, evidence related to COVID-19 associated biomarkers are heterogenous and needs to be interpreted with caveat.

The article also intended to compare clinical symptoms, radiological and laboratory findings of children with adults. In contrast to adults, most children were asymptomatic,[9,11,13,15,20,26,27,28,31,34,35,45] and those with symptoms, commonly observed symptoms were fever, cough and nasal symptoms, which were in accordance with other studies. [48,49,50] Unlike adults, where the substantial number of cases reported to have loss of smell, none of the study selected for the review reported this observation among children. Imaging findings in children were milder and more focal than adults, typically as ground-glass opacities, consolidations with unilateral lower-lobe predominance, and bronchial wall thickening.[25,37,48,49] As indicated by few previous studies the hallmark biochemical markers such as D-dimer and C-reactive protein were also found to increase in children similar to adults.[48,49] However, only two studies [10,22] reported an increase in serum ferritin level among pediatrics, which was commonly elevated in adults. Though numerous characteristic biochemical changes were observed in pediatric COVID patients, none of the study presented observations related to eosinophilia in contrast to adult patients, where it is a

consistent associate of poorer outcome. A recent study published by Licari et al[51] showed that as compared to allergic children, COVID-19 infected children had lower levels of eosinophils ($p<0.0001$). The authors also reported that 12.5% of the pediatric COVID patients had absolute absence of eosinophils. Though this also substantiates the need for further larger studies where COVID infected children are compared with non-COVID patients and the association of the biomarker is investigated using more robust methods.

Four systematic reviews[12, 18, 21, 45] have mentioned details of multisystem inflammatory syndrome (MIS-C) in children infected with COVID-19. There is heterogeneity in terms of prevalence of MIS-C with some reporting it as a rare (0.2 – 0.6%) event[18] and some providing prevalence of 15%[45]. Hoste et al.[21] presented characteristic features of MIS-C in pediatric through systematic review of 68 records. The authors reported that MIS-C in COVID patients is a severe condition, though have favorable short-term outcome coupled with low mortality rate. The disease was frequent in males and black population. However, need for long-term follow up of these cases were highlighted by the study.

So, with this review it is evident that deeper understanding of symptom, clinical and laboratory markers profiling of COVID-19 is extremely vital for pediatric population as nucleic acid test – RT-PCR has its own limitation and is influenced by numerous confounders. Unlike adults where clinical, radiographic and biomarker changes are profound, in children the disease is milder with less specific determinants and identifiers. This might misinterpret the disease as less infective and virulent for pediatrics and hence more robust strategies of screening, diagnosis and management are needed.

Strength and limitations

The major strength of our study is that it is the first global, comprehensive evidence synthesis covering all the aspects of epidemiological and clinical characteristics of COVID-19 infection in children and adolescents. This holds important policy implication especially in the time when we are gradually observing a shift in the age of COVID-19 infection. We were able to include systematic reviews conducted right from initial time of the pandemic to very recent ones. That helped us to map all the transition trends in the disease transmission. Additionally, this allowed us to include a large number of children and adolescents in our analysis further strengthening the review. The umbrella review was conducted using rigorous methodology and hence evidence synthesized can contribute significantly in guiding the policy decisions.

This review has several limitations also. Firstly, only few studies provided detailed information on prevalence, clinical outcome of the disease, age wise clinical manifestation, which could be extracted for the pooled analysis. This has limited our meta-analysis to only two variables. Many of the included studies in systematic reviews had compromised methodological quality, low sample size, and variation in reporting of findings. About 44.7% of total systematic review studies were rated critically low in AMSTAR tool and of these, 50% studies did not assess methodological quality of selected studies. Serious risk of bias was present in about 34.2% of the total studies as per GRADE tool. These introduced significant heterogeneity in the evidence synthesis especially meta-analysis. Secondly, most studies included in systematic reviews were dominantly from China followed by USA and data from other countries are still limited. This limits the generalizability of findings. Third, none of the studies reported COVID-19 in race, indigenous or ethnic minority paediatric populations. Hence, differences in epidemiological, clinical and biomarker profile could not be evaluated. Fourth, this review, though explicitly addressed COVID-19 features in pediatrics,

some reviews have extended age limits, including patients of 18-21 years also. Finally, in few cases, we could not eliminate those patients due to the unavailability of actual data.

CONCLUSION

The current umbrella review provides most updated information regarding characteristics of COVID-19 infection in pediatrics. Important findings of the review are: 1) The disease is relatively less infectious and fatal in pediatrics; however, these statistics are influenced by numerous factors and hence a robust mechanism to identify early signs and symptoms are needed. 2) Children with co-morbid conditions are vulnerable and are susceptible to poorer outcomes. 3) Often biomarkers and radiological findings are overlapped with other viral infections in children and hence dependency on single diagnostic and screen test should be replaced with multiple diagnostic algorithms. 4) Data from larger studies representing various geographic locations are needed to improve generalizability of the findings.

Conflicts of Interest

None declared.

Funding source

No external funding is involved.

References:

1. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. *Acta Biomed*. 2020;91(1):157-160.

2. Dhand R, Li J. Coughs and Sneezes: Their role in transmission of respiratory viral infections, including SARS-CoV-2. *Am J Respir Crit Care Med*. 2020;202(5):651-659.

3. Jayaweera M, Perera H, Gunawardana B, Manatunge J. Transmission of COVID-19 virus by droplets and aerosols: A critical review on the unresolved dichotomy. *Environ Res*. 2020; 188:109819.

4. Ciuca IM. COVID-19 in children: An ample review. *Risk Manag Healthc Policy*. 2020; 13:661-669.

5. Milani GP, Marchisio P, Rocchi A, Bertolozzi G, Furlan L, La Vecchia A, et al. Frequency of asymptomatic carriers of SARS-CoV-2 among children and adults after school reopening. *Ital J Pediatr. 2021;* 47(1):1-4.

6. American Academy of Pediatrics. Children and COVID-19: state-level data report. Accessed October. 2020 Oct;6. https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/

7. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011; 64:383-394.

8. Jung JH, Dahm P. Reaching for the stars - rating the quality of systematic reviews with the Assessment of Multiple Systematic Reviews (AMSTAR) 2. *BJU Int* 2018; 122:717-718.

9. Assaker R, Colas AE, Julien-Marsollier F, Bruneau B, Marsac L, Greff B, et al. Presenting symptoms of COVID-19 in children: a meta-analysis of published studies. *Br J Anaesth*. 2020;125(3): e330-e332.

10. Badal S, Thapa Bajgain K, Badal S, Thapa R, Bajgain BB, Santana MJ. Prevalence, clinical characteristics, and outcomes of pediatric COVID-19: A systematic review and meta-analysis. *J Clin Virol*. 2021; 135:104715.

11. Bhuiyan MU, Stiboy E, Hassan MZ, Chan M, Islam MS, Haider N, et al. Epidemiology of COVID-19 infection in young children under five years: A systematic review and meta-analysis. *Vaccine*. 2021;39(4):667-677.

12. Li B, Zhang S, Zhang R, Chen X, Wang Y, Zhu C. Epidemiological and Clinical Characteristics of COVID-19 in Children: A Systematic Review and Meta-Analysis. *Front Pediatr*. 2020; 8:591132.

13. Castagnoli R, Votto M, Licari A, Brambilla I, Bruno R, Perlini S, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review. *JAMA Pediatr*. 2020;174(9):882-889.

14. Chang TH, Wu JL, Chang LY Clinical characteristics and diagnostic challenges of pediatric COVID-19: A systematic review and meta-analysis. *J Formos Med Assoc*. 2020; 119: 982–989.

15. Christophers B, Gallo Marin B, Oliva R, Powell WT, Savage TJ, Michelow IC. Trends in clinical presentation of children with COVID-19: a systematic review of individual participant data [published online ahead of print, 2020 Sep 17]. *Pediatr Res*. 2020;10.1038/s41390-020-01161-3.

16. Cui X, Zhao Z, Zhang T, Guo W, Guo W, Zheng J, et al. A systematic review and meta-analysis of children with coronavirus disease 2019 (COVID-19). *J Med Virol*. 2020;1–13.

17. Ding Y, Yan H, Guo W. Clinical Characteristics of Children with COVID-19: A Meta-Analysis. *Front Pediatr*. 2020; 8:431.

18. Rodriguez-Gonzalez M, Castellano-Martinez A, Cascales-Poyatos HM, Perez-Reviriego AA. Cardiovascular impact of COVID-19 with a focus on children: A systematic review. *World J Clin Cases*. 2020;8(21):5250-5283.

19. Henry BM, Benoit SW, de Oliveira MH, Hsieh WC, Benoit J, Ballout RA, et al. Laboratory abnormalities in children with mild and severe coronavirus disease 2019 (COVID-19): A pooled analysis and review. *Clin Biochem*. 2020; 81:1-8.

20. Hoang A, Chorath K, Moreira A, Evans M, Burmeister-Morton F, Burmeister F, et al. COVID-19 in 7780 pediatric patients: A systematic review. *EClinicalMedicine.* 2020; 100433.

21. Hoste L, Van Paemel R, Haerynck F. Multisystem inflammatory syndrome in children related to COVID-19: a systematic review [published online ahead of print, 2021 Feb 18]. *Eur J Pediatr*. 2021;1-16.

22. Irfan O, Muttalib F, Tang K, Jiang L, Lassi ZS, Bhutta Z. Clinical characteristics, treatment and outcomes of paediatric COVID-19: a systematic review and meta-analysis [published online ahead of print, 2021 Feb 16]. *Arch Dis Child*. 2021;106(5):440-448.

23. Jahangir M, Nawaz M, Nanjiani D, Siddiqui MS. Clinical manifestations and outcomes of COVID-19 in the paediatric population: a systematic review. *Hong Kong Med J*. 2021;27(1):35-45.

24. Karabay M, Çınar N, Karakaya Suzan Ö, Yalnızoğlu Çaka S, Karabay O. Clinical characteristics of confirmed COVID-19 in newborns: a systematic review [published online ahead of print, 2020 Nov 19]. *J Matern Fetal Neonatal Med*. 2020;1-12.

25. Katal S, Johnston SK, Johnston JH, Gholamrezanezhad A. Imaging Findings of SARS-CoV-2 Infection in Pediatrics: A Systematic Review of Coronavirus Disease 2019 (COVID-19) in 850 Patients. *Acad Radiol*. 2020;27(11):1608-1621.

26. Kumar J, Meena J, Yadav A, Yadav J. Radiological Findings of COVID-19 in Children: A Systematic Review and Meta-Analysis [published online ahead of print, 2020 Jul 21]. *J Trop Pediatr*. 2020; fmaa045.

27. Liu C, He Y, Liu L, Li F, Shi Y. Children with COVID-19 behaving milder may challenge the public policies: a systematic review and meta-analysis. *BMC Pediatr*. 2020; 20:410.

28. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr*. 2020;109(6):1088-1095.

29. Mansourian M, Ghandi Y, Habibi D, Mehrabi S. COVID-19 infection in children: A systematic review and meta-analysis of clinical features and laboratory findings. *Arch Pediatr*. 2021;28(3):242-248.

30. Mantovani A, Rinaldi E, Zusi C, Beatrice G, Saccomani MD, Dalbeni A. Coronavirus disease 2019 (COVID-19) in children and/or adolescents: a meta-analysis. *Pediatr Res*. 2021;89(4):733-737.

31. Mehta NS, Mytton OT, Mullins EW, Fowler TA, Falconer CL, Murphy OB, et al. SARS-CoV-2 (COVID-19): What do we know about children? A systematic review. *Clin Infect Dis*. 2020; 71(9):2469-79.

32. Mustafa NM, A Selim L. Characterisation of COVID-19 Pandemic in Paediatric Age Group: A Systematic Review and Meta-Analysis. *J Clin Virol*. 2020; 128:104395.

33. Nino G, Zember J, Sanchez-Jacob R, Gutierrez MJ, Sharma K, Linguraru MG. Pediatric lung imaging features of COVID-19: A systematic review and meta-analysis. *Pediatric Pulmonology*. 2020;1–12.

34. Patel NA. Pediatric COVID-19: Systematic review of the literature. *Am J Otolaryngol*. 2020; 41:102573.

35. Qi K, Zeng W, Ye M, Zheng L, Song C, Hu S, et al. Clinical, laboratory, and imaging features of pediatric COVID-19: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2021;100(15): e25230.

36. Saleem H, Rahman J, Aslam N, Murtazaliev S, Khan S. Coronavirus Disease 2019 (COVID-19) in Children: Vulnerable or Spared? A Systematic Review. *Cureus*. 2020;12(5): e8207.

37. de Souza TH, Nadal JA, Nogueira RJN, Pereira RM, Brandão MB. Clinical manifestations of children with COVID-19: A systematic review. *Pediatric Pulmonology*. 2020; 55:1892–1899

38. Streng A, Hartmann K, Armann J, Berner R, Liese JG. COVID-19 in hospitalized children and adolescents. [published online ahead of print, 2020 Apr 21]. *Monatsschr Kinderheilkd*. 2020;1-12.

39. Di Toro F, Gjoka M, Di Lorenzo G, De Seta F, Maso G, Risso FM, et al. Impact of COVID-19 on maternal and neonatal outcomes: a systematic review and meta-analysis [published online ahead of print, 2020 Nov 1]. *Clin Microbiol Infect*. 2020.

40. Tsankov BK, Allaire JM, Irvine MA, Lopez AA, Sauvé LJ, Vallance BA, et al. Severe COVID-19 infection and pediatric comorbidities: A systematic review and meta-analysis, *Int. J. Infect. Dis* 2020.

41. Viner RM, Mytton OT, Bonell C, Melendez-Torres GJ, Ward J, Hudson L, et al. Susceptibility to SARS-CoV-2 Infection among children and adolescents compared with adults: A systematic review and meta-analysis [published online ahead of print, 2020 Sep 25]. *JAMA Pediatr*. 2020; e204573.

42. Walker KF, O'Donoghue K, Grace N, Dorling J, Comeau JL, Li W, et al. Maternal transmission of SARS-COV-2 to the neonate, and possible routes for such transmission: a systematic review and critical analysis. *BJOG*. 2020; 127:1324-1336.

43. Wang Z, Zhou Q, Wang C, Shi Q, Lu S, Ma Y, et al. Clinical characteristics of children with COVID-19: a rapid review and meta-analysis. *Ann Transl Med*. 2020; 8(10):620.

44. Williams N, Radia T, Harman K, Agrawal P, Cook J, Gupta A. COVID-19 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review of critically unwell children and the association with underlying comorbidities [published online ahead of print, 2020 Sep 10]. *Eur J Pediatr*. 2020;1-9.

45. Yasuhara J, Kuno T, Takagi H, Sumitomo N. Clinical characteristics of COVID-19 in children: A systematic review. *Pediatr Pulmonol*. 2020;55(10):2565-2575.

46. Yoon S, Li H, Lee KH, Hong SH, Kim D, Im H, et al. Clinical characteristics of asymptomatic and symptomatic paediatric coronavirus disease 2019 (COVID-19): A Systematic Review. *Medicina (Kaunas)*. 2020; 56(9):474.

47. Shah K, Kandre Y, Mavalankar D. Secondary attack rate in household contacts of COVID-19 paediatric index cases: a study from Western India [published online ahead of print, 2021 Jan 18]. *J Public Health (Oxf)*. 2021; fdaa269.

48. Zhang Y, Xie RM, He YL, Xing LH, Dong L, Zhang JZ, et al. Clinical and imaging features of pediatric COVID-19. *Ital J Pediatr*. 2020; 46(1): 1-9.

49. Chen A, Huang JX, Liao Y, Liu Z, Chen D, Yang C, et al. Differences in clinical and imaging presentation of pediatric patients with COVID-19 compared to adults. *Radiology: cardiothoracic imaging*. 2020;2(2):e200117.

50. Du W, Yu J, Wang H, Zhang X, Zhang S, Li Q, et al. Clinical characteristics of COVID-19 in children compared with adults in Shandong Province, China. *Infection*. 2020;48(3):445-452.

51. Licari A, Votto M, Brambilla I, Castagnoli R, Piccotti E, Olcese R, et al. Allergy and asthma in children and adolescents during the COVID outbreak: what we know and how we could prevent allergy and asthma flares. *Allergy*. 2020;75(9):2402-5.

Table 1: Characteristic details of the included systematic reviews and meta-analysis

Sr. No	Authors	Title	Country	Study Population	Study period	Asymptomatic (%)	Mortality (N)
1	Assaker et al., 2020[9]	Presenting symptoms of COVID-19 in children: a meta-analysis of published studies	China, Malaysia, Spain, Italy, and the USA	Children (age not specified)	03-May-20	16%	0
2	Badal et.al.,2021[10]	Prevalence, clinical characteristics, and outcomes of pediatric COVID-19: A systematic review and meta-analysis	USA, Canada	Pediatric (<21 years)	until June 16, 2020	13%	5
3	Bhuiyan et al., 2020[11]	Epidemiology of COVID-19 infection in young children under five years: A systematic review and meta-analysis	Multi country	Children under five years	Until June 4, 2020	43%	1
4	Bingbing Li et al, 2020[12]	Epidemiological and Clinical Characteristics of COVID-19 in	China, USA, Spain, Malaysia	Younger than 18 years old	January 1, 2020 and May 7, 2020	23%	70

		Children: A Systematic Review and Meta-Analysis					
5	Castagnoli et al., 2020[13]	Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents A Systematic Review	China, Singapore	children and adolescents (age ≤19 years)	December 1, 2019, to March 3, 2020	Not Reported	1
6	Chang et al., 2020[14]	Clinical characteristics and diagnostic challenges of pediatric COVID-19: A systematic review and meta-analysis	Taiwan	Younger than 18 years old	January 2020 to February, 2020	26%	0
7	Christophers et al., 2020[15]	Trends in clinical presentation of children with COVID-19: a systematic review of individual participant data	China, Italy, United States, Iran, and Malaysia	Older than 1 month and younger than 19 years	Between December 8, 2019 and April 19, 2020.	21%	0

8	Cui et al., 2020[16]	A systematic review and meta-analysis of children with coronavirus disease 2019 (COVID-19)	Singapore, Korea, Spain, America, Iranian, China.	Under 18 years old	From 25 December 2019 to 30 April 2020	33%	0
9	Ding et al., 2020[17]	Clinical characteristics of children with COVID-19: A meta-analysis	China	0–17 years	January 1, 2020 to April 1, 2020,	17.40%	0
10	Rodriguez-Gonzalez et al., 2020[18]	Cardiovascular impact of COVID-19 with a focus on children: A systematic review	Spain	Children (age not specified)	January 1st, 2020 until July 31st, 2020	Not Reported	0
11	Henry et al., 2020[19]	Laboratory abnormalities in children with mild and severe coronavirus disease 2019 (COVID-19): A pooled analysis and review	China, USA, Italy	0- 17.5 Years	December 1, 2019 to May 1, 2020	Not Reported	Not Reported

12	Hoang et al., 2020[20]	COVID-19 in 7780 pediatric patients: A systematic review	Global	Upper limit of age to 21 years	January 24th to May 11th, 2020.	19.30%	7
13	Hoste et al.,2021[21]	Multisystem inflammatory syndrome in children related to COVID-19: a systematic review	Belgium	0–21 years of age	December 31, 2019, to August 13, 2020	Not Reported	0
14	Irfan et al., 2021 [22]	Clinical characteristics, treatment and outcomes of paediatric COVID-19: a systematic review and meta-analysis	Canada, China, Australia, Pakistan	0–19 years old	from 1 December 2019 to 8 January 2021	13.10%	0
15	Jahangir et al.,2021[23]	Clinical manifestations and outcomes of COVID-19 in the paediatric population: a systematic review	Pakistan	Aged 0-19 years	1 December 2019 until 9 April 2020	Not Reported	Not Reported

16	Karabay et al., 2020[24]	Clinical characteristics of confirmed COVID-19 in newborns: a systematic review	Turkey	Newborns with COVID-19 that confirmed within 28 days of birth are included.	20th August and 23rd September 2020	17.64%	Not Reported
17	Katal et al.,2020[25]	Imaging Findings of SARS-CoV-2 Infection in Pediatrics: A Systematic Review of Coronavirus Disease 2019 (COVID-19) in 850 Patients	USA	<18 years	Conducted on April 5, 2020 and updated on June 10, 2020.	Not Reported	Not Reported
18	Kumar et al., 2020[26]	Radiological Findings of COVID-19 in Children: A Systematic Review and Meta-Analysis	China, Italy, Lebanon	Aged <19 years.	01 December 2019 and 20 May 2020	27.83%	Not Reported
19	Liu et al., 2020[27]	Children with COVID-19 behaving milder may challenge the public	China, Italy, United States,	0–19 years	From December 12,	18.90%	4

		policies: a systematic review and meta-analysis	Canada, Spain, Rome		2019 to May 10, 2020		
20	Ludvigsson et al., 2020[28]	Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults	Sweden	0–19 years		Not Reported	Not Reported
21	Mansourian et al, 2020[29]	COVID-19 infection in children: A systematic review and meta-analysis of clinical features and laboratory findings	China, Iran, the United States and Spain	<18 Years	Until April 14, 2020	Not Reported	Not Reported
22	Mantovani et al., 2020[30]	Coronavirus disease 2019 (COVID-19) in children and/or adolescents: a meta-analysis	Italy	Children (age not specified)		Not Reported	Not Reported
23	Mehta et al., 2020[31]	SARS-CoV-2 (COVID-19): What do we know about children? A systematic review	Predominantly China	Aged under 18 years	Up to 9th March, 2020	Not Reported	Not Reported

24	Mustafa and Selim, 2020[32]	Characterisation of COVID-19 Pandemic in Paediatric Age Group: A Systematic Review and Meta-Analysis	UK and Egypt	0-12 years	Up to 2nd April 2020	Not Reported	Not Reported
25	Nino et al., 2020[33]	Pediatric lung imaging features of COVID-19: A systematic review and meta-analysis	USA	0–18 years of age	December 1, 2019 to July 11, 2020	Not Reported	Not Reported
26	Patel, 2020[34]	Pediatric COVID-19: Systematic review of the literature	USA	0–18 years of age	On April 10, 2020	14.90%	5
27	Qi et al.,2021[35]	Clinical, laboratory, and imaging features of pediatric COVID-19: A systematic review and meta-analysis	China	0–18 years of age	until December 14, 2020	27.70%	0
28	Saleem et al., 2020[36]	Coronavirus Disease 2019 (COVID-19) in Children: Vulnerable or Spared? A Systematic Review	USA	Pediatric patients (age not mentioned)	Not reported	Not Reported	Not Reported

29	Souza et al., 2020[37]	Clinical manifestations of children with COVID-19: A systematic review	China, Italy, Iran, Singapore, Korea, Vietnam	younger than 18 years old	December 1st 2019 and April 6th 2020	14.20%	1
30	Streng et al., 2020[38]	COVID-19 in hospitalized children and adolescents A systematic review of published case series (as of March 31, 2020) and first data from Germany	China	Infants, Children, adolescents (age not mentioned)	Until March 31, 2020	14%	2
31	Toro et al., 2020[39]	Impact of COVID-19 on maternal and neonatal outcomes: a systematic review and meta-analysis	Italy	Pregnant Women and neonates	Until May 8, 2020	Not Reported	Not Reported
32	Tsankov et al., 2020[40]	Severe COVID-19 Infection and Pediatric Comorbidities: A Systematic Review and Meta-Analysis	USA, China, Italy, Spain, France, United Kingdom, Iran, Austria, Brazil,	Below 21 years of age.	January 1st to October 5th, 2020	Not Reported	Not Reported

			India, Turkey, Uruguay				
33	Viner et al., 2020[41]	Susceptibility to SARS-CoV-2 Infection Among Children and Adolescents Compared with Adults A Systematic Review and Meta-analysis	Spain, USA, UK, China, Italy, France	Younger than 20 years	Until July 28, 2020	Not Reported	Not Reported
34	Walker et al., 2020[42]	Maternal transmission of SARS-COV-2 to the neonate, and possible routes for such transmission: A systematic review and critical analysis	Global	Neonates	September 2019 and June 2020	Not Reported	Not Reported
35	Wang et al., 2020[43]	Clinical characteristics of children with COVID-19: a rapid review and meta-analysis	China	aged <18 years	Until March 31, 2020	19%	Not Reported

36	Williams et al., 2020[44]	COVID-19 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review of critically unwell children and the association with underlying comorbidities	Not Reported	under the age of 18	December 1st 2019 to 31st May 2020	Not Reported	17
37	Yasuhara et al., 2020[45]	Clinical characteristics of COVID-19 in children: A systematic review	USA	age <18 years old	Until 20 June 2020	Not Reported	Not Reported
38	Yoon et al., 2020[46]	Clinical Characteristics of Asymptomatic and Symptomatic Pediatric Coronavirus Disease 2019 (COVID-19): A Systematic Review	China, Europe, Malaysia, Korea, USA, Vietnam, Singapore	Children and adolescents (age not mentioned)	From January, 2020; end date not specified	32.27%	Not Reported

Table 2: Symptomatology, key laboratory and radiographic findings of included studies

Sr. No.	Authors	Symptoms (Pooled Prevalence)	Radiographic findings (Pooled Prevalence)	Laboratory findings (Pooled Prevalence)
1	Assaker et al., 2020[9]	Fever: 48% Cough: 40% Sneezing: 23% Rhinorrhoea:16% Headache: 13% Myalgia: 14% Sore throat: 14% Diarrhoea or constipation: 10%	Not reported	Not reported
2	Badal et.al.,2021[10]	Asymptomatic: 13% Headache: 67% Fever: 55% and Cough: 45%	Normal: 33% Consolidation: 29% Ground glass opacification (GGO): 36%	Ferritin 26 %, Procalcitonin 25%, CRP 19 %
3	Bhuiyan et al., 2020[11]	Asymptomatic: 5%, Fever: 38%, Upper respiratory symptoms: 35%, Gastrointestinal symptoms: 7.7%, and	Not reported	Not reported

		Mild or moderate symptoms: 95%		
4	Bingbing Li et al, 2020[12]	Mild to moderate symptoms: 66% Fever: 47% and Cough: 42%	Not reported	Virus particles in their stool: 75% Neutropenia: 34% Lymphocytosis: 26%
5	Castagnoli et al., 2020[13]	Not reported	Not reported	Decreased neutrophil count: 38% Elevated C-reactive protein: 18% Procalcitonin :26% Lactate Dehydrogenase: 28% Lymphopenia: 17%
6	Chang et al., 2020[14]	Symptomatic children: 26% Fever: 59% Cough: 46% and Gastrointestinal symptoms: 12%	Ground glass opacities: 48% Patchy consolidation: 31%	Lymphopenia:32%
7	Christophers et al., 2020[15]	Asymptomatic: 21% Fever: 62% and Cough: 32%	Ground-glass opacities: 62.5%	Elevated white blood cell count :10.4% Elevated ESR :7.2% Elevated C-reactive protein:24.8%

		Other reported symptoms were Headache, Vomiting, Diarrhea, underlying seizure disorders.	Consolidation: 11.2% Pneumonia: 10.4% Patchy shadows: 10.4% Vomiting: 8% Bronchitis: 1.6% Perihilar opacities: 1.6%	Elevated white blood cell counts in children: 6.5% Elevated white blood cell counts in adolescents: 20% Thrombocytosis: 3.3% Thrombocytopenic: 1.6% Elevated lactate dehydrogenase: 12.2% Elevated D-dimer: 6.5%
8	Cui et al., 2020[16]	Fever: 51% Cough: 41% and Vomiting: 33%	Normal images: 41% Ground-glass opacity: 36%	Normal white blood cell 69%, lymphopenia 16% and elevated creatine-kinase MB 37%
9	Ding et al., 2020[17]	Fever: 51.2% Cough: 37.0% Pneumonia: 66.7%	Ground-glass opacities: 53.9%	Leukopenia/lymphopenia: 28.9% Elevated creatine kinase: 20.1%
10	Rodriguez-Gonzalez et al., 2020[18]	Gastrointestinal Symptoms: 100%	Not reported	Not reported

11	Henry et al., 2020[19]	Not reported	Not reported	Elevated WBC: 13% Elevated Neutrophils: 10% Elevated Lymphocytes: 18% Elevated Leukocyte: 13% Elevated C-reactive protein: 18% Elevated ALT:15% Elevated AST:25% Elevated D-dimer: 20% Elevated Procalcitonin:26% Relatively few laboratory changes in children with mild disease.
12	Hoang et al., 2020[20]	Asymptomatic: 19.3% Fever: 59.1% Cough: 55.9% Rhinorrhoea, nasal congestion: 20% Myalgia, fatigue: 18.7% Sore throat: 18.2% Shortness of breath, dyspnea: 11.7% Abdominal pain, diarrhea: 6.5 Vomiting, nausea:	Chest x-ray findings Normal: 23.6% Patchy lesions: 21.0% Ground glass opacities: 6% Consolidation:2.4%	Decreased Neutrophils: 44.4% Elevated Lymphocytes: 39.9% D-dimer: 0.3%

		5.4% Headache, dizziness: 4.3% Pharyngeal erythema:3.3%	Computed tomography findings Normal:18.9% Ground glass opacities: 32.9% Patchy lesions: 10.5 Consolidation:6.5%	
13	Hoste et al.,2021[21]	Fever: 99.4%, Gastrointestinal symptoms: 85.6%, Abdominal pain: 58.4%, Vomiting: 57.5%, Diarrhea: 50.4% (Pooled prevalence is not presented)	Not reported	Not reported
14	Irfan et al., 2021 [22]	Fever: 63.3%, Cough: 33.7%, Nausea or vomiting: 20.0%, and Diarrhea: 19.6%	Ground glass opacities 27.4%	C-Reactive Protein (CRP) 54.2%, Serum-ferritin 46.7%, lactate dehydrogenase (LDH) 36.5%, and d-dimers 35.2%

15	Jahangir et al.,2021[23]	Not reported	Not reported	Not reported
16	Karabay et al., 2020[24]	Respiratory difficulty: 74% Fever: 63% Diarrhea and feeding intolerance and abdominal distension: 50% of newborn.	Not reported	Leucopenia: 11% Lymphopenia: 35% Elevated monocytes concentrations: 12.5% Elevated D dimer concentrations: 67% Elevated ALT: 9% Elevated AST: 58% Elevated PCT: 10% Decreased White blood cell concentrations: 19% Elevated R C-reactive protein: 22%.
17	Katal et al.,2020[25]	Not reported	Not reported	Not reported
18	Kumar et al., 2020[26]	Clinically asymptomatic:19%	Ground glass opacity: 39% Patchy shadows: 44%, Halo sign: 26% Nodules: 25% Consolidation: 23%	Not reported

			Prominent bronchiovascular markings:17% Interstitial infiltration :12% Bronchial wall thickening :11%	
19	Liu et al., 2020[27]	Asymptomatic: 19% Fever: 52.7% Cough: 41.9%	Ground-glass opacity: 35.7% Unilateral compromised lesions: 28.2% Consolidation: 10.5%	Lymphopenia :10.8% Lymphocytosis: 15.4% C-Reactive Protein: 12.3% AST: 10.9% ALT: 6.5% LDH: 23.0%
20	Ludvigsson et al., 2020[28]	Asymptomatic: 15.8% Cough: 48.5% Pharyngeal erythema: 46.2% Tachycardia: 42.1% Tachypnoea: 28.7% Diarrhea: 8.8% Fatigue: 7.6% Rhinorrhea: 7.6% Vomiting: 6.4%	Ground-glass opacities: 33.33% Bilateral patchy shadowing: 12.3%	Lymphocytopenia: 46% Neutropenia :52%
21	Mansourian et al, 2020[29]	Fever: 46% Cough: 37% Diarrhea: 19% Pharyngalgia: 13%	Not reported	RT-PCR test positive results: 43% Low oxygen saturation: 38%

				Elevated D-dimer levels: 36%
22	Mantovani et al., 2020[30]	Fever: 47% Cough: 37% Diarrhea: 4% Nasal congestion: 2% Dyspnea: 1% Mild symptoms: 79% Critical cases: 4%	Unilateral involvement: 26.4% Bilateral involvement: 16% Interstitial pneumonia: 9%	Not reported
23	Mehta et al., 2020[31]	Pooled prevalence not reported. Majority of the cases were asymptomatic. Fever, cough, sore throat, nasal congestion were present in some patients.	Not reported	Not reported
24	Mustafa and Selim, 2020[32]	Cough: 49% Fever: 47% Sore throat: 36% Vomiting or diarrhea: 17% Rhinorrhea: 9%	Not reported	Lymphopenia: 21% Increased Procalcitonin: 28% Leucopenia: 19% Leukocytosis: 11%. Lymphocytosis: 5% Thrombocytopenia: 4% Elevated C-reactive protein: 28%

25	Nino et al., 2020[33]	Not reported	Normal chest CT scans: 35.7% Bilateral lesions: 27.7% Ground-glass opacities: 37.2% Consolidations o pneumonic infiltrates: 22.3%	Not reported
26	Patel, 2020[34]	Asymptomatic: 14.9% Cough: 48% Fever: 47% Sore throat/ pharyngitis: 28.6% Nasal congestion:13.7% Vomiting/nausea:7.8% Diarrhea: 10.1% Comorbidities: 21% The most common were asthma, immunosuppression, and cardiovascular disease.	Computed tomography findings Unilateral: 36% Bilateral: 64%	Not reported
27	Qi et al.,2021[35]	Asymptomatic 27.7%, cough 40.6%, Runny nose 11.0%, headache 9.2%, Sore throat 6.8%	Unilateral lesions 29.4%, bilateral lesions 24.7%, and ground-glass opacity 32.9%	Leukopenia 7.3%, C-reactive protein level 14.0%, high LDH level 17.4%, high creatine kinase MB level 43%,

				high AST level 12.3%, and high erythrocyte sedimentation rate were 29.7%
28	Saleem et al., 2020[36]	Not reported	Not reported	Not reported
29	Souza et al., 2020[37]	Fever: 47.5% Cough: 41.5% Pharyngeal erythema: 20.6% Tachycardia: 18.6% Tachypnea: 13.4% Nasal symptoms :11.2% Upper airway infection: 10.9% Diarrhea: 8.1% Nausea/vomiting :7.1% Fatigue: 5.0% Respiratory distress: 3.5%	Computed tomography findings Pneumonia:36.9% Ground-glass opacities:32.7% Patchy shadowings: 31%	Elevated Procalcitonin levels: 49.8% Laboratory markers levels varied widely with some studies reporting normal levels of white blood cells, platelets, C-reactive proteins and liver enzymes.
30	Streng et al., 2020[38]	Pooled prevalence is not presented	Frosted glass-like shadow: 29–60% Spotty shadows:	No abnormalities in the blood count: 66%. Elevated LDH: upto 50%

			31–67% Unilateral pneumonia: 19–40%, Bilateral pneumonia:12–46% Consolidations with "halo sign": 35%	Elevated D–dimers: upto 50%
31	Toro et al., 2020[39]	Pooled prevalence is not presented	Not reported	Not reported
32	Tsankov et al., 2020[40]	Pooled prevalence is not presented	Not reported	Not reported
33	Viner et al., 2020[41]	Pooled prevalence is not presented	Not reported	Not reported
34	Walker et al., 2020[42]	Not reported	Not reported	Not reported
35	Wang et al., 2020[43]	Fever: 48% Cough 39% Cough and fever: 30% Diarrhea: 7% Nausea/ vomiting: 6%	Ground-glass opacity: 35% Unilateral pneumonia: 31% Bilateral pneumonia: 28%	Not reported

36	Williams et al., 2020[44]	Not reported	Not reported	Not reported
37	Yasuhara et al., 2020[45]	Asymptomatic: 15% Fever: 64% Cough: 35% Rhinorrhea: 16%	Ground-glass opacity: 54%	Lymphopenia: 33% Elevated D-dimer: 52% C-reactive protein: 40%
38	Yoon et al., 2020[46]	Not reported	Not reported	Not reported

Table 3: Key findings and limitations of included studies

Sr. No.	Authors	Key findings	Limitations
1	Assaker et al., 2020[9]	About 75% of patients had a household contact history. At present, there is a lack of evidence on vertical transmission to neonates born to mothers with COVID-19. Relatively high proportion of asymptomatic patients was noted in the literature. Also, due to specificity in COVID-19 symptoms in children, diagnosis is challenging. Disease severity ranged from mild to moderate (98%) and only 2 children received intensive care.	• Short report with brief description of review (systematic) methodology.
2	Badal et.al.,2021[10]	Study shows that all pediatric age groups are prone to COVID-19 infection with the disease usually having a mild clinical presentation and sequelae. Critical illness and death were extremely rare.	• Studies did not report guidelines for testing and quarantine in children.
3	Bhuiyan et al., 2020[11]	Young children with COVID-19 infection are largely asymptomatic. There is the need for ongoing surveillance to monitor COVID-19 disease epidemiology in this paediatric population, strengthening	• Many geographical regions such as the United States and Europe hada resurgence of COVID-19 cases during a second wave were not included in our review.

		prompt laboratory identification for case isolation and clinical management.	• The study included 26 case reports and hence the data could not be used in meta-analysis.Authors did not find articles reporting COVID-19 in Indigenous or ethnic minority paediatric populations, although these groups of children have a higher risk of respiratory infections.
4	Bingbing Li et al, 2020[12]	The mean age of pediatric cases was 6.48 years, 90% had household contact, and 66% presented with mild to moderate clinical syndromes. The pooled mean incubation period was 9.57 days. The shedding of SARS-CoV-2 in the upper respiratory tract lasted 11.43 days. Authors recommended that the transmissibility of pediatric COVID-19 should not be undermined due to the long incubation period, shedding duration, and mild clinical syndromes. Further cohort or case-control studies are urgently needed to establish the causality between COVID-19 and MIS-C.	• Most studies included in the review were retrospective studies, and some were single-center or pre-printed articles without peer review. • Most of the studies came from China and authors could not assess race or ethnicity. • The diagnosis, infection rates, estimated incubation period were limited to the studies describing symptomatic patients admitted to the hospital. • Authors could not assess more detailed clinical information due to limited data.

5	Castagnoli et al., 2020[13]	Children at any age mainly were reported mild respiratory symptoms or were asymptomatic.	• The research occurred over a brief 3-month period. Second, nearly all the articles came from Chinese reports, as European and US studies in children with COVID-19 were unavailable. • Any possible correlation between viral burden and clinical symptoms was not evaluated. • Studies included in the review were observational designs, and many were simple case series or case reports.
6	Chang et al., 2020[14]	The majority of the patients (98%) were in the mild to moderate category and a clear household contact history was reported. There is no gender difference among the studies	• Detailed case descriptions and clinical courses were limited due to the very early compilation of the data. • There are often multiple viral infections that mimic COVID-19 symptoms.
7	Christophers et al., 2020[15]	Most patients with COVID-19 presented with either no symptoms or a single or non-respiratory symptom.	• The study search strategy across six databases may have excluded some publications published before

		Diagnosing COVID-19 in pediatric patients is challenging due to the wider range of symptomatology and poor correlation of imaging findings with symptomatic disease.	May 15 that were not indexed in databases at the time of the literature review. • Few studies included individual patient details or clinical follow-up; thus, our findings may not reflect the true spectrum of disease or post-infection inflammatory sequelae. • Data were not collected prospectively in most studies, so recruitment bias likely exists. • The majority of the patients were from China during the early phase of the pandemic.
8	Cui et al., 2020[16]	Patients with COVID-19 experience milder illness with atypical clinical manifestations and rare lymphopenia. Among children under 1-year old, critical cases account for 14%.	• Few cohort studies available for inclusion, and most of them come from China. • It's hard to standardize the results of laboratory testing and radiographic imaging from different data sources.

			• More detailed patient information in children under 1-year-old is not available in large sample studies at the time of analysis.
9	Ding et al., 2020[17]	Evidence indicates lower risk of developing COVID-19 among children and have a milder disease than adults.	• Although it is noted that children are at a lower risk of developing COVID-19, the current evidence is not satisfactory. Thus, further investigations are urgently needed, and our data will be continuously updated.
10	Rodriguez-Gonzalez et al., 2020[18]	Although the respiratory illness was the dominant clinical manifestation of COVID-19, cardiovascular issues were emerging as one of the most significant complications of SARS-CoV-2 infection in pediatric patients. Patients with pre-existing cardiovascular diseases and with PMIS accounted respectively for 18% and 12% of pediatric deaths associated with COVID-19 and provided a workup strategy for cardiovascular complications in pediatric patients with COVID-19 infection.	• Very few studies have assessed cardiovascular complications in pediatric COVID-19 patients and more research is needed.

11	Henry et al., 2020[19]	Majority of the patients were from mild disease. The age of patients ranged from 0 to 17.5 years old in these studies, with females accounting for around 43% of the pooled cohort.	• A limited number of studies and pooling of analysis from case reports and case series were major limitations of the review. • A considerable amount of heterogeneity existed among the studies and reasons for the heterogeneity were not clearly described in included studies.
12	Hoang et al., 2020[20]	Co-infections were observed in 5.6% of children and 0.14% of children had multisystem inflammatory syndrome. Children with compromised immunity or with respiratory/cardiac disease comprised the largest subset of COVID-19 children with underlying medical conditions (65%). Overall, children diagnosed with COVID-19 have an excellent prognosis.	• Most studies included were case reports or cases with low number of patients. • Overall, the level of evidence was low.
13	Hoste et al.,2021[21]	PIMS-TS/MIS(-C) is a severe, heterogeneous disease with epidemiological enrichment for males, adolescents, and racial and ethnic minorities. However, mortality rate was low and short-term outcome favourable. Authors recommended long-term follow-up of	Lack data reporting association of co-morbid condition apart from obesity. Contribution of genetic predisposition, prior infections, or immunizations as

		chronic complications and additional clinical research to elucidate the underlying pathogenesis.	underlined factor to multisystem inflammatory syndrome vulnerability are unclear with current data.
14	Irfan et al., 2021 [22]	Children presented mild symptoms. Risk of severity may be increased by risk factors such as contact exposure, comorbidities, young age and male sex.	• Most studies included has a smaller sample size. • Considering Multivariate analysis to identify risk factors for severe infection or adverse outcome in children were not carried out due to lack of individual patient data. • The inclusion of asymptomatic cases could have contributed to underestimating the prevalence of clinical characteristics and optimism in the reporting of outcomes. • Lack of generalizability of the findings to countries with a different socioeconomic profile.
15	Jahangir et al.,2021[23]	Pediatric COVID-19 patients had a better prognosis than adults. Children were likely to become a hidden source of infection, which	• No sufficient evidence to study the probability of intrauterine vertical transmission of COVID-19

		may delay the diagnosis of COVID-19, leading to unfavorable outcomes. Evidence indicated that the probability of intrauterine vertical transmission in neonates was low and close contact was only a plausible explanation for the observed positive results in neonates.	
16	Karabay et al., 2020[24]	The most common symptoms during the neonatal period are respiratory tract symptoms and fever. It has been observed that the COVID-19 infection detected in the neonatal period is not fatal.	• Joint pain and sore throat are not evaluated in newborns. • There was incomplete information in some studies about where and how the fever is measured in newborns, how many degrees Celsius and how long it lasts.
17	Katal et al.,2020[25]	Imaging findings in children were milder and more focal than adults, typically as ground-glass opacities and consolidations with unilateral lower-lobe predominance, which regressed during the recovery time. Authors urged to balance the risk of radiation and the need for chest CT.	• Smaller sample sizes and a limited number of studies reporting radiologic manifestations of COVID- 19 in paediatric population. • Lack of consistency in the CT descriptors terms among the available articles.

			• There may be potential bias in the review due to heterogeneity among CT indication criteria.
18	Kumar et al., 2020[26]	A significant proportion (19%) of clinically asymptomatic children had radiological abnormalities too. Computed Tomography is the most commonly used imaging technique detecting pneumonia before the appearance of clinical symptoms.	• Many of the included studies were limited by sample size, methodological quality and variation in reporting of imaging findings. These might have added significant heterogeneity. • We could not correlate the imaging findings with the disease severity, disease progression and outcomes due to limited data availability
19	Liu et al., 2020[27]	Children were also susceptible to SARS-CoV-2; however, critical cases or deaths were rare.	• Most studies were descriptive and retrospective with a varying range of sample size. • Studies reported high heterogeneity. • Most studies were derived from China. Studies and data from other countries were limited.
20	Ludvigsson et al., 2020[28]	Newborn infants have developed symptomatic COVID-19 and evidence of vertical intrauterine transmission is limited. It was noted	• Authors could not read the full text of some of the identified Chinese studies but had to rely on English

		that deaths were extremely rare. Severe cases have increased levels of procalcitonin and young, very sick infants developed high interleukin-6 levels. Oxygen, inhalational support, providing fluids were suggested treatment of COVID-19 in newborn infants.	language summaries or publications that referenced papers published in Chinese.
21	Mansourian et al, 2020[29]	Presentation of symptoms were mild, prognosis was better and mortality rate was low in children with COVID-19. Authors recognized that children are potential carriers and can transmit the infection among the population. Authors advocated early identification and intervention in pediatric patients with COVID-19.	• Few studies were available and most of them were from China. • More detailed data on patient information, and clinical outcomes were unavailable in most studies included in the review.
22	Mantovani et al., 2020[30]	Children tend to have a mild COVID-19 course with a good prognosis.	• Detailed case descriptions and clinical courses are limited. The long-term outcome and sequelae may need further follow-up. • The treatment strategy in children may need additional debate and caution. • There are more asymptomatic and mild cases, which make diagnosis more challenging.

23	Mehta et al., 2020[31]	Very low fatality rate, with only few severe and critical cases. Though milder course of disease, radiological lung changes are present in both milder and asymptomatic cases. Many of the childhood cases are from familial clusters, with the children identified through contact tracing of adult cases.	• Majority of the data was from China an may be subject to ascertainment bias or selective ascertainment and testing bias towards adults with acute respiratory symptoms. • Many pre-print studies those have not been peer reviewed were included in the review.
24	Mustafa and Selim, 2020[32]	Paediatric patients had a good prognosis with less requirement of intensive care and deaths.	• The sample was taken 36 hours after delivery, so the child could be infected by direct contact • Both cord blood and placenta samples were tested negative for SARS-CoV-2. Vertical transmission could not be ruled out entirely as the negative screening in the cord blood and placenta can be attributed to low viral load at the time of delivery below the PCR detection limit.

25	Nino et al., 2020[33]	Chest Computed Tomography manifestations in children with COVID-19 could be used for early identification and prompt intervention.	• This study could not correlate our findings to clinical manifestations and symptom severity. • A limited number of studies reported their imaging findings related to the patient's symptoms.
26	Patel, 2020[34]	Children may play a role in the community spread of COVID- 19 as they can be asymptomatic carriers of the coronavirus.	• The data from case series may be biased as the whole population is not included. • Many chart reviews were based solely on data of children that were symptomatic and were hospitalized and do not represent the population as a whole.
27	Qi et al.,2021[35]	Children with COVID-19 have relatively mild disease, more asymptomatic infections and a very low rate of severe illness. The results of laboratory tests were only slightly abnormal. Chest CT showed no obvious abnormality in quite a part of cases, and the scope of lung injury was limited.	• Low mortality rate of children with COVID-19, so not enough data for synthesis analysis. • Majority of the studies were from one geographic location. • Substantial amount of heterogeneity among studies.
28	Saleem et al., 2020[36]	Children can get coronavirus in the same way as any other age group. They can be carriers of the coronavirus and can spread corona-virus	• Limited data were available to assess the severity of the infection in that patient population.

		to others. Neonates and infants can easily acquire the infection from family members.	• Most studies were from China. As many of the were not translated into English, authors might have missed out relevant studies.
29	Souza et al., 2020[37]	Symptomatology of COVID-19 in children differed widely compared to adults. Mere fever and respiratory symptoms should not be considered as COVID-19 symptoms in children. The review found that in most cases (63%) CT scan presented abnormalities.	• There is a possibility that data from the same patient might be presented in more than one included study. • Most studies were from China, and may not be generalized for other populations. • Most studies presented results from patients who presented to medical attention and likely to overestimate the severity of illness in children. • Comorbidities or hospitalization rates were not explained.
30	Streng et al., 2020[38]	COVID-19 in hospitalized children and adolescents is an uncomplicated febrile disease of the upper or lower respiratory tract. Serious complications or death is very rare in children.	• Overall, the case series were of very heterogeneous quality. Information on previous illnesses and medication were only partially available.

		Upon discharge, 12 of 15 children (on average after 8 days) still showed radiological abnormalities in control CT of the chest, despite the lack of clinical symptoms.	• In some cases, there was a high proportion of "mild" infections in the case series. • Some of the same patients with previous illnesses, co-infections and critical courses in different studies also makes it difficult to assess their actual frequency. • Therapy attempts with antiviral drugs, did not allow any conclusions drawn about their effectiveness due to the lack of controls.
31	Toro et al., 2020[39]	About 8% of women were admitted to the intensive care unit, whereas 2% neonates required admission to neonatal intensive care unit. Three stillbirths, three neonatal deaths and five maternal deaths were reported. Despite need for critical care in some cases, the clinical course of COVID-19 in most women and children was not severe, and the infection did not significantly influence the pregnancy. There was no	• In many studies' patient information regarding some secondary outcomes were missing or unavailable. • Substantial heterogeneity between studies was found in many studies. • Some studies did not explain heterogeneity by the potential confounders analyzed in the meta-regression analysis

		clinical evidence supporting caesarean delivery. The vertical transmission has not been demonstrated.	
32	Tsankov et al., 2020[40]	Severity of COVID-19 and related mortality were high in children with comorbidities compared to those children without underlying disease	• Whether the admission to the Paediatric Intensive Care Unit was due to underlying comorbidities in some children or COVID-19 was not ascertained as COVID-19 infection was subsequently discovered. • Not able to capture the relative risk that comorbidities other than obesity • Heterogeneity in the studies prevented drawing accurate comparisons between the studies.
33	Viner et al., 2020[41]	Available evidence indicates children and adolescents have lower susceptibility to COVID-19, with an odds ratio of 0.56 for being infected compared with adults	• Data on pediatric population remained limited as data continue to evolve. • Unknown factors related to age, transience of infection or waning of immunity, bias findings were challenging.

34	Walker et al., 2020[42]	Neonatal COVID-19 infection is uncommon. Vaginal delivery, breastfeeding and contact with the mother had not impact on vertical transmission of the disease.	• Investigator bias (towards cases or findings of interest) may exist as most of the studies included in the review were case reports and hospital-based series. • Details of outcome of so many neonatal cases born to COVID-19-positive mothers have not been fully reported.
35	Wang et al., 2020[43]	Most paediatric patients had mild symptoms, and many children were asymptomatic. Fever and cough were common symptoms in children.	• Clinical classification of severity of COVID-19 did not exist. Thus, authors combined light, mild and moderate disease into one category (mild), while severe and critical cases were considered severe cases.
36	Williams et al., 2020[44]	Children with lower risk of acquiring the infection appear compared to adults (1% v 3.5%). If infected, the risk of severe disease was almost 25 times lower than adults. Comorbidities especially pre-existing cardiac conditions represented a large proportion of those that became critically unwell.	• Limited data on comorbidities in selected studies.

37	Yasuhara et al., 2020[45]	Children with COVID-19 either had less severe symptoms or asymptomatic. Authors recommended early detection of COVID-19 and early diagnosis of MIS-C. Studies with large cohorts of pediatric patients needed to understand the severity, risk factors, outcomes, and management of children with COVID-19.	• Most studies were reported from Asian countries. Authors purposefully excluded retrospective studies. • Studies included a collection of individual case reports or small case series. It was unclear whether these cases were representative of all pediatric cases or individual cases with novel featured. • Authors were not able to assess more detailed information on the treatment and outcomes. • Data on race or ethnicity was unavailable.
38	Yoon et al., 2020[46]	Most cases recovered. No mortalities were reported. Males were more likely to have an asymptomatic infection, and abnormal lab findings better distinguished symptomatic from asymptomatic pediatric COVID-19.	• Blood laboratory samples and CT were taken at different time points of infection for different patients. The disease progressed from the contraction of illness to the onset of symptoms; laboratory characteristics and radiological features could have changed among cases. • In the review, prospective studies were not included. • Most studies were from China.

Figure 1: Flowchart depicting exclusion criteria and selection process

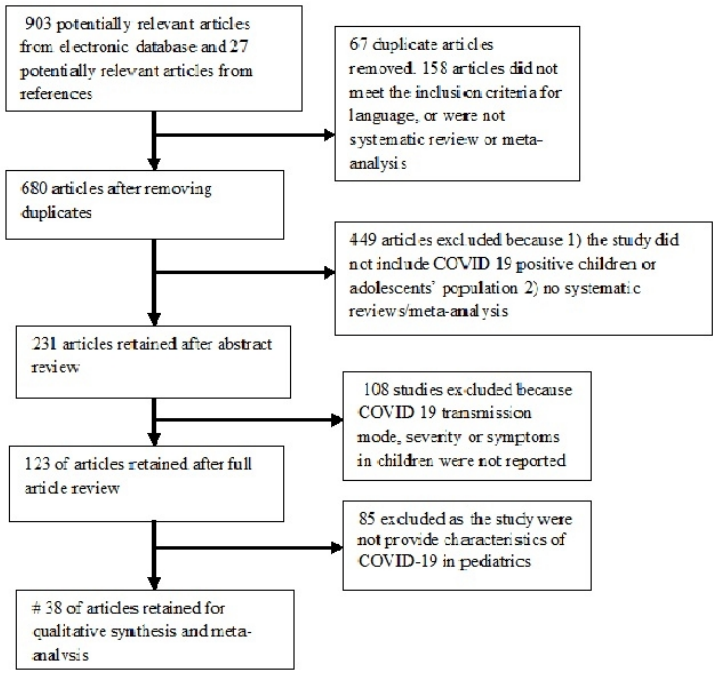
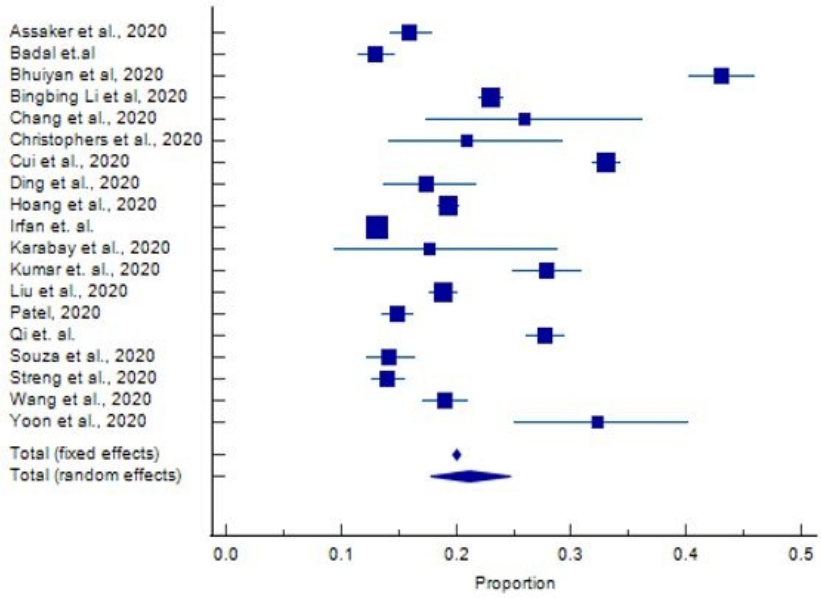


Figure 1

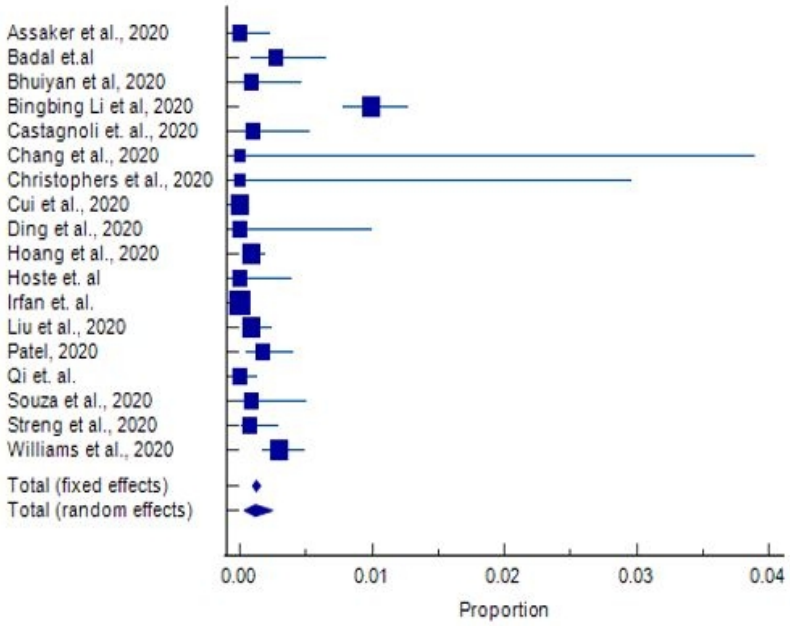
74x54mm (300 x 300 DPI)

Figure 2 A: Forest plot showing results of meta analyses from systematic reviews providing prevalence asymptomatic disease in pediatric patients infected with Covid-19



57x41mm (300 x 300 DPI)

Figure 2 B: Forest plots showing results of meta analyses from systematic review providing mortality prevalence in pediatric patients infected with Covid-19. The pooled proportion percentage are plotted using quantitative data from individual reviews.



52x42mm (300 x 300 DPI)

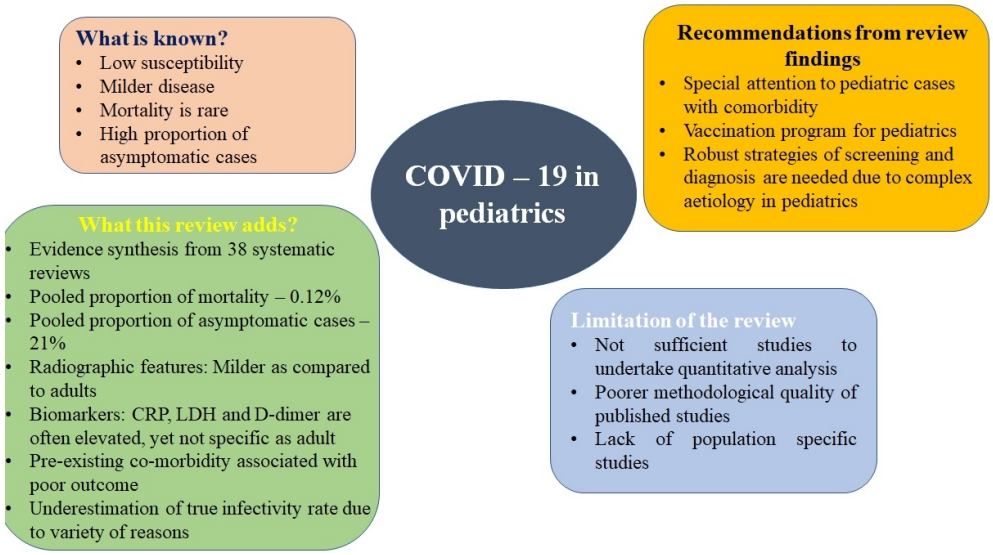


Figure 3

103x57mm (300 x 300 DPI)