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Clinical Features and Illness Severity in Children with COVID-19: A Systematic Review and Meta-Analysis

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Abstract

Background Pediatric patients represent approximately 2% of overall confirmed cases of COVID-19. Illness severity and symptoms differ from adults. Most cases in children are mild but various studies have reported severe and critical cases as well as fatal outcomes. Methods A systematic review and meta-analysis of the available literature was performed. Frequencies were used for reporting categorical variables. Meta-analyses were performed using the binary random effects model for symptoms frequencies in children and illness severity. Results We found 44 studies (n=6026), 38 were used for quantitative synthesis to estimate the frequency of symptoms in the pediatric population with Covid-19 and illness severity, 44 were used for qualitative synthesis. The most common symptoms were fever 64% (CI 95% 54-72%), cough 42% (CI 95% 37-48%) and gastrointestinal symptoms like vomit 31% (CI 95% 17-47%) and diarrhea 28% (CI 95% 17-40%). For illness severity 2% (CI 95%0-5%) were severe and 3% (CI 95% 1-6%) were critical. Children <1-year-old had the higher odds of severe/critical cases with an OR of 2.07 (IC95% 1.40-3.05). All patients were hospitalized, and a total of 10.34% children admitted to PICU. The mortality rate was 0.16% (8/487). A total of 141 patients developed PIMS-TS and only one died. Conclusions: Most cases in children were non-severe, nevertheless children less than 1 year had the higher risk of severe/critical cases. Symptoms frequencies encountered from major to minor were fever, cough and gastrointestinal symptoms. More testing in children should be done in order to understand transmission characteristics in the pediatric population.

Word count: 248

INTRODUCTION

The coronavirus disease 2019 (COVID-19) is a new emerging infectious disease reported in December 2019 to the World Health Organization (WHO) by the Chinese health authorities as a new outbreak of pneumonia-like cases in Wuhan, China [1,2]. The etiologic agent is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 has turned into a pandemic, up until June 19, 2020, there were 8.24 million confirmed cases and 445,535 deaths worldwide [4].

Pediatric patients represent approximately 2.4% of the overall confirmed cases [5]. Illness severity spectrum in children is classified as asymptomatic, mild, moderate, severe and critical disease [6], in contrast, adult clinical classification does not include moderate disease [7,8]. Nevertheless, illness severity among children

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is thought to be mainly a mild disease [7,9], various studies have reported severe and critical cases as well as fatal outcomes [10-12] whereas an important proportion of children cases are asymptomatic [13].

The spectrum of disease in pediatric patients has a very heterogeneous behavior unlike adults, mostly of patients develop asymptomatic and mild disease, where fever, cough and gastrointestinal symptoms predominate, but can also develop severe disease, requiring hospitalization and even mechanical ventilation, less frequently compared to adults (<7%), recently Multi-systemic Inflammatory Syndrome related to SARS-CoV-2 infection has been described how a severe disease in children. [7, 14, 15]

COVID-19 has a different behavior between age groups regarding epidemiological and clinical characteristics, therefore this study aims to provide a qualitative and quantitative analysis to summarize the evidence available in the literature, about epidemiology, illness severity and clinical features among children.

METHODS

Protocol and registration

This Systematic Review of Literature followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16].

Eligibility criteria

We included published and peer-reviewed studies, which were observational, cross-sectional, retrospective, case series, brief reports and letters to the editor that reported clinical features or illness severity among children (<21 y) with COVID-19. Other reviewed items were epidemiological data, pediatric age categories, management, outcomes, imaging and laboratory findings. Due to the limited data of COVID-19 in children outside China, we decided to include letters to the editor from other countries that met the inclusion and exclusion criteria to increase the variability population. Only English language studies were included. Duplicate publications, review articles, case reports, editorials and opinion articles were excluded. We also excluded articles that did not have enough information about children since its main target was the adult population.

Information sources and search strategy

We conducted a systematic search of studies published from February 18th, 2020 to June 8th, 2020 in PubMed and other databases (ScienceDirect, SpringerLink, Ovid and Google Scholar). We used the MeSH terms; ("COVID-19" [Supplementary Concept]) AND "Child"[Mesh]. The search ended on June 8th, 2020. Two different searchers independently evaluated the search results (GCLG, VCJA). Disagreements were resolved by a third searcher (ADL).

Study selection and data selection

First, we appraised the screening strategy by title and abstract, then full texts were evaluated by inclusion criteria, and finally peer reviewed. For each study we obtained the following variables: author´s name, country, year of publication, total number of patients, sex distribution, pediatric age categories (divided according agreement between studies as follows: <1y, 1-5 y, 6-10 y and >10 y), previous contact with a family member infected, mean incubation period, diagnosis by real-time polymerase chain reaction (RT-PCR) and serum antibodies levels (IgM, IgG), illness severity, clinical features, number of patients admitted into the pediatric intensive care unit (PICU), complications, image-laboratory findings and management. We included the analysis of the Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-Cov-2 (PIMS-TS) and their own variables like clinical findings, complications, severity and mortality.

Definition for illness severity, was based on the clinical classification of COVID-19 in children, proposed by Shen K et al. [6] and definition of PIMS-TS reviewed by The Royal College of Pediatrics and Child Health (RCPCH) [17,18]. Available in**Supplementary Material** .

Risk of bias in individual studies

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Two researchers (GCLG and VCJA) assessed the risk of bias by using the appraisal tool to assess the quality of cross-sectional studies (AXIS).**Table 1** . [19].

Statistical Analysis

Meta-analysis of prevalence estimations was done using the Stata command*metaprop,* that allows computation of 95% confidence intervals using the score statistic and the exact binomial method and incorporates the Freeman-Tukey double arcsine transformation of proportions to stabilize the variance and to achieve approximate normality [20]. Meta-analysis of effect sizes that account for the association between age groups and severity of the disease were done by means of random-effects models and the method used for estimating between-study variability was restricted maximum likelihood. Additionally, using I^2 index was obtained to measure heterogeneity.

RESULTS

A total of 287 articles were found in the systematic review of the literature (254 in PubMed and 38 in other databases). After removing duplicates, screening by title and abstract, 58 articles were selected for full-text evaluation, 14 were excluded for different reasons. A total 44 articles were chosen for qualitative analysis, 38 for quantitative analysis of clinical findings [17,18, 21-30,32-38,40,42-48,50-52,54-58,60,62] and 43 for quantitative analysis of illness severity severity[17,18,31-56,58,60-62].**Figure 1.** All were observational studies, twenty-six studies were done in China [21-37,], five were from USA [18,39,50,59,60], five from Italy [40,44,47,56,57], three from Spain [49,51,61], two from France [48,62], one was made in Malaysia [38], Iraqi Kurdistan [41] and UK [17]. The main characteristics of included studies and individual risk of bias are shown in **Table 1** .

Epidemiology

A total of 6026 children with confirmed or suspected COVID-19 were included. 55.25% cases were males. Age ranged from newborn to 21 years, a total of 5754 patients were distributed as follows: 19.09% (< 1 year), 17.18% (1-5 years), 20.17% (6-10 years) and 43.53% (>10 years) [21,27,29-35,38-48,50-52,54,56,59,61]. **Supplementary Material** . Mean incubation period was 6.33 (± 2.48) days. Fourteen studies noted 165 patients with comorbidities [17,21,26,27,30,34,39,41,47-49,51,57], the most common are neoplasms, overweight and obesity, cardiac diseases, neurological and chronic respiratory diseases, mostly asthma. In addition 5 studies reported 6 severe/critical cases with comorbidities, a teenager with obesity, one scholar with acute lymphoblastic leukemia, 3 infants with congenital cardiac disease, one infant with chronic wheezes. [21,27,30,49,58]. A total of 68.48% cases (526/768) had previous contact with an infected family member. Diagnosis was performed with real time polymerase chain reaction (RT-PCR) by nasopharyngeal swab in 1656 patients, 110 patients were diagnosed by serum antibodies (IgM, IgG). [17,18,44,48,61,62]. Seven studies assessed the presence of SARS-CoV-2 in stools [25,29,30,32,45,48,61], finding 18.82% (32/170) positive cases. All RT-PCR tests in stool samples were made in confirmed cases of COVID-19.

Illness severity

Illness severity distribution among 3175 cases (2 lost) [31] were: asymptomatic 6% (CI95% 3-10%), I^2 84.92% p<0.001 (all of them diagnosed after contact with family member), mild disease 28%(CI 95% 19-38%) I^2 92.05% p<0.001, moderate disease 33%(CI 95% 24-43%) I^2 92.20% p<0.001, severe illness 2% (CI 95% 0-5%) I^2 77.52% p<0.001 and critical disease 3% (CI 95% 1-6%) with I^2 90.04% and p<0.001 **Figure 2** .

Hence approximately 89.73% cases in pediatric population were non-severe. Pooled Odds Ratio (OR) of severe or critical illness in children <1y was 2.07 (CI 95% 1.40-3.05) p<0.001, but heterogeneity statistics were unable to calculate since a single study weighs almost 100% and in patients >10y pooled OR was 0.75 (CI 95% 0.16-3.43) but it was not statistically significant.

Figure 3

Clinical Manifestations

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Fever was found to be the most frequent symptom with 64% (CI 95% 54%-72%), I^2 88.18% and p<0.001, followed by cough 42% (CI 95% 37%-48%) I^2 59.54% and p<0.001, vomit 31% (CI 95% 17-47%), $I^2$94.42% p<0.001 and diarrhea 28% (CI 95% 17%-47%) I^2 92.67%, p<0.001. **Figure 4.**Abdominal pain and constipation 27%(CI 95% 12%-45%) I^2 of 95.32% p<0.001, rhinorrhea 19% (CI 95% 12%-28%), I^2 79.74%% p<0.001, fatigue and myalgia 15% (CI 95% 5%-27%) I^2=93.03% p<0.001, tachypnea 13% (CI 95% 0%-45%) I^2= 88.63% p<0.001, and less common symptoms were sore throat 10%, (CI 95% 4%-16%) I^2 82.42% p<0.001, headache 10% (CI95% 4%-19%) I^2 83.30% and p<0.001 and finally expectoration with a frequency of 9% (CI95% 2%-20%) I^2 96.65%, p<0.001. Meta-analysis of other symptoms are shown in **Supplementary Material** .

Image and laboratory findings

The most important laboratory alterations were: lymphopenia 19.55% (124/634) [18,21,22,25,26,28-30,34-36,40,43-47,52,54,58,60,61], lymphocytosis 18.29% (86/470) [21,22,25,26,29,30,33-36,40,43,45,47,52,58,59], neutrophilia 17.84% (58/325) [18,21,22,25,33-36,40,44,45,47,58,62] leucopenia 17.19% (87/506) [24,25,28,29,31,32,33,36,38,43,46,48-50,57,61] and leukocytosis 16.35% (78/477) [21,22,25,26,29,30,32-35,40,43,47,52,58,62]. Pro-inflammatory biomarkers: C-reactive protein increased in 28.55% (205/718) of patients [21-26,28-35,40,43-46,48,52,54,56,58,60-62] and high level of procalcitonin was presented in 18.26% (76/416) of cases. [21,23,24,26,28-30,33,34,40,46,47,54,60-62]. **Supplementary Material** .

Other laboratory findings were: D-dimer was increased in 42.85% (75/175) of patients [21,23,25,28,29,33,36,39,44,47,61,62], alanine- aminotransferase were increased in 22.10% (84/380) [21,25,26,28,29,33-36,40,44,45,47,52,54,62] and high dehydrogenase lactic were presented 21.56% (55/255) of cases [21,25,27,29,33,34,36,40,45-47,52,61]. Patients who reported laboratory results were hospitalized therefore we cannot correlate the laboratory findings with illness severity. **Supplementary Material** .

In respect to image findings a total of 39.61% (353/891) cases had abnormalities in chest CT scan [21-30,33-37,40,43-47,51,52,54,56,57,58,60,62] and 51.10 % (162/317) in chest radiography [18,21-24,29,40,44,52,56-58,62] characterized primarily by ground-glass opacities 35.43% (208/587) [17,21-26,28-30,35,37,40,43,45-47,52,54,60,62]. In some articles the imaging studies were taken from all hospitalized patients, including asymptomatic, in others studies only from those with more severe symptoms.

Bilateral compromise was seen in 34.82% cases 156/448 [18,22,23,27,29,30,34,35,37,40,43-46,54,60] and 25.58% (98/383) cases had unilateral involvement [21,26,27,29,30,33-35,40,43-46,54].**Supplementary Material** .

Management

Patients were treated with interferon, antivirals (lopinavir-ritonavir), steroids and immunoglobulin. So far, we cannot evaluate effectivity of treatments on the outcomes because all studies are observational and not reported individual or aggregate outcomes.

Complications and outcomes

Coinfection with other pathogen was seen in16.77% (104/620) of cases [18,21,22,26,27,30,35,38,43,45,49,56,58,60], the most reported was*Mycoplasma pneumoniae* in 21.95% (72/328) cases [26,27,30,34,35,43,45], Influenza A & B virus and *syncytial respiratory* virus were encountered in 4, 7 and 8 patients, respectively [21,26,30,49,56] Also, Sun D et al. reported 2 patients who developed sepsis. All patients with co-infection were hospitalized, and a total of 10.34% (129/1247) children admitted to the pediatric intensive care unit. [17,18,21,27,35,48-50,56,57,58,60,62], 11.56% (48/415) received mechanical ventilation. In five studies reported deaths, the mortality rate was 0.16% (8/4871) [17,31,39,50,60]

PIMS-ST in COVID-19.

Of the 44 studies included in this systematic review, 5 of them specifically described several patients with Kawasaki disease and/or the presence of PIMS-TS in hospitalized patients with history of SARS-CoV-2 infection. [21,22,47,51,65]. In the largest case series published by Whitaker et al. [17] they included 58

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children, with a median age of 9y, met the criteria for PIMS-TS divided in three patterns; 23 patients presented with fever and elevated pro-inflammatory markers such as RCP, 13 met criteria for complete KD , and 29 presented a toxic shock due to KD or myocardial damage. All patients had fever, 31 developed abdominal pain, 15 headache, 6 sore-throat, 26 patients presented conjunctivitis, 17 had changes in mucus membranes, 9 lymphadenopathy and 9 had swollen extremities. Admission to PICU was required in 29 patients and 25 required mechanical ventilation. All of them had elevated RCP. One patient died. The complete information about these 5 studies is available in **Supplementary Material.** The most relevant in all studies is the severity of illness, 65.5 % of children were admitted to PICU and one dead.

DISCUSSION

We conducted a systematic review and meta-analysis with the current evidence available regarding illness severity and clinical features in children (0-21 years), aiming to provide the most frequent COVID-19 characteristics in the pediatric population in order to bring useful information.

The majority of studies included in this systematic review are from China, and eighteen from other countries, this brought more variability in to our study, in comparison to other systematic reviews that only included Chinese population, nonetheless frequencies for epidemiological data, illness severity and clinical features are similar. Most of the patients in the systematic review published by Castagnoli et. al. were >10 years old (553) [62]. Similarly, we found the higher number of cases in the teenage population (>10 years old) 44.23% (2505). The Korean Society of Infectious Diseases has reported a similar age distribution, this might be associated with teenagers being more active than other pediatric groups [64]. Sex distribution is nearly the same (55.25% vs 57.35% cases in males) in our study compared with the systematic review published by De Souza TH.et al. [65]. Above 85% cases had exposure with a confirmed case in our study. In contrast, a study from Tagarro. A et al. 2020 [49], described 365 suspected cases in children, 41 were positive, 56% of confirmed cases were females and 39% of all confirmed cases had previous contact with a confirmed case versus 61% cases of community transmission. Unlike other respiratory viruses, everything seems to indicate currently, that children are not superspreaders, but they may be the final part of the chain of contagion. This has important implications for school opening policies when the epidemic is controlled locally. [66]

Regarding the illness severity, 95% cases were non-severe, of whom, 6% were asymptomatic and 33% had abnormal findings in chest CT without any serious clinical manifestation, similarly in the systematic review of De Souza TH.et al 96.5% of patients were non-severe but 14.2% were asymptomatic [65]. Asymptomatic cases in the pediatric population possess several challenges to public health, however, it is not clear how this cases in children could affect in the velocity of spread of the virus, besides it would be necessary to stratify the viral load of these patients in order to be able to estimate the risk of infection, in a recent the viral load of SARS-CoV-2 was analyzed by patient age, finding no significance difference in viral load between children and adults, thus children could be as infectious as an adult [67]. On the other hand, our results have shown that children develop non-severe disease in most cases in comparison with adults, who present 81% of mild cases [8] versus almost 95% in pediatric patients. Moreover, severe cases in adults represent 14% and critical cases 5% by contrast only 2% and 3% children cases were severe or critical, respectively. Differences in illness severity between children and adults had brought questions about why severe/critical disease frequency in children is low. Garcia-Salido in their letter to the editor discusses some hypotheses about children having more frequently a mild disease. Firstly, the expression of the angiotensin-converting enzyme (ACE) 2 receptor is lower in nasal fluid when the individual is younger, and it could explain the minor frequency of infection and severe disease in pediatric population. The endothelial damage is higher in adults with diabetes and cardiovascular diseases in comparison with healthy children where is practically absent. Finally, the innate immunity in children is well trained by viral community infections and viral vaccines. [68]

Although the focus of the pandemic is on adults, prevention in the pediatric population should not be neglected. Pathak EB et al. [69] estimated the projected numbers of severe pediatric cases in the USA, under different scenarios of cumulative pediatric infection proportion (CPIP), finding 10,993 projected severe/critical cases among children with a 5% CPIP. Despite non-severe pediatric cases will be the majority, the total number of severe cases will exceed the capacities of a health care system already impaired.

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It is important to emphasize that children are not very symptomatic and not all meet the operational definitions, for example, abdominal pain, vomit and diarrhea have almost the same frequency as cough.**Figure 4** . Unlike adults, in a meta-analysis published by Rodriguez-Morales AJ et al [70] found that 92% of adults presented with fever and 63% with cough, a much higher than children. Other symptoms less frequent in children in contrast with adults are expectoration, fatigue/myalgia, sore throat and dyspnea whereas had equal frequency and gastrointestinal symptoms like diarrhea, vomit and abdominal pain were more frequent in children. **Figure 4** . Hence COVID-19 in children represents a clinical challenge since it is less symptomatic and less severe, making it more difficult to identify. Although the children may spread the virus less, we do not know what will happen when they have more social contact. Unlike Castagnoli study, we observed an increase of severe cases, that are explained by appearance and description of PIMS-TS. Their main clinical features were fever, conjunctivitis, rash, lower limb edema and gastrointestinal symptoms, some of them developing shock and cardiac alterations. Patients presented elevated CRP, ferritin, D-dimer and cardiac enzymes; these clinical findings demonstrated a new phenomenon related to SARS.CoV-2 infection in children. [17,18]

Some clinical features of this new syndrome are KD-like but have some differences, for example this syndrome is related to a specific causal agent; SARS-CoV-2 unlike KD whose etiology is still unknown. KD mainly affects children under 5 years but the prevalence of this syndrome is higher in adolescents, the syndrome manifests itself with greater severity, shock, organ failure, heart dysfunction with decreased ejection fraction and higher prevalence in PICU admission compared to KD. [17,48].

We include five studies that referred specifically to this syndrome, the available information is very limited. These are clinical manifestations of severe COVID-19 in children that can lead systemic complications, admission to ICU and even death, therefore it is important that pediatrician take into account this possible presentation in pediatric patients with symptoms similar to KD and optimize early recognition and management to avoid death.

It is important to mention that our study has several limitations such as letters to the editor, including cases series and in-press articles, having patients diagnosed after a confirmed family member and lastly, heterogeneity among studies goes from medium to high. Nevertheless, this study brings useful epidemiological and clinical information about the pediatric population, for instance, children less than 1 year old could be a group of risk since patients <1y have twice the risk of developing severe or critical illness compared to other pediatric ages**Figure 3.** For this reason, public health authorities take to account that children can and will get severe disease and we must be aware for this target population. Children in most of cases will present a mild disease but with an atypical presentation, where clinicians must identify and discard COVID-19 in children, so testing in the pediatric population must increase.

CONCLUSION

Pediatric patients represent a fundamental population to assess during the COVID-19 pandemic since their characteristics differ from adults. Despite our study has limitations due to the variability among studies, we could summarize the current evidence available, following these key points: A great amount of cases were diagnosed after contact with an infected family member, the majority of cases in children would be non-severe, nevertheless children less than 1 year old could be at higher risk of develop severe/critical disease. Symptoms frequencies encountered in children from major to minor are fever, cough, vomit, diarrhea and abdominal pain. Clinicians have to be aware of atypical presentations among children. Finally, more studies will be necessary to assess the key role of children could play in based-community transmission, more testing in children should be done in order to understand transmission characteristics in the pediatric population. Caution must be taken in children returning to school, they could be the focus of new outbreaks.

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CONFLICT OF INTERESTS

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Figures and tables.

Figure 1. PRISMA flow chart.

Table 1. General characteristics of included studies.

Figure 2. Meta-analysis of illness severity.

Figure 3. Meta-analysis of OR. (<1y and severe/critical disease and >10y severe/critical disease).

Figure 4 . Meta-analysis of clinical manifestations. (Fever, cough, diarrhea and vomit).

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`Figure 3.Meta-analysisi of OR.pptx` available at https://authorea.com/users/348331/articles/473715-clinical-features-and-illness-severity-in-children-with-covid-19-a-systematic-review-and-meta-analysis

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