ORIGINAL ARTICLE

CLINICAL CHARACTERISTICS AND PATIENT SYMPTOMS ASSOCIATED WITH POOR OUTCOMES AMONG CHILDREN WITH COVID-19: A RAPID REVIEW

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ABSTRACT

Objective: To identify specific clinical characteristics and patient signs and symptoms that increase the risk of developing severe/critical COVID-19 disease or death in the pediatric population, and identify strength of these associations

Methodology: A systematic search was done in PubMed, Science Direct, Cochrane Library and grey literature databases focusing on severe and critical COVID-19 disease in the zero to eighteen year old age group until August 26, 2020. Data regarding patient characteristics, signs and symptoms on admission and disease severity were extracted. Outcomes measured were severe or critical COVID-19, Multisystem Inflammatory Syndrome in Children (MIS-C) or death. Results were pooled and meta-analyzed.

Results: Four eligible studies with a total of 292 pediatric patients with COVID-19 were examined. Older children (MD=6.62, 95%CI=4.23 to 9.00, p-value<0.00001, I^2=33%) significantly present with a higher percentage of severe disease. Shortness of breath (OR=8.14, 95%CI=2.33 to 28.47, p-value=0.001, I^2=42%) was also found to be associated with severe COVID-19 disease. The presence of a pre-existing medical condition (OR=4.02, 95%CI=1.55 to 10.43, p-value=0.004, I^2=0%), especially cardiac disease (OR=6.40, 95%CI=1.45 to 28.38, p-value=0.01, I^2=13%) and diabetes (OR=7.01, 95%CI=1.54 to 31.95, p-value=0.01, I^2=0%) was noted to be a risk factor for severe disease.

Conclusion: Based on poor quality observational studies, older age group, shortness of breath, and a pre-existing medical condition, especially cardiac disease or diabetes were found to be associated with poor outcomes in children with COVID-19.

KEYWORDS: *COVID-19, Pediatrics, Disease severity*

INTRODUCTION

The 2019 Novel Coronavirus Disease, now known as Coronavirus Disease 2019 (COVID-19) presents with a wide clinical disease spectrum. Mild disease with fever, cough and fatigue are typically seen, but severe respiratory symptoms associated with other systemic disorders have also been reported.[1] COVID-19 has been a cause of multiple fatalities. More than 23 million cases have already been documented globally as of August 2020, with the pediatric population accounting for 1-5% of cases.[2,3]

Since the start of the pandemic, cases of COVID-19 reported among children have mostly been mild with good prognosis.[3-5]However little is known about the other side of the disease spectrum, and as more individuals are diagnosed, the number of severe and critical cases among children have increased as well. In a nationwide study conducted in China between January 16 to February 8, 2020 among 2,135 pediatric patients with confirmed and suspected COVID-19, more than 80% had mild to moderate disease, 5.2% presented with severe illness, while 0.6% were critical.[6] In another study from a tertiary medical center in New York City, 28% (N=67) of children with positive COVID-19 results necessitated admission to an intensive care unit, with 1 death reported.[7] As of April 2020, there have been reports of a new phenotype of severe to critical pediatric cases occurring weeks after an outbreak of SARS-CoV-2. Disease symptomatologies likened to Kawasaki disease and other hyperinflammatory illnesses were reported with a significant increase in incidence (OR 184, p<0.00001).[8,9] In a report from the United Kingdom, a mortality was attributed to a large cerebrovascular infarction, while another patient developed a giant aneurysm after being discharged from the intensive care unit.[10] This condition is now referred to as Multisystem Inflammatory Syndrome in Children (MIS-C).[9]

It is important to identify the pediatric population at risk of developing severe or critical disease, as delayed recognition may lead to development of complications or death. The objectives of this review are to (1) identify specific clinical characteristics and patient signs and symptoms that increase the risk of developing severe/critical COVID-19 disease or death in the pediatric population, and (2) identify strength of these associations.

MATERIALS AND METHODS

Databases (PubMed, Cochrane Library and Science Direct) and grey literature database (Google Search, ChinaXiv, Medrxiv, Biorxiv) were searched for relevant studies on August 26, 2020 and published studies from December 01, 2019 to August 26, 2020 were reviewed. The pre-defined keywords “Coronavirus Infections", "Coronavirus", “novel coronavirus”, “NCOV”, "COVID-19", “COVID-2019”, "severe acute respiratory syndrome coronavirus 2", “SARS-COV2”, “death”, “mortality”, “critical”, “severe”, “outcomes”, “intensive care unit”, “prognosis”, “signs”, “symptoms”, “pediatric”, “neonates”, “children”, and “adolescents”, with Medical Subject Headings (MeSH terms) and Boolean operators were used for a comprehensive and organized search strategy. Reference lists of studies were reviewed for inclusion. A total of 3,622 articles came up in the initial search. Three review authors (KDC, IGC, CSJ) screened and appraised the articles based on the inclusion criteria:

1. Type of participants: Patients diagnosed with COVID-19 aged 18 years old and below
2. Types of exposure: Epidemiology, clinical characteristics, Signs & symptoms
3. Types of outcome measures: Severe COVID-19, critical COVID-19, MIS-C or death
4. Types of study designs: Systematic reviews and meta-analyses, observational studies

Duplicate articles and studies which did not satisfy the inclusion criteria were removed, as well as reports which only contained abstracts or had insufficient data to be analyzed. From these, 4 studies were considered valid and included in the review. Disagreements among reviewers were discussed and settled through a consensus.

The following items were extracted from each study, if available: journal title, author, date of publication, study design, country in study, time

period, population, epidemiologic data, clinical symptoms, outcomes and risk factor for severe outcomes. If multiple studies were noted to include the same cohort, the most comprehensive and reliable study was selected. The data collated were entered into the Cochrane Collaboration Review Manager Version 5.4 statistical software for data analysis and assessment of level of heterogeneity.[11] Random effects model was utilized during analysis and odds ratios with their 95% confidence intervals were applied to present pooled effect sizes.

RESULTS

Literature Search Yield

After a detailed search for eligible studies, 116 articles were initially considered. Duplicates were removed and records were further screened. Forty-six full-text articles were retrieved and 4 studies were finally deemed eligible. Reasons for exclusion are the following: 1) majority of the sample population are adults (n=7); 2) reported cases are either only non-severe/critical (n=20) or only severe/critical (n=1); 3) no raw data available (n=12); 4) editorial (n=1); and 5) projection study (n=1). An article by Bellino et al. which studied risk factors for disease severity was not included due to lack of available raw data on proportions of severe and critical pediatric cases.[12]

Characteristics of Included Studies

As of August 26, 2020, we included 4 articles, all of which were retrospective cohort studies, with data collated from February to early May 2020 among participants from the United States of America. The sample size of the studies ranged from 19-177, with a total of 292 individuals.[7,13-15]

Three out of 4 studies have a sample population of pediatric individuals with mild to critical COVID-19. One cohort study included children and young adults aged 19 to 34 (n=12), which comprised 6.8% of the sample population.[14] All studies analyzed the epidemiologic and clinical characteristics of individuals. Outcomes noted were severe/critical, and need for mechanical ventilation and admission to pediatric intensive care unit as an indirect measure of the desired outcome.

Critical Appraisal

Studies were assessed using the prognosis guide questions from the book Painless Evidence-Based Medicine.[16] Risk for bias was noted, including: (a) lack of or unclear objective definition of the desired outcome, and where no admission criteria for intensive care was mentioned, or admission to an intensive care unit was based on physician's decision; (b) study population also included young adults, which constituted 4 out of 9 critically ill patients in one study; (c) incomplete follow-up of patients, where outcomes reported were only up to the time of manuscript writing and possible progression of disease was not considered or not mentioned.[7,14-15] Given the appraisal done and possible biases listed, the overall validity assessment of the included studies is moderate.

Prognostic Outcomes[11,16]

Severe/Critical Disease versus Non-severe/critical

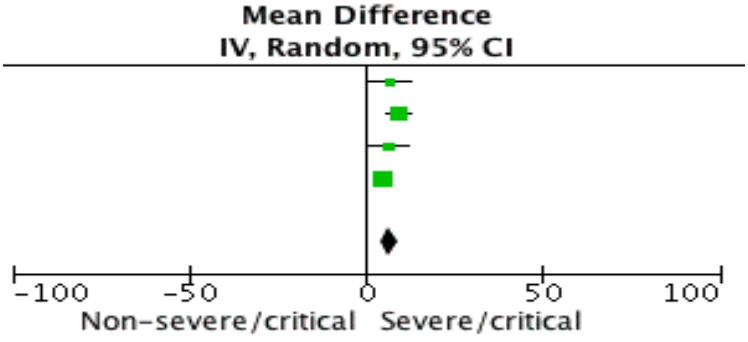
I. Age (4 studies)

Patients with severe/critical disease were significantly older than those with non-severe disease(MD=6.62, 95%CI=4.23 to 9.00, p-value<0.00001) as seen in the 4 pooled studies, with a low heterogeneity of 33%(Table 1).[7,13-15]

Table 1: Age in association with severe/critical COVID-19 disease.

	Severe/critical			Non-severe/critical				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Bhumbra 2020	12	6.1	7	5.4	6.1	12	14.3%	6.60 [0.91, 12.29]
Chao 2020	12.8	5.4	13	3.6	4.3	33	31.1%	9.20 [5.92, 12.48]
De Biasi 2020	15.1	8.5	9	8.7	7.2	168	14.4%	6.40 [0.74, 12.06]
Zachariah 2020	13.7	3.1	9	9	5.2	41	40.2%	4.70 [2.12, 7.28]
Total (95% CI)			**38**			**254**	**100.0%**	**6.62 [4.23, 9.00]**

Heterogeneity: $Tau^2 = 1.95$; $Chi^2 = 4.47$, df = 3 (P = 0.21); $I^2 = 33\%$
Test for overall effect: Z = 5.44 (P < 0.00001)



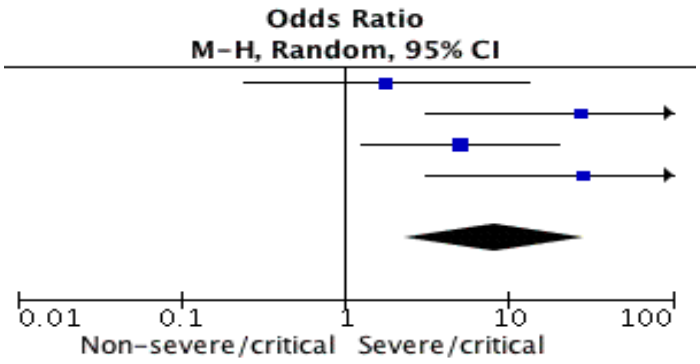
II. Symptoms (3-4 pooled studies)

The forest plot showed that shortness of breath was significantly associated with severe disease (OR=8.14, 95%CI=2.33 to 28.47, p-value=0.001, I^2=42%, n= 4 studies) (Table 2).[7,13-15] Symptoms not associated with severe disease in the pooled studies are fever (OR=2.24, 95%CI=0.71 to 7.07, p-value=0.17, I^2=0%), sore throat (OR=0.87, 95%CI=0.12 to 6.30, p-value=0.89, I^2=57%), cough (OR=1.54, 95%CI=0.71 to 3.32, p-value=0.27, I^2=2%), chest pain (OR=2.77, 95%CI=0.98 to 7.79, p-value=0.05, I^2=0%), and gastrointestinal symptoms, including diarrhea and vomiting (OR=2.77, 95%CI=0.66 to 11.67, p-value=0.17, I^2=40%).[7,13-15]

Table 2: Shortness of breath in association with severe/critical COVID-19 disease

	Severe/critical		Non-severe/critical			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Bhumbra 2020	5	7	7	12	23.6%	1.79 [0.24, 13.21]
Chao 2020	12	13	10	33	21.3%	27.60 [3.15, 241.94]
De Biasi 2020	4	9	23	168	34.3%	5.04 [1.26, 20.18]
Zachariah 2020	8	9	9	41	20.9%	28.44 [3.13, 258.38]
Total (95% CI)		**38**		**254**	**100.0%**	**8.14 [2.33, 28.47]**
Total events	29		49			

Heterogeneity: Tau² = 0.69; Chi² = 5.21, df = 3 (P = 0.16); I² = 42%
Test for overall effect: Z = 3.28 (P = 0.001)



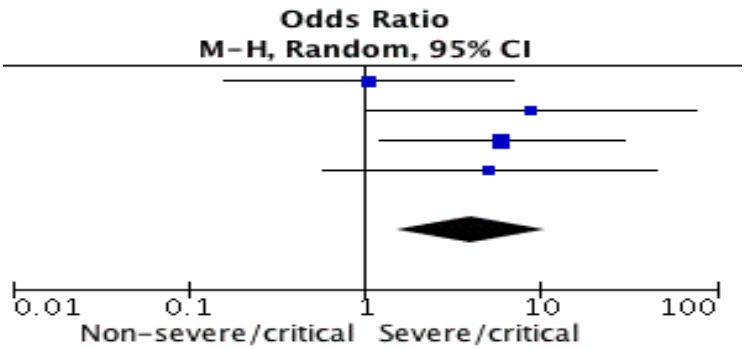
III. Presence of Pre-existing Medical Condition (4 pooled studies)

In the pooled studies of Chao et al., Bhumbra et al., De Biasi et al. and Zachariah et al., presence of any comorbidity was significantly associated with severe disease (OR=4.02, 95%CI=1.55 to 10.43, p-value=0.004) with no heterogeneity (I^2=0%)(Table 3).

Table 3: Impact of a pre-existing medical condition to COVID-19 disease severity

	Severe/critical		Non-severe/critical			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Bhumbra 2020	3	7	5	12	25.6%	1.05 [0.16, 6.92]
Chao 2020	12	13	19	33	19.6%	8.84 [1.03, 76.18]
De Biasi 2020	7	9	62	168	35.5%	5.98 [1.21, 29.71]
Zachariah 2020	8	9	25	41	19.3%	5.12 [0.58, 44.91]
Total (95% CI)		**38**		**254**	**100.0%**	**4.02 [1.55, 10.43]**
Total events	30		111			

Heterogeneity: Tau² = 0.00; Chi² = 2.77, df = 3 (P = 0.43); I² = 0%
Test for overall effect: Z = 2.86 (P = 0.004)



Two specific underlying medical conditions were found to increase the risk of having severe COVID-19 disease. Cardiac disease (OR=6.40, 95%CI=1.45 to 28.38, p-value=0.01, I^2=13%, n=3 studies) and diabetes (OR=7.01, 95%CI=1.54 to 31.95, p-value=0.01, I^2=0%, n=3 studies) were significantly associated with severe disease.[7,13-15] Both showed low to no heterogeneity in their results (Table 4,5). On the other hand, several co-morbidities are not associated with severe disease. The following are:

- Asthma (OR=1.11, 95%CI=0.45 to 2.77, p-value=0.82, I^2=0%)[7,13-15]
- Neurologic condition (OR=4.50, 95%CI=0.83 to 24.39, p-value=0.08, I^2=52%)[7,14,15]
- Hematologic disease (OR=1.35, 95%CI=0.24 to 7.59, p-value=0.73, I^2=0%)[13-15]
- Oncologic disease (OR=5.20, 95%CI=0.55 to 49.36, p-value=0.15, I^2=0%)[7,14]
- Immunosuppression (OR=1.07, 95%CI=0.18 to 6.18, p-value=0.94, I^2=0%)[7,15]
- Obesity (OR=3.46, 95%CI=0.74 to 16.22, p-value=0.12, I^2=57%)[7,13-15]

Table 4: Cardiac disease in association with severe/critical COVID-19 disease

	Severe/critical		Non-severe/critical			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Chao 2020	1	13	0	33	19.1%	8.04 [0.31, 210.67]
De Biasi 2020	2	9	3	168	47.3%	15.71 [2.25, 109.62]
Zachariah 2020	1	9	3	41	33.5%	1.58 [0.15, 17.25]
Total (95% CI)		31		242	100.0%	6.40 [1.45, 28.38]
Total events	4		6			

Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 2.30$, df = 2 (P = 0.32); $I^2 = 13\%$
Test for overall effect: Z = 2.44 (P = 0.01)

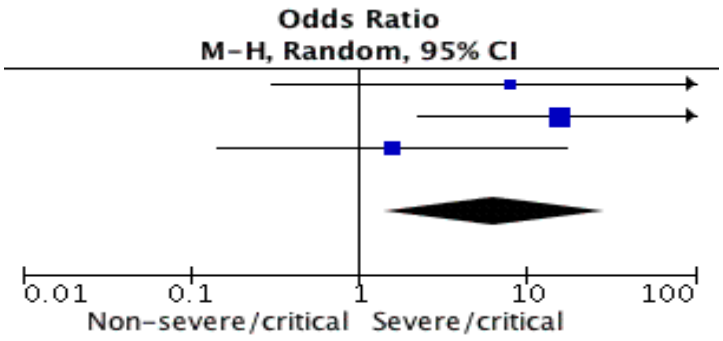
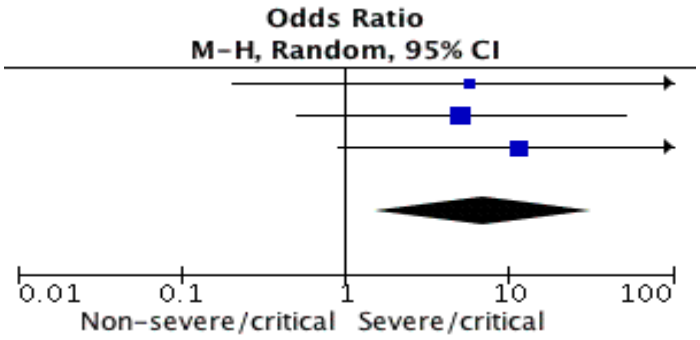


Table 5: Diabetes in association with severe/critical COVID-19 disease

	Severe/critical		Non-severe/critical			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Bhumbra 2020	1	7	0	12	20.7%	5.77 [0.20, 162.48]
De Biasi 2020	1	9	4	168	43.4%	5.13 [0.51, 51.29]
Zachariah 2020	2	9	1	41	35.9%	11.43 [0.91, 143.64]
Total (95% CI)		25		221	100.0%	7.01 [1.54, 31.95]
Total events	4		5			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.23$, df = 2 (P = 0.89); $I^2 = 0\%$
Test for overall effect: Z = 2.51 (P = 0.01)



DISCUSSION

Since COVID-19 is a new disease with the pediatric population contributing only a fraction of cases among affected patients, little is still known of the effect of an individual's profile on severity of disease. In this review, 4 articles were examined to estimate the current available evidence on risk factors for poor outcomes in children afflicted with COVID-19. Three factors including age, symptoms and comorbidities were selected for analysis, and the pooled results revealed significant associations with COVID-19 disease severity in the pediatric population. As of the time of writing, correlation between these factors to COVID-19 prognosis in children has not yet been studied.

This study showed that older age is statistically associated with a poor outcome in children with COVID-19. This is consistent with a study by Sun et al. in China, where 3 (37%) out of 8 severe or critically ill pediatric patients were aged 13–15 years old.[17] In contrast, another study done in France presented severe/critical cases of COVID-19 with a median age of 6 years old (range 0.2-17.8 years old, N=27). However, no available raw data on age was presented. Of the 27 affected children, 5 deaths were reported, with 3 belonging to the adolescent age group (16-17 years old).[18]

Statistically significant moderate heterogeneity was noted in the pooled results of shortness of breath/dyspnea as a risk factor. This may be because dyspnea is a subjective report that an individual can quantify which can point to disease severity.[19] However, in the included studies, signs and symptoms are counted as present or not. On the other hand, fever, sore throat, cough, chest pain and gastrointestinal symptoms showed no statistical difference between the severe/critical and non-severe/critical groups.

Presence of any underlying medical condition increases a child's risk for severe/critical COVID-19. These findings are similar to reports of adult patients from China, where presence of co-morbidities such as cardiovascular disease, hypertension and respiratory system disease may be risk factors for severe disease.[20]

However, in our study, only cardiac disease and diabetes were noted to be risk factors. Focusing on immunosuppression, our results were consistent with a study in a cancer center in New York City, where none of 20 pediatric patients who tested positive for COVID-19 required critical care.[21]

Limitations of this study include 1) studies originated from a single country, and 2) small sample sizes of included pooled articles. Thus, further research is needed to define risk factors for having poorer outcomes in pediatric patients with COVID-19.

Recommendations from Other Guidelines

Presence of an underlying medical condition (serious genetic, metabolic, neurologic disorders, congenital heart disease, obesity, diabetes, asthma, chronic lung disease, or immunosuppression) might increase the risk of having severe COVID-19 disease in children as stated by the Centers for Disease Control and Prevention.[22]

CONCLUSION

Based on poor quality observational studies, older age group, shortness of breath, and a pre-existing medical condition, especially cardiac disease or diabetes were found to be associated with poor outcomes in children with COVID-19. These findings can provide some aid in prognostication and disease management. Further studies with larger sample sizes are recommended.

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