What clinical characteristics and patient symptoms are associated with poor outcomes among children with COVID-19?

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This rapid review summarizes the available evidence on the clinical characteristics including signs and symptoms as risk factors for poorer outcomes of COVID-19 in children.

KEY FINDINGS

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

- Although majority of the pediatric population affected with COVID-1 are classified as mild cases, knowledge of the risk factors for development of severe or critical disease can aid in disease management and prognostication.

- Four cohort studies found that the following clinical characteristics in children are significantly associated with severe to critical COVID-19 disease:
    a. Older age
    b. Shortness of breath
    c. Presence of a pre-existing medical condition, especially cardiac disease or diabetes

- The Center for Disease Control and Prevention reported that having an underlying medical condition may increase the risk of severe COVID-19 disease in the pediatric population.

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 collated data from February to early May 2020 in United States of America. The sample size of the journals ranged from 19-177 [7] [13] [14] [15].

Three out of the 4 studies have a sample population of pediatric individuals with mild to critical COVID-19 disease. One cohort study included children and also young adults aged 19 to 34 (n=12), which comprised 6.8% of the sample population [14]. All studies analyzed epidemiologic and clinical characteristics of the individuals. Outcomes noted were severe/critical, and need for mechanical ventilation and admission to pediatric intensive care unit as indirect measure of the desired outcome. (Appendix 1).

Critical Appraisal

Studies were assessed using the prognosis guide questions from the text authored by Dans et al [16]. Risk for bias was noted, including: (a) lack of or unclear objective definition of the desired outcome, wherein either no admission criteria for intensive care was mentioned [14], or admission to an intensive care unit was based on physician's decision [7], (b) study population also included young adults, which constituted 4 out of the 9 critically ill patients in one study [14], (c) incomplete follow-up of patients, wherein outcomes reported were only up to the time of the study's writing, and possible progression of disease was not taken into consideration [15] or not mentioned [14]. Given the appraisal done and possible biases listed, the overall validity assessment of the included studies is moderate (Appendix 2).

Prognostic Outcomes (Appendix 3, [11] [16])

Severe/Critical Disease versus Non-severe/critical
I. Age (4 studies)
- Patients with severe/critical disease had significantly older ages than those with non-severe condition (MD=6.62, 95%CI=4.23 to 9.00, p-value<0.00001, I^2=33%) [7] [13] [14] [15]

II. Symptoms (3-4 pooled studies)
- Shortness of breath/dyspnea 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) [7] [14] [15] [13]
- Symptoms not associated with severe disease are as follows:
  - Fever (OR=2.24, 95%CI=0.71 to 7.07, p-value=0.17, I^2=0%) [13] [14] [15]
  - Sore throat (OR=0.87, 95%CI=0.12 to 6.30, p-value=0.89, I^2=57%) [13] [14] [15]
  - Cough (OR=1.54, 95%CI=0.71 to 3.32, p-value=0.27, I^2=2%) [7] [13] [14] [15]

- Chest pain (OR=2.77, 95%CI=0.98 to 7.79, p-value=0.05, I^2=0%) [13] [14] [15]
- Gastrointestinal symptoms, including diarrhea and vomiting (OR=2.77, 95%CI=0.66 to 11.67, p-value=0.17, I^2=40%) [13] [14] [15]

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

- Presence of any comorbidity was significantly associated with severe disease (OR=4.02, 95%CI=1.55 to 10.43, p-value=0.004, I^2=0%) [7] [13] [14] [15].

IV. Specific Underlying Medical Condition (2-4 pooled studies)

- Cardiac disease was significantly associated with severe disease (OR=6.40, 95%CI=1.45 to 28.38, p-value=0.01, I^2=13%, n=3 studies) [7] [14] [15]
- Diabetes was significantly associated with severe disease (OR=7.01, 95%CI=1.54 to 31.95, p-value=0.01, I^2=0%, n=3 studies) [13] [14] [15]
- Co-morbidities not associated with severe disease are as follows:
  - Asthma (OR=1.11, 95%CI=0.45 to 2.77, p-value=0.82, I^2=0%) [7] [13] [14] [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] [14] [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] [14] [15]

Recommendations from Other Guidelines

Having 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 Center for Disease Control and Prevention [23].

CONCLUSION

Older age, shortness of breath, or presence of an underlying medical condition, especially cardiac disease and 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 more homogenous data and larger sample sizes are recommended.

Declaration of Conflict of Interest

No conflict of interest

REFERENCES

[1] Rothan, HA, Byrareddy SN, "The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak," *J Autoimmun.,* 2020:109:102433.

[2]   "World Health Organization," 24 August 2020. [Online]. Available: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200711-covid-19-sitrep-173.pdf.

[3]   Ludvigson JF, "Systematic review of COVID-19 in children shows milder cases an6d a better prognosis than adults," *Acta Paediatr,* 2020; 109(6): 1088-1095.

[4]   Tang A, Xu W, Shen M, Chen P, Li G, Liu Y, Liu L, "A retrospective study of the clinical characteristics of COVID-19 infection in 26 children," 2020; 2020.03.08.20029710. [Online]. Available: https://www.medrxiv.org/content/10.1101/2020.03.08.20029710v1.

[5]   Song W, Li J, Zou N, Guan W, Pan J, Xu W, "Clinical features of pediatric patients with coronavirus disease (COVID-19)," *J Clin Virol,* 2020; 127:104377.

[6]   Dong Y, Mo X, Hu Y, et al, "Epidemiology of COVID-19 Among Children in China," *Pediatrics,* 2020; 145(6): e20200702.

[7]   Chao JY, Derespina KR, Herold BC, et al, "Clinical Characteristics and Outcomes of Hospitalized and Critically Ill Children and Adolescents with Coronavirus Disease 2019 (COVID-19) at a Tertiary Care Medical Center in New York City [published online ahead of print, 2020May11]," *J Pediatr,* 2020; S0022-3476(20)30580-1.

[8]   Verdoni L, Mazza A, Gervasoni A, et al, "An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study," *Lancet,* 2020; 395(10239):1771-1778.

[9]   Panupattanapong S, Brooks EB, "New spectrum of COVID-19 manifestations in children: Kawasaki-like syndrome and hyperinflammatory response [published online ahead of print, 2020Jun3]," *Cleve Clin J Med.,* 2020; 10.3949/ccjm.87a.ccc039.

[10] Riphagen S, Gomez X, Gonzales-Martinez C, Wilkinson N, Theocharis P, "Hyperinflammatory shock in children during COVID-19 pandemic," *Lancet,* 2020; 395(10237):1607-1608.

[11] "Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020.".

[12] Bellino S, Punzo O, Rota MC, et al, "COVID-19 disease severity risk factors for pediatric patients in Italy," *Pediatrics,* 2020; doi: 10.1542/peds.2020-009399.

[13] Bhumbra S, Malin S, Kirkpatrick L, et al., "Clinical Features of Critical Coronavirus Disease 2019 in Children," *Pediatr Crit Care Med,* 2020.

[14] DeBiasi RL, Song X, Delaney M, et al, "Severe COVID-19 in Children and Young Adults in the Washington, DC Metropolitan Region [published online ahead of print, 20May13]," *J Pediatr,* 2020; 10.1016/jpeds: 2020.05.007.

[15] Zachariah P, Johnson CL, Halabi KC, et al, "Epidemiology, Clinical Features, and Disease Severity in Patients with Coronavirus Disease 2019 (COVID-19) in a Children's Hospital in New York City, New York [published online ahead of print, 2020Jun3]," *JAMA Pediatr,* 2020;e202430.

[16] Tan NCK, Uy EJB, Dans AL, "Evaluation of Articles on Prognosis.," *Painless Evidence-Based Med,* 2016; 74-86.

[17] D. Sun, H. Li, X. Lu and H. Xiao, "Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study," *World J Pediatr,* vol. 16, no. 3, pp. 251-259, 2020.

[18] M. Oulha, M. Bendavid, L. Berteloot, A. Corsia, F. Lesage, M. Vedrenne and E. Salvador, "Severe and fatal forms of COVID-19 in children," *Arch Pediatr,* vol. 27, no. 5, pp. 235-238, 2020.

[19] J. J. Bass, "Dyspnea," in *Clinical Methods: The History, Physical, and Laboratory Examinations*, 3rd ed., Boston: Butterworths, 1990.

[20] B. Wang, R. Li, Z. Lu and Y. Huang, "Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis," *Aging (Albany NY),* vol. 12, 2020.

[21] N. Dhochak, T. Singhal, S. K. Kabra and R. Lodha, "Pathophysiology of COVID-19: Why Children Fare Better than Adults?," *The Indian Journal of Pediatrics,* vol. 87, no. 8, pp. 537-546, July 2020.

[22] F. Boulad, M. Kamboj, N. Bouvier, A. Mauguen and A. Kung, "COVID-19 in Children With Cancer in New York City," *JAMA Oncol,* 2020.

[23] Centers for Disease Control and Prevention, "Coronavirus Disease: People with Certain Medical Conditions," 14 August 2020. [Online]. Available: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.html#children-underlying-conditions. [Accessed 1 September 2020].

APPENDIX 1. Characteristics of Included Studies

Table 1: Characteristics of Included Studies

No.	Title/Author	Study Design	Country	Population	Outcomes	Prognostic Factors
1	Clinical Characteristics and Outcomes of Hospitalized and Critically Ill Children and Adolescents with Coronavirus Disease 2019 (COVID-19) at a Tertiary Care Medical Center in New York City Chao JY, Derespina KR et al. [7]	Single center Retrospective Cohort	Children's Hospital at Montefiore, New York City	67 confirmed COVID-19 patients (46 hospitalized) by RT-PCR from March 15 to April 13, 2020	Need for Pediatric ICU admission (n=13) All PICU patients had signs of SIRS, and 3 (23.1%) developed septic shock requiring vasopressor support and fluid resuscitation.	The only clinical symptom found to be significantly associated with PICU admission was shortness of breath (92.3% vs. 30.3%, p <0.001). Obesity was present in 14 (30.4%) of admitted patients and asthma in 11 (24.4%) but neither was significantly associated with the need for PICU admission (p<0.99 for both).
2	Clinical Features of Critical Coronavirus Disease 2019 in Children Bhumbra S, Malin S et al. [13]	Single-center Retrospective Cohort Study	Riley Hospital for Children, Indianapolis, U.S.	19 inpatients diagnosed with COVID-19 from February 26 to May 4, 2020	Critical illness is defined as requiring admission to PICU (7 critically ill, 36%; 1 death, 5%)	Pediatric ICU admission is associated with longer duration of symptoms before presentation (p=0.036), lower oxygen saturation on room air (p=0.016), significantly more thrombocytopenia (p = 0.015), higher C-reactive protein (CRP) (p = 0.031). lower WBC (p = 0.039), although interquartile ranges (IQRs) were within normal range for both groups.
3	Severe COVID-19 in Children and Young Adults in the Washington, DC Metropolitan Region DeBiasi RL, Song X, et al. [14]	Single-center Retrospective Cohort Study	Children's National Hospital, Washington, DC	44 hospitalized pediatric and young adult SARS-COV 2 infected patients from March 15 to April 30, 2020	Inpatient critically ill (4 out of 9 was aged 19 years old and above) Of the critically ill patients, 4 required mechanical ventilation (3 ARDS, 2 MODS), 3 on bilevel positive airway pressure, 1 on nasal noninvasive ventilation via RAM cannula, and 1 via high-flow nasal cannula.	Adolescents and young adults >15 years of age represented 66% (6/9) of critical care admissions (P = .02) There was a predominance of males in the critically ill hospitalized cohort (67% male, 33% female), but this difference was not statistically significant (P = .26) Comparing the SARS- CoV-2 infected non-critically ill and critically ill hospitalized patients, there were no significant difference in the presence of underlying conditions overall or any specific underlying diagnosis (asthma, p=0.62; diabetes, p=0.37; neurologic, p=0.33;

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						obesity, p=0.21; cardiac, p=0.18; hematologic, p=0.57; oncologic, p=1.00). Patients in the critically ill cohort were not more likely to have fever or any other specific symptom compared with the non-critically ill cohort (fever, p=0.97; sore throat or congestion, p=0.28; cough, p=0.57; shortness of breath, p=0.13; diarrhea or vomiting, p=0.56; myalgia, 0.59; chest pain, p=0.40; loss of taste and/or smell, p=1.00; headache, p=1.00).
4	Epidemiology, Clinical Features, and Disease Severity in Patients With Coronavirus Disease 2019 (COVID-19) in a Children's Hospital in New York City, New York Zachariah P, Johnson C, et al [15]	Single-center Retrospective Cohort study	New York-Presbyterian Morgan Stanley Children's Hospital, New York City	50 SARS-COV2 confirmed patients aged 21 years and younger between March 1 and April 15, 2020	Severe Illness is defined as requirement for mechanical ventilation (n=9), 1 patient died	Severe disease was significantly higher in adolescents (median age of 14 years old, p<0.001). Obesity was significantly associated with mechanical ventilation in children 2 years or older (6 of 9 [67%] vs 5 of 25 [20%]; p= .03). Disease severity was not significantly higher in patients with asthma (p=0.29), neurologic (p>0.99), sickle cell disease (p=0.33), cardiac disease (p=0.56), diabetes (0.79), genetic syndromes (p=0.22), chronic respiratory disease (p>0.99) and immunosuppression (including solid organ transplantation, hematologic malignancy, solid tumors, hematopoietic stem cell transplant recipients and aplastic anemia p=0.66). Presence of shortness of breath (p<0.001) and gastrointestinal tract symptoms (p=0.01, includes abdominal pain, vomiting, diarrhea) are significantly associated with severe disease. Inflammatory markers (C-reactive protein: median, 8.978 mg/dL vs 0.64 mg/dL; procalcitonin: median, 0.31 ng/mL vs 0.17 ng/mL) were significantly elevated at admission for patients with severe disease (P < .001 for both).