

Infants Hospitalized for Acute COVID-19: Disease Severity in a Multicenter Cohort Study

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Short Report

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Abstract

Age is the most important determinant of COVID-19 severity. Infectious disease severity by age is typically J-shaped, with infants and the elderly carrying a high burden of disease. We report on the comparative disease severity between infants and older children in a multicenter retrospective cohort study of children 0 to 17 year old admitted for acute COVID-19 February 2020 through May 2021 in 17 pediatric hospitals. We compare clinical and laboratory characteristics and estimate the association between age group and disease severity using ordinal logistic regression. We found that infants comprised one third of cases, but were admitted for a shorter period (median 3 days IQR 2-5 versus 4 days IQR 2-7), had a lower likelihood to have an increased C-reactive protein and had half the odds of older children of having severe or critical disease (OR 0.50 (95% Confidence Interval 0.32-0.78)).

Conclusion: When compared to older children, there appeared to be a lower threshold to admit infants but their length of stay is shorter and they have a lower odds than older children of progressing to severe or critical disease.

What Is Known

-A small proportion of children infected with SARS-CoV-2 require hospitalisation for acute COVID-19 with a subgroup needing specialized intensive care to treat more severe disease.

-For most infectious diseases including viral respiratory tract infections, disease severity by age is J-shaped, with infants having more severe disease compared to older children.

What Is New

-One third of admitted children for acute COVID-19 during the first 14 months of the pandemic were infants.

-Infants had half the odds of older children of having severe or critical disease.

Introduction

The distribution of infectious disease severity by age is typically J-shaped [1]. Amongst children, neonates and infants have a high burden of disease [2], particularly with respiratory pathogens, and have the highest hospitalization rates [3]. The objective of this study was to determine whether this is true for coronavirus disease 2019 (COVID-19) in hospitalized children.

Methods

Seventeen pediatric hospitals (15 Canadian and one each in Iran and Costa Rica) included children up to 17 years of age, admitted February 1, 2020 through May 31, 2021 with detection of SARS-CoV-2. Patients

with incidental SARS-CoV-2 infection or who met World Health Organization (WHO) criteria for multisystem inflammatory syndrome in children (MIS-C)) [4] were excluded as acute COVID-19 was not the reason for admission. Following ethics approval at all sites, data were extracted into REDCap from medical records including demographics, role of SARS-CoV-2 in admission, comorbidities (prematurity, malignancy, asthma, chronic pulmonary, heart or renal disease, obesity, or significant congenital anomalies), antibiotic use, clinical presentation and course.

Cases were defined as mild (ward admission without supplemental oxygen), severe (ward admission with supplemental oxygen) or critical (admission to ICU or death) [5].

Children were divided into infants (up to 11 months of age) versus older children for the primary analysis. For those older than 90 days, only month of birth was recorded, so age was the number of months between the birth and admission month. Sensitivity analyses assessed outcomes i) in three age groups: up to 29 days, 30 days to 11 months and 12 months or older and ii) in infants 0 to 5 months versus 6 to 11 months old.

Descriptive statistics were used to summarize baseline characteristics of patients and comparative statistics was performed applying Kruskal-Wallis and chi square test. Associations between age group and disease severity were examined using ordinal logistic regression in STATA 13 (StataCorp), estimating the odds of mild versus severe or critical disease.

Results

There were 117 (36%) infants and 207 (64%) older children admitted for COVID-19 (Figure 1). Eighty-six infants (74%) had no comorbidities, of which 55 (64%) had mild, 18 (21%) severe and 13 (15%) critical disease, compared to 57 (28%) older children, including 32 (56%) with mild, 13 (23%) with severe and 12 (21%) having critical disease. Of 31 (26%) infants with comorbidities, 15 (48%) had mild, 7 (23%) severe and 9 (29%) critical disease. This contrasted to 150 (72%) older children with comorbidities, with mild, severe and critical disease in 55 (37%), 45 (30%) and 50 (33%), respectively.

Symptoms attributable to COVID-19 were similar in infants versus older children (Table 1). CRP was much more likely to be elevated in older children than in infants (67% versus 15%; p -value<0.0001). Similar proportions received antibiotics (67% of infants versus 60% of older children). Length of stay was shorter in infants (median 3 days IQR 2-5 versus 4 days IQR 2-7) (p -value=0.0043). For infants, the odds of having severe or critical disease was half that of older children (OR 0.50 (95%CI 0.32-0.78)). Compared to older children, the ORs for infants up to 29 days old and 30 days to 11 months were 0.56 (95%CI 0.28-1.11) and 0.48 (95%CI 0.29-0.79), respectively. There was insufficient evidence for differing disease severity in infants up to 5 months versus 6 to 11 months old (Supplement). Six deaths occurred in children 14 months to 9 years old.

Table 1

Symptoms, peak CRP values and use of antibiotics in hospitalized infants versus older children with a primary diagnosis of acute COVID-19

	Infants N=117	12 months to 17 years of age N=207
Cough	51 (44%)	135 (65%)
Shortness of breath	49 (42%)	125 (60%)
Rhinitis	49 (42%)	60 (29%)
Vomiting	21 (18%)	51 (25%)
Diarrhea	21 (18%)	49 (24%)
Wheezing	15 (13%)	37 (18%)
Rash	5 (4%)	14 (7%)
New-onset seizures	3 (3%)	5 (2%)
Conjunctivitis	0 (0%)	8 (4%)
Splenomegaly	0 (0%)	3 (1%)
Hepatomegaly	0 (0%)	2 (1%)
Fever history		
Fever documented in hospital	40/106 (38%)	90/182 (49%)
Fever prior to admission only	39/106 (37%)	53/182 (29%)
No fever	27/106 (25%)	39/182 (21%)
Data missing	11/117	25/207
Elevated peak CRP (> 8.0 mg/L)	14/94 (15%)	114/169 (67%)
Antibiotics during admission		
None	39 (33%)	82 (40%)
Started for possible bacterial pneumonia	16 (14%)	75 (36%)
Started for other possible or proven bacterial infection	61 (52%)	49 (24%)
Data missing	1 (1%)	1 (0.5%)
Legend: CRP – C-reactive protein		

Discussion

Over one-third of children admitted with acute COVID-19 were infants. However, the proportion of infants with severe or critical disease was lower than for older children. As far as we are aware, this is the first study to directly compare the severity of illness in infants versus older children. Previous studies that analyzed the severity in admitted infants reported that only 4 of 34 symptomatic infants up to 90 days of age had severe or critical disease [6] and that only 1 of 14 infants was critically ill [7].

CRP was much more likely to be elevated in older children than in infants (67% versus 15%). CRP is a sensitive marker of inflammation even in neonates [8, 9] so we hypothesize a lower level of measurable inflammation in infants compared to older children admitted with COVID-19, but it may reflect admission of infants with milder disease. Less inflammation might partially explain why infants accounted for only 4% of MIS-C cases in a large series [10].

Limitations are that this study is not population based and investigated children admitted primarily to tertiary care centers. The threshold is presumably lower to admit infants versus older children with a similar severity of illness, especially if they are febrile and less than 90 days old [11]. This may explain why admitted infants in our study had less severe disease than did older children. Insufficient power prevents us to provide evidence for additional and more specific age and other subgroups. Furthermore, when the outcome is common, OR's calculated cannot be interpreted as risks.

In conclusion, contrary to what is observed in most other infectious diseases [1], SARs-CoV-2 infection is not more severe in infants admitted with acute COVID-19 compared to older children.

List Of Abbreviation

CI – confidence interval

COVID-19 – coronavirus disease of 2019

CRP – C-reactive protein

ICU – intensive care unit

IQR – inter-quartile range

MIS-C – multisystem inflammatory disorder in children

OR – odds ratio

WHO – World Health Organization

Declarations

Funding/Support:

No funding was secured for this study.

Conflict of Interest/Competing Interest:

The authors have no competing interests to declare that are relevant to the content of this article.

Availability of data and material:

The data are not publicly available

Code availability:

The codes are available on request

Authors' contributions:

Dr Merckx analyzed the data and reviewed and revised the manuscript.

Dr Barton conceptualized and designed the study, collected data and reviewed and revised the manuscript.

Drs Morris, Bitnun, Gill, El Tal, Laxer, Yeh, Yea, Ulloa-Gutierrez, Brenes-Chacon, Yock-Corrales, Ivankovich-Escoto, Soriano-Fallas, Hernandez-de Mezerville, Papenburg, Lefebvre, Nateghian, Aski, Manafi, Dwilow, Bullard, Cooke, Dewan, Restivo, Lopez, Sadarangani, Roberts, Petel, Le Saux, Bowes, Purewal, Lautermilch, Tehseen , Bayliss, Wong, Viel-Thériault, Piche, Top, Leifso , Foo, and Panetta collected data and reviewed and revised the manuscript.

Dr Robinson conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ethics approval:

This study was performed in line with the principles of the Declaration of Helsinki. Ethics approval was obtained primary at the University of Alberta (Pro00099426) and sequentially from all participating sites.

Consent to participate:

Not applicable

Consent for publication:

Not applicable

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References

1. Glynn JR, Moss PA. Systematic analysis of infectious disease outcomes by age shows lowest severity in school-age children. *Sci data*. 2020;7(1):1-3.
2. Paulson KR, Kamath AM, Alam T, Bienhoff K, Abady GG, Abbas J, Abbasi-Kangevari M, Abbastabar H, Abd-Allah F, Abd-Elsalam SM, Abdoli A. Global, regional, and national progress towards Sustainable Development Goal 3.2 for neonatal and child health: all-cause and cause-specific mortality findings from the Global Burden of Disease Study 2019. *The Lancet*. 2021;398(10303):870-905.
3. Goto T, Tsugawa Y, Mansbach JM, Camargo CA Jr, Hasegawa K. Trends in Infectious Disease Hospitalizations in US Children, 2000 to 2012. *Pediatr Infect Dis J*. 2016;35(6):e158-e163
4. World Health Organization. Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. 2020. <https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19>. Accessed August 10, 2021.
5. Kushner LE, Schroeder AR, Kim J, Mathew R. "For COVID" or "With COVID": Classification of SARS-CoV-2 Hospitalizations in Children. *Hosp Pediatr*. 2021 May
6. Shaiba LA, Altirkawi K, Hadid A et al. COVID-19 Disease in Infants Less Than 90 Days: Case Series. *Front Pediatr*. 2021;9.
7. DeBiasi RL, Song X, Delaney M, Bell M, Smith K, Pershad J et al. Severe Coronavirus Disease-2019 in Children and Young Adults in the Washington DC Metropolitan Region. *J Pediatr*. 2020; 223:199-203.
8. Lacaze-Masmonteil T, Rosychuk RJ, Robinson JL. Value of a single C-reactive protein measurement at 18 h of age. *Arch Dis Child Educ Pract Ed*. 2014;99(1):F76-9.
9. Petel D, Winters N, Gore GC et al. Use of C-reactive protein to tailor antibiotic use: a systematic review and meta-analysis. *BMJ open*. 2018;8(12):e022133.
10. Godfred-Cato S, Tsang CA, Giovanni J et al. Multisystem Inflammatory Syndrome in Infants < 12 months of Age, United States, May 2020–January 2021. *Pediatr Infect Dis J*. 2021;40(7):601-5.
11. Pantell RH, Roberts KB, Adams WG, Dreyer BP, Kuppermann N, O'Leary ST, Okechukwu K, Woods CR. Evaluation and management of well-appearing febrile infants 8 to 60 days old. *Pediatrics*. 2021;148(2).

Figures

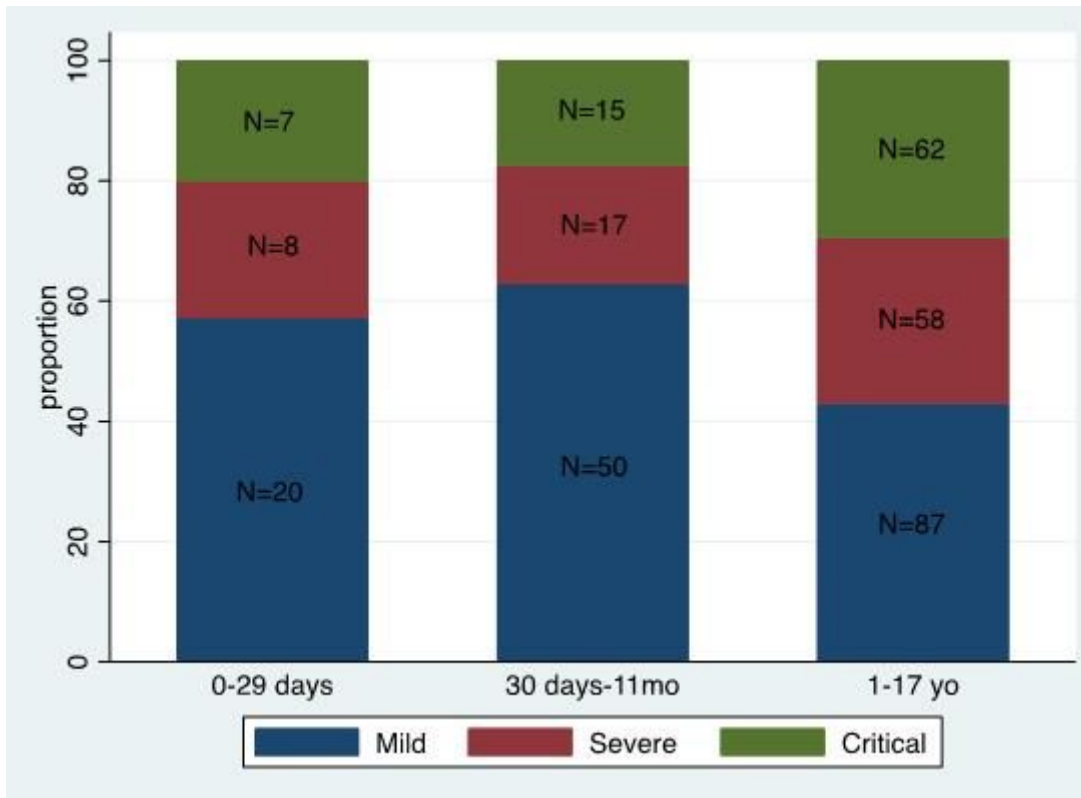


Figure 1

Proportion and absolute number of neonates, infants and children with mild, severe and critical outcome COVID-19 admission. N=absolute number of children included in the group

Supplementary Files

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- [MerckxSupplementNov22COVID19infant.docx](#)