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SHORT COMMUNICATION

Infants hospitalized for acute COVID-19: disease severity in a multicenter cohort study

Joanna Merckx[1] · Shaun K. Morris[2] · Ari Bitnun[2] · Peter Gill[2] · Tala El Tal[2] · Ronald M. Laxer[2] · Ann Yeh[2] · Carmen Yea[2] · Rolando Ulloa-Gutierrez[3] · Helena Brenes-Chacon[3] · Adriana Yock-Corrales[3] · Gabriela Ivankovich-Escoto[3] · Alejandra Soriano-Fallas[3] · Marcela Hernandez-de Mezerville[3] · Jesse Papenburg[1,4] · Marie-Astrid Lefebvre[4] · Alireza Nateghian[5] · Behzad Haghighi Aski[5] · Ali Manafi[5] · Rachel Dwilow[6] · Jared Bullard[6] · Suzette Cooke[7] · Tammie Dewan[7] · Lea Restivo[7] · Alison Lopez[8] · Manish Sadarangani[8,9,10] · Ashley Roberts[8,9] · Michelle Barton[11] · Dara Petel[11] · Nicole Le Saux[12] · Jennifer Bowes[12] · Rupeena Purewal[13] · Janell Lautermilch[13] · Sarah Tehseen[13] · Ann Bayliss[14] · Jacqueline K. Wong[15] · Isabelle Viel-Thériault[16] · Dominique Piche[17] · Karina A. Top[17] · Kirk Leifso[18] · Cheryl Foo[19] · Luc Panetta[20] · Joan Robinson[21]

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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 years old admitted for acute COVID-19 from 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 was shorter and they had 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 hospitalization 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.*

Keywords Infants · COVID-19 · Disease severity · Age

Abbreviations

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

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✉ Joanna Merckx
joanna-trees.merckx@mcgill.ca

Extended author information available on the last page of the article

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 (it was not the reason for admission and did not prolong hospitalization) 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.

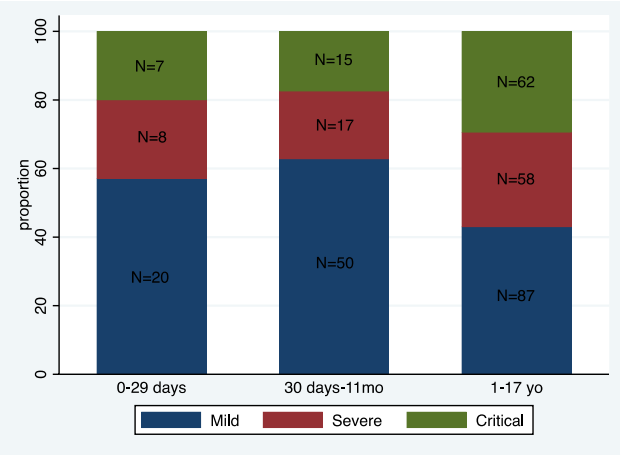
Cases were defined as mild (ward admission without supplemental oxygen), severe (ward admission with supplemental oxygen), or critical (admission to ICU or death) [5].

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 (Fig. 1) after incidental SARS-CoV-2 ($N = 346$) and MIS-C cases ($N = 144$) were excluded



N=absolute number of children included in the group

Fig. 1 Proportion and absolute number of neonates, infants, and children with mild, severe, and critical outcome COVID-19 admission

(Supplement Flow Chart Fig. 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. One older child with severe disease was admitted to ICU for reasons unrelated to COVID-19.

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) (Table 1). The indication was possible bacterial pneumonia in 21% of infants given antibiotics versus 36% of older children. Bacterial coinfection was confirmed in 9 infants (8%) versus 6 older children (3%). Proportions of confirmed viral co-infection were similar in infants and older children, 8% and 9%, respectively.

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; all had comorbidities.

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%)

CRP C-reactive protein

Discussion

Over one-third of children admitted with acute COVID-19 were infants, in a period with wide circulation of wild-type virus and of the variants-of-concern alpha and delta. 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 hospitalized 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 the rare outcome of mortality and 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.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s00431-022-04422-x.

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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.

Availability of data and material The data are not publicly available.

Code availability The codes are available on request.

Declarations

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

Consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no interests.

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Authors and Affiliations

Joanna Merckx[1] · Shaun K. Morris[2] · Ari Bitnun[2] · Peter Gill[2] · Tala El Tal[2] · Ronald M. Laxer[2] · Ann Yeh[2] · Carmen Yea[2] · Rolando Ulloa-Gutierrez[3] · Helena Brenes-Chacon[3] · Adriana Yock-Corrales[3] · Gabriela Ivankovich-Escoto[3] · Alejandra Soriano-Fallas[3] · Marcela Hernandez-de Mezerville[3] · Jesse Papenburg[1,4] · Marie-Astrid Lefebvre[4] · Alireza Nateghian[5] · Behzad Haghighi Aski[5] · Ali Manafi[5] · Rachel Dwilow[6] · Jared Bullard[6] · Suzette Cooke[7] · Tammie Dewan[7] · Lea Restivo[7] · Alison Lopez[8] · Manish Sadarangani[8,9,10] · Ashley Roberts[8,9] · Michelle Barton[11] · Dara Petel[11] · Nicole Le Saux[12] · Jennifer Bowes[12] · Rupeena Purewal[13] · Janell Lautermilch[13] · Sarah Tehseen[13] · Ann Bayliss[14] · Jacqueline K. Wong[15] · Isabelle Viel-Thériault[16] · Dominique Piche[17] · Karina A. Top[17] · Kirk Leifso[18] · Cheryl Foo[19] · Luc Panetta[20] · Joan Robinson[21]

Shaun K. Morris
shaun.morris@sickkids.ca

Ari Bitnun
ari.bitnun@sickkids.ca

Peter Gill
peter.gill@sickkids.ca

Tala El Tal
tala.eltal@sickkids.ca

Ronald M. Laxer
ronald.laxer@sickkids.ca

Ann Yeh
ann.yeh@sickkids.ca

Carmen Yea
carmen.yea@sickkids.ca

Rolando Ulloa-Gutierrez
rolandoug@gmail.com

Helena Brenes-Chacon
helenabrenes@gmail.com

Adriana Yock-Corrales
adriyock@gmail.com

Gabriela Ivankovich-Escoto
givankovich@gmail.com

Alejandra Soriano-Fallas
alejsoriano@gmail.com

Marcela Hernandez-de Mezerville
marcelahdm@hotmail.com

Jesse Papenburg
jesse.papenburg@mail.mcgill.ca

Marie-Astrid Lefebvre
marie-astrid.lefebvre@muhc.mcgill.ca

Alireza Nateghian
alirezanateghian41@gmail.com

Behzad Haghighi Aski
Haghighi.b@iums.ac.ir

Ali Manafi
manafi.a@iums.ac.ir

Rachel Dwilow
Rachel.Dwilow@umanitoba.ca

Jared Bullard
Jared.Bullard@gov.mb.ca

Suzette Cooke
Suzette.Cooke@albertahealthservices.ca

Tammie Dewan
tammie.dewan@albertahealthservices.ca

Lea Restivo
Lea.Restivo@albertahealthservices.ca

Alison Lopez
alison.lopez17@gmail.com

Manish Sadarangani
msadarangani@bcchr.ubc.ca

Ashley Roberts
aroberts6@cw.bc.ca

Michelle Barton
Michelle.BartonForbes@lhsc.on.ca

Dara Petel
darapetel@gmail.com

Nicole Le Saux
lesaux@cheo.on.ca

Jennifer Bowes
jbowes@cheo.on.ca

Rupeena Purewal
rupeenapurewal@gmail.com

Janell Lautermilch
jtl494@mail.usask.ca

Sarah Tehseen
Sarah.Tehseen@saskhealthauthority.ca

Ann Bayliss
Ann.Bayliss@thp.ca

Jacqueline K. Wong
wongj37@mcmaster.ca

Isabelle Viel-Thériault
isabelle.viel-theriault.1@ulaval.ca

Dominique Piche
Dominique.Piche@dal.ca

Karina A. Top
karina.top@dal.ca

Kirk Leifso
Kirk.Leifso@kingstonhsc.ca

Cheryl Foo
cpz.foo@gmail.com

Luc Panetta
luc.panetta@hotmail.fr

Joan Robinson
jr3@ualberta.ca

[1] Department of Epidemiology, Biostatistics and Occupational Health, McGill University, McGill College, Suite 1200, Montreal, QC H3A 1G1, Canada

[2] Department of Pediatrics, University of Toronto, Toronto, ON, Canada

[3] Department of Pediatrics, Caja Costarricense de Seguro Social (CCSS), Hospital Nacional de Niños Dr. Carlos Sáenz Herrera, San José, Costa Rica

[4] Department of Pediatrics, McGill University, Montreal, QC, Canada

[5] Department of Pediatrics, University of Medical Sciences, Tehran, Iran

[6] Department of Pediatrics, University of Manitoba, Winnipeg, MB, Canada

[7] Department of Pediatrics, University of Calgary, Calgary, AB, Canada

[8] British Columbia Children's Hospital, Vancouver, BC, Canada

[9] Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada

[10] Vaccine Evaluation Center, BC Children's Hospital Research Institute, Vancouver, BC, Canada

[11] Department of Pediatrics, Western University, London, ON, Canada

[12] Department of Pediatrics, University of Ottawa, Ottawa, ON, Canada

[13] Department of Pediatrics, University of Saskatchewan, Saskatoon, SK, Canada

[14] Department of Pediatrics, Trillium Health Partners, Mississauga, ON, Canada

[15] Department of Pediatrics, McMaster University, Hamilton, ON, Canada

[16] Department of Pediatrics, CHU de Québec-Université Laval, Québec, QC, Canada

[17] Department of Pediatrics, Dalhousie University, Halifax, NS, Canada

[18] Department of Pediatrics, Queen's University, Kingston, ON, Canada

[19] Department of Pediatrics, Memorial University, St John's, Newfoundland and Labrador, Canada

[20] Department of Pediatrics, Université de Montréal, Montreal, QC, Canada

[21] Department of Pediatrics, University of Alberta, Edmonton, AB, Canada