Pediatric RESEARCH

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CLINICAL RESEARCH ARTICLE

Risk profiles of severe illness in children with COVID-19: a meta-analysis of individual patients

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BACKGROUND: We prepared a meta-analysis on case reports in children with COVID-19, aiming to identify potential risk factors for severe illness and to develop a prediction model for risk assessment.

METHODS: Literature retrieval, case report selection, and data extraction were independently completed by two authors. STATA software (version 14.1) and R programming environment (v4.0.2) were used for data handling.

RESULTS: This meta-analysis was conducted based on 52 case reports, including 203 children (96 boys) with COVID-19. By severity, 26 (12.94%), 160 (79.60%), and 15 (7.46%) children were diagnosed as asymptomatic, mild/moderate, and severe cases, respectively. After adjusting for age and sex, 11 factors were found to be significantly associated with the risk of severe illness relative to asymptomatic or mild/moderate illness, especially for dyspnea/tachypnea (odds ratio, 95% confidence interval, *P*: 6.61, 4.12–9.09, <0.001) and abnormal chest X-ray (3.33, 1.84–4.82, <0.001). A nomogram modeling age, comorbidity, cough, dyspnea or tachypnea, CRP, and LDH was developed, and prediction performance was good as reflected by the *C*-index.

CONCLUSIONS: Our findings provide systematic evidence for the contribution of comorbidity, cough, dyspnea or tachypnea, CRP, and LDH, both individually and jointly, to develop severe symptoms in children with asymptomatic or mild/moderate COVID-19.

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IMPACT:

- We have identified potential risk factors for severe illness in children with COVID-19.
- We have developed a prediction model to facilitate risk assessment in children with COVID-19.
- We found the contribution of five risk factors to develop severe symptoms in children with asymptomatic or mild/moderate COVID-19.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), originated in Wuhan and has rapidly spread to 220 countries, areas, or territories globally, infecting nearly 56 million people of all ages and causing over 1344,003 deaths as of November 20, 2020 (https://www.who.int/emergencies/diseases/novel-coronavirus-2019). Epidemiologic evidence indicates that children are less likely to develop severe COVID-19 than adults, and infected children typically have a good prognosis,[1] with "trained immunity" as a potential explanation.[2] However, controversies remain, as a study from China reported that infants and younger children are more likely to develop severe clinical manifestations than older children, likely due to immature immune system.[3] Despite children represents about 1–2% of total COVID-19 burden,[4] the actual fatality figure is relatively high. In the medical literature, reports regarding the clinical features of children with COVID-19 are scarce, with the majority arising from studies of cases report and case series. Thus the aggregation of these cases via a meta-analysis may help to better understand its clinical features and risk profiles. Although most pediatric COVID-19 patients are not severe,[3,5–7] a serious COVID-19 illness could result in severe outcomes, including an intensive care unit (ICU) admission and even death in children. Considering the fact that the respiratory structural characteristics and immune response system differ remarkably between children and adults,[8–10] one of the most urgent tasks facing us is to seek potential predictors that can assist in improving clinical management of children with COVID-19.

To yield more information, we prepared a meta-analysis on case reports in children with COVID-19, aiming to test the hypothesis that some potential risk factors can lead to severe COVID-19 of children, and if this hypothesis is confirmed, we further develop a prediction model to facilitate risk assessment.

METHODS

Literature search

Case reports, published in English or Chinese language, were identified by retrieving PubMed, EMBASE (Excerpt Medica Database), and Web of Science databases before May 1, 2020, using key terms "COVID-19," "2019-nCoV," "SARS-CoV-2," "children," and "pediatric." Literature search was independently

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Table 1. The baseline characteristics of study children with COVID-19 from 52 case reports.

Characteristics	Asymptomatic COVID-19 ($n = 26$)	Mild/moderate COVID-19 ($n = 160$)	Severe COVID-19 ($n = 15$)	*P*
Demographic information				
Age (months)	72 (12.96, 120)	48 (12, 108)	12.96 (8.04, 96)	0.458
Age				0.594
≤1 year	5 (19.2%)	37 (23.9%)	5 (33.3%)	
>1 year	21 (80.8%)	118 (76.1%)	10 (66.7%)	
Boys	10 (40%)	74 (48.1%)	12 (80%)	0.037
Day to negative	8.5 (6.5, 15)	10 (5, 13)	5 (5,5)	0.658
Comorbidity	0 (0, 0)	0 (0, 0)	0 (0,1)	<0.001
Temperature	36.4 (36, 36.7)	38.1 (37.6, 38.55)	39 (37.9, 40)	<0.001
Clinical symptoms				
Fever	0 (0%)	97 (60.6%)	11 (73.3%)	<0.001
Nose symptoms	0 (0%)	20 (12.5%)	0 (0%)	0.058
Throat symptoms	0 (0%)	22 (13.8%)	2 (13.3%)	0.132
Cough	0 (0%)	58 (36.3%)	11 (73.3%)	<0.001
Phlegm sputum	0 (0%)	3 (1.9%)	4 (26.7%)	<0.001
Asthma/wheeze	0 (0%)	4 (2.5%)	0 (0%)	0.593
Short of breath	0 (0%)	2 (1.3%)	1 (6.7%)	0.203
Dyspnea/tachypnea	0 (0%)	2 (1.3%)	13 (86.7%)	<0.001
diarrhea	0 (0%)	12 (7.5%)	5 (33.3%)	0.001
Nausea/vomiting	0 (0%)	13 (8.1%)	6 (40%)	<0.001
Abdominal pain	0 (0%)	3 (1.9%)	0 (0%)	0.677
Headache	0 (0%)	4 (2.5%)	1 (6.7%)	0.418
Fatigue symptoms	0 (0%)	6 (3.8%)	2 (13.3%)	0.104
Chest radiography features				
Abnormal chest X-ray	1 (4.3%)	81 (65.3%)	12 (92.3%)	<0.001
Normal chest X-ray/CT	22 (95.7%)	43 (34.7%)	1 (7.7%)	<0.001
X-ray/CT unilateral injury	0 (0%)	23 (18.5%)	3 (23.1%)	
X-ray/CT bilateral injury	0 (0%)	15 (12.1%)	7 (53.8%)	
GGO (CT)	0 (0%)	43 (26.9%)	7 (46.7%)	0.002
Laboratory biomarkers				
WBC ($\times 10^9$/L)	8.14 (6.5, 9.42)	6.7 (5.45, 8.6)	9 (4.43, 11.96)	0.173
LYMPH (%)	59.9 (25.4, 66.7)	51 (42.3, 56.5)	NA	0.933
LYMPH ($\times 10^9$/L)	2.89 (2.4, 3.7)	2.69 (1.75, 4.05)	1.76 (0.8, 2.47)	0.042
NEUT (%)	27.8 (25.4, 32.1)	34.2 (25, 42)	NA	0.568
NEUT ($\times 10^9$/L)	3.2 (2.1, 5.56)	2.49 (1.3, 3.6)	3.8 (1.27, 7.77)	0.226
MONO	NA	1.26 (0.95, 7.45)	0.89 (0.08, 1.69)	0.643
HGB (g/L)	133 (128, 142)	126 (115, 136)	108 (100, 153)	0.378
PLT ($\times 10^9$/L)	278 (260, 358)	256 (188, 311)	193 (183.5, 216)	0.131
CRP (mg/mL)	0.71 (0.2, 3.58)	2.01 (0.5, 8)	24.6 (6.48, 24.8)	0.019
PCT (ng/mL)	0.08 (0.04, 0.14)	0.07 (0.03, 0.1)	0.25 (0.11, 0.43)	0.070
ALT (U/L)	15.74 (13, 25.7)	15.74 (13, 23)	20 (12, 88)	0.787
AST (U/L)	33.21 (23.19, 42)	31.36 (24, 40.8)	63 (63, 63)	0.373
Cr (μmol/L)	78 (75, 81)	29 (22.8, 48)	224 (45, 224.5)	0.005
LDH (U/L)	175 (159.4, 218)	229.35 (177.1, 367.5)	485 (361, 609)	0.104
CK (U/L)	68 (68, 85)	75 (46, 112)	62 (50.5, 80.4)	0.540
CKMB (U/L)	52 (34, 76)	23 (12.3, 30)	NA	0.010
D-dimer (mg/L)	0.25 (0.16, 0.3)	0.33 (0.25, 0.6)	NA	0.095
NEUT/LYMPH	1.14 (1, 1.99)	0.93 (0.46, 2.02)	3.13 (0.02, 6.84)	0.428
PLT/LYMPH	114.29 (77.42, 151.16)	101.92 (61.67, 175.86)	106.43 (74.14, 212.93)	0.957
LYMPH/MONO	NA	2.32 (0.19, 2.87)	4.11 (1.47, 6.75)	0.563
WBC/LYMPH	2.13 (1.91, 2.64)	2.27 (1.84, 3.17)	4.83 (3.03, 8.2)	0.089

The *p* value was calculated using the rank sum test or χ^2 test where appropriate. Data are expressed as median (interquartile range) or count (percentage), if appropriate.
GGO ground-glass opacity, *CT* computed tomography, *WBC* white blood cell, *NEUT* neutrophil, *LYMPH* lymphocyte, *MONO* monocyte, *HGB* hemoglobin, *PLT* platelet, *CRP* C-reactive protein, *PCT* procalcitonin, *ALT* alanine transaminase, *AST* aspartate aminotransferase, *Cr* creatinine, *LDH* lactate dehydrogenase, *CK* creatine kinase, *CKMB* creatine phosphokinase-isoenzyme-MB.

done by two authors (B.Z. and Y.Y.), and disagreement was resolved by consensus.

Diagnosis
For each eligible case report or case series, COVID-19 should be diagnosed by high-throughput sequencing or real-time PCR kit for nasal/pharyngeal swab specimens.

Clinical classification of COVID-19
The severity of COVID-19 was defined according to clinical features, laboratory testing, and chest X-ray imaging, including asymptomatic infection, mild, moderate, severe, and critical cases.[11]

Asymptomatic infection: without any clinical symptoms and signs and the chest imaging is normal, while the 2019-nCoV nucleic acid test is in a positive period.

Mild: symptoms of acute upper respiratory tract infection, including fever, fatigue, myalgia, cough, sore throat, runny nose, and sneezing. Physical examination shows congestion of the pharynx and no auscultory abnormalities. Some cases may have no fever or have only digestive symptoms, such as nausea, vomiting, abdominal pain, and diarrhea.

Moderate COVID-19: with pneumonia, frequent fever and cough, mostly dry cough, followed by productive cough, some may have wheezing, but no obvious hypoxemia such as shortness of breath, and from the lungs one can hear sputum or dry snoring and/or wet snoring. Some cases may have no clinical signs and symptoms, but chest CT shows lung lesions, which are subclinical.

Severe COVID-19: early respiratory symptoms such as fever and cough and may be accompanied by gastrointestinal symptoms, such as diarrhea. The disease usually progresses around 1 week, and dyspnea occurs, with central cyanosis. Oxygen saturation is <92%, with other hypoxia manifestations.

Critical COVID-19: children can quickly progress to acute respiratory distress syndrome or respiratory failure and may also have shock, encephalopathy, myocardial injury or heart failure, coagulation dysfunction, and acute kidney injury. Organ dysfunction can be life threatening.

Selection process
For each retrieved case report or case series, two authors (B.Z. and Y.Y.) independently reviewed title and abstract for initial selection, and if necessary full text for eligibility. Disagreement was discussed between the two authors until a consensus on eligibility was attained. In case of more than one report of the same patients, we abstracted data from the most complete report.

Data extraction
Data from each eligible patient were independently extracted by two authors (B.Z. and Y.Y.), and they were typed into a predesigned Microsoft Office ExcelTM spreadsheet, including first author's name, year of publication, country where participants were enrolled, study type, sex, age, clinical symptoms and signs, laboratory findings, imaging features, and severity. Extracted data were compared for consistency using the kappa statistic, and any divergence was resolved by a third author (W.N.).

Quality assessment
The Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI)[12] scale was employed for critical appraisal, and this scale ranges from 0 (the worst) to 16 points (the best).

Statistical analysis
Based on the severity of COVID-19, all study children were classified into three groups (asymptomatic, mild/moderate, and severe/critical). Continuous variables were tested for normality by using skewness and kurtosis test. Skewed continuous variables are expressed as median (interquartile range) and normally distributed variables as mean (standard deviation or SD). Categorical variables are expressed as number (percentage). Between-group comparisons were implemented by rank-sum test or χ^2 test, where appropriate. Potential risk factors for severity were selected by logistic regression analyses at a statistical significance level of 5% before and after adjusting for confounding factors, including age and sex. The magnitude of risk association is quantified by odds ratio (OR) and 95% confidence interval (95% CI).

Finally, on the basis of significant risk factors, a prediction nomogram, generated by the R programming environment version 3.5.2 for Windows, was established to enhance clinical application, and calibration curve and the *C*-index were used to assess prediction performance.

Unless otherwise reported, statistical analyses were completed using the STATA software version 14.0 (Stata Corp, TX) for Windows. Two-sided *P* value <5% was reported to be statistically significant. The power to detect statistical significance was estimated by using the PS Power and Sample Size Calculations software version 3.0.

RESULTS

Baseline characteristics
After comprehensive literature search, 52 case reports were eligible for inclusion,[4,13–63] including 203 children (mean age: 5.46 years, 96 boys and 98 girls) with COVID-19. By severity, 26 (12.94%), 160 (79.60%), and 15 (7.46%) children were diagnosed as asymptomatic, mild/moderate, and severe cases, respectively, and their baseline characteristics are provided in Table 1. As assessed by the JBI-MAStARI scale,[12] the quality score of all case reports ranged from 13 to 16.

Identification of potential risk factors
After adjusting for age and sex, 11 factors were found to be significantly associated with the risk of severe illness relative to asymptomatic or mild/moderate illness (Table 2), especially for dyspnea/tachypnea (OR, 95% CI, *P*: 6.61, 4.12–9.09, <0.001) and abnormal chest X-ray (3.33, 1.84–4.82, <0.001). The power to detect significance was >90% for the above comparisons.

Table 2. Identification of significant factors in association with severe COVID-19 relative to mild/moderate or asymptomatic COVID-19.

Significant factors	Unadjusted			Adjusted*		
	OR	95% CI	*P*	OR	95% CI	*P*
Comorbidity	2.74	1.41–4.07	<0.001	2.76	1.39–4.13	<0.001
Fever	2.53	1.45–3.60	<0.001	2.64	1.52–3.75	<0.001
Temperature	2.29	1.00–3.60	0.001	2.15	0.81–3.49	0.002
Cough	2.39	1.29–3.48	<0.001	2.27	1.15–3.38	<0.001
Phlegm/sputum	3.12	1.51–4.72	<0.001	2.89	1.09–4.69	0.002
Dyspnea/tachypnea	6.40	4.36–8.44	<0.001	6.61	4.12–9.09	<0.001
Diarrhea	2.08	0.92–3.25	<0.001	1.95	0.61–3.29	0.004
Abnormal chest X-ray	3.32	1.84–4.79	<0.001	3.33	1.84–4.82	<0.001
GGO (CT)	1.59	0.68–2.50	0.001	1.63	0.65–2.59	0.001
CRP	2.23	0.57–3.89	0.009	2.17	0.51–3.84	0.011
LDH	1.97	0.02–4.15	0.007	1.60	0.94–4.51	0.017

The *P* value was calculated after adjusting for age and sex.
OR odds ratio, *95% CI* 95% confidence interval, *GGO* ground-glass opacity, *CT* computed tomography, *WBC* white blood cell, *LYMPH* lymphocyte, *CRP* C-reactive protein, *LDH* lactate dehydrogenase.

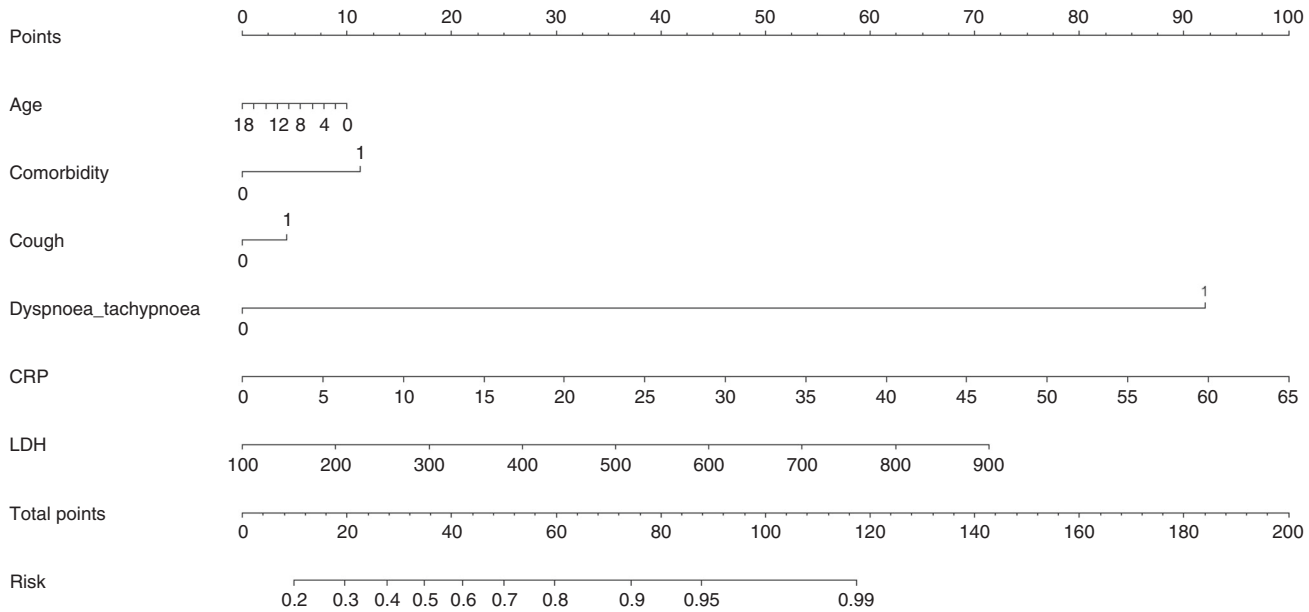

Fig. 1 Development of a nomogram model in predicting the severe illness in children with COVID-19. CRP C-reactive protein, LDH lactate dehydrogenase.

Prediction nomogram model

Due to missing values or establishment of some radiographic features such as abnormal chest X-ray, five factors, including comorbidity, cough, dyspnea or tachypnea, C-reactive protein (CRP), and lactate dehydrogenase (LDH), were retained for further model development, together with age.

To facilitate clinical application, a nomogram model regressing age, comorbidity, cough, dyspnea or tachypnea, CRP, and LDH was developed (Fig. 1), and the prediction performance was good, as revealed by the calibration curve (Supplementary Fig. 1) and the *C*-index (80.1%).

Taking the prediction nomogram model for pediatric COVID-19 severity as an example, assuming a child aged 9 years (5 points), with other comorbidities (11 points), with cough (5 points), with dyspnea or tachypnea (92 points), with circulating CRP of 30 mg/mL (45 point), and with LDH of 200 mg/mL (8 points), the probability of having severe pediatric COVID-19 was estimated to be >99%.

DISCUSSION

The findings of this meta-analysis can enrich our understanding on the risk profiling of children with COVID-19 in predisposition to severe illness. In particular, we have identified five clinical characteristics or biomarkers in significant and independent association with COVID-19 severity, in line with the findings of some previous studies.[64,65] Importantly, their prediction, together with age, was particularly evident in a nomogram model. To the best of our knowledge, this is the first study that has interrogated the possible risk factors of pediatric COVID-19 severity.

Although there are currently no effective antiviral drugs for SARS-CoV-2, prompt identification and early respiratory supportive care would provide relief in severe cases and reduce mortality. Recent studies estimated that 26–32% of adults were committed to ICU, and 1% patients with COVID-19 were asymptomatic.[66] In contrast, we found only 7.5% of children with severe illness and 12.9% of children were completely asymptomatic, in agreement with a previous report.[67] In this study, we found that children with COVID-19 who had clinical features such as fever, cough, phlegm/sputum, and dyspnea/tachypnea and chest radiography features such as abnormal chest X-ray, bilateral injury, or ground-glass opacity tended to develop into serious conditions, the findings consistent with that in adults.[68–70]

The findings of this present study, along with other studies,[1,71] supported the note that children may have a better prognosis for COVID-19, when compared to adults. The reasons behind this claim are manifold, mainly because the SARS-CoV-2 S protein attaches to the angiotensin-converting enzyme 2,[1,71,72] which is less developed at a younger age,[73] and the percentage of children infected with COVID-19 having an exaggerated inflammatory response against the virus are not commonly described thus far.[71,74]

This meta-analysis of individual participant data was limited by the clinical heterogeneity of different reports, measurement bias of circulating biomarkers, and the limited number of assessable children with COVID-19, especially with severe illness.

Despite these limitations, our findings provide evidence for the contribution of comorbidity, cough, dyspnea or tachypnea, CRP, and LDH, both individually and jointly in a model, to develop severe symptoms in children with asymptomatic or mild/moderate COVID-19. Practically, we hope this meta-analysis will not represent just an endpoint of research but a start to construct the list of determinant factors in predicting the severe illness among children with COVID-19.

DATA AVAILABILITY

Data involved in this meta-analysis are available upon reasonable request.

AUTHOR CONTRIBUTIONS

W.N. planned and designed the study and directed its implementation. B.Z., Y.Y., Z.Z., S.W., M.Y., and X.D. contributed to data acquisition. B.Z. and Y.Y. conducted statistical analyses. B.Z., Y.Y., Z.Z., and X.D. performed the data preparation and quality control. B.Z. and W.N. wrote the manuscript. All authors read and approved the final manuscript prior to submission.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41390-021-01429-2.

Competing interests: The authors declare no competing interests.

Patient consent: As it is a meta-analysis of individual participant data from case reports, patient consent was not required.

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