CLINICAL RESEARCH ARTICLE

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

Bo Zhou1,2, Yuan Yuan1,2, Shunan Wang1,2, Zhixin Zhang2, Min Yang1,2, Xiangling Deng1,2 and Wenquan Niu3

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.

Pediatric Research (2021) 90:347–352; https://doi.org/10.1038/s41390-021-01429-2

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 represent 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,5,6,7 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 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
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 ≤1 year     | 5 (19.2%)                     | 37 (23.9%)                       | 5 (33.3%)                | 0.594 |
| Age >1 year     | 21 (80.8%)                    | 118 (76.1%)                      | 10 (66.7%)               | 0.037 |
| 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 |
| diarhea         | 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%) | 0.466 |
| X-ray/CT bilateral injury | 0 (0%) | 15 (12.1%) | 7 (53.8%) | 0.002 |
| GGO (CT)        | 0 (0%)                        | 43 (26.9%)                       | 7 (46.7%)                | 0.002 |
| **Laboratory biomarkers** | | | | |
| WBC (×10⁹/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 (×10⁹/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 (×10⁹/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 (×10⁹/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 (1.199)                  | 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 χ² 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 auscultatory 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 wheezing, but no obvious hypoxemia such as shortness of breath, and sneezing. Physical examination shows congestion of the pharynx and no auscultatory abnormalities. Some cases may have no fever or have only digestive symptoms, such as nausea, vomiting, abdominal pain, and diarrhea.
- **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 (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 χ² 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 included in the study, 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 or mild/moderate illness (Table 2), especially for dyspnea/tachypnea (3.33, 1.84–4.82, <0.001). The power to detect significance was >90% for the above comparisons.

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 1.61 4.12–9.09 <0.001 |
| Diarrhea            | 2.08 0.92–3.25 0.001 | 1.95 0.61–3.39 0.04 |
| 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 0.17 |

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.
with a previous report. In this study, we found that children with 12.9% of children were completely asymptomatic, in agreement contrast, we found only 7.5% of children with severe illness and recent studies estimated that 26% care would provide relief in severe cases and reduce mortality. SARS-CoV-2, prompt identi the possible risk factors of pediatric COVID-19 severity. To the best of our knowledge, this is the first study that has interrogated some previous studies. 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. 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. 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. The findings of this present study, along with other studies, 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, which is less developed at a younger age, and the percentage of children infected with COVID-19 having an exaggerated inflammatory response against the virus are not commonly described thus far. 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.

**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. 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. 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. 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.

The findings of this present study, along with other studies, 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, which is less developed at a younger age, and the percentage of children infected with COVID-19 having an exaggerated inflammatory response against the virus are not commonly described thus far.

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.
REFERENCES

1. Castagnoli, R. et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. JAMA Pediatr. 174, 882–889 (2020).

2. Midulla, F. Cristiani, L. & Mancino, E. Will children reveal their secret? The coronavirus dilemma. Eur. Respir. J. 55, 2000749 (2020).

3. Dong, Y. et al. Epidemiology of COVID-19 among children in China. Pediatrics 145, e20200702 (2020).

4. Li, Y. et al. Insight into COVID-19 for pediatricians. Pediatr. Pulmonol. 55, E1–E4 (2020).

5. Qiu, H. et al. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect. Dis. 20, 689–696 (2020).

6. Tagarro, A. et al. Screening and severity of coronavirus disease 2019 (COVID-19) in children in Madrid, Spain. JAMA Pediatr. https://doi.org/10.1001/jamapediatrics.2020.1346 (2020).

7. Ding, Y., Yan, H. & Guo, W. Clinical characteristics of children with COVID-19: a meta-analysis. Front. Pediatr. 8, 431 (2020).

8. Shen, K. et al. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts’ consensus statement. World J. Pediatr. 16, 223–231 (2020).

9. Shen, K. L. & Yang, Y. H. Diagnosis and treatment of 2019 novel coronavirus infection in children: a pressing issue. World J. Pediatr. 16, 219–221 (2020).

10. Chen, Z. M., Fu, J. F. & Shu, Q. New coronavirus: new challenges for pediatricians. Pediatr. Pulmonol. 55, 1424–1429 (2020).

11. Munn, Z. et al. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. Int. J. Evid. Based Health Care 13, 147–153 (2015).

12. Alzamora, M. C. et al. Severe COVID-19 during pregnancy and possible vertical transmission. Am. J. Perinatol. 37, 861–865 (2020).

13. An, P. & Zhang, M. Novel coronavirus SARS-CoV-2: familial spread resulting in COVID-19 pneumonia in a pediatric patient. Diagn. Interv. Radiol. 26, 262–263 (2020).

14. Cai, J. H. et al. [First case of 2019 novel coronavirus infection in children in Shangh hai]. Zhonghua Er Ke Za Zhi 58, E002 (2020).

15. Canarutto, D. et al. COVID-19 infection in a paucisymptomatic infant: Raising the index of suspicion in epidemic settings. Pediatr. Pulmonol. 55, E4–E5 (2020).

16. Chen, F. et al. [First case of severe childhood novel coronavirus pneumonia in China]. Zhonghua Er Ke Za Zhi 58, E005 (2020).

17. Chen, Z. et al. [COVID-19 with post-chemotherapy agranulocytosis in childhood acute leukemia: a case report]. Zhonghua Xue Ye Xue Za Zhi 41, E004 (2020).

18. Cui, Y. et al. A 55-day-old female infant infected with COVID-19: presenting with pneumonia, liver injury, and heart damage. J. Infect. Dis. 221, 1775–1781 (2020).

19. Dong, L. et al. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. JAMA 323, 1846–1848 (2020).

20. Feng, K. et al. [Analysis of CT features of 15 children with 2019 novel coronavirus infection]. Zhonghua Er Ke Za Zhi 58, E007 (2020).

21. Genovese, G., Colonna, C. & Marzano, A. V. Varicella-like exanthem associated with COVID-19 in an 8-year-old girl: a diagnostic clue? Pediatr. Dermatol. 37, 435–436 (2020).

22. Guqing, H. E., Sun, W., Jing, W. U. & Cai, J. Serial computed tomography manifestations in a child with coronavirus disease (COVID-19) pneumonia. Indian Pediatr. 57, 467–468 (2020).

23. Huang, O. et al. Flash survey on severe acute respiratory syndrome coronavirus-2 infections in paediatric patients on anticonvulsant treatment. Eur. J. Cancer 132, 11–16 (2020).

24. Ji, L. et al. Clinical features of pediatric patients with COVID-19: a report of two family cluster cases. World J. Pediatr. 16, 267–270 (2020).

25. Jiang, S. et al. Co-infection of SARS-CoV-2 and multiple respiratory pathogens in children. Clin. Chem. Lab. Med. 58, 1160–1161 (2020).

26. Kam, K. Q. et al. A well infant with coronavirus disease 2019 (COVID-19) with high viral load. Clin. Infect. Dis. 71, 847–849 (2020).
60. Tan, X. et al. Clinical features of children with SARS-CoV-2 infection: an analysis of 13 cases from Changsha, China. Zhongguo Dang Dai Er Ke Za Zhi 22, 294–298 (2020).
61. Sun, D. et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center’s observational study. World J. Pediatr. 16, 251–259 (2020).
62. Xing, Y. H. et al. Prolonged viral shedding in feces of pediatric patients with coronavirus disease 2019. J. Microbiol. Immunol. Infect. 53, 473–480 (2020).
63. Zheng, F. et al. Clinical characteristics of children with coronavirus disease 2019 in Hubei, China. Curr. Med. Sci. 40, 275–280 (2020).
64. Li, Y. et al. Immune-related factors associated with pneumonia in 127 children with coronavirus disease 2019 in Wuhan. Pediatr. Pulmonol. 55, 2354–2360 (2020).
65. Abdel-Mannan, O. et al. Neurologic and radiographic findings associated with COVID-19 infection in children. JAMA Neurol. 77, 1–6 (2020).
66. Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua Liu Xing Bing Xue Za Zhi 41, 145–151 (2020).
67. Wang, Z. et al. Clinical characteristics of children with COVID-19: a rapid review and meta-analysis. Ann. Transl. Med. 8, 620 (2020).
68. Chen, G. et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J. Clin. Invest. 130, 2620–2629 (2020).
69. Li, X. et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J. Allergy Clin. Immunol. 146, 110–118 (2020).
70. Wu, C. et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern. Med. 180, 934–943 (2020).
71. Ludvigsson, J. F. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr. 109, 1088–1095 (2020).
72. Wrapp, D. et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 367, 1260–1263 (2020).
73. Simon, A. K., Hollander, G. A. & McMichael, A. Evolution of the immune system in humans from infancy to old age. Proc. Biol. Sci. 282, 20143085 (2015).
74. Henry, B. M., Lippi, G. & Plebani, M. Laboratory abnormalities in children with novel coronavirus disease 2019. Clin. Chem. Lab. Med. 58, 1135–1138 (2020).