Letter to the Editor

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Laboratory abnormalities in children with novel coronavirus disease 2019

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To the Editor,

The novel coronavirus disease 2019 (COVID-19), a cause of respiratory and systemic illness, continues to progress toward global pandemic. As of March 6, 2020, the World Health Organization has reported over 98,000 confirmed cases globally, with as many as 3380 related deaths [1]. However, there has been a limited number of reported COVID-19 cases in children and adolescents [2].

In a report of 44,672 laboratory-confirmed cases of COVID-19 in China, only 2.1% were in those ≤19 years of age [3]. Although the reason for this remains unknown, a similar epidemiologic pattern has been observed in the severe acute respiratory syndrome (SARS) and Middle Eastern respiratory syndrome (MERS) outbreaks [4–6]. Moreover, like in both MERS and SARS, milder symptoms and less hospitalizations are reported in children as compared to adults [2, 4–6].

Nonetheless, severe illness has been observed in 2.5% of pediatric cases, and mortality in children and adolescents has also been reported [2]. To date, there is limited data on children available in the literature. Moreover, most studies on this patient group have been published in Chinese, perpetuating a knowledge deficit among the pediatric health community at large.

The etiological diagnosis of COVID-19 encompasses real-time reverse transcription polymerase chain reaction (rRT-PCR), which allows direct identification of viral RNA in nasopharyngeal and oropharyngeal swabs. Importantly, neither quantitative rRT-PCR can provide data on disease severity, whereby no clear association has been found between viral load and individual clinical phenotype. However, laboratory medicine proffers more than etiological diagnosis and disease surveillance, and may provide insights into evaluating disease severity, assessing prognosis, and therapeutic monitoring [7]. Moreover, laboratory data may provide hints to underlying pathophysiology and the body's immunological response. In this article, we aimed to provide a concise overview of laboratory abnormalities in children and adolescents with COVID-19.

We performed an electronic search of PubMed (MEDLINE), CNKI (China National Knowledge Infrastructure), WanFang, and the Chinese Medical Journal Network through March 5, 2020 for case reports or case series reporting laboratory data in symptomatic or asymptomatic children and adolescents (0–≤19 years of age) with confirmed COVID-19. No language restrictions were applied. Search terms included the keywords: "coronavirus", "COVID-19", "SARS-CoV-2", "pediatrics", "neonates", "infants", "children", and "adolescents". Articles were screened by title, abstract, and full text for pediatric laboratory data. Articles in Chinese were screened by a healthcare professional fluent in both Chinese and English. When data describing laboratory data in pediatric patients were identified, the article was translated to English to enable data collection. If an article reported laboratory data in both children and adults, it was included only if the pediatric case data were able to be retrieved. The references of all included articles were searched to identify additional studies.

A total of 1189 studies were identified in the search, of which 1180 were excluded following study screening as they did not report relevant data. Two articles reported data in adult patients, but in which one pediatric case was retrievable [8, 9]. One additional article was

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found by reference search. As such, a total of 12 articles were included with a total sample size of n = 66 pediatric patients [8–19]. The age of patients ranged from 2 weeks to 17 years. Females accounted for 54.5% of cases. Symptoms were present in 72.7% of cases, whilst radiologic abnormalities were observed in 53.0%. A summary of findings is shown in Table 1.

No consistent derangements were observed in leukocyte indices. A normal leukocyte count was found in 69.6%, with 15.2% having an increased count and 15.2% a decreased count relative to the locally defined reference limits. The majority of patients had normal neutrophil counts, with only 4.6% above the normal range and 6.0% below the normal range. On the contrary, it was noted in a review of adult labs that increased leukocyte and neutrophil counts were common in patients with unfavorable COVID-19 progression [20]. While minimal data on severe cases of children were available for analysis, in Cai et al. [10], which provided individual patient data in 10 symptomatic children, only one of the three cases that had alternations in leukocyte or neutrophil counts also had radiologic changes suggestive of pneumonia.

Only 3.0% (n = 2) infants experienced lymphopenia. Both were from the study by Wang et al. [15], which included only patients with mild, moderate, or asymptomatic disease. The lack of significant lymphopenia may in part explain the limited number of severe COVID-19 in children. Yang et al. [21] reported that 80% of critically ill adult COVID-19 patients had lymphopenia, whereas Chen et al. [22] reported that only 25% of patients with mild COVID-19 had lymphopenia, suggesting that lymphopenia may correlate with severity of infection. In both SARS and MERS, lymphopenia was a predominant feature, due to a combination of viral particle-induced cytoplasmic damage and apoptosis [23–25]. In very young children, however, lymphopenia may not occur due to the relative immaturity of their immune system and differences in their immune response compared to adults [12, 26].

When comparing COVID-19 and SARS, significant differences are apparent with respect to alterations in leukocyte indices. In a summary of 80 laboratory-confirmed cases of SARS in children, leukopenia was observed in 47%, neutropenia in 52%, and lymphopenia in 46%. The dissimilarity in leukocyte aberrations between the variable, inconsistent changes in COVID-19 and the more consistent changes in SARS suggests an underlying difference in the immunologic response in children to each virus.

The inflammatory markers C-reactive protein (CRP) and procalcitonin (PCT) were elevated in 13.6% and 10.6% of cases, respectively. In the study by Cai et al. [10], two of the four patients with radiologic abnormalities had elevated CRP, with a third patient hovering 1 mg/L below the assay-specific cut-off. In adults, both CRP and PCT have been observed to be elevated in cases of unfavorable progression [20]. In a meta-analysis of adult COVID-19 patients, PCT was observed to be associated with a near 5-fold increase in risk of severe infection (OR: 4.76) [27]. While not observed in the presented cases, in children with viral lower respiratory tract infections in the intensive care unit (ICU), elevated PCT is strongly suggestive of bacterial co-infection [28].

Only one case report presented a clearly defined severe COVID-19 case in a 1-year-old child who presented with a 6-day history of vomiting and diarrhea, followed by a rapidly developing pneumonia [12]. Although no major leukocyte aberrations could be found, low natural killer (NK) cell count and high CRP values were observed throughout hospitalization. The authors suggested that the leukocyte indices in this case differed from those of severe adults due to the young age of the patient. Interestingly, interleukin-6 (IL-6) was significantly elevated in days 1–5 of hospitalization, and its trend followed that of CRP. IL-6 is reported to be elevated in other viral respiratory tract infections in children, and high IL-6 levels are associated with increased mortality in children <5 years of age with severe pneumonia necessitating mechanical ventilation [29, 30]. Further case reports are needed to evaluate the laboratory abnormalities and potential prognostic indicators in children with severe cases of COVID-19.

There are some limitations to our findings. All data were obtained through case reports and case series. Laboratory parameters of interest were not consistently reported. Only 10 reports were included, with a small total number of patients and no cases from outside of East Asia. Moreover, laboratory methods and reference ranges may have differed between centers and were not always clearly defined. Importantly, a lack of granularity of data prevents comparison of laboratory values between symptomatic and asymptomatic children or analysis based on severity of illness. Efforts should focus on this in the coming weeks and months.

In summary, and unlike in adults, consistent pattern of laboratory derangements has yet to be observed in children with confirmed COVID-19. The laboratory alternations reported in children with SARS are not consistent with the early observations in cases of COVID-19. We recommend clinicians to monitor lymphocyte count and CRP as signs for severe infection, while monitoring PCT for potential bacterial co-infection. IL-6 should be investigated as a potential prognostic indicator in severe COVID-19.

Table 1: Characteristics of the included studies.

Characteristics	Cai et al. [10]	Cai et al. [11]	Chen et al. [12]	Feng et al. [13]	Wang et al. [15]	Zeng et al. [17]	Zhang et al. [16]	Liu et al. [8]	Kam et al. [14]	Chan et al. [9]	Zhang et al. [18]	Zhao et al. [19]
Location	China	China	China	China	China	China	China	China	Singapore	China	China	China
Number of cases	10	1	1	15	31	1	1	1	1	1	2	1
Age, range	Median: 6 years (3 months–11 years)	7 years	13 months	12 years	Median: 7 years (6 months–17 years)	2 weeks	3 months	7 years	6 months	10 years	14 months (twins)	13 years
Males, %	40	100	100	33.3	48.4	100	0	100	100	100	0	100
Symptomatic, %	100	100	100	20	87.1	100	100	100	0	0	100	100
Radiologic abnormalities, %	40	100	100	60	45.2	100	100	100	0	100	50	100
Laboratory data												
Leukocytes	↑30%, ↓10%	↑100%	↑100%	↓46.7%	↑9.7%, ↓6.5%	↔	↔	↔	↓100%	↔	↑100%	↔
Neutrophils	↑10%, ↓30%	NR	↑100%	NR	NR	NR	NR	↔	↓100%	↔	NR	↓100%
Lymphocytes	↑10%	NR	↔	NR	↑12.9%, ↓6.5%	NR	NR	↔	NR	↔	NR	↔
Platelets	↑20%, ↓10%	↑0%, ↓100%	↔	NR	↑6.5%	↑100%	↑100%	↔	↓100%	↔	↑100%	↔
Hemoglobin	↔	NR	↓100%	NR	NR	↔	↔	NR	NR	↔	↔	↔
CRP	↑30%	↑100%	↑100%	NR	↑9.7%, NR 3.2%	↔	↔	↔	NR	↔	↑50%	↔
PCT	↔	↔	↑100%	NR	↑12.9%, NR 9.7%	↔	↑100%	↔	NR	NR	↑50%	↔
ESR	NR	NR	NR	NR	↑12.9%, NR 32.3%	NR	NR	NR	NR	NR	NR	↔
Albumin	NR	NR	NR	NR	NR	NR	NR	↔	NR	↔	NR	↔
ALT	↑10%	↔	NR	NR	↑22%	NR	NR	↔	NR	↔	↔	↔
AST	↑20%	↔	NR	NR	↑22%	NR	NR	↔	NR	↔	↑100%	↔
Bilirubin	NR	NR	NR	NR	NR	NR	NR	NR	NR	↔	NR	↔
Creatinine	↔	NR	↑100%	NR	NR	NR	NR	↔	NR	↔	↔	↔
Creatine kinase	↑50%	↑100%	↑100%	NR	↑12.9%, NR 12.9%	NR	NR	↑100%	NR	NR	NR	↔
LDH	↑30%	NR	NR	NR	NR	NR	NR	↑100%	NR	↔	↑100%	↔
D-dimer	↑20%	NR	↔	NR	↑6.5%	NR	NR	NR	NR	NR	NR	↔
Urea	↓30%	NR	↑100%	NR	NR	NR	NR	NR	NR	↔	NR	↔

Data are presented as percent of patients with abnormalities defined by local reference ranges. ↔, 100% within the normal reference range; NR, not reported; CRP, C-reactive protein; PCT, procalcitonin; ESR, erythrocyte sedimentation rate; ALT, alanine transaminase; AST, aspartate transaminase; LDH, lactate dehydrogenase.

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