Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Biochemistry 81 (2020) 1–8

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Review

Laboratory abnormalities in children with mild and severe coronavirus disease 2019 (COVID-19): A pooled analysis and review

Brandon Michael Henry[a,1,*], Stefanie W. Benoit[b,c,1], Maria Helena Santos de Oliveira[d], Wan Chin Hsieh[e], Justin Benoit[f], Rami A. Ballout[g], Mario Plebani[h], Giuseppe Lippi[i]

[a] Cardiac Intensive Care Unit, The Heart Institute, Cincinnati Children's Hospital Medical Center, OH, USA
[b] Division of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, OH, USA
[c] Department of Pediatrics, University of Cincinnati, College of Medicine, OH, USA
[d] Department of Statistics, Federal University of Parana, Curitiba, Brazil
[e] Pediatric COVID-19 Open Data Analysis Group, Cincinnati, OH, USA
[f] Department of Emergency Medicine, University of Cincinnati, College of Medicine, OH, USA
[g] Lipoprotein Metabolism Section, Translational Vascular Medicine Branch, National Heart, Lung and Blood Institute (NHLBI), National Institutes of Health, Bethesda, MD, USA
[h] Department of Laboratory Medicine, University Hospital of Padova, Padova, Italy
[i] Section of Clinical Biochemistry, Department of Neuroscience, Biomedicine and Movement, University of Verona, Verona, Italy

ARTICLE INFO

Keywords:
Clinical chemistry
Biomarkers
Inflammation
Pediatrics
SARS-CoV-2

ABSTRACT

Limited data exists to-date on the laboratory findings in children with COVID-19, warranting the conduction of this study, in which we pool the currently available literature data on the laboratory findings seen in children with mild and severe COVID-19. Following an extensive literature search, we identified 24 eligible studies, including a total of 624 pediatric cases with laboratory-confirmed COVID-19, which report data on 27 different biomarkers. We then performed a meta-analysis to calculate the pooled prevalence estimates (PPE) for these laboratory abnormalities in mild COVID-19. As data was too limited for children with severe COVID-19 to allow pooling, results were presented descriptively in a summary of findings table. Our data show an inconsistent pattern of change in the leukocyte index of mild and severe cases of COVID-19 in children. Specifically, changes in leukocyte counts were only observed in 32% of the mild pediatric cases (PPE: 13% increase, 19% decrease). In mild disease, creatine kinase-MB (CK-MB) was frequently elevated, with a PPE of 33%. In severe disease, c-reactive protein (CRP), procalcitonin (PCT), and lactate dehydrogenase (LDH) were frequently elevated. Based on data obtained from early COVID-19 studies, leukocyte indices in children appear inconsistent, differing from those reported in adults that highlight specific leukocyte trends. This brings into question the utility and reliability of such parameters in monitoring disease severity in the pediatric population. Instead, we suggest physicians to serially monitor CRP, PCT, and LDH to track the course of illness in hospitalized children. Finally, elevated CK-MB in mild pediatric COVID-19 cases is indicative of possible cardiac injury. This highlights the importance of monitoring cardiac biomarkers in hospitalized patients and the need for further investigation of markers such as cardiac troponin in future studies.

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is now a global pandemic that is challenging modern medicine in many aspects [1]. The disease initially presents as a mild respiratory illness, developing into viral interstitial pneumonia, which may in turn, further progress into acute respiratory distress syndrome and multiple organ failure (MOF) in 10–15% of adults [2].

Interestingly, the course of the disease in children is generally mild compared to that seen in adults, for reasons that are yet to be clearly elucidated [3]. Nonetheless, severe and fatal cases have been reported in children and are expected to continue to increase with the growing community transmission and overall current disease prevalence. In fact,

* Corresponding author at: Brandon Michael Henry, Cardiac Intensive Care Unit, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229, USA.
E-mail address: Brandon.henry@cchmc.org (B.M. Henry).
[1] These authors share first authorship for this work.

https://doi.org/10.1016/j.clinbiochem.2020.05.012
Received 2 May 2020; Received in revised form 16 May 2020; Accepted 22 May 2020
Available online 27 May 2020

a recent report from China on 2143 children with suspected COVID-19, described a particularly concerning rate of severe disease in young children, stratified by several age sub-categories [4]. Specifically, the proportions of severe and critical cases by age group were 10.6% for < 1 years, 7.3% for 1–5 years, 4.2% for 6–10 years, 4.1% for 11–15 years, and 3.0% for ≥16 years [4].

In a previous report, we briefly summarized the laboratory findings reported in the early case studies from China on children with COVID-19, which despite the limited sample at the time, clearly suggested that children with COVID-19 have different laboratory profiles compared with adult patients [3]. Although a limited number of pediatric cases continue to be described in the current literature, the growing number of such reports allowed us to conduct this updated data synthesis. In this pooled analysis of literature data, we report the most common laboratory abnormalities observed in children with COVID-19. Moreover, because sex and age have been shown to factor into incidence and outcomes of COVID-19 in adults, we also compared the laboratory findings across different age subgroups and across the sexes in children with COVID-19. Finally, for children with severe disease, we summarized the most frequently observed laboratory abnormalities, highlighting the biomarkers that may be the best indicators at present, to monitor disease severity.

2. Methods

2.1. Search strategy

An electronic search of Medline (PubMed interface), Scopus, Web of Science, and China National Knowledge Infrastructure (CNKI), was performed using the keywords “children” OR “pediatrics” OR “infant” OR “neonate” OR “laboratory” OR “chemistry” OR “clinical” AND “coronavirus 2019” OR “COVID-19” OR “2019-nCoV” OR “SARS-CoV-2”, between December 1, 2019 and May 1, 2020. No language restrictions were applied. The reference lists of all identified potentially relevant studies were reviewed to identify any additional eligible studies. This systematic review and meta-analysis was reported in conformity with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplement 1).

2.2. Selection criteria

All studies were evaluated for inclusion by two independent reviewers. Each reviewer screened the titles and abstracts of retrieved references for relevance and possible eligibility. Full texts were then retrieved for references deemed eligible by at least one reviewer and screened for inclusion. Studies were deemed eligible for inclusion if they were case reports, case series, or observational studies that report clear and extractable data on laboratory findings in RT-PCR confirmed cases of COVID-19 in pediatric patients. Editorials and reviews were excluded. Cases of the Multi-System Inflammatory Syndrome in Children (MIS-C) potentially linked to COVID-19 were not included in this investigation. Studies in the Chinese language were evaluated by a medical professional fluent in both Chinese and English, who translated the article into English when data on laboratory parameters in children were reported in these studies. Inter-reviewer disagreements were resolved by discussion among the reviewers, and in certain cases, with a third author. Given the limited data available to date on pediatric COVID-19 cases, we decided to include single case reports and case series. As a result, we did not assess the risk of bias or grade the level of the generated evidence.

2.3. Data collection and outcomes

Two reviewers independently extracted data from the included studies, which covered the following information: study authors, sample size, country of study, sex and mean age of participants, disease severity, and laboratory tests performed with their corresponding values. The primary outcome was frequency of laboratory abnormalities, with mean laboratory values being collected whenever available, to allow for comparisons between different age and sex groups. Individual patient data was also extracted whenever possible. When the mean and standard deviations (SDs) of laboratory values were not reported, we extrapolated these values from sample size, median, and interquartile range (IQR), using the method suggested by Hozo et al. [5]. Additional data was sought from original study authors when appropriate. Severe disease was defined in our analysis as having any of the following: hypoxemia (oxygen saturation of ≤92%), central cyanosis, acute respiratory distress syndrome (ARDS), need for ventilation support, need for vital life support, need for intensive care unit (ICU) support, or any combination of these. Mild disease was defined as COVID-19 with any severity below that as defined for severe.

2.4. Data synthesis and analysis

Studies were grouped into two separate cohorts for analyses: a ‘mild cohort’ and a ‘severe cohort’, which include studies reporting relevant data on children having mild and severe COVID-19, respectively. For the mild cohort, a meta-analysis was performed to calculate pooled prevalence estimates (PPE) with their 95% confidence interval (95% CI) for each of the laboratory parameters reported in the relevant studies. Laboratory data was pooled whenever two or more studies reported a specific variable. For some parameters, appropriately, only increased or decreased values were reported by the studies, as such PPE represents prevalence estimate percentage of patients outside the normal ranges for a given value. Increased and/or decreased laboratory values were defined according to the cut-off values reported in their corresponding study. To accommodate for any heterogeneity arising from using different cut-offs or measuring methods in the different studies, a random effects model was applied. Heterogeneity among the included studies was assessed using the Chi-square test and the I^2 statistic. For the Chi-square test, significant heterogeneity among studies is indicated by a Cochran’s Q p-value of < 0.10. As for the I^2 statistic, heterogeneity was classified as results were interpreted as 25%, 50% and 75%, representing low, moderate, and high heterogeneity, respectively [6].

Given that sex and age have each been found to affect COVID-19 severity and outcomes, subgroup analyses were performed to compare mean lab values by age (< 1 vs. > 1 year) and sex (female vs. male). Using inverse variance, we calculated a weighted mean difference (WMD) with a 95% CI, for each laboratory parameter assessed in each of these subgroups. Statistical analysis was performed using the MetaXL, software Version 5.3 (EpiGear International Pty Ltd., Sunrise Beach, Australia). Due to the nature of the included studies, i.e., case reports and case series mainly, and the types of outcomes evaluated in this analysis, we did not investigate publication bias.

Additionally, given the limited number of studies reporting laboratory abnormalities in children with severe COVID-19, with available ones showing marked variability across patients, we did not conduct a meta-analysis for studies evaluating severe COVID-19 patients. Instead, we only descriptively report the findings on such patients in a summary of findings table.

3. Results

3.1. Study identification and characteristics of included studies

Supplementary Fig. 1 shows the flow diagram for this review. After removing duplicate references, a total of 553 articles were identified for title and abstract screening. Among these, 117 were excluded for being review articles, 292 for not reporting data on COVID-19, 44 for not providing lab data on pediatric patients with COVID-19, and 79 for being editorials and/or commentaries. When we screened the reference lists of the 21 remaining articles eligible for inclusion, we identified

Table 1
Characteristics of Included Studies.

Study Name	Sample Size	Age (months)	Female (%)
Cai J et al.	10	3–131	6 (60)
Chen F. et al.	1	13	0
Cui Y et al.	1	2	1 (100)
Du W et al.	14	0–192	8 (57)
Feng K et al	15	48–168	10 (67)
Han Y et al.	7	2–156	3 (43)
Liu H et al	4	2–108	2 (50)
Liu W et al.	6	12–84	4 (67)
Lu et al	171	0–180	67 (39)
Ma Y et al.	115	Not Reported	42 (37)
Munoz A et al.	1	0.75	0
Parri N et al.	100	0–210	43 (43)
Qiu H et al.	36	12–192	13 (36)
Shen Q et al.	9	12–144	6 (67)
Su L et al.	9	11–108	6 (67)
Sun D et al.	8	2–180	2 (25)
Tan Y et al.	10	12–144	7 (70)
Wang D et al.	31	6–204	16 (52)
Xia W et al.	20	0–175	7 (35)
Xu Y et al.	9	2–180	4 (44)
Zeng L et al.	3	Newborns	0
Zheng F et al.	25	48–108	11 (44)
Zhou Y et al.	9	7–36	5 (56)
Zhu L et al.	10	19–204	5 (50)

three additional eligible studies. As a result, our final pooled analysis included 24 studies, which together covered a total of 624 laboratory-confirmed pediatric cases of COVID-19, reporting data on 27 different laboratory parameters [7–30]. All studies were from China, except for two: one from the United States [17] and the other from Italy [30]. The age of patients ranged from 0 to 17.5 years old in these studies, with females accounting for around 43% of the pooled cohort. Three patients with severe disease were included in the mild cohort analysis, as data was not able to be removed individually. The basic characteristics of the included studies are summarized in Table 1.

3.2. Laboratory abnormalities in mild COVID-19

Twenty out of the 24 included studies, totaling 610 pediatric patients with mild COVID-19, reported on laboratory abnormalities [7,9,11–16,18–20,22–30]. Their pooled results are presented in Table 2 with their corresponding forest plots in Supplement 3. The most common hematologic aberration was a decreased neutrophil count with PPE of 38% (95% CI: 19–60%). Elevations in the levels of C-Reactive Protein (CRP), Procalcitonin (PCT), and Lactate Dehydrogenase (LDH) were also seen, with PPEs of 18%, 26%, and 28%, respectively. Interestingly, creatine kinase-MB (CK-MB) was also elevated in one-third of patients (PPE, 33%; 95% CI, 25–42%). Heterogeneity varied between the parameters analyzed, but trended higher for inflammatory biomarkers.

Subgroup analyses by age and sex are presented in Tables 3 and 4, respectively. With respect to age, infants (< 1 year) had significantly higher leukocyte, lymphocyte, and platelet counts, along with elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), and LDH levels, without any of these changes being significant. However, they had significantly reduced hemoglobin and creatinine levels. No differences were observed with respect to CRP, PCT, or CK-MB. Relatively lower heterogeneity was observed for the age-specific subgroup analyses, suggesting that laboratory findings are influenced by age, with infants having a slightly different biochemical presentation compared with children older than 1 year of age. With respect to sex, females had significantly higher leukocyte and neutrophil counts, with lower CK levels, compared with males. Here too, heterogeneity trended lower for several variables suggesting that sex may also account for the variability observed for some variables in the main analysis.

Table 2
Results of meta analysis for pediatric patients with mild COVID-19.

Measure	Total No Studies	Sample Size	Pooled Prev %	95% CI	I^2	Cochran's Q, p-value*
Hematologic						
↑ WBCs	13	194	13	8, 19	15%	0.29
↓ WBCs	16	416	19	12, 26	61%	0.00
↑ Neutrophils	5	36	10	2, 23	0%	0.87
↓ Neutrophils	6	50	38	19, 60	57%	0.04
↑ Lymphocytes	10	108	18	9, 30	45%	0.06
↓ Lymphocytes	16	421	17	8; 28	83%	0.00
↑ Platelets	6	77	10	4, 18	0%	0.57
↑ Hemoglobin	4	39	10	0, 27	44%	0.15
↓ Hemoglobin	3	25	5	0, 16	0%	0.37
Biochemical						
↑ ALT	14	503	15	10, 20	43%	0.05
↑ AST	12	357	25	17, 35	63%	0.00
↓ Creatinine	3	23	39	0, 100	91%	0.00
↑ CK	7	84	15	3, 32	66%	0.01
↑ CK-MB	6	200	33	25, 42	22%	0.27
↑ LDH	8	119	28	17, 41	50%	0.05
Inflammation/Coagulation						
↑ D-dimer	8	247	20	12, 29	43%	0.09
↑ CRP	13	336	18	10, 28	66%	0.00
↑ ESR	7	96	20	4, 42	79%	0.00
↑ Procalcitonin	12	331	26	9, 46	91%	0.00

*p-value < 0.10 is considered as significant.

3.3. Laboratory abnormalities in severe COVID-19

Only 6 out of the 24 included studies, covering a total of 14 pediatric patients, addressed laboratory abnormalities in children with severe COVID-19 [8,10,17,21,26,27]. Table 5 summarizes the characteristics and laboratory findings of these studies. Given the limited data and high variation across these studies, we did not analytically pool their data together. Nonetheless, certain trends could be noted from generally observing their reported findings and deserve to be mentioned. Alterations in leukocyte count were observed at lower-than-expected frequency, with few patients having elevated counts (4/16, 25%). Interestingly, increased and decreased lymphocyte count were observed at equal frequency (18.7%). In 2 studies (n = 9 patients) [10,21] that reported lymphocyte subsets, 44.4% of patients had an increase in CD4 + cell counts, with only 1 patient (11.1%) increased CD8 + cell count. However, 66.6% (6/9) had decreased counts of natural killer cells. When reported, CRP (5 studies, n = 13, ↑61.5%), PCT (4 studies, n = 11 ↑72.7%), and LDH (3 studies, n = 11, ↑72.7%) were commonly elevated. Only 2 studies (n = 9 patients) reported on cytokines [10,21], with Interleukin-10 (IL-10) being the most frequently elevated cytokine, seen in up to 75% of cases. IL-6 and interferon-gamma (IFN-gamma) were also elevated, though in only 37% and 25% of cases, respectively. All other cytokine levels were normal. Though only reported in one severe case report, CK-MB and troponin was elevated, in congruence with our observations of frequently elevated CK-MB in 1/3rd of the mild cohort. Additionally, a trend of elevated D-Dimer and prothrombin time (PT) could also be seen in severe cases.

4. Discussion

Although laboratory abnormalities in adults with mild and severe COVID-19 have been widely reported and appear to be somewhat consistent, little is known about the laboratory findings in children with COVID-19. While the disease burden seems to be significantly lower in the pediatric population, with many children being almost completely asymptomatic or only mildly affected, the number of cases continues to increase. Recent data has shown that up to 10% of infants testing positive for COVID-19 may be at risk for developing severe disease that

Table 3
Results of Meta-Analysis Comparing Laboratory Values in Mild COVID-19 Patients Under One Year Old versus Older Pediatric Patients.

Measure	Total No Studies	Sample Size	WMD	95% CI	I^2 %	Cochran's Q p-value
Hematologic						
WBC	4	36	3.11 × 10^9/L	0.69, 5.53	53	0.09
Neutrophils	2	20	−1.13 × 10^9/L	−4.34, 2.08	0	0.42
Lymphocytes	3	27	2.17 × 10^9/L	1.11, 3.24	0	0.55
Platelets	2	19	103.13 × 10^9/L	18.33, 187.94	0	0.96
Hemoglobin	3	27	−9.66 g/L	−17.61, −1.7	0	0.59
Biochemical						
ALT	2	18	52.81 U/L	20.92, 84.71	0	0.99
AST	4	36	12.06 U/L	7.63, 16.50	10	0.34
Creatinine	2	18	−26.78 μmol/L	−36.06, −17.50	0	0.49
CK-MB	2	19	8.03 U/L	−5.15, 21.20	4	0.31
LDH	2	16	378.22 U/L	308.55, 447.90	98	0.00
Inflammation/Coagulation						
Procalcitonin	2	18	0.04 ng/mL	−0.01, 0.09	0	0.32
CRP	2	18	−4.24 mg/L	−12.18, 3.71	0	0.78

*WMD – Weighted mean difference.

necessitates supplemental oxygen and other aggressive interventions [4]. Nonetheless, the majority of laboratory data on COVID-19 pediatric patients stems from case reports and case series, with very few small-sized observational studies contributing such data. Thus, given that data on children with COVID-19 is lacking and urgently needed to inform patient care, we conducted this pooled analysis in the hope that we may provide some insights into the expected laboratory abnormalities or trends for this cohort.

Table 6 provides a summary of the most common laboratory abnormalities seen in children with mild and severe COVID-19. Overall, children with mild disease have relatively few laboratory changes. Leukocyte count is elevated with a PPE of only 13%, with an inconsistent overall pattern of derangement in white blood cell (WBC) indices in this category, compared with adults having mild disease [31]. Unlike a summary of 80 laboratory-confirmed pediatric cases of SARS that observed leukopenia in 47% of cases, the PPE for leukopenia was only 19% in this study [32]. Moreover, while neutropenia and lymphopenia were reported in 52% and 46% of SARS cases, respectively, the generated PPEs corresponding to these abnormalities in our study were 38% and 17%, respectively. These changes emphasize notable differences between SARS and mild COVID-19 in children, despite the high genetic and molecular similarity between the two underlying viruses [32]. In influenza, leukopenia is common occurring in ~1/3rd of hospitalized children. However, when compared to COVID-19, a similar rate of leukocytosis (3–10%) and neutropenia (14–26%) are observed in influenza [33].

Of interest, CRP was not found to be as frequently elevated in mild COVID-19 cases as would be expected, yielding a PPE of only 18%. In children hospitalized with influenza, the rate of elevated CRP ranges from 37 to 67%) [33]. In contrast, we found an elevation in PCT level of 26% PPE, suggesting the possibility of a secondary bacterial infection in children hospitalized with COVID-19 pneumonia. This is higher than that noted in children hospitalized with influenza, in which PCT elevations were noted in 6%-12% [33]. Importantly, bacterial and viral co-infections at the time of admission have been reported as being common in children with COVID-19 [24]. In adults, elevated PCT was found to be associated with a nearly 5-fold increased risk of severe disease [34]. Hence, we propose serially monitoring PCT levels in children hospitalized with COVID-19, as a potential biomarker of bacterial super-infection (either pulmonary or systemic) and consequent clinical deterioration.

Additionally, CK-MB levels were found to be increased over local thresholds in one-third of mild pediatric cases of COVID-19, which resembles the case of adults with COVID-19, in whom acute cardiac injury, demonstrated as elevated cardiac biomarkers, has been reported as a common finding that is associated with poorer outcomes. As such, the elevated CK-MB level may suggest either viral infiltration of cardiac tissue, which is among the organs known to express the viral receptor (i.e., angiotensin converting enzyme 2; ACE2), or cardiac ischemia due to the frequent intravascular coagulopathy that is seen with this

Table 4
Results of meta-analysis comparing laboratory values in female versus male mild COVID-19 pediatric patients.

Measure	Total No Studies	Sample Size	WMD	95 CI	I^2 %	Cochran's Q, p-value
Hematologic						
WBC	8	71	1.34 × 10^9/L	0.09, 2.60	45	0.08
Neutrophils	4	33	1.83 × 10^9/L	0.99, 2.67	57	0.07
Lymphocytes	7	62	0.37 × 10^9/L	−0.41, 1.15	0	0.54
Platelets	4	34	32.59 × 10^9/L	−14.08, 79.26	0	0.93
Hemoglobin	5	42	−4.37 g/L	−9.94, 1.19	0	0.62
Biochemical						
ALT	7	62	−2.89 U/L	−6.71, 0.94	0	0.62
AST	7	61	−2.30 U/L	−8.46, 3.86	7	0.37
BUN	2	19	−0.57 mmol/L	−1.42, 0.27	0	0.99
Creatinine	3	24	0.74 μmol/L	−6.58, 5.09	0	0.41
CK	3	23	−47.52 U/L	−94.63, −0.4	0	0.91
CK-MB	4	35	2.61 U/L	−5.41, 10–64	44	0.14
LDH	5	41	37.06 U/L	10.76, 63.35	0	0.84
Inflammation/Coagulation						
D-Dimer	3	24	0.04 mg/L	−0.06, 0.13	36	0.21
Procalcitonin	4	30	−0.01 ng/mL	−0.03, 0.01	0	0.61
CRP	5	42	0.03 mg/L	−0.04, 0.10	58	0.05

*WMD – Weighted mean difference.

Table 5
Characteristics of Laboratory Findings in Severe COVID-19 Pediatric Patients.

Measure (reference range)		Sun D et al	Zheng F et al	Cui Y et al	Zeng L et al	Munoz A et al	Chen F et al
Number of Patients		8	2*	1	1**	1	1
Age (months; min,max)		2, 180	10, 12	2	Newborn	0.75	13
Hematologic							
WBCs (x10^9/L)	↑, n (%)	2 (25)	1 (50)	0	1 (100)	–	0
	↓, n (%)	0	0	0	0	–	0
	Mean (SD)	8.1 (4.0)	8.0 (5.3)	8.0	20.4	4	12.0
Neutrophils (x10^9/L)	↑, n (%)	2 (25)	–	0	–	–	1 (100)
	↓, n (%)	1 (12.5)	–	0	–	–	0
	Mean (SD)	4.3 (3.5)	–	1.9	–	0.8	7.8
Lymphocytes (x10^9/L)	↑, n (%)	2 (25)	0	1 (100)	0	–	0
	↓, n (%)	1 (12.5)	1 (50)	0	1 (100)	–	0
	Mean (SD)	3.0 (1.7)	2.0 (0.7)	5.2	8	2.2	2.48
Hemoglobin (g/L)	↑, n (%)	1 (12.5)	0	0	–	–	–
	↓, n (%)	3 (37.5)	1 (50)	0	–	–	–
	Mean (SD)	119.4 (27.6)	126.5 (37.5)	112	–	–	108
Platelets (x10^9/L)	↑, n (%)	–	0	1 (100)	–	–	–
	↓, n (%)	–	0	0	–	–	–
	Mean (SD)	–	193 (12.7)	406	230	212	186
CD3 + T (%)	↑, n (%)	3 (38)	–	–	–	–	0
	↓, n (%)	0	–	–	–	–	1 (100)
	Mean (SD)	68.7 (9.9)	–	–	–	–	38.1
CD8 + T (%)	↑, n (%)	1 (13)	–	–	–	–	0
	↓, n (%)	0	–	–	–	–	0
	Mean (SD)	30.7 (11.5)	–	–	–	–	16.7
CD4 + T (%)	↑, n (%)	4 (50)	–	–	–	–	0
	↓, n (%)	0	–	–	–	–	0
	Mean (SD)	34.0 (6.1)	–	–	–	–	20.2
CD16 + CD56 + T (%)	↑, n (%)	0	–	–	–	–	0
	↓, n (%)	5 (63)	–	–	–	–	1 (100)
	Mean (SD)	7.3 (5)	–	–	–	–	6.2
CD4+/CD8 + T (%)	↑, n (%)	0 ±	–	–	–	–	0
	↓, n (%)	3 (43) ±	–	–	–	–	0
	Mean (SD)	1.3 (0.5)	–	–	–	–	1.21
Biochemical							
ALT (U/L)	↑, n (%)	4 (50)	0	1 (100)	–	–	1 (100)
	↓, n (%)	2 (25)	0	0	–	–	–
	Mean (SD)	43.5 (32.3)	16 (5.7)	84	88	21	54
AST (U/L)	↑, n (%)	0	0	1 (100)	–	–	1 (100)
	↓, n (%)	4 (50)	0	0	–	–	–
	Mean (SD)	24.8 (11.2)	–	100	63	21	124
Bilirubin (μmol/L)	↑, n (%)	0	–	1 (100)	–	–	–
	Mean (SD)	11.3 (5.1)	–	33.7	–	–	–
Blood urea nitrogen (BUN) (mmol/L)	↑, n (%)	–	–	–	–	–	1 (100)
	Mean (SD)	–	–	–	–	–	15.91
Creatinine (μmol/L)	↑, n (%)	2 (25)	1 (50)	0	–	–	1 (100)
	↓, n (%)	2 (25)	0	0	–	–	–
	Mean (SD)	40.8 (21.8)	134.8 (126.9)	20	–	–	224.5
Creatine Kinase (U/L)	↑, n (%)	1 (12.5)	2 (100)	1 (100)	–	–	1 (100)
	↓, n (%)	2 (25)	0	0	–	–	–
	Mean (SD)	91.7 (82.2)	80.4 (26.0)	46	39	–	177
Creatine Kinase – MB (U/L)	↑, n (%)	–	–	–	–	–	1 (100)
	Mean (SD)	–	–	–	–	–	98
Troponin (ng/ml)	↑, n (%)	–	–	–	–	–	1 (100)
	Mean (SD)	–	–	–	–	–	0.272
LDH (U/L)	↑, n (%)	5 (62.5)	2 (100)	–	–	–	1 (100)
	↓, n (%)	0	0	–	–	–	–
	Mean (SD)	461.5 (280.5)	485 (175.4)	–	–	–	751
Inflammation/Coagulation							
Prothrombin Time (s)	↑, n (%)	–	2 (100)	0	–	–	1 (100)
	↓, n (%)	–	0	0	–	–	–
	Mean (SD)	–	14.2 (0.2)	9.7	21	–	14.3
D-dimer (mg/L)	↑, n (%)	2 (40)***	–	0	–	–	–
	Mean (SD)	8.9 (17.6)	–	0.5	–	–	–
Procalcitonin (ng/mL)	↑, n (%)	5 (62.5)	–	1 (100)	–	1 (100)	1 (100)
	Mean (SD)	2.2 (6.0)	–	0.2	–	6.5	0.43
CRP (mg/L)	↑, n (%)	5 (62.5)	1 (50)	0	–	1 (100)	1 (100)
	Mean (SD)	25.8 (36.8)	12.6 (17.0)	0.6	–	172	24.3
IL-2 (ng/L)	↑, n (%)	0	–	–	–	–	0
	Mean (SD)	2.13 (0.84)	–	–	–	–	1.0
IL-4 (ng/L)	↑, n (%)	0	–	–	–	–	0
	Mean (SD)	3.53 (1.38)	–	–	–	–	4.0
IL-6 (ng/L)	↑, n (%)	2 (29) ±	–	–	–	–	1 (100)
	Mean (SD)	114.6 (217.8)	–	–	–	–	120.3

(*continued on next page*)

Table 5 (*continued*)

Measure (reference range)		Sun D et al	Zheng F et al	Cui Y et al	Zeng L et al	Munoz A et al	Chen F et al
IL-10 (ng/L)	↑, n (%)	5 (71) ±	–	–	–	–	1 (100)
	Mean (SD)	7.8 (4.6)	–	–	–	–	33.4
TNF-α (ng/L)	↑, n (%)	0	–	–	–	–	0
	Mean (SD)	3.2 (1.7)	–	–	–	–	4.5
INF-γ (ng/L)	↑, n (%)	2 (28.6) ±	–	–	–	–	0
	Mean (SD)	12.1 (11.6)	–	–	–	–	1.9

*2 of the 25 patients in this study had severe disease.
**1 of the 3 patients in this study had severe disease.
*** only measured in 5 patients.
± only 7 of the 8 patients have lab values.

Table 6
Summary of Common Laboratory Changes in Pediatric Patients with COVID-19 based on current reported data.

Mild Disease	Severe Disease
↓ ↔WBC Count	↑ ↔ WBC Count
↓ Neutrophils	
↔ Lymphocytes	↔ Lymphocytes
↑ AST	
↑ ALT	↑ ALT
↑ LDH	↑ LDH
↑ CK-MB	↑ CK-MB
↑ D-dimer	↑ D-dimer
↑ ESR	
↑ CRP	↑ CRP
↑ Procalcitonin	↑ Procalcitonin
	↑ IL-10

↔ no change, ↑ increase, ↓ decreased.

enigmatic disease. While the data on CK-MB presents potential evidence of cardiac damage in children affected by COVID-19, more sensitive and specific cardiac biomarkers, like cardiac troponins (both cTnI and T), need to be measured in a pediatric cohort. Recently, a new hyperinflammatory shock phenomenon, referred to as MIS-C has been reported in children and is likely associated with COVID-19. In these patients, significant cardiac dysfunction and high levels of troponins have been observed [35]. As such, we suggest that clinicians regularly monitor cardiac troponins in hospitalized children with COVID-19, as a likely indicator of ongoing or imminent cardiac injury.

When we conducted a subgroup analysis in children with mild COVID-19 by age, increased leukocyte counts, LDH levels, and liver enzymes were noted in infants (i.e., < 1 year). This may reflect a higher viral burden in this age group, given that infants have been reported to have higher risk of developing severe disease. Importantly, low heterogeneity was observed when comparing laboratory values across different age groups, suggesting that age may explain some of the differences seen between the various laboratory variables included in the primary analysis.

Moreover, since males have been reported to exhibit higher severity and mortality with COVID-19 compared with females across all age groups, with numerous hypotheses attempting to explain this sex-specific discrepancy such as differences in ACE2 expression, heterogeneous immune responses, presence of co-morbidities, and sex hormones variabilities, we also conducted a subgroup analysis by sex to check for such discrepancies in the pediatric population [36]. Paradoxically, our pooled analyses showed that female children actually have higher leukocyte and neutrophil counts, as well as LDH levels, compared with males. All other parameters had low or non-significant differences between the sexes.

Table 6 highlights the most common laboratory findings in children with severe COVID-19. Despite the limited data on this category of patients, we were able to note some meaningful trends. First, unlike the case of adults with severe COVID-19 who show significant lymphopenia, a near equal frequency of increased and decreased lymphocyte counts were seen in children with severe COVID-19, with the majority having normal counts. In a limited analysis of T-lymphocyte subsets, 44% of patients showed an increase in CD4+ cell counts. Because lymphopenia and immune dysregulation may impact disease severity, the differences between children and adults require further investigation, especially because SARS-CoV-2 has been found capable of directly infecting T-lymphocytes, which may be the mechanism underlying this lymphopenia [37]. Lymphopenia in adults has been shown to correlate with increased risk of in-hospital mortality, whilst this association remains to be tested in pediatric patients [31]. However, it may be possible that the relative immaturity of the immune system in young children, accounts for differences in viral susceptibility or response to infection, possibly explaining the differences in laboratory trends seen in the pediatric versus adult population of COVID-19 patients [3]. Overall, based on our analysis, leukocyte indices do not appear to be reliable indicators of disease severity in children.

Children with severe COVID-19 showed somewhat consistent trends of elevated LDH, CRP, and PCT levels, similar to what has been reported in adult patients with COVID-19 [31]. Additionally, trends of elevated D-dimer and PT were noted in children with severe COVID-19, although these variables have not been consistently measured across studies. Nonetheless, these also overlap with findings reported in adult patients, which have been suggested as markers of the recently highlighted hypercoagulability status seen in patients with severe disease [37].

It is worth mentioning that further information on other biomarkers that may help in COVID-19 prognostication, such as IL-6 and serum ferritin levels, remains limited in children. Only two studies reported data on IL-6 in COVID-19, with none reporting data on serum ferritin. Of note, IL-6 was only elevated in 37.5% of severe pediatric cases. Additional studies should therefore incorporate measurements of IL-6, given that this biomarker is commonly elevated in viral respiratory tract infections, and perhaps plays an important role in the cytokine storm seen with the disease, which may make it part of a risk stratification test [3]. In children aged < 5 years with severe pneumonia requiring mechanical ventilation, elevated IL-6 is in fact associated with increased mortality [38]. Interestingly, IL-10 levels were elevated in 75% of severe cases reported in two studies included in this review. IL-10 is an anti-inflammatory cytokine which at high levels may contribute to or reflect a state of immunoparalysis in critically ill children, increasing the risk for secondary nosocomial infections [39]. This further supports the importance of serially monitoring PCT levels in children hospitalized with severe disease. The use of IL-10 as a measure of pediatric disease severity should also be further investigated in future studies.

The major limitation of this study is the small number of relevant references that could be included, and their erratically observational nature. In fact, it is imperative to keep in mind when interpreting our results, that our pooled analyses included case reports and case series, which reduce our level of confidence in the generated estimates. Nonetheless, we provide in this report, the most comprehensive summary to date, on the laboratory abnormalities seen in children with

COVID-19. The heterogeneity detected in our primary analyses, could be explained by different influences of age and sex, as differences were noted in subgroup analyses. Moreover, heterogeneity may stem from differences among studies with regards to their outcome measures, such as the timing of specimen collection and measurement assays used, which were not clearly described in most of the included studies. Lastly, as reference ranges and cut-offs used in the pediatric population for laboratory measures are traditionally heterogenous and may differ from institution to institution, this may partially explain the elevated levels of heterogeneity see for some measurements. Importantly, however, as leukocyte indices appear to be unreliable markers of disease severity based on early data, urgent identification of reliable prognostic biomarkers should be a top priority of future studies in this population.

5. Conclusions

Despite the increasing number of pediatric COVID-19 cases, little is known about the laboratory profiles of these patients. Based on data available to date within the literature, alterations in leukocyte indices appear to be mostly inconsistent in children, unlike the case of adults with COVID-19. Therefore, leukocyte indices in children do not appear to be reliable markers of disease severity. Instead, we propose that physicians serially monitor CRP, PCT, and LDH levels, to monitor the course of the disease in children hospitalized with COVID-19. Finally, elevated CK-MB levels in children with mild COVID-19 suggest the possibility of cardiac injury, highlighting the importance of monitoring cardiac biomarkers in hospitalized patients and the need for further investigation in future studies.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinbiochem.2020.05.012.

References

[1] G. Lippi, F. Sanchis-Gomar, B.M. Henry, Coronavirus disease 2019 (COVID-19): the portrait of a perfect storm, Ann. Transl. Med. 8 (2020) 497, https://doi.org/10.21037/atm.2020.03.157.
[2] WHO-China Joint Mission, Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19), (2020). https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf (accessed March 1, 2020).
[3] B.M. Henry, G. Lippi, M. Plebani, Laboratory abnormalities in children with novel coronavirus disease 2019, Clin. Chem. Lab. Med. (2020), https://doi.org/10.1515/cclm-2020-0272.
[4] Y. Dong, X. Mo, Y. Hu, X. Qi, F. Jiang, Z. Jiang, S. Tong, Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China, Pediatrics (2020), https://doi.org/10.1542/peds.2020-0702.
[5] S.P. Hozo, B. Djulbegovic, I. Hozo, Estimating the mean and variance from the median, range, and the size of a sample, BMC Med. Res. Method. 5 (2005) 13, https://doi.org/10.1186/1471-2288-5-13.
[6] J.P.T. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman, Measuring inconsistency in meta-analyses, BMJ 327 (2003) 557–560, https://doi.org/10.1136/bmj.327.7414.557.
[7] J. Cai, J. Xu, D. Lin, Z. Yang, L. Xu, Z. Qu, Y. Zhang, H. Zhang, R. Jia, P. Liu, X. Wang, Y. Ge, A. Xia, H. Tian, H. Chang, C. Wang, J. Li, J. Wang, M. Zeng, A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features, Clin. Infect. Dis. (2020), https://doi.org/10.1093/cid/ciaa198.
[8] Y. Cui, M. Tian, D. Huang, X. Wang, Y. Huang, L. Fan, L. Wang, Y. Chen, W. Liu, K. Zhang, Y. Wu, Z. Yang, J. Tao, J. Feng, K. Liu, X. Ye, R. Wang, X. Zhang, Y. Zha, A 55-Day-Old Female Infant Infected With 2019 Novel Coronavirus Disease: Presenting With Pneumonia, Liver Injury, and Heart Damage, The Journal of Infectious Diseases. (n.d.). https://doi.org/10.1093/infdis/jiaa113.
[9] W. Du, J. Yu, H. Wang, X. Zhang, S. Zhang, Q. Li, Z. Zhang, Clinical characteristics of COVID-19 in children compared with adults in Shandong Province, China, Infection (2020), https://doi.org/10.1007/s15010-020-01427-2.
[10] C. Feng, L. Zhisheng, Z. Furong, X. Ruihua, C. Yang, C. Xingfeng, W. Wenyong, R. Jie, First case of severe childhood novel coronavirus pneumonia in China, Chinese Journal of Pediatrics. 58 (2020) 179–182, https://doi.org/10.3760/cma.j.issn.0578-1310.2020.03.003.
[11] K. Feng, Y.X. Yun, X.F. Wang, G.D. Yang, Y.J. Zheng, C.M. Lin, L.F. Wang, Analysis of CT features of 15 Children with 2019 novel coronavirus infection, Zhonghua Er Ke Za Zhi. 58 (2020) E007, https://doi.org/10.3760/cma.j.issn.0578-1310.2020.0007.
[12] Y. Han, Z. Feng, L. Sun, X. Ren, H. Wang, Y. Xue, Y. Wang, Y. Fang, A comparative-descriptive analysis of clinical characteristics in 2019-coronavirus-infected children and adults, Journal of Medical Virology. n/a (n.d.). https://doi.org/10.1002/jmv.25835.
[13] H. Liu, F. Liu, J. Li, T. Zhang, D. Wang, W. Lan, Clinical and CT imaging features of the COVID-19 pneumonia: Focus on pregnant women and children, J. Infect. (2020), https://doi.org/10.1016/j.jinf.2020.03.007.
[14] W. Liu, Q. Zhang, J. Chen, R. Xiang, H. Song, S. Shu, L. Chen, L. Liang, J. Zhou, L. You, P. Wu, B. Zhang, Y. Lu, L. Xia, L. Huang, Y. Yang, F. Liu, M.G. Semple, B.J. Cowling, K. Lan, Z. Sun, H. Yu, Y. Liu, Detection of Covid-19 in children in early January 2020 in Wuhan, China, New Engl. J. Med. (2020), https://doi.org/10.1056/NEJMc2003717.
[15] X. Lu, L. Zhang, H. Du, J. Zhang, Y.Y. Li, J. Qu, W. Zhang, Y. Wang, S. Bao, Y. Li, C. Wu, H. Liu, D. Liu, J. Shao, X. Peng, Y. Yang, Z. Liu, Y. Xiang, F. Zhang, R.M. Silva, K.E. Pinkerton, K. Shen, H. Xiao, S. Xu, G.W.K. Wong, SARS-CoV-2 Infection in Children, New Engl. J. Med. (2020), https://doi.org/10.1056/NEJMc2005073.
[16] X.S.-Y. MA Yao-Ling, Clinical features of children with SARS-CoV-2 infection: an analysis of 115 cases, Chinese Journal of Contemporary Pediatrics. 22 (n.d.) 290–293. https://doi.org/10.7499/j.issn.1008-8830.2003016.
[17] A. Coronado Munoz, U. Nawaratne, D. McMann, M. Ellsworth, J. Meliones, K. Boukas, Late-onset neonatal sepsis in a patient with Covid-19, New Engl. J. Med. (2020) e49, https://doi.org/10.1056/NEJMc2010614.
[18] H. Qiu, J. Wu, L. Hong, Y. Luo, Q. Song, D. Chen, Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study, Lancet. Infect. Dis (2020), https://doi.org/10.1016/S1473-3099(20)30198-5.
[19] Q. Shen, W. Guo, T. Guo, J. Li, W. He, S. Ni, X. Ouyang, J. Liu, Y. Xie, X. Tan, Z. Zhou, H. Peng, Novel coronavirus infection in children outside of Wuhan, China, Pediatric Pulmonology. n/a (n.d.). https://doi.org/10.1002/ppul.24762.
[20] L. Su, X. Ma, H. Yu, Z. Zhang, P. Bian, Y. Han, J. Sun, Y. Liu, C. Yang, J. Geng, Z. Zhang, Z. Gai, The different clinical characteristics of corona virus disease cases between children and their families in China – the character of children with COVID-19, Emerg. Microbes Infect. 9 (2020) 707–713, https://doi.org/10.1080/22221751.2020.1744483.
[21] D. Sun, H. Li, X.-X. Lu, H. Xiao, J. Ren, F.-R. Zhang, Z.-S. Liu, Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study, World J. Pediatrics. (2020), https://doi.org/10.1007/s12519-020-00354-4.
[22] Y. Tan, B. Tan, J. Pan, J. Wu, S. Zeng, H. Wei, Epidemiologic and clinical characteristics of 10 children with coronavirus disease 2019 in Changsha, China, J. Clin. Virol. 127 (2020) 104353, , https://doi.org/10.1016/j.jcv.2020.104353.
[23] D. Wang, X.L. Ju, F. Xie, Y. Lu, F.Y. Li, H.H. Huang, X.L. Fang, Y.J. Li, J.Y. Wang, B. Yi, J.X. Yue, J. Wang, L.X. Wang, B. Li, Y. Wang, B.P. Qiu, Z.Y. Zhou, K.L. Li, J.H. Sun, X.G. Liu, G.D. Li, Y.J. Wang, A.H. Cao, Y.N. Chen, Clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous region) of northern China, Zhonghua Er Ke Za Zhi. 58 (2020) E011, https://doi.org/10.3760/cma.j.cn112140-20200225-00138.
[24] W. Xia, J. Shao, Y. Guo, X. Peng, Z. Li, D. Hu, Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults, Pediatric Pulmonology. n/a (n.d.). https://doi.org/10.1002/ppul.24718.
[25] Y. Xu, X. Li, B. Zhu, H. Liang, C. Fang, Y. Gong, Q. Guo, X. Sun, D. Zhao, J. Shen, H. Zhang, H. Liu, H. Xia, J. Tang, K. Zhang, S. Gong, Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding, Nat. Med. 26 (2020) 502–505, https://doi.org/10.1038/s41591-020-0817-4.
[26] L. Zeng, X. Tao, W. Yuan, J. Wang, X. Liu, Z. Liu, China's first neonatal coronavirus pneumonia, Chin. J. Pediatrics. 58 (2020).
[27] F. Zheng, C. Liao, Q. Fan, H. Chen, X. Zhao, Z. Xie, X. Li, C. Chen, X. Lu, Z. Liu, W. Lu, C. Chen, R. Jiao, A. Zhang, J. Wang, X. Ding, Y. Zeng, L. Cheng, Q. Huang, J. Wu, X. Luo, Z. Wang, Y. Zhong, Y. Bai, X. Wu, R. Jin, Clinical characteristics of children with coronavirus disease 2019 in Hubei, China, Curr. Med. Sci. (2020), https://doi.org/10.1007/s11596-020-2172-6.
[28] L. Zhu, J. Wang, R. Huang, L. Liu, H. Zhao, C. Wu, C. Zhu, Clinical characteristics of a case series of children with coronavirus disease 2019, Pediatric Pulmonology. n/a (n.d.). https://doi.org/10.1002/ppul.24767..
[29] Yun Zhou, G. Yang, K. Feng, H. Huang, Y. Yun, X. Mou, Wang LF, Clinical features and chest CT findings of coronavirus disease 2019 in infants and young children, Chinese Journal of Contemporary Pediatrics. 22 (n.d.) 215–220. https://doi.org/10.7499/j.issn.1008-8830.2020.03.007.
[30] N. Parri, M. Lenge, D. Buonsenso, Children with Covid-19 in Pediatric Emergency Departments in Italy, New England Journal of Medicine. 0 (2020) null. https://doi.

org/10.1056/NEJMc2007617.
[31] B. Henry, M. Olivera, S. Benoit, M. Plebani, G. Lippi, Hematologic, biochemical, and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis, Clin. Chem. Lab. Med. (2020), https://doi.org/10.1515/cclm-2020-0369.
[32] L.J. Stockman, M.S. Massoudi, R. Helfand, D. Erdman, A.M. Siwek, L.J. Anderson, U.D. Parashar, Severe acute respiratory syndrome in children, Pediatr. Infect. Dis. J. 26 (2007) 68–74, https://doi.org/10.1097/01.inf.0000247136.28950.41.
[33] M. Acar, M. Sütçü, H. Aktürk, S.H. Törün, M. Uysalol, S. Meşe, N. Salman, A. Somer, Clinical differences of influenza subspecies among hospitalized children, Turk Pediatri Ars. 52 (2017) 15–22, https://doi.org/10.5152/TurkPediatriArs.2017.4695.
[34] G. Lippi, M. Plebani, Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis, Clin. Chim. Acta (2020), https://doi.org/10.1016/j.cca.2020.03.004.
[35] S. Riphagen, X. Gomez, C. Gonzalez-Martinez, N. Wilkinson, P. Theocharis, Hyperinflammatory shock in children during COVID-19 pandemic, The Lancet. (2020), https://doi.org/10.1016/S0140-6736(20)31094-1.
[36] J. Vikse, G. Lippi, B. Henry, Do sex-specific immunobiological factors and differences in ACE2 expression explain increased severity and mortality of COVID-19 in males?, Diagnosis. (2020).
[37] B.M. Henry, J. Vikse, S. Benoit, E.J. Favaloro, G. Lippi, Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: A novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis, Clin. Chim. Acta 507 (2020) 167–173, https://doi.org/10.1016/j.cca.2020.04.027.
[38] T. Nguyen Thi Dieu, A. Pham Nhat, T.J. Craig, S. Duong-Quy, Clinical characteristics and cytokine changes in children with pneumonia requiring mechanical ventilation, J Int Med Res. 45 (2017) 1805–1817. https://doi.org/10.1177/0300060516672766.
[39] M.L. Allen, J.A. Hoschtitzky, M.J. Peters, M. Elliott, A. Goldman, I. James, N.J. Klein, Interleukin-10 and its role in clinical immunoparalysis following pediatric cardiac surgery, Crit. Care Med. 34 (2006) 2658–2665, https://doi.org/10.1097/01.CCM.0000240243.28129.36.