Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.62, No.6(2022). p.411-21; DOI: https://doi.org/10.14238/pi62.6.2022.411-21

Original Article

# Inflammatory and coagulation marker profiles in severe pediatric COVID-19 patients: a systematic review

**Tartila Fathan[1], Antonius Hocky Pudjiadi[1], Nina Dwi Putri[1], Nindya Permata[2], Yosilia Nursakina[2]**

## Abstract

***Background*** Children are susceptible to SARS-CoV-2 infection and often present mild manifestations. However, severe and critical cases have also been reported. The inflammation and coagulation marker profile pattern in these patients along with the white blood cell differential count in critical PICU cases with non-COVID-19 etiology is not entirely clear.

***Objective*** To evaluate the inflammation and coagulation profiles in children presenting with severe/critical SARS-CoV-2 infection.

***Methods*** A systematic search and review of scientific literature was conducted following the PRISMA guidelines using *ProQuest, SCOPUS, EBSCOHost, ScienceDirect, Cochrane, EMBASE,* and *Pubmed* databases. All relevant original studies until March 11, 2021, were included. The risk of bias was appraised using the *Modified Newcastle Ottawa Scale* and *JBI Critical Appraisal Checklist* tools.

***Results*** We identified 14 studies across 6 countries, including a total sample of 159 severe and critically ill pediatric COVID-19 patients. Most of the subjects showed normal leukocytes, but increased CRP, procalcitonin, ferritin, and IL-6. Studies on coagulation profiles showed normal platelets, PT, aPTT, and inconsistent D-dimer results.

***Conclusion*** Inflammation and coagulation parameters in severe/critically ill children with COVID-19 are atypical. Several inflammatory markers were elevated, including CRP, ferritin, procalcitonin, and IL-6. However, the elevated marker values are still lower compared to non-COVID infection patients. Further investigation of the parameters need to be done in serial examination multicenter studies, which include control subjects. **[Paediatr Indones. 2022;62:411-21; DOI: https://doi.org/10.14238/pi62.6.2022.411-21** ].

***Keywords:*** *inflammatory marker; coagulation marker; severe pediatric COVID-19*

In late December 2019, China first reported pneumonia cases of unknown cause in Wuhan. The next month, the *WHO* declared the coronavirus outbreak to be a worldwide public health emergency. The *WHO* announced the official disease name to be *Coronavirus Disease 2019* (COVID-19), and the etiologic agent name to be *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2), as proposed by *The International Committee on Taxonomy of Viruses*.[1,2] Pneumonia due to SARS-CoV-2 infection is still a global concern and there has not been a significant transmission reduction. As of February 8, 2021, there were 105,805,951 confirmed cases of COVID-19, with 2,312,278 deaths.[3]

Coronavirus disease (COVID) 19 is transmitted by droplets and aerosols released by infected patients when they cough, sneeze, or speak. Airborne transmission is less common, mainly in procedures that generate aerosols. Viruses in droplet and aerosol particles attach to human mucosal surfaces, such as the mouth, nose, and eyes. The symptoms found in

From the Department of Child Health, Universitas Indonesia Medical School/Dr. Cipto Mangunkusumo Hospital[1] and Faculty of Medicine Universitas Indonesia[2], Jakarta, Indonesia.

**Corresponding author:** Tartila Fathan. Department of Child Health, University of Indonesia Medical School/Dr. Cipto Mangunkusumo Hospital, Jl. Diponegoro No. 71, Jakarta. Email: dr.tartila@gmail.com.

Submitted October 19, 2021. Accepted December 15, 2022.

COVID-19 patients vary. Mild symptoms include headache, anosmia, loss of taste, rhinorrhea, myalgia, sore throat, fever, and diarrhea. Patients with severe symptoms may develop dyspnea, hypoxia, respiratory failure, shock, and multi-organ dysfunction.[4]

Children are susceptible to SARS-CoV-2 infection. Their clinical manifestations are often mild, but severe and critical cases have also been reported. Fewer pediatric studies of severe/critical subjects have been done than adult studies. Based on adult reports, inflammation and coagulation profiles hallmark the differences between mild and severe-critical cases. Inflammation profiles include C-reactive protein, ferritin, as well as cytokine and chemokine profiles. Recent studies highlight coagulopathy as the main factor for organ failure in COVID-19 in adults.[5]

However, the pattern of clinical manifestations, inflammation markers, and coagulation profiles are not well established in children with severe/critical COVID-19 disease. We aimed to elucidate the clinical manifestations, inflammation, and coagulation profiles in children presenting with severe/critical SARS-CoV-2 infection, as better knowledge of these profiles may translate to better treatment for patients.

## Methods

In this systematic review, the inclusion criteria were: 1) original study (e.g., cohort, cross-sectional, case series, case reports) conducted in pediatric COVID-19 patients aged 0-18 years; 2) available in full text and English language; and 3) date of publication in the previous 2 years (March 11, 2018 to March 11, 2021).

Subjects were severe and critically pediatric COVID-19 patients. According to the WHO in 2021, severe COVID-19 was defined if pediatric patients showed clinical signs of pneumonia and at least one of the following criteria: (1) central cyanosis or $SpO_2$<90%, severe respiratory distress, a general danger sign, inability to breastfeed, or drink, lethargy or unconsciousness or convulsions; (2) fast breathing: <2 month-olds: ≥ 60 times/min; 2 to 11-month-old: ≥ 50 times/min; 1-5 years: ≥ 40 times/min. The diagnosis of severe COVID-19 may be assisted by chest imaging (radiograph, CT scan, ultrasound). Diagnoses of critically ill pediatric COVID-19 patients included sepsis, septic shock, acute thrombosis, and MIS-C.[5]

We systematically searched *ProQuest, SCOPUS, EBSCOHost, ScienceDirect, Cochrane, EMBASE,* and *Pubmed* with the search terms "covid 19" AND ("child*" OR "pediatric") AND ("inflammatory marker" OR "procalcitonin" OR "crp" OR "ferritin" OR "interleukin" OR “leukocyte” OR “neutrophil” OR “lymphocyte” OR “platelet” OR “prothrombin time” OR “APTT” OR “D-dimer” OR “fibrinogen”) as shown in **Table 1**. Duplicate articles were removed. The remaining articles were independently screened by two authors (NP and YN) for their abstracts' relevance. Selection was made through title and abstract screening, followed by full-text screening according to the inclusion criteria. A third investigator (TF) checked the article list and corresponding data to ensure that no duplications were made and adjudicated any discrepancies. Any conflicting decisions found in the articles were settled by the other reviewers (NDP and AHP). The search was finalized on March 11, 2021. The study was conducted according to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines.[6]

Data extraction was performed independently by two reviewers. We used standardized extraction forms that included study design, sample size, as well as inflammatory and coagulation markers. The quality and risk of bias assessment of included studies was performed using the *Modified Newcastle-Ottawa Quality Assessment Form* for cohort, case control, and cross-sectional studies,[7-9] and the *JBI Critical Appraisal Checklist for Case Series* for case series studies.[10]

*The Modified Newcastle-Ottawa Scale* was a risk-of-bias assessment tool for observational studies (i.e., cohort and case control studies) which includes three categories of evaluation: patient selection, comparability, and outcome. Criteria of *Modified Newcastle Ottawa Scale* for cohort studies were as follows: 1. Representativeness of the exposed cohort, 2. Selection of the non-exposed cohort, 3. Ascertainment of exposure, 4. Demonstration that outcome of interest was not present at the start of the study, 5. Comparability of cohorts on the basis of the design or analysis, 6. Assessment of outcome, 7. Was follow-up long enough for outcomes to occur?, and 8. Adequacy of follow up cohorts.[7] On the other hand, the criteria of *Modified Newcastle Ottawa Scale* for case control studies differed. The criteria

**Table 1.** Keywords for search strategies.

| Database | Search query | Hits |
|---|---|---|
| Cochrane | ab(covid 19) AND ab(children OR child OR pediatric) AND ab(inflammatory marker OR procalcitonin OR CRP OR ferritin OR blood OR interleukin OR leukocyte OR lymphocyte OR platelet OR prothrombin time OR APTT OR D-dimer OR fibrinogen) | 36 |
| EBSCOHost | covid 19 AND (child OR children) AND (procalcitonin OR ferritin OR CRP OR interleukin OR blood OR leukocyte OR lymphocyte OR platelet OR prothrombin time OR APTT OR D-dimer OR fibrinogen) | 61 |
| Scopus | TITLE-ABS-KEY ("covid 19" AND (children OR child) AND (procalcitonin OR CRP OR interleukin OR ferritin OR blood OR leukocyte OR lymphocyte OR platelet OR prothrombin time OR APTT OR D-dimer OR fibrinogen) AND NOT adult) | 330 |
| ProQuest | ab(covid 19) AND ab(children OR child OR pediatric) AND ab(inflammatory marker OR procalcitonin OR CRP OR ferritin OR blood OR interleukin OR leukocyte OR lymphocyte OR platelet OR prothrombin time OR APTT OR D-dimer OR fibrinogen) | 83 |
| Science Direct | TITLE-ABS-KEY covid 19 AND ( child OR children OR pediatric ) AND ((inflammatory marker OR procalcitonin OR ferritin OR CRP OR interleukin OR leukocyte OR lymphocyte OR platelet OR prothrombin time OR APTT OR D-dimer OR fibrinogen)) | 35 |
| PubMed | (covid 19[Title/Abstract] AND (child [Title/Abstract] OR children [Title/Abstract] OR pediatric) [Title/Abstract]) AND ((inflammatory marker OR procalcitonin OR ferritin OR CRP OR interleukin OR leukocyte OR lymphocyte OR platelet OR prothrombin time OR APTT OR D-dimer OR fibrinogen) | 352 |
| EmbaseEMBASE | 'covid 19':ab AND (severe OR critical) AND (child:ab OR children:ab) AND (procalcitonin:ab OR ferritin:ab OR crp:ab OR interleukin:ab OR blood:ab OR leukocyte:ab OR lymphocyte:ab OR platelet:ab OR 'prothrombin time':ab OR aptt:ab OR 'd dimer':ab OR fibrinogen:ab) AND [embase]/lim | 628 |

were as follows: 1. Is the case definition adequate?, 2. Representativeness of the cases, 3. Selection of controls, 4. Definition of controls, 5. Comparability of cases and controls on the basis of the design or analysis, 6. Ascertainment of exposure, 7. Same method of ascertainment for cases and controls, and 8. Non-response rate.[8] Lastly, criteria of Modified Newcastle Ottawa Scale for cross-sectional studies included: 1. Representativeness of the sample, 2. Sample size, 3. Non-respondents, 4. Ascertainment of exposure, 5. The subjects in different outcome groups were comparable based on the study design or analysis. Confounding factors were controlled., 6. Assessment of the outcome, 7. Statistical test.[9]

The JBI critical appraisal tool was an internal validity and risk of bias assessment tool especially designed for case series studies which included questions regarding confounding, selection, and information bias, in addition to the importance of clear reporting. Criteria of *JBI Critical Appraisal Checklist* for case series studies were as follows: 1. Were there clear criteria for inclusion in the case series?, 2. Was the condition measured in a standard, reliable way for all participants included in the case series?, 3. Were valid methods used for identification of the condition for all participants included in the case series?, 4. Did the case series have consecutive inclusion of participants?, 5. Did the case series have complete inclusion of participants?, 6. Was there clear reporting of the demographics of the participants in the study?, 7. Was there clear reporting of clinical information of the participants?, 8. Were the outcomes or follow up results of cases clearly reported?, 9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?, 10. Was statistical analysis appropriate?[10]

In order to interpret the assessment results according to AHRQ standards, several thresholds were defined: good, fair, and poor. The study was considered as good quality if it gained 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain. Whereas, the study was considered fair quality if it gained 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain. Lastly, poor quality study would gain 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.7 On the other hand, there was no standardized method or guideline to interpret the results of *JBI Critical Appraisal Checklist*, resulting in ramification for how appraisers interpret the results after using the tool.[10]

The primary endpoint of the study was

inflammatory and coagulation markers, including leukocytes, lymphocytes, neutrophils, CRP, ferritin, procalcitonin, natural killer (NK) cells, interferon gamma, TNF-alpha, interleukin, platelets, PT, aPTT, D-dimer, and fibrinogen.

## Results

A total of 1525 citations were found by literature search with the additional 4 records identified by manual searching. After removing duplicates, these records were screened, with only 86 full-text articles assessed for their eligibility. Among them, 72 articles were excluded for various reasons, including not being available in the English language, irrelevant outcomes, and review articles. Finally, 14 articles were included in our systematic review (**Figure 1**).

The included studies were conducted in the USA, Spain, China, and the Middle East, including Turkey, Kuwait, and the Kingdom of Saudi Arabia. The study designs were 11 cohort studies, 2 case control studies, and 1 case series. All studies involved pediatric patients under the age of 21 years. Sample sizes ranged from 1 to 30 severe/critical cases per study, with a total sample of 163 severe and critically ill pediatric COVID-19 patients (**Table 2**). Risk of bias analyses revealed that all studies were eligible for further analysis, as shown in **Tables 3, 4, 5,** and **6**.

We extracted descriptive data from all studies on the inflammatory marker profiles, including leukocyte count, lymphocyte count, neutrophil count,

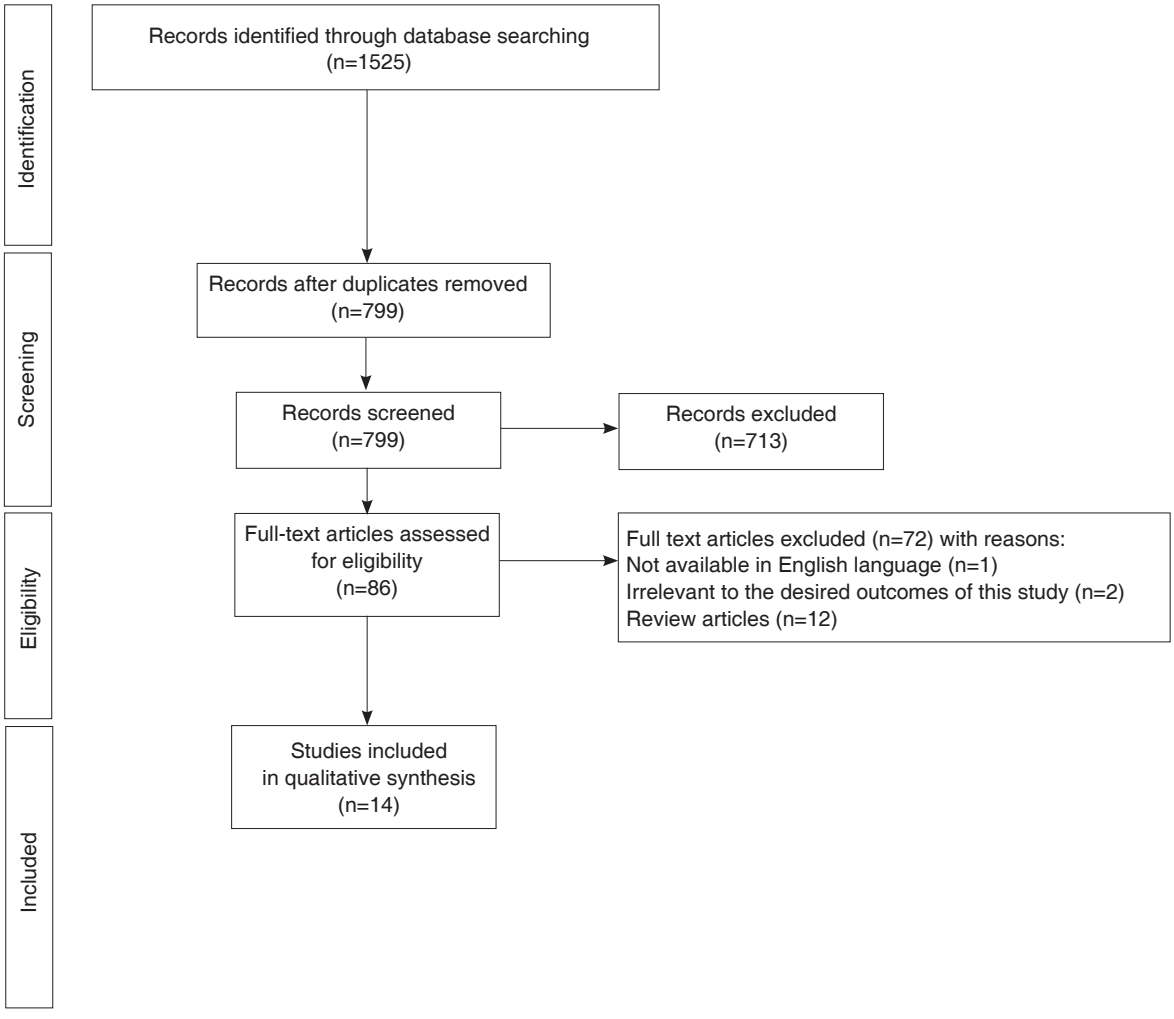


**Figure 1**. PRISMA flow diagram of study selection process

**Table 2**. Characteristics of included studies

| Author, year | Origin | Study design | Sample size of severe and critically ill | Mean age (SD), years | Male (%) |
|---|---|---|---|---|---|
| Alfraij *et al.*[11] | Kuwait and Kingdom of Saudi Arabia | Multicenter retrospective cohort | 25 | 2.78 (0.21 - 8.51)* | 60 |
| Fisler *et al.*[12] | USA | Retrospective cohort | 30 (47 non-PICU) | 12** | 37 |
| Chao *et al.*[13] | USA | Retrospective | 13 (33 medical unit) | 14.8 (11.6 - 15.9)* | 62 |
| Storch-de-Gracia *et al.*[14] | Spain | Retrospective | 15 (24 uncomplicated) | 9 (12 days - 16 years)* | 59 |
| Ren *et al.*[15] | China | Multicenter retrospective cohort | 1 (40 COVID pneumonia 284 other viral pneumonia) | COVID-19 pneumonia cohort : 6.4* | |
| Lu *et al.*[16] | China | Retrospective | 12 severe 8 critical | 6.36 (3.08)+ 2.71 (2.96)++ | 85 |
| Al Yazidi *et al.*[17] | Middle East | Multicenter retrospective | 13 severe | 1.8 (0.2-6.9)* | 64 |
| Zachariah *et al.*[18] | USA | Cohort | 9 severe | 14 (8 -19)* | 44 |
| Diorio *et al.*[19] | USA | Cohort | 11 severe | 15 (14-17)* | 45 |
| Sun *et al.*[20] | China | Case series | 8 severe | 5.04 (0.8-13.9)* | 75 |
| Wang *et al.*[21] | China | Case control | 8 severe | 5.06 (0.97–13.83)* | 75 |
| Ozenen *et al.*[22] | Turkey | Case control | 1 severe, 3 critical | 15.1 (2.1) | 40 |
| Dul *et al.*[23] | China | Cohort | 1 severe, 3 critical | 4.5 (0.8-13.4)* | 75 |
| Zheng *et al.*[24] | China | Cross-sectional | 2 critical | 0.67 (1) | 100 |

*Data presented in median (IQR), +severe group, ++critically ill group, **Data presented in mean (without available SD)

**Table 3**. Critical appraisal of cohort studies using the Modified Newcastle Ottawa Scale

| Author | Selection comparability outcome | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | |
| Alfraij *et al.*[11] | * | | * | | | * | * | * | ***** |
| Fisler *et al.*[12] | * | | * | | | * | * | * | ***** |
| Chao *et al.*[13] | * | | * | | | * | * | * | ***** |
| Storch-de-Gracia *et al.*[14] | * | | * | | | * | * | * | ***** |
| Ren *et al.*[15] | * | * | * | | * | * | * | * | ****** |
| Lu *et al.*[16] | * | | * | | | * | * | * | ***** |
| Al Yazidi *et al.*[17] | * | | * | | * | * | * | * | ****** |
| Zachariah *et al.*[18] | * | * | * | | | * | * | * | ****** |
| Diorio *et al.*[19] | * | | * | | | * | * | * | ***** |
| Dul *et al.*[23] | * | | * | | * | * | * | * | ****** |

**Table 4**. Critical appraisal of case-control studies using *Modified Newcastle Ottawa Scale*

| Author | Selection comparability exposure | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | |
| Wang *et al.*[21] | * | * | * | | ** | * | * | * | ******** |
| Ozenen *et al.*[22] | * | * | * | | | * | * | * | ****** |

**Table 5**. Critical appraisal of cross-sectional studies using *Modified Newcastle Ottawa Scale*

| Author | Selection comparability exposure | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | |
| Zheng et al.24 | * | | * | ** | | * | | ***** |

**Table 6**. Critical appraisal of case series study using *JBI Critical Appraisal Checklist*

| Author | Selection comparability exposure | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Sun *et al.*[20] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

CRP level, ferritin level, procalcitonin level, NK cell count, IFN gamma level, TNF alpha level, and interleukin levels (IL-1, IL-6, IL-8 and IL-10). We also extracted descriptive data regarding the coagulation marker profiles, including platelet count, PT, APTT, D-dimer level and fibrinogen level. Each study fulfilled a minimum of two parameters, and no study had fulfilled all the parameters analyzed in this review. Most data were presented in mean (SD), and some were presented in median (IQR), as shown in **Table 6**. The majority of studies showed normal leukocyte counts, increased CRP, procalcitonin, ferritin, and IL-6. Studies for coagulation profiles showed normal platelet count, PT, aPTT, and inconsistent results in D-dimer.

## Discussion

While severe/critical SARS-CoV-2 infection in children is not prevalent, children are more susceptible to SARS-CoV-2 than adults. Most pediatric patients present with milder symptoms and relatively good prognoses. In a previous study in an adult cohort, significantly elevated inflammatory markers suggest a hyperinflammatory state seen in severe patients.[25] In this systematic review, we examined 14 studies conducted in pediatric cohorts, which reported 159 severe/critical cases in total. Patient ages varied among studies, while the male gender was predominant.

Like previous reports, males were deemed more vulnerable to COVID-19 in our systematic review. A large-scale meta-analysis showed that male sex is highly correlated with the development of severe disease, as measured by intensive treatment unit (ITU) admission (OR 2.84; 95%CI 2.06 to 3.92; P<0.001) and death (OR 1.39; 95%CI 1.31 to 1.47; P=5.00 × 10-30).[21] This observation might have been caused by sex differences in innate and adaptive immune systems. Females have higher numbers of CD4+ T cells and more active CD8+.[26]

Elevation in CRP was found in a Chinese adult cohort study and associated with higher mortality.[27] In a pediatric COVID-19 cohort, high CRP was also associated with the need for mechanical ventilation.[28] Laboratory testing revealed that initial C-reactive protein, leukocyte count, and presenting thrombocytopenia were significantly associated with the presence of organ dysfunction (P=0.001, P=0.034, and P=0.003, respectively).[7] Another study also noted that PICU admission was associated with high C-reactive protein [median 6.6 (range 2.0-11.8) mg/dL)], high procalcitonin [median 11.5 (range 1.4-21.5) ng/mL], and low platelet counts [median 194,000 (range 138.000-238.000) /mm3].[8] Moreover elevated CRP might be predictive of mortality in severe pediatric sepsis and septic shock.[29] Compared to other studies of inflammatory markers in non-COVID-19 pneumonia, CRP and IL-6 were higher in non-COVID-19 pneumonia patients, with a median of 40 (range 12-157) mg/dL and 248.39 (range 92.33-473.9) pg/mL, respectively.[30] A high level of procalcitonin is not specific, as inflammatory cytokines can trigger it as a response to severe bacterial infection. It is also found in severe respiratory viral infection, e.g., severe pneumonia cases caused by human adenovirus.[31] Like CRP, procalcitonin was also a predictor for mortality and need for intensive care in adult COVID-19 patients.[32]

The finding of thrombocytopenia in children is not prevalent in severe adult COVID-19 patients.[32] Such findings highlight the differences

in pathophysiology compared to adults, which seems to have thrombotic microangiopathy (TMA) as the underlying mechanism for the severity. Compared to immunophenotypes in children with sepsis, we noted that thrombocytopenia associated multi-organ failure (TAMOF) was not the underlying pathophysiology for severe and critically ill pediatric conditions due to COVID-19. Consistently increased ferritin found in our study may relate to macrophage activating syndrome in sepsis immunophenotypes. Nevertheless, other immunophenotypes such as immune paralysis and sequential multi-organ failure need to be explored more fully.[33]

Leukocyte, lymphocyte, and neutrophil counts were in the normal range. In contrast, reduced lymphocyte and neutrophil counts were observed in other types of viral respiratory infection in children, including influenza.[34] A high neutrophil/lymphocyte ratio has also been described as a helpful marker in diagnosing other illnesses, such as influenza and sepsis.[35] It can also be found in adult COVID-19 patients, where leukopenia is prevalent in severe adult cases.[36]

An increase in cytokines was not prevalent in children, indicating that SARS-CoV-2 infection has a more negligible effect on excessive activation of children's innate immune systems, thus rarely triggering a cytokine storm. Hence, milder manifestations are seen in pediatric COVID-19 patients, whereas high levels of cytokines were usually detected in severe adult COVID-19 patients.[36] However, in critically ill patients, cytokine storms resulting from lung injury can be more pronounced, leading to increased plasma concentrations of pro-and anti-inflammatory cytokines.[37] We also found several studies that showed an increase in IL-6 and IL-10,38 as well as IFN-γ and IL-8 in a few studies.[39] Laboratory testing conducted by Ren et al. showed significantly higher levels of IL-6 (120.31 ng/L), IL-10 (33.38 ng/L), and procalcitonin (0.43 ng/mL) in their patients compared to those with mild and moderate symptoms.[10]

In conclusion, inflammation and coagulation parameters in severe/critically ill COVID-19 children are atypical. To review, several inflammatory parameters in the literatures included are increased, namely, CRP, ferritin, procalcitonin, and IL-6. Compared to other non-COVID infection conditions, these values are still much lower. A limitation of this systematic review was the high variations in underlying disease or comorbidities of subjects, including in each study, as well as performing the laboratory examinations at different times, and not having a full understanding of COVID-19 as a newly emerging disease. Further investigations of the parameters need to be done in serial examination multicentre studies, including control subjects.

## Conflict of interest

None declared.

### Funding acknowledgment

This study received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

## References

1. Ryan GA, Purandare NC, McAuliffe FM, Hod M, Purandare CN. Clinical update on COVID-19 in pregnancy: a review article. J Obstet Gynaecol Res. 2020;46:1235-45. DOI: https://doi.org/10.1111/jog.14321.
2. Rasmussen SA, Smulian JC, Lednicky JA, Wen TS, Jamieson DJ. Coronavirus Disease 2019 (COVID-19) and pregnancy: what obstetricians need to know. Am J Obstet Gynecol. 2020;222:415-26. DOI: https://doi.org/10.1016/j.ajog.2020.02.017.
3. World Health Organization. WHO coronavirus disease (COVID-19) dashboard. Geneva. 2020. [cited 2021 March 11]. Available from: https://covid19.who.int.
4. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review Clin Immunol. 2020:108427. DOI: https://doi.org/10.1016/j.clim.2020.108427.
5. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, Baxter-Stoltzfus A, Laurence J. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. Transl Res. 2020 Jun;220:1-13. DOI: https://doi.org/10.1016/j.trsl.2020.04.007.
6. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021; n71. DOI: https://doi.org/10.1136/bmj.n71.

**Table 6**. Laboratory findings of severe and critically ill pediatric COVID-19 patients from 14 studies

| Author | Alfraji *et al.*[11] | Fisler *et al.**12 | Chao *et al.**13 | Storch-de-Gracia *et al.** 14 | Ren *et al.*[15] | Lu *et al.*** [16] | Al Yazidi *et al.**[17] | Zachariah *et al.**[18] | Diorio *et al.**[19] | Sun *et al.*[20] | Wang *et al.*[21] | Ozenen *et al.**[22] | Dul *et al.*[23] | Zheng *et al.*[24] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sample size (severe and critical) | 25 | 30 | 13 | 15 | 1 | 20 | 13 | 9 | 11 | 8 | 8 | 8 | 4 | 2 |
| **Inflammation marker** | | | | | | | | | | | | | | |
| Leukocyte, x $10^9$/L | 10.0 (8.8) | 7.8 (5.4-17.1) | 9.7 (6.9-17.1) | 8.0 (7.5-10.3) | | S: 6.0 (2.2) C: 4.0 (2.5) | | | 8.1 (4.0) | 6.65 (5.11-10.81) | 13.07± 7.5 | 6.3 (4.6) | 4.43 (11.96) | |
| Lymphocyte, x $10^9$/L | 2.68 (2.5) | | 1.18 (0.88-2.53) | 0.75 (0.35-1.8) | | S: 1.5 (0.6) C: 1.7 (1.4) | | | | 3.0 (1.7) | 2.80 (1.87-7.00) | 7.26±6.1 | 2.5 (1.8) | 1.46 (2.47) |
| Neutrophil, x $10^9$/L | 6.16 (6.2) | | | 6.72 (6.2-9.4) | | S: 4.0 (2.0) C: 1.8 (1.6) | 11.9 (5.4-17.1) | | | | | 11.5± 7.68 | 3.1 (3.4) | |
| CRP, ug/dL | 84.7 (107) | 54.10 (13.90-161.90) | 6.6 (2.0-11.8) | 20.6 (15.3-34.2) | | S: 36.0 (23.9) C: 22.5 (20.0) | 116 (25-171) | 18.825 (12.69-25.78) | 30.3 (7-34.9) | 25.8 (36.8) | 6.48 (0.23-29.20) | 78.2± 67.4 | 11.4 (10.5) | 0.5 (24.6) |
| Ferritin, ng/mL | 1229 (1689) | 446.05 (307.35-809.35) | | 686 (255-1392) | | S: 198 (109) C: 3230 (5350) | | 432.55 (178-1374) | 419 (164-2747) | | | | | |
| Procalcitonin, ng/mL | 10.2 (21.2) | | 11.5 (1.4-21.5) | 5.73 (1.77-14.08) | 0.43 | S: 0.248 (0.193) C : 15.3 (34.4) | | 5.3 (0.13-29.89) | | 2.2 (6.0) | | 3.5± 5.6 | 0.2 (0.2) | |
| NK cells, /µL | | | | S: 157.3 (105.1) C: 91.0 (83.9) | | | | | | | | 141.00 (11.00-253.00)† | | 4.6 (4.0) |
| IFN gamma, pg/mL | | | | S: 58.8 (141.1) C: 274.6 (664.6) | | | | | | | | 12.1 (11.6) | | 1.7 (2.3) |
| TNF alpha, pg/mL | | | | S: 1.6 (0.5) C: 2.1 (1.1) | | | | | | 54 (12-100) | 3.2 (1.7) | | | 2.2 (2.6) |
| **Interleukin** | | | | | | | | | | | | | | |
| IL-6, pg/mL | | | 120.31ng/L | S: 25.2 (24.5) C: 569.1 (1337.3) | | | | 139.52 (11.2-315.0) | | | 23.75 (6.53-1057.45) | | 31.9 (59.0) | |
| IL-8, pg/mL | | | | | | | | | | 32.7 (12.3-124) | | | | |

**Table 6**. Laboratory findings of severe and critically ill pediatric COVID-19 patients from 14 studies (continued)

| Author | Alfraji *et al.*[11] | Fisler *et al.**12 | Chao *et al.**13 | Storch-de-Gracia *et al.** 14 | Ren *et al.*[15] | Lu *et al.*** [16] | Al Yazidi *et al.**[17] | Zachariah *et al.**[18] | Diorio *et al.**[19] | Sun *et al.*[20] | Wang *et al.*[21] | Ozenen *et al.**[22] | Dul *et al.*[23] | Zheng *et al.*[24] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IL-10, pg/mL | | | | | 33.38 ng/L | S 9.9 (15.8)<br>C: 262.1 (536.1) | | | | | 7.8 (4.6) | 8.92 (3.18-106.77) | | 9.2 (16.2) |
| **Coagulation marker** | | | | | | | | | | | | | | |
| Platelet count, x $10^9$/L | 243 (167) | 231 (182-206)* | 194 (138-238) | | | S: 253.3 (60.1)<br>C: 210.6 (129.2) | | | Lowest: 128 (78-165)<br>Highest: 311 (223-347) | | | 225± 80.8 | | 202 (184) |
| PT, s | | | | | | | | 17.32 (13.7-20.7) | 16 (13.2-31) | | | | | 14 (14.3) |
| APTT, s | | | | | | | | 47.77 (32.4-108.5) | 52.4 (37.5-78.8) | | | | | |
| D-dimer, ng/dL | 3,106 (3,491) | | 800 (700-2,300) | 3,960 (2,210-6,660) | | | | 4,870 (950-18,775) | 2,530 (600-20,500) | 8,900 17,600) | 3 (37.5%) | 2,500± 2006 | 44.000 (27,000-78,000) | |
| Fibrinogen, mg/dL | | | | | | | | | Lowest 297 (239-332)<br>Highest 488 (305-890) | | | 444± 212.3 | | |

Data presented in mean (SD); *Data presented in median (IQR); ****Data were separated for each subject classification, S=severe; C=critically ill

7. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, *et al*. Newcastle-Ottawa quality assessment scale cohort studies. University of Ottawa. [Cited 2021 Mar 11]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK99082/bin/appb-fm4.pdf.
8. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, *et al.* The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [cited 2021 March 11]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
9. Luchini C, Stubbs B, Solmi M, Veronese N. Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale. World Journal of Meta-Analysis. 2017;5:80-84. DOI: https://doi.org/10.13105/wjma.v5.i4.80.
10. Munn Z, Barker TH, Moola S, Tufanaru C, Stern C, McArthur A, *et al.* Methodological quality of case series studies: an introduction to the JBI critical appraisal tool. JBI Evidence Synthesis. 2020;18: 2127-2133. DOI: https://doi.org/10.11124/JBISRIR-D-19-00099.
11. Alfraij A, Bin Alamir A, Al-Otaibi A, Alsharrah D, Aldaithan A, Kamel A, *et al*. Characteristics and outcomes of coronavirus disease 2019 (COVID-19) in critically ill pediatric patients admitted to the intensive care unit: A multicenter retrospective cohort study. Journal of Infection and Public Health. 2021;14:193-200. DOI: https://doi.org/10.1016/j.jiph.2020.12.010.
12. Fisler G, Izard S, Shah S, Lewis D, Kainth M, Hagmann S, *et al*. Characteristics and risk factors associated with critical illness in pediatric COVID-19. Annals of Intensive Care. 2020;10. DOI: https://doi.org/10.1186/s13613-020-00790-5.
13. Chao J, Derespina K, Herold B, Goldman D, Aldrich M, Weingarten J, *et al.* Clinical Characteristics and Outcomes of Hospitalized and Critically Ill Children and Adolescents with Coronavirus Disease 2019 at a Tertiary Care Medical Center in New York City. The Journal of Pediatrics. 2020;223:14-19. DOI: https://doi.org/10.1016/j.jpeds.2020.05.006.
14. Storch-de-Gracia P, Leoz-Gordillo I, Andina D, Flores P, Villalobos E, Escalada-Pellitero S, *et al.* Clinical spectrum and risk factors for complicated disease course in children admitted with SARS-CoV-2 infection. Anales de Pediatría (English Edition). 2020;93:323-33. DOI: https://doi.org/10.1016/j.anpede.2020.07.005.
15. Ren G, Wang X, Xu J, Li J, Meng Q, Xie G, *et al.* Comparison of acute pneumonia caused by SARS-COV-2 and other respiratory viruses in children: a retrospective multi-center cohort study during COVID-19 outbreak. Military Medical Research. 2021;8. DOI: https://doi.org/10.1186/s40779-021-00306-7.
16. Lu W, Lu W, Yang L, Yang L, Li X, Li X, *et al.* Early Immune Responses and Prognostic Factors in Children with COVID-19: A Single-center Retrospective Analysis. 2020;. DOI: https://doi.org/10.21203/rs.3.rs-101151/v1.
17. Al Yazidi L, Al Hinai Z, Al Waili B, Al Hashami H, Al Reesi M, Al Othmani F, *et al.* Epidemiology, characteristics and outcome of children hospitalized with COVID-19 in Oman: A multicenter cohort study. International Journal of Infectious Diseases. 2021;104:655-660. DOI: https://doi.org/10.1016/j.ijid.2021.01.036.
18. Zachariah P, Johnson C, Halabi K, Ahn D, Sen A, Fischer A, *et al.* Epidemiology, clinical features, and disease severity in patients with coronavirus disease 2019 (COVID-19) in a children's hospital in New York City, New York. JAMA Pediatrics. 2020;174):e202430. DOI: https://doi.org/10.1001/jamapediatrics.2020.2430.
19. Diorio C, McNerney K, Lambert M, Paessler M, Anderson E, Henrickson S, *et al*. Evidence of thrombotic microangiopathy in children with SARS-CoV-2 across the spectrum of clinical presentations. Blood Advances. 2020;4:6051-6063. DOI: https://doi.org/10.1182/bloodadvances.2020003471.
20. Sun D, Li H, Lu X, Xiao H, Ren J, Zhang F, *et al*. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. World Journal of Pediatrics. 2020;16:251-259. DOI: https://doi.org/10.1007/s12519-020-00354-4.
21. Wang Y, Zhu F, Wang C, Wu J, Liu J, Chen X et al. Children Hospitalized With Severe COVID-19 in Wuhan. Pediatric Infectious Disease Journal. 2020;39:e91-e94. DOI: https://doi.org/10.1097/inf.0000000000002739.
22. Ozenen G, Sahbudak Bal Z, Umit Z, Bilen N, Yildirim Arslan S, Yurtseven A, *et al.* Demographic, clinical, and laboratory features of COVID-19 in children: The role of mean platelet volume in predicting hospitalization and severity. Journal of Medical Virology. 2021;. DOI: https://doi.org/10.1002/jmv.26902.
23. Du H, Dong X, Zhang J, Cao Y, Akdis M, Huang P, *et al.* Clinical characteristics of 182 pediatric COVID-19 patients with different severities and allergic status. Allergy. 2020;76:510-32. DOI: https://doi.org/10.1111/all.14452.
24. Zheng F, Liao C, Fan Q, Chen H, Zhao X, Xie Z, *et al.* Clinical characteristics of children with coronavirus disease 2019 in Hubei, China. Current Medical Science. 2020;40:275-80. DOI: https://doi.org/10.1007/s11596-020-2172-6.
25. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.

Lancet. 2020;395:1054-62. DOI: https://doi.org/10.1016/S0140-6736(20)30566-3.

26. Peckham H, Gruijter NM, Raine C, Radziszewska A, Clurtin C, Wedderburn L, *et al.* Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission 2020;11:6317. DOI: https://doi.org/10.1038/s41467-020-19741-6.
27. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46:846-8. DOI: https://doi.org/10.1007/s00134-020-05991-x.
28. Zachariah P, Johnson CL, Halabi KC, Ahn D, Sen AI, Fischer A, *et al.* Epidemiology, clinical features, and disease severity in patients with Coronavirus disease 2019 (COVID-19) in a children's hospital in New York City, New York. JAMA Pediatr. 2020;174:e202430. DOI: https://doi.org/10.1001/jamapediatrics.2020.2430.
29. Carcillo JA, Sward K, Halstead ES, Telford R, Jimenez-Bacardi A, Shakoory B, *et al*. A systemic inflammation mortality risk assessment contingency table for severe sepsis. Pediatr Crit Care Med. 2017;18:143-50. DOI: https://doi.org/10.1097/PCC.0000000000001029.
30. Khattab AA, El- Mekkawy MS, Shehatab AM, Whdan NA. Clinical study of serum interleukin-6 in children with community-acquired pneumonia. Egyptian Pediatric Association Gazette. 2018;66:43-8. DOI: https://doi.org/10.1016/j.epag.2018.03.003.
31. Guervilly C, Coisel Y, Botelho-Nevers E, Dizier S, Castanier M, Lepaul-Ercole R, *et al*. Significance of high levels of procalcitonin in patients with influenza A (H1N1) pneumonia. J Infect. 2010;61:355-8. DOI: https://doi.org/10.1016/j.jinf.2010.07.013.
32. Almazeedi S, Al-Youha S, Jamal MH, Al-Haddad M, Al-Muhaini A, Al-Ghimlas F, *et al.* Characteristics, risk factors and outcomes among the first consecutive 1096 patients diagnosed with COVID-19 in Kuwait. EClinicalMedicine. 2020;24:100448. DOI: https://doi.org/10.1016/j.eclinm.2020.100448.
33. Carcillo J, Halstead ES, Hall M W, Nguyen TC, Reeder R, Aneja R, *et al.* Three hypothetical inflammation pathobiology phenotypes and pediatric sepsis-induced multiple organ failure outcomes. Pediatr Crit Care Med. 2017;18: 513-3. DOI: https://doi.org/10.1097/PCC.0000000000000112230.
34. Cao B, Li XW, Mao Y, Wang J, Lu HZ, Chen YS, et al. Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. N Engl J Med. 2009;361:2507-17. DOI: https://doi.org/10.1056/NEJMoa090661.
35. Russell CD, Parajuli A, Gale HJ, Bulteel NS, Schuetz P, de Jager CPC, *et al.* The utility of peripheral blood leucocyte ratios as biomarkers in infectious diseases: a systematic review and meta-analysis. J Infect. 2019;78:339-48. DOI: https://doi.org/10.1016/j.jinf.2019.02.006.
36. Jesenak M, Brndiarova M, Urbancikova I, Rennerova Z, Vojtkova J, Bobcakova A, *et al*. Immune parameters and COVID-19 infection - associations with clinical severity and disease prognosis. Front Cell Infect Microbiol 2020;10:364. DOI: https://doi.org/10.3389/fcimb.2020.00364.
37. Huang CL, Wang YM, Li XW, Ren LL, Zhao JP, Hu Y, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506. DOI: https://doi.org/10.1016/S0140-6736(20)30183-5.
38. Dhar SK, K V, Damodar S, Gujar S, Das M. IL-6 and IL-10 as predictors of disease severity in COVID-19 patients: results from meta-analysis and regression. Heliyon. 2021;7: e06155. DOI: https://doi.org/10.1016/j.heliyon.2021.e06155.
39. Li L, Li J, Gao M, Fan H, Wang Y, Xu X, *et al*. Interleukin-8 as a biomarker for disease prognosis of coronavirus disease-2019 patients. Frontiers in Immunology. 2021;11: 602395. DOI: https://doi.org/10.3389/fimmu.2020.602395.