International Journal of Contemporary Pediatrics
Bari A et al. Int J Contemp Pediatr. 2024 Jan;11(1):8-13
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20233953

Original Research Article

Neutrophil lymphocyte ratio and platelet lymphocyte ratio as a marker for disease severity in children with COVID-19

Attia Bari[1], Tooba Fateen[2]*, Aimen Ch[1]

[1]Department of Pediatric Medicine, University of Child health Sciences, The Children Hospital Lahore, Pakistan
[2]Department of Pathology. University of Child health Sciences, The Children Hospital Lahore, Pakistan

Received: 30 October 2023
Revised: 02 December 2023
Accepted: 06 December 2023

***Correspondence:**
Dr. Tooba Fateen,
E-mail: drtoobafateen@gmail.com

ABSTRACT

Background: It had been observed that there is relationship of neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) with disease severity in children with COVID-19 and post-COVID, multisystem inflammatory disease in children (MIS-C). Study conducted to determine NLR and PLR correlation with this disease severity.
Methods: Prospective descriptive analytical study conducted at the children's hospital and university of child health sciences, Lahore. Consecutive confirmed cases of COVID-19 infection and post-COVID, MIS-C diagnosed on the basis of RT-PCR from nasopharyngeal swab and antibody test admitted from March 2020 to October 2021 were included through consecutive sampling. Complete blood (CBC) was done and NLR and PLR was determined
Results: Majority 198 (74.2%) of the 267 patients had a diagnosis of COVID-19 and 69 (25.8%) were post-COVID MIS-C. There was a male preponderance 177 (66.3%) and the mean age was 6.1±4.7 years (95% CI: 5.62-6.74). Majority children had mild disease 80 (30%), 34 (12.7%) were critical and there were 37 (13.8%) deaths. Underlying comorbidity was present in 55 (20.6%). As the severity of symptoms changed from asymptomatic to severe disease, there was a significant rise of mean NLR from 1.88±1.40 to 5.47±4.77 respectively ($p<0.001$). PLR however, failed to show any kind of association with severity of the symptoms ($p=0.922$).
Conclusions: NLR served as a marker of disease severity among pediatric patients suffering from COVID-19 and MIS-C. However, PLR failed to show any relation with disease severity.

Keywords: COVID-19, MIS-C, Children, Blood picture, Neutrophil, Platelet

INTRODUCTION

Coronavirus (COVID-19) has resulted in a drastic result on health care facilities. It causes severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] COVID-19 is often severe in advanced age patients, particularly those with medical comorbidities. It has been an observation that pediatric patients present with milder form of disease. Few children have hyperinflammatory shock called as MIS-C or atypical Kawasaki like syndrome.[2] Presentations and severity related factors of this disease are evolving. The levels of CRP, D-dimer, are clearly elevated and blood cell count showed leukopenia or leukocytosis, and lymphopenia in critical disease.[3]

In human body, platelets are essential immune cells that plays a significant role in blood clotting mechanism and maintenance of vascular lining, new vessel formation, natural immunity and reaction in inflammation. Variation in their count is markedly related to a spectrum of illnesses. Lymphocyte count and platelet count can be utilized in early detection of inflammation and as marker to indicate regulation during infective process. In patients with COVID-19 temporal pattern of falling platelet counts could indicate a worsening thrombotic state.[4]

A novel biomarker of inflammation, PLR and NLR is inexpensive and readily available in hospital setting. In multiple studies such as cardiovascular diseases and autoimmune diseases, NLR and PLR have been taken into use in recent years as indicator to see different disease progress related to heart, malignancies and severe infections.[5] NLR and PLR has been used to see severity of inflammation and death risk related to it. Severe COVID-19 admitted patients have shown raised PLR and NLR because of increase in severity of respiratory disease. There are different results on significance of PLR for using it as an indicator for severe disease, as in 1 study was stated that PLR has no observed value for identifying severe patients and predicting death of COVID-19 patients.[6] Another study reported a significant difference in both NLR and PLR between more serious advanced disease and less serious patients with COVID-19.[7] An increased risk of mortality was associated with high PLR at time of admission.[8]

Raised NLR and PLR levels in admitted patients can be utilized in under resourced countries so that medical attention and health care facilities can be justified and more directed towards those patients who are vulnerable to severe form of disease.[8] Since COVID-19 is a new pandemic disease, information and data on this disease is scarce, particularly in children, our study will analyze the relationship between NLR and PLR with the severity of its manifestations and prognosis of children having COVID-19 and MIS-C presented to our hospital.

METHODS

This descriptive cross sectional prospective study was conducted in Corona isolation ward of university of child health sciences, the children's hospital Lahore. This study had been approved by institutional ethical review board. Confirmed cases of COVID-19 infection and post-COVID MIS-C of either sex up to the age of 16 years, diagnosed on the basis of RT-PCR from nasopharyngeal swab and Antibody test admitted in nineteen months duration from March 2020 to October 2021 were included through consecutive sampling. CBC was done. Cases whose parents failed to give consent were excluded from the study.

Disease was categorized as mild, moderate, severe disease and critical disease:

Mild: Mild respiratory tract symptoms, moderate: Fast breathing according to age and radiological evidence of pneumonia, severe disease: Dyspnea, hypoxia, or >50% lung involvement on imaging within 24 to 48 hours and critical disease: ARDS with respiratory failure, shock, or multiorgan dysfunction.

Information about demographic profile was collected. Laboratory tests including CBC, X-ray chest, PLR and NLR was determined. The NLR is measured as the ratio of absolute count of neutrophils and absolute count of lymphocyte, while the PLR is taken as ratio of absolute count of platelets and absolute count of lymphocyte.

Patient response was taken as home isolation, discharged or expired. The data was analyzed by using statistical software SPSS-22. The quantitative variables like age and laboratory parameters were presented as mean and the SD. Qualitative variables like gender, disease severity and outcome were presented by calculating frequency and percentages. The independent T test was used for the difference in mean scores, Chi square test was employed for the categorical variables as well as the $p<0.05$ was considered as significant. One-way ANOVA was used to see the difference in means values of multiple categories.

RESULTS

Total patients included in the study were 267, out of which 198 (74.2%) were COVID-19 and 69 (25.8%) were MISC cases. There was male preponderance 177 (66.3%). Mean age of these patients was 6.1±4.7 years and majority 86 (32.2%) were 5-10 years old. Underlying comorbidity was present in 55 (20.6%). Majority children had mild disease 80 (30.0%), 34 (12.7%) were critical and there were 37 (13.8%) deaths (Table 1).

Table 2 shows mean NLR and PLR in different categories of disease severity.

Comparison of mean NLR in different categories of symptomatic showed that NLR is very much associated with the severity of symptoms. Table 3 shows the details of mean NLR in different categories of symptomatic patients comparing asymptomatic patients with mild, moderate, severe and critical patients. Results showed that as the severity of symptoms change from asymptomatic to critical the mean NLR value rises from 1.88(±1.40) to 5.47(±4.77) for severe symptomatic patients and rise in this mean value was found to be statistically significant (Table 3)

PLR however failed to show any kind of association with severity of the symptoms and was found to have insignificant association with symptoms. Table 4 shows the details of mean PLR values in different groups of patients according to the severity of symptoms along with mean difference of PLR values (Table 4).

NLR and PLR. NLR rise with increasing disease severity ($p<0.001$) and slight drop in the critical patients but there is no significant association of PLR with disease severity ($p=0.922$) shown in (Figure 1).

PLR however failed to show any kind of association with severity of the symptoms and was found to have insignificant association with symptoms. Table 4 shows the details of mean PLR values in different groups of patients according to the severity of symptoms along with mean difference of PLR values (Table 4).

Table 1: Demographic characteristics of admitted children with COVID-19 and MIS-C, n=267.

Demographic characteristics	N (%)
COVID-19/ post-COVID	
COVID-19	198 (74.2)
Post COVID/Kawasaki like illness	69 (25.8)
Age (In years)	
Mean age (SD)	6.1±4.7
<1	56 (21.0)
1-5	59 (22.1)
5-10	86 (32.2)
10-16	66 (24.7)
Gender	
Male	177 (66.3)
Female	90 (33.7)
Co-morbidity	
No co-morbidity	114 (42.7)
Present	55 (20.6)
Surgical cases	98 (36.7)
Disease severity	
Asymptomatic	40 (15.0)
Mild	80 (30.0)
Moderate	65 (24.3)
Severe	48 (18.0)
Critical	34 (12.7)
Total duration of stay	
Mean days	6.8±1.8
Outcome	
Home isolation	80 (30)
Discharged	150 (56.2)
Died	37 (13.8)

Table 2: Mean of NLR and PLR in different categories of disease severity.

Variables	Disease severity	Mean	SD	95% CI for mean	
				Lower bound	Upper bound
NLR	Asymptomatic	1.8833	1.39942	1.4357	2.3308
	Mild	2.8255	3.92131	1.9528	3.6981
	Moderate	4.2364	3.67982	3.3246	5.1482
	Severe	5.4665	4.77639	4.0795	6.8534
	Critical	4.5815	4.42661	3.0370	6.1260
PLR	Asymptomatic	130.2295	112.70748	94.1839	166.2751
	Mild	130.0419	110.32481	105.4903	154.5935
	Moderate	115.4506	89.66637	93.2324	137.6689
	Severe	120.4123	82.78707	96.3734	144.4512
	Critical	138.8626	269.18349	44.9401	232.7852

Table 3: Comparison of mean NLR in different categories of disease severity.

Comparisons	Group	N	NLR mean (SD)	Mean difference	P value
Asymptomatic and mild	Asymptomatic	40	1.88 (1.40)	0.94	0.14
	Mild	80	2.83 (3.92)		
Asymptomatic and moderate	Asymptomatic	40	1.88 (1.40)	2.35	<0.001
	Moderate	65	4.23 (3.68)		
Asymptomatic and severe	Asymptomatic	40	1.88 (1.40)	3.58	<0.001
	Severe	48	5.47 (4.77)		
Asymptomatic and critical	Asymptomatic	40	1.88 (1.40)	2.70	<0.001
	Critical	34	4.58 (4.42)		

Table 4: Comparison of mean PLR in different categories of disease severity.

Comparisons	Group	N	PLR mean (SD)	Mean difference	P value
Asymptomatic and mild	Asymptomatic	40	130.2 (112.71)	0.18	0.99
	Mild	80	130.04 (110.32)		
Asymptomatic and moderate	Asymptomatic	40	130.2 (112.71)	14.77	0.459
	Moderate	65	115.4 (89.66)		
Asymptomatic and severe	Asymptomatic	40	130.2 (112.71)	9.81	0.639
	Severe	48	120.41 (82.78)		
Asymptomatic and critical	Asymptomatic	40	130.2 (112.71)	0.064	<0.001
	Critical	34	138.86 (269.18)		

Table 5: Comparison of mean NLR and PLR between COVID-19 and MIS-C patients.

Variables	Group	Mean (SD)	Mean difference	P value
NLR	**COVID-19**	2.94 (3.12)	3.015	<0.001
	MIS-C	5.96 (5.15)		
PLR	**COVID-19**	125.32 (84.4)	0.794	0.966
	MIS-C	126.11 (146.2)		

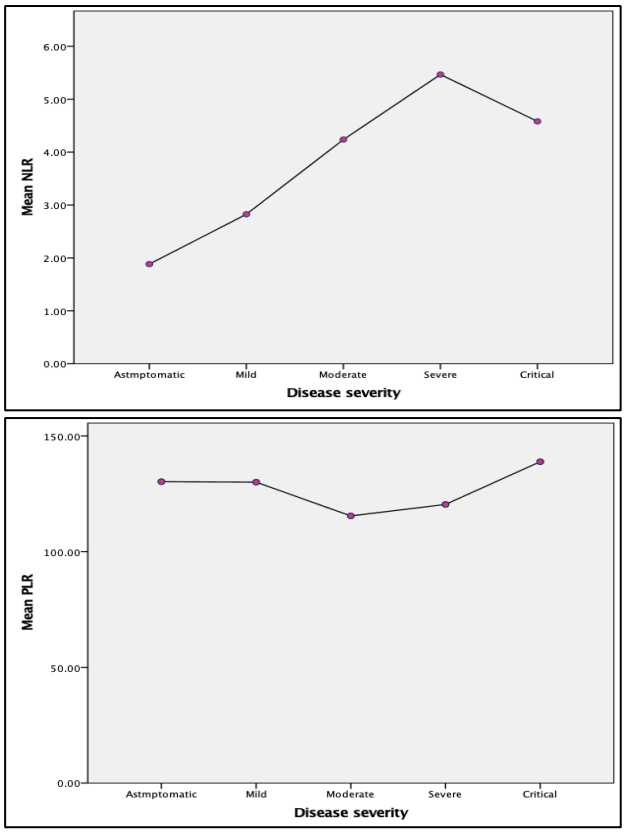

Figure 1: Mean NLR and PLR in different disease severity.

One-way ANOVA: p≤0.001, p=0.922.

DISCUSSION

Our research showed that children with multiple comorbidities had COVID 19 infections and there was statistically significant relationship between levels of NLR and severity of the disease while PLR did not show any statistically significant trend with the severity of the disease. COVID-19 has a relatively lesser vigorous clinical course and manifestations in pediatric age group with quicker recovery and a much better outlook overall when in comparison to adults age group, according to investigations.[9] Nevertheless, pediatric research findings are sparser than those conducted in the elderly populations.

In principle, decrease in lymphocyte counts implies a lack of cell-mediated immunity, whereas a raised neutrophil count shows a responsiveness to inflammatory responses. The relationship between these two numbers might be regarded as indicating the effectiveness of the cell-mediated immunity in accordance to the degree of inflammatory responses. Indeed, findings indicate that these statistics could be utilized to forecast the outcome of a variety of disorders, including coronary heart disease, malignancies, and autoimmune disorders.[10]

Multivariate logistic analysis was utilized to examine data from 153 cases of acute pulmonary embolism (PE) in a retrospective analysis, and it was concluded that NLR could be employed as a predictive marker determining 30-day death in pulmonary embolism.[11] Furthermore, it has been demonstrated that NLR may be employed as a measure of inflammatory responses to screen individuals contaminated with COVID-19 and can indicate poor outcome even during admission.[12] It has also been claimed that NLR may predict outcome in people beyond the age of 50.[13]

On the other hand, evidence on the connection among COVID-19 and NLR in children is limited. According to our research, NLR is raised in children with COVID-19, and except from those having mild symptoms, all the children had raised NLR i.e. >2 and it was even more in those with severe and critical disease. This discovery should spur additional investigation.

Our results is in line with another study done in pediatric age group by Yildiz et al.[14] They also showed that a threshold of 3.13 could be taken as being symptomatic and it has also been shown in adults.[8]

NLR was a particularly reliable marker that was primarily used in malignancies, autoimmune disorders, pathogenic infectious bronchitis, and tuberculosis.[12-17] Nevertheless, the use of NLR in other types of viral pneumonia has been rare. We discovered that NLR can be employed as a predictive biomarker for COVID-19 in our research. Eventually, this study found that increased NLR was a potential predictive screening tool for COVID-19 patient populations. NLR can improve clinician's assessed potential on COVID-19 patient populations. As a result, the utilizable NLR and age are suggested as useful tools for assessing prognostic value and assessing the magnitude of clinical manifestations in COVID-19 patients.

PLR did not show any significant relation with the severity of disease in our study as shown by NLR. It showed very mixed trend among the patients with different grades of diseases. Globally the researches done on significance of PLR have been very variable and inconsistent. A few really research findings seem to suggest that the PLR is an effective predictor of the magnitude and death rates of COVID-19, which appears to be different from our findings.[18,19] Be sides the small group of patients, which may be accountable for the absence of power introduced in these research findings and describe the disparity in outcomes, it is crucial to remember that the eligible participants in another research were also distinctive. Matter of fact, some scientists have compared COVID-19-negative patients to a control group.[19] Moreover, PLR appeared to be raised and eventually useful biomarker in distinguishing COVID-19 negative cases form positive ones especially those who had moderate symptoms and were meeting hospital admission criteria. But unfortunately, its specificity was not up to the mark in deciding patients between severe forms and those who need mechanical ventilation or ICU care. The study done by Wang et al involved patient selection like ours and their findings are also in line with our findings.[20]

Numerous pathophysiological explanations for low lymphocytes and platelet counts have been proposed. Lymphopenia might be caused by a cell-exhaustion process, increasing the viral activity and lymphocyte infection, bone marrow infectious disease, lymphocyte suicide triggered by inflammation, or leukocyte suppression caused by biochemical dysregulation.[21,22] Thrombocytopenia is primarily associated with platelet eating, but it is also associated with reduced production levels of platelets owing to marrow injury and an immune phenomenon that leads to platelet destruction.[23] Nevertheless, because these two distinct defects do not arise from the exact same source, their beginning times vary. Several investigations have been carried out to investigate the development of these biological anomalies during infections. Furthermore, the amount of platelets and lymphocytes varies dramatically with passing time, especially during the early stages of the illness of inflammatory origin.[24,25] This highlights the issue of PLR heterogeneity and perception. Based on our findings, we may also consider the value of this ratio and, more generally, the significance of biological proportions that have appeared in recent decades, for instance the NLR, the LMR, and the systemic immune-inflammation index (SII). Like NLR and PLR, D dimers have been reported in a study by Saqlain et al that increase in D-dimers at the time of indoor admission to hospital is a reliable predictive bio-marker for disease severity and in-hospital mortality for both pediatric COVID-19 and MIS-C patients.[26]

CONCLUSION

It is concluded that NLR can be used as a marker of severity of disease among pediatric patients suffering from COVID-19 disease. However, PLR failed to show any relation with severity of disease among pediatric patients suffering from COVID-19 disease and our study does not recommend it to use it as a marker of severity of disease.

Limitations

The basic limitations of retrospective studies extend to this study as well. Another constraint that may be addressed is the respondents' absence of cultural knowledge. As a result, the existence of some other fundamental disease cannot be ruled out. Because the patient category to be institutionalized and managed even during pandemic was selected by the National Ministry of Health's guidelines, inactive and milder patients in the later stages of the epidemic were observed on an outpatient setting and were excluded from this research. This is one of our study's limitations.

ACKNOWLEGMENTS

The author would like to acknowledge Dr Sohail and Dr Ahsan for statistical support.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Sharma A, Tiwari S, Deb MK, Marty JL. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2): a global pandemic and treatment strategies. Int J Antimicrobial Agents. 2020;56(2):106054.
2. Sadiq M, Aziz OA, Kazmi U, Hyder N, Sarwar M, Sultana N et al. Multisystem inflammatory syndrome

associated with COVID-19 in children in Pakistan. Lancet Child Adolescent Heal. 2020;4(10):e36-7.
3. El-Kady AM, Aldakheel FM. Clinical Characteristics, Outcomes and Prognostic Factors for Critical Illness in Hospitalized COVID-19 Patients in Saudi Arabia: A Retrospective Cohort Study. 2022;15:6945-63.
4. Wool GD, Miller JL. The Impact of COVID-19 Disease on Platelets and Coagulation. Pathobiology. J Immunopathology. Molecular Cellular Biol. 2021;88(1):15-27.
5. Chan AS, Rout A. Use of Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios in COVID-19. J Clin Med Res. 2020;12(7):448-53.
6. Wang X, Li X, Shang Y, Wang J, Zhang X, Su D et al. Ratios of neutrophil-to-lymphocyte and platelet-to-lymphocyte predict all-cause mortality in inpatients with coronavirus disease 2019 (COVID-19): a retrospective cohort study in a single medical centre. Epidemiol Infect. 2020;148:e211.
7. Xia LJ, Li W, Zhai JC, Yan CW, Chen JB, Yang H. Significance of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio and prognostic nutritional index for predicting clinical outcomes in T1-2 rectal cancer. BMC Cancer. 2020;20(1):208.
8. Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol. 2020;84:106504.
9. Li Y, Guo F. Insight into COVID-2019 for pediatricians. Pediatr Pulmonol. 2020;55(5):E1-4.
10. Asghar MS, Asghar MZ, Zahid A, Shah HSZA, Khan H, Zia H. Inflammatory mediators as surrogates of malignancy. J Pak Med Asso. 2022;72(11):2259-63.
11. Jia D, Liu F, Zhang Q, Zeng GQ, Li XL, Hou G. Rapid on-site evaluation of routine biochemical parameters to predict right ventricular dysfunction in and the prognosis of patients with acute pulmonary embolism upon admission to the emergency room. J Clin Lab Anal. 2018;32(4):e22362.
12. Pimentel GD, Dela Vega MCM, Laviano A. High neutrophil to lymphocyte ratio as a prognostic marker in COVID-19 patients. Clin Nutrit ESPEN. 2020;40:101-2.
13. Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C et al. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. J Transl Med. 2020;18(1):206.
14. Yildiz E, Cigri E, Dincer Z, Narsat MA, Calisir B. High Neutrophil/Lymphocyte Ratios in Symptomatic Pediatric COVID-19 Patients. J College Physicians Surgeons-Pak. 2021;31(7):S93-8.
15. Ying H-Q, Deng Q-W, He B-S, Pan Y-Q, Wang F, Sun H-L et al. The prognostic value of preoperative NLR, d-NLR, PLR and LMR for predicting clinical outcome in surgical colorectal cancer patients. Med Oncol. 2014;31:1-8.
16. Uslu AU, Küçük A, Şahin A, Ugan Y, Yılmaz R, Güngör T et al. Two new inflammatory markers associated with Disease Activity Score-28 in patients with rheumatoid arthritis: neutrophil-lymphocyte ratio and platelet-lymphocyte ratio. Int J Rheumatic Dis. 2015;18(7):731-5.
17. Jeon YL, Lee W-I, Kang SY, Kim MH. Neutrophil-to-monocyte-plus-lymphocyte ratio as a potential marker for discriminating pulmonary tuberculosis from nontuberculosis infectious lung diseases. Lab Med. 2019;50(3):286-91.
18. Sun S, Cai X, Wang H, He G, Lin Y, Lu B et al. Abnormalities of peripheral blood system in patients with COVID-19 in Wenzhou, China. Clinica chimica acta. Int J Clin Chem. 2020;507:174-80.
19. Seyit M, Avci E, Nar R, Senol H, Yilmaz A, Ozen M et al. Neutrophil to lymphocyte ratio, lymphocyte to monocyte ratio and platelet to lymphocyte ratio to predict the severity of COVID-19. Am J Emergency Med. 2021;40:110-4.
20. Wang R, He M, Yin W, Liao X, Wang B, Jin X et al. The Prognostic Nutritional Index is associated with mortality of COVID-19 patients in Wuhan, China. Cell Biol Int. 2020;34(10):e23566.
21. Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang YQ et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduction Targeted Therapy. 2020;5(1):33.
22. Barale C, Melchionda E, Morotti A. Prothrombotic Phenotype in COVID-19: Focus on Platelets. Int J Mol Sci. 2021;22(24).
23. Yang X, Yang Q, Wang Y, Wu Y, Xu J, Yu Y et al. Thrombocytopenia and its association with mortality in patients with COVID-19. J Thrombosis Haemostasis. 2020;18(6):1469-72.
24. Li Q, Cao Y, Chen L, Wu D, Yu J, Wang H et al. Hematological features of persons with COVID-19. Leukemia. 2020;34(8):2163-72.
25. Saqlain N, Bari A, Aimen C, Sadiq M. D-dimer: a biomarker for predicting disease severity and outcome in hospitalized children with COVID-19 and post COVID multisystem inflammatory syndrome. Int J Contemp Pediatr. 2023;10:995-1001.

Cite this article as: Bari A, Fateen T, Ch A. Neutrophil lymphocyte ratio and platelet lymphocyte ratio as a marker for disease severity in children with COVID-19. Int J Contemp Pediatr 2024;11:8-13.