EVALUATION OF HEMATOLOGICAL PARAMETERS AND INFLAMMATORY MARKERS IN CHILDREN WITH COVID-19

By

Ahmed Ibrahim Ahmed[1], Mohsen Taha El-Keiy[1], Mohamed Ahmed Shahin[3] and Mohamed Baha Al-Amir Al-Hawary[2]

Pediatrics[1] Department Faculty of Medicine, Al-Azhar University

Pediatrics[2] Department Faculty of Medicine, Aswan University

Clinical Pathology[3] Department Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Corresponding author: Ahmed Ibrahim Ahmed Hamed,

Mobile: (+02) 01097902401, **E-mail:** dr.ahmed201313@gmail.com

ABSTRACT

The aim of this study was to evaluate hematological parameters in children with COVID-19 and determine the effects of inflammatory biomarkers on the severity of the disease and hospitalization.

Methods: *This is retrospective study on 80 COVID-19 pediatric Egyptian patients, managed in the I.C.U of the Pediatric department (Luxor Fever Hospital) during the period between May 2020 to May 2021, Egypt, the studied patients were classified into non-severe and severe/critical cases. The patient's laboratory assessment, included total leucocyte count (TLC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC), neutrophil to lymphocyte ratio (NLR), derived neutrophil to lymphocyte ratio (d-NLR), lymphocyte to monocyte ratio (LMR), and platelets to lymphocyte ratio (PLR), as well as C reactive protein (CRP), D-dimer and serum ferritin.*

Results: *The severe/critical group had the highest total leucocyte count (TLC), ANC, AMC, neutrophil to lymphocyte ratio (NLR), derived neutrophil to lymphocyte ratio (d-NLR), and platelets to lymphocyte ratio (PLR), but the lowest acute lymphocytic count (ALC) and lymphocyte to monocyte ratio (LMR) (p=0.618 and 0.001, respectively). In the severe/critical group, C - reactive protein (CRP) and d-dimer levels were found to be elevated (p0.001). In addition, the severe group had greater ferritin levels than the non-severe groups (p=0.012). We determined the appropriate cut-off values for the hematological ratios: neutrophil to lymphocyte ratio (NLR) (1.61), derived neutrophil to lymphocyte ratio (d-NLR) (1.12), platelets to lymphocyte ratio (PLR) (101) and lymphocyte to monocyte ratio (LMR) (0.61). (2.73). the specificity of derived neutrophil to lymphocyte ratio (D-NLR) was the highest (87.8%), although the sensitivity of neutrophil to lymphocyte ratio (NLR) was the highest (87.2%).*

Conclusions: *The predominant hematological results in our study were lymphopenia and thrombocytosis, which may be associated to the milder clinical course of COVID-19 in children. We propose that age and platelet count can be utilized as independent predictors of hospitalization in COVID-19-affected children. NLR is the main predictor of COVID-19 severity. Also neutrophil to lymphocyte ratio (d-NLR), lymphocyte to monocyte ratio (LMR), and platelets to lymphocyte ratio (PLR) were mild to moderate predictor.*

Key words: *Children, COVID-19, Hematological parameters, Hospitalization, Inflammatory marker.*

INTRODUCTION

An outbreak of coronavirus disease 2019 (COVID-19) is rapidly spreading across the globe and affecting people of all ages. Epidemiology studies have indicated that the prevalence of COVID-19 in children is lower than in adults. In addition, it has been discovered that, compared to adults, children have a milder clinical course or are asymptomatic carriers and rarely suffer severe sickness **(Ladhani et al., 2020)**.

In the United States, 22% of the population consists of children under the age of 18. Comparatively, the Centers for Disease Control and Prevention (CDC) COVID-19 Response Team reported that 1.7% (2572/149,082) of the COVID-19 cases were reported as of April 2, 2020, for which the age was available, involved individuals younger than 18 years of age. The CDC COVID-19 Response Team assessed that 20% of pediatric patients with known hospitalization status were hospitalized, compared to 33% of adults aged 18 to 64 **(Mahmoudi et al., 2021)**.

Among immunocompetent adults and children, coronaviruses (229E, OC43, NL63, and KHU1) are ubiquitous and are responsible for a considerable proportion of all common colds. SARS-CoV-2, a new coronavirus discovered in 2019, can be transferred directly from person to person via respiratory droplets and may exploit the ACE2 receptor to infect people. The clinical course of SARS-CoV-2 is more varied than that of the common cold **(Moorthy et al., 2021)**.

Unresolved is whether children are also less susceptible to SARS-CoV-2 infection. Extensive epidemiological studies indicate that only 1% to 2% of SARS-CoV-2 cases include youngsters. Nevertheless, these estimates vary largely on testing criteria, and in many cases, testing was conducted

primarily on symptomatic or hospitalized adults, which is less common for children. Several research indicate that youngsters have the same likelihood of contracting SARS-CoV-2.9 as adults. However, more recent research indicates that children who come into contact with a SARS-CoV-2-positive person are less likely to become infected **(Ong et al., 2020)**.

It has been suggested that children and adolescents have similar viral loads and may therefore be as likely to transmit SARS-CoV-2 as adults. In addition, the viral load may be similar in asymptomatic and symptomatic individuals **(Peaper et al., 2021)**. However, reassuringly, transmission in schools from children either to other children or to adults has been rare **(Peng et al., 2021)**.

In up to 45 percent of instances, the symptoms of COVID-19 in children range from asymptomatic to severe (in up to 90 percent). Fever, dry cough, shortness of breath, and exhaustion are prevalent, as are gastrointestinal symptoms including diarrhea, nausea, and vomiting. While the vast majority of children identified with mild or moderate COVID-19 will not develop severe illness, treatment focuses mostly on supportive care, including the prevention and control of complications **(Cho et al., 2021)**.

Infants with underlying chronic illnesses (neurometabolic disorders like obesity or asthma) as well as immunosuppression or congenital heart disease may be at an elevated risk for severe disease. With the exception of severe pediatric cases, the majority of children with non-severe COVID-19 disease, particularly febrile newborns, will require hospitalization for supportive therapy and close observation **(Alkan et al., 2021)**.

PATIENTS AND METHODS

Ethical Considerations:

1. A written informed consent was obtained from patients or their legal guardians.
2. An approval by the local ethical committee was obtained before the study.
3. The authors declared no potential conflicts of interest with respect to the research, authorship, and/ or publication of this article.
4. All the data of the patients and results of the study are confidential and the patients have the right the patient has the right to keep it.

5. The researcher explains the aim of the study to the patient.

Calculation Of Sample Size:

The sample size estimation was done using the Epi info7 program for sample size calculation, with 0.05 alpha error, confidence interval of 0.95 and the power of the study 0.80. The minimum sample size calculated to evaluate hematological parameters and inflammatory markers in children with COVID-19 is 80 confirmed COVID-19 cases

Study Design:

Our study was a retrospective observational study conducted at Critical care unit of Pediatric department, (Luxor fever Hospital). All participants signed written informed consents, study procedures were conducted in accordance with this Code of Ethics of the World Medical Association (Declaration of Helsinki), all information/images were anonymized, and the privacy rights of study participants were properly done.

Inclusion Criteria:

All patients who presented to the hospital with per Patients aged 0-18 years who were hospitalized in the Children's COVID-19 service with positive SARS-CoV-2 RT-PCR test result from the nasopharyngeal swab, between May, 2020 and May, 2021 were evaluated retrospectively.

Exclusion Criteria:

Those with lung involvement (bronchitis or pneumonia), bacterial coinfections, an underlying disease, or Down syndrome were excluded from the study.

Study Procedure:

Our study was retrospective study on 80 COVID-19 pediatric Egyptian patients, managed in the I.C.U of the Pediatric department (Luxor Fever Hospital) during the period from May 2020 to May 2021, Egypt, and the studied patients were classified into non-severe and severe/critical cases.

The following data was obtained retrospectively from hospital records from day 1 of hospitalization.

The age of the patients (in years), length of hospitalization, sex, age group, the severity of the disease, and details of family members with COVID-19 who have improved, were gathered as data.

1. Arterial blood gas analysis, pulse oxygen saturation, complete blood picture, inflammatory markers including D-dimer, ferritin, and CRP, IL-6, and blood glucose levels. White blood

cell (WBC) count in peripheral blood, neutrophil, monocyte, and lymphocyte counts, Hgb level, platelet value, mean platelet volume (MPV), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), serum ferritin level, lactate dehydrogenase (LDH) level, and prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio, fibrinogen, and D-dimer levels from coagulation tests were examined in the study.

2. Details of oxygen therapy, CPAP, non-rebreather mask or even mechanical ventilation SBT.
3. Computed tomography (CT) image findings suggestive of viral pneumonia, and; positive result of real-time polymerase chain reaction (RT-PCR) for SARS-CoV-2 RNA. Sputum and throat swab specimens were collected from all patients on admission and tested by RT-PCR within 3 hours.

The patients were divided to:

Group 1 (non-sever group) had mild or moderate symptom symptoms.

Group 2 (sever critical group) had severe and critical symptoms.

All patients were treated according to the World Health Organization's provisional guidelines (WHO) **(Organization, 2019)**.

Statistical Analysis:

SPSS version 25.0 was used for data management and data analysis. Quantitative variables will be first subject to the normality test (Kolmogorov v Simonov). Continuous variables were present mean ±SD, and their differences were assessed by the independent T-test. Categorical variables were described as numbers (percentage), and were compared by chi-squared test and fisher`s Exact test. The optimal cut-off values of the continuous NLR, d-NLR, PLR, and LMR were calculated by applying the receiver operating curve (ROC) analysis. The demographics and laboratory data with significant differences between the three groups were assessed by univariate and multivariate logistic regression analysis to discover the independent early predictors and risk factors associate with the disease severity of COVID-19. A two-sided $P<0.05$ will be consider statistically significant.

RESULTS

Our results will be demonstrated in the following tables and figures:

Table (1): Demographic and clinical data in the two studied groups

Variables		Group				*p value*
		Non-severe group (N=40)		Severe/critical group (N=40)		
Age (years)		8.63 ±4.10		4.52 ±3.71		**<0.001**
		N	%	N	%	
Gender	male	25	62.5%	21	52.5%	0.178
	female	15	37.5%	19	47.5%	
Risk factors	Congenital heart disease	2	5.0%	9	22.5%	**0.023**
	Bronchial asthma	3	7.5%	10	25.0%	**0.034**
	Immunocompromised	0	0.0%	6	15.0%	**0.011**
Clinical Picture	Fever	18	45.0%	30	75.0%	**0.006**
	Cough	4	10.0%	14	35.0%	**0.007**
	pneumonia	1	2.5%	13	32.5%	**<0.001**
	GIT symptoms	18	45.0%	4	10.0%	**<0.001**
	Seizures	1	2.5%	3	7.5%	0.166

*Statistically significant as $p<0.05$.

This table shows a significant difference between severe (critical) and non-sever groups regarding demographical and Clinical data except gender.

Table (2): Comparison between Hematological parameter and inflammatory markers in the two studied groups

Variables	Group		*p value*
	Non-severe group (N=40)	**Severe/critical group (N=40)**	
CBC (mean ±SD)			
HB (g/dL)	12.31 ±2.97	11.95 ±2.24	0.550
Platelets (10^3/µL)	197.43 ±89.36	283.57 ±36.22	**0.001**
TLC (10^3/µL)	4.61 ±1.96	9.28 ±7.82	**<0.001**
ANC (10^3/µL)	2.13 ±1.36	6.79 ±6.65	**<0.001**
ALC (10^3/µL)	1.92 ±0.95	1.80 ±1.18	0.618
AMC (10^3/µL)	0.61 ±2.09	0.72 ±0.87	0.763
NLR	1.27 ±0.83	4.47 ±1.05	**<0.001**
dNLR	0.89 ±0.54	3.70 ±5.33	**0.001**
PLR	122.75 ±68.04	222.21 ±78.83	**0.002**
LMR	5.91 ±3.27	3.42 ±2.21	**<0.001**
Inflammatory markers (mean ±SD)			
CRP	14.91 ±6.96	72.72 ±12.98	**<0.001**
Ferritin	125.07 ±28.96	328.42 ±88.39	**0.012**
D- dimer	4.07 ±6.63	20.97 ±7.12	**0.038**

Values are presented as mean ± SD
P value is significant if <0.05
Abbreviations: ALC, absolute lymphocyte count; AMC, absolute monocyte count; ANC, absolute neutrophil count; CRP,C-reactive protein. d-NLR, derived neutrophil to lymphocyte ratio; HB, hemoglobin; LMR, lymphocyte to monocyte ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelets to lymphocyte ratio; TLC, total leukocyte count.

This table shows statistically significant differences between sever (critical) and non-sever groups regarding Hematological parameter and inflammatory markers except, absolute lymphocyte count (ALC), absolute monocyte count (AMC).

Table (3): Univariate and multivariate logistic regression analysis of risk factors

Variables	Univar able Odds ratio	95% C.I		P value	Multivariable Odds ratio	95% C.I		P value
		Lower	upper			lower	upper	
Age	0.772	0.677	0.881	**<0.001***	0.738	0.565	0.963	**0.026***
platelets (103/µL)	1.007	1.002	1.011	**0.003***	1.026	1.001	1.051	**0.043***
TLC (103/µL)	1.564	1.253	1.951	**<0.001***	.632	0.119	3.363	0.590
ANC (103/µL)	1.946	1.440	2.630	**<0.001***	1.836	0.187	17.998	0.602
NLR	3.009	1.727	5.244	**<0.001***	1.197	0.112	12.758	0.882
dNLR	3.645	1.790	7.424	**<0.001***	3.911	0.134	14.495	0.429
PLR	1.008	1.002	1.013	**0.005***	.982	0.945	1.019	0.335
LMR	0.685	0.550	0.852	**<0.001***	.647	0.302	1.383	0.261
CRP (mg/L)	1.040	1.018	1.062	**<0.001***	1.018	0.993	1.044	0.161
Ferritin	1.003	1.000	1.007	**0.025***	1.007	1.000	1.015	0.052
D- dimer	1.086	1.023	1.154	**0.007***	1.079	0.921	1.265	0.344

*Statistically significant as $p<0.05$.

This table shows that age and platelets represent univariate and multivariate risk factors.

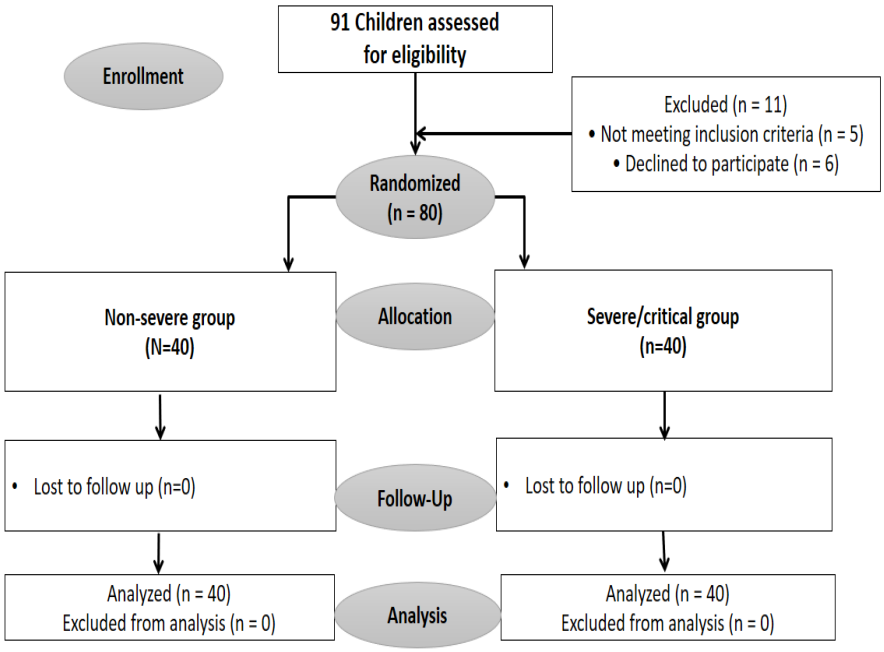

Figure (1): The CONSORT flowchart of the patients

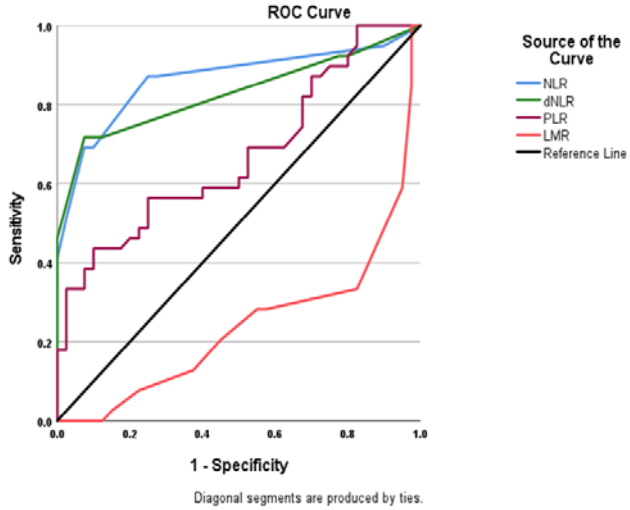

Figure (2): ROC curve was used to study the optimal cut off values of different hematological ratio. Notes: The test variable(s): NLR, d-NLR, PLR and LMR has at least one tie between the positive actual state group and the negative actual state group. P value is significant if <0.05. Abbreviations: d-NLR, derived neutrophil lymphocyte ratio; LMR, lymphocyte monocyte ratio; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; PV, ROC, receiver operating characteristics.

DISCUSSION

An outbreak of coronavirus disease 2019 (COVID-19) is rapidly spreading across the globe and affecting people of all ages. Epidemiology studies have indicated that the prevalence of COVID-19 in children is lower than in adults. In addition, it has been discovered that, compared to adults, children have a milder clinical course or are asymptomatic carriers and rarely suffer severe sickness **(AlHajri et al., 2021)**.

The SARS-CoV-2 virus has many clinical manifestations affecting different organ systems, including the hematological system. Adults with COVID-19 have frequently reported lymphopenia and hypercoagulability, both of which are thought to be indicators of poor outcomes **(Balasubramanian et al., 2020)**.

In the acute phase of COVID-19, it is anticipated that many inflammatory indicators may increase. Unrestrained systemic inflammation may result in organ damage. C-reactive protein (CRP), ferritin, D-dimer, a reduced platelet count, and elevated levels of a number of pro-inflammatory cytokines have been linked to the severity of COVID-19 disease **(Asakura and Ogawa, 2021)**. In a few studies, biomarkers of inflammation derived from the peripheral blood, such as neutrophil to lymphocyte ratio (NLR), neutrophil to monocyte ratio (NMR), lymphocyte to monocyte ratio (LMR), platelet to lymphocyte ratio (PLR), and lymphocyte to CRP ratio (L/CRP), were evaluated as prognostic factors of the severity of COVID-19 disease in adults **(Asakura and Ogawa, 2021)**.

A limited number of pediatric COVID-19 studies have rarely reported hematological involvement, possibly due to the immature immune systems of the patients or to the lesser severity of the disease. In the present study, our main goal was to the relation between neutrophil to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) and severity of COVID 19 infection.

In the current study, the severe/critical group's mean age was 4.52 3.71 years, significantly older than the non-severe group's mean age of 8.63 4.10 years (p 0.001). These results corroborate the ideas of Storch-de-Gracia et al., 2020 who suggested that mean age of non-severe group was 9.4 years while that of severe/critical group was 3.5 years **(Storch-de-Gracia et al., 2020b)**.

During the Omicron surge, weekly hospitalization rates were particularly high in children age zero to four years, who were not eligible for vaccination (15.6 per 100,000 population) **(Marks et al., 2022)**. Underlying conditions are associated with higher rates of hospitalization and intensive care unit (ICU) admission. Whether underlying conditions are associated with increased severity or a lower threshold for admission (e.g., because of concern for complications) is unclear. Age <1 year has also been associated with increased rates of hospitalization, although hospitalization of infants may not reflect severity of illness **(Wanga et al., 2021)**.

Regarding as gender, 25 cases (62.5%) in non-severe group and 21 cases (52.5%) in severe/critical group were male individuals. Also, based on information from medical records and the findings of a survey conducted in the children's isolation unit at Pasar Rebo Hospital in Jakarta, it was determined that 24 of 150 children (or 57%) who were confirmed to have COVID-19 in March–May 2021 were male **(Purwati et al., 2022)**.

A possible explanation for this might be that gender-related changes in the immune system. To a greater extent than men, women are protected from viral infections. The X chromosome heavily influences the pathophysiology of viral diseases and female sex hormones, which play crucial roles in the innate (nonspecific) immune response and the adaptive (specific) immune response. Because females have an X chromosome and the hormone progesterone, they are more resistant to contracting COVID 19 **(Graff et al., 2021)**. Males made up the majority of children with COVID-19 diagnoses, but this did not mean that they had a more severe case than females **(Hidayani, 2020)**.

Another desirable ratio is the LMR, which was observed to have lower values in patients with COVID-19 who were critically ill. This finding was previously detected but concerning community-acquired pneumonia without identification of the causative pathogen **(Alkan et al., 2022)**.

LIMITATIONS OF THE STUDY

The first limitation of our study was its retrospective nature. second, it was limited by relatively small number of patients as epidemiological studies have confirmed a lower prevalence of COVID-19 in children who tend to have a milder clinical course or asymptomatic carriers and rarely

develop critical illness compared with adults.

CONCLUSIONS

Neutrophil to lymphocyte ratio (NLR) is a predictor for severity in COVID-19. Lymphocyte to monocyte ratio (LMR), derived neutrophil to lymphocyte ratio (d-NLR), and platelet to lymphocyte ratio (PLR) may assist in risk stratification. According to our observations in this study, NLR can improve risk stratification of COVID-19 severity; LMR, d-NLR, and PLR can be quick, cost-effective, and interesting potential markers.

RECOMMENDATION

We can use NLR as a useful assessment tool to map out COVID-19 related disease severity and mortality outcomes.

Embedding NLR into routine clinical management can help clinicians to identify potentially sever cases earlier and facilitate risk stratification to initiate prompt therapeutic intervention.

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