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Original Article

Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio in Pediatric Acute Respiratory Distress Syndrome

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Abstract

OBJECTIVE: Acute respiratory distress syndrome (ARDS) is a clinical picture that indicates severe acute hypoxemic respiratory insufficiency. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are convenient, uncomplicated, and inexpensive parameters that can be used in detecting the severity of the disease. The prognostic role of NLR and PLR in patients with pediatric ARDS is unknown. The aim of this study was to investigate if there was any relationship between initial hematological parameters and the stages of ARDS, duration of mechanical ventilation and the length of intensive care stay in pediatric ARDS.

MATERIAL AND METHODS: Of 34 patients diagnosed with ARDS, 5 excluded, a total of 29 patients who were followed in our pediatric intensive care unit between 2016 and 2018 were retrospectively enrolled. Patients were retrospectively registered in terms of demographical features, disease severity scores (PIM2, PRISM III, PELOD scores), lymphocyte, neutrophil and platelet counts and NLR, PLR values in complete blood count during intensive care unit stay and on the day of discharge, the stages of ARDS, duration of mechanical and the length of intensive care stay.

RESULTS: There was a significant relationship between NLR values and ARDS stages on the first day of the admittance ($P = .003$). There was a moderate correlation between NLR and PELOD scores on the day of admittance and it was statistically significant ($r = 0.45$, $P = .026$). There was no correlation between mechanical ventilation time and the length of intensive care stay and NLR-PLR values. Platelet-to-lymphocyte ratio was not identified as a prognostic factor in our study.

CONCLUSION: In diagnosis of the severity of ARDS with severe acute hypoxemic respiratory insufficiency, NLR is a convenient and inexpensive parameter that can only be calculated by complete blood count.

KEYWORDS: Child, neutrophil, lymphocyte, platelet, acute respiratory distress syndrome
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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a condition that occurs due to disruption of the alveolar-capillary membrane that causes diffuse pulmonary infiltration resulting in pulmonary impairment of gas transfer and severe hypoxemic respiratory failure.[1] As a result of the differentiation of stem cells in bone marrows, leucocytes, erythrocytes, and platelets are produced. The intensity of the leukocytic series is age-related and consists mostly of neutrophils. In the case of inflammation, lymphocyte count decreases while neutrophil and platelet count increase. Increase in neutrophil count occurs as a result of the delay in apoptosis, demargination of neutrophils, and stimulation of stem cells by growth factors.[2] Neutrophil-to-lymphocyte ratio (NLR) is calculated by neutrophil and lymphocyte values in complete blood count, and it is a convenient, new biomarker that can predict the progression and mortality rate in many inflammatory rheumatic, dermatological, cardiac, endocrinological diseases that have become popular lately and it is considered to indicate the severity of inflammation. Platelet-to-lymphocyte ratio (PLR) is used to predict inflammatory period, disease activity, treatment response, and prognosis in inflammatory diseases and malignancies.[3]

ARDS is accepted as a worldwide spreading important clinical problem in today's world; and its mortality and morbidity rates are known to be rather high.[1] Identifying the effective factors on the severity of the disease helps to predict the bad clinical course of disease and organ failure, and helps the precautions to be taken with the necessary treatment manipulations. This study aims to evaluate associations between the NLR, PLR and outcomes: the stages of ARDS, duration of mechanical ventilation, and the length of intensive care stay in pediatric ARDS patients.

MATERIAL AND METHODS

A retrospective observational cohort study was performed in our pediatric intensive care unit between January 2016 and August 2018. Patients admitted to pediatric intensive care unit with diagnosed of ARDS were retrospectively registered

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in terms of demographical features, disease severity scores (PIM2, PRISM III, PELOD), leucocyte, lymphocyte, neutrophil and platelet counts, and NLR, PLR values in complete blood count during intensive care unit stay and on the day of discharge, the stages of ARDS,[1] duration of mechanical and the length of intensive care stay.

ARDS were determined using the recently developed pediatric ARDS criteria from the Pediatric Acute Lung Injury Consensus Conference.[4] In addition, to determine if there is a worsening in the patient's condition and to assess the risk of mortality in the patients admitted to the PICU (Pediatric Intensive Care Unit), pediatric risk of mortality (PRISM III),[5] and pediatric index of mortality (PIM2)[6] scores were used, and pediatric logistic organ dysfunction (PELOD)[7] score was used to evaluate dysfunctions of the organs.

All patients were under 18 years old, had neutrophil, lymphocyte, and platelet counts results within first hour of intensive care unit admission and within 24 hours before discharge. Both on the first day and on the day of discharge, NLR1 (first day) and NLR2 (discharge) were calculated by the division of the neutrophil count to the lymphocyte count; and PLR1 and PLR2 were calculated by the division of platelet count to the lymphocyte count. The complete blood parameters were examined with the Beckman Coulter Unicel DxH 800 Coulter® Cellular Analysis System (DxH 800; Miami, FL, USA) device at our university hospital biochemistry laboratory. This Analysis System complete blood cell counter combines advanced technology, innovative computer algorithms, impedance technology, flow cell volume, conductivity, and 5 light scatter measurements to analyze platelets, neutrophils and lymphocytes. Conditions that may affect the hematological parameters of patients (chemotherapy, immunosuppressive therapy and conditions, hematological malignancy, immunodeficiency) were searched and excluded from the study. Ethical approval was obtained from clinical researches ethics committee.

Statistical Analysis

All statistical analyses were carried out with the Statistical Package for Social Sciences version 20.0 software (IBM Corp.; Armonk, NY, USA). The numerical measurements were given as mean ± standard deviation, minimum, maximum values. The data's convenience to normal distribution was evaluated by one-sample Kolmogorov–Smirnov test. The Kruskal–Wallis test was used to evaluate the relationship between the stages of ARDS and NLR-PLR values. Spearman's correlation test was used to evaluate the relationship between the length of intensive care stay, the mechanic ventilation time and PLR, NLR, and PELOD. The significance level was reported as $P < .05$.

MAIN POINTS

- Acute respiratory distress syndrome is accepted as a worldwide spreading important clinical problem in today's world.
- NLR and PLR are convenient, uncomplicated, and inexpensive parameters that can be used in detecting the severity of the disease.
- NLR can be used in predicting the bad clinical course in critically ill children diagnosed with ARDS.

RESULTS

Between the study period, 34 patients diagnosed with primary ARDS were followed in our pediatric intensive care unit. A total of 3 patients with acute lymphoblastic leukemia who had immunosuppressive therapy, 1 patient with renal transplantation who had immunosuppressive therapy and 1 patient with immunodeficiency was excluded. A total of 29 patients with ARDS were included in the study. Among 29 patients in our study, underlying diseases were as follows; 3 patients had metabolic diseases, 4 patients had chronic renal diseases, 12 patients had epilepsy, and/or mental motor retardation, 5 patients had no underlying diseases but pneumonia, 5 patients had chronic lung diseases. All patients were taking antibiotherapy on admission to intensive care unit. Neither of the patients were on immunosuppressive therapy nor corticosteroid therapy on admission.

The patients ages were median 36 months (min: 4-max: 204) IQR (20-127 months), and 15 of them (51.7%) were female. When disease severity scores were evaluated, mean PIM2 score was 19.6 ± 8.3 (min: 6-max: 40), mean PRISM III score was 22.60 ± 8.3 (min: 7.8-max: 43), median PELOD score was 20 (IQR 12-30.5). The median length of pediatric intensive care stay was 15 days (IQR 12.5-34.5 days), while median mechanic ventilation time was 10 days (IQR 5.5-21.5 days). Classification according to ARDS stages were as follows: 10 patients (34.5%) were classified as mild ARDS, 14 patients (48.3%) were moderate ARDS, 5 patients (17.2%) were severe ARDS. The mortality rate of our patients followed in the pediatric intensive care unit due to ARDS was 6.9%. Among 5 patients with severe ARDS, 2 patients were expired. All patients with mild and moderate ARDS were alive. The average minimum and maximum neutrophil, lymphocyte, platelet, NLR1, NLR2, PLR1, and PLR2 values of patients were given in Table 1.

There was no difference between males and females in terms of NLR and PLR values ($P = .78$ and $P = .74$, respectively). There was a significant relationship among NLR1 values and ARDS stages ($P = .003$). The median NLR ratio in severe ARDS was 7.41, while in mild ARDS was 2.62. When mild and severe ARDS compared, the NLR1 value was higher in severe ARDS ($P = .003$). There were significant differences between NLR1 and NLR2, PLR1 and PLR2 among in each ARDS groups ($P < .001$). However, there were no differences across the stages of ARDS and NLR2 and PLR2. There were no difference between PLR1 and PLR2 values in mild, moderate, and severe ARDS groups (Table 2). In terms of age, there was no correlation between NLR1-NLR2 values and age of patients. There was a moderate correlation between NLR1 and PELOD scores on the day of admittance, and it was statistically significant ($r = 0.45$, $P = .026$). There were no correlation among mechanical ventilation time and the length of intensive care stay and NLR-PLR values. Due to the low mortality rate (6.9%, $n = 2$), the factors effecting mortality were not examined.

Table 1. Complete Blood Count Parameters on the First Day and on the Day of Discharge

	Minimum	Maximum	Mean ± SD	*P*
WBC1	1.700	45.430	13.973 ± 11.231	.699
WBC2	0.200	29.670	11.820 ± 6.348	
ANC1	0.700	34.050	9.768 ± 8.834	.768
ANC2	0.100	53.000	8.866 ± 9.677	
ALC1	0.200	54.901	4.554 ± 9.448	.584
ALC2	1.000	9.410	3.078 ± 2.229	
PLT1	47.000	655.000	273.205 ± 150.224	.169
PLT2	30.000	830.000	329.823 ± 203.681	

1, admission; 2, discharge.
WBC, white blood cell; ANC, absolute neutrophil count; ALS, absolute lymphocyte count; PLT, platelet.

DISCUSSION

ARDS is a damage in alveolar epithelium and pulmonary endothelium caused by an inflammatory response. With the inflammatory response, the capillary permeability increases, endothelial and epithelial cells are damaged, microthrombuses are formed, ventilation-perfusion mismatch occurs, resulting in the occurrence of alveolar edema, decreased pulmonary compliance, and persistent hypoxia. At the time, there is noncardiogenic pulmonary edema, severe hypoxia, and extensive bilateral infiltration in chest radiography.[8,9]

NLR is a new biomarker that can predict the progression and mortality rate in many inflammatory rheumatic, dermatological, cardiac, endocrinological diseases.[3] It is considered that NLR indicates the severity of inflammation.[10] NLR, which is prominent due to rapidity, easy detection and cost-effectiveness, is being reported with increasing frequency as a reliable biomarker of systemic inflammation.[11-13] PLR is used to predict inflammatory period, disease activity, treatment response, and prognosis.[3]

NLR and PLR values can easily be used in diagnosis and progression follow-ups of diseases like Henoch–Schönlein purpura, asthma, acute pyelonephritis, acute appendicitis, vesicoureteral reflux, atopic dermatitis, obesity and Type 1 diabetes mellitus, which are dominated by systemic inflammation.[14-18] Along with this, NLR is identified as a factor that effects mortality and morbidity in patients staying in intensive care.[19] A study shows a relation between high NLR rates of patients staying in intensive care due to pneumonia and their high mortality rates.[20] Another study on adult patients with ARDS also shows a relation between high NLR rates in critically ill patients and their bad clinical course. In the same study, high NLR rate is identified as an independent prognostic factor to estimate the 28 day-rate in patients diagnosed with ARDS.[21] In another study on adult patients with miliary tuberculosis with developed ARDS indicated that NLR can be a useful biomarker for mortality rates and ARDS development.[22]

We have not encountered any study in literature observing the relation between ARDS and NLR-PLR rates in the pediatric age group during our literature research. As far as we are concerned, our study is the first study conducted on the relationship between NLR and PLR rates in patients admitted to pediatric intensive care due to ARDS. Our results show a significant relationship between NLR1 rates on the day of admittance and the severity of ARDS. In our study NLR1 rate in severe ARDS was statistically significantly higher than the rates in moderate and mild stages of ARDS ($P = .003$). There was a statistically significant, moderate correlation between NLR1 rates and PELOD scores of our patients ($r = 0.45$, $P = .026$).

Another hematological parameter that changes in inflammations is the platelet count. Thrombocytosis occurs not only in the condition of acute inflammations but also during chronically inflammatory diseases.[23] PLR can be used in predicting the inflammation period disease activity, response to treatment and prognosis, and there is data on its effect in mortality and morbidity in inflammatory diseases and cancer.[24,25] In our study, there were no difference between patients with moderate and severe ARDS in terms of PLR1 and PLR2 values. Along with this, PLR was not identified as a prognostic factor in our study because no correlation was found among PLR and PELOD scores and mechanical ventilation time and the length of intensive care stay.

Finally, in ARDS with severe acute hypoxemic respiratory insufficiency, NLR is a convenient, uncomplicated and inexpensive parameter that can be used in detecting the severity of the disease. According to our findings, we consider that NLR can be used in predicting the bad clinical course

Table 2. Comparison of PLR 1-2 and NLR 1-2 Median Values According to Mild, Moderate, and Severe ARDS Groups

	Mild ARDS	Moderate ARDS	Severe ARDS	*P*
NLR1 median (IQR)	2.24 (0.93-3.14)	2.62 (1.49-9.47)	7.41 (4.1-25.3)	**.003**
NLR2 median (IQR)	1.33 (0.72-5.33)	1.95 (1.01-4.11)	9.32 (3.21-21)	.049
PLR1 median (IQR)	84.2 (39.6-119.2)	146.80 (81.1-205.2)	272 (71.6-481.3)	.86
PLR2 median (IQR)	111.6 (91-258.8)	104 (59.3-172.4)	97.7 (86-323.9)	.92

1, admission; 2, discharge.
NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.
The significance level is reported as $p < .05$; so this level is bold in the table.

in critically ill children diagnosed with ARDS. Prospective studies, which will be conducted particularly with a broader range of patients, will be beneficial in clarifying the relationship between ARDS and NLR.

There were several limitations to this study that should be taken into consideration when interpreting the results. The major limitations of our study are retrospective design and the small number of patients. The NLR and PLR are influenced by several conditions, including medications and comorbidities that affect the neutrophil and lymphocyte count, but we did not record medications, although we excluded the patients who had malignancy, immunodeficiency (receiving steroid, chemotherapy). Further investigations with larger and stratified samples are needed. In a larger series, a receiver operator characteristic (ROC) curve analysis can be performed in order to identify the optimal cut-off point of NLR that predicts the stages of ARDS.

CONCLUSION

Neutrophil-to-lymphocyte ratio is a convenient, uncomplicated, and inexpensive parameter that can be used in detecting the severity of the disease. NLR can be used in predicting the bad clinical course in critically ill children diagnosed with ARDS.

Ethics Committee Approval: The study was approved by the ethical committee of the Cukurova University (Approval No 2018/78-24).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer Review: Externally peer-reviewed.

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