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Could the systemic immune-inflammation index be a new biomarker of inflammation in children with asthma?

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Abstract

Asthma is a disease with a complex etiology that is caused by genetic and environmental factors. More recently, the importance of changes related to the systemic immune-inflammation (SII) index has been recognized. The aim of this study was to investigate SII as a potential novel biomarker of the inflammatory process in children with asthma. This study included 60 children hospitalized with asthma exacerbation between February and September 2021. Complete blood counts of the patient group were obtained during the exacerbation period and during the asymptomatic period of 3 months after exacerbation. Furthermore, SII, C-reactive protein (CRP), eosinophil-to-lymphocyte ratio (ELR), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) values were compared in both periods. All values of the patient groups were compared with the healthy control group (n=60). CRP, SII, NLR and ELR levels were significantly higher in the asymptomatic period compared to the control group (All of them, $p<0.001$), whereas no significant difference was found in PLR levels. This study indicates that CRP, SII, NLR and ELR may be helpful and practical, measurable biomarkers for assessing inflammation in children with asthma during acute exacerbation. Nevertheless, their further detailed analysis in prospective studies with larger cohorts is needed.

Keywords: Asthma, eosinophil lymphocyte ratio, neutrophil lymphocyte ratio, platelet lymphocyte ratio systemic immune-inflammation index

Introduction

Asthma is a disease with a complex etiology that is caused by genetic and environmental factors with recurrent wheezing, shortness of breath, chest tightness and cough with variable restriction of expiratory airway flow. Findings and airflow limitation improve spontaneously or with treatment [1]. In Türkiye, 8-15% 60-80% begins before the age of 4-5. Y/N=2/1. Approximately ~30% of children with atopic dermatitis develop asthma. The majority of asthmatics (~80%) have allergic rhinitis [2].

Asthma diseases need to be diagnosed correctly, and appropriate treatments should be applied. Especially in children with asthma conditions, it may not be seen during the examination and can be seen later. Diagnoses can be made when wheezing, shortness of breath, and difficulty in breathing occur during certain periods [3-5]. The tests performed in the laboratory are performed to support the diagnosis and monitor the diseases. Asthma is reversible in the respiratory tract [6]. There are different methods of airflow restrictions. Two different methods are used in pulmonary function test (PFT) for children over the age of 5 [7]. The first is spirometry (FEV1) (forced expiratory volume in one second), the second is forced viral capacity (FVC) and peak flow rate (PEF) measurements.

The most important pathological feature in asthma patients is chronic airway inflammation. Sputum assays is one of the most common techniques used to evaluate the airways in

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asthmatic patients. But sputum analysis is usually laborious and inappropriate for children [7,8]. Therefore, blood samples are commonly used in children.

Asthma is a chronic inflammatory disease of the airways in which many cellular elements are involved, particularly mast cells, eosinophils and T lymphocytes [9]. Neutrophil/lymphocyte ratio (NLR) is a cheap and easily available non-specific inflammation marker. NLR value is found to be higher in asthma patients. C-reactive protein (CRP) is the first protein identified to act as a positive acute phase reactant indicating inflammation and is widely used in the routine laboratory. Since NLR and CRP are increased in asthma, there is a need to find a new specific marker, a combined score of CRP level and NLR, that can fully utilize NLR and CRP during acute exacerbations and stable periods in children with asthma [9,10].

This study aimed to compare serum CRP, complete blood count and hematologic indices in children aged 6-12 years with and without asthma exacerbation.

Material and Methods

Ethics committee approval was obtained from Istanbul Atlas University Ethics Committee (Approval date: 30.06.2022 and No: E-22686390-050.99-18388). This study was conducted at Medicine Hospital, Department of Pediatrics, İstanbul, Türkiye. A total of 120 children were retrospectively included from February 2021 to September 2021.

Gender, age, history of atopy, severity of asthma (n=60) of patients aged 6-12 years who presented to the allergy polyclinic of the Medicine Hospital, were diagnosed with asthma according to the international guidelines, and were followed up for at least one year, and laboratory values (eosinophil count in peripheral blood) were taken from their files.

Patients' files contain both attack and asymptomatic periods. Sixty children hospitalized with an asthma exacerbation from February to September 2021 were included. Patient samples were obtained during the period of exacerbation and the asymptomatic period of the following 3 months after the exacerbation. Control group (n=60) included healthy children without allergic disease (asthma, allergic rhinitis, eczema) or signs of infection.

Inclusion Criteria: Children aged 6-12 years without diseases other than asthma.

Exclusion Criteria:

- Patients who have taken systemic steroids in the last month have other systemic diseases such as acute/chronic infections, cardiovascular, liver and kidney disorders, diabetes mellitus, cancer, and systemic inflammatory diseases,
- Individuals with anemia, leukopenia, leukocytosis, and thrombocytosis,
- Because NLR levels may be altered by drugs such as Nebivolol, patients taking such drugs,
- Patients who are unable to obtain permission from their parents.

Total immunoglobulin E (IgE) values were analyzed by Immunofluorescence analysis (IFA) method (using PHARMACIA UniCAP 100 instrument). Serum CRP was determined by nephelometric method on an autoanalyzer (Siemens dade behring BN 2, USA). Complete blood count (CBC) was determined by hematology analyzer (Sysmeks XN-1000, Germany). The SII, NLR, LMR, PLR, mean platelet volume (MPV)/PLT ratio (MPVPR) and ELR value were calculated from neutrophil, lymphocyte, monocyte, MPV, PLT counts. NLR, LMR and PLR were determined. SII was obtained by dividing the multiplied number of platelets and neutrophils by the number of lymphocytes, and NLR was obtaned by dividing the number of neutrophils by the number of lymphocytes. SIRI was caalculated as follows: SIRI=(neutrophil×monocyte)/lymphocyte).

Statistical Analysis

For the statistical analysis of the data obtained, SPSS Statistics (Version 26.0. Armonk, NY: IBM Corp.) software was used. A non-parametric test, the Mann-Whitney U test, was employed for the purpose of comparing the study groups, while the Wilcoxon signed-ranks test was utilised for the within-group comparison between the attack and healthy periods of the patients. Pearson's correlation coefficient was employed to assess the strength of the relationship between the variables under investigation. In the context of statistical analysis, a p-value of less than 0.05 was considered statistically significant.

Results

Demographic characteristics, CRP levels and mean and standard deviation of CBC parameters of the study groups are presented in Table 1. No significant difference was observed between the patient and control groups in terms of age and gender ($p<0.05$). IgE and eosinophil values were significantly higher in the patient groups. However, PLT and MPV levels were lower than in the control group. IgE, CRP, neutrophil, monocyte and eosinophil levels were significantly higher in the exacerbation group compared to the AS group.

NLR, ELR and SII values were significantly higher in the exacerbation group compared to asymptomatic asthma patient groups (Table 2). SII levels were lower in the asymptomatic group than in the exacerbation group, but not significant in the healthy group. No statistically significant difference was found in PLR and MPVPR levels between all groups.

A positive correlation was found between NLR-IgE ($r=0.792$; $p<0.001$), NLR-SII ($r=0.857$; $p<0.001$), and NLR-ELR ($r=0.762$; $p<0.001$ in patients in the exacerbation period.

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Table 1. Demographic data of groups, mean and standard deviation of complete blood count and CRP levels

	Control group (n=60)	Patient group (exacerbations) (n=60)	Patient group (asymptomatic) (n=60)
Gender (F/M)	27/33	25/35	25/35
Age (month)	8.77±2.91	9.52±2.56	9.45±2.63
IgE (kU/L)	20 (0.01-223)	254 (0.03-1570)^{a***}	40 (0.03-356)^{a*,b**}
CRP (mg/L)	1.03±0.89	24.05±37.02^{a***}	3.55±2.23^{a**,b***}
Leukocyte (×10^3/µL)	8.43±1.34	14.49±6.33^{a***}	8.88±1.40^{a***}
Hemoglobin (gr/dL)	12.94±1.04	11.72±1.30^{a***}	11.70±0.98^{a***}
Hematocrit (%)	37.62±2.80	35.55±3.39^{a***}	34.34±2.83^{a***,b*}
Platelet (K/µL)	298±66	251±69^{a***}	276±45^{a*,b*}
Lymphocyte (×10^3/µL)	4.24±1.80	3.52±1.37^{a**}	4.01±1.51^{b*}
Neutrophil (×10^3/µL)	4.25±1.73	13.37±6.87^{a***}	4.73±1.24^{b***}
Monocyte (×10^3/µL)	0.78±0.38	1.49±0.87^{a***}	0.86±0.96^{b***}
Eosinophil (mm^3/L)	94.23±26.47	332.26 ±149.72^{a***}	124.19±38.85^{a**,b***}

IgE: immunoglobulin E, CRP: C-reactive protein; a vs. C; b vs. EX; *<0.05, **<0.01, ***<0.001

Table 2. The means and standard deviations of the hematological indices of the groups

	Control group (n=60)	Patient group (exacerbations) (n=60)	Patient group (asymptomatic) (n=60)
NLR	1.00±0.96	4.23±2.55^{a***}	1.35±0.64^{a*,b***}
PLR	70±37	82±40	78.48±29.94
ELR	26.96±15.73	116.70±82.74^{a***}	38.81±23.63^{a**,b***}
SII	315±116	1035±688^{a***}	364±149^{b***}

NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio, ELR: eosinophil lymphocyte ratio, SII: systemic immune-inflammation; a vs. C; b vs. EX; *<0.05, **<0.01, ***<0.001

Discussion

Studies on NLR have shown that both local and systemic inflammatory responses increase during exacerbations in patients with a variety of inflammatory lung pathologies due to toxic particles penetrating the lungs [11,12]. The pathophysiology of asthma includes inflammation, but this becomes more apparent when triggered by infection. In present study, NLR, ELR and SII were significantly higher in the exacerbation group compared to asymptomatic asthma patient groups. SII levels were lower in the asymptomatic group than in the exacerbation group. A positive correlation was found between NLR-IgE, NLR-SII, and NLR-ELR in patients in the exacerbation period. According to the results of this study, CRP, SII, NLR and ELR may be helpful and practical, measurable biomarkers for assessing inflammation in children with asthma during acute exacerbation.

Zhang et al. [5] compared the ratio of neutrophils and eosinophils in blood counts with sputum cytology. They reported that patients with neutrophilic asthma had higher NLR values. Drews et al. [7] found sputum neutrophil levels higher in children with non-atopic asthma, while sputum eosinophil levels were higher in children with atopic asthma. Fu et al. [10] found an increase in sputum neutrophil counts in 50 adult asthmatic subjects with systemic inflammation.

In this study, IgE, WBC, CRP, neutrophil, monocyte, and eosinophil counts were found to be helpful in the diagnosis and follow-up of asthma in children with asthma, whereas the change in PLT level did not contribute to the diagnosis and follow-up of asthma. Moreover, in this study, whole blood count parameters and CRP were found to be significantly higher during acute asthma exacerbation compared to those in the control group, which is also in line with the literature. SII, IgE, ELR, and NLR were found to be biomarkers of inflammation in asthma correlated with inflammation in asthma during exacerbation.

During acute exacerbation of asthma, NLR, ELR, or SII can be used as biomarkers to indicate inflammation. A statistically significant association between NLR and general asthma severity, asthma exacerbation severity, annual number of exacerbations, pulmonary function tests or CRP levels has not yet been established. On the other hand, Furukawa et al. found increased sputum neutrophil granulocyte counts in asthmatic children and a relatively weak but significant association between NLR and hospitalization [13].

Asthma is a clinical syndrome characterized by reversible or persistent airway obstruction [1,2]. SII is one of the inflammation parameters developed in recent years and is calculated with platelet, lymphocyte and neutrophil values. Neutrophils,

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lymphocytes and platelets, all involved in the pathogenesis of asthma, are used to calculate the SII value. Increased SII levels in patients usually result in a stronger inflammatory and weaker immune response [14]. In the literature review, no study investigating the SII value in children with asthma was found.

Erdoğan et al. [14] investigated the potential use of SII, a marker of systemic inflammation and prognosis in different types of cancer and vasculitis, to discriminate between asthma and nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (NERD). This study is the first to evaluate the SII to differentiate asthma phenotypes. There was no significant difference between the clinical characteristics of the study groups. Asthma Control Test (ACT) score, eosinophil level, total IgE level, NLR, PLR and SII were analyzed. However, NLR was found to be a risk factor affecting only SII. Pan et al. [15] showed that the combination of NLR, NLR-alanine aminotransferase ratio (NAR) and NLR-albumin ratio (NBR) biomarkers distinguished asthmatics suffering from disease exacerbations from healthy children. Therefore, their results suggest that NLR + NAR + NBR can be used as a clinical biomarker for asthma in children. Radhapyari et al. [16] also reported a significant relationship between NLR and type of asthma severity, but no relationship between NLR and age, gender, BMI, concomitant allergic rhinitis, or asthma exacerbation. According to their results, NLR in pediatric asthma may be an efficient and beneficial biomarker for predicting systemic inflammation in pediatric asthma during acute exacerbation. Our results confirm the results of Radhapyari et al. [16]. In another study, NLR was found to be higher in asthmatic children compared to controls. NLR can be used to assess systemic inflammation in asthmatic patients [17]. However, further studies are needed to assess airway and systemic inflammation in addition to NLR in asthmatic children.

Conclusion

Consequently, SII, ELR, and NLR may be effective and useful biomarkers for determining systemic inflammation during an exacerbation in asthma. In children with asthma, NLR, ELR and SII may be potent and beneficial biomarkers for ascertaining systemic inflammation during an exacerbation. The biomarkers SII, ELR, and NLR offer complementary information when used together as a panel and SII can be used for asthma assessment and follow-up. However, prospective studies with larger samples are needed to compare different types and to determine the optimal cut-off value for SII.

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Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
Ethics committee approval was obtained from Istanbul Atlas University Ethics Committee (Approval date: 30.06.2022 and No: E-22686390-050.99-18388).

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