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Original article

The evaluation of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in asthma control

Évaluation des ratios neutrophiles pour évaluer le contrôle de l'asthme

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ABSTRACT

Aim. – Asthma is a chronic disease of the airways characterized by inflammation. Neutrophils and platelets play a role in the inflammatory process. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have recently been evaluated in various chronic diseases. However, there are only limited data on the association between NLR, PLR and asthma in adult patients. Our aim was to investigate the role of blood NLR and PLR in asthma control.

Materials and methods. – Eighty patients with asthma and 23 healthy controls were included in the study. Complete blood count (CBC), neutrophil count, lymphocyte count, platelet count, C-reactive protein (CRP), and NLR and PLR values were recorded for the study group and controls. An asthma control test (ACT) was performed by a pulmonologist. Patients with asthma were divided into two groups: those with and without controlled asthma.

Results. – The mean age in the patient and control groups was 41.5 ± 11.6 years and 42.0 ± 10.5 years, respectively. Median PLR was significantly higher in the asthma group at 111.9 (range: 82.6–154.9) compared with the control group at 95.9 (range: 89.3–109.0) ($P = 0.048$). Median platelet count was higher in the asthma group than in the control group ($P = 0.009$). Median platelet count and PLR in the uncontrolled group were significantly higher than those in the controlled group ($P = 0.039$; $P < 0.001$). A negative correlation was found between PLR and ACT, FEV₁/FVC and FEV₁ (%), FEV₁ (L), MMEF (%) and MMEF (L) in the asthma group ($P < 0.05$).

Conclusion. – According to our data, PLR may be of value in prediction of asthma control in asthma patients. PLR can be assessed quickly and easily to evaluate asthma control.

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1. Introduction

Asthma is a heterogeneous disease characterized by reversible airway obstruction and chronic inflammation. There are currently some 300 million patients with chronic asthma worldwide. The Global Initiative for Asthma (GINA) guideline is used in the management and treatment of asthma. A key aim of asthma treatment is to control asthma symptoms and minimize the risk of flare-ups [1]. Various surveys have assessed control of the disease. The Asthma Control Test (ACT) is useful for evaluating daytime and nighttime symptoms, daily use of beta-2 agonists, and daily activity [2].

In addition to characteristic chronic airway inflammation, systemic inflammation is also present in patients with asthma. Mast-cell activation, mediated by a variety of cells, cytokines, and numerous mediators, has been described as key to the development of clinical asthma [3,4]. Neutrophils and platelets also play a role in asthma disease. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have recently been evaluated in various chronic diseases. NLR was investigated to determine its association with clinical symptoms in asthmatic children in comparison with a control group, and mean NLR was found to be higher in children with asthma [5]. In a study of 262 asthma patients, NLR and PLR were significantly higher in patients in a critical condition than in patients in non-critical conditions and controls [6]. However, there are only scant data on the association between NLR/PLR and asthma control in adult patients. Our aim was to determine the association between asthma control and NLR/PLR.

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2. Materials and methods

2.1. Study patients

Eighty asthma patients referred to our pulmonology outpatient clinics between June 2017 and September 2018 were enrolled, together with 23 age- and sex-matched healthy volunteers. The study group comprised patients presenting physician-diagnosed asthma in accordance with the GINA criteria and evidence from a bronchodilator reversibility test. The exclusion criteria were respiratory infection, pregnancy, chronic obstructive pulmonary disease (COPD), and asthma exacerbations or hospitalization for asthma in the 4 weeks prior to ratio measurement. All patients provided a detailed history including disease duration, and each underwent a physical examination and pulmonary function tests. CBC, neutrophil count, lymphocyte count, C-reactive protein (CRP), and NLR/PLR values for the study group and controls were recorded. Body mass index (BMI) was determined for all patients. ACT was performed by a pulmonologist. Patients with asthma were divided into two groups based on ACT results: controlled asthma (complete or partial) and uncontrolled asthma. The institutional review board approved the study, and all patients provided written informed consent before the study began.

2.2. Pulmonary function testing

All patients underwent pulmonary function tests according to the American Thoracic Society criteria using spirometry to assess forced expiratory volume in 1 s (FEV₁) as well as other pulmonary function parameters [7].

2.3. Asthma Control Test (ACT)

The ACT includes 5 questions designed to evaluate daytime and nighttime symptoms, frequency of use of beta-2 agonists as rescue medication, and restriction of daily activities. A score of 25 points indicates “complete control”, 20–24 points indicates “partial control”, and <20 points is taken to indicate “uncontrolled” asthma [2].

2.4. Laboratory tests

Blood samples were collected in a hematology sample tube containing anticoagulant for the CBC. Neutrophil, lymphocyte and platelet counts were done using a Coulter LH 780 analyzer, CRP was determined using a Siemens BNII analyzer, and immunoglobulin (Ig)-E values were analyzed using a Beckman Coulter AU5600. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count obtained in a CBC, and PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count.

2.5. Statistical analysis

SPSS software version 15.0 was used for the statistical analyses. The data were assessed for normal distribution. Descriptive statistics are shown as mean and standard deviation for normally distributed data and as median (minimum–maximum) for non-normally distributed data. Pearson's Chi² and Fisher's exact test were used for comparisons in 2 × 2 contingency tables. A *t*-test for independent samples was used to compare the means of the two groups for normally distributed continuous variables. Measurable parameters that were not normally distributed were assessed using the Mann-Whitney U test for comparisons between two groups.

To determine the threshold PLR value in asthma control, receiver operating characteristics (ROC) curve analysis was used, and

sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) are presented. Correlations between normally distributed data were tested using Pearson's correlation test, while Spearman's correlation test was used for non-normal data. The significance level was set at *P* < 0.05.

3. Results

In all, 80 patients with asthma were included in the study: 57 women (71.3%) and 23 men (28.7%), along with 22 controls. The mean age of the patient and control groups was 41.5 ± 11.6 years and 42.0 ± 10.5 years, respectively. No differences were found between the groups in terms of age and sex.

The demographic and clinical characteristics, laboratory values and respiratory function values for all subjects are given in Table 1.

Median PLR was significantly higher in the asthma group at 111.9 (range: 82.6–154.9) compared with the control group at 95.9 (range: 89.3–109.0) (*P* = 0.048). Median platelet count was higher in the asthma group than in the control group (*P* = 0.009). No significant difference regarding NLR was seen between the asthma and control groups (*P* = 0.994). There were no significant differences between the uncontrolled asthma group and the controlled asthma group regarding sex, age, neutrophils, lymphocytes, eosinophils, IgE, BMI, CRP or NLR (Table 2).

Median platelet count and PLR in the uncontrolled group were significantly higher than in the control group (*P* = 0.039; *P* < 0.001) (Figs. 1 and 2).

A negative correlation was found between PLR and ACT, FEV₁/forced vital capacity (FVC) and FEV₁ (%), FEV₁ (L), maximal (mid-)expiratory flow (MMEF) (%) and MMEF (L) in the asthma group (*P* < 0.05) (Table 3). No statistically significant correlation was found between PLR and pulmonary function test results in the controlled group.

PLR values of 100 relative to the ROC curve may be considered as a threshold in uncontrolled asthma. The sensitivity, specificity, and positive and negative predictive values were 93.5%, 91.2%, 93.5%, and 91.2%, respectively.

4. Discussion

Our results show significantly higher platelet counts and PLRs for asthma patients than for controls; however, there were no statistically significant differences between patients and controls in terms of CRP, neutrophils or NLRs. Moreover, higher PLRs were found in patients with uncontrolled asthma than in those with controlled asthma. PLR may be of value in the prediction of asthma control and this requires confirmation in further clinical trials. However, there is scant research on NLR and PLR in patients with atopic diseases, including asthma and allergic rhinitis. A study in 469 children with asthma and 170 controls identified a significant difference in mean NLR between asthmatic children and controls. Moreover, mean NLR was positively correlated with the number of asthma attack-related hospitalizations [5]. In another study, NLR was found to be higher in patients with allergic rhinitis compared with the control group, and NLR was shown to increase with disease severity [8]. NLR of asthma patients was significantly higher during asthma attacks compared with patients in asymptomatic periods and with controls [9]. Another study showed higher NLR in asthmatic children than in healthy controls. An association was thus established between the presence of systemic inflammation in these diseases and disease severity [10].

In asthma, chronic inflammation of the airways results in airway obstruction. Cytokines, which regulate host responses to infection, immune response and inflammation, play a key role in the pathogenesis of asthma by eliciting an increase in neutrophils. NLR was

Table 1

Demographic characteristics, laboratory parameters, and respiratory function findings for all subjects.

	Asthma group(n = 80)	Control group(n = 22)	P
Age (years)	41.5 ± 11.6	42.0 ± 10.5	0.852
BMI	27.6 ± 5.5	27.0 ± 2.6	0.574
Female/male	57/23 (71.3/28.7)	15/7 (68.2/31.8)	0.780
Atopy history (n)	75 (93.75%)	0 (0%)	<0.001
Smoking status (packs/year)	2 ± 0.3	3 ± 0.2	0.121
FEV ₁ /FVC ratio	77.5 ± 8.0	81.8 ± 4.7	0.019
FEV ₁ predicted (%)	85.6 ± 14.1	97.6 ± 11.2	<0.001
FEV ₁ (L/s)	2.5 ± 0.6	3.1 ± 0.7	0.001
MMEF predicted (%)	61.5 ± 22.7	88.7 ± 17.3	<0.001
MMEF (L/s)	2.2 (1.5–3.0)	3.4 (2.8–3.7)	<0.001
Neutrophils (10 ³ /μL)	4.2 (3.5–5.7)	4.2 (3.4–5.1)	0.657
Lymphocytes (10 ³ /mm ³)	2.4 ± 0.6	2.5 ± 0.6	0.370
Platelets (10 ³ /μL)	268.5 (220.0–322.5)	238.0 (201.0–263.0)	0.009
Neutrophil/lymphocyte ratio	1.8 (1.3–2.2)	1.8 (1.5–2.0)	0.994
Platelet/lymphocyte ratio	111.9 (82.6–154.9)	95.9 (89.3–109.0)	0.048
Eosinophils (10 ³ /mm ³)	0.2 (0.1–0.4)	0.2 (0.1–0.3)	0.696
CRP (mg/L)	3.0 (3.0–4.0)	3.0 (3.0–5.0)	0.226

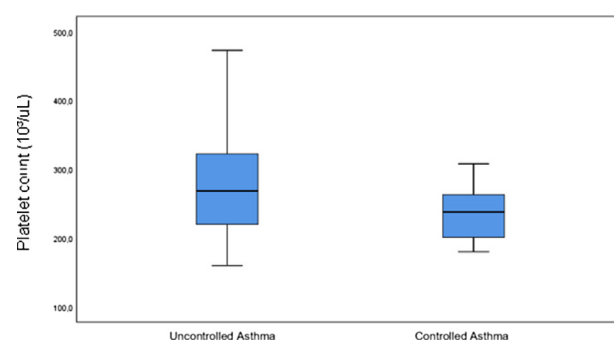
Bold values denote statistically significance at the $P < 0.05$ level**Table 2**

Demographic characteristics of patients with uncontrolled and controlled asthma.

	Uncontrolled asthma(n = 46)	Controlled asthma(n = 34)	P
Age (years)	43.1 ± 12.0	39.4 ± 10.9	0.159
BMI	27.7 ± 6.6	27.5 ± 3.8	0.846
Sex n (%)			
Female	35 (61.4)	22 (38.6)	0.266
Male	11 (47.8)	12 (52.2)	
Smoking status n (%)			
Non-smoker	43 (60.6)	28 (39.4)	0.159
Smoker	3 (33.3)	6 (66.7)	
FEV ₁ /FVC ratio	75.4 ± 8.2	80.4 ± 6.8	0.005
FEV ₁ predicted (%)	83.4 ± 15.5	88.7 ± 11.5	0.094
FEV ₁ (L/s)	2.3 ± 0.6	2.7 ± 0.6	0.005
FVC (%)	95.0 (84.0–103.0)	89.0 (83.0–98.0)	0.405
FVC (L)	3.1 ± 0.8	3.4 ± 0.7	0.137
MMEF predicted (%)	54.6 ± 22.5	70.8 ± 19.7	0.001
MMEF (L/s)	1.7 (1.3–2.6)	2.9 (2.1–3.6)	<0.001
Total IgE	88.5 (26.0–203.0)	67.0 (40.0–133.0)	0.486
Eosinophils (10 ³ /mm ³)	0.2 (0.1–0.4)	0.2 (0.1–0.3)	0.459
Neutrophils (10 ³ /μL)	4.5 ± 1.5	4.9 ± 1.5	0.228
Lymphocytes (10 ³ /mm ³)	2.3 ± 0.6	2.5 ± 0.5	0.075
Platelets (10 ³ /μL)	271.0 (222.0–342.0)	248.5 (218.0–283.0)	0.039
Neutrophil/lymphocyte ratio	1.9 (1.3–2.4)	1.6 (1.4–2.0)	0.051
Platelet/lymphocyte ratio	153.4 ± 41.9	81.2 ± 11.2	<0.001
CRP	3.0 (3.0–5.0)	3.0 (3.0–4.0)	0.226
ICS – daily use (n)	46 (100%)	30 (88%)	0.124

found to play an important role in inflammation; however, there is a paucity of data on NLR and PLR evaluation in adult asthma. In one study, the effect of NLR on disease control status was assessed in asthma patients. NLR was higher in asthma patients than in controls. In addition, as asthma becomes uncontrolled, NLR increases [11]. Zhang et al. demonstrated that NLR was higher in asthma patients than in controls and that it was associated with hospitalization [10]. As in our own study, no relation between asthma and NLR was reported in a study evaluating the association between NLR and chronic disease in adults [12]. Contrary to our study, Hendy et al. found that NLR was higher in patients with asthma than in controls and that NLR was increased in uncontrolled asthma [13]. In another study, NLR was found to be significantly correlated with severe asthma exacerbations [14]. Further, a significant correlation was reported between ACT > 20 and ACT < 20 and NLR in adults with asthma [11].

Like NLR, PLR is an inflammatory marker for chronic inflammation; evaluation is inexpensive and is easily performed on blood samples. Both NLR and PLR have served as inflammatory biomarkers in many diseases. The role of platelets in inflammation has also been evaluated in other earlier studies. Certain platelets

**Fig. 1.** Platelet counts in the uncontrolled and controlled asthma groups.

are activated during inflammation. Platelets form chemotaxis signals by interacting with endothelium and induce the secretion of adhesion molecules. They promote inflammation by increasing pro-inflammatory mediators [15,16]. A study reported elevated platelet counts in allergic hospitalized asthma patients. The authors also found no significant differences in platelet counts between

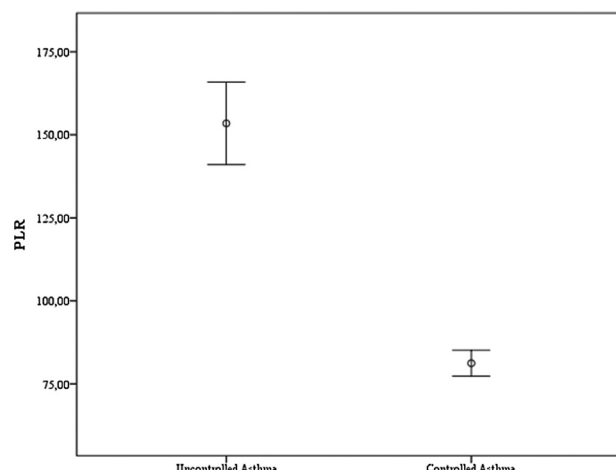


Fig. 2. PLR in the uncontrolled and controlled asthma groups.

Table 3
Correlation between PLR, pulmonary function tests and ACT.

	PLR	
	<i>r</i>	<i>p</i>
FEV ₁ /FVC ratio	−0.255	0.022
FEV ₁ predicted (%)	−0.226	0.044
FEV ₁ (L/s)	−0.317	0.004
FVC predicted (%)	−0.065	0.569
FVC (L)	−0.189	0.093
MMEF predicted (%)	−0.332	0.003
MMEF (L/s)	−0.349	0.001
Asthma control test (ACT)	−0.752	0.001

non-allergic asthma patients compared with controls [17]. In our study, the median platelet count was higher in the asthma group than in the control group.

Studies in the literature report higher PLR values in adults with asthma compared with controls. PLRs were also significantly higher in asthmatics in a critical condition than in asthmatics in a non-critical condition [6]. Similarly, we found median PLR to be higher in patients with stable asthma compared with controls. Further, PLR was higher in the uncontrolled group compared with the controlled group. This study is the first to investigate the association between PLR and asthma control in adults.

5. Conclusion

In our study, median platelet count and PLR were higher in the asthma group than in the control group, and these values were higher in the uncontrolled asthma group than in the controlled asthma group. Our data suggests that PLR may be of value in

predicting asthma control and this requires confirmation in further clinical trials. PLR offers a quick and easy method to evaluate asthma control. Nevertheless, further large-scale studies are warranted to investigate airway and systemic inflammation in relation to PLR in asthma patients.

Disclosure of interest

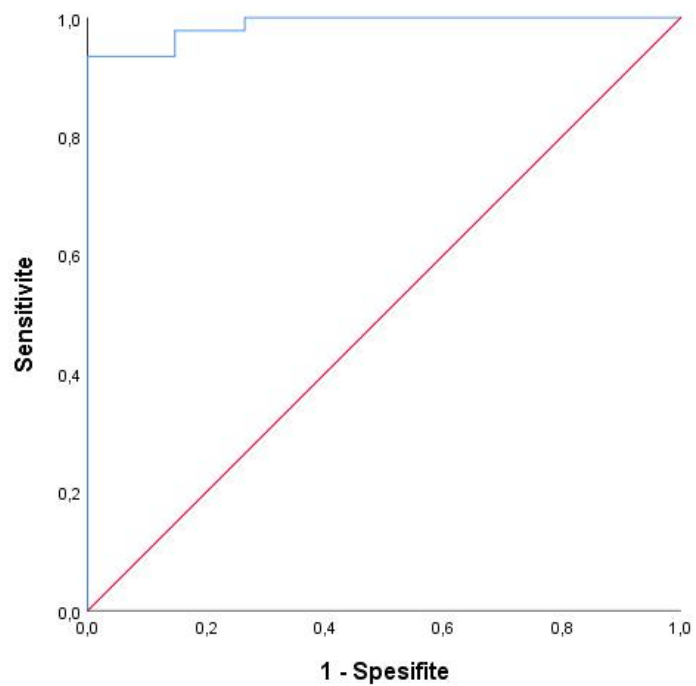
The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at: <https://doi.org/10.1016/j.reval.2019.09.001>.

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	Value	SEN (%)	SPE (%)	PPV (%)	NPV (%)	Under curve area (%)	%95 CI		p
PLR	100	93,5	91,2	93,5	91,2	0,988	0,971	1,000	<0,001