

PREDICTIVE VALUE OF PLATELET-TO-LYMPHOCYTE RATIO AND NEUTROPHIL-TO-LYMPHOCYTE RATIO IN PATIENTS WITH HYPERSENSITIVITY PNEUMONIA

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ABSTRACT. *Aim:* To evaluate Platelet-to-Lymphocyte Ratio (PLR) and Neutrophil-to-Lymphocyte Ratio (NLR) in patients with HP. *Method:* A sample of 140 total patients, 50 having chronic HP and 20 having acute HP, and a control group of 70 more patients were included in this retrospective study conducted with hospital Ethical Committee approval. *Results:* PLR and NLR values were significantly higher in all HP patients than in the control group ($p < 0.001$). In addition, these biomarkers were significantly higher in patients with acute HP than in the chronic HP group ($p = 0.017$ and $p = 0.044$, respectively). The cutoff values for PLR and NLR were: (1) 177 ($p = 0.020$) and 2.76 ($p < 0.0001$) between the HP patients and the control group, and, (2) 110 ($p = 0.0054$) and 2.15 ($p = 0.03$), between the acute and chronic HP groups. *Conclusion:* PLR and NLR values are inexpensive and easy parameters that can guide in diagnosing hypersensitivity pneumonia in combination with clinical, radiological and pathology findings and the acute-chronic differentiation of the disease. (*Sarcoidosis Vasc Diffuse Lung Dis* 2020; 37 (4): e2020012)

KEY WORDS: platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, acute/chronic hypersensitivity pneumonia

INTRODUCTION

Hypersensitivity pneumonia (HP) is an immune-mediated disease that occurs upon exposure to particles of animal or vegetable origin and/or chemical agents in patients who are shown to be genetically sensitive to those antigens. The severity and duration of the disease and how a patient presents with symptoms in the clinic can vary. The intensity and duration of antigen exposure is dependent upon

many factors, including, but not necessarily limited to, the type of antigen and patient specific host factors (1,2). The development of HP disease in patients is not yet completely understood. However, T-cell hyperreactivity and the immune complex-mediated immune response formation are believed to play a significant role. Previous research classified disease progression into three groups:

- (1) acute,
- (2) subacute,
- (3) and chronic (3).

Current thinking is to approach the disease more practically into two groups:

- (1) Acute/inflammatory/nonfibrotic HP, and,
- (2) Chronic/fibrotic HP.

based on the clinical-radiological-pathological correlation(4).

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While neutrophil and platelet levels increase in inflammation, lymphocyte levels decrease. Systemic inflammation can be determined using PLR and NLR that are easy and inexpensive to obtain. Many observational studies emphasize that PLR is an inflammatory marker of immune-mediated, metabolic, prothrombotic and neoplastic diseases. It has diagnostic and prognostic value in many diseases (5-8). In those studies, the NLR value was found to be higher in sarcoidosis patients than in the control group and in those patients without extrapulmonary involvement. Research shows NLR may be used as a biomarker in determining the progression in sarcoidosis (9). Another research also showed that increasing PLR can facilitate sarcoidosis diagnosis, and in gauging the extent of lung involvement (8). However, there is little research on the use and value of PLR and NLR ratios in diagnosing or predicting the progression of hypersensitivity pneumonia. The purpose of this study is to evaluate the diagnostic value of these inflammatory serum markers in hypersensitivity pneumonia.

MATERIALS/METHODS

Patients

This study was conducted using retrospective patient data from a tertiary teaching, high bed capacity hospital for the period between August 2013 through December 2017. This study included 70 HP patients.

All clinical and radiologic data together with a full occupational, exposure, smoking, family and drug history were collected. Lung biopsies were examined in the Department of Pathology.

70 healthy individuals who applied to our outpatient clinic were included as the control group. Patients exhibiting the following symptoms were included in the acute HP subgroup:

- (1) Patients with a symptom duration of less than 6 months,
- (2) upper-middle zone weighted GGO,
- (3) Patients having acentrilobular nodule, mosaic attenuation, air trapping or consolidation on HRCT

Patients exhibiting the following symptoms or pathology were included in the chronic HP subgroup:

- (1) patients with symptoms longer than 6 months,
- (2) patients having upper middle zone-weighted fibrosis; and,
- (3) patients with honeycomb, mosaic attenuation, air trapping and centrilobular nodules.

In all patients definitive diagnosis reached by multidisciplinary diagnosis(MDD), confirmed by guidelines (10)

Patients presenting with following diseases which can affect inflammatory processes and bleeding were excluded from the study:

- (1) rheumatoid arthritis,
- (2) vasculitis,
- (3) inflammatory bowel diseases,
- (4) hematologic diseases,
- (5) chronic respiratory diseases,
- (6) malignancies,
- (7) autoimmune diseases,
- (8) chronic heart diseases, and,
- (9) anyone having had a blood transfusion in the last 3 months.

Collection of Blood and Inflammatory-Marker Data

Complete blood counts were determined by spectrophotometry/impedance (Beckman Coulter LH 780 Analyzer; Beckman Coulter, Inc., CA, USA). Venous blood samples were collected and placed into ethylenediaminetetraacetic acid tubes. The following hematological parameters were recorded at the time of diagnosis:

- (1) leukocyte count,
- (2) neutrophil count and percentage,
- (3) lymphocyte count and percentage,
- (4) hemoglobin,
- (5) Hematocrit levels,
- (6) mean corpuscular volume,
- (7) red cell distribution width,
- (8) Platelet counts,
- (9) mean platelet volume (MPV),
- (10) platelet distribution width,
- (11) NLR, and,
- (12) PLR.

The NLR and PLR were defined as follows:

- NLR = neutrophil count divided by the lymphocyte count, and,
- PLR = platelet count divided by the lymphocyte count.

C-Reactive Protein (CRP) was determined by the turbidimetric method (Cobas c 702, cobas 8000 ISE; Hitachi High-Technologies Corporation, Tokyo, Japan). Peripheral blood was obtained at the time of diagnosis. Electron Spin Resonance (ESR) was determined by spectrophotometric method (Alaris, ALS 100, Auto ESR Analyzer, Turkey).

Pulmonary Function Tests (PFTs)

Pulmonary function data was collected by performing PFTs using a ZAN 300 device (ZAN Messgerate, Oberthulba, Germany), in the sitting position. The highest value of Forced Expiratory Volume in 1 second (FEV1) and Forced Vital Capacity (FVC), was recorded after patients performed at least three technically satisfactory maneuvers differing by less than 5%.

Statistical Analysis

Statistical analysis was performed using 'SPSS 18.0 for Windows'. The means, standard deviations, medians and the minimums and maximums were calculated. Normality was evaluated using the Kolmogorov–Smirnov test. Comparison of results between groups was performed using Analysis of Variance (ANOVA) for parametric results and the Kruskal–Wallis test for nonparametric results. For ANOVA values with $p < 0.05$, an unpaired Student's *t*-test was used for parametric results. The Mann–Whitney *U*-test for nonparametric results was used for pair-wise comparisons. Categorical comparisons were performed using the Chi-squared test. Relationship between the parameters were evaluated using the Spearman Rank Correlation test for normally distributed results. The Pearson Correlation coefficient was calculated for abnormally distributed results. The predictive significance of the NLR and PLR was analyzed by graphically plotting Receiver Operating Characteristic (ROC) curves. Sensitivity, specificity and likelihood ratios were calculated using different cutoff values.

ETHICS

This study was designed and performed in accordance with The Helsinki Declaration and good clinical practices, and approved by our hospital Ethics Committee.

RESULTS

Of the 70 HP patients, the mean age was 58.9 with a standard deviation of 13.4. Females represented 52.9% ($n=37$) while 47.1% ($n=33$) of our patients were males. Half of the patients ($n=35$) were smokers. History of contact with birds was determined for 39 (55.7%) patients. 20 (28.6%) patients were found to have exposure to organic antigens. 11 (15.7%) patients had other antigenic exposure. The most common symptoms were cough and dyspnea. HRCT findings in 50 (71.4%) of patients revealed predominant ground glass opacity associated with other pathologies.

Traction bronchiectasis was detected in 43 (61.4%), honeycomb 25 (32.9%), centrilobular nodule 17 (24.3%) and mosaic attenuation in 16 (22.9%) patients. Upper-middle-lower zone involvement was seen in 25 (35.7%), upper-middle zone involvement was 7 (10.0%), middle-lower zone involvement was 25 (35.7%) and lower zone involvement was seen in only 13 (18.6%) patients. Pathological diagnosis was used to confirm the diagnosis in 43(61%) patients. Medical thoracoscopy was used for obtaining a lung biopsy in 23 (32.8%) patients. Transbronchial lung biopsy (TBLB) was used for 15 (21.4%) patients. Video Assisted Thoracoscopic Surgery (VATS) was used for 5 (7.1%) patients

Comparison of the hemogram parameters of the 70 HP patients with the 70 patients in the control group is shown in Table 1. In comparison with the control group, PLR ($p = 0.000$) and NLR ($p = 0.000$) values were significantly higher in all HP patients. Also leucocyte, neutrophil, PLT count, MCV, MPV, RDW and PDW levels were significantly higher in patients with HP than in the control group. In the ROC analysis between patients with HP and the control group:

- (1) the PLR cutoff was 177, sensitivity 32.8%, specificity 95.7%, AUC 0.61 (0.51-0.70) ($p = 0.020$), and,
- (2) the NLR cutoff was 2.76, sensitivity 52.8%, specificity 82.8%, AUC 0.72 (0.63-0.80) ($p < 0.0001$) (Figure 1).

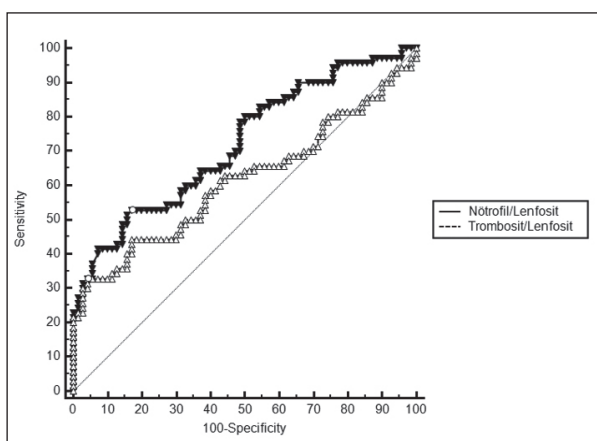
50 patients (71.4%) were diagnosed as being in the chronic HP subgroup. 20 (28.6%) were placed in the acute HP subgroup.

Comparative demographic data and laboratory findings of acute and chronic HP patients are given

Table 1. Comparison of hemogram parameters in Hypersensitivity Pneumonia patients and the patient control group

	HP(n:70)	Control(n:70)	p value
Age (years) mean (min;max)	63 (18 ; 82)	58 (24 ; 77)	0.12
Leucocyte ($\times 10^3/\mu\text{l}$) (min;max)	9 (3.8 ; 24.1)	7 (4.4 ; 10.9)	0.000
Hb(gr/dl)	13.7 \pm 1.9	13.9 \pm 1.1	0.49
Hct(%)	41.2 \pm 5.4	41.6 \pm 3	0.51
MCV(fl)	84.5 \pm 6.2	86.6 \pm 4.5	0.025
RDW(fl)	14.2 (10.2 ; 20)	13.3 (11.2 ; 18.6)	0.000
PLT($\times 10^3/\mu\text{l}$)	270 (122 ;742)	245 (149; 393)	0.016
MPV(fl)	8.5 \pm 1	9.1 \pm 1	0.001
PDW(fl)	16.7 (11.5 ;19)	16.5 (9.4 ;22)	0.012
Neutrophile ($\times 10^3/\mu\text{l}$) (min;max)	5.5 (2.2 ;20.7)	4.1 (2.2 ;6.9)	0.000
Lymphocyte ($\times 10^3/\mu\text{l}$) (min;max)	2.1 (0.8 ;4.5)	2.1 (1.3 ;3.6)	0.41
NLR	2.8 (0.9 ;18.8)	1.9 (0.6 ;3.9)	0.000
PLR	129 (37.8 ;573.4)	114 (50.8 ;220)	0.021

Hb: Hemoglobin;Hct:Hematocrit; MPV: Mean platelet volume; MCV: Mean corpuscular volume; NLR: Neutrophil-to-lymphocyteratio; PDW: Plateled distribution width; PLR: Platelet-to-lymphocyte ratio; PLT: Platelet; RDW: Red cell distribution width.

**Fig. 1.** ROC analysis for PLR / NLR values of all patients with hypersensitivity pneumonia and the control group.

in Table 2. When acute and chronic HP cases are compared; the mean age was significantly higher in the chronic group ($p = 0.006$). Steroid treatment was given to 30 of the 70 patients (42.8%). Of those 30 patients, 20 (66.7%) of the treated subjects were chronic HP and 10 (33.3%) were acute HP. In the acute HP group, PLR ($p = 0.017$) and NLR ($p = 0.044$) values were significantly higher than the

chronic group. In the ROC analysis between the chronic HP and acute HP:

- (1) the PLR cutoff was 110, sensitivity 44%, specificity 90%, AUC 0.68 (0.56-0.79) ($p = 0.0054$), and,
- (2) the NLR cutoff was 2.15 sensitivity 42%, specificity 85%, AUC 0.65 (0.53-0.76) ($p = 0.03$) (Figure 2).

NLR was correlated with ESR, PLR, MCV, RDV and PDW, and $p = 0.03$, $p < 0.0001$, $p = 0.013$, $p = 0.017$ and $p = 0.028$, respectively. PLR was also correlated with ESR, NLR, MCV, MPV and PDW, and $p = 0.04$, $p < 0.0001$, $p = 0.001$, $p = 0.001$ and $p < 0.0001$, respectively.

DISCUSSION

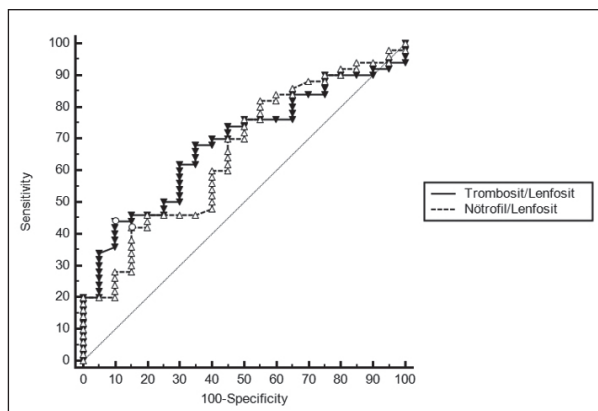
In this study, PLR and NLR, leucocyte and neutrophile count, PDW levels were significantly higher in patients with HP than in the control group. PLR and NLR were significantly higher in patients with acute HP than those having chronic HP.

Previous studies showed that NLR and PLR increased in sarcoidosis, COPD, pulmonary embolism,

Table 2. Demographics of chronic and acute HP patients

	Chronic HP n: 50	Acute HP n: 20	p value
Age (years)(min;max)	65 (18 ;82)	52 (22 ; 71)	0.006
Gender			
Male	29 (%58)	4 (%20)	0.009
Female	21 (%42)	16 (%80)	
Cigarette			
Non-smoker	22 (%44)	13 (%65)	0.242
Smoker	5 (%10)	2 (%10)	
Ex-smoker	23 (%46)	5 (%25)	
BMI	27.3 (15.1; 41.5)	27.4 (18.3; 44.2)	0.98
FEV1%	74 (39;135)	65.5 (33;114)	0.08
FVC %	69 (34;120)	65.5 (45;94)	0.25
FEF25-75 %	88 (22;181)	70 (13;117)	0.024
DLCO%	44.5 (3;114)	39.5 (18;102)	0.71
ESR(mm/h)	21.5 (8;93)	27.5 (8;74)	0.19
CRP(mg/dl)	0.75 (0.05;23)	1 (0.05;3.8)	0.58
Hb(gr/dl)	14.3 (10.2 ;17.2)	13.5(7.9;16.5)	0.04
Hct(%)	42 (31;52)	39.9 (24;48)	0.10
MCV(fl)	86 (73;96)	82 (60;92)	0.016
RDW(fl)	14 (10;17)	14.4 (13;20)	0.15
PLT($\times 10^3/\mu\text{l}$)	265 (122;567)	313 (217;742)	0.06
MPV(fl)	8.4 (6.4;12.6)	8.4 (6.8;10.7)	0.90
PDW(fl)	16.8 (11.5;19)	16.6 (13.5; 17.8)	0.53
Neutrophile($\times 10^3/\mu\text{l}$)(min;max)	5.3 (2.2;20.7)	6.1 (2.4; 16.2)	0.32
Lymphocyte($\times 10^3/\mu\text{l}$)(min;max)	2.2 (0.8;4.5)	1.8(1.1;3)	0.19
PLR	124 (37;573)	176 (85;352)	0.017
NLR	2.7 (0.9; 18.8)	3.5 (1.7;10.8)	0.04

CRP: C-reactive protein; DLCO: Diffusing capacity of carbon monoxide; ESR: Erythrocyte sedimentation rate; FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; Hb: Hemoglobin; Hct: Hematocrit; MPV: Mean platelet volume; MCV: Mean corpuscular volume; NLR: Neutrophil-to-lymphocyt ratio; PDW: Platelet distribution width; PLR: Platelet-to-lymphocyte ratio; PLT: Platelet; RDW: Red cell distribution width, BMI: Body mass index.

**Fig. 2.** ROC analysis for PLR and NLR values in patients with chronic and acute HP

lung cancer, and inflammatory / rheumatological diseases. This is associated with poor prognosis (11-14). Various cells have been investigated in serum and BAL samples in hypersensitivity pneumonia patients (15,16). Our study is the first to evaluate PLR and NLR in HP patients.

Yalniz et al. found PLR and NLR significantly higher in all sarcoidosis patients compared to the control group. They found these biomarkers significantly higher in sarcoidosis patients (stage 2,3,4) with parenchymal involvement compared to those without parenchymal involvement (stage 0,1). In predicting the diagnosis of sarcoidosis, they determined the cutoff value for PLR and NLR as 158 (with

57% sensitivity and 93% specificity and positive and negative predictive values 93% and 59% respectively), and the cut-off value for NLR as 2.4 (87% sensitivity and 58% specificity with ppv and npv 64 and 85% respectively) (8). In our study, we determined the cut-off for NLR as 2.76, with the sensitivity of 52.8%, specificity of 82.8%, and plr cut-off was 177 with the sensitivity of 32.8%, specificity of 95.7% for the diagnosis of HP. When we compared with the sarcoidosis study, the sensitivity of both plr and nlr was lower whereas specificity was higher for HP in our study. Karadeniz et al. Showed that PLR increased in COPD patients compared to the control group, and it was higher in the AE-COPD group than stable COPD. In addition, they observed a negative correlation between PLR and FEV1 (11). Sakurai et al. also found that NLR predicted the exacerbations and severity of COPD (17). In acute pulmonary embolism, it is reported that the increase in NLR and PLR is related to all-cause mortality (18).

Hypersensitivity pneumonia is an inflammatory disease that develops against an inhaled antigen. Neutrophils may also increase in inflammatory diseases. In addition, platelets also increase in many inflammations with an acute phase reactant-like effect. We also found that neutrophil and platelet counts increased significantly in HP patients compared to the control group. We believe that, as a result, PLR and NLR values have increased. In addition, studies in sarcoidosis patients have reported that a peripheral lymphopenia may develop due to lymphocyte accumulation in the granulomas, and, consequently, an increase in PLR and NLR was seen (8,19). Similar to sarcoidosis in HP, lymphocytes may decrease in peripheral blood due to lymphocytic inflammation and granulomas developing in the lung. Consequently, PLR and NLR are higher in HP patients than in the control group. In addition, as the disease progresses to chronic HP, granulomas and inflammation in the lung decrease gradually and they are replaced by fibrosis (chronic / fibrotic HP) (4). As a result, we believe that PLR and NLR decreases in the chronic period compared to the acute period.

While lymphocytic alveolitis is mostly seen in the BAL of HP patients, sometimes neutrophilic alveolitis can also be seen (15,16). According to clinical, radiological and BAL findings, differentiating between acute and chronic HP can be difficult. Therefore, we PLR and NLR biomarkers can be used

as predictors both in the diagnosis of HP and in the distinction between acute and chronic HP.

Serum KL-6 and SP-D produced from type II pneumocytes are biomarkers that can be used in the differential diagnosis of ILD. T. Okamoto et al. determined serum KL-6 and SP-D levels significantly higher in acute HP and chronic HP than in patients with IPF, CVD-IP, sarcoidosis. For patients in the chronic HP group who had acute exacerbation (AE), KL-6 level was significantly higher than KL-6 level one month before AE (20). Precipitating antibodies were used to differentiate chronic HP from other fibrotic interstitial lung diseases and it was concluded that serum precipitating antibodies have no role in the diagnostic approach to chronic HP (21). In a study in which Cathepsin-K was used as an immunohistochemical marker, Cathepsin-K was found to be a sensitive and specific marker that detects granulomatous reactions in chronic HP (22).

We found that PLR and NLR values were higher in HP patients compared to the control group, and were significantly higher in acute HP than chronic HP. PLR and NLR cutoff values between the HP and the control group 177 and 2.76, respectively. We also found the cutoff values for PLR and NLR to predict acute HP and chronic HP differential diagnosis were 110 and 2.15, respectively.

LIMITATIONS OF THE STUDY

There were limitations to this study: it was retrospective, in the control group, laboratory values such as ESR and CRP showing inflammation and respiratory function test parameters could not be examined, the lack of cell analysis in the BAL fluid of all patients. And the value of both ratios to diagnose HP and to differentiate between AHP and CHP is characterized by a low sensitivity which could lead to a number of false negative results.

CONCLUSION

Sometimes there may be difficulties in the diagnosis and differentiation of acute vs. chronic HP. Other biomarkers such as KL-6 and SP-D are difficult to obtain and are expensive. PLR and NLR values, which are inexpensive and easily accessible, can guide

us both in the diagnosis and the distinction of acute vs. chronic HP forms together with clinical, imaging, BAL findings and with the history of exposure.

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