

# Can We Estimate the Recurrence of Primary Spontaneous Pneumothorax With Simple Blood Tests?

Fatih Selvi<sup>1</sup>, Cihan Bedel<sup>1\*</sup>, Muharrem Özkaya<sup>2</sup>

<sup>1</sup>Health Science University Antalya Training and Research Hospital, Department of Emergency Medicine

<sup>2</sup>Health Science University Antalya Training and Research Hospital, Department of Thoracic Surgery

## ABSTRACT

Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are associated with inflammatory diseases and inflammation plays an important role in primary spontaneous pneumothorax (PSP). Therefore, this study evaluated the relationship between estimating recurrence risk and simple blood test such as NLR and PLR in patients with PSP.

We designed a retrospective study examining the benefit of NLR and PLR in estimating recurrence in PSP patients. Patients were divided into 3 groups according to their recurrence: Group 1 (132 patients; defined as no recurrence); Group 2 (46 patients; defined as one recurrence); Group 3 (16 patients; defined as two or more recurrence). The clinical blood parameters were compared among the groups. Mann-Whitney U test, Chi-square and ANOVA test were used to analyze data.

NLR and PLR were significantly elevated in patients with recurrent PSP ( $p < 0.001$  and  $p < 0.001$ , respectively). The best NLR cut-off value for predicting recurrence was 3.5 with 87% sensitivity and 63% specificity, and the best PLR cut-off value was 144.5 with 75% sensitivity and 66% specificity.

NLR and PLR may have clinical importance, because the early markers of recurrent PSP.

**Key Words:** Recurrence, primary spontaneous pneumothorax, neutrophil, lymphocyte, platelet, ratio

## Introduction

Primary spontaneous pneumothorax (PSP) is a life-threatening condition associated with the presence of air in the pleural space in the absence of a known significant pulmonary disease or trauma. A study reported that the incidence was 22.7 in 100,000 and predominant in men (1). PSP usually occurs in thin and tall men under 40 years of age (2).

The recurrence rate of PSP varies according to studies range from 16% to 52%, but it is generally accepted to be about 30% and the majority of recurrences occur within the first two years (3-7). Therefore, recurrence is the major concern associated with PSP. It not only affects the quality of patient's life but also causes an economic burden. Predicting recurrence and conducting appropriate treatment options would be crucial in the management of PSP.

Many studies have shown that inflammation plays an important role in PSP (8-10). Neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) are defined as new signs of inflammation and markers of thrombotic events that can be easily measured from routine blood

tests taken in emergency departments (ED) (11-17). Therefore, this study evaluated the importance of PLR and NLR in patients with recurrent PSP and this is the first study to evaluate the relationship between PSP and the markers mentioned above.

## Materials and Methods

In our retrospective study, the tenets of the Helsinki Declaration were followed. We carried out a retrospective hospital record review of the data between January 2013 and November 2017. During this period, all patients who presented with a PSP were included. Inclusion criteria of the study were: (1) admission with PSP, (2) presence of PSP on x-ray and X-ray or computed tomography (CT), (3) age over 18 years. Patients with missing data of clinical, laboratory or radiographic findings and those who had a pneumothorax other than PSP were excluded from the study.

Demographic characteristics of patients (age and sex), location of pneumothorax, lateralization (ipsilateral, contralateral or both), recurrence time, episode of recurrence frequency (first, second or

\*Corresponding Author: Cihan Bedel, Health Science University Antalya Training and Research Hospital, Kazım Karabekir Street postal zip code: 07100, Muratpaşa, Antalya, Turkey

E- mail: cihanbedel@hotmail.com Phone: +90 (507) 564 12 54, Fax: +90 (242) 249 44 87

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**Table 1.** Demographic and clinical characteristics of patients with PSP, stratified by recurrence

Parameter		Recurrence (n =62 )	Non-recurrence (n = 132)	p value
Age (years)		32.1 ±9.3	30.2±8.4	0.255
Gender	Male	54(87.1%)	121(91.7%)	0.318
	Female	8(12.9%)	11(8.3%)	
Location of pneumothorax, n (%)				0.676
Right				
Left		30(48.4%)	69(52.3%)	
Bilateral		32(51.6%) 0(0%)	62(47%) 1(0.7%)	
Time of recurrence	Week(n)	23.42±48.91		
Neutrophil count (×10 <sup>3</sup> /mm <sup>3</sup> )		8.72±4.92	7.07±3.05	0.063
Lymphocyte count(×10 <sup>3</sup> /mm <sup>3</sup> )		1.75±1.07	2.22±0.79	<0.001
Platelet count (×10 <sup>3</sup> /mm <sup>3</sup> )		294.48±285.39	240.22±77.92	0.67
MPV (fL)		8.82±1.2	9.2±1.32	0.075
PLR		204.58±201.57	124.63±73.64	<0.001
NLR		6.03±4.44	4.04±4.49	<0.001

(PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; MPV: mean platelet volume; SD: standard deviation)

**Table 2.** Comparison of demographic and laboratory parameters between groups

Parameter		Group 1 n=132	Group 2 n=46	Group 3 n=16	p
Age (years)		30.2±8.4	31.4±9.6	33.9±8.4	0.238
Gender	Male	121(91.7%)	38(82.6%)	16(100%)	0.08
	Female	11(8.3%)	8(17.4%)	0(0%)	
Time of recurrence	Weeks,n		27.29±97.7	12.29±14.11	0.295
Neutrophil count (×10 <sup>3</sup> /mm <sup>3</sup> )		7.07±3.05	8.56±4.56	9.17±5.97	0.387
Lymphocyte count(×10 <sup>3</sup> /mm <sup>3</sup> )		2.22±0.79	1.75±0.64	1.72±1.86	0.003b
Platelet count (×10 <sup>3</sup> /mm <sup>3</sup> )		240.2±77.92	290.5±320.8	305.9±148.7	0.132
PLR		124.6±73.6	186.9±208.4	255.3±176.7	<0.001a
NLR		4.03±4.49	5.65±4.04	7.11±5.43	<0.001a
MPV (fL)		9.2±1.3	8.86±1.18	8.7±1.31	0.146

Post hoc Tukey test;

<sup>a</sup>Significant differences between all 3 groups

<sup>b</sup>Nonsignificant difference between group 2 and 3

(PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio MPV: mean platelet volume; SD: standard deviation; IQR: Interquartile Range; NS: nonsignificant)

more), laboratory results were noted. Primary attack of PSP was defined as first episode of PSP. Secondary or tertiary attacks of PSP were defined as recurrence of pneumothorax either in the ipsilateral or in the contralateral side, occurring after initial treatment of first episode of PSP in two years of follow up. In our study, three groups were formed according to the episodes of

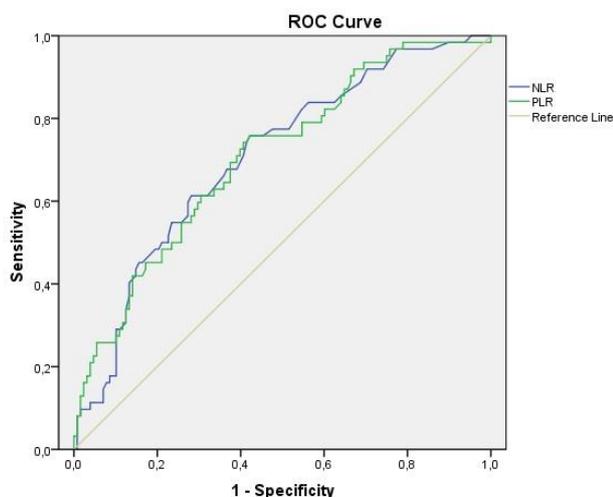
pneumothorax; patients with the first PSP episode were in Group 1; patients with the second episode of PSP were in Group 2; patients with three or more episodes of PSP were in Group 3.

Treatment modalities applied for the first episode of patients with PSP were bed rest with supplemental oxygen, needle aspiration, tube thoracostomy and video-assisted thoracoscopic

**Table 3.** Prediction performance of the NLR and PLR for recurrence

	NLR (Cut-off: 3.5)	PLR (Cut-off: 144.5)
Sensitivity (%)	87	75
Specificity(%)	63	66
Positive likelihood ratio	2.35	2.21
Negative likelihood ratio	0.21	0.38
Positive Predictive Value (%)	70.16	68.81
Negative Predictive Value (%)	82.89	72.53
Accuracy(%)	75	70.5

(NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio)



**Fig. 1.** Area under the receiver operating characteristic curve (AUC) for NLR and PLR in predicting recurrence of PSP. PLR had the highest AUC in predicting mortality (AUC=0.771) followed by NLR (AUC=0.728). (NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio)

surgery (VATS). Asymptomatic patients with small pneumothorax were observed and treated with supplemental oxygen and in two patients simple aspiration was required. On the other hand, symptomatic patients were treated by tube thoracostomy. VATS was performed in patients with 4-5 days of prolonged air leakage, tension pneumothorax, hemopneumothorax or high-risk occupation.

The laboratory results of first venous blood samples, which were obtained on admission to the ED, were evaluated. Our samples were analyzed within 1 hour of collection in ED. Reference values were  $2.1\text{--}6.1 \times 10^3/\text{mm}^3$  for neutrophils,  $1.3\text{--}3.5 \times 10^3/\text{mm}^3$  for lymphocytes,  $156\text{--}373 \times 10^3/\text{mm}^3$  for platelets. The definition of NLR: the ratio of neutrophil count to lymphocyte count and the definition of PLR: the ratio of platelet count to lymphocyte count.

**Statistical Analysis:** Analysis was performed using SPSS 18.0 and parameters were expressed as mean and standard deviation. Variables were compared according to their suitability using independent t-test or chi-square test. ANOVA was used for multiple group comparisons. To predict the recurrence of PSP, the ROC curve analysis was performed to identify the optimal value of NLR and PLR, and a P value less than 0.05 was considered statistically significant.

## Results

In our study, a total of 194 patients with the diagnosis of PSP were included. There were 175(90.2%) male and 19(9.8%) female. Their age mean of  $30.82 \pm 8.75$  (range 18 to 59). There were 62 (32%) had recurrence PSP and patients 132 (68%) had no recurrence. The comparison of demographic and clinical characteristics of patients is shown in Table 1. There were statistically significant differences between patients with and without recurrences and lymphocyte count were significantly lower and PLR, NLR were significantly higher in patients with recurrences.

When we compared the groups; lower mean of lymphocyte count and higher mean of NLR and PLR were found in patients of PSP who developed two or more recurrences (Group 3) when compared with one (Group 2) or no recurrence (Group 1). The mean age of patients and neutrophil, platelet, MPV counts were not statistically significant ( $p > 0.05$ ) (Table 2).

The cut off NLR and PLR were obtained regarding the differences between the groups predict recurrences. For the NLR, the AUC was estimated as 72.8% (sensitivity 87%; specificity 63%) (Table 3, Figure 1). For the PLR, the AUC was measured as 77.1% (sensitivity 75%; specificity 66%) (Table 3, Figure 1).

In the univariate analysis demonstrated that NLR (OR: 2.93; 95% CI: 1.29-6.68;  $p=0.01$ ), PLR (OR: 1.86; 95% CI: 0.84-4.09;  $p<0.001$ ) were independently associated with recurrences.

## Discussion

Studies have shown that high NLR levels are associated with autoimmune diseases (11–15). Platelets play an active role in inflammation and have regulatory roles in the immune system, therefore, PLR has been proposed to determine inflammation. Similar to NLR, PLR has been used for the differential diagnosis of various diseases such as cancer, metabolic syndrome and inflammatory diseases (16–18). PSP is more common in men and its annual incidence was reported 22.7 per 100,000. The actual incidence in Turkey is not known. As in our study, PSP is commonly seen in men (1,19,20).

Although some of the studies have reported right lung predominance for spontaneous pneumothorax, others found no difference between right and left lungs (21). This study had a minor dominance in the right lung.

When a patient has a SP, the risk of recurrence rates after the first part of PSP varies between 16% to 52% (the average 30%). Most recurrences occur within 2 years (3,4). After the first recurrence, the next recurrence incidence increases gradually 62 to 83 (22). In our study first recurrent rate is 23.8% and similar to the literature.

NLR is a basic and efficient biomarker that has been studied thoroughly in the literature in order to predict multiple diseases, including inflammatory conditions, such as neoplastic diseases (23,24). But there is also no data about serum biomarkers for predict of recurrent PSP. According to the results, NLR were a useful indicator for predict of recurrent PSP. In this study, we found that the sensitivity, specificity, NPV and PPV of NLR were 87; 63; 82.89 and 70.16%, respectively, with a cut-off value of 3.5.

PLR has been identified and used for a sign of severe inflammation. In previous studies PLR were also investigated in various diseases such as myocardial infarction, end-stage renal diseases, malignancies (25-27). The lack of literature on the relationship between serum biomarkers and recurrence of PSP did not allow us to accurately compare our results, so that in our discussion we mainly presented our results about this topic. According to the results of our study, PLR were a

useful indicator for predict recurrence of PSP and the sensitivity, specificity, NPV and PPV of PLR count were 75, 66, 72.53 and 68.81%, respectively, with a cut-off value of 144.5.

The limitations of study: (1) this is a retrospective study over a long period of time during which the management for PSP has evolved (2). Small sample size and the results are only from one center. Nevertheless, our study revealed the potential relationship recurrence of PSP with NLR and PLR. (3) it was also thought that evaluating blood values of these patients separately for pre-treatment and post-treatment might give more beneficial results in terms of inflammatory process (4). Prospective studies with larger study populations are needed.

As a result, NLR and PLR values in cases of recurrent PSP were higher than the cases with non-recurrent PSP. NLR and PLR is a predictor of the development of recurrence in subjects with PSP.

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