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TANAFFOS

Prognostic Value of Platelet to Lymphocyte Ratio (PLR) and Neutrophil to Lymphocyte Ratio (NLR) in Patients with Pulmonary Hypertension

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Background: Pulmonary hypertension (PH) is a hemodynamic and pathophysiological disease defined by a mean pulmonary artery pressure of ≥20 mm Hg. Pulmonary hypertension severity and prognosis play an essential role in the management of these patients. The aim of this study was to evaluate the prognostic value of platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) in patients with PH referred to Masih Daneshvari Hospital, Tehran, Iran.

Materials and Methods: A total of 61 patients with PH referred to Masih Daneshvari Hospital in Tehran were enrolled. Patients' information such as age, sex, type of PH, echocardiographic data, and blood cell count, including platelet, lymphocyte, and neutrophil count, hemoglobin, and RDW, were collected in each follow-up.

Results: Out of 61 patients with PH, 27 (44.3%) were male, and 34 (55.7%) were female. The mean age of the patients was 43.19 ± 2.25 years. Our results showed that during hospitalization, PLR decreased from 13.2 to 9.7, and NLR also decreased from 4.49 to 3.08. Neither PLR nor NLR was associated with gender. However, both PLR and NLR showed a significant difference between deceased vs. discharged patients and were significantly lower in the patients who died.

Conclusion: Both PLR and NLR decreased during hospitalization in patients with PH, and this decrease was greater in the patients who died, suggesting these indicators as potential prognostic markers for the disease.

Keywords Pulmonary hypertension; Platelet to lymphocyte ratio; Neutrophil to lymphocyte ratio; Prognosis

INTRODUCTION

Pulmonary hypertension (PH) is characterized by increased blood pressure in pulmonary arteries (1) and presents with dyspnea, syncope, fatigue, chest pain, swelling of the legs, and tachycardia (2). Patients with PH have difficulties in doing exercise. The onset of the disease usually follows a gradual course, and its cause often remains unknown (1). Risk factors include a positive familial history, hypercoagulation in the lungs, HIV/AIDS, sickle cell disease, cocaine use, chronic obstructive pulmonary disease (COPD), sleep apnea, living in altitude, and mitral valve disorders. The underlying mechanism generally involves the inflammation of pulmonary arteries (3, 4).

The incidence of PAH is about five cases in 1 million people annually, with a frequency of about 25 cases in 1 million people (5).

In addition, PH can be seen in the context of a variety of other diseases. In systemic scleroderma, PH prevalence has been estimated at 8 to 12%. Although it is rarely seen in patients with rheumatoid arthritis, 4 to 14% of those with systemic lupus erythematosus suffer from PH. In patients with sickle cell disease, the prevalence has been reported 20 to 40%. Overall, up to 4% of people with pulmonary embolism develop chronic thromboembolic disease, including PH, and a small ratio of patients with COPD develops PH. Moreover, right heart failure due to PH is a well-characterized complication in individuals with obesity-disability syndrome (6, 7).

The prevalence and incidence of pulmonary arterial hypertension (PAH) in North America is unknown. Studies from Scotland and France indicated a prevalence of 2.5-7.1 cases per million, reaching 52.5 per million in adults (8). Approximately half of the patients diagnosed with PAH suffer from either idiopathic (IPAH) or heritable (HPAH) form of the disease. The most common cause of PAH includes connective tissue disease (particularly scleroderma), followed by congenital heart disease. In a study in France population and compared to reports from the United States, PAH was more commonly associated with anorexic drug use (9.5% vs. 3.3%) and HIV infection (6.2% vs. 1-2.3%). In China, congenital heart disease was the most common cause of PAH, a finding that differed from that of other countries (9, 10). Recent evidence shows that PAH epidemiology has changed significantly over the past three decades. In recent registries from Western countries, the mean age of patients with IPAH or HPAH has been between 45 and 65 years (11, 12). The female-to-male ratio in individuals with PAH has been reported 1.7, indicating a higher prevalence in women.

Recently, two hematologic indices, platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR), have been reported to be valuable prognostic indicators in a variety of diseases. However, the ability of these markers to predict the outcome of patients with PH is not known (13, 14). Therefore, in the present study, we aimed to investigate the prognostic value of PLR and NLR in patients with PH referred to Masih Daneshvari Hospital, Tehran, Iran.

MATERIALS AND METHODS

Study Population

This was a descriptive-analytical study performed to determine the prognostic value of PLR and NLR in patients with PH referred to Masih Daneshvari Hospital, Tehran, Iran, during 2019-2020. Patients who were diagnosed with PH and had a MAP score of greater than 20 according to the definition of the World Health Organization (WHO) were included. The patients were divided into five groups (according to WHO criteria) as follows: only PAH, PH associated with left heart failure, PH due to chronic lung disease and hypoxia, chronic thromboembolic pulmonary hypertension (CTEPH), and PH due to unclear or multifactorial etiologies.

Sample Size Calculation

The minimum sample size required in this study was decided based on the following statistical calculations. Based on a study by Hampole et al. (15), in which RDW was used to predict the survival of patients with PH, the mean baseline RDW values were 16.3±2.4% in the patients who survived and 17.8±2.6% in those who died. Considering the highest standard deviation related to the deceased patients, the study power of 80% (type 1 error=20%), and the significance level of 95%, the statistical sample size was calculated n=25 using the following formula:

$$n = \frac{\sigma^2 Z^2_{1-\frac{\alpha}{2}}}{d^2}$$

Where "α" represents type 1 error at the level of 0.05; "Z" is the study power (80%); "d" shows the degree of freedom, and "σ" is the standard deviation.

Data Collection

After recruiting the patients, the required data, including age, sex, type of PH, echocardiographic findings, and blood cell count (platelet, lymphocyte, and neutrophil count, hemoglobin, pro-BNP, and RDW) were recorded in each follow-up. Also, baseline (i.e., admission) and final (i.e., before discharge or death) values of PLR, NLR, and RDW were recorded for each patient. PLR and NLR were evaluated 3 times because we wanted to evaluate the mean value of these methods. We could not make a mean by performing these tests fewer than 3 times and more than 3 times was not cost-benefit for us and our patients.

The data about the New York Heart Association's (NYHA) functional classification (16) were extracted.

A 6-minute walk test was performed for all patients at the end of the study to evaluate the capacity of patients for exercise. This test was performed based on ATS (American Thoracic Society) protocol (17).

The patients were under evaluation from one year to five years from diagnosis. During this time, the number and causes of hospitalizations were recorded for each patient in a checklist. The cause of death was also recorded for deceased patients.

All patients were followed up in our center every one or two months, routinely. If we needed an evaluation, it was requested for them.

Inclusion and Exclusion Criteria

Inclusion criteria were a MAP score above 20, and consent to participate in the study. The exclusion criterion was the diagnosis of concomitant pneumonia or sepsis.

Statistical Analysis

Data were analyzed in SPSS software version 20. Data distribution was evaluated by the Kolmogorov-Smirnov test, and based on data distribution (i.e., normal or non-normal), either independent samples student t-test or Mann-Whitney U test was used, respectively. Also, Receiver Operating Curve (ROC) was plotted for each variable to determine its diagnostic sensitivity and specificity.

RESULTS

In the present study, 61 patients were enrolled, of whom 27 (44.3%) were male, and 34 (55.7%) were female. The mean age of the patients was 43.19 ± 2.25 years. The youngest patient was a 10-year-old boy, and the oldest was a 78-year-old woman.

Regarding the type of PH, the highest frequency was related to IPAH. Regarding different NYHA functional classes, 11 (18%), 28 (46%), 14 (23%), and 8 (13%) patients belonged to classes I, II, III, and IV, respectively (Table 1). The patients were hospitalized an average of 6.19 times. At the end of the study, 14 patients (23%) were alive, and 47 patients (77%) died. The mean survival time (from diagnosis to death) in deceased patients was 4.26 ± 1.77 months.

Table 1. The Underlying Causes of Pulmonary Hypertension in the Studied Population

Causes	Number	Percentage
Bronchiectasis	5	8
Left heart involvement	1	1.6
IPAH	42	68.8
CTPEH	10	16.4
Other causes	3	5.2
Total	61	100

IPAH: Idiopathic pulmonary artery hypertension, CTPEH: Chronic thromboembolic pulmonary hypertension

Laboratory Findings

Patients' hematological parameters at admission, during hospitalization, and at discharge (for those who survived) have been mentioned in Table 2.

A 6-minute walk test (6MWT) was performed for all patients and total mean of 6MWT was 323.6 meters. Mean pulmonary artery pressure (mPAP) in the patients was obtained 76.17 cm/H_2O. Level of pro-brain natriuretic peptide (Pro-BNP) was 271.5 mg/Dl. Table 3 shows the values of pro-BNP, 6MWT, and mPAP in different groups of patients with PH.

Table 2. Patients Hematological Parameters

Indices	Admission	During hospitalization	Discharge (for live patients)
Platelet count (×103/µL)	239	218	173
Neutrophil %	79	63	61
Lymphocyte %	24	26	30
RDW	19	18	18

Table 3. The Results of Pro-brain Natriuretic Peptide, the 6-minute Walk Test, and Pulmonary Artery Pressure in Patients with Pulmonary Hypertension Due to Various Reasons

Causes	Pro-brain natriuretic peptide (mg/dL, Mean)	6-minute walk test (meters, Mean)	Pulmonary artery pressure (cm/H2O, Mean)
Bronchiectasis (N=5)	295.3	311.2	75.19
Left heart involvement (N=1)	222.4	309.3	74.21
IPAH (N=42)	283.5	349.9	76.92
CTPEH (N=10)	265.4	314.4	78.12
Other causes (N=3)	291.3	333.2	76.45
Total (N=61)	271.5	323.6	76.17

PLR and NLR

The values of PLR and NLR in the patients on three occasions (i.e., admission, during hospitalization, and discharge) have been presented in Table 4 and Figure 1.

Table 4. Platelet to Lymphocyte Ratio and Neutrophil to Lymphocyte Ratio in Patients with Pulmonary Hypertension

Indices	Admission	During hospitalization	Discharge (for live patients)
PLR (Mean ± SD)	13.2 ± 2.1	9.71 ± 1.1	11.41 ± 3.65
NLR (Mean ± SD)	4.49 ± 0.85	3.08 ± 0.33	7.93 ± 4.2

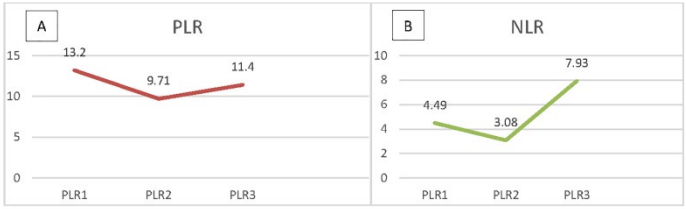

Figure 1. The trends of platelet to lymphocyte ratio (A) and neutrophil to lymphocyte ratio (B) in patients with pulmonary hypertension

Neither PLR nor NLR was associated with gender. However, both PLR and NLR showed a significant difference in disease outcome. In this regard, PLR at admission (i.e., PLR1) and NLR during hospitalization (i.e., NLR2) were significantly higher in discharged patients (Table 5).

Table 5. The Association of Platelet to Lymphocyte Ratio and Neutrophil to Lymphocyte Ratio with Gender and Disease Outcome in Patients with Pulmonary Hypertension

Variables		NLR		PLR	
		NLR 1 (admission)	NLR 2 (hospitalization)	PLR 1 (admission)	PLR 2 (hospitalization)
Gender	Male	5.11	3.39	12.68	9.76
	Female	3.77	2.70	13.84	9.66
	P value	0.19	0.46	0.68	0.05
Disease outcome	Deceased	4.17	2.8	11.6	9.5
	Discharged	6.3	4.4	20.2	11.4
	P value	0.46	0.001	0.006	0.37

DISCUSSION

Pulmonary hypertension is a hemodynamic and pathophysiological disease defined as an increase in mean pulmonary artery pressure ≥25 mmHg at rest (18). Evaluation of PH severity and prognosis plays an essential role in the management of these patients, especially in the choice of therapeutic course. In patients with untreated IPAH, mean survival has been reported as six months for WHO functional class IV, 2.5 years for class III, and six years for functional class I or II (19). Pulmonary hypertension etiology also affects the prognosis of the disease. Patients with congenital heart disease have a better prognosis, and survival has been significantly higher in those with Eisenmenger syndrome than in IPAH patients treated with routine protocols or epoprostenol (20).

The predictors of mortality and prognosis in patients with PAH are not completely known. A recent meta-analysis (21) reported that there are about 107 factors linked to mortality in patients with PH; however, there are

conflicting reports about the prognostic value of many of them. The first ten prognostic factors included functional class, heart rate, 6MWT, pericardial effusion, mPAP, right atrial pressure, cardiac index, stroke volume index, PVR, and mixed venous oxygen pressure and saturation. Likewise, a study highlighted the role of echocardiographic and hemodynamic parameters in predicting adverse outcomes in patients with either idiopathic or secondary PH. Consistently, we here identified a significant relationship between these parameters and mortality, the need for hospitalization, hospitalization duration, the need for inotropic support and mechanical ventilation, and the incidence of non-cardiac events (19).

The pathogenic mechanism of PAH (WHO functional class I) in part is related to the narrow blood vessels supplying the lungs, which prevents blood from returning to the heart by being pumped from the lungs (i.e., water recirculation is harder in narrow vs. wide tubes). Over time, damaged pulmonary blood vessels become harder and thicker (i.e., fibrosis). The mechanisms underlying vascular narrowing include vasoconstriction, thrombosis, and vascular regeneration (vascular epithelial cells' hyperproliferation, fibrosis, and reduced apoptosis/programmed cell death secondary to inflammation, dysregulated metabolism, and abnormal production of growth factors) (22). Vascular regeneration gradually causes the affected blood vessels to become harder and thicker, which further increases pulmonary blood pressure, disrupts blood flow in the lungs, and boosts the workload of the right heart (23). The right ventricle is generally a part of a low-pressure system, which faces low pressures (compared to the high systolic pressures endured by the left ventricle) and cannot endure high pressures. In addition, although ventricular adaptation mechanisms (e.g., hypertrophy and increased myocardial contraction) initially help maintain stroke volume, they are usually insufficient. Therefore, the right ventricular muscle receives inadequate oxygen, leading to right heart failure. A fall in pulmonary blood supply causes the left heart to receive less blood (that may even be less than normal saturated with oxygen), making it difficult for the left side to effectively pump blood to warrant adequate oxygenation of body organs, especially during exercise (24).

Recently, PLR and NLR have been proposed as prognostic factors in various diseases, including heart failure, as reported by Durmus et al. (25) and Balci et al. (26). Considering the importance of inflammation in the initiation and progression of PH, it seems that such parameters can be regarded as cheap and widely accessible prognostic factors. The aim of this study was to determine the prognostic value of PLR and NLR in patients with PH.

In a study on 56 patients with heart failure and 40 individuals as the control group, Durmus et al. assessed the role of NLR and PLR in predicting the rate of readmission, cerebrovascular events, and mortality and reported that both NLR and PLR were higher in patients with heart failure compared to age- and sex-matched controls. They also suggested that NLR was a better prognostic factor in this condition (25).

In the present study, we enrolled 61 patients with PH, of whom 27 (44.3%) and 34 (55.7%) were males and females, respectively. This finding was consistent with previous studies, showing a higher prevalence of PH in women compared to men. The mean age of our patients was 43.19 ± 2.25 years, which showed a slightly lower mean age compared to the studies conducted in Western countries, reporting an age of onset between 45 and 65 years. This suggests that the mean age of PH presentation in Iran is lower than the global mean, which is a concerning issue.

Our findings showed that in our patients, platelet count decreased during hospitalization (i.e., from admission to discharge). The pathophysiology of PAH is based on three basic mechanisms: vascular thrombotic lesions, stenosis, and vascular regeneration. Platelets, through the accumulation, production, storage, and release of several mediators, can be involved in these pathogenic mechanisms. The role of platelets is particularly prominent

in secondary PAH due to inflammatory and infectious diseases, hemoglobinopathies, essential thrombocythemia, medications, thromboembolism, and cardiac surgery. In fact, most antihypertensive drugs administered for PH are supposed to at least in part suppress platelet function (27). Pulmonary vascular thrombotic lesions and exacerbated vascular regeneration and repair are the main vascular pathologic events in PH, and platelets can contribute to these mechanisms through different pathways. Platelet functional abnormalities, endothelial dysfunction, and dysregulated fibrinolysis/antithrombotic events have been reported in idiopathic PH; however, it is not yet clear whether these abnormalities play key roles in the development of PH or themselves are events secondary to the disease.

One of the main objectives of the present study was to determine the prognostic value of PLR and NLR in PH patients. This index was calculated based on the results of cell blood count on two occasions (i.e., admission and during hospitalization) for all patients and an additional occasion (i.e., discharge) for those who survived. The results showed that during hospitalization, PLR decreased from 13.2 to 9.7, which could be attributed to a decrease in platelet count after the administration of antihypertensive drugs. Also, NLR decreased during hospitalization from 4.49 to 3.08, which can be justified by a decrease in neutrophil count following the control of inflammation by anti-inflammatory drugs.

Neither PLR nor NLR was significantly associated with gender; however, there was a significant difference between discharged and deceased patients in PLR1 (i.e., admission) and NLR2 (i.e., during hospitalization), and both indices were significantly lower in the deceased. In a study by Durmus et al. on 56 patients with heart failure and 40 control subjects, PLR and NLR were calculated for all the participants, showing higher NLR and PLR in patients with heart failure than in age- and sex-matched controls, highlighting these parameters as potential prognostic factors (25).

CONCLUSION

Based on our study, PLR decreased from 13.2 to 9.7 and NLR from 4.49 to 3.08 during hospitalization of patients with pulmonary hypertension. Gender was not associated with PLR and NLR. Disease outcome had a significant association with PLR at admission and NLR during hospitalization. Our results showed that PLR1 and NLR2 were significantly lower in patients who died. So, these indicators may be useful as prognostic factors in patients with PH.

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