Novel predictor of pulmonary arterial hypertension
Monocyte to HDL cholesterol ratio

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Abstract

Monocyte to HDL cholesterol ratio (MHR), lymphocyte to monocyte ratio (LMR), and neutrophil to lymphocyte ratio (NLR) have been proposed as novel systemic inflammatory markers. The aim of this study was to explore the association between MHR, LMR and NLR with pulmonary arterial hypertension (PAH). The study is a single-center, retrospective Cross-sectional study. The study group consisted of 73 patients with PAH and the control group 77 participants without cardiac pathology as determined by echocardiography. On admission, blood sampling to calculate MHR, LMR, NLR, and detailed clinical data were obtained. According to the Pearson test, systolic pulmonary artery pressure (PAP) value Higher MHR, NLR and lower LMR that indicates an enhanced inflammation were significantly increased in patients with PAH when compared with controls. Compared to many other inflammatory markers, these markers are widely available.

positively correlated with the MHR and NLR (r:.35, $P < .001$ and r:.33, $P < .001$, respectively), but negatively correlated with LMR (r: −.26, $P = .001$). After multivariate logistic regression analysis, MHR, LMR, and NLR remained as significant predictors of PAH (OR: 2.651, 95% CI: 1.227–5.755, $P = .007$; OR: 0.647, 95% CI:0.450–0.931, $P = .005$; OR: 1.350, 95% CI: 1.054–1.650 $P = .030$, respectively).

Abbreviations: MHR = monocyte to HDL cholesterol ratio,LMR = lymphocyte to monocyte ratio,NLR = neutrophil to lymphocyte ratio,PAH = pulmonary arterial hypertension,OR = odds ratio,CI = confidence interval.

Keywords: pulmonary arterial hypertension, monocyte to HDL cholesterol ratio, lymphocyte to monocyte ratio

1. Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by increased pulmonary vascular resistance (PVR), right ventricular (RV) failure and eventually death if left untreated.[1] Undue vasoconstriction, thrombosis and unusual vascular remodeling result in increased PVR and RV pressure load.[2] PAH has many etiologies; it can be idiopathic, familial, drug and toxin induced or associated with connective tissue diseases, congenital heart diseases, portal hypertension and HIV infection.[3] Previously vasoconstriction was regarded as the main causative of PAH, but it is now considered to be a vasculopathy which excessive vascular cell growth and chronic inflammation play major role causing these structural changes.[2] Local inflammation may induce neutrophils and platelets which may participate in plugging of the microvasculature and further vasoconstriction. The resulting vascular remodeling and proliferation cause a chronic elevation in PVR, RV failure and eventually death.[4] Although considerable advances occurred in the understanding of PAH pathophysiology and several PAH-specific therapies developed, the desired results are still not achieved.

Endothelin receptor antagonists, phosphodiesterase 5 inhibitors, prostacyclin analogues and guanylate cyclase activator are used as PAH-specific therapy. Balloon atrial septostomy and heart-lung transplantation are other treatment options in patients whom medical treatment has been inadequate to relieve symptoms. Understanding the pathophysiology of the disease is very important in terms of guiding new treatment options.

The neutrophil to lymphocyte ratio (NLR) is accepted as a new indicator of systemic inflammation. NLR, which can be obtained from the white blood cell count (WBC), is shown to have predictive and prognostic value in several cardiovascular diseases.[5,6] In these studies, NLR has been associated with coronary artery disease, rheumatic mitral valve stenosis, non-valvular atrial fibrillation, ventricular premature contraction, ST-segment elevation myocardial infarction (STEMI) and pre-eclampsia development.

The lymphocyte to monocyte ratio (LMR) has been proposed as a novel systemic inflammatory marker. LMR is calculated as lymphocyte count divided by monocyte count. It has been widely studied in cancer, infectious, autoimmune and

cardiovascular diseases.[7,8] Derivatives of peripheral blood cells, such as NLR and LMR, can be used as markers of systemic inflammation. Lymphocytes, neutrophils, and monocytes play a pivotal role in the inflammatory cascade. Lymphocytes and monocytes are important cells for innate and acquired immunity, and the LMR shows the balance of immune disorder.[9] Therefore, the increased monocyte number may be caused by immune disease progression. The decreased lymphocyte number in blood may be associated with their migration to the inflammation area.[10] So, the combination of elevated monocyte and decreased lymphocyte counts into a single combined inflammatory marker could provide more contribution than either parameter alone, which can show inflammation severity better.

Monocytes and differentiated macrophages are main components of innate immunity and can adjust inflammatory cytokine secretion and tissue remodeling, which results in chronic inflammation and cardiovascular events.[11] Monocytes have an essential role in every stage of atherosclerosis from foam cell formation to plaque rupture.[12] Circulating monocytes migrate to the subendothelial space by interacting with proinflammatory cytokines secreted by damaged or activated endothelial cells. High-density lipoprotein (HDL) cholesterol have antiinflammatory, antioxidant and antithrombotic effects.[13] HDL prevents monocyte recruitment into the arterial wall via inhibiting adhesion of monocytes to endothelium.[14] Besides, increased HDL particles suppress the proliferation of hematopoietic stem cells and inhibit monocyte production and mobilization.[15] Thus, HDL acts as a reversal factor for proinflammatory and pro-oxidant effects of the monocytes. The monocyte to HDL cholesterol ratio

MHR has emerged as a novel prognostic marker that has been reported to be related to cardiovascular outcomes in various cardiovascular diseases.[16]

There is no cure for pulmonary hypertension, but early diagnosis and treatment can help to reduce patients' symptoms, also can improve quality of life and may slow the progression of pulmonary hypertension.

Because of the need for continuous treatment and high mortality rate in patients with PAH, early recognition of these patients is very important. Inflammation has long been known to play a role in the pathogenesis of PAH. So, in this study, we aimed to investigate the effectiveness of MHR, LMR, and NLR, which are new inflammatory markers that have been shown to be effective in various diseases and inexpensive screening tool, in the diagnosis of PAH.

2. Methods

2.1. Study population

The present study is a single-center, cross-sectional study. We retrospectively collected data of patients with PAH between January 2016 and December 2019. The study group consisted of 73 patients with PAH and the control group consisted of 77 participants. PAH patients aged 18 years and over who underwent physical examination, echocardiography and diagnostic cardiac catheterization were included in the study group. All PAH patients were class-1 PAH according to 2015 pulmonary hypertension European Society of Cardiology (ESC) guideline and on pulmonary-specific therapy.[17] PAH was defined as mean pulmonary arterial pressure (mPAP) ≥25 mm Hg at rest detected by cardiac catheterization.[3] The control group was obtained by retrospectively collecting the records of patients aged 18 and over who presented to the cardiology outpatient clinic with atypical cardiac complaints. Echocardiographic examination of the participants included in this group were normal.

Exclusion criteria for both groups were cardiogenic shock, valvular heart diseases, hematological diseases, malignancy, severe liver or renal disease, systemic inflammatory diseases

or active infection, hypothyroidism, hyperthyroidism, current therapy with corticosteroids and nonsteroidal antiinflammatory drugs and autoimmune diseases. In addition, patients with PAH associated with connective tissue diseases were not included in the patient group of the study because they were associated with systemic inflammatory disease.

The study was approved by the local ethics committee (Dicle University Medical Faculty Ethics Committee for Non interventional Studies, No: 2020-107).

2.2. Biochemical and hematological parameters

Venous blood samples were drawn in the morning from the antecubital vein after a fasting period of 12 hours. Venous blood samples were collected in a tube containing K3 EDTA for measurement of hematologic indices in all patients. The blood collection process that we defined in the method section is the process that is routinely applied in our unit. Patients who we were sure that the process worked in this way were included in the study. Total and differential leukocyte counts were measured by an automated hematology analyzer (Abbott Cell- Dyn 3700; Abbott Laboratory, Abbott Park, Illinois). Absolute cell counts were used in the analyses. Standard methods were used for routine biochemical tests including glucose, urea, creatinine and lipid profile. The NLR was calculated by dividing neutrophil count to lymphocyte count. LMR was calculated by dividing lymphocyte count to monocyte count. MHR was calculated by division of monocyte count to HDL (mg/dl).

2.3. Statistical analysis

Data were analyzed with the SPSS software version 18.0 for Windows (SPSS Inc, Chicago, IL). The Kolmogorov-Smirnov test was used to verify the normality of the distribution of continuous variables. Continuous variables were defined as means ± standard deviation (SD) or median (interquartile range) values; categorical variables were given as percentages. The independent sample t-test or the Mann–Whitney U test was used for continuous variables and the Chi-square test for categorical variables. The Pearson test was used for correlation analysis. Statistical significance was defined as $P < .05$. Multivariate logistic regression analysis was performed to assess the independent predictors of PAH. In addition to MHR, LMR, and NLR, general factors affecting cardiovascular mortality were included in the univariate analysis. All variables found significant in the univariate analysis were included in the logistic regression model, and the results are shown as odds ratio (OR) with 95% confidence intervals (CIs). Receiver-operating characteristic (ROC) curve analysis was used to determine the optimum cut off levels of the MHR and LMR in association with PAH.

3. Results

This study consisted of 73 patients with PAH and 77 subjects in the control group. The mean age (± SD) of the patients with PAH was 49.52 (±17.03) years, and the mean age (± SD) of the control group was 48.95 (±16.16) years ($P = .833$). The baseline demographic, biochemical, hematological, and echocardiographic data of the patients according to the groups are presented in Table 1. There was no significant difference between 2 groups in terms of gender and comorbidities.

Hematological and biochemical parameters were similar in both groups, except for lymphocyte count, monocyte count and HDL cholesterol level. The patients with PAH were more likely to have higher monocyte counts, systolic pulmonary arterial pressure (PAP), right atrial diameters, right ventricular diameters, NLR, and MHR. But the patients with PAH were more likely to have lower lymphocyte counts, HDL levels, and LMR.

Table 1

Clinical, hematologic, and demographic characteristics of study groups.

Variables	Controls (n = 77)	PAH (n = 73)	P
Age, yr	48.95 ± 16.16	49.52 ± 17.03	0.833
Female gender, n (%)	48 (62.3)	52 (71.2)	0.299
Hypertension, n (%)	18 (23.4)	19 (26)	0.850
Diabetes mellitus, n (%)	11 (14.3)	12 (16.4)	0.822
Coronary artery disease, n (%)	15 (19.5)	15 (20.8)	0.841
Hemoglobin, g/dL	13.30 ± 1.88	13.21 ± 2.31	0.779
White blood cell count, $10^3/\mu L$	8.01 ± 1.76	7.82 ± 2.22	0.551
Neutrophil count, $10^3/\mu L$	4.80 ± 1.60	4.98 ± 1.77	0.518
Lymphocyte count, $10^3/\mu L$	2.32 ± 0.64	1.98 ± 0.78	**0.004**
Monocyte count, $10^3/\mu L$	0.58 ± 0.15	0.68 ± 0.26	**0.003**
Platelet count, $10^3/\mu L$	252.28 ± 53.03	248.27 ± 70.34	0.695
Creatinine, mg/dL	0.71 ± 0.19	0.75 ± 0.21	0.171
Glucose, mg/dL	106.79 ± 28.03	108.38 ± 35.78	0.762
HDL, mg/dL	48.26 ± 12.46	43.34 ± 11.46	**0.013**
Left ventricular EF, %	59.32 ± 5.43	58.18 ± 6.13	0.227
PAP systolic, mm Hg	23 (20–30)	65 (49.5–85)	**<0.001**
Right atrial diameter, mm	36.28 ± 0.50	45.97 ± 0.89	**<0.001**
Right ventricular diameter, mm	32.42 ± 0.49	42.79 ± 0.86	**<0.001**
NLR	1.99 (1.63–2.68)	2.42 (1.88–3.25)	**0.012**
PLR	109.13 (95.37–141.62)	120.88 (85.54–182.56)	0.394
MHR	1.31 (0.91–1.55)	1.49 (1.15–2.10)	**0.003**
LMR	4.24 ± 1.32	3.13 ± 1.30	**<0.001**

Data are presented as number (percentage) and mean ± standard deviation or median (interquartile range) values.

EF = ejection fraction, HDL = high-density lipoprotein, LMR = lymphocyte to monocyte ratio, MHR = monocyte to HDL cholesterol ratio, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio.

After multivariate logistic regression analysis, MHR, LMR, and NLR remained significant predictors of PAH (OR: 2.651, 95% CI: 1.227–5.755, P = .007; OR: 0.647, 95% CI:0.450–0.931, P = .005; OR: 1.350, 95% CI: 1.054–1.650, P = .030, respectively, Table 2). In ROC analysis, LMR < 3.50 had 74% sensitivity and 63% specificity (ROC area under curve: 0.725, 95% CI: 0.645–0.806, P < .001; Fig.1A), MHR > 1.32 had 60% sensitivity and 55% specificity in accurately predicting PAH diagnosis (ROC area under curve: 0.639, 95% CI: 0.550–0.728, P = .003; Fig. 1B) and NLR > 2.07 had 60% sensitivity and 56% specificity in accurately predicting PAH diagnosis

(ROC area under curve: 0.618, 95% CI: 0.528–0.708, P = .012; Fig. 1C).

We analyzed the correlation between systolic PAP with MHR, LMR and NLR by Pearson test. According to the Pearson test, systolic PAP value positively correlated with the MHR and NLR (r:.35, P < .001 and r:.33, P < .001, respectively), whereas it negatively correlated with LMR (r: −.26, P = .001) (Table 3).

4. Discussion

The aim of our study was to investigate the value of hematological inflammatory markers as an additional diagnostic tool in patients with PAH. We have found that MHR levels were significantly higher in the PAH group when compared to the control group. To the best of our knowledge, this is the first study to determine the association between MHR and PAH. Also, LMR levels were found to be statistically lower in the PAH group when compared to the control group. Again, as far as we know, this is the first study to show the relationship between LMR and PAH. In addition, we have found that high NLR was independently associated with PAH. Moreover, in the correlation analysis we showed that MHR and NLR are positively correlated with systolic PAP and LMR is negatively correlated with systolic PAP. We also demonstrated that higher MHR and NLR and lower LMR are significant independent predictors of high systolic PAP.

PAH, characterized by pulmonary vascular remodeling which mainly affects the small and medium pulmonary arteries ultimately leading to increased PAP and PVR, eventuate in progressive right heart failure and decreased functional capacity.[18] In previous studies, it was found that interleukin (IL)-1, IL-6, tumor necrosis factor alpha (TNF-α) and monocyte chemoattractant protein-1 levels were increased in patients with idiopathic PAH.[19,20] In another study, serum levels of IL-2, IL-4, IL-8, IL-10, and IL-12p70 were found to be significantly higher than the control group. It has also been shown that levels of these interleukins are predictors of survival in this cohort.[21] As these studies have shown, inflammation has long been recognized to play a key pathogenic role in PAH.[22]

In a meta-analysis made by Lu et al, low LMR was associated with poor survival rates in patients with ovarian cancer.[23] In a meta-analysis performed in patients with Hodgkin lymphoma, low LMR at diagnosis was found to be associated with poor overall survival and poor progression-free survival.[24]

In a recent study involving 221 patients with stable coronary artery disease and a control group of 72 patients with normal coronary arteries, LMR was significantly lower in the group with coronary artery disease compared to the control group.[5] Also in this study, lower LMR was detected in patients with high

Table 2

Significant predictors of PAH in univariable and multiple logistic regression analyses.

|	Univariate analysis OR (95% CI) P		Multiple logistic regression analysis OR (95% CI) P	
Age	1.002 (0.983–1.022)	0.832	1.004 (0.979–1.030)	0.740
Male gender	1.496 (0.754–2.968)	0.249	2.315 (1.040–5.152)	0.066
HT	1.153 (0.549–2.424)	0.707	1.055 (0.387–2.873)	0.916
DM	1.180 (0.485–2.872)	0.715	1.061 (0.338–3.325)	0.919
CAD	1.088 (0.488–2.423)	0.837	1.084 (0.371–3.166)	0.883
MHR	3.020 (1.615–5.647)	**0.001**	2.651 (1.227–5.755)	**0.007**
LMR	0.526 (0.395–0.698)	**<0.001**	0.647 (0.450–0.931)	**0.005**
NLR	1.426 (1.109–1.835)	**0.006**	1.350 (1.054–1.650)	**0.030**
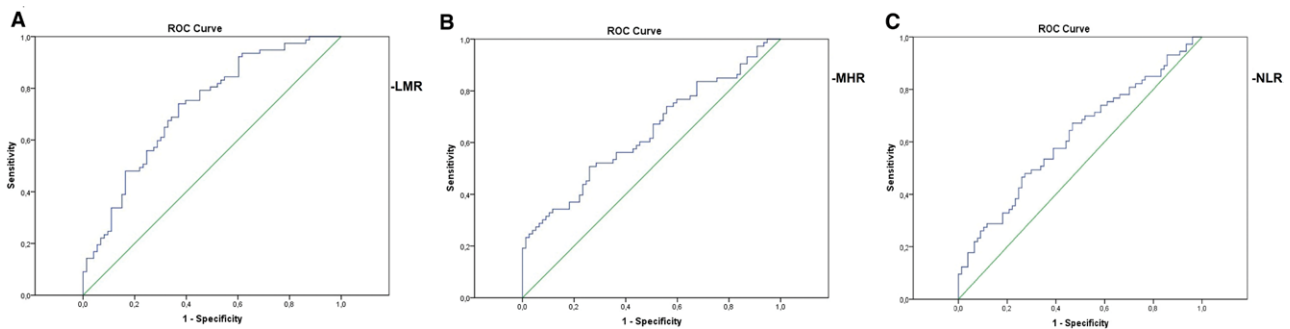
Figure 1. Receiver-operating characteristics curve of lymphocyte to monocyteratio (A), Monocyte to HDL cholesterol ratio (B), and neutrophil to lymphocyte ratio (C) for predicting pulmonary arterial hypertension.

Table 3

Pearson correlation analysis of systolic PAP is associated with variables.

Variables	Pearson correlation analysis	
	r value	*P* value
MHR	0.35	<0.001
NLR	0.33	<0.001
LMR	−0.26	0.001

LMR = lymphocyte to monocyte ratio, MHR = monocyte to HDL cholesterol ratio, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio.

syntax score, a scoring system used to rate the anatomical severity of coronary artery disease, (>32) and speculated as LMR was an independent predictor of high syntax score in patients with stable angina pectoris. In our study, lymphocyte count and LMR level were found to be statistically significantly lower in patients with PAH compared to the control group. So, our results are in line with the literature.

In a study conducted in STEMI patients, the admission MHR was independently correlated with in-hospital major adverse cardiovascular events (MACEs) and stent thrombosis as well as mortality.[26] Canpolat et al[27] reported that MHR was an independent predictor of atrial fibrillation recurrence after cryo-balloon-based catheter ablation. In another study conducted by Dogan et al, it was found that MHR were significantly higher in patients with cardiac syndrome X who had normal angiogram but had ischemia in exercise test or myocardial perfusion scintigraphy compared to the control group.[28] In our study, the monocyte count and MHR value were found to be higher in patients with PAH when compared with the control group. However, HDL was found to be significantly lower in patients with PAH compared to the control group. The results which we have found, support the presence of inflammation in the pathogenesis of PAH, in accordance with the literature.

As an indicator of systemic inflammation, NLR shows the balance between neutrophil and lymphocyte levels in circulation.[29] In a study conducted by Kaya et al high NLR were found as an independent predictor of atherosclerosis.[5] In another study NLR levels were significantly higher in patients with rheumatic mitral stenosis and correlated with the severity of the disease.[30] In a study involving a small number of patients with PAH, NLR was found to be significantly higher in patients with PAH than in the control group.[4] In another study investigating the prognostic value of NLR in patients with PAH, NLR was correlated with important prognostic markers in PAH such as New York Heart Association functional capacity (NYHA FC), brain natriuretic peptide (BNP) and tricuspid annular plane systolic excursion (TAPSE).[31] Similarly to the

previous 2 studies, in our study, the NLR was found to be statistically significantly higher in the PAH group compared to the control group. In these 3 studies conducted in the PAH group, the higher NLR compared to the control groups is promising for the reproducibility of this marker.

To the best of our knowledge there is no other study showing the association of PAH with MHR, LMR. So, this is the first study that investigates the relationship between PAH and MHR, LMR which is the strength of our study.

5. Study limitations

This study has several limitations. The study demonstrated a single-center experience and it conducted on a small patient group due to the rarity of the disease. It doesn't provide information regarding the cause or effect relationship between MHR, LMR, NLR, and PAH. Usage of a single blood sample does not anticipate the persistence of these markers over time. We did not evaluate inflammatory markers such as C-reactive protein (CRP), interleukins and TNF-α and we also did not analyze the correlation of these parameters with MHR, LMR, and NLR. In patients with longer disease duration, inflammatory biomarkers may not be sensitive in detecting inflammation. Therefore, the difference in duration of illness in the patient population of our study is another limitation of our study. In addition, the effect of treatment with PAH-specific agents on hematolic parameters and markers derived from these parameters is not exactly known.

6. Conclusions

We demonstrated that MHR and NLR were significantly increased in patients with PAH compared with controls. But LMR is significantly decreased in patients with PAH compared with controls. In addition, systolic PAP and LMR correlation was found to be weaker than systolic PAP and MHR and NLR correlations. This suggests that MHR and NLR may be better than LMR in predicting PAH. Although these data may support previous trials reporting that hematological parameters may be involved directly in the pathogenesis of PAH, this needs to be confirmed in larger randomized studies. Early diagnosis is very important as patients with PAH need continuous care and aggressive treatments to reduce the high risk and mortality rate. We believe that these inexpensive and noninvasive hematological markers may be helpful in the diagnosis of patients with PAH.

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