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Association of the Monocyte to HDL-cholesterol Ratio with Idiopathic Pulmonary Arterial Hypertension and Disease Severity

Monosit HDL-kolesterol Oranının İdiyopatik Pulmoner Arteriyel Hipertansiyon ve Hastalık Şiddeti ile İlişkisi

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ABSTRACT

Objective: Idiopathic pulmonary arterial hypertension (IPAH) is a disease characterized by abnormal vascular changes in the pulmonary arteries, leading to elevated pulmonary artery pressure. In this retrospective study, we investigated the role of monocyte to high-density lipoprotein-cholesterol ratio in predicting IPAH and disease severity.

Methods: Thirty-three patients with IPAH were compared with the 25 healthy controls according to their demographic characteristics, laboratory and echocardiographic parameters. Baseline and year 1 data of patients with pulmonary hypertension who received drug-therapy were also compared. The predictive value of the monocyte to high-density lipoprotein-cholesterol ratio for IPAH and its change with disease severity were examined.

Results: The monocyte to high-density lipoprotein-cholesterol ratio was significantly higher in patients with IPAH (p=0.009). In receiver operating characteristic curve analysis, monocyte to high-density lipoprotein-cholesterol ratio >11.05% predicted idiopathic pulmonary hypertension. In drug-treated patients, monocyte to high-density lipoprotein-cholesterol ratio in year 1 was significantly lower than the baseline (p<0.001). Among the patients with pulmonary hypertension, the group in which risk stratification improved from high risk to low showed the greatest reduction in monocyte to high-density lipoprotein-cholesterol ratio. A significant positive correlation was found between the percentage reduction in monocyte to high-density lipoprotein-cholesterol ratio and the percentage reduction in pulmonary vascular resistance from baseline to year 1 (p=0.003).

Conclusion: Monocyte to high-density lipoprotein-cholesterol ratio may be a promising parameter in the assessment and management of patients with IPAH.

Keywords: HDL-C, monocyte, pulmonary hypertension

ÖZ

Amaç: İdiyopatik pulmoner arteriyel hipertansiyon (İPAH), pulmoner arterlerde pulmoner arter basıncının yükselmesine neden olan anormal vasküler değişikliklerle karakterize bir hastalıktır. Bu retrospektif çalışmada, İPAH ve hastalık şiddetini öngörmede monosit yüksek yoğunluklu lipoprotein-kolesterol oranının rolünü araştırmayı amaçladık.

Yöntem: İPAH'li 33 hasta, 25 sağlıklı kontrol grubu ile demografik özellikleri, laboratuvar ve ekokardiyografik parametreleri açısından karşılaştırıldı. İlaç tedavisi alan PAH'li hastaların başlangıç ve 1. yıl verileri de karşılaştırıldı. İPAH için monosit yüksek yoğunluklu lipoprotein-kolesterol oranının prediktif değeri ve hastalık şiddeti ile değişimi incelendi.

Bulgular: İPAH'li grupta monosit yüksek yoğunluklu lipoprotein-kolesterol oranı anlamlı olarak daha yüksektir (p=0,009). Monosit yüksek yoğunluklu lipoprotein-kolesterol oranının %11,05 seviyesi üzerindeki değerlerde İPAH öngördürücü olarak tespit edilmiştir. İlaçla tedavi edilen hastalarda, 1. yılda monosit yüksek yoğunluklu lipoprotein-kolesterol oranı bazale göre anlamlı ölçüde düşüktür (p<0,001).

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İPAH'li hastalar arasında, risk sınıflandırmasının yüksek riskten düşüğe doğru iyileştiği grup, monosit yüksek yoğunluklu lipoprotein-kolesterol oranında en büyük azalmayı göstermiştir. Monosit yüksek yoğunluklu lipoprotein-kolesterol oranındaki azalma yüzdesi ile başlangıçtan 1. yıla kadar pulmoner vasküler dirençteki azalma yüzdesi arasında anlamlı bir pozitif korelasyon bulunmuştur (p=0,003).

Sonuç: Monosit yüksek yoğunluklu lipoprotein-kolesterol oranı, İPAH'li hastaların değerlendirilmesinde ve yönetiminde umut verici bir parametre olabilir.

Anahtar Kelimeler: HDL-K, monosit, pulmoner hipertansiyon

INTRODUCTION

Pulmonary arterial hypertension (PAH) is an uncommon and progressive disorder marked by pulmonary arteriole remodeling, which leads to proliferation, dysfunction and inflammation in endothelial and smooth muscle cells. Due to this process, pulmonary arterial pressure and pulmonary vascular resistance (PVR) rise.[1] If left untreated, it can cause right ventricular failure, resulting in eventual death.[1] According to studies, adults with PAH have an incidence of 2.5 to 7.1 cases per million and prevalence of 5-52 instances per million, with around half of the patients having idiopathic PAH (IPAH) or hereditary PAH.[2] The contribution of oxidative stress and inflammation to the development and progression of PAH has been demonstrated in many observational and experimental studies.[3-9]

Leukocytes and their subtypes are biomarkers of inflammation, and their activation releases inflammatory cytokines and an increase in inflammatory markers. It has been shown that monocytes play a key role in inflammatory and vasculogenetic processes and initiation of vascular endothelial dysfunction in many diseases.[10-13] However, high-density lipoprotein-cholesterol (HDL-C) has been found to play a role in reversing the processes implicated in the pathogenesis of PAH by reducing endothelial dysfunction[14,15], prolonging the half-life of prostacyclin[16], increasing nitric oxide production and stimulating nitric oxide biological activity[17,18], with regard to its antioxidant and anti-inflammatory properties.[19,20]

In support of all data mentioned above, the predictive and prognostic usefulness of the monocyte to HDL-C ratio (MHR), which is a simple and easily accessible marker of inflammation, has recently been demonstrated in different diseases.[21-25]

To our knowledge, MHR has not been studied in patients with IPAH, which is a rare disease and a subclass of PAH with no detectable cause. The goal of this study was to determine the role of MHR in IPAH and its predictive role in disease severity through treatment response.

METHODS

In this retrospective and two center studies, 38 subjects 18 years of age and older with IPAH diagnosed between January 2017 and January 2021 according to the updated clinical classification of pulmonary hypertension (PH)[26] on regular follow-up were recruited from the cardiology department. However, two subjects were ineligible due to subsequent identification of an associated cause of their PAH and three subjects were ineligible due to the lack of certain variables required for the assessment. Finally, 33 eligible IPAH patients were compared with 25 healthy controls who were age, gender, and body mass index (BMI) matched. Demographic characteristics, laboratory and echocardiography-derived parameters, and cardiac catheterization data of all patients were retrospectively evaluated from the hospital database. IPAH has been defined by the presence of PAH due to an unknown mechanism having a resting mean pulmonary artery pressure of ≥25 mmHg and normal pulmonary artery wedge pressure of ≤15 mmHg in diagnostic right heart catheterization, in addition to elevated PVR of ≥3 wood units.[27]

Patients having any other PH cause, including such left heart disease, lung disease and/or hypoxia, pulmonary artery obstructions, unclear and/or multifactorial processes, were excluded from the study. Patients with coronary and peripheral artery disease, cerebrovascular disease, renal or hepatic dysfunction, systemic inflammatory disease, acute inflammatory conditions, unstable coronary syndromes, history of malignancy, recent operation (<3 months) and trauma were also excluded from the study. Additionally, patients with smoking habits and patients under statin treatment were excluded from the study.

After 12 h of fasting, blood samples were obtained from the antecubital vein in the morning. Routine hematological and biochemical parameters including NT-pro brain natriuretic peptide (BNP) were performed. An automated hematology analyzer was used to get both the total and differential leukocyte counts (Beckman Coulter Ireland Inc, Mervue, Galway, Ireland). The results are based on absolute cell numbers. An AU 5800 chemistry analyzer was used for biochemical analysis (Beckman Coulter- Brea, California, United States). Serum lipid levels, blood urine nitrate and creatinine levels were measured using standard methods, and eGFR was calculated. Monocyte count divided by HDL-C was used to determine serum MHR.

All of the IPAH patients were under the targeted drug therapy, and they were receiving endothelin receptor

antagonists, phosphodiesterase-5 enzyme inhibitors, prostacyclin analogs, or a combination of these drug classes. They underwent clinical assessments, echocardiographic evaluation and 6-minute walking test (6MWT) at baseline and at three months of follow-up. The World Health Organization's (WHO) functional classification was used to determine the functional capacity (FC). Control right and left heart catheterizations were applied to IPAH patients during their first year follow-up. The risk assessment was performed in accordance with a simplified and practical version of the European Society of Cardiology (ESC) / European Respiratory Society (ERS) PH 2015 risk stratification strategy. This strategy included six variables to classify patients as having a "Low risk", a "Intermediate risk", or a "High risk" as per their estimated one-year mortality rate.[27] These six variables include clinical (WHO FC), exercise-related (6MWD), biochemical (plasma levels of NT-proBNP) and hemodynamic (CI, RAP, SvO_2) indicators, all of which have predictive values used and verified in recent investigations.

MHR was compared between the control and IPAH groups. Among the IPAH patients, changes from the baseline to the first year in MHR and PVR were evaluated based on risk stratification groups.

Calculated using the G power 3.1 tool with an alpha level of 0.05, a power of 0.80, and an effect size of 0.2, the minimum number of samples that needed to be included in each group was 20.

Ethical approval was obtained from the Ethics Committee of İzmir Tepecik Training and Research Hospital, in Turkey (protocol no: 2022/03-10, date 15.03.2022).

Statistical Analysis

Statistical Package for the Social Sciences software version 26 was used for statistical analyzes (IBM Corp., 2017). Since the number of populations per group in the study represented a relatively small sample size, it was deemed appropriate to use nonparametric tests. For categorical data comparisons, the chi-square testing was performed. Numbers and percentages were used to represent categorical data. Descriptive analyses were presented using means and standard deviations, and using medians. Mann-Whitney U test for nonparametric measurements was performed to compare parameters between groups. To compare how variables changed over time, the Wilcoxon signed-rank test was used. The Spearman correlation test was used to determine the correlation coefficients and their significance. The best cut-off value of MHR to predict the existence of IPAH was determined using receiver operating characteristic (ROC) curve analysis. A 5% type-1 error level was used to infer statistical significance.

RESULTS

Table 1 shows the baseline characteristics of the study population. While 22 of 33 participants were female (66.7%) in the IPAH group and 14 of 25 participants were female (56%) in the control group, there were no statistically significant differences in gender between the two groups (x^2=0.309, p=0.578). The mean age and BMI of the two study populations were similar (61.27±10.94 vs. 57.04±7.66, p=0.058, and 25.59±3.5 vs. 25.36 ± 2.39, p=0.485) for patients with IPAH and control groups, respectively. Although the LVEF (55.09±9.94 vs. 61.2±2.74, p<0.001) of the IPAH group was significantly lower than the control group, respectively, all obtained LVEF values were preserved. According to the blood cell counts, monocyte values (0.62±0.25 vs. 0.48±0.13, p=0.016) were significantly higher in the IPAH group than the control group, and HDL-C values (45.26±10.97 vs. 49.96±5.56, p=0.013) were significantly lower in the IPAH group than the control group, respectively. When groups were compared according to the MHR value, the MHR of the IPAH group was found to be significantly higher than that of the control group (14.02±5.26 vs. 10.44±2.59, p=0.009), respectively. In ROC curve analysis, MHR>11.05% predicted IPAH with sensitivity of 69.7% and a specificity of 76.7% (area under the curve=0.702; 95% CI=0.566-0.838, p=0.004) (Figure 1). A comparison of IPAH patients' baseline and the first year clinical, echocardiographic, laboratory and hemodynamic parameters is shown in Table 2. At the time of diagnosis, while 19 (57.6%) of the 33 IPAH patients were at the intermediate risk group, 14 (42.4%) of the 33 IPAH patients were at the high-risk group. At the time of year 1, after drug therapy, while 22 (66.7%) of 33 IPAH patients were at low-risk, 8 (24.2%) of 33 IPAH patients were at the intermediate risk group, and 3 (9.1%) of the 33 IPAH patients were at the high-risk group. In drug-treated IPAH patients, was found that MHR values (11.33±4.44 vs. 14.02±5.26, p<0.001) in year 1 was significantly lower than the baseline values, respectively. In targeted drug-treated patients with IPAH, the percentage change in MHR from baseline to year 1 varied with the change in patient's risk stratification groups (Table 3). The group in which risk stratification improved from high risk to low showed the greatest reduction in MHR, and the group in which risk stratification worsened from intermediate risk to high showed an increase in MHR. A significant positive correlation was also found between the percentage reduction in MHR from baseline to year 1 and the percentage reduction in PVR from baseline to year 1 (r=0.504, p=0.003).

DISCUSSION

In the present study, MHR, a simple indicator of inflammation and endothelial dysfunction, was shown to be significantly higher in IPAH patients compared to

Table 1. Baseline characteristics and laboratory parameters of the groups					
	IPAH group (n=33)		Control group (n=25)		p
	Median	Mean±SD or n (%)	Median	Mean±SD or n (%)	
Age, years	64	61.27±10.94	57	57.04±7.66	**0.058**
Gender, female (n)		22 (66.7%)		14 (56%)	**0.578**
BMI, kg/m^2	25.26	25.59±3.5	24.97	25.36±2.39	**0.485**
WBC, ×10^3/µl	7.42	7.3±1.41	6.60	6.61±1.34	**0.079**
Lymphocytes, ×10^3/µl	1.69	1.78±0.69	2.05	2.09±0.61	**0.062**
Neutrophil, ×10^3/µl	4.90	4.81±1.33	3.80	3.94±1.03	**0.014***
Monocyte, ×10^3/µl	0.60	0.62±0.25	0.50	0.48±0.13	**0.016***
Hb, gr/dL	13.20	13.29±1.73	13.70	14.03±1.2	**0.036***
Htc, %	40.90	41.02±5.59	40.60	41.36±2.9	**0.470**
T. chol, mg/dL	195.00	198±36.75	211	210±32.45	**0.321**
TRG, mg/dL	140.00	139.01±50.84	123.00	146.96±72.67	**0.643**
LDL, mg/dL	127.00	125.44±34.02	144.00	142.96±34.47	**0.053**
HDL, mg/dL	42.30	45.26±10.97	47.00	49.96±5.56	**0.013***
MHR	13.35	14.02±5.26	10.00	10.44±2.59	**0.009***
BUN mg/dL	36.00	37.94±12.24	26.00	29.08±8.62	**0.003***
Cre, mg/dL	0.78	0.8±0.19	0.79	0.84±0.18	**0.524**
LVEF, %	55.00	55.09±9.94	60.00	61.2±2.74	**0.000***
GFR, mL/min/1.73 m^2	88.05	84.75±17.08	85.52	83.59±13.83	**0.577**

*Statistically significant.

IPAH: Idiopathic pulmonary arterial hypertension, BMI: Body mass index, WBC: White blood cell, Hb: Hemoglobin, Htc: Hematocrit, TRG: Trigliseride, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, MHR: Monocyte to HDL-C ratio, BUN: Blood urea nitrogen, GFR: Glomerular filtration rate, SD: Standard deviation, LVEF: Left ventricular ejection fraction, Cre: Creatinine, T. chol: Total cholesterol

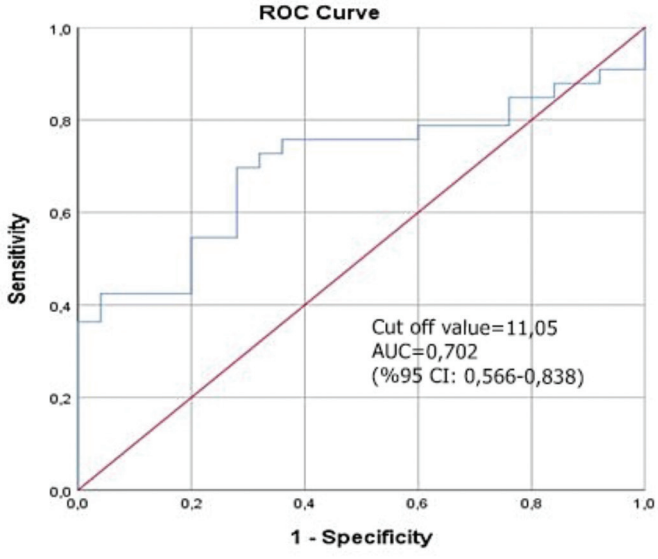

Figure 1. Receiver-operating characteristic curve analysis for monocyte count to high density lipoprotein-cholesterol ratio predicting IPAH

ROC: Receiver-operating characteristic, AUC: Area under the curve, CI: Confidence interval

controls, and that the percentage change in MHR was consistent with the drug response and correlated with disease severity in targeted drug-treated patients with IPAH. According to our knowledge, this study is first to evaluate the MHR in patients diagnosed with IPAH.

Inflammation and endothelial disunction are important processes in the development of IPAH.[27] While inflammation has a prognostic value in IPAH[28,29], it is unclear whether inflammation is the reason or the result of pulmonary vascular remodeling. Regardless of the answer, it is inevitable that any predictor of the disease itself and its course will contribute to the management of this highly fatal disease.

Among the measured variables, monocyte, HDL-C and MHR values were observed to be significantly different between the two groups, and while monocyte and MHR values were found to be higher, HDL-C was found to be lower in patients with IPAH. The low HDL-C concentration has been shown to be directly related to vascular endothelial dysfunction, which is one of the fundamental mechanisms that contribute to PH.[30] In a study by Heresi et al.[31], low HDL-C was found to play a crucial role in the onset

Table 2. The comparison of IPAH patients' baseline and year 1 clinical, echocardiographic, laboratory and hemodynamic parameters

	Baseline		Year 1		p
	Median	Mean±SD or n (%)	Median	Mean±SD or n (%)	
Hb, gr/dL	13.20	13.29±1.73	13.70	13.5±1.72	**0.893**
Htc, %	40.90	41.02±5.59	42.70	40.31±8.86	**0.979**
WBC, $\times10^3$/µl	7.42	7.3±1.41	6.92	6.89±1.75	**0.195**
Lymphocytes, $\times10^3$/µl	1.69	1.78±0.69	1.54	1.68±0.65	**0.491**
Neutrophil, $\times10^3$/µl	4.90	4.81±1.33	4.68	4.61±1.71	**0.464**
Monocyte, $\times10^3$/µl	0.60	0.62±0.25	0.50	0.51±0.16	**0.002***
HDL-C, mg/dL	42.30	45.26±10.97	45.50	48.2±14.25	**0.032***
LDL-C, mg/dL	127.00	125.44±34.02	120.00	119.51±34.46	**0.228**
TRG, mg/dL	140.00	139.01±50.84	133.00	141.55±54.27	**0.802**
BUN, mg/dL	36.00	37.94±12.24	34.00	37.61±13.12	**0.963**
Cre, mg/dL	0.78	0.8±0.19	0.73	0.78±0.2	**0.557**
LVEF, %	55.00	55.09±9.94	55.00	56.7±3.22	**0.587**
MHR	13.35	14.02±5.26	10.40	11.33±4.44	**<0.001***
sPAP, mmHg	59.00	61.97±18.78	38.00	44.52±14.85	**<0.001***
mPAP, mmHg	39.00	42.27±11.48	26.00	28.3±8.89	**<0.001***
dPAP, mmHg	24.00	25.91±7.47	19.00	19.27±5.4	**<0.001***
sAoP, mmHg	113.00	115.79±20.11	110.00	113.15±17.88	**0.113**
LVEdP, mmHg	8.00	10.3±10.17	8.00	8.09±2.14	**0.209**
PVR	6.90	8.8±4.93	4.81	5.84±3.18	**<0.001***
TRV, m/s	3.60	3.59±0.5	2.90	2.97±0.62	**<0.001***
6MWD, m	165.00	192.85±95.31	380.00	356.11±104.62	**<0.001***
RAP, mmHg	17.00	16.61±4.54	11.00	11.12±4.62	**<0.001***
CI, L/min/m^2	2.04	2.13±0.47	2.59	2.56±0.41	**<0.001***
SvO_2, %	64.67	62.9±7.74	69.50	68±5.66	**<0.001***
Nt-proBNP, ng/L	437.00	918.63±1485.52	180.67	266.99±308.08	**<0.001***
FC	3.00	2.67±0.48	2.00	1.94±0.5	**<0.001***
TAPSE, mm	18.00	16.49±4.88	24.00	22.62±6.92	**<0.001***
ESC/ERS risk stratification groups - Low risk - Intermediate risk - High risk		 19 (57.6%) 14 (42.4%)		 22 (66.7%) 8 (24.2%) 3 (9.1%)	

*Statistically significant.

IPAH: Idiopathic pulmonary arterial hypertension, WBC: White blood cell, Hb: Hemoglobin, Htc: Hematocrit, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, TRG: Trigliseride, sPAP: Systolic pulmonary artery pressure, mPAP: Mean pulmonary artery pressure, dPAP: Diastolic pulmonary artery pressure, sAoP: Systolic aortic pressure, LVEdP: Left ventricular end-diastolic pressure, PVR: Pulmonary vascular resistance, TRV: Tricuspid regurgitation velocity, 6MWD: 6 minute walking distance, RAP: Right atrial pressure, CI: Cardiac index, FC: Functional capacity, TAPSE: Tricuspid annular plane systolic excursion, SvO_2: mix venous O_2 saturation, MHR: Monocyte to HDL-C ratio

and/or progression of pulmonary arterial disease, and this association was found to be irrespective of the existence of other cardiovascular risks. These results may be primarily due to the anti-inflammatory properties of HDL-C because they observed elevated markers of inflammatory responses and endothelial activity in individuals with PAH who had low HDL-C levels. In another study by Zhao et al.[32], low levels of HDL-C were shown to be related to a shorter 6DWD, lower cardiac index, lower mixed venous oxygen saturation, and higher PVR in patients with PAH. In the two-year follow-up, HDL-C was found to be an independent predictor of event-free survival. In a recent study reported by Jonas et al.[33], HDL-C was shown to predict pulmonary artery vasoreactivity and long-term responsiveness to

Table 3. Percent change in MHR from baseline to year 1 according to change in risk stratification group of patients with IPAH					
		MHR% change baseline to year 1			
		Median	Mean±SD	F	P
Change of risk stratification groups	High to intermediate (n=5, 15.2%) (reduction)	4.98	5.31±9.5	23.43	**<0.001***
	High to low (n=9, 27.3%) (reduction)	37.64	36.51±20.49		
	Intermediate to low (n=16, 48.5%) (reduction)	18.52	18.65±12.56		
	Intermediate to high (n=3, 9.1%) (increase in)	41.94	47.96±20.19		
*Statistically significant. MHR: Monocyte to high-density lipoprotein cholesterol ratio, SD: Standart deviation, IPAH: Idiopathic pulmonary arterial hypertension					

calcium channel blocker medication. In this study, elevated concentrations of inflammatory indicators were related to reduced levels of HDL-C; therefore, it can be assumed that chronic inflammation may modulate the association between HDL-C and pulmonary artery vasoreactivity. Looking at the relationship of HDL-C with prostacyclin analogs, it has been shown that the biological and chemical half-life of prostaglandin I2 (PGI2), which is a potent vasodilator, was prolonged by HDL-C and that a decrease in PGI2 stability may lead to insufficient PGI2 activity at the site of vascular injury.[17] However, it has been shown that monocytes trigger inflammation and oxidation in various diseases by initiating vascular inflammatory responses.[34,35] In a study by Yamamoto et al.[10], cardiovascular events were observed to be considerably more common in individuals with coronary artery disease (CAD) who had high monocyte counts compared with low monocyte counts. At this point, it can be speculated that elevated monocyte counts could play a role in the development of atherosclerotic and cardiovascular events in patients with CAD. Additionally, pulmonary inflammation mediated by pulmonary perivascular macrophages originating from monocytes has been demonstrated to be an important pathogenic driver of pulmonary vascular remodeling that increases right ventricular systolic pressure.[36-39] In another study by Ataga et al.[40], it was found that the median absolute monocyte count in sickle cell disease (SCD) patients with PH was higher than in SCD patients without PH.

According to our findings, ROC curve analysis indicated MHR larger than 11.05 percent as a threshold value for predicting IPAH. A recent study pointed to pathobiological overlap in PAH and CAD and shared mechanisms between pulmonary vascular remodeling and coronary remodeling.[41] In a recent study of patients with acute ST-segment elevation myocardial infarction managed with primary PCI, MHR at admission was shown to be independently correlated with in-hospital adverse cardiovascular events, stent thrombosis, and death.[42] In this study, MHRs more than 17.1 were determined to be the threshold for mortality, whereas MHRs greater than 20.4 were shown to be the threshold for MACE. In another study, participants with mitral annulus calcification (MAC), a form of atherosclerosis, showed significantly higher MHR than controls.[25] In the same study, systolic pulmonary artery pressure was also found to be significantly higher in participants with MAC.

When the baseline and year 1 data were compared in IPAH patients receiving targeted drug therapy, monocyte, HDL-C and MHR values were found to be significantly lower in the year 1. Additionally, among the IPAH patients receiving the targeted drug therapy, MHR showed the greatest decrease in the group in which the risk stratification improved from high risk to low, and an increase in MHR was observed in the group where the risk stratification worsened from intermediate risk to high, indicating that MHR followed a course in parallel with the treatment response. However, the positive correlation between the percentage reduction in MHR from baseline to year 1 and the percent reduction in PVR from baseline to year 1 also supports this implication. In a recent study by Badagliacca et al.[43], it was reported that treatment failure would be due to insufficient reduction in PVR. We know that, the main goal of targeted drug therapy in PAH is to shift patients to lower risk status and a greater reduction in PVR, thereby allowing for improved right heart structure and function.

We realized that there were several limitations to our study. Due to the limited sample size and the fact that this was a retrospective research, we need a study with a bigger sample size and one that is prospective to validate our findings. Another limitation is that it is not evaluated whether the result would change if the MHR was calculated using data from multiple blood samples rather than from a single blood sample. Additionally, data of other inflammatory indicators such as sedimentation and high-sensitivity C-reactive protein were excluded from the study owing to a lack of data due to the retrospective design of the study. In this study, we were unable to recruit a participant group that was completely homogenous due to the variety of target drugs used by the patients. Various PH medications may can alter the inflammatory signature in different directions and influence the findings.

CONCLUSION

The trigger role of monocytes in pathogenic components in pulmonary vascular remodeling and their proinflammatory and prooxidative effects are evaluated together with the effects of HDL-C on the reduction of endothelial dysfunction and the increase of prostacyclin and nitric oxide, it seems useful to combine these two parameters as a ratio in IPAH. MHR could be a promising, inexpensive and accessible parameter in the assessment and management of IPAH patients receiving targeted drug therapy in addition to conventional parameters.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of İzmir Tepecik Training and Research Hospital, in Turkey (protocol no: 2022/03-10, date: 15.03.2022).

Informed Consent: Consent forms were not obtained from the participants because of the retrospective study design.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: H.S., Design: H.S., Data Collection or Processing: H.S., M.A., Analysis or Interpretation: H.S., M.A., Literature Search: H.S., Writing: H.S.

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