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RESEARCH

Relationship between monocyte-HDL ratio and disease process and pulmonary functions and pulmonary hypertension in stable COPD patients

Stabil KOAH'lılarda monosit-HDL oranı ile hastalık süreci ve solunum fonksiyonları arasındaki ilişki ve pulmoner hipertansiyon

Efraim Güzel[1], Burak Mete[2], Sedat Kuleci[1], Yasemin Saygıdeğer[1], Oya Baydar Toprak[1]

[1]Cukurova University, Faculty of Medicine, Department of Chest Diseases, 2Department of Public Health, Adana, Turkey

Abstract

Purpose: Inflammation is a major factor in the pathophysiology of chronic obstructive pulmonary disease (COPD), and molecules implicated in inflammation include monocytes and high-density lipoprotein-cholesterol (HDL-C). The primary goal of the study was to look at the relationship between pulmonary function and pulmonary hypertension (PH) in COPD and the monocyte to HDL ratio (MHR).

Materials and Methods: The study was conducted by acquiring retrospective data from previously recorded questionnaires and hospital databases for 239 individuals over the age of 40 with a diagnosis of COPD who admitted to the outpatient clinic. Patients whose data were missing were not included in the analysis. Two groups of patients were created: those with high MHO levels and those without. Analysis was done on the correlation between high MHO and COPD and pulmonary function tests. The presence of PH in COPD patients was analyzed in the second stage.

Results: The median age of the patients was 62.22 ± 9.37 year and 88.7% of them were male. With the exception of smoking, there was no statistically significant link between high MHR and COPD in the analyses, however there was a negative connection between post-bronchodilation (post-BD) FEV1/FVC and MHR. Additionally, the statistically significant negative association was found between the absolute monocyte value and RV/TLC. However, older age (OR=0.949, 95% CI (0.915, 0.984)), having more than three comorbidities (OR=2.174, 95% CI (1.045, 4.521)), and having a body mass index (BMI) below 25 have all been linked to an increased risk of PH in COPD patients.

Conclusion: Although the link between MHR and COPD was not conclusively established, it was linked to

Öz

Amaç: Monositler ve yüksek yoğunluklu lipoprotein-kolesterol (HDL-C) inflamasyonda görevi olan moleküllerdir ve inflamasyon kronik obstrüktif akciğer hastalığı (KOAH) patogenezinde önemli bir role sahiptir. Çalışmanın temel amacı, KOAH'ta monosit/HDL oranının (MHO) solunum fonksiyonları ve pulmoner hipertansiyon (PH) ile ilişkisini araştırmaktır.

Gereç ve Yöntem: Polikliniğe başvuran KOAH tanılı 40 yaş üstü 239 hastanın retrospektif verileri daha önce kayıt altına alınan anket formları ve hastane veri tabanından temin edilerek çalışma gerçekleştirildi. Verileri eksik hastalar çalışma dışı bırakıldı. Hastalar MHO yüksek olan ve olmayan şeklinde 2 gruba ayrıldı. MHO yüksekliğinin KOAH ve solunum fonksiyon testleri ile ilişkisi analiz edildi. İkinci aşamada KOAH'lılarda PH varlığı için analizler yapıldı.

Bulgular: Hastaların ortanca yaşı 62,22 ± 9,37 yaş ve %88,7'si erkekti. Yapılan analizlerde yüksek MHO ile KOAH arasında sigara dışında istatistiksel olarak anlamlılık bulunmamasına rağmen, bronkodilatasyon sonrası (post-BD) FEV1/FVC ile MHO arasında negatif bir korelasyon bulunmuştur. Ayrıca mutlak monosit değeri ile RV/TLC arasındaki negatif korelasyon da anlamlı bulunmuştur. Diğer yandan ileri yaşın (OR=0.949, 95% CI (0.915, 0.984)), üçten fazla komorbidite varlığının (OR=2.174, 95% CI (1.045, 4.521)) ve vücut kitle indeksi (VKİ) <25 olmasının (OR=0.419, 95% CI (0.219, 0.804)) KOAH hastalarında PH için risk faktörü olabileceği bulunmuştur.

Sonuç: Çalışmamızda MHO'nin KOAH ile ilişkisi net olarak kanıtlanamamış, ancak MHO'nin solunum fonksiyonları üzerine etkisi olabileceği bulunmuştur. Bunun yanında ileri yaş, çoklu komorbidite ve düşük vücut ağırlığının PH için önemli bir risk oluşturabileceği tespit edilmiştir. Ancak bu konuların çok merkezli daha geniş

Address for Correspondence: Efraim Guzel, Cukurova University, Faculty of Medicine, Department of Chest Diseases, Adana, Turkey E-mail: efraimguzel@gmail.com
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pulmonary functions. The study that was presented also came to the conclusion that PH may be significantly increased by advanced age, numerous comorbidities, and low body weight. These problems must be investigated and validated in larger, multicenter patient populations.
Keywords:. COPD, HDL-C, MHR, monocytes, pulmonary hypertension, pulmonary function test

hasta gruplarında çalışılması ve doğrulanması gerekmektedir.

Anahtar kelimeler: KOAH, HDL-C, MHO, monositler, pulmoner hipertansiyon, solunum fonksiyon testi

INTRODUCTION

Chronic obstructive pulmonary disease (COPD), an extremely common and heterogeneous disease that disproportionately affects poor and vulnerable people, is associated with significant morbidity, disability and mortality globally[1]. It is characterized pathologically by different degrees of persistent inflammation, modification of the small airways (bronchiolitis), and devastation of the alveolar walls (emphysema)[2]. Among the cells involved in chronic inflammation, monocytes and macrophages are active members of inflammation in systemic diseases and play a crucial role in the pathophysiology of COPD[3].

High-density lipoprotein cholesterol (HDL-C), which inhibits the migration of macrophages and promotes the efflux of cholesterol from these cells, also has an indirect role in inflammation[4]. An experimental study demonstrated that HDL-C exerts its anti-inflammatory effect on human monocytes by inhibiting CD11b activation[5]. However, HDL-C levels have also been shown to be lower in smokers and those with sedentary lifestyles[6-8]. It is thought that HDL-C levels are lower in COPD patients than in healthy people due to smoking history and sedentary lifestyle and this may have a significant effect on inflammation.

There are some studies that provide evidence that the ratio of monocyte molecules involved in inflammation and HDL-C with an anti-inflammatory role (MHR) is an indicator of inflammation[9,10]. There are many studies showing that MHR, which is thought to be associated with inflammatory systemic diseases, predicts cardiovascular disease (CVD) in various patient groups[11,12].

On the other hand, it has been proven that complications that arise during the disease process have significant effects on prognosis and increase the risk of death in COPD patients[13]. Pulmonary hypertension (PH), a common complication of COPD, is a pathophysiological disorder characterized by abnormally high pulmonary artery pressure, defined as a resting mean pulmonary artery pressure (mPAP) > 20 mmHg[14]. Literature data on the prevalence of PH in COPD patients are highly variable. A review of a meta-analysis of 38 studies showed that the prevalence of COPD-related PH varies depending on regional differences, with the highest in Africa (64%) and lowest in Europe (30.4%)[15]. In various studies, the presence of PH has been associated with decreased exercise tolerance in COPD[16] and increased rates of hospitalization for acute exacerbation of COPD[17], and negative effects such as decreased survival rate[18,19].

Although there are a limited number of studies investigating the association between MHR and COPD patients, to the best of our kwowledge, there is no study that examined the relationship between MHR and both pulmonary function and PH. In a progressive airway disease such as COPD, a biomarker is needed to predict disease progression and mortality. By examining the impact of MHR on pulmonary function, PH, and PH risk factors in individuals with stable COPD, we intended to add to the literature.

MATERIALS AND METHODS

The study is a retrospective study approved by the non-interventional ethics committee of Cukurova University Hospital (approval number 124/2022). All actions taken during the course of the study that involved human subjects were in compliance with hospital and national research committee ethical standards as well as the 1964 Helsinki declaration. Informed consent forms were also obtained from the participants along with the previous questionnaire forms.

Study design

This study included 239 patients who admitted to the chest diseases outpatient clinic of a tertiary university hospital, Cukurova University Balcalı Hospital, between April 2016 and December 2022 and were

diagnosed with COPD based on clinical findings and pulmonary function tests. The study was carried out in Cukurova University Faculty of Medicine, Balcalı Hospital, chest diseases department. This institution is a well-known tertiary health institution and carries out service, education and research activities simultaneously. Qualified personnel and research assistants within the institution take an active role in the execution of the practices in this institution and the additional supervision of the faculty members. Detailed anamnesis and physical examination findings including socio-demographic and clinical characteristics of the patients were recorded. In addition to sociodemographic data including age, gender, marital status, body mass index (BMI), comorbidities, smoking history (pack/year) and occupational history, laboratory parameters including complete blood count, renal-liver function tests, C-reactive protein (CRP) and detailed lipid profile (high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), triglyceride and total cholesterol levels) were recorded. Monocyte level was calculated by routine hemogram with Pentra 120 Retic Hematology Analyzer (ABX, France). The monocyte reference range in laboratory is 2-10%. Monocyte/HDL ratio (MHR) was calculated as the ratio of absolute monocyte level to HDL-C level in the laboratory. Based on similar studies in the literature, a mean cut-off value of 12.50 and above was accepted as high MHR[10-12].

The ultimate indicator of progressive course in COPD is mortality. Although there are conflicting data in COPD-mortality studies, it has been estimated that the overall mortality rate is around 4 percent on average[1,20,21]. According to the data of the Turkish Statistical Institute for 2022, the crude mortality rate in the general population was determined as 5.9 per thousand[22]. In order to reach the most accurate results with these findings, we had to include at least 194 patients according to the results of our power analysis with an absolute value (+/- %(d)) of 5% and a confidence interval of 95%.

Study population

COPD patients were divided into ABE groups according to the current GOLD 2023 report[23]. In this classification, group A represented patients with few symptoms (modified Medical Research Council (mMRC) 0-1 and The COPD Assessment Test (CAT) <10), while group B represented patients with excessive symptoms (mMRC≥2 and CAT≥10). Both groups were below the table, as in the previous classification (patients with no hospitalization, no exacerbation or 1 moderate exacerbation in the last 1 year). Group E, on the other hand, represented the patients who had 2 or more moderate exacerbations in the last 1 year or who had been hospitalized 1 or more times in the last 1 year, regardless of symptoms, with the combination of C and D groups[23]. The results of mMRC according to dyspnea severity, disease severity and BODE index ((B) body mass index; (O) forced expiratory volume in one second (FEV1) measurement of airflow obstruction; (D) mMRC scale measurement of dyspnea; and (E) 6-minute walk distance (6-MWD) measurement of exercise capacity) score results according to mortality expectancy were used in the study.

Patients over 40 years of age, with a history of smoking, biomass or occupational exposure for more than 10 years and a pulmonary function test FEV1/FVC ratio below 70% were considered to have COPD and included in the study.

The study excluded 48 patients with incomplete data, 14 patients with hyperlipidemia, 25 patients with structural diseases (bronchiectasis, CF, etc.), 36 patients with COPD exacerbation or acute infection in the previous month, 8 patients with hematological diseases, and 14 patients with hyperlipidemia. Thus, 137 of the 376 patients who were planned to be enrolled in the study with the diagnosis of COPD were excluded from the study and 239 patients were included in the study.

Pulmonary function tests (PFT), diffusion tests and lung volumes were performed in the PFT laboratory in accordance with the standards set in the international ATS/ERS guidelines[24], and the data were recorded on questionnaire forms and in the hospital data recording system.

Patients with pulmonary artery pressure of 25 mmHg or more on Echocardiography (ECHO) findings were considered to have PH[25]. ECHO and 6-MWD results from the hospital data recording system were used for the presence and severity of PH. We identified the deceased patients by telephone or through the inter-hospital data recording system.

Primary outcome was to document the association between MHR and pulmonary function and PH. Oth the other hand, the secondary outcome was to identify the PH risk factors in COPD.

Statistical analysis

In order to conduct statistical analyses, SPSS version 22.0 (SPSS, Inc. Chicago, Illinois) was used. Using the Kolmogorov-Smirnov test, the distributional properties of the variables were examined. The mean and standard deviation (SD) of the parametric data were reported. Parametric tests were preferred for quantitative data conforming to normal distribution, non-parametric tests were preferred for non-conforming data and categorical data. Analysis of variance (ANOVA) was used to compare multiple mean values. Chi-square tests were used to compare percentage summaries of categorical variables. To examine the relationship between MHR and COPD, the Pearson correlation coefficient was determined. To determine PH risk factors in COPD patients, multivariate regression analyses were conducted. Statistics were considered significant for P values below 0.05.

RESULTS

The median age of the 239 patients with COPD included in the study was 62.22 ± 9.37 years and 88.7% of them were male. Of the patients in the study, 89.5% were married, 59.8% were active smokers and 42.7% had low income. Among patients, 33.1% had more than three comorbidities and 36.8% had a BMI <25. According to the GOLD 2023 classification, 19.7% of patients were in Group A, 35.1% in Group B and 45.2% in Group E. PH was observed in 42.7% of the participants, while 9.6% of them has died. Analyses did not find statistical significance between high MHR and COPD patients' disease course and progression (including COPD subgroups, exacerbations, hospital readmissions, PH and mortality). The MHR elevation was statistically significant only in those with COPD who continued to smoke and were married (p=0.001, p=0.0029, respectively). Extensive information including the socio-demographic and clinical characteristics of the patients, as well as analyzing the association of these data with MHR elevation is presented in Table 1.

In the analysis concerning the effects of monocytes, HDL and MHR on PFT parameters; IC-RV-TLC-RV/TLC values for monocytes (p=0.041, p=0.007, p=0.002 and p=0.001, respectively), TLC for HDL (p=0.012) and postBD FEV1/FVC for MHR (p=0.029) were statistically significant. IC, RV, TLC parameters were positively correlated with monocyte levels, while RV/TLC parameter was negatively correlated. HDL and TLC were positively correlated, whereas MHR and postBD FEV1/FVC were negatively correlated. The relationship between PFT parameters and monocytes, HDL and MHR is shown in Table 2.

Another endpoint of our study was the presence of PH in stable COPD patients and we found the prevelance of pH in COPD was 42.7%. The COPD patients with PH were more frequently older (p=0.016), had a higher likelihood of having more than three comorbid conditions (p=0.001), and had a BMI of less than 25 (p=0.016), had more severe airway obstruction (p=0.025), had high BODE score (p=0.007), had higher risk of presence of anxiety (p=0.028) and depression (p=0.029). We also observed that mortality rates were higher in the group with PH among those with stable COPD, but this was of low statistical significance (p=0.052). The characteristics of the patients according to the presence of PH are shown in detail in table 3.

The independent variable in the logistic regression analysis to estimate the risk of pulmonary hypertension in COPD patients is pulmonary hypertension status (risk category: PH +). The independent variables included in the model were age, comorbidity, BMI, Monocyte to HDL-C ratio, anxiety and depression status. Stepwise model was used in the selection of independent variables. The model was found to be significant (omnibus test p<0.001).

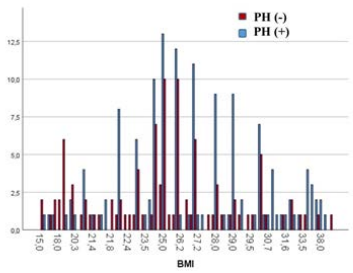

Figure 1. BMI values according to presence of Pulmonary Hypertension in COPD ptients

In our multivariate logistic regression analysis for the presence of PH in COPD patients, older age (odds ratio=0.949, 95% CI (0.915, 0.984), p=0.005), presence of more than three comorbidities (odds ratio=2.174, 95% CI (1.045, 4.521), p=0.038) and BMI <25 (odds ratio=0.419, 95% CI (0.219, 0.804), p=0.009) were found to be risk factors for PH in

stable COPD. The findings of the multivariate logistic regression analysis are shown in Table 4. In multivariate analysis, an increased risk of PH was found in low-weight individuals and the correlation between PH and BMI is shown in figure 1.

Table 1. Socio-Demographic and Clinic data of patients according to Elevated MHR

Characteristics	All patients	Group 1 (Non-elevated MHR) (n=46)	Group 2 (Elevated MHR) (n=193)	p
	Mean±S.D. or n(%)			
Age (year)	62.22 ± 9.368	65.35 ± 9.638	61.47 ± 9.511	0.526
Male	212 (88.7)	44 (20.8)	168 (79.2)	0.073
Female	27 (11.3)	2 (7.4)	25 (92.6)	
Active smoker	143 (59.8)	37 (25.9)	106 (74.1)	0.001
Ex smoker	96 (40.2)	9 (9.4)	87 (90.6)	
Maried	214 (89.5)	37 (17.3)	177 (82.7)	0.029
Single	25 (10.5)	9 (36)	16 (64)	
Low income	102 (42.7)	20 (19.6)	82 (80.4)	0.515
Medium-good income	137 (57.3)	26 (19)	111 (81)	
≤3 Comorbidity	160 (66.9)	34 (21.3)	126 (78.8)	0.173
>3 Comorbidity	79 (33.1)	12 (15.2)	67 (84.8)	
<25 BMI	88 (36.8)	16 (18.2)	72 (81.8)	0.445
≥25 BMI	151 (63.2)	30 (19.9)	121 (80.1)	
Mild Obstructive (PostFEV1 ≥80)	31 (13)	3 (9.7)	28 (90.3)	0.204
Moderate Obstructive (PostFEV1 50-80)	114 (47.7)	20 (17.5)	94 (82.5)	
Severe Obstructive (PostFEV1 30-50)	79 (33.1)	18 (22.8)	61 (77.2)	
Very Severe Obstructive (PostFEV1 30-50)	15 (6.3)	5 (33.3)	10 (66.7)	
BODE Stage 1	122 (51)	17 (13.9)	105 (86.1)	0.160
BODE Stage 2	51 (21.3)	13 (25.5)	38 (74.5)	
BODE Stage 3	46 (19.2)	10 (21.7)	36 (78.3)	
BODE Stage 4	20 (8.4)	6 (30)	14 (70)	
GOLD Group A	47 (19.7)	6 (12.8)	41 (87.2)	0.114
GOLD Group B	84 (35.1)	13 (15.5)	71 (84.5)	
GOLD Group E	108 (45.2)	27 (25)	81 (75)	
Exacerbation (-)	59 (24.7)	10 (16.9)	49 (83.1)	0.379
Exacerbation (+)	180 (75.3)	36 (20)	144 (80)	
Readmission (-)	225 (94.1)	42 (18.7)	183 (81.3)	0.272
Readmission (+)	14 (5.9)	4 (28.6)	10 (71.4)	
Anxiety (-)	197 (82.4)	35 (17.8)	162 (82.2)	0.149
Anxiety (+)	42 (17.6)	11 (26.2)	31 (73.8)	
Depression (-)	182 (76.2)	34 (18.7)	148 (81.3)	0.412
Depression (+)	57 (23.8)	12 (21.1)	45 (78.9)	
PH (-)	137 (57.3)	26 (19)	111 (81)	0.515
PH (+)	102 (42.7)	20 (19.6)	82 (80.4)	
Survivor	216 (90.4)	41 (19)	175 (81)	0.465
Died	23 (9.6)	5 (21.7)	18 (78.3)	

BMI: Body Mass Index, post-FEV1: After bronchodilation test Forced Expiratory Volume in One Second, BODE: body mass index-obstruction-dyspnea-exercise capacity, GOLD: Global Initiative for Chronic Obstructive Lung Disease, PH: Pulmonary Hypertension

Table 2. Effects of monocytes, HDL and MHR on Pulmonary Function Test Parameters

		Monocytes	HDL	MHR
PreBD-FEV1 (lt)	r	.028	.026	-.086
	p	.669	.686	.187
PostBD-FEV1 (lt)	r	-.006	-.006	-.088
	p	.923	.931	.173
PreBD-FEV1 (%)	r	.008	.024	-.100
	p	.903	.707	.124
PostBD-FEV1 (%)	r	-.002	-.015	-.060
	p	.970	.818	.358
PreBD-FVC (lt)	r	.009	-.008	-.045
	p	.885	.907	.484
PostBD-FVC (lt)	r	.025	.029	-.078
	p	.704	.652	.232
PreBD-FVC (%)	r	.020	-.030	.024
	p	.762	.642	.710
PostBD-FVC (%)	r	.081	.022	.025
	p	.214	.735	.696
PreBD-FEV1/FVC (%)	r	-.041	.000	-.094
	p	.527	.999	.149
PostBD-FEV1/FVC (%)	r	-.076	-.024	-.142
	p	.241	.717	.029
DLCO	r	.047	.027	.002
	p	.470	.682	.980
DLCO_VA	r	.047	.034	-.001
	p	.466	.602	.993
IC	r	.132	.028	.053
	p	.041	.666	.414
RV	r	.174	.125	.059
	p	.007	.054	.360
TLC	r	.203	.161	.005
	p	.002	.012	.935
RV/TLC	r	-.210	-.101	-.102
	p	.001	.118	.117

preBD: before bronchodilation test, postBD: after bronchodilation test FEV1: Forced Expiratory Volume in One Second, FVC: Forced Vital Capacity, DLCO: Transfer factor of the lung for carbon monoxide, IC: Inspiratory Capacity, RV: Residual Volume, TLC: Total Lung Capacity

Table 3. Characteristics of patients according to the presence of pulmonary hypertension

Characteristics	All patients	Non-PH	PH	p
Mean±S.D. or n(%)				
Age (year)	62.22 ± 9.368	60.37 ± 9.495	64.70 ± 9.309	0.016
Male	212 (88.7)	118 (55.7)	94 (44.3)	0.105
Female	27 (11.3)	19 (70.4)	8 (29.6)	
Active smoker	143 (59.8)	81 (56.6)	62 (43.4)	0.451
Ex smoker	96 (40.2)	56 (58.3)	40 (41.7)	
Maried	214 (89.5)	127 (59.3)	87 (40.7)	0.052
Single	25 (10.5)	10 (40)	15 (60)	
Low income	102 (42.7)	55 (53.9)	47 (46.1)	0.216
Medium-good income	137 (57.3)	82 (59.9)	55 (40.1)	
≤3 Comorbidity	160 (66.9)	105 (65.6)	55 (34.4)	<0.00
>3 Comorbidity	79 (33.1)	32 (40.5)	47 (59.5)	1
<25 BMI	88 (36.8)	42 (47.7)	46 (52.3)	0.016
≥25 BMI	151 (63.2)	95 (62.9)	56 (37.1)	
Mild Obstructive (PostFEV1 ≥80)	31 (13)	23 (74.2)	8 (25.8)	0.025
Moderate Obstructive (PostFEV1 50-80)	114 (47.7)	65 (57)	49 (43)	
Severe Obstructive (PostFEV1 30-50)	79 (33.1)	45 (57)	34 (43)	
Very Severe Obstructive (PostFEV1 30-50)	15 (6.3)	4 (26.7)	11 (73.3)	
BODE Stage 1	122 (51)	78 (63.9)	44 (36.1)	0.007
BODE Stage 2	51 (21.3)	33 (64.7)	18 (35.3)	
BODE Stage 3	46 (19.2)	18 (39.1)	28 (60.9)	
BODE Stage 4	20 (8.4)	8 (40)	12 (60)	
GOLD Group A	47 (19.7)	32 (68.1)	15 (31.9)	0.123
GOLD Group B	84 (35.1)	50 (59.5)	34 (40.5)	
GOLD Group E	108 (45.2)	55 (50.9)	53 (49.1)	
Exacerbation (-)	59 (24.7)	35 (59.3)	24 (40.7)	0.420
Exacerbation (+)	180 (75.3)	102 (56.7)	78 (43.3)	
Readmission (-)	225 (94.1)	131 (58.2)	94 (41.8)	0.197
Readmission (+)	14 (5.9)	6 (42.9)	8 (57.1)	
Anxiety (-)	197 (82.4)	119 (60.4)	78 (39.6)	0.028
Anxiety (+)	42 (17.6)	18 (42.9)	24 (57.1)	
Depression (-)	182 (76.2)	111 (61)	71 (39)	0.029
Depression (+)	57 (23.8)	26 (45.6)	31 (54.4)	
Monocyte	645.77 ± 255.235	655.11 ± 261.355	633.24 ± 247.555	0.675
HDL-C	43.67 ± 11.025	43.98 ± 9.885	43.25 ± 12.430	0.416
MHR	15.58 ± 7.151	15.51 ± 7.043	15.67 ± 7.327	0.493
Survivor	216 (90.4)	128 (59.3)	88 (40.7)	0.052
Died	23 (9.6)	9 (39.1)	14 (60.9)	

BMI: Body Mass Index, post-FEV1: After bronchodilation test Forced Expiratory Volume in One Second, BODE: body mass index-obstruction-dyspnea-exercise capacity, GOLD: Global Initiative for Chronic Obstructive Lung Disease, PH: Pulmonary Hypertension, HDL-C: high-density lipoprotein-cholesterol, MHR: Monocyte to HDL-C ratio

Table 4. Multivariate analysis of pulmonary hypertension risk factors in COPD patients

Variables	B	*p*	OR	95% CI for OR	
				Lower	Upper
Advanced Age	-0.052	**0.005**	0.949	0.915	0.984
>3 Comorbidity	0.776	**0.038**	2.174	1.045	4.521
<25 BMI	-0.869	**0.009**	0.419	0.219	0.804

BMI: Body Mass Index, MHR: Monocyte to HDL-C ratio

DISCUSSION

This study revealed that there was no significant relationship between high MHR and stable COPD patients except smoking. It also found that it could have a minor effect on pulmonary function parameters. On the other hand, mortality was higher in patients with PH, suggesting that PH may be associated with increased mortality in COPD patients.

There are very few studies in the literature examining the relationship between COPD and MHR, and to the best of our knowledge, there is a very limited data study that specifically describes the relationship between MHR and PFT parameters. In a prospective cohort study of 185 COPD and 89 non-COPD controls, they found that high MHR had a high sensitivity to predict cardiovascular disease, especially in COPD patients[26]. Many studies have examined the relationship between MHR and cardiovascular diseases. A retrospective study of 34.335 participants over the age of 20 showed a significant increase in mortality, particularly from cardiovascular disease, in people with high MHR values compared to those with low MHR values[27]. Another study of 552 heart failure patients with low ejection fraction found a positive correlation between MHR and mortality, suggesting that MHR can be used as a predictor of mortality in cardiovascular diseases[28]. In our study, we could not find a significant relationship between COPD and MHR, including pulmonary hypertension and mortality. Although the relationship of MHR, which shows the ratio of inflammatory parameters, with cardiovascular diseases has been clearly proven, its place in COPD has not yet been clarified, except for a limited number of studies. Perhaps the fact that our patients were stable in terms of COPD and their examination in this period may have prevented us from reaching more accurate results regarding MHR. Therefore, multicenter cohort studies with large participants are needed to support this situation.

There are few studies that directly examine the relationship between monocyte, HDL or MHR and PFT. Higher HDL cholesterol levels were shown to be associated with a faster decline in FEV1 and FEV1/FVC ratio, according to data from an investigation of a sizable sample of patients during a 7-year follow-up period[29]. In a different study, healthy male teenagers were shown to have lower lung function (FVC and FEV1) when their HDL cholesterol levels were higher[30]. Another study found a negative link between HDL levels and lung function, with patients with low HDL levels performing better on spirometric tests (FEV1, FVC, and FEV1/FVC ratio) than those with normal HDL levels[31]. According to a different study, the lymphocyte to HDL ratio may be the best indicator of lung function in people with COPD[32]. We also found a negative correlation between MHR and postBD FEV1/FVC in our study. We interpreted this result as "if the severity of chronic inflammation increases, it may accelerate the loss of respiratory function". We also found a negative correlation between monocyte levels and RV/TLC. The RV/TLC ratio is one of the important PFT parameters that show air trapping and the extent of emphysema. In this case, low monocyte levels may be associated with predisposition and prevalence of emphysema. In this respect, we think that these two results we have found are valuable and should be documented with prospective studies.

Despite the fact that the prevalence of PH in COPD is unclear, a research on the topic noted that it may fall within a wide range, such as 20-91%[33]. According to studies, the prevalence of PH may rise by up to 90%, particularly in people with end-stage COPD.[34,35]. In addition, the prevalence of PH was found to be around 50% in a small group of COPD patients who underwent procedures such as lung transplantation and volume reduction surgery[35-37]. In a meta-analysis of 38 studies and 16,345 participants, the combined prevalence of PH associated with COPD was 39.2%[15]. We also found the prevalence of PH to be 42.7% in our study, which was consistent with the literature data.

Many studies have shown an increased incidence and severity of PH in patients with advanced COPD [15,35,36]. It has also been shown in many studies that the presence of PH in COPD causes an increased risk of mortality[18,19,37]. A study comparing patients with moderate to severe PH in COPD with those with IPAH found that PH was more common in COPD patients of male gender and older age group[38]. Compared to patients with IPAH, patients with PH in COPD had more severe airflow obstruction, lower diffusion capacity (DLCO), lower partial pressure of oxygen (PaO_2) and higher partial pressure of carbon dioxide ($PaCO_2$)[38]. A comprehensive meta-analysis of studies published between 1980 and 2015 found that comorbidities such as DM and HT and smoking were associated with an increased risk of cardiovascular diseases, including pulmonary circulatory diseases, in

COPD patients[39]. Hawkins et al.[40] found in one study that smoking, advanced age, and markers of systemic inflammation may pose a risk for the development of PH in COPD. In addition, many studies have shown that the incidence of PH increases as the degree of airflow limitation and therefore the severity of the disease increases[37-41]. In our study, we found an increased risk of PH in patients with advanced age, multiple comorbidities, and low BMI. Although we have similar results with the literature, to the best of our knowledge, we present the first study showing that low BMI is a risk factor for PH.

Although our study has some striking results, it also has some limitations such as being single centered and based on retrospective data. At this point, pulmonary artery catheterization, the gold standard diagnostic method for the diagnosis of pulmonary hypertension, could not be performed in all patients. Because of the high expectation of pulmonary hypertension in COPD patients and the retrospective nature of the data, the diagnosis of pulmonary hypertension was based on clinical and ECHO findings. Therefore, we think that it would be good to investigate this issue in a multicenter, prospective, larger patient population in which there is a chance to perform pulmonary artery catheterization.

In conclusion, the negative connection of post-BD FEV1/FVC with MHR and again monocyte levels with RV/TLC ratio also detracts from the assumption that there is no relationship at all, even if our study was unable to draw a definitive conclusion about the relationship of MHR with COPD. The results of our study show that individuals with COPD who have low BMI, advanced age, and other comorbidities are more likely to develop PH. Therefore, it is important to maintain control of COPD, ensure more frequent hospital visits, and integrate ECHO-cardiographic tests in long-term treatment and follow-up programs, particularly for this patient group.

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