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Relationship of Clinical Parameters and Inflammation Markers with Pulmonary Hypertension in Patients with Stable Chronic Obstructive Pulmonary Disease

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ABSTRACT

Aim: Inflammation is an important mechanism in the development of pulmonary arterial hypertension (PAH) in patients with COPD. In this study, we investigated the relationship of disease severity parameters and inflammation with PAP in COPD patients.

Material and Methods: A patient group consisting of 80 patients with stable COPD including who were obtaining treatment at the outpatient clinic of Kırıkkale University Faculty of Medicine Department of Pulmonary Medicine were included in the study along with a control group of 46 individuals who were compatible with the patient group in terms of age and gender and did not have any airway obstruction. Spirometry measurements were performed (FEV1, FVC, FEV1/FVC, MEF and PEF). Systolic pulmonary artery pressure (sPAP) measurements and standard doppler echocardiography were performed at the outpatient clinic of the department of cardiology.

Results: CRP was found to be significantly higher in patients with stable COPD compared to the control group. sPAP values of COPD patients were significantly higher than those of the control group. A statistically significant positive relationship was observed between the sPAP value and age ($p = 0.006$). There was no statistically significant relationship between sPAP and MCIRS score ($p = 0.700$). A statistically weak negative relationship was observed between sPAP and FVC% ($p = 0.053$)

Conclusion: Development of PAH increases morbidity and mortality. Therefore, patients with advanced stages of COPD should be screened using echocardiography, which is an easy-to-use, fast and repeatable measurement method to check for PAH development.

Keywords: Chronic obstructive pulmonary disease; inflammation; pulmonary arterial hypertension

Stabil Kronik Obstrüktif Akciğer Hastalığı Olan Hastalarda Klinik Parametreler ve İnflamasyon Belirteçlerinin Pulmoner Hipertansiyon ile İlişkisi

ÖZ

Amaç: Kronik obstrüktif akciğer hastalığı (KOAH), tamamen geri dönüşümlü olmayan ilerleyici hava akımı kısıtlaması ile karakterizedir. Bu çalışmada, KOAH hastalarında hastalık şiddeti parametreleri ve inflamasyonun PAP ile ilişkisini araştırdık.

Gereç ve Yöntemler: Kırıkkale Üniversitesi Tıp Fakültesi Göğüs Hastalıkları Anabilim Dalı polikliniğinde tedavi görmekte olan 80 KOAH'lı hasta grubu ile uyumlu 46 kişilik kontrol grubu çalışmaya dahil edildi. Spirometri ölçümleri yapıldı (FEV1, FVC, FEV1 / FVC, MEF ve PEF). Kardiyoloji Anabilim Dalı polikliniğinde sistolik Pulmoner Arter Basıncı (sPAP) ölçümleri ve standart doppler ekokardiyografi yapıldı.

Bulgular: CRP stabil KOAH'lı hastalarda kontrol grubuna göre anlamlı olarak yüksek bulundu. KOAH hastalarının sPAP değerleri kontrol grubuna göre anlamlı derecede yüksekti. Yaş, cinsiyet ve VKİ değerleri dikkate alınarak sPAP ile Modifiye Kümülatif Hastalık Derecelendirme Ölçeği (MCIRS) puanı ile FVC% arasındaki ilişki lineer regresyon analizi ile değerlendirildi. SPAP değeri ile yaş arasında istatistiksel olarak anlamlı pozitif bir ilişki gözlendi ($p=0,006$). SPAP ve MCIRS skoru arasında istatistiksel olarak anlamlı bir ilişki yoktu ($p=0,700$). SPAP ile FVC% arasında istatistiksel olarak zayıf bir negatif ilişki gözlendi ($p=0,053$)

Sonuç: PAH gelişimi KOAH hastalarında morbidite ve mortaliteyi artırmaktadır. Bu nedenle KOAH'ın ileri evrelerinde olan hastalar, PAH gelişimini kontrol etmek için kullanımı kolay, hızlı ve tekrarlanabilir bir ölçüm yöntemi olan ekokardiyografi ile taranmalıdır.

Anahtar Kelimeler: Kronik obstrüktif akciğer hastalığı; inflamasyon; pulmoner hipertansiyon

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow restriction, which is not fully reversible. This disease is caused by an inflammatory process that occurs against harmful gases and particles, particularly cigarette smoke. This inflammation is not limited to the lungs; it also shows systemic characteristics (1). Symptoms of chronic systemic inflammation should be investigated by performing a detailed clinical and functional examination of the respiratory, cardiovascular and metabolic system in addition to COPD testing in people who have smoked for a long time, are over 40 years of age and have symptoms of COPD (2). These systemic effects are associated with impaired functional capacity, increased shortness of breath, deterioration in the quality of life and increased mortality in most patients (3).

Patients with COPD have elevated levels of inflammatory mediators in their blood (4). Inflammation of the lung periphery releases cytokines such as tumor necrosis factor-a (TNF-a), interleukin-lb (IL-lb) and interleukin-6 (IL-6) into circulation, thereby increasing acute phase proteins such as C-reactive protein and fibrinogen. Extrapulmonary effects that develop as a result of systemic inflammation in COPD are called the systemic effects of COPD (4).

Changes in pulmonary vessels in COPD are characterized by thickening of the vascular wall, which begins in the early stages of the natural development of the disease, with thickening in the intima being the first structural change to occur (5).

Inflammation is an important mechanism in the development of pulmonary arterial hypertension (PAH) in patients with COPD [With ECHO, sPAP is defined as normal PAH <35 mmHg, mild PAH of 36-50 mmHg, and severe PAH> 50 mmHg (6,7)]. Inflammation causes endothelial cell damage and dysfunction. Endothelial dysfunction causes an imbalance between vasoactive factors. The balance between vasoconstrictors, such as ET-1 and angiotensin, and vasodilators, such as NO, is disturbed (8,9). Detection of PAH, one of the most important complications of COPD, and adopting early measures are important for the prognosis of the disease. Changing the natural course of COPD in patients through a more comprehensive approach that considers comorbidities such as PAH and cor pulmonale may reduce morbidity and mortality.

In this study, we investigated the relationship of disease severity parameters and inflammation with PAP in COPD patients.

MATERIAL AND METHODS

Patient Selection

A patient group consisting of 80 patients with stable COPD including 75 men and 5 women who were obtaining treatment at the outpatient clinic of Kırıkkale University Faculty of Medicine Department of Pulmonary Medicine between July 2013 and June 2014 were included in the study along with a control group of 46 individuals including 40 men and 6 women who were compatible with the patient group in terms of age and gender and did not have any airway obstruction.

COPD was diagnosed based on GOLD criteria (10).

Exacerbation of COPD was defined as pronounced and acute events requiring changes in treatment unlike usual daily changes during the natural course of the disease, characterized by shortness of breath, cough and/or change in sputum.

Individuals who had parenchymal lung disease, pulmonary embolism, obesity or sleep-related breathing disorders, diastolic or systolic dysfunction of the left ventricle, malignancy, autoimmune diseases, endocrine diseases, severe liver or kidney disease, cardiac valve diseases, infectious diseases and those who had any lung and heart disease other than COPD in the control group were not included in the study. The patients were given an informed consent form and the written consent of the patients was obtained.

Study Protocol

Laboratory results were obtained for CRP, serum NO, NT-proBNP and ABG (pH, Pa02, PaC02, Sa0 2, HC03). Spirometry measurements were performed using Microlab 3500 spirometer in the Pulmonary function test (PFT) laboratory (Kırıkkale University Faculty of Medicine Department of Pulmonary Medicine). FEV1, FVC, FEV1/FVC, MEF and PEF were measured.

Six minute walking test (6MWT): The patient is asked to walk for 6 minutes in a 30m straight corridor and how many meters she has walked is measured.

Medical Research Council (MRC) dyspnea scale: She questions the relationship between the daily activity of the patient and shortness of breath (Picture 1). MRC dyspnea scale and 6MWT tests were performed to evaluate the individuals shortness of breath severity and exercise capacity.

BODE index: BODE index form was filled in with MRC dyspnea scale, 6MWT, FEV 1% and Body Mass Index (BMI) results (Picture 2). With the BODE index, respiratory and systemic symptoms of COPD patients are categorized better than FEV1 (11,12).

CAT score: CAT questionnaire includes 8 different items such as cough, sputum, feeling of congestion in the chest, shortness of breath when climbing or climbing stairs, difficulty in movements at home, fear of leaving home, sleep state and feeling energetic. Each item is graded from 0 to 5. They were asked to score in the patient and control groups. The scores 0-10, 11-20, 21-30 and 31-40 indicate mild, moderate, severe and very severe clinical effects, respectively (13).

Modified Cumulative Illness Rating Scale (MCIRS): The test, which is conducted for the purpose of comprehensively examining medical problems and evaluating morbidity, includes 14 anatomical organ systems, and the disease rating in each system was determined between 0-4 points according to the severity of the disease. The total score of the test ranges from 0 to 56. Higher scores in each category indicate more severe disease severity (Picture 3) (14,15).

PAP measurements and standard doppler echocardiography were performed at the outpatient clinic of the Department of Cardiology at the Faculty of Medicine of Kırıkkale University. All echocardiographic assessments and measurements were performed using the GE-Vingmed Vivid 7 system (GE-Vingmed)

echocardiography machine while the patient was lying in the left lateral decubitus position. sPAP was determined as a numerical value based on the tricuspid insufficiency flow.

Statistical Analyses

Statistical assessment was performed using the statistical analysis software, Statistical Package for Social Sciences (SPSS) 15.0 (Inc. Chicago, Illinois, USA). Mean and standard deviation values of the groups were calculated. The means of the two groups were analysed via the "Student t-test" for variables that fulfill parametric assumptions and via the "Mann–Whitney U-test" for those that do not fulfill the parametric assumptions. The means of more than two groups were compared through variance analysis. The relationship between variables was evaluated using the Pearson correlation test. Multiple logistics regression analysis was performed to investigate the determinants of the groups. The results of the analysis were expressed as mean ± standard deviation (Mean ± SD), and $p<0.05$ was considered statistically significant.

Ethics Committee Approval

This study was approved by the Ethics Committee of the Faculty of Medicine of Kırıkkale University with the decision numbered 14/07 and dated 17.07.2013

RESULTS

Statistically, age (p=0.0001) and cigarette packs/year (p=0.0001) were significantly higher in patients with COPD than individuals from the control group. There was no statistically significant difference between the two groups in terms of gender distribution (p=0.200). Statistically, BMI was significantly lower in the COPD group than in the control group (p=0.040). CRP (p=0.0001), sPAP (p=0.001) and NT-proBNP (p=0.0001) were statistically significantly higher in the COPD group than in the control group. 6MWT (p=0.0001) was statistically significantly lower in the COPD group than in the control group. There was no statistically significant difference between the groups in terms of NO (Table 1). Statistically, age (p=0.003) was significantly higher in COPD patients with PAH than in COPD patients without PAH. There was no statistically significant difference between the groups in terms of gender distribution (p=0.100), cigarette packs/year (p=0.300) and BMI (p=0.400). FVC% was statistically significantly lower in COPD patients with PAH than in COPD patients without PAH (p=0.030). There was no statistically significant difference between COPD patients with and without PAH in terms of FEV1/FVC (p=0.200), FEV 1% (p=0.500), PEF% (p=0.300), MEF% (p=0.300) and MEF% (p=0.300). Furthermore, there was no statistically significant difference between the groups in terms of CRP (p=0.300) and NO (p=0.900). Statistically, sPAP (p=0.0001), NT-proBNP (p=0.030), BODE index (p=0.020) and MRC score (p=0.020) were significantly higher in COPD patients with PAH than in COPD patients without PAH.

Table 1. Comparison of demographic and clinical characteristics of the COPD patients and the control group.

	COPD n=80 Mean±SD	Control group n=46 Mean±SD	P value
Age	63.09 ± 10.7	50.7 ±7.8	0.0001
Gender (male/female) (male%)	75/5 (93.7%)	40/6 (86.9%)	0.200
Cigarette packs/year	34.5 ± 13.9	18.1 ± 16.8	0.0001
BMI	25.4 ± 4.9	27.2 ± 4.9	0.040
CRP	5.4 ± 3.8	2.5 ± 2.0	0.0001
NT-proBNP	327 ± 363.1	45.2 ± 31.7	0.0001
sPAP	28.64 ± 9.2	22.9 ± 4.5	0.001
NO	118.5 ± 616.0	35.7 ± 25.4	0.100
6MWT	327 ± 69.4	463 ± 58.8	0.0001

Statistical Significance $p < 0.05$, SD: Standard Deviation BMI: Body Mass Index, CRP: C-Reactive Protein
NT-proBNP: N-Terminal Pro-Brain Natriuretic Peptide sPAP: Systolic Pulmonary Artery Pressure
NO: Nitric Oxide
6MWT: Six Minute Walk Test

6MWT (p=0.004) and Pa02 (p=0.010) were statistically significantly lower in COPD patients with PAH than in COPD patients without PAH. There was no statistically significant difference between the groups in terms of PaC02 (p=0.300), sat02 (p=0.100), CAT score (p=0.600) and MCIRS score (p=0.100) (Table 2).

There was a statistically significant positive relationship between sPAP and NT-proBNP (p=0.020) and age (p=0.006). No statistically significant relationship was observed between sPAP and NO (p=0.400), CRP (p=0.100), gender (p=0.100), BMI (p=0.900) and cigarette packs/year (p=0.600). There was a statistically significant positive relationship between NT-proBNP and age (p=0.030). There was no statistically significant correlation between NT-proBNP and NO (p=0.090), CRP (p =0.400), gender (p=0.800), BMI (p=0.400) and cigarette packs/year (p=0.800). No statistically significant relationship was observed between NO and sPAP (p=0.400), NT-proBNP (p=0.090), CRP (p=0.300), age

Table 2. Comparison of demographic and clinical data of COPD patients with and without PAH

	COPD patients with PAH n = 18	COPD patients without PAH n = 62	P value
	Mean ± SD	Mean ± SD	
Age	69.8 ± 8.2	61.2 ± 10.7	0.003
Gender (male/female) (male%)	14/3 (82.4%)	61/2 (96.8%)	0.100
Cigarette packs/year	31.4± 17.1	35.3 ± 13.06	0.300
BMI	24.6 ± 5.7	25.6 ± 4.7	0.400
FEVI/FVC	62.2 ± 14.8	66.3 ± 11.4	0.200
FEVI%	45.5 ±29.1	48.6 ± 16.8	0,500
FVC%	51.8 ± 17.1	61.7 ± 16.2	0.030
PEF%	42.4 ±20.1	48.1 ± 20.5	0.300
MEF%	24.8 ± 15.8	29.1 ± 17.9	0.300
CRP	6.3 ± 3.2	5.2 ± 4.0	0.300
sPAP	42.3 ± 8.0	24.7 ± 4.5	0.0001
NT-proBNP	522.4 ± 506.1	270.2 ± 291.2	0.003
BODE	2.6 ± 1.6	1.8 ± 1.2	0.020
NO	38.3 ± 22.2	138.8 ± 689.5	0.900
MRC	M ± 1.1	1.7 ± 1.1	0.030
CAT	14.4 ± 8.4	15.3 ± 8.7	0.600
6MWT	285 ± 78.4	339 ± 62.2	0.004
Pa02	57.7 ± 9.2	66.1 ± 13.2	0.010
PaC02	41.7 ± 8.2	39.5 ± 6.4	0.300
Sat 02%	85.1 ± 14.6	91.3 ± 5.9	0.100
MCIRS	17.4 ± 2.0	16.6 ± 2.3	0.100

Statistical Significance p<0.05; SD: Standard Deviation; BMI: Body Mass Index; FEVI Forced Expiratory Volume in the 1st Second; FVC: Forced Vital Capacity; PEF: Peak Expiratory Flow; MEF: Maximal Expiratory Flow (MMFR: Maximal Midexpiratory Flow Rate, FEF: Forced Expiratory Flow 25%–75%); CRP: C-Reactive Protein; NT-proBNP: N-Terminal Pro-Brain Natriuretic Peptide; sPAP: Systolic Pulmonary Artery Pressure; NO: Nitric Oxide; 6MWT: Six Minute Walk Test; CAT: COPD Assessment Test; Pa02: Arterial Blood Gas Partial Oxygen Pressure; PaC02: Arterial Blood Gas Partial Carbon Dioxide Pressure sat02%: Oxygen Saturation MCIRS: Modified Cumulative Illness Rating Scale

(p=0.500), gender (p=0.600), BMI (p=0.900) and cigarette packs/year (p=0.200) (Table 3).

Table 3. The relationship between sPAP, NT-proBNP, NO and sPAP, NT-proBNP, NO, age, gender, CRP, BMI and cigarette packs/year

	sPAP	NO	proBNP	CRP	Age	Gender	BMI	Cigarette packs/ year
	r p	r p	r p	r p	r p	r p	r p	r p
sPAP		−0.090 0.400	0.250 0.020	0.140 0.100	0.300 0.006	−0.170 0.100	−0.009 0.900	−0.040 0.600
proBNP	0.240 0.030	0.200 0.090		0.090 0.400	0.240 0.030	−0.010 0.800	−0.080 0.400	−0.020 0.800
NO	−0.090 0.400		0.200 0.090	0.100 0.300	0.070 0.500	−0.050 0.600	0.005 0.900	0.140 0.200

Statistical Significance p<0.05
CRP: C-Reactive Protein
NT-proBNP: N-Terminal Pro-Brain Natriuretic Peptide
sPAP: Systolic Pulmonary Arterial Pressure NO: Nitric Oxide BMI: Body Mass Index

A statistically significant positive correlation existed between sPAP and BODE index (p=0.006), MRC (p=0.040), stage of COPD (p=0.020) and the number of attacks (p=0.006). A statistically significant negative relationship was observed between sPAP and 6MWT (p=0.010). There was no statistically significant relationship between sPAP and CAT score (p=0.800) and the MCIRS score. There was a statistically significant positive relationship between NT-proBNP and BODE index (p=0.020) and the stage of COPD (p=0.040). A statistically borderline negative correlation existed between NT-proBNP and 6MWT (p=0.053). There was no statistically significant correlation between NT-Pro BNP and MRC (p=0.070), CAT score (p=0.500), number of attacks (p=0.100) and MCIRS score (p=0.200). A statistically significant positive correlation was observed between NO and CAT score (p=0.004). There was a statistically significant negative relationship between NO and 6MWT (p = 0.030). There was no statistically significant relationship between NO and BODE index (p=0.400), MRC (p=0.070), stage of COPD (p=0.600), number of attacks (p=0.300) and MCIRS score (p=0.200) (Table 4).Considering age, gender and BMI values, the relationship between sPAP and MCIRS score and FVC% was evaluated via linear regression analysis. A statistically significant positive relationship was observed between the sPAP value and age (p=0.006). There was no statistically significant relationship between sPAP and MCIRS score (p=0.700). A statistically weak negative relationship was observed between sPAP and FVC% (p=0.053) (Table 5).

Table 4. The relationship between sPAP, NT-proBNP, MRC, NO and BODE index, 6MWT, COPD stage, number of attacks and MCIRS score

	BODE index	MRC	6MWT	Stage	CAT Score	Number of attacks	MCIRS
	r p	r p	r p	r p	r p	r p	r p
sPAP	0.300 0.006	0.220 0.040	-0.270 0.010	0.240 0.020	0.020 0.800	0.300 0.006	0.100 0.300
proBNP	0.250 0.020	0.080 0.400	-0.210 0.053	0.230 0.040	0.060 0.500	0.160 0.100	0.130 0.200
NO	0.100 0.400	0.210 0.070	-0.250 0.030	0.050 0.600	0.330 0.004	0.120 0.300	0.120 0.200

Statistical Significance p < 0.05
CRP: C-Reactive Protein
NT-proBNP: N-Terminal Pro-Brain Natriuretic Peptide
sPAP: Systolic Pulmonary Artery Pressure
NO: Nitric Oxide
BODE Index: COPD Functional Assessment Test
6MWT: Six-Minute Walk Test
CAT: COPD Assessment Test
Stage: GOLD Disease Severity Rating (A, B, C, D)
mMRC: Modified Medical Research Council (MRC) Dyspnea Scale *MCIRS: Modified Cumulative Illness Rating Scale*

Table 5. Clinical determinants of pulmonary artery pressure

	sPAP B P		sPAP B P		sPAP B P		sPAP B P
Age	0.300 0.006	Age	0.300 0.006	Age	0.230 0.040	Age	0.250 0.020
Gender	−0.16 0.100	Gender	−0.160 0.100	Gender	−0.060 0.500	Gender	−0.140 0.100
BMI	0.160 0.100	BMI	0.160 0.100	BMI	0.110 0.300	BMI	0.160 0.100
MCIRS	0.040 0.700	MCIRS	0.040 0.700	MCIRS	−0.040 0.600	MCIRS	0.004 0.900
FVC%	−0.200 0.053	proBNP	0.180 0.100	Sat 02%	−0.290 0.009	BODE Index	0.250 0.020

Statistical Significance p < 0.05
SD: Standard Deviation,
BMI: Body Mass Index,
FVC: Forced Vital Capacity,
sPAP: Systolic Pulmonary Artery Pressure,
MCIRS: Modified Cumulative Illness Rating Scale

Grade	Dyspnea Related to Activity
0	Breathlessness only on strenuous exercise
1	Breathless when hurry on the level or walking up a slight hill
2	Walks slower than other people of same age on the level due to shortness of breath or need to stop for breath when walking at own pace
3	Short of breath after walking few minutes on the level or about 100 yards (90m)
4	Too breathless to leave the house, or breathless when dressing or undressing

Figure 1. Medical Research Council (MRC) dyspnea scale

Variable	0	1	2	3
FEV_1 (% of predicted)	≥ 65	50-64	36-49	≤ 35
Distance walked in 6 min (m)	≥350	250-349	150-249	≤149
MMRC Dispne score	0-1	2	3	4
Body mass index (BMI) (kg/m2)	> 21	≤ 21		

Figure 2. BODE index

(FEV1: forced expiratiory volüme of air in 1 second. Adapted from Celli et al. 2004 Massachusetts Medical Society. Repirented with permission)

Modified Cumulative Illness Rating Scale (MCIRS)

It is the examination of patients according to their comorbidities. (Total score 56)

Rating scale

0- no problem
1- 1- slight trouble or past major problem
2- 2- moderate disability or morbidity requiring treatment for the first time
3- 3-severe / constant major illness / uncontrolled chronic problems
4- 4- extremely common / urgent treatment / end organ damage / widespread irreparable function

POINT

Cardıac Dısease.....
Vascular..... ……
Hematopoietic system.....
Respiratory system.....
Eye, Ear Nose Throat and Larynx..... ……
Upper and Lower Gastrointestinal system.....
Derm .....
Liver.....
Kidney.....
Genitourinary system.....
Musculoskeletal system.....
Neurological disease.....
Endocrinology / metabolism and Breast.....
Psychiatric illnesses..... ……
Total number of unapproved categories.....
Total score.....

The severity index: total score / total number of unapproved categories……

Figure 3. Modified Cumulative Illness Rating Scale (MCIRS)

DISCUSSION

In the present study, CRP was found to be significantly higher in patients with stable COPD compared to the control group. To date, numerous studies have shown that inflammation in the lungs observed in COPD accompanies a "systemic inflammation" load and is the leading cause of mortality and morbidity in COPD (16,17).

Elevated CRP, leukocyte and platelet counts that are associated with airflow obstruction have been found in such cases (18).

Elevated CRP is associated with undesirable events in patients with COPD and increased mortality in female patients at advanced ages (19).

Herein, NT-proBNP values were higher in COPD patients compared to the control group. Phua et al. reported that BNP and NT-proBNP may not only increase in cardiac diseases but also in several pulmonary diseases (20).

In the present study, sPAP values of COPD patients were significantly higher than those of the control group. (sPAP was 28.64 ± 9.2 in the COPD group and 22.9 ± 4.5 in the control group) (Table 1). Mild PAH diagnosis with ECHO; sPAP is defined as 36-50 mmHg at rest (6).

Spirometry values have not been shown to be reliably associated with the presence of underlying PAH, but further investigation is particularly in patients with advanced stage COPD (GOLD 3-4 Severe-Very severe group FEV1 <50) and hypoxic respiratory failure (10) and in patients with low DLCO. and PAH follow-up has been recommended. (21).

Another factor in the development of PAH is hypoxia. While acute hypoxia causes pulmonary vasoconstriction, chronic hypoxia leads to remodeling of the pulmonary vascular bed (8). Pulmonary vascular remodeling is the most prominent cause of increased pulmonary artery pressure (PAP). It is thought that the increase in PAP is caused by chronic hypoxia, inflammation, and capillary loss in emphysema (22).

.Detecting PAH, which is one of the most important complications of COPD, and taking early precautions are important in terms of disease prognosis. Changing the natural history of COPD patients with a more comprehensive approach that takes into account comorbidities such as PAH and corpulmonale may provide an opportunity to reduce morbidity and mortality.

Hypoxia is a strong vasoconstricting factor. Therefore, hypoxemia and the presence of PAH are associated in patients with COPD. Fayngersh et al. investigated the prevalence of pulmonary hypertension in COPD patients, and the mean sPAP was calculated to be 45 ± 6 mmHg in COPD patients with pulmonary hypertension (23).

Similarly, in the present study, the age of COPD patients with PAH was statistically significantly higher than that of COPD patients without PAH. Pearson correlation analysis revealed a significant positive relationship between sPAP and age. Additionally, when the relationship between the sPAP value and age, as clinical determinants of PAP in COPD patients, was evaluated via linear regression analysis, a statistically significant positive relationship was revealed between sPAP and age. Similarly, it was reported in a study that hypoxic PAH and cor pulmonale associated with COPD were mostly observed in elderly patients (24).

Herein, there was no statistically significant difference between the COPD group with PAH and the COPD group without PAH in terms of CRP and NO values. In addition, no significant correlation was observed between the sPAP value and CRP and NO values in the Pearson correlation analysis. Unlike the results of the present study, inflammatory cytokines such as CRP, TNF and IL-6 were found to have been elevated in COPD patients with PAH compared to COPD patients without PAH in previously conducted studies (25).

Chronic inflammation can contribute to pulmonary vascular remodeling. CRP levels have been reported to be an independent determinant for PAP in COPD patients with PAH (26).

In patients with COPD, endothelial dysfunction is caused by the release of vasoactive mediators of endothelial origin. The levels of CRP and ET-1, a potent vasoconstrictor produced from the vascular endothelium, were higher in COPD patients with PAH than those without (27).

The extent of the systemic inflammation in COPD is associated with the elevated levels of CRP and other inflammatory markers in circulation in addition to being associated with the severity of airflow obstruction (28,29).

Numerous studies have shown that pulmonary expression of NO paradoxically increases owing to chronic hypoxia. Although some studies have shown that NO activity and cGMP, its mediator, increase, in numerous other studies, NO production decreased. PAH secondary to chronic hypoxia is accompanied by increased pulmonary expression of NOS enzymes. Increased PAP affects the mechanism of NO, which has a strong vasodilator effect. A previous study showed that the pulmonary production of NO decreased (22).

In the animal study conducted by Sandimo et al., the group with PAH showed lower NO activity than those without (30).

NO is a highly labile molecule and its actual levels are difficult to detect. One of the most important reasons underlying the detection of different NO levels in the literature is methodological differences. Various studies have shown that both increased and decreased NO levels can cause increased damage. In the present study, there was no correlation between sPAP values and serum NO values in patients with COPD. This could be due to the lability of the NO molecule and our selected measurement method.

Herein, BODE index was higher in COPD patients with PAH compared to those without. Pearson correlation and linear regression analyses revealed a negative correlation between sPAP and BODE index. In a previous study, sPAP > 40 mmHg, right ventricle (RV) wall thickness > 0.7mm, RV diastolic dysfunction, FEV1 < 40%, sat02 < 90 and 6MWT < 300 m were assessed to be the prognostic factors in COPD patients; furthermore, when BODE index was compared with the above data, its reliability in COPD as a prognostic factor was found to be higher (31).

Grabicki et al. examined the relationship between BODE index and the prevalence of the diseases accompanying COPD in 80 COPD patients, wherein COPD patients with high BODE index were found to have a high correlation in terms of certain comorbidities (32). The 6MWT test is not only used to measure the patient's level of shortness of

breath. It is also known that patients with a bad 6-minute walk test have a poor prognosis. In addition, the 6-minute walking test is also performed in addition to the pulmonary function tests to understand whether the patients respond to the treatment given. Periodic follow-up checks are made. If the walking distance is significantly increased, it is interpreted as the benefit of the treatment. The repeatability of 6MWT and its correlation with other functional capacity measurements is good (33,34).

One study involving only 45 COPD patients showed that patients with a mPAP> 35 mmHg had a significantly shorter 6-minute walking distance than patients with a lower mPAP (35). Spirometry is mandatory for the diagnosis of COPD; however, there is no use of VC, FEV1 and FEV1 / VC ratio to predict PAP in COPD. This is not surprising, as PAH has little effect on lung mechanics (36). According to the ATS / ERS 2005 consensus reports, stage determination based on FEV1 may be insufficient in advanced stage diseases. The FEV1% predicted value does not correlate well with the symptoms and may be insufficient to clinically determine the severity and prognosis of the disease. Therefore, evaluation of further pulmonary function tests is recommended (37).

In this study, 6MWT was found to be lower in COPD patients with PAH than those without. In the Pearson correlation analysis, PAP value was negatively correlated with 6MWT; however, this relationship could not reach statistical significance in linear regression analysis. Golpe et al. showed that 6MWT was very significant in determining the prognosis in PAH in their study conducted on 60 patients with PAH. They revealed that walking less than 400 m was associated with mortality (6).

Herein, the NT-proBNP value was found to be higher in patients with PAH than those without. In Pearson correlation analysis, a positive relationship existed between sPAP and NT-proBNP. However, linear regression analysis did not reveal any correlation between sPAP and NT-proBNP. Myocardial wall stress causes increased synthesis of BNP and NT-proBNP. Increased right atrial pressure is observed as a result of pulmonary vascular and parenchymal damage due to COPD. The results of the present study suggest that plasma NT-proBNP may be a useful prognostic marker for monitoring COPD progression and determining secondary PAH cases in patients with stable COPD. A significant positive correlation was observed between NT-proBNP concentrations and sPAP (38). In a previous study investigating the use of prognostic plasma NT-proBNP in severe COPD with chronic respiratory failure and PAH, plasma NT-proBNP levels were higher in stage IV and stage III COPD patients compared to stage II COPD patients according to the GOLD classification of COPD. The plasma NT-proBNP level is significantly increased in case of an increase in the severity of COPD, progression of chronic respiratory failure and the presence of secondary PAH in patients with stable COPD. A significant positive correlation was observed between NT-proBNP concentrations and sPAP. These results suggest that plasma NT-proBNP may be a useful prognostic marker for monitoring COPD progression and determining secondary PAH cases in patients with stable COPD (26). Chi et al. reported that NT-proBNP increased with the severity of the disease in patients with COPD who developed PAH. Based on these findings, they reported that NT-proBNP may be a prognostic indicator in stable COPD patients with PAH (39). In the present study, a positive correlation was found between NT-proBNP and age through Pearson correlation analysis. This correlation was also observed in linear regression analysis. Similarly, Sanchez-Marteles et al. detected significant changes in NT-proBNP with respect to age groups (40).

CONCLUSIONS

In the present study, CRP was higher in patients with stable COPD than in the control group. The level of CRP is an indicator of systemic inflammation, and given that it increases the frequency of exacerbations and mortality in patients with COPD (18,41), evaluating COPD patients in terms of "systemic inflammatory-COPD phenotype" would be useful in clinical practice. 6MWT is the basic criterion in PAH studies. Owing to its easy applicability and higher contribution to clinical evaluation compared to SFT, 6MWT should be periodically performed and recorded during follow-up visits at the outpatient clinic.

While evaluating the severity of the disease in patients with COPD, evaluation using BODE index and its sub-parameters would be a more appropriate approach.

Development of PAH increases morbidity and mortality in COPD patients. Therefore, patients with advanced stages of COPD should be screened using echocardiography, which is an easy-to-use, fast and repeatable measurement method to check for PAH development.

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