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STATISTICAL EVALUATION OF COPD PATIENTS WITH RESPECT TO GENDER: A CROSS-SECTIONAL STUDY

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ABSTRACT

This study has been conducted to evaluate chronic obstructive pulmonary disease (COPD) patients in Turkey in terms of gender. This cross-sectional study was performed on 416 COPD patients during January 2014 to January 2016. The various clinical parameters of the patients were obtained from the electronic data bank of the Kars Harakani State Hospital, Kars, Turkey. Patients' number of hospitalization, one-year mortality, complete blood cell count, blood gas parameters, and the relationship of these parameters with gender was evaluated. Around 38% of the patients were found to be female. The association of height, body mass index (BMI), and forced expiratory volume in 1 s (FEV₁) with gender is found statistically significant (p < 0.001). The results further indicated that the association of FEV₁ with BMI and weight is directly proportional and FEV₁ has a moderate positive correlation with weight and BMI (p < 0.001, r=0.250; p < 0.001, r=0.371). The association of FEV₁ levels with gender are also found statistically significant (p < 0.001). FEV₁ level are found to be related with smoking status (p < 0.001) and co-morbidity (p = 0.001)and thus affects in terms of the severity of the disease. No relationship between gender and the outcome of the present hospitalization, mortality or being referred to a more advanced health institution (p=0.202) has been observed. The association of whether mortality occurred or not in a year after the present hospitalization with the gender is statistically significant (p < 0.011). The association of C-reactive protein (CRP), platelet, platelet distribution width (PDW), plateletcrit (PCT), hemoglobin, and hematocrit values with gender are also statistically significant (p=0.009, p=0.004, p=0.048, and p<0.001). Eosinophile count has a weak positive correlation with the number of hospitalizations. On the basis of the findings of the study it is concluded that a number of studied parameters affect the severity of COPD and male patients are more affected than females.

Keywords: Chronic obstructive pulmonary disease, FEV1, gender.

1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a condition with acute exacerbation and is followed by chronic and progressive inflammation¹. Gases like cigarette smoke and inhaled particulates result in inflammation in lungs and airways, which causes totally irreversible progressive airway restriction¹. COPD is currently considered as the fifth common cause of death and is predicted to become the third common death cause in 2020². Acute exacerbation in COPD patients is the leading cause of death. Therefore, it is very important to check acute

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complications¹ and inflammation² in the COPD patients. COPD highly reduces one's quality of life. At the same time, frequent hospitalizations of COPD patients cause high health expenses².

The markers such as C-reactive protein (CRP) and white blood cells (WBC) are expected to increase in COPD². In order to ascertain the presence of the disease in patients, forced expiratory volume in 1 s (FEV₁) is one of the measurements that have been used for a long time³. FEV₁ is effective in determining the severity of the disease and the efficiency of the

treatment. Declined FEV₁ level is associated with mortality³. The aim of this study is to statistically evaluate a relationship between the clinical parameters such as routine blood count components, blood gas, CRP, and FEV₁ with patients' gender in order to assess whether the gender has any impact on the disease and its symptoms.

2. METHODS

2.1. Patient Selection

This cross-sectional study was performed on 416 patients with known COPD. The study included only those patients who were diagnosed with COPD at the Chest Diseases Clinic and Emergency Room in Kars Harakani State Hospital, Kars, Turkey and who were hospitalized just after their admission to the hospital during January 2014 to January 2016.

2.2. Confirmation of COPD

COPD was confirmed on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for the diagnosis, classification and severity⁴. Spirometry was done with Spirolab III-MIR (Italy). Subsequently, patients were staged according to the severity criteria of GOLD⁴; stage I (FEV₁ \ge 80%), stage II (50% \le FEV₁ < 80%), stage III (30% \le FEV₁ < 50%) and stage IV (FEV₁ < 30%)⁴.

2.3. Clinical Parameters

The clinical parameters of the patients were obtained from the electronic data bank of the hospital. The parameters evaluated included the following:

- Hospital admission date
- Age
- Gender
- Height (meters)
- Weight (kg)
- BMI (kg/m^2)
- Co-morbidity
- Smoking status (non-smoker, smoker, ex-smoker)
- Number of hospitalizations in the last one year
- Results of the present hospitalization (discharge, being referred to a more advanced health institution or mortality)
- Whether there was hospitalization in the intensive care unit or not in the last one year

- Results of sputum culture
- Clinical findings including the results of complete blood cell count of the patients provided hemoglobin (g/dL), hematocrit (%), white blood cell (WBC, $\times 10^3 \mu$ L), mean platelet volume (MPV, fL), platelet count ($\times 10^3 \mu$ L), lymphocyte count ($\times 10^3$ µL), lymphocyte percent (%), platelet/lymphocyte rate (division of platelet count in lymphocyte count, TLR) neutrophile count ($\times 10^3$ µL), neutrophile percent (%), neutrophile/lymphocyte rate (division of neutrophile count in lymphocyte rate, NLR), eosinophile count ($\times 10^3 \mu$ L), eosinophile percent (%), platelet distribution width (PDW, fL) plateletcrit (PCT, %). Besides, C-reactive protein (CRP, m/L), pH from blood gas, partial pressure of carbon dioxide (pCO₂, mmHg) and partial pressure of oxygen (pO₂, mmHg) were evaluated.

2.4. Statistical Analysis

The studied parameters were analyzed using SPSS for Windows (version 23.0, IBM, New York, USA). The mean of the continuous variables in descriptive statistics was expressed with standard deviation; categorical variables were expressed with numbers and percentages. The comparison of two independent groups was performed with chi-square test. Mann–Whitney U test was used for comparison of binary groups (nonparametric test). The nonparametric comparison of three independent groups was performed using the Kruskal–Wallis test. *p*-value of less than 0.005 was accepted to be statistically significant. Spearman correlation analysis was performed for data that was not consistent with the normal distribution.

3. RESULTS AND DISCUSSION

In this study, patients with COPD have been evaluated in terms of gender, smoking status, comorbidities, hospitalization, clinical and microbial parameters. A total of 416 patients with COPD have been included in the study where male gender is found to be more affected with the disease (62.3%) among the studied patients. The average age of females was 69.6 ± 9 years and that of the males was 68.1 ± 9.9 years. The results indicated statistically

significant (p < 0.001) association of height, BMI and FEV1 with gender. The values of BMI and FEV1 are observed to be higher in females as compared to male patients (Table 1). In this study, the age, weight, BMI, and FEV1 levels of the female patients are found higher comparatively to those of the male patients (Table 1). However, Olafsdottir et al.⁵ observed that a decline in FEV1 was substantially associated with the increase of BMI in both genders. Whereas de Torres et al.⁶ noted lower BMI of females with same FEV1 level in both genders. A higher BMI has been reported in male patients by Harik-Khan et al.⁷ whereas no relationship between gender and FEV₁ has been observed by Watson et al.⁸. In the study of Ekstrom et al.⁹, females were younger than males and they had a lower mean absolute

FEV1 but similar predicted FEV1.

It is reported that among the clinical parameters, CRP, platelet count, PDW, PCT, hemoglobin, hematocrit values has a statistically significant association⁹. However, in the study of Olafsdottir et al.⁵, there was an insignificant relationship between CRP level and gender (p=0.91) whereas no relationship between PDW level and gender was observed by Bialas et al.¹⁰. In the present study, the values of CRP, platelet count, PDW and PCT, hemoglobin and hematocrit indicated statistical relevance with gender (p=0.009, p=0.004, p=0.048, and p<0.001). The other clinical parameters such as complete blood count and blood gas are found to be statistically non-significant with gender (Table 1).

	Total		Gender				
Parameters			Female		Male		p
	Mean	±SD	Mean	±SD	Mean	±SD	
Age	68.7	9.6	69.6	9.0	68.1	9.9	0.186
Height (m)	1.6	0.1	1.6	0.1	1.7	0.1	< 0.001
Weight (kg)	72.3	15.9	73.1	16.1	71.8	15.9	0.431
BMI (kg/m ²)	27.3	6.4	30.1	6.8	25.5	5.5	< 0.001
FEV ₁ (%)	38.8	14.5	44.9	14.8	35.2	13.1	< 0.001
WBC (×10 ³ µL)	11.4	5.6	11.2	6.9	11.5	4.7	0.102
MPV (fL)	8.2	1.0	8.3	1.1	8.2	1.0	0.117
Platelet (×10 ³ μ L)	246.2	81.9	255.8	70.1	240.3	87.9	0.004
Lymphocyte (×10 ³ μ L)	1.6	1.4	1.7	1.7	1.5	1.2	0.381
Lymphocyte (%)	15.2	9.9	16.1	9.4	14.7	10.2	0.079
TLR	235.3	268.6	230.4	244.7	238.3	282.6	0.616
Neutrophile (×10 ³ μ L)	8.8	4.7	8.6	5.2	8.9	4.4	0.224
Neutrophile (%)	76.4	26.0	74.9	13.2	77.4	31.4	0.433
NLR	9.1	11.7	8.9	13.3	9.2	10.7	0.084
Eosinophile (×10 ³ μ L)	0.2	1.0	0.2	1.3	0.2	0.7	0.329
Eosinophile (%)	1.6	4.5	2.0	6.9	1.3	1.8	0.616
PDW (fL)	16.8	0.8	16.8	0.6	16.8	0.9	0.048
PCT (%)	0.2	0.1	0.2	0.1	0.2	0.1	< 0.001
CRP (m/L)	6.0	7.4	4.8	6.4	6.7	7.9	0.009
pCO ₂ (mmHg)	41.5	8.2	41.7	8.2	41.4	8.2	0.565
pO ₂ (mmHg)	53.1	11.7	53.4	10.5	52.9	12.4	0.418
Hemoglobin (mg/dL)	15.2	2.0	14.8	2.0	15.5	2.0	< 0.001
Hematocrit (%)	47.2	15.6	45.3	6.2	48.4	19.0	< 0.001

Table 1. The association of gender with age, BMI, FEV₁, and clinical parameters

Month of Hospitalization	n	%
January	30	7.2
February	38	9.1
March	37	8.9
April	38	9.1
May	51	12.3
June	47	11.3
July	19	4.6
August	20	4.8
September	34	8.2
October	20	4.8
November	56	13.5
December	26	6.2

Table 2. Distribution rates of hospitalized COPD patients with respect to the months

It has been observed that there are number of cases for hospitalization of COPD patients throughout the year but the number is highest in the month of November followed by May probably due to seasonal changes and lowest from July to August (Table 2).

On the basis of severity criteria of GOLD⁴, all 416 COPD patients have been diagnosed with a severity stage of II to IV (Table 3). The relationship between moderate, severe and very severe FEV₁ levels and gender is found to be statistically significant (p < 0.001). The results indicated male population more affected to severe and very severe conditions as compared to females (Table 3). Previously, Shimray et al.¹¹ has reported an association of FEV₁ levels with gender as females have lower levels of FEV_1 as compared to male patients. On the contrary, Dal Negro et al.¹² observed no association between FEV_1 levels and gender. Similarly, in the study of Bednarek et al.¹³, COPD patients underwent spirometric categorization and were categorized into mild, moderate, severe and very severe. However, no relationship was found between the categorization and gender¹³.

The association of smoking status and presence of co-morbidity with gender is also found to be significant in this study (p < 0.005, p < 0.001). Male patients are found to be more prone to smoking and absence of co-morbidities as compared to females (Table 3). No relationship between gender and the outcome of the present hospitalization, mortality or being referred to a more advanced health institution (p=0.202) has been observed. The association of whether mortality occurred or not in a year after the present hospitalization with the gender is statistically significant (p<0.011).

The sputum culture results showed isolation of normal flora in vast majority of the patients (87.4%) indicating very limited role of the infectious organisms with respect to gender in the occurrence of the disease (Table 3). However, the increased number of male patients could be due to their presence in majority in this study. Among the different clinical pathogens isolated, *Escherichia coli* is found in ~4% (n=17) and *Pseudomonas aeruginosa* in ~3 of the patients (Table 3).

Table 3. The association of FEV	levels, co-morbidity, smoking status,	hospitalization outcomes and
	one-year mortality with gender	

Paramatars	Total		Gender				n
			Female		Male		P
FEV ₁ level	n	%	n	%	n	%	-
Moderate COPD (50% ≤ FEV ₁ < 80%)	102	24.5	64	15.4	38	9.1	-
Severe COPD (30%≤FEV ₁ <50 %)	175	42.1	62	14.9	113	27.2	< 0.001
Very severe COPD (FEV ₁ <30 %)	139	33.4	31	7.4	108	26.0	
Smoking status							
Smoker	74	17.8	14	3.4	60	14.4	
Ex-smoker	206	49.5	31	7.4	175	42.1	< 0.005
Non-smoker	136	32.7	112	26.9	24	5.8	
Co-morbidity							
Present	180	43.3	96	23.1	84	20.2	< 0.001
Absent	236	56.7	60	14.4	175	42.1	
The outcome of the present hospitali	zation ^a	1	I	1	I	1	
Discharge	407	99.3	155	37.8	252	61.5	
Mortality	2	0.5	0	0.0	2	0.5	0.202
Being referred to a more advanced health institution	1	0.2	0	0.0	1	0.2	
Mortality through a year after the p	resent ho	spitalizat	tion ^a		I	1	
Present	76	18.5	19	4.6	57	13.9	< 0.011
Absent	334	81.5	136	33.2	198	48.3	
Reproduction in culture of sputum ^b							
Normal upper respiratory tract flora	359	87.4	144	35.0	215	52.3	
Escherichia coli	17	4.1	4	1.0	13	3.2	
Staphylococcus aureus	3	0.7	2	0.5	1	0.2	
Pseudomonas aeruginosa	14	3.4	2	0.5	12	2.9	
Candida species	2	0.5	1	0.2	1	0.2	
Serratia marcescens	3	0.7	0	0.0	3	0.7	
Enterobacter species	3	0.7	1	0.2	2	0.5	
Klebsiella species	3	0.7	1	0.2	2	0.5	_
Proteus species	3	0.7	0	0.0	3	0.7	1
Acinetobacter species	1	0.2	0	0.0	1	0.2	1
Coagulase negative Staphylococcus species	1	0.2	0	0.0	1	0.2	1
Streptococcus pneumoniae	1	0.2	0	0.0	1	0.2	1
Stenotrophomonas maltophilia	1	0.2	0	0.0	1	0.2	1

^a In 6 patients, the outcome was not obtained from the hospital records. The percentages calculated are from the mean of 410.

^b The sputum culture results of 5 patients was missing from the hospital records. The percentages calculated are from the mean of 411.

In the present study, the smoking habit is noted to be more common in male patients as compared to female patients (Table 3). Similar higher rates were observed prevously in males as compared to females by other workers^{7,13}. FEV₁ level is associated with smoking status (p < 0.005). The FEV₁ values for smokers, ex-smokers and non-smokers are found to be 37.3±13.7, 36.2±13.2, and 43.8±15.7, respectively. The FEV₁ value for non-smokers is found comparatively better whereas nearly similar values are obtained for both smokers and ex-smokers (p=0.486, p=0.004). This study has found that around 67% of the patients who smokes or used to smoke have critical COPD condition as compared to nonsmokers (~33%) indicating the harmful effects of smoking on the disease (Table 4). Majority of the patients have been diagnosed with severe COPD (42.1%) followed by very severe (33.4%) and moderate (24.5%) conditions with highest number of cases in ex-smokers (Table 4). Previously, it has been reported by some workers that there is no significant relationship between decline in FEV₁ level and smoking^{5,8} or between gender and smoking⁶. However, Prescott et al.¹⁴ have stated that continuous smoking can cause decline in FEV₁ levels. Smoking with increasing age particularly in females can result in substantial decline in FEV_1 levels¹⁵. The results of this study clearly indicates that there is a significant relationship between FEV₁ levels and smoking. However, as majority of the patients in this category are male (~89%) and females $(\sim 11\%)$ are few (Table 3), it is difficult to conclude the results on the basis of gender.

 FEV_1 level is also noted to be associated with comorbidity (p < 0.001) and has a significant relationship with the severity of the disease (Table 5). In about 57% of the patients co-morbidities are found to be absent whereas some patients ($\sim 43\%$) are found to have different co-morbidities along with COPD (Table 5). These findings are in accordance with the observation of Dal Negro et al.¹² who also reported an association between co-morbidities and COPD. Majority of the patients without co-morbidities are found to have severe (25.5%) and very severe (21.4%) COPD (Table 5). In case of patients with co-morbidities there is not much difference among the various types, however, comparatively severe (16.6%) and moderate (14.4%) COPD are found to be the most prevalent conditions (Table 5). In the present study, both male and female patients are in almost similar numbers (20-23%) in terms of comorbidities (Table 3), therefore, a conclusive statement on the basis of gender cannot be made. de Torres et al.⁶ noted that co-morbidity was less in female patients than male while Ekstrom et al.⁹ found more co-morbidities in females in terms of hypertension, mental disorders, osteoporosis and rheumatoid arthritis, but less for arrhythmias, cancer, ischemic heart disease and renal failure when compared to males. They found no significant genderrelated differences for anemia, cerebrovascular disease, diabetes mellitus, digestive organ disease, heart failure, lung cancer or pulmonary embolism⁹.

	Smoking Status					
FEV ₁	Smoker n (%)	Ex-smoker n (%)	Non-smoker n (%)	Total n (%)	p	
Moderate COPD	17 (4.1)	36 (8.6)	49 (11.8)	102 (24.5)		
$(50\% \le FEV_1 \le 80\%)$						
Severe COPD	30 (7.2)	87 (20.9)	58 (13.9)	175 (42.1)		
(30%≤FEV ₁ <50 %)					< 0.005	
Very severe COPD	27 (6.5)	83 (20.0)	29 (7.0)	139 (33.4)		
(FEV ₁ <30 %)						
Total	74 (17.8)	206 (49.5)	136 (32.7)	416 (100.0)		

Table 4. The association of FEV₁ levels with smoking

		Co-morbidity		
FEV ₁	Present n (%)	Absent n (%)	Total n (%)	p
Moderate COPD	60 (14.4)	42 (10.1)	102 (24.5)	
$(50\% \le FEV_1 \le 80\%)$				
Severe COPD	69 (16.6)	106 (25.5)	175 (42.1)	<0.005
(30%≤FEV ₁ <50 %)				<0.005
Very severe COPD	51 (12.3)	88 (21.1)	139 (33.4)	
(FEV ₁ <30 %)				
Total	180 (43.3)	236 (56.7)	416 (100.0)	

Table 5. The association of FEV_1 with co-morbidity

 FEV_1 level is found to be inversely proportional to height with a weak negative correlation (p < 0.001, r = -0.225). The results further indicated that the values of FEV₁ increases with an increase in weight and BMI thus showing a direct proportionality between them (p<0.001, r=0.250; p<0.001, r=0.371). The statistical correlation of clinical parameters with FEV_1 and the number of hospitalizations are shown in Table 6. Platelet and lymphocyte count has a positive weak correlation with FEV_1 (r=0.098, r=0.100). MPV and lymphocyte count showed a weak positive correlation to the number of hospitalizations in a year (r=0.099). Previously, no correlation between exacerbation of the COPD and MPV level has been observed by Gunay et al.¹⁶ whereas significantly lower MPV levels were noted by Agapakis et al.¹⁷ and Ulasli et al.¹⁸ in the exacerbation period compared with stable COPD. According to Duman et al.¹⁹, the association of readmission to hospital after the discharge with MPV was statistically significant. There was a statistically significant relationship between gender and whether mortality occurred or not in a year after the present hospitalization. Duman et al.¹⁹, stated that mortality of COPD patients in 6 months after the discharge was associated with male gender.

Eosinophile count and its percent has also been found to have a weak positive correlation with the number of hospitalization in the last one year before the last hospital admission (r=0.125, r=0.145). It has been reported by Bafadhel et al.²⁰ that the length of hospital stay (in days) was shorter in eosinophilic-associated exacerbations than non-eosinophilic exacerbations of COPD. However, the 12 month readmission rate and time to other exacerbation did not show differentiation between the index eosinophilic and non-eosinophilic COPD exacerbation²⁰ while Duman et al.¹⁹ observed that the length of stay was significantly shorter in the eosinophilic group. The duration was 6.6 (4.6–8.0) days in the eosinophilic group and 7.0 (5.5-9.0) days in the non-eosinophilic group $(p < 0.001)^{19}$. Contrary to this, the readmission rate is found to be significantly higher in the non-eosinophilic patients in this study. Readmission in 6 months was 1 (0-3) for the eosinophilic and 2 (0-4) for the noneosinophilic group (p < 0.01).

PDW, platelet count, lymphocyte count, and CRP showed a weak negative correlation with FEV₁. PDW has a weak positive correlation with the number of hospitalization in the last one year before the last hospital admission (Table 6). These findings are in accordance to the observations of Bialas et al.¹⁰ who also found a non-significant relationship of PDW with FEV₁. In the study of Olafsdottir et al.⁵, the patients whose CRP value was over 0.46 mg/L were noted to have substantially low FEV₁. The negative relationship between CRP and FEV₁ was substantially more in males than females (p=0.04)⁵. Male patients whose CRP value was over 0.46 mg/L have a great decline in FEV₁. However, no

relationship between the decline in female patients' pulmonary functions and CRP was observed⁵. In the study of Gunay et al.¹⁶, CRP levels in patients with grade 4 COPD were significantly higher when compared to the other groups (p=0.040). No correlations between FEV₁ and CRP levels and no significant correlations between CRP and complete blood cell count and disease severity either in patients with stable COPD or those with exacerbation were noted by Ulsali et al.¹⁸.

 pCO_2 indicated a negative weak correlation with FEV_1 and also showed a weak positive correlation

with the number of hospitalizations in the last one year before the last hospital admission and the number of hospitalization in the last one year (Table 6). On the other hand, pO₂ showed a weak positive correlation with FEV₁ and a weak negative correlation with the number of hospitalization in the last one year (r=0.270, r=-0.134). Prescot et al.¹⁴, has reported that FEV₁ level is a strong predictor for hospitalization. Hemoglobin and hematocrit values indicated a weak negative correlation with FEV₁ and weak positive correlation with the number of hospitalization in the last one year (r=-0.168, r=0.103) (Table 6).

Parameters	FEV ₁		Num Hospitaliz Year Befor Hospital A	ber of zation in a re the Last Admission	Number of Hospitalization in the Last One Year (Including the Present Hospitalization)		
	r	р	r	р	R	р	
WBC (×10 ³ µL)	-0.031	0.528	0.066	0.184	0.046	0.356	
MPV (fL)	-0.03	0.542	0.088	0.076	0.099*	0.045	
Platelet (×10 ³ μ L)	0.098^{*}	0.047	-0.023	0.650	-0.022	0.659	
Lymphocyte ($\times 10^3 \mu$ L)	0.100*	0.043	0.067	0.177	0.06	0.226	
Lymphocyte (%)	0.074	0.136	0.021	0.676	0.016	0.743	
TLR	-0.045	0.365	-0.074	0.138	-0.048	0.332	
Neutrophile (×10 ³ μ L)	-0.018	0.722	0.062	0.211	0.054	0.278	
Neutrophile (%)	-0.023	0.648	-0.02	0.685	-0.004	0.928	
NLR	-0.08	0.105	-0.004	0.929	-0.003	0.957	
Eosinophile (×10 ³ μ L)	0.016	0.744	0.125*	0.011	0.145**	0.003	
Eosinophile (%)	0.03	0.543	0.08	0.105	0.097*	0.050	
PDW (fL)	-0.119*	0.016	0.131**	0.008	0.069	0.163	
PCT (%)	0.083	0.093	0.004	0.932	0.016	0.741	
CRP (m/L)	-0.191**	< 0.001	0.00	0.993	0.001	0.979	
pCO ₂ (mmHg)	-0.361**	< 0.001	0.147**	0.003	0.225**	< 0.001	
pO ₂ (mmHg)	0.270**	< 0.001	-0.074	0.141	-0.134**	0.007	
Hgb (mg/dL)	-0.098^{*}	0.047	0.005	0.917	0.065	0.192	
Hematocrit (%)	-0.168**	0.001	0.061	0.216	0.103*	0.037	

Table 6. The statistical correlation of clinical parameters with FEV_1 and the number of hospitalizations

 * Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

4. CONCLUSION

Patients with COPD have been evaluated in terms of gender. The findings of this study indicates that the severity of COPD is affected by a number of conditions such as BMI, FEV₁, smoking status, comorbidity, and some other parameters. Male gender is found to be more affected by some of the studied parameters. Further evaluation of such parameters on a larger population may help in ascertaining the association of gender with the progression of COPD with respect to gender.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICAL APPROVAL

The study was approved by the Ethics Committee of the Kafkas University, Kars, Turkey.

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