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Carotid intima-media thickness in chronic obstructive pulmonary disease and survival: A multicenter prospective study

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Abstract

Introduction: Chronic obstructive pulmonary disease (COPD) is associated with increased cardiovascular morbidity and mortality. Carotid intima-media thickness (CIMT) is a noninvasive method assessing atherosclerosis.

Objective: It was aimed to determine relationship and survival between COPD and CIMT.

Methods: CIMT was measured using Doppler ultrasound (USG) in 668 stable COPD patients at 24 centers. Patients were followed-up for 2 years.

Results: There were 610 patients who completed the study. There were 200 patients CIMT with <0.78 mm (group 1), and 410 with CIMT ≥ 0.78 mm (group 2). There was a significant difference at the parameters of age, gender, smoking load, biomass exposure, GOLD groups and degree of airway obstruction (FEV1) between groups 1 and 2. Our results revealed positive correlations between mean CIMT and age, smoking load (pack-years), biomass exposure (years), exacerbation rate (last year), duration of hypertension (years) and cholesterol level; negative correlations between CIMT and FEV_1 ($P < 0.05$). According to logistic regression model, compared with group A, risk of CIMT increase was 2.2-fold in group B, 9.7-fold in group C and 4.4-fold in group D ($P < 0.05$). Risk of CIMT increase was also related with cholesterol level ($P < 0.05$). Compared with infrequent exacerbation, it was 2.8-fold in the patients with frequent exacerbation ($P < 0.05$). The mean survival time was slightly higher in group 1, but not significant (23.9 vs 21.8 months) ($P > 0.05$).

Conclusion: This study is the first regarding CIMT with combined GOLD assessment groups. It has revealed important findings supporting the increase in atherosclerosis risk in COPD patients. We recommend Doppler USG of the carotid artery in COPD patients at severe stages.

KEYWORDS
carotid intima-media, COPD, exacerbation, survival

1 | INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic form of lung disease that is characterized by progressive airflow limitation, and is known to be a significant cause of mortality and morbidity worldwide.[1] COPD is associated with several comorbidities, but mainly with those related to diseases of the cardiovascular system.[2] Cardiovascular diseases represent an important cause of death in COPD patients, and increase the rates of both emergency admissions and hospitalizations.[3]

Smoking has been identified as a common risk factor in the pathogenesis of cardiovascular diseases accompanying COPD. By the way, this coexistence cannot be explained by the effects of smoking alone. The effects of COPD are not only limited to the respiratory system, it may also lead to systemic inflammation. In this regard, apart from smoking, hypoxia and chronic systemic inflammation secondary to COPD are also suggested to have potential effects on the development of cardiovascular disease and atherosclerosis, which may increase the rates of mortality and morbidity by the association with cardiovascular events.[4,5]

While several parameters have been investigated in the recent years to identify subclinical vascular disease, the role of these parameters in estimating cardiovascular risk among COPD patients is still unclear. Carotid intima-media thickness (CIMT) is known to be a simple and noninvasive method of assessment for atherosclerosis.[5]

Both retrospective and prospective studies reported in recent years have emphasized the importance of subclinical atherosclerosis in COPD, and have provided evidence that COPD patients should be more closely monitored for the risk of cardiovascular disease. However, as the majority of these studies were performed on small patient groups and in the presence of multiple confounding factors, there is still insufficient data for the development of an effective strategy aiming to reduce COPD-related morbidity and mortality.[6,7]

The present study investigates CIMT and subclinical atherosclerosis, as well as the accompanying characteristics, in patients with different stages of COPD.

2 | MATERIALS AND METHODS

2.1 | Patients and study protocol

This multicenter, prospective cohort study was conducted between March 2015 and February 2017, and was granted approval by the ethics committee of Selcuk University, Konya, Turkey (2015/100), and the review boards and the patients of the 31 participating centers all provided written informed consent. The study was carried out as detailed in Figure 1.

A COPD diagnosis was based on a post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio of <70%, in the absence of a primary diagnosis of bronchiectasis, asthma or any other significant respiratory disease. The patients also had symptoms and a history compatible with COPD (disease onset after 40 years of age, smoking history of at least 10 packs/year, or occupational exposure to irritant or toxic gases or biomass exposure), and had to have been in a stable state for at least 6 weeks without exacerbation.

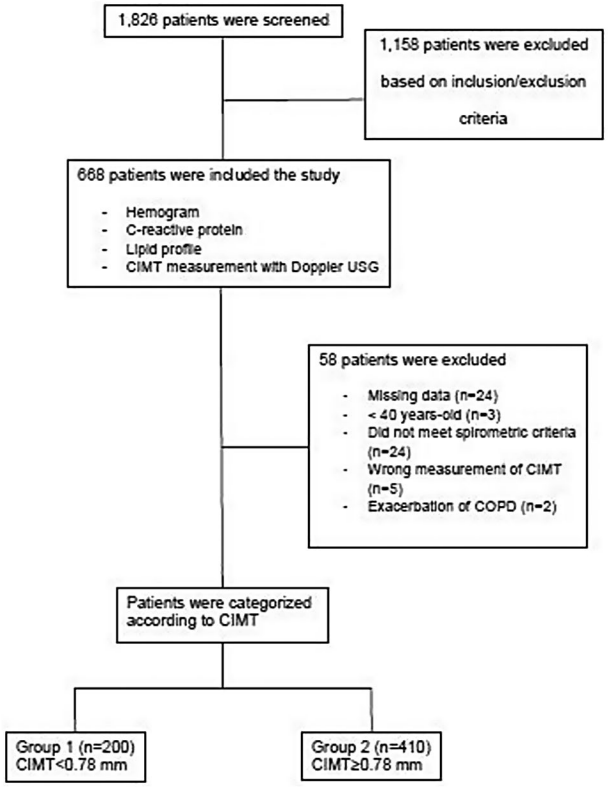

FIGURE 1 Flowchart of patient enrollment
CIMT, carotid intima-media thickness; COPD: Chronic obstructive pulmonary disease; USG, ultrasonography

Patients were excluded on the basis of the following criteria: (1) presence of a systemic inflammatory disease, (2) undergoing regular anti-inflammatory drug therapy, (3) presence of diabetes mellitus, (4) presence of heart failure and atherosclerotic heart disease, (5) regular antihyperlipidemic treatment and 6) presence of plaque formation at intima, based on a previous Doppler ultrasonography (USG).

All patients were assessed based on exacerbation history over the previous year, physical examination findings, pulmonary function test results and dyspnea score, identified from the modified Medical Research Council (mMRC) scale. The patients were divided into combined assessment groups of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2015,[8] based on pulmonary function tests, the mMRC scale and exacerbation history over the last year.

2.2 | Data collection

The following demographical and clinical data were collected for all patients: age; sex; smoking history (pack-years); body mass index (kg/m^2); history of biomass exposure (years); history of hypertension (years); exacerbation rate over the last year; mMRC score; spirometric stage; and combined COPD assessment classification according to GOLD 2015.

Each patient was evaluated at intervals of 3-6 months for 2 years. In the event of death, the date of death was confirmed from the death information system.

2.3 | Measurements

In line with the recommendations of the ATS/ERS Task Force, a post-bronchodilator spirometry test was performed after four separate salbutamol doses (total dose 400 mg) were delivered at 30-second intervals. The patients had the diagnosis of COPD with a post-bronchodilator FEV_1/FVC less than 70%. Patients were categorized based on a combined COPD assessment according to the 2015 GOLD classification.[8]

Venous blood samples were obtained and analyzed for plasma levels of fibrinogen, C-reactive protein (CRP), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides. Resting arterial blood gas levels while breathing room air were analyzed only for GOLD C and D patients.

All measurements of CIMT were made by the same radiologist in each center who was blinded to all patient data. The patients were examined in the supine position, and CIMT was measured bilaterally using a high-resolution Doppler USG device with, at minimum, 8-12 MHz linear array probes. Measurements were taken from at least 10 mm proximal to the carotid bifurcation, in the left and right common carotid artery, with three measurements obtained from both the left and right common carotid artery, and the average value of the three measurements used for analysis.[9]

2.4 | Statistical analysis

Data obtained from 610 participants were used for the statistical analysis which was carried out using SPSS V22.0 software (SPSS Inc. Chicago, Illinois, United States), and the baseline characteristics of the participants were presented as mean ± standard deviation and numerically (%). Frequency distributions were given for the categorical variables, and the data were compared using an independent-samples *t* test for categorical variables between two groups and a one-way analysis of variance (ANOVA) for categorical variables for more than two groups, while a chi-squared test was used to analyze the relationship between two categorical variables. Correlations between CIMT and the other variables were evaluated using a Pearson's correlation test.

The mean survival was given as mean ± standard deviation (SD), and a binary logistic regression method was used to analyze any factors that may cause a CIMT increase. A Hosmer-Lemeshow test was carried out to evaluate goodness of fit for the logistic regression models. The binary logistic regression model included age, smoking load, hypertension history, CRP, cholesterol value and the combined COPD assessment classification groups (according to GOLD 2015). The survival of the patients was analyzed using the Kaplan-Meier method, and a two-sided *P* value of <0.05 was considered statistically significant.

3 | RESULTS

The study included 668 patients who were followed up at 24 clinical centers with taken informed consent. There were 58 patients who were excluded from the study because of missing data or incorrect records (related to age, gender, smoking history or spirometry test results; $n = 24$), those who were younger than 40 years of age ($n = 3$), those who did not meet the GOLD spirometry criteria ($n = 24$), those in whom CIMT was not measured bilaterally ($n = 5$), or those who had an exacerbation of COPD ($n = 2$).

The final study population comprised 610 patients, with 539 (88.4%) men and 71 (11.6%) women. The mean age of patients was 65.4 ± 9.8 years (range: 40-94 years). There were 565 (92.7%) patients with smoking history; 45 (7.3%) participants were nonsmokers. Patients were categorized according to the 2015 GOLD classification as 188 (30.8%), 181 (29.7%), 73 (12.0%) and 168 (27.5%) in groups A-D, respectively. Spirometric stages were assessed based on a post-bronchodilator spirometry test, with 61 (10%), 312 (51.1%), 174 (28.5%) and 63 (10.3%) patients found to be at stages 1-4, respectively.

There were 200 patients with CIMT <0.78 mm (group 1), and 410 with CIMT ≥ 0.78 mm (group 2). There were significant differences in the baseline characteristics of the groups, such as age, smoking load (pack-years), forced vital capacity (FVC) (%), FEV_1 (mL), FEV_1 (%), FEV_1/FVC and hypertension (years) variables ($P < 0.05$) (Table 1).

Table 2 summarizes the nonparametric variable data of the study groups, of which, gender, age, biomass exposure, spirometric stage and GOLD classification were found to differ significantly among the groups ($P < 0.05$).

Of the total, 338 (54.7%) patients were aged 65 years or above, and CIMT was seen to be significantly higher in this patient group than in the younger patients (0.92 ± 0.21 vs 0.85 ± 0.22 mm, respectively; $P < 0.001$). The mean CIMT was 0.81 ± 0.20 mm in women and 0.90 ± 0.21 mm in men ($P = 0.001$). In total, there were 524 (85%) heavy smokers (at least 20 pack-years), and the mean CIMT was significantly higher in this group when compared to all other patients (0.90 ± 0.22 vs 0.81 ± 0.18 mm, respectively; $P < 0.004$). According to the GOLD criteria, 28% of the patients ($n = 167$) had a history of at least two exacerbations or one hospitalization within the last year. Patients with frequent exacerbations had a higher mean CIMT when compared to all other patients, but the difference was not significant (0.91 ± 0.21 vs 0.88 ± 0.21 mm, respectively; $P = 0.107$). There was a significant difference between the mean CIMT values of GOLD groups A and C, and of groups A and D (0.86 ± 0.24, 0.88 ± 0.20, 0.93 ± 0.22 and 0.92 ± 0.20 mm, respectively; $P = 0.033$), and also in the mean CIMT by spirometric stage (stage 1-4; 0.84 ± 0.20, 0.87 ± 0.22, 0.92 ± 0.23 and 0.93 ± 0.16 mm, respectively; $P = 0.019$).

When the patients were divided into groups as low (≤18.5 kg/m^2), normal (>18.5 to <30 kg/m^2) and high (≥30 kg/m^2) BMI, no significant difference was found in the mean CIMT values of the three groups (0.89 ± 0.20, 0.89 ± 0.23 and 0.89 ± 0.23 mm, respectively; $P = 0.999$). According to the results of arterial blood gases, the normoxemic group had a higher mean CIMT without a significant difference (0.92 ± 0.23 vs 0.90 ± 0.20 mm, respectively; $P = 0.536$).

In a Pearson's correlation test, no significant correlations were identified between mean CIMT and BMI, FVC, reversibility, pH, partial carbon dioxide pressure (PCO_2), PO_2, oxygen saturation (SO_2), fibrinogen, triglyceride, HDL, LDL or long-term oxygen treatment (LTOT) ($P > 0.05$). In contrast, positive correlations were noted between mean CIMT and age, smoking load (pack-years), biomass exposure (years), exacerbation rate over the last year, duration of hypertension (years), and cholesterol level and negative correlations between CIMT and FEV_1 (mL), FEV_1 (%), and FEV_1/FVC ($P < 0.05$). Table 3 shows the relationships between mean CIMT and the parametric variables.

Of all the patients, 434 were followed for a mean duration of follow-up of 15.7 ± 4.6 months (range: 0.5-27.5

TABLE 1 Clinical characteristics of study groups

	Group 1	Group 2		
	CIMT with <0.78 mm	CIMT with ≥0.78 mm	*t* test	*P* value
Age (years)	62.69 ± 10.61	66.81 ± 9.10	−4.594	**0.000*****
BMI (kg/m^2)	26.25 ± 4.34	26.20 ± 5.13	0.115	0.908
Smoking load (packs-years)	38.34 ± 19.45	47.45 ± 25.92	−4.034	**0.000*****
Exacerbation rate (over previous year)	0.98 ± 1.57	1.18 ± 1.65	−1.319	0.188
FVC (%)	73.92 ± 18.16	69.46 ± 20.38	2.551	**0.011***
FEV_1 (mL)	1662 ± 708	1462 ± 609	3.318	**0.001****
FEV_1 (%)	59.47 ± 18.20	53.99 ± 18.84	3.321	**0.001****
FEV_1/FVC	62.44 ± 10.25	59.91 ± 9.34	2.969	**0.003****
Reversibility (%)	6.17 ± 6.98	5.31 ± 5.77	1.185	0.238
pH	7.41 ± 0.04	7.41 ± 0.04	0.470	0.377
pCO_2 (mm Hg)	39.34 ± 7.14	40.63 ± 8.90	−0.949	0.344
pO_2 (mm Hg)	65.85 ± 20.84	67.49 ± 18.56	−0.541	0.589
SaO_2 (%)	91.67 ± 7.10	92.87 ± 5.50	−1.372	0.173
HT (years)	1.71 ± 4.66	2.68 ± 5.67	−2.121	**0.035***
Fibrinogen (mg/dL)	377.75 ± 144.316	374.59 ± 128.28	0.222	0.825
Cholesterol (mg/dL)	183.55 ± 41.19	187.69 ± 49.03	−0.954	0.341
Triglycerides (mg/dL)	134.43 ± 73.42	130.85 ± 67.84	0.554	0.579
HDL (mg/dL)	49.64 ± 21.28	47.86 ± 15.06	1.110	0.268
LDL (mg/dL)	114.26 ± 37.15	115.81 ± 43.46	−0.398	0.691
LTOT (years)	1.44 ± 2.65	1.51 ± 2.73	−0.142	0.887

Abbreviations: BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; HDL, high-density lipoprotein; HT, Hypertension; LDL, low-density lipoprotein; LTOT, long-term oxygen treatment; PCO_2, partial carbon dioxide pressure; PO_2, partial oxygen pressure; SO_2, oxygen saturation.
Note. Significant *P* values were specified with bold charecters.
**P* < 0.05, ***P* < 0.01, ****P* < 0.001.

months). Of the total study population ($N = 610$), 12.6% died during follow-up, while the mean survival of the whole group was 24.5 (range 23.8-25.2) months. The mean survival time of group 1 was slightly higher than that of group 2, which was not statistically significant [23.9 (22.7-25.3) and 21.8 (21.1-22.5) months in groups 1 and 2, respectively] ($P > 0.05$). Figure 2 shows the Kaplan-Meier survival curves of the groups.

The risk factors for CIMT increase in COPD patients were analyzed with a binary logistic regression approach. According to the results of a Hosmer-Lemeshow test, the goodness of fit of the logistic regression models was sufficient. Risk of CIMT increase was related with cholesterol level (RR; 1.008; $P = 0.038$). group B (RR: 2.209; $P = 0.002$), group C (RR: 9.751; $P = 0.009$) and group D (RR: 4.452; $P = 0.013$) were also associated with CIMT increase when compared with group A. As the risk of increase at CIMT level (>0.78 mm) in frequent exacerbators was 2.8 times of which in infrequent exacerbators, it makes frequent exacerbation as a risk factor for increased CIMT (RR: 2.798; $P = 0.040$) (Table 4).

4 | DISCUSSION

The present study revealed a significant difference at the parameters of age, smoking load, the presence of biomass exposure, GOLD groups and degree of airway obstruction between groups 1 and 2 [CIMT < or ≥0.78 mm].[10] On the other hand, frequency of exacerbation (in the last year), duration of hypertension (years) and serum cholesterol levels were among the other parameters found to be positively correlated with CIMT.

COPD is a progressive disease that is characterized with airway obstruction associated with abnormal inflammation, which does not only affects the lungs but also has systemic effects.[11] Aside from smoking as a common etiology, the increased frequency of comorbidities, such

TABLE 2 Distribution of non-parametric variables in study groups

		Group 1	Group 2		
		n (%)	n (%)	$\chi 2$	p value
Sex	Female	33 (45.7)	38 (54.3)	7.256	**0.007***
	Male	156 (29.8)	368 (70.2)		
Age (years)	< 65	105 (39.8)	159 (60.2)	14.494	**0.000****
	≥ 65	83 (25.2)	247 (74.8)		
Smoking load (packs-years)	< 20	19 (42.2)	26 (57.8)	3.227	0.072
	≥ 20	145 (29.4)	349 (70.6)		
Biomass Exposure	(-)	155 (35.9)	277 (64.1)	12.723	**0.000****
	(+)	25 (19.2)	105 (80.8)		
mMRC	1	73 (35.8)	131 (64.2)	4.245	0.236
	2	66 (28.8)	163 (71.2)		
	3	25 (25.5)	73 (74.5)		
	4	10 (27.8)	26 (72.2)		
Spirometric Stages	1	22 (41.5)	31 (58.5)	15.528	**0.001***
	2	112 (36.1)	198 (63.9)		
	3	45 (26.5)	125 (73.5)		
	4	8 (14)	49 (86)		
GOLD Groups	A	76 (41.8)	106 (58.2)	18.579	**0.000****
	B	57 (32.8)	117 (67.2)		
	C	16 (22.9)	54 (77.1)		
	D	35 (21.7)	126 (78.3)		
LTOT	Non-user	146 (31.7)	315 (68.3)	1.010	0.315
	User	18 (25.7)	52 (74.3)		

Abbreviations: mMRC: modified Medical Research Council, GOLD: Global Initiative for Chronic Obstructive Lung Disease, LTOT: Long-term oxygen treatment.
*$P < 0.01$, **$P < 0.001$.

as osteoporosis, depression and cardiovascular diseases accompanying COPD, are attributed to systemic inflammation. While atherosclerosis plays an important role in these diseases, its relationship mechanism with COPD has not yet been fully understood. Besides, the inflammatory processes that are present in both diseases are believed to contribute to its pathogenesis. It has also been emphasized that COPD represents an independent risk factor for atherosclerotic diseases.[12]

The increased risk of cardiovascular disease in COPD patients highlights the importance of monitoring these risk factors, and the identification of subclinical atherosclerosis is important in the prediction of cardiovascular risk.[13] Recent years have seen several studies investigating subclinical atherosclerosis accompanying COPD, which have reported that high CIMT is an important marker reflecting the early subclinical phase of atherosclerotic disease.[14-16] In a review investigating the presence of subclinical atherosclerosis in COPD patients, 22 studies were examined, and it was found that CIMT was significantly higher in COPD patients than in the control groups in all of studies in which CIMT was measured.[14]

In the present study, we found a positive correlation between CIMT and age. The risk of atherosclerosis increases with age (also correlated with the rate of smoking), and secondary effects of COPD may be seen frequently over years. Furthermore, the CIMT measurements of COPD patients with a smoking history of >20 packs-years were found to be higher. While smoking is a fundamental risk factor in both diseases, there have been several studies reporting that the relationship between COPD and cardiovascular disease is independent of smoking history.[17-20] A significant relationship between CIMT and biofuel exposure was also observed in the present study. Biofuel exposure also presents a significant risk, both for COPD and for atherosclerotic changes,[21] and chronic biofuel exposure has been shown to be associated with a higher prevalence of increased CIMT and atherosclerotic plaque.[22] As biofuels are in common use in our country, people who fall under in risk groups should be monitored for atherosclerosis risk, even in the absence of a COPD diagnosis.[23]

We have showed gender variation in CIMT values; males were found to have significantly higher values than females.

TABLE 3 Relationship between mean thickness of CIM and parametric variables

	Mean thickness of CIM, mm		
	n	***R***	***P* value**
Age (years)	594	0.220	**0.000*****
BMI (kg/m^2)	592	−0.077	0.062
Smoking load (packs-years)	539	0.206	**0.000*****
Biomass (years)	537	0.202	**0.000*****
Exacerbation rate (in last year)	572	0.087	**0.037***
FVC (%)	590	−0.074	0.071
FEV_1 (mL)	584	−0.123	**0.003****
FEV_1 (%)	590	−0.097	**0.019***
FEV_1/FVC	591	−0.158	**0.000*****
Reversibility (%)	422	−0.043	0.377
pH	229	−0.102	0.124
pCO_2 (mm Hg)	229	0.020	0.761
pO_2 (mm Hg)	229	0.038	0.572
SaO_2 (%)	336	0.101	0.064
HT (years)	558	0.094	**0.026***
Fibrinogen (mg/dL)	404	−0.024	0.629
Cholesterol (mg/dL)	541	0.113	**0.008****
Triglycerides (mg/dL)	541	0.044	0.311
HDL (mg/dL)	541	−0.039	0.368
LDL (mg/dL)	538	0.048	0.271
LTOT (years)	165	−0.049	0.530

Abbreviations: BMI, body mass index; CIM, carotid intima-media; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HDL, high-density lipoprotein; HT, hypertension; LDL, low-density lipoprotein; LTOT, long-term oxygen treatment; PCO_2, partial carbon dioxide pressure; PO_2, partial oxygen pressure; SO_2, oxygen saturation.
Note. Significant *P* values were specified with bold charecters.
**P* < 0.05, ***P* < 0.01, ****P* < 0.001.

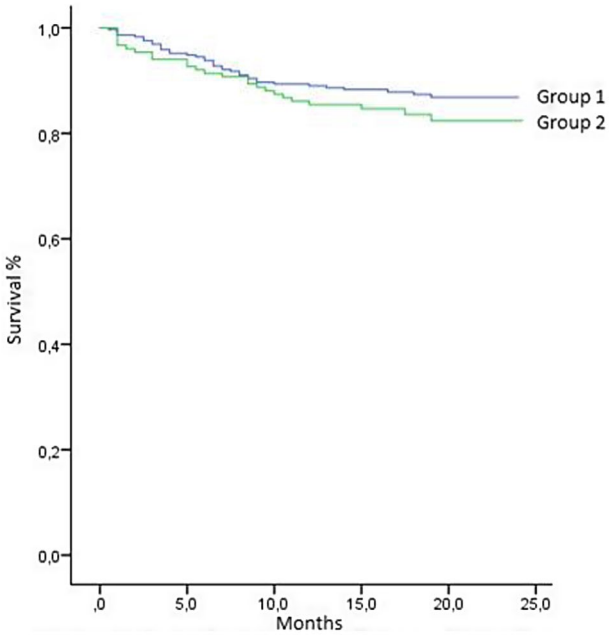

FIGURE 2 Kaplan-Meier curve showing mortality rates

Most of the studies support this result. Baroncini et al specifies that male sex is one of the strongest cardiovascular risk factors that increases CIMT.[24] It may be related with the higher endothelial dysfunction rates in males.

While contradictory results have also been reported,[6] there have been several studies identifying a negative correlation between FEV_1 level and CIMT measurements.[17,25] FEV_1 is known to be an independent predictor of cardiovascular morbidity and mortality risk.[26] Previous studies also reported a significant relationship between decreased FEV_1 levels and endothelial dysfunction, vascular wall stiffness and the presence of atherosclerosis.[27] Ambrosino et al found that the risk of carotid plaque development was significantly high in spirometric stage III and IV COPD patients.[13] In addition, the levels of systemic inflammatory markers were found to be high in patients with severe COPD, which may affect the atherosclerotic process and eventually increase the rate of cardiovascular complications in COPD.[28] In line with this data from literature, a negative correlation was found between FEV_1 levels and CIMT in the present study. Additionally, CIMT was found to be significantly associated with GOLD-combined assessment groups, as there was a significantly difference at CIMT between groups A and C, and between groups A and D. A logistic regression analysis also indicated that the risk of CIMT increased in groups B, C and D when compared to group A. The highest risk increase seen in group C was probably related to the low number of patients in this group. This assumption is further supported by the wide range of confidence intervals. This is the first study to investigate the potential relationship between CIMT and the GOLD groups. This significant association identified between GOLD groups indicates that the number and severity of exacerbations may also contribute to the pathogenesis of atherosclerosis in COPD patients, apart from FEV_1 values. Although previous studies reported no relationship between COPD exacerbations and CIMT, it has also been suggested that the increased systemic inflammatory response during exacerbations may contribute to the activation of an atherosclerotic process.[29,30]

Kiechl et al suggest that repetitive and chronic diseases may activate atherogenesis, particularly in smokers.[31] In the presence of hypertension, long-term endothelial dysfunction leads to atherosclerosis.[32] The presence of hypertension is a parameter that increases cardiovascular risk, and a positive correlation was found between CIMT and duration of hypertension in the present study. Moreover, a positive correlation was observed between CIMT and cholesterol levels, which is also a known risk factor for atherosclerosis. That said, no

TABLE 4 Binary logistic regression analysis for multiple independent parameters associated with carotid intima-media thickness increase

	95% confidence interval		
	Relative risk	**Lower-Upper**	**p-value**
Age years	1.813	0.941-3.491	0.075
Smoking load pack-years	1.085	0.273-4.310	0.907
Hypertension	1.066	0.519-2.188	0.862
CRP	0.777	0.402-1502	0.453
Cholesterol	1.008	1.000-1.016	**0.038***
Hypoxemia	1.400	0.617-3.174	0.421
GOLD			**0.027***
Group B	2.209	0.919-5.307	**0.002****
Group C	9.751	1.764-53.890	**0.009****
Group D	4.452	1.376-14.411	**0.013***
Infrequent exacerbation	0.357	0.134-0.952	**0.040***
Model χ^2 = 19.178	Cox & Snell R^2 = 0.074	Nagelkerke R^2 = 0.113	Hosmer and Lemeshow Test
P = 0.038*	Square = 0.074	Square = 0.113	χ^2 = 6.201 p= 0.625

Abbreviations: CRP: C reactive protein, GOLD: Global Initiative for Chronic Obstructive Lung Disease.
*$P < 0.05$, **$P < 0.01$.

previous studies have reported significant increases in cholesterol levels in COPD patients, which has been attributed to the anaerobic changes that occur in carbohydrate and lipid metabolism after hypoxia.[33,34]

In our study, the effects of CIMT on survival were analyzed with a Kaplan-Meier survival analysis, and the mean 2-year survival time was found to be longer in the group with lower CIMT measurements. A relationship between increased CIMT and high rates of cardiovascular mortality in COPD patients has been reported in the literature.[25] Van Gestel et al demonstrated that carotid wall measurements could be used as an accurate predictor of cardiovascular mortality and morbidity in COPD patients.[35] In our study, the difference between the groups was not significant, which may be because of the short follow-up duration.

This study has revealed important findings supporting the increase in atherosclerosis risk in the presence of COPD. The relationship between CIMT and the combined GOLD assessment groups is established for the first time in the literature. In order to investigate the presence of subclinical atherosclerosis, a Doppler USG of the carotid artery is recommended, especially in COPD patients with severe stages and frequent exacerbation. The main limitations of this study include the absence of a control group and short-term duration of follow-up.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

Designed research/study, performed research/study, contributed important reagents, collected data: Gulbas, Turan, Sarioglu, Diken, Ogan, Kadioglu, Kurtipek, Bozkus, Demirci Yilmaz, Coskun Beyan, Mutlu, Duyar, Deniz, Fazlioglu, Aysun, Tanriverdi, Okutan, Turan, İnonu, Ortakoylu, Lakadamyali, Kivanc, Atlí, Özdemir, Koşar, Mirici, Suerdem
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ETHICS

This was approved by Suerdem (Selcuk University, Konya, Turkey).

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