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ORIGINAL RESEARCH

The Effects of Smoking and Airway Restriction on Subclinical Atherosclerosis

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Purpose: Chronic obstructive pulmonary disease (COPD) is a chronic disease associated with systemic inflammation that may accelerate the atherosclerotic process. Smoking is a common risk factor for COPD and atherosclerosis. The goal of this study was to investigate the effects of COPD and smoking on carotid intima–media thickness (CIMT), in order to emphasise their importance in terms of subclinical atherosclerosis.

Materials and Methods: The study involved 208 male patients aged 45–65 years and was designed as a prospective, observational case-control study. Patients were separated into three groups, as follows: Group 1—non-smokers without airway obstruction (control) (n= 70); Group 2—smokers without airway obstruction (n= 70); and Group 3—smokers with airway obstruction(COPD) (n= 68). They were also classified into thickened CIMT (≥0.8mm) and normal CIMT (<0.8mm) groups. Pulmonary function tests (PFT), carotid Doppler ultrasound, and biochemical and haematological tests were applied to all the participants.

Results: CIMT values were markedly increased in the COPD group (1.00 [0.90–1.30] mm), compared to the smoker group without airway obstruction (0.70 [0.58–0.90] mm) and the non-smoker control group (0.60 [0.50–0.70] mm). The factors associated with CIMT were FEV_1/FVC ratio (Exp B 0.0952, p=0.003), age (Exp B 1.082, p<0.001), and cigarette pack-years (Exp B 1.030, p=0.020). In feature importance analysis, the most influential factor on CIMT was the FEV_1/FVC ratio (0.54) indicating COPD, followed by age (0.33) and cigarette pack-years (0.13).

Conclusion: Among the factors influencing CIMT, the impact of a decreased FEV_1/FVC ratio was found to be the highest. Therefore, screening with carotid US should be considered for the early detection of subclinical atherosclerosis in patients with COPD.

Keywords: atherosclerosis, CIMT, COPD, pulmonary function, smoking

Introduction

Chronic obstructive pulmonary disease (COPD) is considered to be a prevalent systemic disease linked to considerable mortality and morbidity.[1–3] It has been demonstrated in numerous studies that cardiovascular disease (CVD) is a highly prevalent comorbidity among patients diagnosed with COPD.[4] Furthermore, it is one of the primary causes of mortality in this patient population.[5,6] There are also suggestions that COPD is an independent risk factor for both atherosclerosis and cerebrovascular ischaemic stroke induced by atherosclerosis.[7,8] The pathophysiological processes underlying the relationship COPD and atherosclerosis are complex and multi-factorial. Both disorders are related to common risk factors such as cigarette smoking, chronic systemic inflammation, oxidative stress and a sedentary lifestyle. COPD is thought to accelerate the ageing process, and cellular ageing mechanisms have a major role in the underlying pathogenesis of subclinical atherosclerosis.[9–11] Furthermore, in recent years, it has been hypothesised that COPD causes a systemic inflammatory state that may increase the risk of cardiovascular disease.[12,13]

COPD is characterised by chronic airway obstruction due to abnormal and exaggerated inflammatory responses in the lungs, especially with respect to cigarette smoke and other environmental pollutants.[14] Although cigarette smoking is a known

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important risk factor for COPD and CVD, it does not fully explain the increased cardiovascular risk observed in people with COPD. Cardiovascular disease in people with COPD is likely to be influenced by many factors in addition to smoking.[15]

Intrinsic factors associated with COPD pathology are thought to contribute to cardiovascular risk beyond traditional factors. In this context, several studies have sought to ascertain whether airway limitation represents an independent risk factor for CVD and its association with pulmonary function tests (such as FEV1 and FEV1/FVC).[16]

In COPD, increased inflammatory markers such as C-reactive protein (CRP) and pro-inflammatory cytokines which are markers of systemic inflammation are associated not only with pulmonary complications but also with increased cardiovascular risk. In particularly, increased levels of CRP have been shown to be related to an excess risk of cardiovascular disease and a poorer prognosis in patients with COPD.[17,18] Persistent low-grade systemic inflammation has been proposed as a common mechanism that may explain the link between COPD and cardiovascular diseases.[19]

Atherosclerosis is a major contributor to coronary heart disease and stroke,[20] and subclinical carotid atherosclerosis is recognised as a potential indicator of future cardiovascular events.[21,22] CIMT can be reliably and non-invasively measured using carotid Doppler ultrasound, and is commonly accepted as an identifier of subclinical atherosclerosis and vascular remodelling.[23–25] Research investigating the association between carotid atherosclerosis and lung function has proposed that individuals with lower FEV_1 in the general population tend to have greater IMT thickness and are at higher risk for carotid plaque formation.[26–28]

In this present study, we analysed the combined effects of smoking, airway obstruction, age, and inflammatory markers on subclinical atherosclerosis, and in particular, to determine whether COPD is an important determinant of increased CIMT and subclinical atherosclerosis through analysing the role of decreased FEV_1/FVC ratios.

Materials and Methods

Study Population and Design

Our study was approved by the Necmettin Erbakan University Faculty of Medicine Ethics Committee with the decision dated 13.11.2015 and numbered 2015/357. All procedures involving human subjects were conducted in accordance with the ethical standards of the relevant institutional and/or national research committees and the ethical principles and standards of the Declaration of Helsinki. For the clinical trial, 208 male patients between the ages of 45 and 65 were enrolled. The research was designed as a prospective, matched, case-control, observational study. Patients were divided into three groups according to the following criteria: Group 1(control)—non-smokers without airway obstruction (n = 70); Group 2—smokers without airway obstruction (n = 70); and Group 3—smokers with airway obstruction (COPD) (n = 68).

All the participants underwent pulmonary function testing (PFT), carotid Doppler ultrasound, biochemistry (low-density lipoprotein (LDL), high-density lipoprotein (HDL, triglycerides, total cholesterol, glucose), complete blood count, CRP and other blood tests. Inclusion criteria were male patients aged 45 to 65 years with complete data on necessary investigations. Exclusion criteria were history of hypertension or hyperlipidaemia, lipid-lowering medication, diabetes or antidiabetic medication, unstable COPD, chronic infection, haematological or oncological illness, coronary or peripheral arterial disorder, hepatic or renal failure, history of cerebrovascular illness and conditions causing platelet dysfunction.

Spirometric Analysis

Pulmonary function tests were conducted after admission to the pulmonology outpatient clinic. FEV_1 (forced expiratory volume in one second), FVC (forced vital capacity) and FEV_1/FVC ratio were measured for all participants using a computerised spirometer (BTL-08 Spiro and BTL-08 Spiro Pro, Turkey). Spirometric measurements were performed as previously recommended by the European Respiratory Society, and the highest value obtained from at least three measurements was taken into consideration.[28] Before spirometry, participants were required to avoid short-acting and long-acting beta-2 agonists or theophylline, as well as physical exercise, heavy meals and smoking. Lung function test measurements included forced expiratory lung volume %FEV_1, FVC and FEV_1/FVC ratio. Patients were assessed according to the GOLD 2019 guidelines, and COPD was defined as $FEV_1/FVC < 70\%$.

Radiologic Analysis

All CIMT measurements were performed by an experienced radiologist. The clinical conditions of the patients were not known to the radiologist. Measurements were performed using an ultrasound device (Aplio 500; Toshiba Medical Systems, Tokyo, Japan) that included a 12 MHz linear probe. Measurements were obtained at three separate sites: the left and right and common carotid arteries, the bifurcation, and the first 2 cm of the internal carotid artery, with the patients in the supine position and the neck tilted approximately 20°, evaluating only the posterior wall. CIMT measurements were performed using B-mode imaging, which measures the distance between the intima–lumen and media–adventitia interfaces in the longitudinal plane. The average of three measurements from the thickest part of each carotid artery was used to calculate the mean CIMT. The CIM was considered thickened if the measurement was ≥0.8 mm.[29,30]

Statistical Analysis

Statistical analyses were carried out utilizing IBM's Statistical Package for Social Sciences (SPSS), version 25.0 (Chicago, IL, USA). The normality of the distribution of numerical variables was tested by performing the Shapiro–Wilk test. An independent samples *t*-test or one-way analysis of variance was employed for the comparison between groups of normally distributed variables, while a Mann–Whitney *U*-test or Kruskal–Wallis test was used for variables that did not show normal distribution. Binary logistic regression analysis was employed for the purpose of evaluating the risk factors associated with CIMT. Pearson's or Spearman correlation analysis applied to assess relationships between continuous variables, depending on the normality of their distribution. Python 3.7.9 (Delaware, USA) software was used to calculate the significance of variables. The effect percentages of variables affecting the dependent variable were calculated using Gradient Boosting Regressor, and these are shown in the variable significance graph. For the dependent variable CIMT, the contribution of each independent variable to the model was expressed with a significance score reflecting the percentage role of each variable in predicting CIMT. Continuous data are represented as mean ± standard deviation (SD), while categorical data are shown as median (Q1-Q3). Statistical significance was considered to be $p < 0.05$.

Results

Demographic and Clinical Characteristics

The demographics of the patient groups involved in the study are shown in Table 1. The mean age difference was highly significant between the patient groups ($p < 0.001$). The mean age of smokers with COPD (60 [57–65] years) was significantly higher than that of smokers without airway obstruction (51.5 [57–65] years) and the control group of non-smokers without airway obstruction (49 [57–65] years). Body mass index (BMI) was not markedly different between the study groups ($p = 0.809$). Nevertheless, pack-years of smoking which may reflect the progressive effect of smoking-related diseases over time was considerably increased in the COPD group ($p < 0.001$).

Table 1 Demographic Characteristics and Comparison of the Parameters in the Groups of Participants

	Group 1 (n=70)	Group 2 (n=70)	Group 3 (n=68)	p-Value
Age (years)	49.00 (46.00–57.00)[a]	51.50 (46.00–59.00)[a]	60.00 (57.00–65.00)[b]	**<0.001**[α]
BMI (kg/m^2)	26.42 ± 3.72	26.38 ± 3.15	26.05 ± 4.11	0.809[β]
Glucose (mg/dL)	92.50 (84.75–102.00)	88.50 (84.00–100.25)	92.50 (86.00–102.00)	0.913[α]
LDL cholesterol (mg/dL)	117.50 (99.75–136.25)	118.00 (96.75–148.25)	110.50 (96.00–132.00)	0.101[α]
HDL cholesterol (mg/dL)	45.50 (37.75–55.25)[a]	41.00 (35.00–47.00)[ab]	39.50 (35.00–48.75)[b]	**0.013**[α]
TG (mg/dL)	150.00 (100.25–200.00)	149.00 (101.00–194.50)	130.50 (102.50–177.25)	0.757[α]
Total cholesterol (mg/dL)	191.00 (159.50–216.25)	186.50 (152.75–216.75)	177.50 (154.00–218.50)	0.406[α]
Cigarette pack-years	0.00 (0.00–0.00)[a]	25.00 (20.00–30.00)[a]	35.00 (30.00–45.00)[b]	**<0.001**[γ]
FEV1 (%)	88.50 (83.50–94.25)[a]	84.00 (78.00–93.25)[b]	58.00 (44.00–65.00)[c]	**<0.001**[α]
FVC (%)	89.00 (81.75–96.25)[a]	88.00 (77.75–96.00)[a]	55.00 (48.00–65.75)[b]	**<0.001**[α]

(*Continued*)

Table 1 (Continued).

	Group 1 (n=70)	Group 2 (n=70)	Group 3 (n=68)	p-Value
FEV_1/FVC ratio (%)	98.00 (93.75–100.00)[a]	90.00 (85.00–98.00)[b]	69.00 (66.25–70.00)[c]	**<0.001**[α]
CIMT	0.60 (0.50–0.70)[a]	0.70 (0.58–0.90)[b]	1.00 (0.90–1.30)[c]	**<0.001**[α]
CRP (mg/L)	3.27 (3.02–4.51)[a]	3.27 (3.11–3.90)[a]	4.22 (3.27–14.20)[b]	**<0.001**[α]
WBC ($\times 10^3$ /μL)	7.07 (6.03–8.13)[a]	8.45 (7.54–9.56)[b]	8.59 (7.25–11.32)[b]	**<0.001**[α]
Hb (g/dL)	15.20 (13.98–16.20)[a]	15.75 (15.00–16.53)[b]	15.10 (13.83–15.90)[a]	**0.002**[α]
Htc (%)	45.40 (42.08–46.53)	46.05 (43.90–47.73)	45.70 (43.65–48.75)	0.061[α]
Neutrophil (/μL)	3.89 (3.02–5.03)[a]	4.78 (3.88–5.84)[b]	5.33 (4.09–7.16)[b]	**<0.001**[α]
Lymphocyte (/μL)	2.28 (2.02–2.67)[a]	2.67 (2.07–3.13)[b]	2.32 (2.00–2.87)[ab]	**0.047**[α]
PLT ($\times 10^3$ /μL)	250.00 (214.75–286.25)	241.50 (206.75–284.25)	263.00 (213.25–310.00)	0.528[α]
MPV (fL)	10.30 ± 0.79	10.35 ± 0.82	10.16 ± 0.75	0.344[β]

Notes: Continuous variables are presented as mean ± standard deviation or median (Q1-Q3): categorical variables are presented as number (%). Statistically significant p values (p<0.05) are shown in bold. [α] Kruskal–Wallis test was applied. [β] One-way ANOVA was applied. [γ] Mann–Whitney *U*-test was applied. a, b, c shows statistical significance (p <0,05).

Abbreviations: BMI, body mass index; CRP, C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; MPV, mean platelet volüme; PLT, platelet; CIMT, carotid intima–media thickness; TG, triglycerides; WBC, white blood cell; Hb, haemoglobin; Htc, haematocrit; FEV_1; 1 second forced expiration; FVC; forced vital capacity.

Lung Function Tests

The %FEV_1, %FVC, and FEV_1/FVC ratios were significantly lower among smokers with COPD compared to smokers and non-smokers without airway obstruction ($p < 0.001$). In addition, the FEV_1/FVC ratio and %FEV_1 values differed significantly between smokers without airway obstruction and non-smokers without airway obstruction ($p < 0.001$). However, %FVC values were not significantly different in smokers without airway obstruction compared to non-smokers (p=0.14).

Laboratory Data

No important differences in fasting glucose, LDL cholesterol, total cholesterol, and triglyceride values were found between the three groups (p= 0.913, p= 0.101, p= 0.406, p= 0.757). However, there was a higher level of HDL cholesterol in COPD smokers as opposed to non-smoking controls, which was statistically significant between groups (p= 0.013). CRP, WBC, Hb (haemoglobin), neutrophil and lymphocyte values were significantly different between the three groups (p< 0.001, p< 0.001, p= 0.002, p< 0.001, p= 0.047). Levels of CRP, WBC, and neutrophils were notably elevated in COPD smokers, compared to non-smokers.

Carotid Intima-Media Thickness

The median CIMT was considerably increased in smokers with COPD (1.00 [0.90–1.30] mm), when compared to smokers without airway obstruction (0.70 [0.58–0.90] mm) and non-smokers (60 [0.50–0.70] mm) ($p < 0.001$). In addition, CIMT values in the smoker group without airway obstruction were also significantly higher than in the non-smoker control group (Table 1). All patients were also stratified according to CIMT alone and divided into two groups: normal CIMT (<0.8 mm) and thickened CIMT (≥0.8 mm) (Table 2). Age, cigarette pack-years, %FEV_1, %FVC and FEV_1/FVC ratios were significantly different in the thickened CIMT group ($p < 0.001$). Among the laboratory parameters, CRP, WBC, haemoglobin, neutrophil levels and NLR were statistically markedly different between the two groups (p=0.001, p=0.001, $p < 0.001$, p = 0.004), while glucose and lipid levels including LDL, HDL, triglycerides and total cholesterol were not different (p=0.391, p=0.601, p=0.486, p=0.862, p=0.230).

Multivariate Analysis

The findings of multivariate logistic regression analysis assessing the variables influencing CIMT and their correlations are displayed in Table 3. In all patients, age, smoking pack-years and FEV_1/FVC ratio were independently associated

Table 2 Comparison of All Patients According to CIMT

	Normal CIMT (<0.8 mm)	Thickened CIMT (≥ 0.8 mm)	p
Age (years)	49.00 (46.00–57.00)	59.00 (54.00–65.00)	**<0.001**[γ]
BMI (kg/m^2)	26.47±3.66	26.07±3.67	0.438[&]
Glucose (mg/dL)	90.00 (86.00–103.00)	94.00 (88.00–101.25)	0.391[γ]
LDL cholesterol (mg/dL)	110.00 (90.00–130.25)	115.00 (97.00–142.00)	0.601[γ]
HDL cholesterol (mg/dL)	42.00 (36.00–51.00)	41.00 (35.00–49.00)	0.486[γ]
TG (mg/dL)	150.00 (95.50–199.25)	135.00 (106.25–195.25)	0.862[γ]
Total cholesterol (mg/dL)	183.00 (152.75–210.75)	189.00 (156.00–219.25)	0.230[γ]
Cigarette pack-years	0.00 (0.00–30.00)	30.00 (20.00–40.00)	**<0.001**[γ]
FEV$_1$ (%)	86.00 (78.00–94.00)	69.00 (55.00–84.00)	**<0.001**[γ]
FVC (%)	88.00 (77.00–96.00)	67.50 (52.00–87.00)	**<0.001**[γ]
FEV$_1$/FVC ratio (%)	96.00 (87.00–99.00)	70.00 (68.00–89.50)	**<0.001**[γ]
CRP (mg/L)	3.27 (3.11–4.05)	3.60 (3.23–8.18)	**0.001**[&]
WBC (×10^3 /μL)	7.69 (6.39–8.91)	8.49 (7.28–9.97)	**0.001**[&]
Hb (g/dL)	15.30 (14.30–16.22)	15.50 (14.00–16.00)	0.416[γ]
Htc (%)	45.50 (43.00–47.02)	45.60 (43.75–46.82)	0.858[γ]
Neutrophil (×10^3 /μL)	4.20 (3.27–5.24)	5.11 (3.98–6.28)	**<0.001**[γ]
Lymphocyte (×10^3 /μL)	2.35 (1.99–2.97)	2.44 (2.02–2.83)	0.933[γ]
PLT (×103 /μL)	250.00 (208.50–289.25)	244.00 (212.50–289.50)	0.894[γ]
MPV (fL)	10.28 ±0.82	10.25 ±0.75	0.847[&]
NLR	1.78 (1.38–2.20)	1.97 (1.55–2.89)	**0.004**[γ]
PLR	107.69 (82.02–127.55)	103.77 (80.85–127.75)	0.748[γ]
MPV/PLT ratio	0.04 (0.03–0.05)	0.04 (0.03–0.04)	0.930[γ]

Notes: Continuous variables are presented as mean ± standard deviation or median (Q1-Q3): categorical variables are presented as number (%). Statistically significant p values (p<0.05) are shown in bold. [γ] Mann–Whitney *U*-test was applied. [&] Independent samples *t*-test.

Abbreviations: BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, Triglycerides; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; CRP, C-Reactive Protein; WBC, white blood cell; Hb, haemoglobin; Htc, haematocrit; PLT, platelet; MPV, mean platelet volüme; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; CIMT, carotid intima–media thickness.

Table 3 Logistic regression analysis for variables affecting CIMT

	B	Wald	Sig.	Exp(B)	95% C.I. for EXP(B)	
					Lower	Upper
Age	0.076	11.990	0.001	1.079	1.034	1.127
Cigarette pack-years	0.028	4.801	0.028	1.028	1.003	1.054
Total Cholesterol	0.005	1.774	0.183	1.005	0.998	1.013
FEV$_1$/FVC Ratio	-0.049	8.336	0.004	0.952	0.921	0.984
CRP	0.024	0.472	0.492	1.025	0.956	1.099
MPV/PLT Ratio	14.961	0.985	0.321	3143312.642	0.000	2145E+19
Constant	-2.538	1.180	0.277	0.079		

Abbreviations: FEV1/FVC Ratio, forced expiratory volume in 1 second/forced vital capacity ratio; CRP, C-Reactive Protein; MPV/PLT Ratio, mean platelet volume/platelet count ratio; B, coefficient; Wald, Significance test; Sig., p value; Exp(B), exponentiated coefficient (odds ratio); C.I., confidence interval for Exp(B).

with CIMT after adjustment for all variables. The parameters most strongly associated with thickened CIMT were age (ExpB: 1.082, p< 0.001), smoking pack-years (ExpB: 1.030, p = 0.020) and FEV$_1$/FVC ratio (ExpB: 0.0952, p = 0.003).

An analysis of the factors affecting the dependent variable CIMT was performed, and the significance percentages were calculated and presented as a "feature importance" plot (Figure 1). The most influential factor on CIMT was the FEV$_1$/FVC ratio indicating COPD (0.54), followed by age (0.33) and smoking pack-years (0.13). Although age and

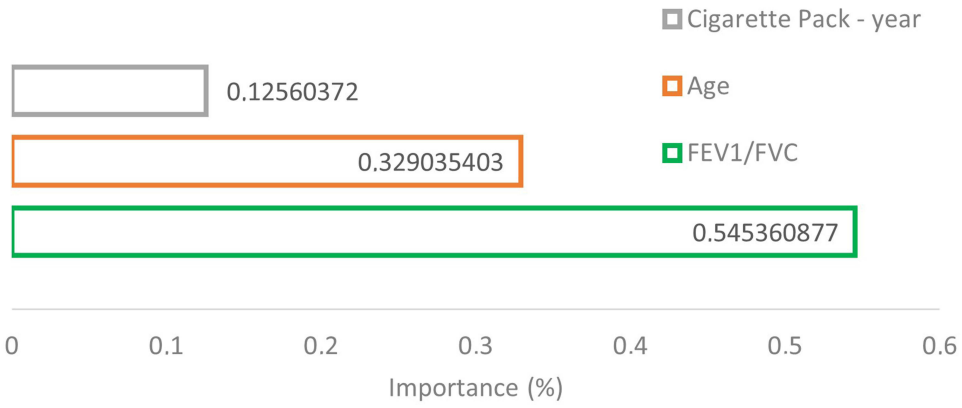

Figure 1 Feature Importance Graph.

smoking pack years were also found to be associated, they were not as influential as COPD status, as reflected by the lower FEV_1/FVC ratio.

Correlation Analysis

Table 4 presents the outcomes of the correlation analysis, showing the relationships between CIMT and age, smoking pack-years, FEV_1, FVC, FEV_1/FVC ratio, CRP, WBC, and neutrophil count. Significantly negative correlations were found between CIMT and FEV_1 (r= −0.416), FVC (r= −0.406), and FEV_1/FVC ratio (r= −0.499), while positive correlations were found between CIMT and age (r= 0.515), pack-years of smoking history (r= 0.491), CRP (r= 0.284), and neutrophil count (r= 0.329).

Discussion

This research investigates the impact of smoking and airway obstruction (COPD) on subclinical atherosclerosis, and examines the potential impacts of these factors on CIMT. Our findings show that patients who smoke and have been diagnosed with COPD exhibit significantly higher CIMT values, when compared to smoking and non-smoking controls without airway obstruction. These associations emphasise that smoking and airway obstruction may act as independent and combined factors in increasing cardiovascular risk. Importantly, our analyses suggest that COPD as reflected by decreased FEV_1/FVC ratios may have a more pronounced effect on CIMT than smoking alone.

CIMT is a potential indicator of vascular remodelling in the early stages of atherosclerosis,[24] and may predict plaque formation.[25] Subclinical carotid atherosclerosis has been shown to have a good correlation with cerebrovascular and

Table 4 Spearman Correlation Test

Variables(r)	Age	Cigarette Pack-Years	FEV_1	FVC	FEV_1/FVC Ratio	CIMT	CRP	WBC	Neutrophil
Age	1								
Cigarette pack-years	0.36**	1							
FEV_1	−0.39**	−0.56**	1						
FVC	−0.34**	−0.56**	0.84**	1					
FEV_1/FVC ratio	−0.43**	−0.64**	0.79**	0.77**	1				
CIMT	0.51**	0.49**	−0.41**	−0.40**	−0.49**	1			
CRP	0.27**	0.28**	−0.45	−0.47**	−0.45**	0.28**	1		
WBC	0.16*	0.33**	−0.26**	−0.22*	−0.22**	0.30*	0.29**	1	
Neutrophil	0.24**	0.30**	−0.29**	−0.24**	−0.25**	0.32**	0.33**	0.82**	1

Notes: *: $p < 0.05$, **: $p < 0.0001$.
Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; CIMT, carotid intima–media thickness; CRP, C-reactive protein; WBC, white blood cell; r, correlation coefficient.

coronary atherosclerosis[21] and, thus, is considered a predictor of future cardiovascular diseases.[22] A meta-analysis reported that CIMT was 0.77 mm ± 0.18 in patients with cerebrovascular stroke, 0.76 mm ± 0.17 in patients with myocardial infarction, and 0.82 mm ± 0.17 in patients with both myocardial infarction and cerebrovascular stroke.[31] These findings suggest that COPD is a systemic disease characterised by persistent and progressive airway obstruction, exacerbations and comorbidities may be more closely associated with subclinical atherosclerosis.[32] Comorbidities such as arrhythmias, myocardial infarction, ventricular hypertrophy, and cerebrovascular stroke are primarily responsible for the morbidity and mortality observed in patients with COPD.[33] A number of research studies have shown an increased risk of cardiovascular morbidity and mortality in patients with COPD.[34,35] It has also been found that mild and moderate COPD patients are more commonly at risk of death from cardiovascular disease than death from respiratory failure.[36] Increased CIMT values have been reported in individuals with stable COPD compared with healthy people, regardless of smoking status. In addition, significantly higher CIMT values have been observed in patients diagnosed at an early stage of COPD, but not yet treated, compared to healthy control subjects.[37,38] Increased CIMT in COPD has been demonstrated to be correlated with a high risk of cardiovascular mortality.[39] Hafez et al reported a CIMT of 0.85 ± 0.18 mm in COPD patients and 0.63 ± 0.076 mm in controls.[40] In our study, the mean CIMT (1.00 mm) in the smokers with COPD group was significantly increased, when compared to the smokers without airway obstruction group (0.70 mm) and the control group without airway obstruction (0.70 mm). These findings suggest that subclinical atherosclerosis may be more prevalent in smokers with COPD.

There is a well-documented, powerful association between low FEV_1 and cardiovascular mortality and morbidity. It has been demonstrated that the potential for the occurrence of a fatal myocardial infarction in COPD patients is high, independent of smoking, and the risk of developing cardiovascular disease increases with the severity of COPD.[41] Some academic studies have indicated an adverse correlation between elevated CIMT and %FEV1 in COPD patients, as well as an elevated risk of cardiovascular mortality in patients with low %FEV1.[42–44] The current study showed a very significant adverse association between %FEV1 and increased CIMT. Chronic low-grade systemic inflammation has been reported to be a common pathologic mechanism in both COPD and atherosclerotic cardiovascular disease.[34] The presence of elevated serum platelets, fibrinogen, leukocytes, chemokines, cytokines, and acute phase proteins strongly suggests that it may be associated with systemic inflammation of COPD.[45] Low-grade systemic inflammation has also been demonstrated in non-smoking COPD patients.[46] In our study, CIMT was positively correlated with CRP and negatively correlated with FEV_1, which is similar to the literature reporting associations between CRP, FEV_1, and IMT. In addition, CRP, WBC, neutrophil and NLR values were markedly higher in patients with thickened IMT. These results indicated that the relationships between decreased FEV_1 and FEV_1/FVC ratios and subclinical atherosclerosis may be related to inflammatory markers, such as elevated CRP, and support the view that inflammation accelerates the atherosclerotic process in COPD patients. Smoking is known to trigger vascular damage and atherosclerosis,[47] probably through its effects on endothelial dysfunction, inflammation and oxidative stress.[48] In our study, mean CIMT was significantly greater in the smoking group of COPD than in the two other groups. In addition, CIMT values in the smoker group without airway obstruction were also significantly higher than in the non-smoker control group. These findings support that although smoking has an effect on subclinical atherosclerosis, airway obstruction may be a more influential factor.

In our feature importance analysis, conducted to identify the primary factors influencing subclinical atherosclerosis (CIMT), the importance percentages were as follows: FEV_1/FVC ratio (0.54), age (0.33) and smoking pack-years (0.13). These findings indicate that airway limitation (COPD) has a stronger effect on CIMT than smoking status. Additionally, these results emphasise that COPD, smoking and increased age each contribute to the increase in CIMT, with their combined effects further elevating the risk of atherosclerotic disease.

Several previous studies have reported inconsistent results regarding cholesterol levels, one of the traditional risk factors for atherosclerosis, in COPD patients. The results of these studies varied, with LDL cholesterol levels in COPD patients being increased, decreased, or no difference compared to healthy individuals.[49–51] In our study, there was no meaningful difference in lipid profiles in patients with COPD and controls. The exclusion of participants with hyperlipidemia was thought to be an important factor in this situation. Although there were no significant differences in lipid profiles, the observation of elevated CIMT values in COPD patients suggests the involvement of different mechanisms in the pathogenesis of subclinical atherosclerosis in these individuals. Several studies have indicated that

CIMT increases gradually with age, and age is one of the strongest predictors of subclinical atherosclerosis.[8,52] With advancing age, arterial stiffening, endothelial dysfunction and vascular remodelling occur, all of which contribute to increased IMT.[53] The age-related increase in CIMT has been demonstrated to although there were no significant differences in lipid profiles, the observation of elevated CIMT values in COPD patients indicates the involvement of distinct mechanisms in the pathogenesis of atherosclerosis in these patients particularly stroke and myocardial infarction.[54] In our present study, age was a very important predictor of increased CIMT. The positive correlation between age and CIMT was interpreted as an indicator of cumulative vascular changes over time.

Given the strong association between airway obstruction and subclinical atherosclerosis, it is proposed that COPD patients should be investigated for atherosclerosis, in order to determine the risk of developing subclinical atherosclerosis. Carotid ultrasound is an accessible, affordable, and reliable imaging modality for the assessment of carotid atherosclerosis through measuring CIMT and atheromatous plaques. Despite minor differences between study participants, the results presented in our study were obtained by averaging the CIMT measurements from three different segments of the carotid artery.

Although our study provides important findings, it has some limitations. First, this is not a long-run prospective study, so it cannot confirm whether the association between smoking, COPD and atherosclerosis increases the risk of cardiovascular disease. Second, our study population was limited to male patients aged 45–65 years. The results cannot be extrapolated to women. Third, the sample size is relatively small, which affects the power of the study.

Conclusion

In this study, a low FEV_1/FVC ratio (COPD), smoking, and age were identified as significant determinants of subclinical atherosclerosis. However, among these factors, the most substantial contributor to increased CIMT was found to be a decrease in the FEV_1/FVC ratio, indicating COPD. Although smoking is recognised as an independent risk factor for increased CIMT, our findings suggest that COPD plays a more prominent role in subclinical atherosclerosis. Therefore, patients with COPD should be checked for subclinical atherosclerosis at an earlier phase, with carotid Doppler ultrasonography serving as an accessible and appropriate screening method. In conclusion, to better understand the mechanisms of atherosclerosis in COPD patients, reduce cardiovascular mortality and develop improved treatment strategies, there is a need for more extensive and long-term research in the future.

Data Sharing Statement

The dataset used in this study is available from the corresponding author upon reasonable request.

Ethical Approval

The study was conducted according to the principles of the Declaration of Helsinki and approved by the local ethics committee (Approval number: 357/2015). Written informed consent was obtained from all participants before inclusion in the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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