













# Cardiovascular Prognosis of Subclinical Chronic Obstructive Pulmonary Disease in Patients with Suspected or Confirmed Coronary Artery Disease

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**Background:** Chronic obstructive pulmonary disease (COPD) worsens prognosis in patients with coronary artery disease (CAD). However, the cardiovascular prognosis in patients with stable or mildly symptomatic COPD remains unclear. Here, we sought to determine the long-term cardiovascular events in patients with subclinical or early-stage COPD with concomitant CAD.

**Methods:** This was a longitudinal analytical study involving 117 patients with suspected or established CAD who underwent assessment of pulmonary function by spirometry and who were followed up for six years (March 2015–January 2021). The patients were divided into two groups, one comprising COPD (n=44) and the other non-COPD (n=73) patients. Cox regression was used to evaluate the association between COPD and cardiovascular events, with adjustment for the established CAD risk factors, and the effect size was measured by the Cohen test.

**Results:** COPD patients were older ( $p=0.028$ ), had a greater frequency of diabetes ( $p=0.026$ ), were more likely to be smokers ( $p<0.001$ ), and had higher modified Medical Research Council scores ( $p<0.001$ ). There was no difference between the groups regarding gender, body mass index, hypertension, dyslipidemia, family history of CAD, and type of angina. CAD frequency and the proportion of patients with severe and multivessel CAD were significantly higher among COPD than among non-COPD patients (all  $p<0.001$ ). At six-year follow-up, patients with COPD were more likely to have experienced adverse cardiovascular events than those without COPD ( $p<0.001$ ; effect size, 0.720). After adjusting for established CAD risk factors, COPD occurrence remained an independent predictor for long-term adverse cardiovascular events (OR: 5.13; 95% CI: 2.29–11.50;  $p<0.0001$ ).

**Conclusion:** COPD was associated with increased severity of coronary lesions and a greater number of adverse cardiovascular events in patients with suspected or confirmed CAD. COPD remained a predictor of long-term cardiovascular events in stable patients with subclinical or early-stage of COPD, independently of the established CAD risk factors.

**Keywords:** COPD, coronary artery disease, risk factors, ischemic heart disease, myocardial infarction

## Introduction

Despite being preventable and treatable, chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide and the fourth leading cause of death in Brazil.<sup>1-3</sup> This is mainly due to the chronic systemic inflammatory response induced by COPD and its promotive and aggravating effect on conditions such as pulmonary hypertension, lung cancer, and cardiovascular diseases (CVD).<sup>4-6</sup>

COPD is a risk factor for the development of coronary artery disease (CAD) independently of other cardiovascular risk factors and its occurrence worsens prognosis in patients with CAD.<sup>7,8</sup> Excess or chronic inflammation can result in damage to the pulmonary and cardiovascular systems. The inflammatory environment is characterized by the recruitment of inflammation-associated immune cells, which further increases the inflammatory response, leading to atherosclerosis, increased platelet activation, thrombosis, and the accelerated evolution and ultimate rupture of vascular plaques.<sup>9–11</sup> The shared risk factors between COPD and CAD, such as smoking and pulmonary malfunction, can further heighten the inflammatory response. Smoking disrupts the lipid profile, making it more atherogenic, thereby inducing changes in platelet function and causing endothelial damage. Lung malfunction, in turn, is associated with an increased risk for diabetes, hypertension, stroke, and CVD.<sup>12</sup> Moreover, studies have shown that the prevalence of these comorbidities increases with the severity of the disease as well as the extent of COPD exacerbation.<sup>13</sup>

Despite being underdiagnosed, COPD is common in patients with CAD. Indeed, airflow limitation is not detected in 60% to 87% of patients with ischemic heart disease. The rates of underdiagnosis are even higher among former smokers, mildly symptomatic individuals, and patients with mild airflow limitation. Conversely, COPD is incorrectly diagnosed in a small proportion of CAD patients. This inaccuracy may be explained by the overlap in the clinical presentation of the two diseases, such as breathlessness and chest pain, which results in the lack of a second diagnosis once one has already been made.<sup>10,14,15</sup>

Large population-based studies have demonstrated that patients with COPD are at increased risk for cardiovascular events and associated mortality, particularly following COPD exacerbation, hospitalization, acute coronary syndrome, and cardiac revascularization.<sup>16,17</sup> However, the cardiovascular prognosis of patients with mild/moderate or stable COPD remains unclear. Thus, the objective of this study was to assess the long-term cardiovascular events in patients with subclinical COPD or those in the initial stages of the disease with a concomitant diagnosis of CAD.

## Methods

### Study Design and Population

This was a longitudinal and analytical study, carried out from March 2015 to January 2021, involving a cohort of 117 patients with suspected or established CAD who underwent assessment of pulmonary function by spirometry and who were subsequently followed up for six years. These patients were referred by their physician for the evaluation of myocardial ischemia using the ergometric test or exercise stress echocardiography. At the time of the noninvasive cardiac test, spirometry was performed for all the patients (COPD or non-COPD). The inclusion criteria were patients older than 40 years who had stable cardiac and pulmonary disease (ie, those who did not present with clinical evidence of acute coronary syndrome, heart failure, respiratory infection, or recent hospitalization) at least eight weeks before data collection. The exclusion criteria were patients with a previous diagnosis of COPD, asthma or reversible obstruction, allergy, hyperreactivity, occupational lung disease, or sequelae of pulmonary pathologies such as tuberculosis or pulmonary fibrosis. Informed consent was obtained from all the participants and the study protocol was approved by the Research Ethics Committee of the Federal University of Sergipe as well as the local ethics committee of each participating institution and complies with the Declaration of Helsinki.

### Demographic and Clinical Characteristics

Demographic and clinical data were collected via a structured case report form and included age, gender, weight, height, cardiovascular risk factors (such as diabetes, hypertension, dyslipidemia, family history of CAD), life habits, the medication used, actual symptoms, and assessment of limitation in activities of daily living imposed by dyspnea according to modified Medical Research Council (mMRC) criteria.<sup>18,19</sup>

### Diagnosis of COPD

The diagnosis of COPD was established by spirometry, which was performed for all participants according to American Thoracic Society performance criteria.<sup>20</sup> A post-bronchodilator ratio of forced expiratory volume in 1s (FEV1) to forced vital capacity (FVC) of less than 70% of the predicted value confirmed the presence of persistent airflow limitation,

which was compatible with COPD diagnosis.<sup>21</sup> COPD severity was evaluated following GOLD recommendations and the patients were categorized into four severity classes (GOLD I–IV) according to spirometric criteria.<sup>22</sup>

## Diagnosis of CAD

All the patients included in this study had either suspected CAD based on a medical history of angina and/or inducible myocardial ischemia in the stress test (ergometric test or exercise stress echocardiography) or confirmed CAD with evidence of coronary atherosclerotic lesions by coronary computed tomography angiography or invasive coronary angiography.<sup>23</sup> Among patients with known coronary anatomy, CAD was classified according to the degree of stenosis, severity, and extent of coronary lesions. Non-obstructive CAD was defined by the detection of lesions with a degree of luminal stenosis of less than 50%; the criterium for obstructive CAD was a degree of luminal stenosis of 50% or more in at least one of the coronary arteries. Meanwhile, CAD severity was graded according to the degree of luminal obstruction, as follows: discrete CAD, lesions with a degree of stenosis of less than 39%; moderate CAD, lesions with a degree of stenosis of 40% to 69%; and severe CAD, lesions with a degree of stenosis of 70% or more in at least one coronary segment. The criteria for determining the extent of CAD were based on the number of affected major epicardial vessels and the detection of disease in the left main coronary artery. Thus, the extent of CAD was classified as univessel, bivessel, trivessel, or left main CAD. The multivessel pattern represents obstructive CAD in two or more major epicardial vessels, including or not the left main coronary artery.<sup>24,25</sup>

## Follow-Up and Adverse Cardiovascular Events

During the six years of follow-up, the patients were monitored for adverse cardiovascular events, including the need for invasive coronary angiography, cardiac revascularization, myocardial infarction, cardiac hospitalization, and cardiac death. The decision for invasive coronary angiography was taken by the patient's cardiologist or, in an emergency, by the attending physician, according to standard clinical practice. Cardiac revascularization was described as any clinically driven revascularization event, including percutaneous coronary intervention (PCI) or bypass surgery. The diagnosis of myocardial infarction was defined as new Q waves, new persistent ST-segment or T-wave changes, or elevated troponin levels. Cardiac hospitalization was described as any hospitalization in which a suspected diagnosis of cardiac disorder was the primary reason for admission. Finally, cardiac death was diagnosed as an unexplained death without an identifiable non-cardiac cause.<sup>26,27</sup>

## Statistical Analysis

Continuous variables were expressed as means  $\pm$  standard deviation. The Kolmogorov–Smirnov test was applied to evaluate the normality of distribution. According to the normality of the sample, the Student's *t*-test or the Mann–Whitney test was used for independent groups. For categorical variables, the results are presented as absolute frequency or percentage; the chi-square test or Fisher's exact test was employed for comparisons between the two groups, as appropriate. The Kaplan–Meier method was used to estimate adverse cardiovascular event-free survival and the Log rank test was used to test the differences between the groups. Cox regression was used to assess the association between COPD and the occurrence of combined adverse cardiovascular events, adjusting for the variables age, gender, diabetes, hypertension, and dyslipidemia. The effect size was measured by the Cohen test and Cohen's *h* was categorized as a small ( $<0.25$ ), medium ( $0.25 < 0.50$ ), or large ( $\geq 0.50$ ) effect size, based on benchmarks suggested by Cohen.<sup>28</sup> Statistical analyses were performed using SPSS for Windows, version 26 (IBM Corporation, Armonk, NY, USA) and WINPEPI, version 11.65 (Copyright J.H Abramson, 23 August 2016). A *p*-value  $< 0.05$  was considered significant and the statistical power was 0.80 or higher.

## Results

The demographic, clinical and spirometric data of all the patients (with or without COPD) are shown in Table 1. Patients with COPD were older ( $62 \pm 9$  vs  $58 \pm 10$  years,  $p=0.028$ ) and had a higher frequency of diabetes (47.7% vs 27.4%;  $p=0.026$ ). There was also a greater proportion of current smokers (31.8% vs 2.7%;  $p<0.001$ ) and higher mMRC scores ( $p<0.001$ ) among the COPD patients. Additionally, patients with COPD had lower FEV1 and FEV1/FVC ratio ( $p<0.001$ )

**Table 1** Demographic and Clinical Characteristics of Patients with and without COPD

Variable	Total (n = 117)	COPD (n = 44)	Non-COPD (n = 73)	p-value*
Age (years)	59 ± 10	62 ± 9	58 ± 10	0.028
Male, n (%)	63 (53.8)	26 (59.1)	37 (50.7)	0.377
BMI (kg/m <sup>2</sup> )	27.82 ± 4.66	27.96 ± 4.89	27.74 ± 4.56	0.930
Cardiovascular risk factors, n (%)				
Hypertension	93 (79.5)	38 (86.4)	55 (75.3)	0.153
Dyslipidemia	78 (66.7)	32 (72.7)	46 (63.0)	0.280
Diabetes mellitus	41 (35.0)	21 (47.7)	20 (27.4)	0.026
Family history of CAD	75 (64.1)	26 (59.1)	49 (67.1)	0.380
Life habits, n (%)				
Current smoking	16 (13.7)	14 (31.8)	02 (2.7)	< 0.001
Sedentary lifestyle	66 (56.4)	23 (52.3)	43 (58.9)	0.483
Alcoholism	39 (33.3)	16 (36.4)	23 (31.5)	0.589
Angina, n (%)				
Typical	44 (37.6)	18 (40.9)	26 (35.6)	0.550
Atypical	33 (28.2)	09 (20.5)	24 (32.9)	0.160
mMRC score, n (%)				< 0.001
0	37 (33.0)	00 (00.0)	37 (54.4)	–
1	46 (41.1)	21 (47.7)	25 (36.8)	–
2	20 (17.9)	14 (31.8)	06 (8.80)	–
3	09 (8.00)	09 (20.5)	00 (00.0)	–
Spirometric data				
VEF1 (L)	–	1.86 ± 0.59	2.62 ± 0.58	< 0.001
VEF1 predicted (%)	–	69.80 ± 16.76	90.85 ± 9.97	< 0.001
FVC (L)	–	2.89 ± 0.78	3.17 ± 0.76	0.053
FVC predicted (%)	–	86.37 ± 12.30	89.10 ± 9.10	0.169
VEF1/ FVC ratio (%)	–	63.20 ± 6.89	83.47 ± 7.04	< 0.001

**Notes:** \*p-value referring to the comparison of COPD with the non-COPD group; Student's t-test, chi-square test or Fisher's exact test was used for statistical analyses, as appropriate.

**Abbreviations:** COPD, chronic obstructive pulmonary disease; BMI, body mass index; CAD, coronary artery disease; mMRC, modified medical research council; VEF1, forced expiratory volume in one second; FVC, forced vital capacity.

than patients without lung disease. There was no difference between the two groups regarding gender, body mass index, hypertension, dyslipidemia, family history of CAD, and type of angina. In the COPD group, 15 patients (34.1%) had mild lung disease (GOLD I), 23 (52.3%) had moderate disease (GOLD II), and 6 (13.6%) had severe disease (GOLD III). None of the patients had very serious disease (GOLD stage IV).

Information relating to the presence, extent, and severity of CAD, as determined by invasive coronary angiography or coronary computed tomography angiography, is presented in Table 2. CAD frequency was significantly higher in patients with COPD than in those without COPD (90.9% vs 39.7%;  $p < 0.001$ ). Additionally, patients with COPD had a greater number of lesions with a degree of luminal stenosis of 50% or more (65.7% vs 17.8%;  $p < 0.001$ ) and greater proportions of severe CAD (54.5% vs 11.0%;  $p < 0.001$ ) and trivessel CAD (31.8% vs 11.0%;  $p < 0.001$ ) compared with non-COPD patients.

At the six-year follow-up, patients with COPD were more likely to have experienced adverse cardiovascular events compared with patients without COPD (52.3% vs 11.0%;  $p < 0.001$ ), with an effect size of 0.720, which was characterized as a large effect. During follow-up, more than one-third of COPD patients underwent invasive coronary angiography (36.4% vs 9.6%;  $p < 0.001$ ). Moreover, the occurrence of myocardial infarction (27.3% vs 6.8%;  $p = 0.002$ ), cardiac revascularization (25.0% vs 5.5%;  $p = 0.002$ ), and cardiac hospitalization (27.3% vs 8.2%;  $p = 0.019$ ) was significantly higher in the COPD group than in the non-COPD group (Table 3). There was one cardiac death in the study population, followed in the COPD group.

**Table 2** Presence, Extent and Severity of CAD in Patients with and without COPD

Variable	Total (n = 117)	COPD (n = 44)	Non-COPD (n = 73)	p-value*	W-Cohen <sup>§</sup>
CAD <sup>†</sup> , n (%)	69 (59.0)	40 (90.9)	29 (39.7)	< 0.001	0.825
Degree of luminal stenosis, n (%)					
Lesion < 50%	27 (23.1)	11 (25.0)	16 (21.9)	0.620	–
Lesion ≥ 50%	42 (35.9)	29 (65.7)	13 (17.8)	< 0.001	0.786
Severity of CAD, n (%)					
Mild	17 (14.5)	7 (15.9)	10 (13.7)	0.550	–
Moderate	20 (17.1)	9 (20.5)	11 (15.1)	0.620	–
Severe	32 (27.4)	24 (54.5)	8 (11.0)	< 0.001	0.761
Extent of CAD, n (%)					
Univessel	18 (15.4)	8 (18.2)	10 (13.7)	0.230	–
Bivessel	16 (13.7)	10 (22.7)	6 (8.2)	0.050	–
Trivessel	22 (18.8)	14 (31.8)	8 (11.0)	0.010	0.379
LMCA + 03 vessels	13 (11.1)	8 (18.2)	5 (6.8)	0.090	–

**Notes:** \*p-value referring to the comparison of COPD with the non-COPD group; <sup>§</sup>adjusted for table size; <sup>†</sup>CAD was evaluated by CCTA or invasive coronary angiography; chi-square test or Fisher's exact test was used for statistical analyses, as appropriate.

**Abbreviations:** COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; LMCA, left main coronary artery.

**Table 3** Adverse Cardiovascular Events at Six-Years Follow-Up in Patients with and without COPD

Adverse Cardiovascular Events	Total (n = 117)	COPD (n = 44)	Non-COPD (n = 73)	p-value*	W-Cohen <sup>§</sup>
Composite cardiovascular events, n (%)	31 (26.5)	23 (52.3)	8 (11.0)	< 0.001	0.720
Coronary angiography, n (%)	23 (19.7)	16 (36.4)	7 (9.6)	< 0.001	0.488
Cardiac revascularization <sup>†</sup> , n (%)	15 (12.8)	11 (25.0)	4 (5.5)	0.002	0.417
Myocardial Infarction, n (%)	17 (14.5)	12 (27.3)	5 (6.8)	0.002	0.414
Cardiac hospitalization, n (%)	18 (15.4)	12 (27.3)	6 (8.2)	0.019	0.374
Cardiac death, n (%)	1 (0.9)	1 (2.3)	0 (0)	0.185	–

**Notes:** \*p-value referring to the comparison of COPD with the non-COPD group; <sup>§</sup>adjusted for table size; <sup>†</sup>cardiac revascularization by PCI or bypass surgery; chi-square test or Fisher's exact test was used for statistical analyses, as appropriate.

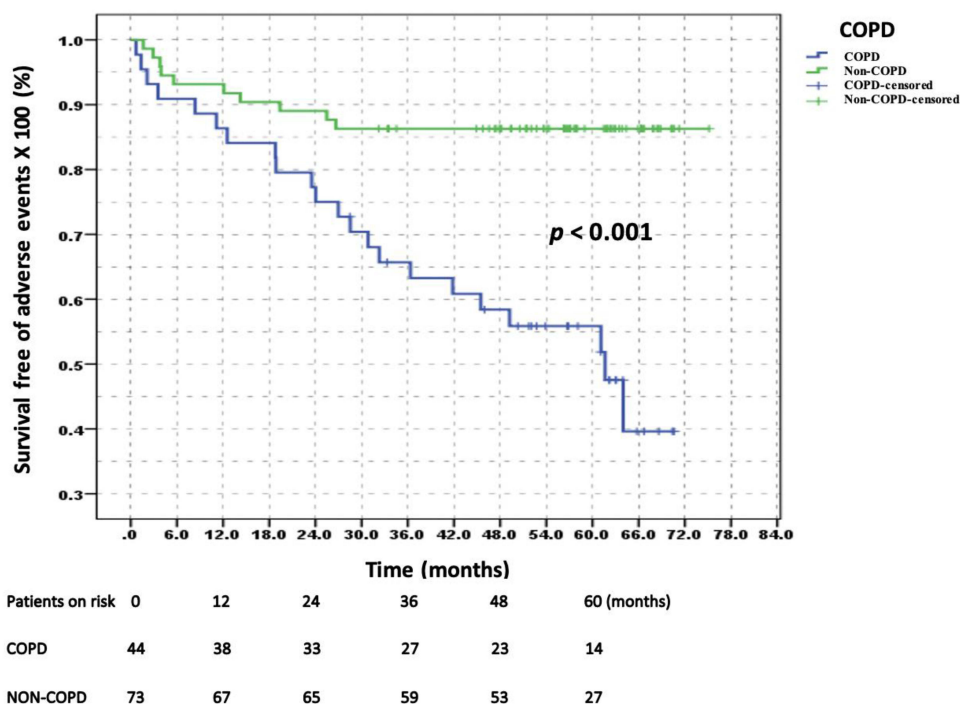
**Abbreviations:** COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention.

The relationship between COPD and adverse cardiovascular events was evaluated using the Kaplan–Meier method. At six-year follow-up, event-free survival was significantly higher in the non-COPD group than in the COPD group (86% vs 40%;  $p < 0.001$ ) (Figure 1). After adjusting for established risk factors for CAD, the presence of COPD remained an independent predictor for long-term adverse cardiovascular events (OR: 5.13, 95% CI: 2.29–11.50;  $p < 0.0001$ ).

In the COPD group, there was a higher frequency of long-term adverse cardiovascular events among patients with moderate to severe pulmonary disease (GOLD stages II and III); than among those with mild disease (GOLD I) however, the difference was not significant (Table 4).

## Discussion

In the present study, we demonstrated that patients with suspected or confirmed CAD and concomitant diagnosis of COPD have an adverse cardiovascular prognosis. The diagnosis of COPD in patients classified as stable or mildly symptomatic and with suspected or confirmed CAD was significantly associated with an increase in the number of long-term cardiovascular events requiring invasive coronary angiography, cardiac revascularization, cardiac hospitalization, and myocardial infarction during follow-up. Patients in the COPD group were older and had a higher frequency of diabetes compared with those in the non-COPD group; however, COPD remained an independent predictor of long-term cardiovascular events even after adjusting for established risk factors for CAD such as age, gender, hypertension, diabetes, and dyslipidemia. Patients with COPD also had a higher frequency of CAD, mainly severe and multivessel,



**Figure 1** Kaplan Meier curves of survival free of adverse cardiovascular events in COPD patients and non-COPD patients during six-year follow-up ( $p < 0.001$ ).

and the more advanced the degree of COPD, the greater the severity of the coronary lesions and the extent of calcification, as previously suggested by us<sup>29</sup> and others.<sup>30</sup>

Epidemiologic studies have identified a strong association between COPD and CAD, leading to the proposition that patients with COPD might be at higher risk of developing CAD and vice versa.<sup>31</sup> However, in clinical practice, there is substantial underdiagnosis of COPD among individuals with CAD. In a population-based survey, CAD was reported in only 7% to 13% of patients diagnosed with COPD, and COPD was reported in 26% to 35% of patients with CAD. Studies have reported that persistent airflow limitation is not recognized in 60% to 87% of patients with CAD, especially those who are former smokers or have mild symptoms.<sup>14,32</sup> In the present study, the presence of COPD was assessed by spirometry in patients categorized as stable or mildly symptomatic and who had not previously been diagnosed with COPD during routine and non-invasive investigation for myocardial ischemia by exercise stress echocardiography. Among the 117 patients, 44 (37%) were diagnosed with COPD, 86% of which exhibited mild or moderate airflow limitation and were classified as having COPD GOLD stage I or II.

**Table 4** Adverse Cardiovascular Events at Follow-Up of COPD Patients According GOLD Class

Variable	Total (n = 44)	GOLD I (n = 15)	GOLD II and III (n = 29)	p-value*
Composite cardiovascular events, n (%)	23 (52.3)	6 (40)	17 (58.6)	0.241
Coronary angiography, n (%)	16 (36.4)	5 (33.3)	11 (37.9)	0.764
Cardiac revascularization <sup>†</sup> , n (%)	11 (25.0)	2 (13.3)	9 (31.0)	0.199
Myocardial Infarction, n (%)	12 (27.3)	3 (20)	9 (31)	0.436
Cardiac hospitalization, n (%)	12 (27.3)	2 (13.3)	10 (34.5)	0.225
Cardiac death, n (%)	1 (2.3)	1 (6.7)	0 (0)	0.292

**Notes:** \*p-value referring to the comparison within the GOLD stage groups; <sup>†</sup>cardiac revascularization by PCI or bypass surgery; chi-square test or Fisher's exact test was used for statistical analyses, as appropriate.

**Abbreviations:** COPD, chronic obstructive pulmonary disease; GOLD, global initiative for obstructive lung disease; PCI, percutaneous coronary intervention.

Our results suggested the existence of inherent and reciprocal influences between COPD and CAD. Although the shared underlying pathogenic mechanisms are not fully understood, chronic and systemic inflammation, which affects both cardiovascular endothelial cells and the lung parenchyma, has been proposed to be the main causative factor in both diseases. Several studies have shown that patients with stable COPD and comorbid CAD have higher levels of inflammatory markers, including C-reactive protein (CRP); interleukins 6, 7, and 8; and fibrinogen, compared with patients without COPD. In addition, in COPD patients, elevated levels of inflammatory markers, especially CRP, have been associated with the exacerbations of pulmonary disease and worse long-term outcomes.<sup>9–12</sup> Thus, more episodes of COPD exacerbation translate into more cardiovascular events, more hospital admissions, and a notable increase in the cost of medical care.<sup>33–36</sup>

CVD represents the major cause of hospitalization and death among COPD patients and the morbimortality rate is higher among these patients than among the general population. Furthermore, COPD has been determined to be a strong predictor of mortality, recurrent infarction, cardiovascular shock, and bleeding complications in patients suffering from myocardial infarction.<sup>30,37–40</sup> Zhang et al<sup>6</sup> found that the rate of in-hospital cardiovascular events, including myocardial infarction and heart failure, was increased in COPD patients undergoing PCI. Meanwhile, patients with more frequent or more recent hospitalizations due to COPD exacerbation within one year before PCI were at a higher risk of major adverse cardiovascular and cerebrovascular events (ie, myocardial infarction, repeat revascularization, stroke, and death) during follow-up, especially those with two exacerbations within one year or any exacerbation within one month before PCI.<sup>41</sup>

Most studies on COPD and CVD to date have focused on advanced or acute stages of one or both diseases, including hospitalization, respiratory infection, acute coronary syndrome, or after coronary revascularization.<sup>6,8,13,37–43</sup> Here, we showed that stable patients with subclinical or early-stage of COPD and concurrent CAD were increased risk of long-term cardiovascular events. These results support the relevance of screening for COPD in cardiac patients and could be useful for guiding novel approaches in the patient's lifestyle and prompting medical treatment to control risk factors, thereby reducing cardiovascular morbimortality.

Cardioprotective medications such as antiplatelets, statins, and cardioselective beta-blockers are rarely used in COPD patients despite the evidence of their safety. Aspirin is mandatory for the treatment of patients with CAD, predominantly after myocardial infarction and cardiac revascularization. Furthermore, the results of observational studies and meta-analyses have suggested that antiplatelet therapy is beneficial for COPD patients, independently of CAD.<sup>44</sup> An observational cohort study involving 1343 patients with known thrombocytosis and hospitalized for acute exacerbation of COPD found that antiplatelet therapy was correlated with lower one-year mortality, while the results of another national prospective multicenter study also suggested that antiplatelet medication reduced mortality among COPD patients.<sup>45,46</sup>

Statins are used primarily in the treatment of hypercholesterolemia and the prevention of cardiovascular events. However, they also have recognized pleiotropic immunomodulatory and anti-inflammatory properties, which may be useful for mitigating the chronic systemic inflammation found in patients with COPD. Data from a large case-control study (Rotterdam Study), which enrolled 7983 participants older than 55 years, showed that long-term statin therapy was associated with a 39% decrease in the risk of all-cause death among COPD patients, independently of age, gender, the use of other drugs, the duration of COPD, pack years, total serum cholesterol, and cardiovascular covariables. This protective effect of statins was even more pronounced in patients with high levels of inflammatory markers (CRP >3 mg/dL), who obtained a 78% reduction in the risk of death.<sup>47</sup> Meanwhile, other observational studies reported that only 42% of COPD patients who had any degree of angiographic CAD were receiving statin therapy and 67% among those with angiographically proven severe CAD. The inconsistency of statin prescription may be explained by the more favorable lipid profiles found in COPD patients compared with general population.<sup>46,47</sup>

Beta-blockers are a standard class of anti-ischemic drugs historically prescribed to patients with CAD and heart failure, for whom they are known to reduce mortality. However, their use among COPD patients remains controversial owing to their potential for inducing acute bronchospasm via the non-selective blockade of  $\beta_2$  subtype receptors, which consequently also inhibits the action of beta-agonist drugs.<sup>48,49</sup> Another aspect refers to the heterogeneity of COPD presentation; for instance, studies have reported degrees of pulmonary disease and asthma overlap ranging from 6% to 55%.<sup>50</sup>

Selective  $\beta_1$  blockers, such as metoprolol and bisoprolol, are significantly less likely to induce bronchoconstriction. They also exert potentially beneficial effects in COPD patients by decreasing heart rate acceleration caused by

bronchodilators and may increase the sensitivity of  $\beta_2$  receptors for beta-agonists. Clinical trials and large meta-analyses have shown that cardioselective beta-blockers are safe and are associated with a better prognosis in patients with stable COPD and concurrent CAD, particularly those with milder COPD, even though some results may have been affected by the bias inherent in observational studies.<sup>51–58</sup> In contrast, a recent randomized controlled trial (BLOCK-COPD) found no effect of metoprolol in reducing the incidence of exacerbations among patients with moderate to severe COPD who did not have an established indication for the beta-blocker treatment.<sup>59</sup>

In summary, in the present study, we showed that COPD was undiagnostic in cardiac patients, especially in individuals with stable and mildly symptomatic disease. Additionally, cardiac patients with concurrent COPD were older, had a higher frequency of diabetes, and exhibited more progressive and more severe coronary atherosclerosis than patients without pulmonary disease. COPD was an independent predictor of long-term cardiovascular events requiring coronary angiography, cardiac revascularization, cardiac hospitalization, and myocardial infarction; this adverse cardiovascular prognosis was found even in patients with subclinical and early-stage lung disease. Combined, these results suggest that screening for COPD in cardiac patients may be beneficial to improving their treatment and preventing the occurrence of cardiovascular events.

## Study Limitations

This study was a nonrandomized and retrospective cohort and has inherent limitations, including selection bias. Additionally, the diagnosis of COPD was determined by spirometry in patients with stable and mildly symptomatic disease during routine and non-invasive investigation for myocardial ischemia by exercise stress echocardiography; consequently, patients with severe pulmonary disease (GOLD stages III and IV) may have been underrepresented, which may have affected the assessment of the relationship between COPD grades and cardiovascular outcomes. Despite these limitations, we believe that the major strength of this study lies in the quality of the reported event data used to assess the impact of COPD on long-term clinical outcomes. Future prospective and randomized clinical trials will be necessary to confirm these observations.

## Conclusions

COPD was associated with an increase in the severity of coronary lesions and adverse cardiovascular events in patients with suspected or confirmed CAD. In addition, COPD was a predictor of long-term cardiovascular events in patients with subclinical or early-stage of lung disease, independently of the established risk factors for CAD. Our findings suggest that screening for COPD in cardiac patients could be useful in risk stratification as well as in determining the appropriate treatment for controlling risk factors and reducing cardiovascular morbimortality.

## Disclosure

The authors report no conflicts of interest in this work.

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