

Underdiagnosis and prognosis of chronic obstructive pulmonary disease after percutaneous coronary intervention: a prospective study

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Background: Retrospective studies based on clinical data and without spirometric confirmation suggest a poorer prognosis of patients with ischemic heart disease (IHD) and chronic obstructive pulmonary disease (COPD) following percutaneous coronary intervention (PCI). The impact of undiagnosed COPD in these patients is unknown. We aimed to evaluate the prognostic impact of COPD – previously or newly diagnosed – in patients with IHD treated with PCI.

Methods: Patients with IHD confirmed by PCI were consecutively included. After PCI they underwent forced spirometry and evaluation for cardiovascular risk factors. All-cause mortality, new cardiovascular events, and their combined endpoint were analyzed.

Results: A total of 133 patients (78% male, with a mean (SD) age of 63 (10.12) years were included. Of these, 33 (24.8%) met the spirometric criteria for COPD, of whom 81.8% were undiagnosed. IHD patients with COPD were older, had more coronary vessels affected, and a greater history of previous myocardial infarction. Median follow-up was 934 days (interquartile range [25%–75%]: 546–1,160). COPD patients had greater mortality ($P=0.008$; hazard ratio [HR]: 8.85; 95% confidence interval [CI]: 1.76–44.47) and number of cardiovascular events ($P=0.024$; HR: 1.87; 95% CI: 1.04–3.33), even those without a previous diagnosis of COPD ($P=0.01$; HR: 1.78; 95% CI: 1.12–2.83). These differences remained after adjustment for sex, age, number of coronary vessels affected, and previous myocardial infarction ($P=0.025$; HR: 1.83; 95% CI: 1.08–3.1).

Conclusion: Prevalence and underdiagnosis of COPD in patients with IHD who undergo PCI are both high. These patients have an independent greater mortality and a higher number of cardiovascular events during follow-up.

Keywords: ischemic heart disease, mortality, myocardial infarction, prognosis

Background

Ischemic heart disease (IHD) and chronic obstructive pulmonary disease (COPD) are within the top causes of mortality worldwide.¹ The prevalence of IHD is considered increased in patients with COPD and is one of the most frequent causes of death across the entire spectrum of COPD severity.² Nevertheless, the inverse situation – that is, a greater prevalence of COPD and a worse prognosis in IHD patients – has been less studied.

In the past decade, only retrospective studies have indicated that COPD worsens the prognosis of patients with IHD. For example, Berger et al found greater mortality in patients with a previous diagnosis of COPD and IHD who underwent percutaneous coronary intervention (PCI);³ these data were corroborated in subsequent studies.^{4,5} Prior diagnosis of COPD has also been related to a greater number of complications and increased mortality in patients with acute myocardial infarction.^{6–12}

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As mentioned, all these studies were retrospective and the diagnosis of COPD was based on clinical history only, without spirometric confirmation, which likely led to an evident underdiagnosis; this explains in part why the prevalence of COPD in these studies is often less than that found in the general population.^{13,14}

To our knowledge only one previous study – based in 119 patients – has examined the real prevalence of COPD in patients with IHD as demonstrated with PCI by means of spirometry, revealing a COPD prevalence of 34%, of which 87% were not previously diagnosed.¹⁵

We aimed to evaluate whether patients with IHD, demonstrated by PCI, along with COPD confirmed by spirometry – with or without previous diagnosis – had a worse prognosis in terms of mortality and increased number of cardiovascular events than patients with IHD alone.

Methods

All patients admitted at the hemodynamic unit of the Mutua de Terrassa University Hospital due to IHD who underwent a PCI revealing stenosis above 50% in primary arteries, from January to June 2011, and gave their informed consent, were included. Patients with significant valvulopathy, persistent signs of heart failure, unable to carry out spirometry, and those diagnosed with asthma or bronchiectasis as the main respiratory disease were excluded. Data collected included the characteristics of the PCI, number of arteries affected and treated, stents implanted, and postprocedural flow. At the time of the PCI, the logistic EuroSCORE was calculated, the prognostic evaluation according to the GRACE scale was also recorded and the SYNTAX and ACA/AHA (American College of Cardiology/American Heart Association) coronary lesion complexity indices were analyzed.^{16–21} Analytical variables were drawn at the time of the PCI.

One month after PCI, a postbronchodilator spirometry was performed according to international guidelines, and reviewed by an experienced pulmonologist (JLLH).²² We used a standardized questionnaire to assess the previous diagnosis of COPD.^{15,23} Other cardiovascular and COPD risk factors alongside other comorbidities, both included or not in the Charlson index, were recorded.²⁴ COPD was defined as a post-bronchodilator forced expiratory volume in the 1st second (FEV₁)/forced vital capacity (FVC) ratio <0.70. Spirometric severity was stratified in accordance with the Global initiative for chronic Obstructive Lung Disease (GOLD) normative.²⁵ The lower limit of normality (LLN) was also calculated, using the Global Lung Function Initiative software (<http://www.lungfunction.org>). The patients' regular physicians

were informed of their spirometric data, without posterior intervention on the part of the researchers in their medication or additional tests performed on the patients. Follow-up was carried out based upon the information contained in the clinical record and by means of telephone contact. Data and cause of death were collected, as was information on admissions for cardiovascular or respiratory reasons. A combined mortality/major cardiovascular event (MACE) variable including death or hospital admission for a new acute coronary syndrome, heart failure, or cerebral vascular event, was calculated. A study based on the number of MACE events was also performed. The relationship between predicted FEV₁%, predicted FVC%, and FEV₁/FVC, expressed as a continuous variable stratified for events, was also examined.

Statistical analysis

Data are presented as means and standard deviation (SD) for continuous variables, or as totals and percentages for qualitative variables. Differences within groups were compared with Student's *t*-test or non-parametric tests and the chi-squared test for continuous and categorical variables, respectively. Time-dependent variables were analyzed with Kaplan–Meier curves and Cox logistic regression analysis. Statistical significance was determined for *P*-values below 0.05. All patients signed their informed consent. The study was approved by the ethical and clinical trial committee of the Mutua de Terrassa University Hospital.

Results

A total of 171 patients were initially studied, of whom 38 were then excluded. Excluded patients were older: 63 (10.12) vs 67.64 (12.42) years (*P*=0.022), although there were no differences in terms of sex, history of cardiovascular risk, or number of treated arteries. Finally, 133 patients were included (78.2% males) with a global mean (SD) age of 63.03 (10.12) years and 33 (24.8%) met the spirometric criteria for COPD. Ten patients had mild COPD (30.3%), 19 moderate COPD (57.6%), and four severe COPD (12.1%). The global prevalence of underdiagnosis was 81.8%. All of the severe COPD patients had been previously diagnosed, while underdiagnosis in patients with moderate and mild COPD was 89.5% and 100%, respectively (Figure 1).

The main characteristics of the participants in the presence or not of COPD are presented in Table 1. Patients with COPD were significantly older and had a more frequently history of previous myocardial infarction, while the Charlson index was similar between groups. Previous use of antiplatelets and statins, and other indicators of cardiovascular risk, was not significantly

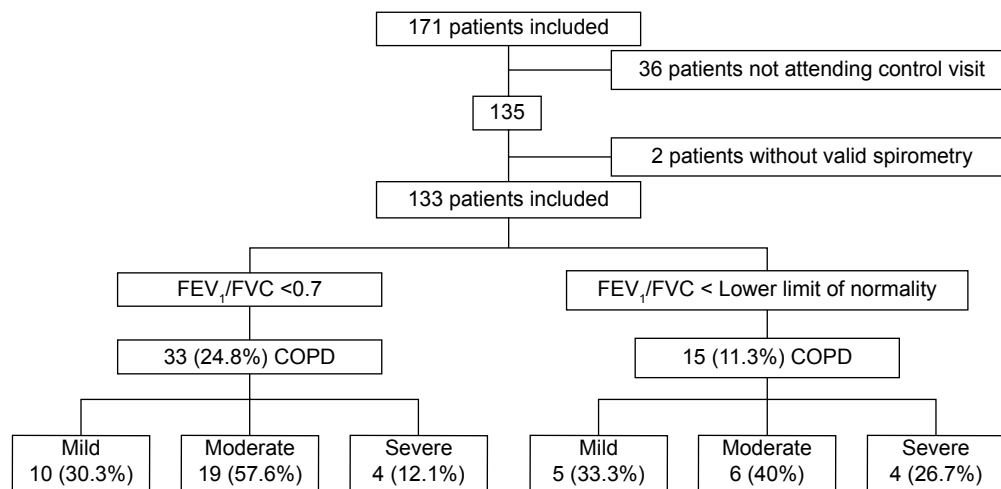


Figure 1 Flowchart of patients.

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in the 1st second; FVC, forced vital capacity.

different. Findings obtained in the PCI are shown in Table 2. COPD patients had a greater number of affected coronary arteries, although there were no differences in the number of arteries or lesions treated, the percentage of patients achieving total revascularization, the number of stents implanted – drug-eluting or otherwise – or the ejection fraction (Table 2).

In accordance with the ACC/AHA classification, 7% had type a lesions, 60% type b, and 33% type c, with no difference between the COPD patients and the rest; similarly scoring

was similar for those with and those without COPD on the Syntax index in grouping those at low risk (0–22), medium risk (23–32), and high risk (≥ 33).

Analytic parameters were likewise comparable. Those patients with COPD had lower total cholesterol levels although this difference disappeared when subjects with a prior diagnosis of dyslipidemia or under treatment with statins were analyzed (Table 3). We did not find differences between patients with and without COPD at the time of discharge after

Table 1 Demographic and clinical characteristics of participants according to spirometry FEV₁/FVC <0.70

	COPD (n=33)	Non-COPD (n=100)	Total (n=133)	P-value
Male sex (n) (%)	28 (84.8)	76 (76)	78.2%	ns
Age, years (SD)	67.48 (9.91)	61.56 (9.79)	63.03 (10.1)	0.003
BMI (kg/m ²)	28.91 (5.43)	31.3 (14.74)	30.71 (13.01)	ns
Smoking				ns
Current	6 (18.2%)	17 (17%)	23 (17.3%)	
Ex-smoker	21 (63.65%)	57 (57%)	78 (58.6%)	
Pack-years	35.23 (20.63)	27.79 (25.62)	29.82 (24.5)	ns
Charlson's index	1.87 (1.49)	1.48 (1.26)	1.57 (1.32)	ns
Waist circumference	100.77 (10.57)	103.71 (9.68)	103 (9.94)	ns
Dyslipidemia ^a	22 (66.7%)	62 (62%)	84 (63.2%)	ns
Peripheral vasculopathy ^a	3 (9.1%)	5 (5%)	8 (6%)	ns
Hypertension ^a	23 (69.7%)	100 (69%)	92 (69.2%)	ns
Diabetes mellitus ^a	12 (36.4%)	27 (27%)	39 (29.3%)	ns
Heart failure ^a	6 (18.2%)	9 (9%)	15 (11.3)	ns
Stroke ^a	3 (9.1%)	3 (3%)	6 (4.5%)	ns
AMI ^a	14 (42.4%)	24 (24%)	38 (28.6%)	0.03
Angina ^a	22 (66.7%)	54 (54%)	76 (57.1%)	ns
Cardiac surgery ^a	8 (24.2%)	21 (21%)	29 (21.8%)	ns
Previous use statins	17 (51.5%)	65 (65%)	82 (61.7%)	ns
Previous use antiplatelets	18 (54.5%)	60 (60%)	78 (58.6%)	ns
Depression: Yesavage scale, mean (SD)	3.82 (2.82)	4.05 (3.8)	3.99 (3.56)	ns

Notes: ^aPrevious diagnosis of dyslipidemia, arterial peripheral vasculopathy, diabetes mellitus, hypertension, heart failure, stroke, acute myocardial infarction (AMI), angina or cardiac surgery.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in the 1st second; FVC, forced vital capacity; ns, non-significant; SD, standard deviation.

Table 2 Characteristics of the PCI, according to spirometry FEV₁/FVC <0.70

	COPD (n=33)	Non-COPD (n=100)	Total (n=133)	P-value
GRACE score at hospital (SD) ¹⁸	16.36 (26.96)	10.23 (5.44)	14.4	ns
GRACE score at 6 months (SD) ¹⁸	25.21 (21.18)	19.8 (8.43)	21.20 (12.96)	ns
Logistical EuroSCORE (median and IQR) ¹⁷	11 (6–15)	2 (2–3.8)	3 (2–10)	0.006
SYNTAX (SD) ¹⁹	13.77 (10.81)	13.09 (10.42)	13.25 (10.46)	ns
Number of arteries affected (SD)	1.91 (0.84)	1.56 (0.7)	1.64 (0.75)	0.04
Number of arteries treated (SD)	1.3 (0.47)	1.23 (0.48)	1.25 (0.47)	ns
Number of lesions treated (SD)	1.47 (0.67)	1.44 (0.69)	1.45 (0.68)	ns
Number of stents (SD)	1.47 (0.69)	1.4 (0.66)	1.42 (0.67)	ns
Number of drug-eluting stents (SD)	1.21 (0.92)	0.96 (0.89)	1.01 (0.89)	ns
Ejection fraction (SD)	56.67 (13.26)	60.20 (13.31)	59.26 (13.32)	ns
Complete revascularization (%)	10 (30.3%)	46 (46%)	56 (42.1%)	ns

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in the 1st second; FVC, forced vital capacity; IQR, interquartile range (25%–75%); PCI, percutaneous coronary intervention; SD, standard deviation.

PCI or during follow-up in the prescription of antiplatelets, statins, beta-blockers, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II inhibitors, or calcium antagonists (Figure 2). There were, however, differences in the use of bronchodilators and inhaled corticosteroids, both more frequent among the patients with COPD ($P < 0.001$).

The median follow-up period was 974 (interquartile range: 546–1,160) days. During follow-up eight deaths occurred, six in the COPD group (18.2%) and two in the non-COPD group (2%) ($P = 0.003$). There were 88 new events, of which 35 were in the COPD group and 53 in the non-COPD group ($P = 0.015$), as well as a greater number of events per patient: 1.36 (0.29) vs 0.63 (0.97) ($P = 0.02$).

When analyzing survival and MACE using a Cox regression model, COPD patients showed a worse prognosis with regard to mortality ($P = 0.008$; hazard ratio [HR]: 8.85; 95% confidence interval [CI]: 1.76–44.47) and to the MACE variable ($P = 0.024$; HR: 1.87; 95% CI: 1.04–3.33). These differences were sustained when the total number of events in the MACE variable was examined in relation to whether or not the patient had COPD ($P = 0.003$; HR: 1.84; 95% CI: 1.14–2.74) (Figure 3). COPD patients without a

prior diagnosis also showed a worse prognosis with the MACE variable ($P = 0.001$; HR: 1.78; 95% CI: 1.12–2.83) (Figure 4A). The significance of COPD was maintained after adjusting for age, sex, previous myocardial infarction, and number of arteries affected (Table 4 and Figure 5).

When classifying the COPD patients in terms of LLN the prevalence observed went down to 15 patients (11.3%), five with mild COPD, six with moderate, and four with severe, thereby reducing the underdiagnosis to 67%. In terms of LLN, no differences in mortality were found, although statistical significance was maintained for the MACE variable ($P = 0.03$; HR: 2.26; 95% CI: 1.1–4.68) and for the total number of events in the non-adjusted analysis ($P = 0.002$; HR: 2.37; 95% CI: 1.48–3.83). However, this significance disappeared in the multivariate model (Table 4 and Figure 5). The number of arteries with stenosis maintained its statistical significance in both multivariate models.

Subjects with discordant results (obstructive by fixed ratio but normal by LLN) had a greater number of events than patients without COPD and a smaller number than the patients meeting both criteria ($P < 0.002$). Total number

Table 3 Blood analysis of participants according to spirometry FEV₁/FVC <0.70

	COPD (n=33)	Non-COPD (n=100)	Total (n=133)	P-value
Total cholesterol (mg/dL)	161.33 (46.29)	182.86 (42.92)	177.24 (44.64)	0.02
HDL cholesterol (mg/dL)	45.46 (12.97)	45.98 (11.98)	45.85 (12.182)	ns
LDL cholesterol (mg/dL)	90 (32.59)	106.35 (39.78)	102.41 (38.66)	ns
Triglycerides (mg/dL)	105.69 (92.46)	134.29 (73.26)	127.02 (79.14)	ns
CRP	2 (5.45)	0.87 (2.1)	1.13 (3.21)	ns
BNP (pg/mL)	1,839 (4,137)	832 (2,437)	1,092 (2,984)	ns
Total cholesterol ^a (mg/dL)	167 (40.37)	181 (43.95)	177 (43.2)	ns
HDL cholesterol ^a (mg/dL)	46.24 (11.25)	44.68 (11.65)	45.1 (11.5)	ns
LDL cholesterol ^a (mg/dL)	96.82 (31.8)	102.9 (41.2)	101.49 (38.99)	ns

Note: ^aTotal cholesterol levels and fractions in patients with previously prescribed statins. Data are presented as mean (standard deviation).

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in the 1st second; FVC, forced vital capacity. BNP, brain natriuretic peptide; CRP, c-reactive protein; HDL, high density lipoprotein; LDL, low density lipoprotein; ns, non-significant.

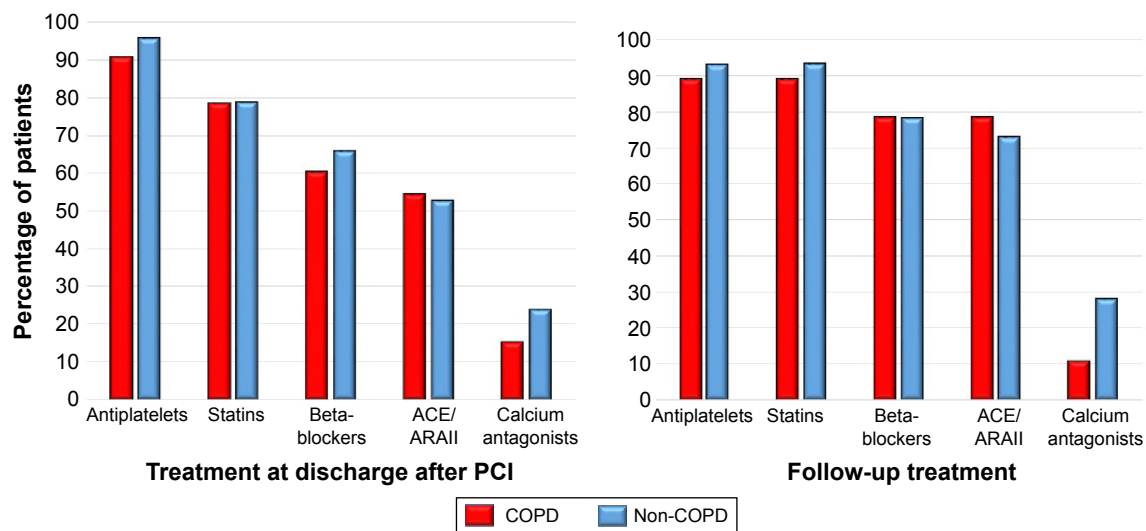


Figure 2 Treatment at discharge and during patient follow-up.

Abbreviations: ACE, angiotensin converting enzyme inhibitors; ARAI, angiotensin II receptor antagonist; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention.

of events with Cox regression in the discordant patients were similar to those with the COPD according to the fixed ratio.

The relationship within percent predicted FVC, FEV₁, and FEV₁/FVC with the number of stratified events was a statistically significant inverse one (Figure 6). Finally when using both the fixed ratio and the lower limit for normality in defining obstruction, the number of events increased with the severity of COPD (both $P < 0.0001$) (Figure 4B).

Discussion

Our study demonstrates high rates of prevalence (25%) and underdiagnosis (82%) of COPD in patients with IHD leading to PCI, as well as lower survival and a greater number of cardiovascular events in patients with COPD, including those who were not previously diagnosed. To our

knowledge, this is the first study in which this prognostic relationship has been demonstrated conjointly using the two techniques considered as GOLD standards: PCI in IHD and spirometry in COPD.

It is well established that COPD is associated with IHD even after adjustment for confounding variables, and that the presence of IHD worsens the prognosis in COPD.^{26–30} The inverse situation – an increase in the risk of COPD in patients with a history of cardiovascular disease – has been shown in other studies.^{14,31,32} The worsened prognosis for patients with IHD and COPD together has been demonstrated in various studies carried out in patients with IHD who have undergone PCI.^{3–5,9,11,12} Other studies have shown a worse prognosis for patients with COPD and acute myocardial infarction, revealing greater risk of heart failure, bleeding, cardiogenic shock, and mortality.^{6–8,10} Unfortunately, none of these studies included a systematic use of spirometry to confirm or rule out the diagnosis of COPD. Rather, they were based solely on a prior diagnosis of COPD in the patient's clinical record or the previous use of bronchodilators, which likely produced a bias and an evident underdiagnosis. Recent studies have shown that, although the specificity of the prior diagnosis of COPD in patients with IHD is high, previous diagnosis sensitivity is very low (23%), with a positive predictive value of 53%.³³ In our study, the prevalence of underdiagnosis was similar to what was seen in a previous study.¹⁵

Our data demonstrate that both mortality and the number of events of patients with COPD – with or without previous diagnosis – and concomitant IHD were greater than in IHD patients without COPD. COPD patients were similar to the others except for their more advanced age, a higher number

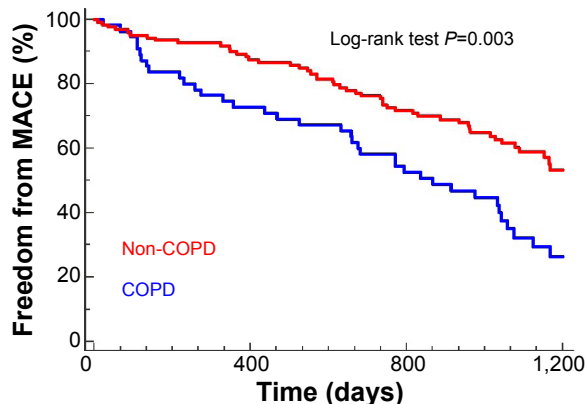


Figure 3 Kaplan–Meier survival curves for the mortality/major cardiovascular event variable (MACE).

Abbreviation: COPD, chronic obstructive pulmonary disease.

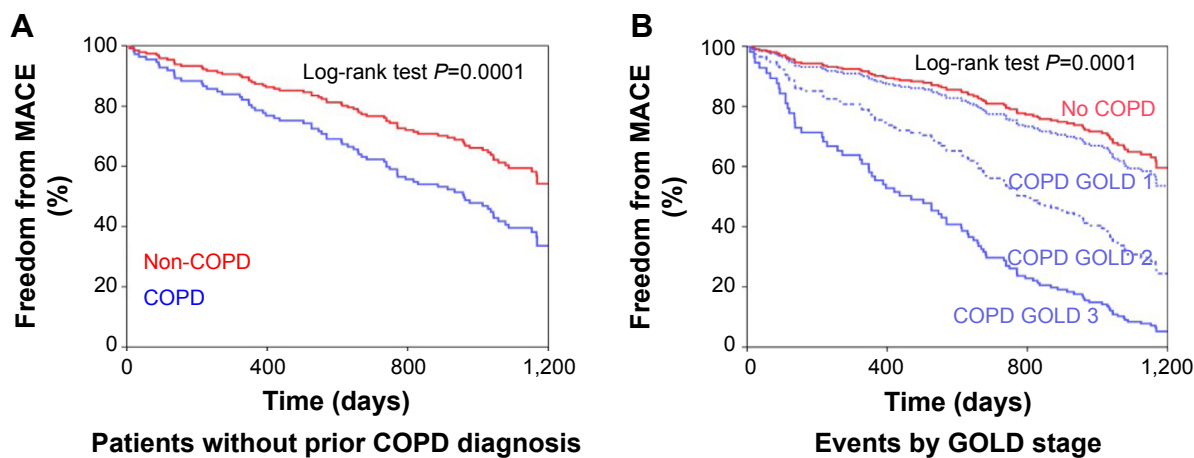


Figure 4 Kaplan–Meier curves for (A) Patients without prior diagnosis of COPD. (B) Total number of events by GOLD stage.
Abbreviations: COPD, chronic obstructive pulmonary disease; GOLD, Global initiative for chronic Obstructive Lung Disease; MACE, mortality/major cardiovascular event variable.

of previous incidents of infarction, and a greater number of stenosed arteries. Several previous retrospective studies have also found a greater prevalence of prior infarction in patients with COPD, although data concerning the number of stenosed arteries, the complexity of the coronary lesions, and the procedures for revascularization in these studies were variable.^{3–5,9,11} Nevertheless, the rest of the parameters analyzed in our study, including the GRACE risk and the Syntax and ACC/AHA coronary complexity scales, were similar. Only the logistic EuroSCORE was higher in COPD patients, although this difference may be explained by the older age and prior diagnosis of COPD in some patients, variables that are included in this index.

The number of arteries with stenosis was related to a higher number of events during follow-up, in both the crude and the adjusted analysis, which is in agreement with other studies.³⁴ However, the number of arteries treated and the

number of stents implanted were somewhat greater in those patients with COPD, albeit short of statistical significance, which suggests that the worse prognosis of COPD patients is not attributable to lessened treatment during the PCI of other arteries with stenosis not responsible for the current coronary event. Recent studies have shown that non-treatment of these arteries is associated with a poor prognosis during follow-up.³⁵

The causes of this worse prognosis for patients with IHD and COPD are not entirely clear. Some population-based studies have pointed to poorer adherence to treatment guidelines for IHD in patients with COPD, with less use of statins and beta-blockers, but this was not confirmed in our study, in which the treatment at discharge following PCI and the follow-up with statins, antiplatelets, beta-blockers, calcium antagonists, and ACE inhibitors were comparable.^{36,37} Other possible explanations might include a greater arterial stiffness and higher platelet aggregation and inflammation, all of which are aggravated during COPD exacerbations, with an increased incidence of cardiovascular events in the following weeks after COPD exacerbation.^{29,38–41} This increase in platelet aggregation in COPD patients has also been demonstrated in patients with IHD leading to PCI.⁴²

Finally, in our study the use of LLN reduced the level of underdiagnosis but also excluded a sub-group of patients with a greater number of cardiovascular events and their relationship with the number of events in the multivariate model was not significant. These data had already been suggested by other studies that demonstrated an increase in the mortality due to IHD with the reduction of pulmonary function, and higher mortality in those patients classified as non-COPD by LLN but with obstruction criteria from the fixed ratio.^{43,44}

Table 4 Multivariate analysis by event using Cox regression

	HR	95% CI	P-value
COPD fixed ratio			
COPD	1.83	1.08–3.1	0.025
Sex	1.1	0.62–1.99	ns
Age	1.01	0.98–1.03	ns
AMI ^a	1.16	0.68–1.98	ns
Number of stenosed arteries	1.45	1.08–3.11	0.03
COPD lower limit of normality			
COPD	1.47	0.77–2.81	ns
Sex	1.18	0.66–2.13	ns
Age	1.01	0.99–1.04	ns
AMI ^a	1.27	0.74–2.18	ns
Number of stenosed arteries	1.45	1.01–2.1	0.046

Note: ^aHistory of previous acute myocardial infarction (AMI).
Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; ns, non-significant.

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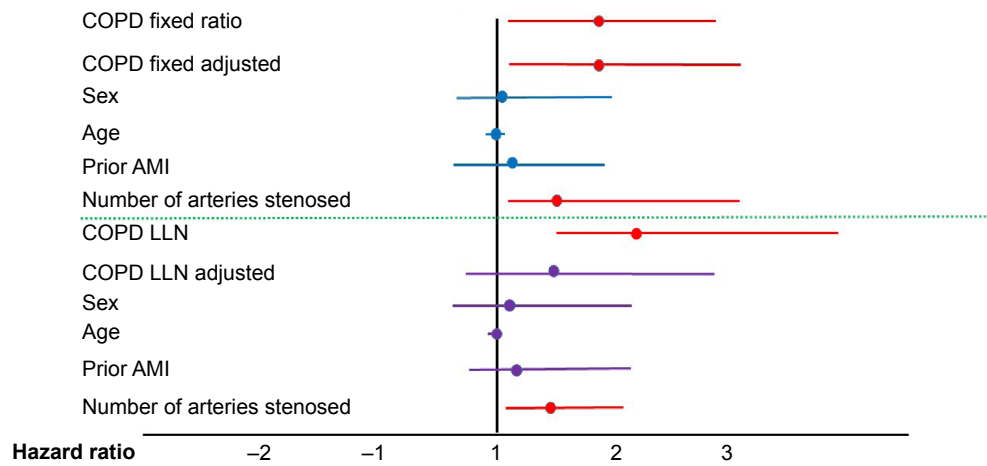


Figure 5 Hazard ratio and 95% CI for COPD by the fixed ratio and the LLN index both raw and adjusted by sex, age, number of arteries with stenosis, and history of AMI. **Abbreviations:** AMI, acute myocardial infarction; COPD, chronic obstructive pulmonary disease; LLN, lower limit of normality; CI, confidence interval.

Our study has some limitations. Only IHD patients who underwent PCI were included, so that our conclusions may not be generalized to all patients with IHD; in all likelihood, the oldest patients and those with the most comorbidities were not included as they were not referred for PCI. Although the average age observed in our study was similar to the age in the other studies carried out among PCI patients, it is lower than the overall age for patients with IHD.^{5,11,45} Secondly, by being a single center study we maximize internal consistency in procedures and treatments, but the limited size of

the sample may mean that some of the differences observed in the characteristics of patients failed to reach statistical significance. Finally, some classic studies have suggested that myocardial infarction may transiently affect respiratory function, although the FEV₁/FVC is usually less affected.⁴⁶ In our study, spirometry was performed 1 month after the PCI and recent publications demonstrate that after an acute coronary syndrome treated with PCI, spirometric values performed at this time are similar to those observed during follow-up.⁴⁷

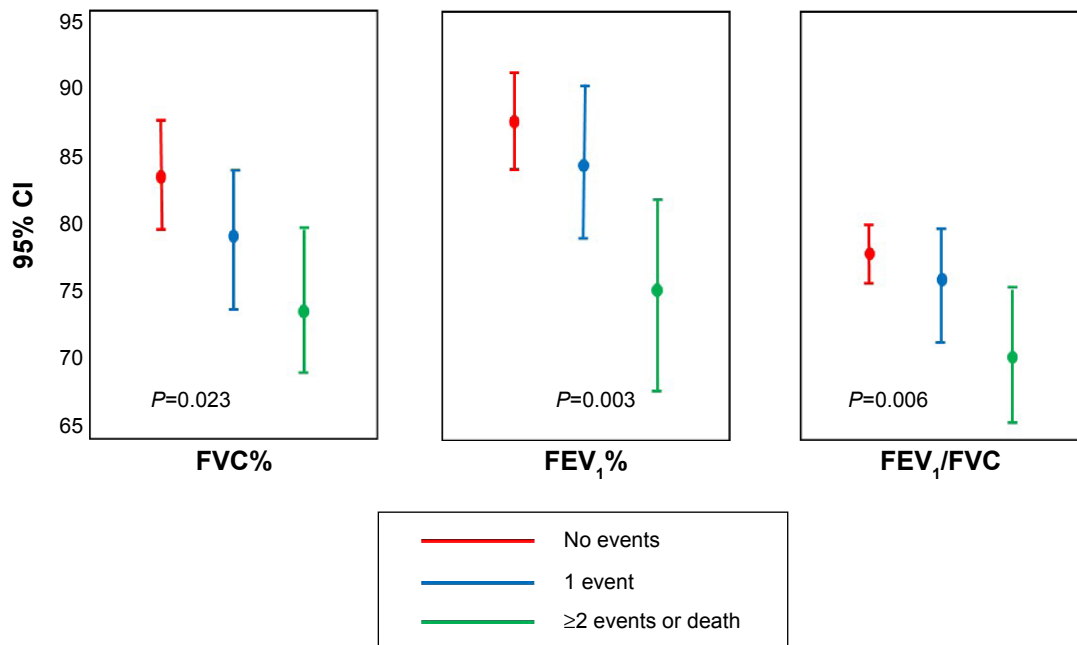


Figure 6 Relationship between number of events (MACE) and percent predicted FVC, FEV₁, and FEV₁/FVC. **Abbreviations:** CI, confidence interval; MACE, combined mortality/major cardiovascular event; FEV₁, forced expiratory volume in the 1st second; FVC, forced vital capacity.

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Conclusion

Despite these limitations, we believe that our study demonstrates the poorer prognosis of patients with COPD – with or without previous diagnosis – both in terms of mortality and in cardiovascular events during follow-up independently of other variables, which highlights the need to carry out spirometric studies in order to detect COPD in IHD patients for their prognostic and possibly therapeutic implications.⁴⁸

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Author contributions

Conception and design: PA, AL, JP, FP, JLH, AD, JBS; Analysis and interpretation: PA, AL, JP, SY, MEG, FP, JLH, AD, JBS; Drafting the manuscript for important intellectual concept: PA, AL, JP, SY, MEG, FP, JLH, AD, JBS. PA had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosure

The authors report no conflicts of interest in this work.

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