

Impact of Spirometrically Confirmed Chronic Obstructive Pulmonary Disease on Arterial Stiffness and Surfactant Protein D After Percutaneous Coronary Intervention. The CATEPOC Study

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Background: Several mechanisms have been proposed to explain why chronic obstructive pulmonary disease (COPD) impairs the prognosis of coronary events. We aimed to explore COPD variables related to a worse prognosis in patients undergoing percutaneous coronary intervention (PCI).

Methods: Patients with an acute coronary event treated by PCI were prospectively included. One month after discharge, clinical characteristics, comorbidities measured with the Charlson index, and prognostic coronary scales (logistic EuroSCORE; GRACE 2.0) were collected. Post-bronchodilator spirometry, arterial stiffness, and serum inflammatory and myocardial biomarkers were measured. Lung plasmatic biomarkers (Surfactant protein D, desmosine, and Clara cell secretory protein-16) were determined with ELISA. COPD was defined by the fixed ratio (FEV1/FVC <70%). Spirometric values were also analyzed as continuous variables using adjusted and non-adjusted ANCOVA analysis. Finally, we evaluated the presence of a respiratory pattern defined by non-stratified spirometric values and pulmonary biomarkers.

Results: A total of 164 patients with a mean age of 65 (± 10) years (79% males) were included. COPD was diagnosed in 56 (34%) patients (68% previously undiagnosed). COPD patients had a longer smoking history, higher scores on the EuroSCORE ($p < 0.0001$) and GRACE 2.0 ($p < 0.001$) scales, and more comorbidities ($p = 0.006$). Arterial stiffness determined by pulse wave velocity was increased in COPD patients (7.35 m/s vs 6.60 m/s; $p = 0.006$). Serum values of high sensitive T troponin ($p = 0.007$) and surfactant protein D ($p = 0.003$) were also higher in COPD patients. FEV1% remained significantly associated with arterial stiffness and surfactant protein D in the adjusted ANCOVA analysis. In the cluster exploration, 53% of the patients had a respiratory pattern.

Conclusion: COPD affects one-third of patients with an acute coronary event and frequently remains undiagnosed. Several mechanisms, including arterial stiffness and SPD, were increased in COPD patients. Their relationship with the prognosis should be confirmed with longitudinal follow-up of the cohort.

Keywords: acute coronary event, chronic obstructive pulmonary disease, ischaemic heart disease, percutaneous coronary intervention, arterial stiffness, surfactant protein D

Introduction

According to the Global Burden of Disease Study data, ischaemic heart disease (IHD) and chronic obstructive pulmonary disease (COPD) are the first and third causes of global mortality for chronic diseases.¹ Their joint prevalence exceeds that expected for their shared risk factors and impairs the prognosis of subjects affected by the two pathologies.² In COPD patients, the prevalence of IHD is two-fold higher than that observed in the general population, while a third of patients

with IHD have COPD.^{3–6} Several previous studies have shown that IHD accounts for a third of COPD deaths and suggest that COPD increases coronary events and cardiovascular mortality risk.^{7–10}

An essential component of COPD is the presence of airway obstruction defined by a spirometric fixed ratio FEV1/FVC lower than 0.7. Without spirometric data, COPD underdiagnosis reaches figures of 70% in both general populations and IHD patients.^{2,3,11} Hence, the relevance of COPD in studies performed on IHD patients without spirometric tests is challenging to assess. Although some studies suggest that COPD worsens the prognosis after an acute coronary event, nearly all of them had a retrospective design, and the diagnosis of COPD was based only on clinical criteria without any pulmonary function data.¹² Previous studies of IHD patients have shown that this approach has a very low sensitivity (23%).¹³ Moreover, the reported COPD prevalence in these studies is around 10% compared to the 30% observed in IHD patients with spirometric evaluation.^{14–16} Therefore, it seems likely that in studies without pulmonary function data, two-thirds of COPD patients were undiagnosed and hence analyzed as non-COPD.

In a recent meta-analysis performed to evaluate the prognostic relevance of COPD after a percutaneous coronary intervention (PCI), only one of the ten studies included had a prospective design with spirometric confirmation of COPD.¹² The follow-up of this cohort showed an increased risk of new coronary events and cardiovascular mortality in COPD patients, independent of IHD treatment.^{15,17}

Furthermore, the relationship between pulmonary function and cardiovascular risk is non-dichotomic. FEV1/FVC is a continuous variable that usually descends progressively during the evolution of the disease. Some patients may have significant radiologic lung pathology and symptoms before reaching the accepted threshold of airway obstruction, and the incidence of cardiovascular events increases progressively with pulmonary function impairment.^{18–21} More recent studies have shown that even in the absence of rapid pulmonary function loss (the primary mechanism traditionally related to COPD development), some subjects with incomplete lung development in early adulthood present an earlier incidence of COPD and cardiovascular comorbidities.^{22,23}

Multiple variables have been proposed to explain the increased risk of cardiovascular events in COPD patients, including arterial stiffness and inflammatory, cardiac, and respiratory biomarkers.^{24–34} However, their association in patients with a coronary event and concomitant COPD remains unclear.^{35,36}

Our main objective was to explore the differences between patients with and without COPD in several variables previously considered relevant to explain the risk of new coronary events in those with IHD treated by PCI. Differences in lung function data were analyzed as continuous variables and dichotomized according to the fixed ratio (FEV1/FVC <0.7). Finally, we aimed to investigate the existence of respiratory clusters based on the combination of non-dichotomized lung function parameters and serum pulmonary biomarkers.

Methods

We prospectively studied patients admitted due to an acute coronary event diagnosed and treated by PCI at the University Hospital Mutua de Terrassa. Our study accomplishes the criteria of the Declaration of Helsinki. The ethical and clinical trial committee of the Mutua de Terrassa University Hospital approved the study, and all patients signed the informed consent form. Only patients with a significant coronary obstruction (>50%) in the main coronary arteries and attending the follow-up visit were included. The reason for performing PCI, the number of arteries stenosed and treated, and the left ventricular ejection fraction were recorded. Logistic EuroSCORE and Global Registry of Acute Coronary Events (GRACE 2.0) risk scores were calculated after PCI, while the complexity of coronary artery disease was evaluated using the SYNTAX 1.0 score.^{37–39}

A month after discharge, all patients completed a standardized questionnaire including cardiovascular and respiratory variables. A complete physical examination was performed. The Charlson index was used to measure comorbidities.⁴⁰ Scores on the Charlson index represent clinical history previous to the coronary event and spirometry.

Evaluation of Arterial Stiffness

Arterial stiffness was determined in the follow-up visit through two different methods. First, carotid-femoral pulse wave velocity (cfPWV) was measured by applanation tonometry using a Sphygmocor Xcel device (AtCor Medical Pty Ltd). Augmentation index (AIx), central systolic pressure, and central pulse pressure were also calculated with the Sphygmocor

device. Aix measures the supplementary increase in blood pressure during systole due to the reflection of the forward-travelling pressure waves from the peripheral circulation.⁴¹ Secondly, the cardio-ankle vascular index (CAVI) was obtained using a VaSera 1500 (Fukuda Denshi, Tokyo) device. CAVI measures arterial stiffness using extrapolated brachial-ankle pulse and ankle/brachial index (ABI) values.⁴²

Evaluation of Pulmonary Function

Postbronchodilator spirometry was performed according to international guidelines after evaluation of arterial stiffness.⁴³ Airway obstruction was diagnosed using the fixed ratio (FEV1/FVC <0.7), while obstruction severity was stratified according to FEV1% predicted values from the Global Obstructive Lung Disease (GOLD) thresholds.⁴⁴ COPD diagnosis was confirmed by airway obstruction and compatible clinical criteria. A separate analysis was made using continuous values of lung function (FEV1, FVC, and FEV1/FVC).

Evaluation of Blood and Urine Biomarkers

A fasting blood sample was obtained in the follow-up visit. Red and white blood cell count, renal and hepatic function, inflammatory serum parameters [high sensitivity C reactive protein (Hs-CRP) and fibrinogen], cardiac biomarkers [brain natriuretic peptides (NT-proBNP), high sensitivity troponin (Hs-TNT)], and urine albumin-creatinine ratio in urine sample were measured with standard routine methods. In a subgroup of patients, surfactant protein D (SPD), desmosine, and Clara cell secretory protein-16 (CC-16) were analyzed with ELISA immunoassay (DYNEX technologies).

Statistical Analysis

Data are presented as means \pm standard deviation (S.D.) for symmetric continuous variables or as medians and interquartile ranges for non-symmetric continuous variables. Because of its strongly asymmetric distribution, the albumin-creatinine ratio was log-transformed and expressed as the geometrical mean. Differences were compared with robust Welch's *t*-test or non-parametric Wilcoxon test. Frequency distribution (number and percentages) was provided for qualitative variables. The Chi-2 test or the Fisher exact test was used to compare proportions.

We performed an ANCOVA analysis to study the association between unstratified lung function and the rest of the variables. In this analysis, FEV1% and FEV1/FVC analyzed as continuous variables were the dependent factors, while the rest of the measures—adjusted for age and gender—were the independent variables. Coefficients and 95% confidence intervals were reported.

Finally, to explore the latent groups of patients based on their respiratory profile, including non-stratified lung function values and biomarkers of pulmonary damage, we used hierarchical unsupervised learning algorithms based on the combination of FEV1%, FVC%, FEV1/FVC, CC-16, SPD, and package-years. In this analysis, the chained equation for multivariate imputation was used to replace missing values (R package mice used with this goal). A case-complete approach is provided as supplementary material. The numbers of groups were determined after a visual inspection of the resulting dendrogram. A forest plot describing the mean and 95% confidence intervals of the standardized measures represents the differences among the resulting groups. R (www.r-project.org) was used for statistical analysis. Two-sided *p*-values are provided, and those below 0.05 were considered significant.

Results

A total of 170 patients were evaluated during the follow-up visit. Of these, six were excluded (4 for non-valid spirometry and 2 with coronary obstruction below 50%). The mean age of patients included was 65 \pm 10 years, and 79% were males. The main reasons for performing PCI were myocardial infarction without ST-elevation (NSTEMI) in 70 (42.7%), myocardial infarction with ST-elevation (STEMI) in 67 (40.9%), and unstable angina in 27 (16.5%). Respiratory biomarkers (CC-16, Desmosine and SPD) were obtained in 101 (61.6%) patients. No differences were observed between patients with and those without respiratory biomarker determination regarding age, FEV1%, FEV1/FVC, cfPWV, CAVI, Charlson index, Hs-TNT, NT-proBNP, or Hs-CRP.

Prevalence and Previous Underdiagnosis of COPD

A total of 56 (34.1%) patients met the spirometric criteria for COPD, according to the fixed ratio (FEV1/FVC <0.7). Thirty-eight (67.9%) had not been previously diagnosed. All of them presented clinical criteria compatible with COPD. Eight patients classified with COPD were never smokers; none of them had asthma or bronchiectasis as the predominant disease. Four had a previous diagnosis of COPD. In the rest, the symptoms, radiological findings, and subsequent spirometries were compatible with the diagnosis.

According to the GOLD spirometric criteria, nineteen (33.9%) had mild COPD, twenty-five (44.6%) had moderate COPD, and twelve (21.5%) had severe or very severe airway obstruction. Two patients with severe COPD had not been previously diagnosed, while a lack of a previous diagnosis accounted for 76% and 89% of those with moderate or mild COPD (**Figure 1**). Respiratory biomarkers were available for 35 (62.5%) COPD patients and 66 (61.1%) ($p = 0.862$) non-COPD patients.

Differences Between COPD and Non-COPD Patients According to the Fixed Ratio

Compared to non-COPD patients, those with COPD diagnosed by fixed ratio were older, with greater tobacco history, and higher logistic EuroSCORE and GRACE 2.0 score (**Table 1**). COPD patients had more comorbidities measured by adjusted and non-adjusted Charlson indexes and presented peripheral arterial disease ($p = 0.035$) and arrhythmias ($p = 0.012$) more frequently (**Table S1**; **Supplementary Material**). According to the fixed ratio, no other demographic or clinical characteristics differed significantly between patients with and those without COPD.

Measures of Arterial Stiffness

As shown in **Table 2**, cfPWV was significantly higher in COPD compared to non-COPD patients: 7.35 m/s (IQR: 6.40–8.70) vs 6.60 m/s (IQR: 5.73–7.88) ($p = 0.006$). Likewise, CAVI was also higher in COPD patients: 9.70 (IQR: 8.63–10.80) vs 9.01 (IQR: 8.40–9.99) ($p = 0.023$). Other values of central hemodynamics, such as central systolic, pulse pressure, and AIx, did not differ between patients with and those without COPD. cfPWV and CAVI measures were moderately correlated [$\rho = 0.18$; $p = 0.043$ (95% CI: 0.005–0.038)], and both were related with FEV1% and FEV1/FVC values. **Figure S1** (**Supplementary material**). Since carotid-femoral wave velocity is correlated with age and blood pressure values, we performed a logistic regression analysis adjusted for age and central blood pressure. In this analysis pulse wave velocity and age remained statistically significant [PWV ($p = 0.022$); age ($p = 0.001$), central blood pressure ($p = 0.058$)]. Given that the CAVI index is independent of blood pressure, we did not perform additional adjustment analysis.

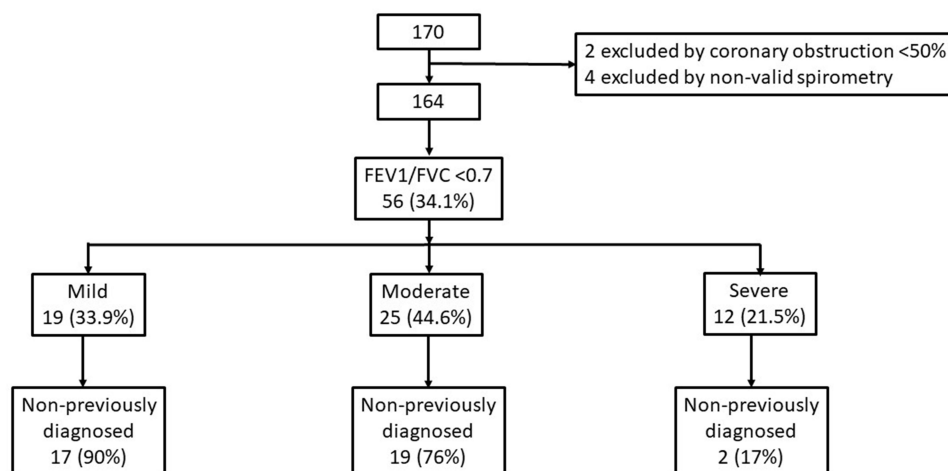


Figure 1 Flowchart of participants, COPD prevalence, and underdiagnosis levels according to the fixed ratio (FEV1/FVC <0.7).

Table 1 Differences in Demographic and Clinical Characteristics of Patients with and without COPD

	Total (n=164)	COPD (n=56)	Non-COPD (n=108)	P-value
Age, years^a	65.0±10.2	69.0±8.3	62.9.0±10.6	<0.0001
Gender, male	130 (79%)	47 (84%)	83 (77%)	0.487
Body mass index^a	28.3±5.2	28.9.0±4.3	27.9±5.6	0.270
Non-adjusted Charlson index^b	1 [0–3]	2 [1–4]	1 [0–3]	0.006
Age-adjusted Charlson index^b	4 [2–6]	4 [3–7]	3 [2–5]	<0.001
Waist circumference^a	103.3±11.4	103.5±11.8	103.2±11.2	0.881
Smoking status				
Never	45 (27.6%)	8 (14.3%)	37 (35.2%)	0.008
Former	86 (52.4%)	37 (66.0%)	49 (45.4%)	0.011
Current	32 (19.6%)	10 (17.9%)	22 (20.4%)	1.000
Package-years^{b/c}	30.0 [18.2–46.0]	40.0 [20.6–60.0]	30.0 [15.0–40.0]	0.015
Respiratory variables				
FVC mL^a	3413.3±967.9	3181.9±972.0	3533.3±947.9	0.027
FVC %^a	85.4±16.9	81.6±18.7	87.4±15.7	0.040
FEV1 mL^a	2475.2±806.7	2020.0±737.1	2711.3±739.8	<0.0001
FEV1%^a	82.4±19.7	69.9±20.9	88.9±15.6	<0.0001
FEV1/FVC^b	72.50 [67.66–77.68]	65.59[59.32–67.78]	75.89[72.52–79.94]	<0.0001
Cardiovascular variables				
Number of coronary stenosed arteries^b	2.0 [1.0–3.0]	1.5 [1.0–3.0]	2.0 [1.0–3.0]	0.131
Number of coronary lessons treated^b	1.0 [1.0–2.0]	1.0 [1.0–2.0]	1.0 [1.0–2.0]	0.867
Left ventricular ejection fraction^a	53.0±12.7	52.0±11.8	53.5±13.3	0.545
EuroSCORE^b	2.5 [1.5–5.1]	3.6 [2.1–6.2]	2.1 [1.3–4.3]	<0.0001
GRACE score^b	104.0 [85.0–119.0]	114.0[94.3–125.8]	97.0[78.0–116.0]	0.001
SYNTAX score^b	13.0 [7.0–21.0]	11.5 [7.0–19.9]	13.0 [7.0–23.5]	0.290

Notes: ^aValues expressed as mean and standard deviation. ^bValues expressed as median and interquartile range (IQR) 25–75%, and compared through Wilcoxon test. ^cPackage-years are computed just on ever smoker patients.

Biomarkers

In the analysis of serum biomarkers, COPD patients had higher serum values of Hs-TNT: 14.19 (IQR: 10.28–24.26) ng/mL vs 10.97 (IQR: 7.42–18.06) ng/mL ($p = 0.007$) and SPD: 19.64 (IQR: 15.01–26.01) ng/mL vs 14.71 (IQR: 11.67–18.39) ng/mL ($p = 0.003$) (Table 2).

ANCOVA Analysis

ANCOVA analysis was used to explore the association between FEV1/FVC ratio and FEV1% values expressed as continuous values in relation to the rest of the variables. In this analysis, FEV1% was significantly associated with cfPWV, Hs-TNT, Hs-CRP, SPD, GRACE, and the non-adjusted Charlson index. FEV1/FVC ratio was associated with cfPWV, Hs-TNT, EuroSCORE, GRACE, and non-adjusted Charlson index.

After adjusting for age and gender, FEV1% remained significantly associated with cfPWV, Hs-CRP, SPD, and Charlson index, while FEV1/FVC was associated with cfPWV, SYNTAX, and Charlson index (Table 3).

Cluster Analysis

Finally, we performed a cluster analysis to explore the existence of different subgroups among the patients according to pulmonary variables, including respiratory function continuous values (FEV1%, FVC%, and FEV1/FVC ratio) and serum biomarkers of lung damage (SPD and CC-16). This analysis did not include desmosine due to the lack of significance in the previous explorations. Three clusters of patients were identified after an exploratory visualization of the dendrogram, although one had a small number of patients (5). (Figure 2) The other two clusters included 82 and 77 patients. The first of these was characterized by a respiratory pattern with decreased pulmonary function values, higher accumulated smoking

Table 2 Descriptive Statistics for Arterial Stiffness, Analytic Parameters, and Serum Biomarkers for the Total Cohort Stratified by COPD Diagnosis

	Total (n =164)	COPD (n=56)	Non-COPD (n=108)	P-value
Arterial stiffness				
Arterial pulse wave velocity (m/s) ^b	6.90 [6.00–8.17]	7.35 [6.40–8.70]	6.60 [5.73–7.88]	0.006
Central systolic pressure (mmHg) ^a	119.83 ± 15.75	118.76 ± 16.46	120.38 ± 15.42	0.534
Central pulse pressure ^a	47.45 ± 13.27	47.29 ± 13.78	47.53 ± 13.07	0.912
Augmentation index ^a	35.64 ± 12.61	34.29 ± 12.09]	36.34 ± 12.87	0.326
Cardio-ankle vascular index mean ^b	9.40 [8.70–10.80]	9.70 [8.63–10.80]	9.01 [8.40–9.99]	0.023
Ankle-brachial pressure index mean ^b	1.11 [0.98–1.19]	1.07 [0.92–1.16]	1.12 [0.99–1.20]	0.065
Analytic parameters				
Hemoglobin (g/L) ^a	13.99 ± 1.70	13.95 ± 2.00	14.01 ± 1.54	0.835
Leukocytes (10 ⁹ L) ^a	7.98 ± 2.17	7.96 ± 1.90	7.99 ± 2.31	0.939
Creatinine (mg/dL) ^a	1.03 ± 0.33	1.04 ± 0.33	1.03 ± 0.33	0.777
Glomerular filtration rate (mL/min) ^a	59.52 ± 28.56	57.41 ± 27.26	60.61 ± 29.27	0.498
Albumin-creatinine ratio (mg/g) ^{a,c}	1.20 ± 0.68	1.27 ± 0.67	1.16 ± 0.7	0.245
Total cholesterol (mg/dl) ^b	138.4 [118.3–162.8]	138.4 [118.3–167.0]	138.2 [118.0–161.4]	0.893
HDL cholesterol (mg/dl) ^b	42.9 [36.0–52.6]	42.9 [35.6–53.7]	42.7 [36.1–52.1]	0.899
LDL cholesterol (mg/dl) ^b	65.7 [49.5–81.2]	65.7 [48.7–85.1]	65.7 [49.9–81.1]	0.628
Serum inflammatory biomarkers				
Fibrinogen (g/L) ^a	4.47 ± 0.87	4.40 ± 0.89	4.51 ± 0.87	0.472
Hs-CRP(mg/L) ^b	2.45 [0.93–6.06]	2.83 [1.17–7.97]	2.12 [0.79–5.85]	0.245
Myocardial biomarkers				
NT-proBNP(pg/mL) ^b	228 [93.75–744.15]	279.50 [134.50–816.50]	197.50 [70.00–699.00]	0.064
Hs-TNT(ng/mL) ^b	11.97 [8.19–20.83]	14.19 [10.28–24.26]	10.97 [7.42–18.06]	0.007
Respiratory biomarkers				
CC-16 (ng/mL) ^b	8.59 [6.23–14.33]	8.59 [5.86–14.27]	8.57 [6.34–14.95]	0.808
Desmosine (ng/mL) ^b	119.34 [81.24–189.72]	144.68 [92.09–203.28]	116.64 [79.37–185.46]	0.224
SPD (ng/mL) ^b	18.24 [13.55–22.29]	19.64 [15.01–26.01]	14.71 [11.67–18.39]	0.003

Notes: ^aValues expressed as mean and standard deviation. ^bValues expressed as the median and interquartile range (IQR) 25–75%, and compared through Wilcoxon test. ^cLogarithmic transformation.

Table 3 Standardized Beta Coefficient for the Unadjusted and Adjusted (Age and Gender) Models. ANCOVA Analysis

	FEV1%				FEV1/FVC			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value
cfPWV (m/s)	-0.27	<0.001	-0.24	0.003	-0.25	0.001	-0.16	0.037
CAVI	-0.12	0.142	-0.05	0.503	-0.16	0.04	-0.1	0.195
Hs-TNT (ng/mL)	-0.17	0.033	-0.10	0.237	-0.16	0.039	-0.07	0.374
NT-proBNP (pg/mL)	0.04	0.610	0.13	0.123	-0.06	0.430	0.08	0.330
Hs-CRP (mg/L)	-0.25	0.001	-0.23	0.003	-0.12	0.111	-0.06	0.465
SPD (ng/L)	-0.33	0.002	-0.30	0.004	-0.16	0.167	-0.1	0.402
LVEF	0.03	0.718	0.00	0.978	0.08	0.413	0.05	0.570
EUROSCORE	-0.13	0.091	-0.06	0.553	-0.22	0.004	-0.06	0.503
Charlson	-0.26	0.001	-0.21	0.008	-0.28	<0.001	-0.19	0.016
SYNTAX	0.05	0.563	0.09	0.271	0.08	0.285	0.17	0.026
GRACE	-0.16	0.044	-0.09	0.370	-0.28	<0.001	-0.12	0.213
Fibrinogen	-0.09	0.262	-0.09	0.300	-0.03	0.727	0.04	0.654

Abbreviations: cfPWV, arterial carotid-femoral pulse wave velocity; CAVI, Cardio-ankle vascular index; Hs-TNT, High sensitivity Troponin T; NT-proBNP, Brain natriuretic peptide; Hs-CRP, High sensitivity C reactive protein; SPD, Surfactant protein D; LVEF, Left ventricular ejection fraction; Charlson, Charlson index without age adjustment.

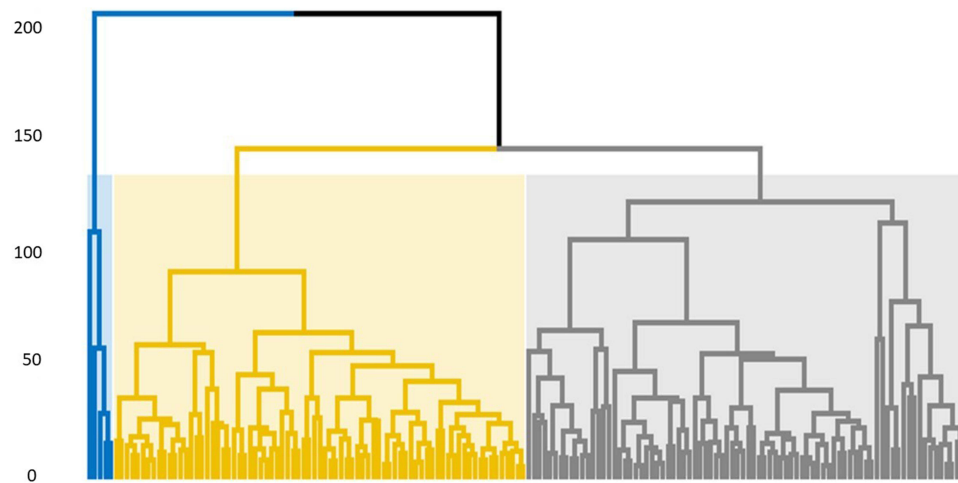


Figure 2 Dendrogram according to pulmonary related measures (FEV1%, FEV1/FVC, SPD and CC-16).

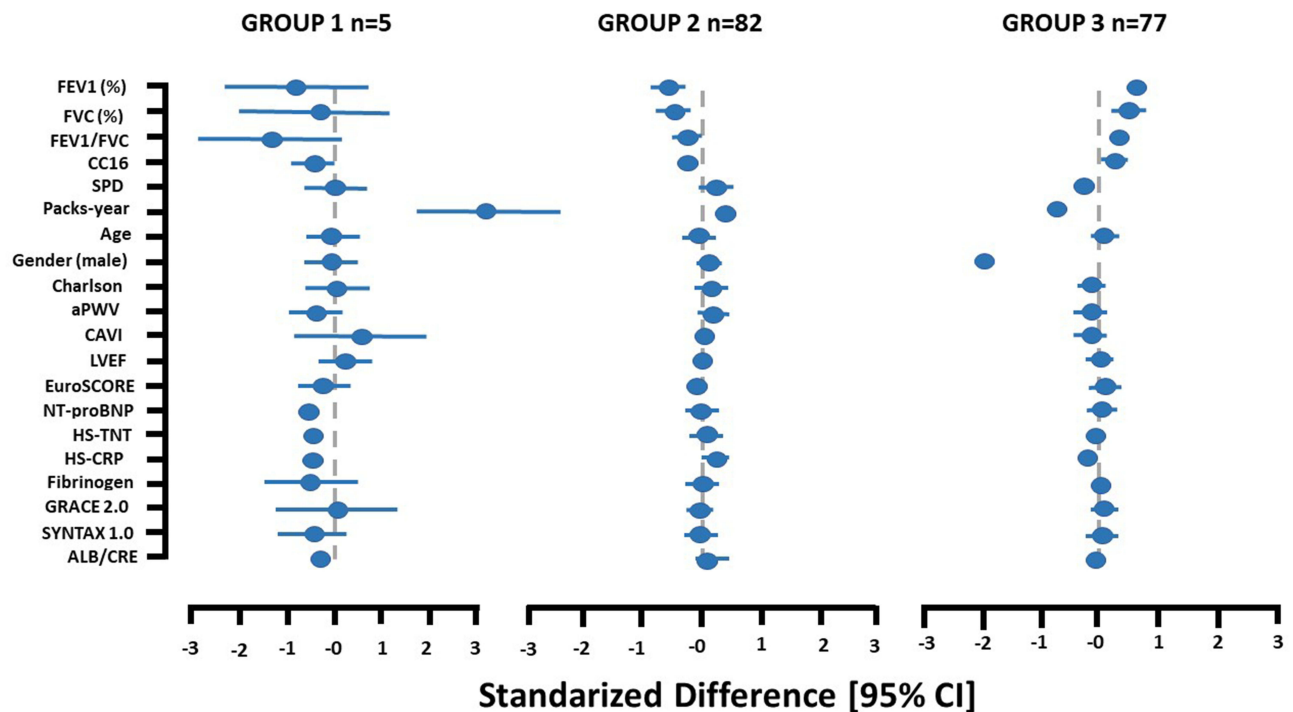


Figure 3 Forest plot with mean and 95% confidence interval comparison between selected variables stratified by clusters.

history, increased inflammatory serum parameters (Hs-CRP and fibrinogen), and SPD in blood serum, and augmented values of arterial stiffness measured with cfPWV (Figure 3; Tables 4 and Table S2 Supplementary Material). The case-complete analysis is shown in the supplementary material (Table S3; Figure S3 Supplementary Material).

Discussion

Our results demonstrate that after an acute coronary event treated by PCI, arterial stiffness, Hs-TNT, and SPD are increased in COPD patients, even those without a previous COPD diagnosis. SPD and cfPWV remain significantly related to unstratified postbronchodilator FEV1% after adjustment for age and gender. Moreover, in the cluster analysis, nearly half of the patients present a respiratory pattern defined by lower lung function parameters and higher serum biomarkers of pulmonary damage (SPD and CC-16).

Table 4 Differences in Relevant Variables According to Cluster Group

	Group 1 N=5		Group 2 N=82		Group 3 N=77		p-value
	Mean	SD	Mean	SD	Mean	SD	
FEV1 (%)	66.60	25.02	71.89	17.22	94.62	14.14	0.0000
FVC (%)	80.60	22.14	77.23	14.60	94.42	14.37	0.0000
FEV1/FVC	59.83	12.45	69.43	9.86	74.97	6.31	0.0000
CCI6	8.57	5.00	10.62	10.51	16.27	12.89	0.0070
SPD	20.00	7.69	22.24	15.33	16.14	7.67	0.0077
Packs-year	110.00	31.50	37.00	18.95	7.09	10.98	0.0000
Age	64.40	5.03	64.18	9.92	65.94	10.81	0.5567
Gender, male %	100%		85%		71%		0.0487
Charlson	2.00	1.00	2.15	1.90	1.55	1.54	0.0908
acfPWV	6.46	0.79	7.49	2.04	6.87	1.56	0.0673
CAVI	10.13	1.74	9.40	1.48	9.03	1.44	0.1146
LVEF	55.38	5.38	52.73	11.55	53.07	10.75	0.8691
EuroSCORE	3.03	2.14	4.10	5.77	4.94	5.51	0.5381
NT-pro BNP	130.00	60.15	588.09	850.40	626.43	938.11	0.4768
Hs-TNT	9.68	1.86	22.04	32.42	16.70	16.37	0.2989
Hs-CRP	1.65	1.46	8.00	11.33	3.24	6.05	0.0032
Fibrinogen	3.11	1.45	4.05	1.98	4.02	1.48	0.5064
GRACE 2.0	106.80	28.96	102.61	27.45	106.19	24.85	0.6783
SYNTAX	10.70	7.03	15.67	11.12	15.90	11.57	0.6057
ALB/CRE	12.57	16.42	88.87	236.42	41.04	101.91	0.2087

The COPD prevalence observed in our cohort (34%) is similar to that reported in prospective studies performed on IHD patients after spirometric evaluation, both in stable conditions and after PCI.^{14–17,45} This prevalence drops to around 10% in retrospective cohorts without lung function data, suggesting that in these studies, two-thirds of COPD patients were non-diagnosed and consequently analyzed as non-COPD.^{12,13} To our knowledge, only one prospective study performed on patients treated by PCI and with spirometric evaluation has demonstrated that COPD patients—with or without a previously known diagnosis—have a higher number of new coronary events and increased mortality after median follow-up of 3 and 6 years.^{15,17}

Given the lack of previous prospective studies with confirmed COPD in this population, the reasons for this adverse prognosis remain unclear.² Our study is an attempt to explore possible mechanisms to explain the worse evolution after a PCI procedure in COPD patients. IHD and COPD share an increased prevalence of classic cardiovascular risk factors, including arterial hypertension, diabetes mellitus, dyslipidemia, smoking, and low-grade systemic inflammation.^{3,6,46} More recently, other variables, such as arterial stiffness and myocardial or pulmonary serum biomarkers, have been related to a worse prognosis in patients with IHD or COPD.

Arterial stiffness is a significant predictor of cardiovascular events in the general population and in patients with established IHD.²⁶ The most widely validated method for evaluating arterial stiffness is pulse wave velocity, measured between the carotid and femoral arteries.^{26,28,41} Greater values for cfPWV reflect impairment of aortic distensibility, which is associated with arterial ageing and atherosclerosis.^{41,47,48} An alternative way to calculate arterial stiffness is the cardio-ankle vascular index, which uses extrapolated values from the ascending aorta to the ankle arteries.^{29,42} Previous studies have shown that arterial stiffness is inversely related to lung function parameters and is a predictor of 3-year mortality in COPD patients.^{27,28,48}

Similarly, in several prospective cohorts, arterial stiffness measured with cfPWV or CAVI was an independent predictor of major cardiovascular events in IHD patients treated by PCI.^{29,33,49–51} Arterial stiffness measured by other methods such as magnetic resonance or arteriography was also related to new coronary events, stent occlusion, and

decreased survival after an acute coronary event.^{52–54} Regrettably, in none of these studies was pulmonary function explored. In our cohort, cfPWV and CAVI were increased in patients with IHD and COPD, offering a possible explanation for the increased risk of cardiovascular events in COPD patients.

Hs-TNT and SPD were also increased in our study in COPD patients. Hs-TNT measures cardiomyocyte damage and is related to the risk of cardiovascular death both in patients with a coronary event and in the general population.^{55,56} Higher values of Hs-TNT have also been related to COPD patients' prognosis in the stable phase and after an acute exacerbation.^{30,56} In a cohort study performed on patients with severe exacerbations of COPD and elevated levels of troponins at admission, coronary angiography showed significant coronary stenosis in 67% of patients, suggesting an imbalance between coronary flow and oxygen demand.⁵⁷

SPD is a highly lung-specific glycoprotein secreted by type-2 pneumocytes, and it is also expressed in the endothelium of the cardiovascular system. Serum levels of SPD are increased in COPD patients, and these high levels have been associated in longitudinal studies with increased cardiovascular mortality.^{25,58} Circulating SPD levels are also a strong independent predictor of 10-year cardiovascular mortality in patients referred for selective coronary angiography, although, again, lung function was not assessed in this cohort.³²

Beyond lung function, arterial stiffness, troponins, and SPD are correlated.^{33,59} A longitudinal study performed on COPD patients has shown that arterial stiffness and troponins increase simultaneously during acute exacerbations of COPD compared with their values in the stable phase.³⁴ Similarly, SPD values are also increased during COPD exacerbations and are related to arterial stiffness.^{58,59}

Inflammatory biomarkers (Hs-CRP and fibrinogen) are associated with the risk of cardiovascular events in the general population, and they predict mortality in patients with IHD or COPD.^{24,25,60,61} In our study, no differences in inflammatory biomarkers were found between COPD and non-COPD patients defined according to the fixed ratio. However, Hs-CRP was related significantly to airway obstruction measured by post-bronchodilator FEV1% values after adjusting for age and gender.

Finally, in the cluster analysis, a 53% of included patients had a respiratory pattern characterized by a combination of non-dichotomized lung function values and serum pulmonary biomarkers, suggesting that pulmonary damage may be more frequent than previously reported in this population.

Our study has several limitations. First, it was performed in a single centre, and in predominantly male patients. This low percentage of women in IHD patients treated by PCI is similar to that reported in similar cohorts with spirometric confirmation.^{14,16} It may be partially explained by the underuse of PCI in women with an acute coronary event.^{62,63} Finally, our study assessed variables previously recognized as being related to IHD patients' prognosis, but the follow-up was insufficient to confirm their relationship with new coronary events and mortality.

In conclusion, our results confirm the high prevalence of COPD in patients treated by PCI and the increased values of arterial stiffness and serum biomarkers in COPD patients. Their relationship with the occurrence of new coronary events and mortality should be confirmed with longitudinal follow-up of the cohort.

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Disclosure

The authors declare that they have no conflict of interest in this article.

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