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Chest CT-assessed comorbidities and all-cause mortality risk in COPD patients in the BODE cohort

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Abstract

Background and objective: The availability of chest computed tomography (CT) imaging can help diagnose comorbidities associated with chronic obstructive pulmonary disease (COPD). Their systematic identification and relationship with all-cause mortality have not been explored. Furthermore, whether their CT-detected prevalence differs from clinical diagnosis is unknown.

Methods: The prevalence of 10 CT-assessed comorbidities was retrospectively determined at baseline in 379 patients (71% men) with mild to severe COPD attending pulmonary clinics. Anthropometrics, smoking history, dyspnoea, lung function, exercise capacity, BODE (BMI, Obstruction, Dyspnoea and Exercise capacity) index and exacerbations rate were recorded. The prevalence of CT-determined comorbidities was compared with that recorded clinically. Over a median of 78 months of observation, the independent association with all-cause mortality was analysed. A 'CT-comorbidome' graphically expressed the strength of their association with mortality risk.

Results: Coronary artery calcification, emphysema and bronchiectasis were the most prevalent comorbidities (79.8%, 62.7% and 33.9%, respectively). All were underdiagnosed before CT. Coronary artery calcium (hazard ratio [HR] 2.09; 95% CI 1.03–4.26, $p = 0.042$), bronchiectasis (HR 2.12; 95% CI 1.05–4.26, $p = 0.036$) and low psoas muscle density (HR 2.61; 95% CI 1.23–5.57, $p = 0.010$) were independently associated with all-cause mortality and helped define the 'CT-comorbidome'.

Conclusion: This study of COPD patients shows that systematic detection of 10 CT-diagnosed comorbidities, most of which were not detected clinically, provides information of potential use to patients and clinicians caring for them.

KEYWORDS
all-cause mortality, chest CT, comorbidity, COPD, tomography

INTRODUCTION

Chronic obstructive pulmonary disease (COPD), the third cause of death worldwide,[1] is frequently associated with a wide group of comorbidities that contribute substantially to its poor outcome.[2,3]

Our group has identified the most prevalent clinically detected comorbidities in COPD and defined the ones with an independent impact on long-term mortality.[3] Some of these are identifiable using validated chest computed tomography techniques (CT chest). These include coronary artery disease (CAD),[4] pulmonary hypertension (PH),[5] lung cancer,[6]

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interstitial lung disease,[7] osteoporosis[8] and liver disease.[9] They may impair functional capacity, reduce quality of life and increase hospitalizations and importantly mortality risk.[10]

In patients with COPD, chest CT is frequently used to evaluate lung parenchyma and airways, presence of pulmonary infections and/or embolism.[11] In addition, multiple associations support the use of CT scan as a screening tool for early lung cancer detection.[6,12] Several experts have expressed the convenience of doing a chest CT in COPD patients to make use of the information available in those studies.[13,14]

We conducted this study in a cohort of patients with COPD attending pulmonary clinics to (1) define the prevalence of CT-assessed comorbidities, (2) compare the CT-determined prevalence with their clinical recognition and (3) determine the association of these comorbidities with all-cause mortality.

SUMMARY AT A GLANCE

This multicentric study shows that chest computed tomography (CT) to evaluate the presence of 10 comorbidities detects important pathologies not diagnosed in the clinical management of those patients. While emphysema, coronary artery calcification (CAC) and bronchiectasis were the most prevalent CT-detected comorbidities, CAC, bronchiectasis and low Psoas muscle density were independently associated with all-cause mortality.

METHODS

Participants

This was a retrospective analysis of a multicentre, observational study, involving COPD outpatients prospectively enrolled between June 2012 and 2015 and followed up until January 2021. All patients had mild to severe airway limitation followed by pulmonologists from the BODE (BMI, Obstruction, Dyspnoea and Exercise capacity) collaborative group (Pamplona, Las Palmas, Tenerife and Zaragoza in Spain).

COPD was defined according to the GOLD criteria[10] and had to be stable (without exacerbations) for at least 8 weeks while receiving therapy according to the same guidelines.[10] Exclusion criteria were the presence of uncontrolled comorbidities such as malignancy including the working diagnosis of lung cancer. At baseline, age, gender, height, weight, BMI, body surface area, smoking status and pack-year history and previous year exacerbations were recorded. Lung functions were measured following the ATS/ERS standards.[15] Patients' dyspnoea was evaluated with the modified Medical Research Council (mMRC) scale,[16] and 6-min walking distance (6MWD) was performed following the ATS recommendations.[17] The forced expiratory volume in 1 s (FEV_1%), BMI, 6MWD and mMRC scale values were integrated into the BODE index.[18] CT-diagnosed comorbidities were compared with those previously recorded in patient's medical records.

Patients were followed up for a median of 78 (50–116) months. During this time, the investigators at each site determined the patient's survival status by reviewing medical records or contacting patient's family members as previously reported.[18]

Chest CT protocol and CT-assessed comorbidities

At baseline, while supine, subjects underwent a low-dose chest CT examination acquired at end-inspiration, using multidetector-row (16-detector or 64-detector) CT scans, ordered following the discretion of the attending physician. The examination extended from the thoracic inlet to the upper abdomen. The following parameters were employed: 120 kV, 40 mAs, 32 × 0.6 mm detector collimation, pitch 1. Images were reconstructed with 5 mm and 1 mm slice thickness using soft tissue (B31f) and high-resolution (B60f) reconstruction algorithms to evaluate the mediastinum and lung parenchyma, respectively. CT scans were retrospectively evaluated by two chest radiologists (AE and GB),

TABLE 1 Demographic characteristics and functional data of participants at baseline ($n = 379$)

Variables	
Age in years, median (IQR)	66 (59–72)
Male sex, *n* (%)	297 (78.4%)
Pack-years, median (IQR)	50 (36–75)
Current smoker, *n* (%)	136 (37.3)
BMI kg/m^2, median (IQR)	27 (23.7–30.1)
BSA (kg/m^2), mean (SD)	1.9 (0.3)
FEV_1/FVC (%), median (IQR)	55 (44–63)
FEV_1 %, mean (SD)	64.4 (21.9)
FVC %, mean (SD)	93.6 (22.4)
TLC %, median (IQR)	107 (96–116)
DLCO %, mean (SD)	62.1 (46.8)
6MWD (m), median (IQR)	480 (403–545)
MMRC, median (IQR)	1 (0–2)
BODE, median (IQR)	1 (0–2)
Spirometric GOLD stages (%)	I (36.2) II (47.9) III (13.3) IV (2.7)
Exacerbations in the previous year, median (IQR)	0 (0–1)
Exacerbations in the previous year, yes (%)	97 (37.9)
Charlson index, median (IQR)	1 (0–2)

Abbreviations: 6MWD, 6-min walking distance; BODE, BMI, Obstruction, Dyspnoea and Exercise capacity, GOLD Global Initiative for Obstructive Lung Disease; BSA, body surface area; DLCO, diffusion capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IQR, interquartile range; mMRC, modified Medical Research Council; TLC total lung capacity.

blinded to clinical data. The 10 radiological variables with validated methodology and that are potentially useful for COPD prognosis were established by the same radiologists (AE and GB) and by COPD expert pulmonologists (BRC and JPdT; see Appendix S1 in the Supporting Information). They included lung abnormalities (emphysema, interstitial lung abnormalities [ILA] and bronchiectasis)[19–22]; cardiovascular abnormalities (ascending aorta and pulmonary artery enlargement [PAE] and coronary artery calcification [CAC])[4,23–26]; low liver density[9,27]; musculoskeletal abnormalities (osteoporosis and low psoas muscle density)[8,13,28–31]; and hiatus hernia.[32]

Statistical analysis

To explore the normality of the data distribution, we used the Kolmogorov–Smirnov test. Quantitative data with a normal distribution were described as mean and SD and, with non-normal distribution, as median and interquartile range (IQR). Categorical data were described using relative frequencies (%).

The prevalence of each morbidity (as categorical variable) in survivors versus non-survivors and between clinically diagnosed versus CT-detected comorbidities was compared using chi-square test. To evaluate the independent association of the detected comorbidities with all-cause mortality, a Cox proportional regression analysis was performed. The relationship was adjusted by age, BMI, FEV_1 and sex. Statistical analysis was performed with IBM SPSS Statistics for Macintosh, version 25.0 (IBM Corp., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant.

Development of the 'CT-comorbidome'

To evaluate the strength of the association of the comorbidities with the risk of death, we performed multivariate

TABLE 2 Prevalence of the different CT-assessed comorbidities

Morbidity detected	% of patients
Emphysema	62.7
Bronchiectasis	33.9
ILA	9.2
CAC	79.8
PAE (≥30 mm)	15.6
Ascending aorta enlargement	16
Hiatal hernia	24.2
Liver steatosis	23.4
Osteoporosis	25.7
Low PsD	15.8

Abbreviations: CAC, coronary artery calcification; CT, computed tomography; ILA, interstitial lung abnormalities; PAE, pulmonary artery enlargement; PsD, Psoas density.

TABLE 3 Contribution of chest CT to the diagnosis of comorbidities

Morbidity	Clinically diagnosed	Radiologically detected	p-value
Emphysema, %	34.4	62.7	0.011
Bronchiectasis, %	25.9	33.9	<0.001
ILA, %	4.2	9.2	<0.001
CAC, %	15.6	79.8	<0.001
PAE (≥30 mm), %	9	15.6	<0.001
Ascending aorta enlargement, %	7.1	16	<0.001
Hiatal hernia, %	21.6	24.2	<0.001
Liver steatosis, %	15	23.4	0.018
Osteoporosis, %	12.9	25.7	0.039
Muscle weakness versus low PsD, %	0.3	15.8	0.021

Abbreviations: CAC, coronary artery calcification; CT, computed tomography; ILA, interstitial lung abnormalities; PAE, pulmonary artery enlargement; PsD, Psoas density.

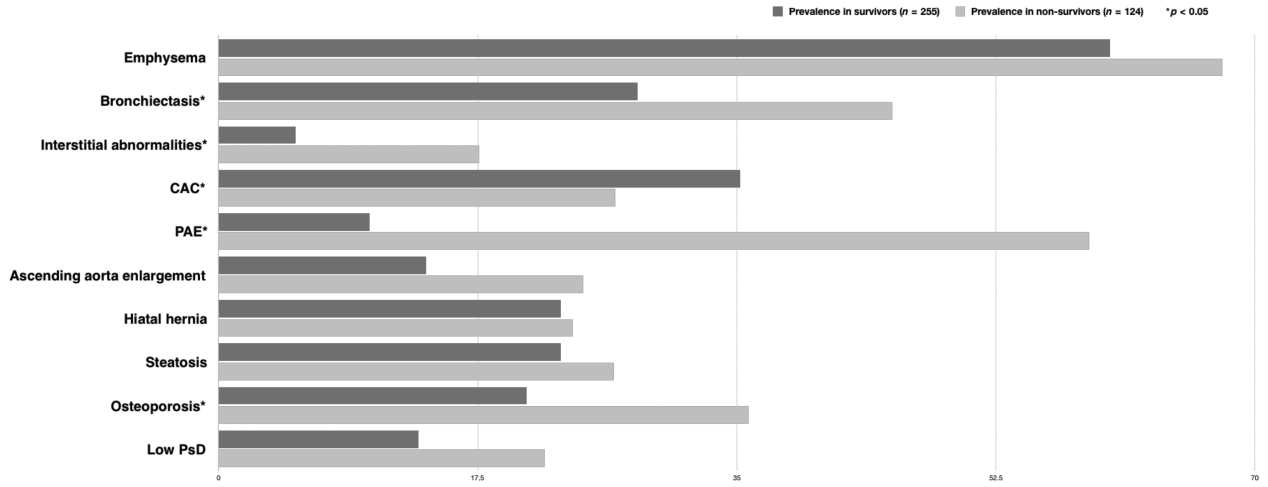

FIGURE 1 Prevalence of chest computed tomography-assessed comorbidities in survivors and non-survivors

analyses using Cox proportional hazards regression including all 10 CT-diagnosed comorbidities. A second multivariate analysis was performed including smoking status and FEV_1 (%, already adjusted by sex, age and BMI). We integrated this information with the prevalence of the disease to construct the 'CT-comorbidome', a graphical expression (orbital bubble chart) of the CT-diagnosed comorbidity prevalence and risk of death.

RESULTS

Cohort characteristics

From a total of 406 patients, we obtained appropriate radiological information in 379 participants (Figure S1 in the Supporting Information). The patients' clinical and functional data are provided in Table 1. The sample included 297 men and 82 women, with a median age of 66 years (IQR, 60–73) with a good exercise capacity at the time of enrolment. One third of the subjects were current smokers with a median history of 50 pack-years (IQR, 36–75). The mean FEV_1% predicted value was 64.4 (22.1)%, with a low BODE score and less than one exacerbation in the year prior to enrolment. During the follow-up time (78; 50–116 months), 32.7% ($n = 124$) of the participants died.

Prevalence of chest CT-assessed comorbidities

The prevalence of the 10 CT-assessed comorbidities is summarized in Table 2 and its specific prevalence in survivors

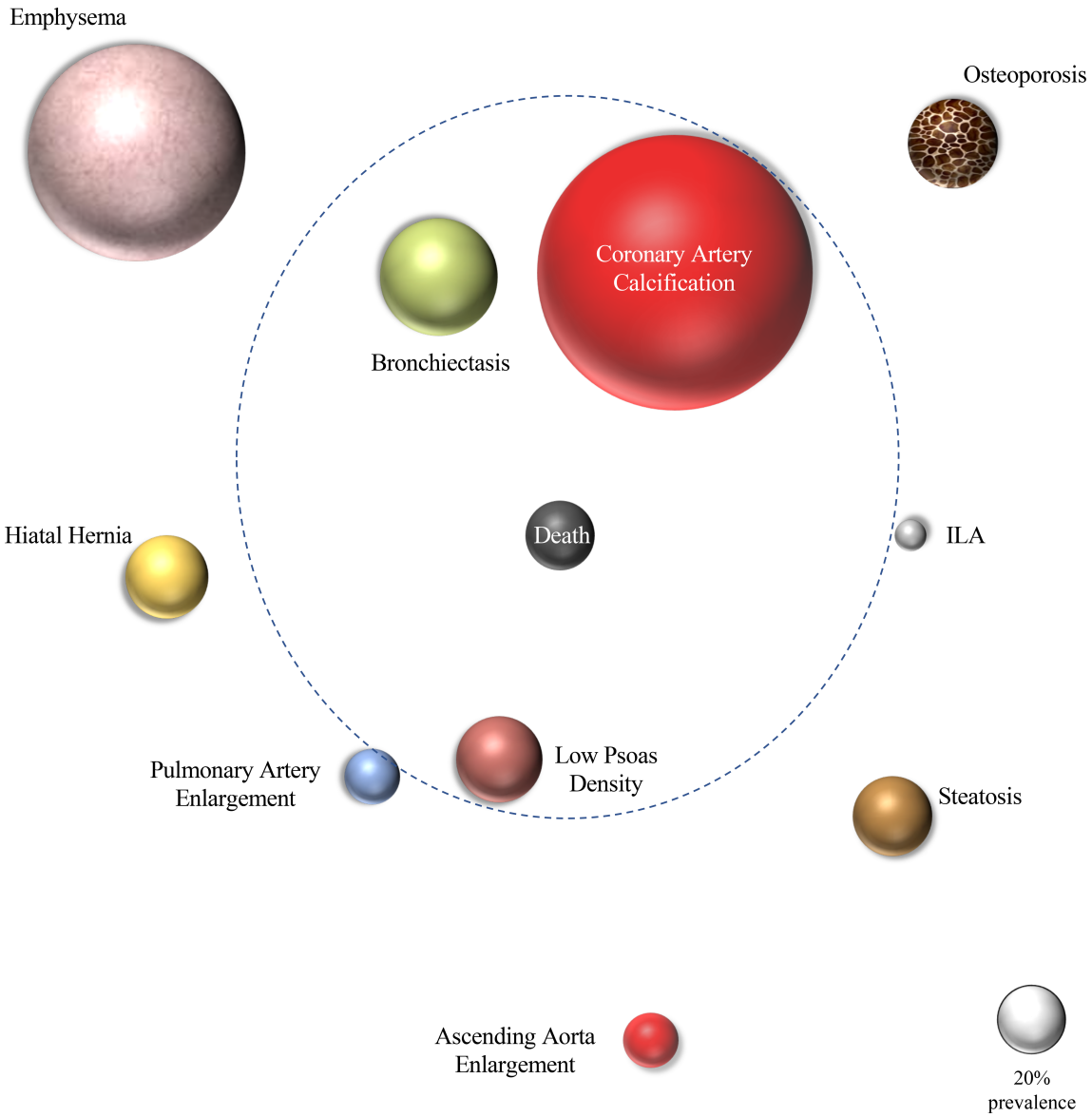

FIGURE 2 'Computed tomography (CT)-comorbidome': an orbital bubble chart showing the prevalence of the 10 CT-assessed comorbidities and the strength of their association with all-cause mortality

TABLE 4 Multivariate analysis exploring the CT-determined comorbidities and risk of all-cause mortality

Variables	HR (95% CI)	*p*-value
Emphysema (yes vs. no)	1.06 (0.53–2.14)	0.89
Bronchiectasis (yes vs. no)	**2.12 (1.05–4.26)**	**0.036**
ILA (yes vs. no)	1.93 (0.79–4.74)	0.151
CAC (low risk vs. high risk)	**2.09 (1.03–4.26)**	**0.042**
PAE (≥30 mm)	1.98 (0.69–5.73)	0.21
Ascending aorta enlargement (yes vs. no)	1.18 (0.48–2.90)	0.724
Hiatus hernia (yes vs. no)	1.53 (0.69–3.36)	0.269
Liver steatosis (yes vs. no)	1.39 (0.66–2.94)	0.392
Osteoporosis by CT (yes vs. no)	1.09 (0.44–2.68)	0.864
Low PsD (yes vs. no)	**2.61 (1.23–5.57)**	**0.013**

Note: Adjusted for age, sex, BMI, pack-year history and FEV_1.
Abbreviations: CAC, coronary artery calcification; CT, computed tomography; FEV_1, forced expiratory volume in 1 s; HR, hazard ratio; ILA, interstitial lung abnormalities; PAE, pulmonary artery enlargement; PsD, Psoas density.

versus non-survivors is shown in Figure 1. A statistically significant higher prevalence was observed in non-survivors for bronchiectasis, ILA, CAC, PAE and osteoporosis. Table S1 in the Supporting Information shows the prevalence of CT-assessed comorbidities by sex. A higher prevalence of bronchiectasis and borderline higher prevalence of low Psoas density (PsD) was found in men while a higher prevalence of osteoporosis was found in women.

Table S2 in the Supporting Information shows no significant differences in the treatment of comorbidities between survivors and non-survivors, except for emphysema and CAD. Surprisingly, a significantly higher proportion of non-survivors was receiving treatment for CAD perhaps reflecting more severe CAD and, thus, a higher mortality risk.

As shown in Table 3, chest CT increased the diagnostic prevalence for all the comorbidities compared to the clinically recognized diseases.

The independent association between CT-detected morbidity with all-cause mortality is displayed in Figure 2 as an orbital bubble chart ('CT-comorbidome'). The bigger the size of the bubble, the higher the prevalence. The closer to the centre, the higher the hazard ratio (HR) for mortality risk, with those included within the dotted orbit reaching statistical significance. CAC, emphysema and bronchiectasis were present in 79.8%, 62.7% and 33.9% of the patients, respectively. The distribution of the visually assessed emphysema severity was mild (51.5%), moderate (31.2%) and severe (17.3%) disease. Adjusting for other important cofounders (age, sex, BMI, pack-years history and FEV_1), bronchiectasis, CAC and low PsD were independently associated with all-cause mortality (Table 4 and Figure 2). CAC had added prognostic value to patients with low BODE index (BODE ≤ 4) (Figures S2–S4 and Tables S3–S5 in the Supporting Information).

DISCUSSION

This study shows that, in COPD patients, the systematic evaluation of data obtained from a chest CT significantly increases the prevalence of clinically unrecognized comorbidities. Importantly, we observed a significant association between these comorbidities and the risk of death after a median follow-up of 6 years. The graphical representation of their prevalence and the strength of association with all-cause mortality ('CT-comorbidome') provides a novel visualization of the relevance of these comorbidities in COPD patients.

Three comorbidities deserve special attention, because they were independently associated with increased risk of death, but also because they were significantly under-recognized clinically and all of which can be treated, thus able to modify their outcome. As expected, the added prognostic value of these comorbidities (especially CAC) was found in patients with low BODE index (BODE ≤ 4).[3]

The strongest association to risk of death was observed for bronchiectasis, a finding that has been previously described.[22] However, our study highlights how frequently it is under-recognized clinically (known vs. unknown: 25.6% vs. 33.9%, $p < 0.001$). In this cohort, the systematic CT detection of bronchiectasis increased up to 34% the percentage of patients who could benefit from its recognition as there currently are available and effective treatments for its occurrence.[33]

The prevalence of chest CT-defined low PsD was significantly higher in non-survivors compared with survivors. Muscle weakness, which seems to occur in 22% of COPD patients, has been related to exercise intolerance and increased mortality in COPD.[30,34] Chest CT-assessed PsD, which can be a marker of muscle weakness, is independently associated with long-term mortality in COPD patients.[29] Because a regimen of rehabilitation and nutritional support may help revert muscle dysfunction and atrophy,[35] identification of PsD is clinically meaningful.

In our study, CAC reached a statistically significant independent association with mortality ($p = 0.042$). Importantly, CT increased the diagnostic prevalence by five times compared with the known clinical diagnosis (15.6% in clinical compared with 79.8% by CT). CAC is a marker of coronary atherosclerosis associated with both all-cause and cardiovascular mortalities.[4,36–38] Although CAC is highly prevalent in COPD patients, it remains largely underdiagnosed clinically. CAC identification should lead to the implementation of different interventions for secondary prevention of myocardial injury.[35,38]

PH was underdiagnosed in our cohort (known vs. unknown: 9% vs. 15.6%, $p < 0.001$), with a higher percentage of non-survivors having PAE (Figure 2). PH is associated with reduced exercise capacity, increased number of exacerbations and mortality.[24,25,39] In this study, we did not find an increased risk of death for this finding likely because

previous studies[24,25] did not compare this parameter with other important comorbidities. Although there have been no studies evaluating specific therapies for this image finding, potentially reversible causes should be explored and treated, including hypoxaemia and obstructive sleep apnoea.[40]

The finding of other comorbidities that were not associated with mortality over 6 years cannot be minimized, because several of them impact health status and functional capacity.

We found that 25.7% of the patients had CT-defined osteoporosis, a prevalence similar to other studies[31] and double the number of clinically diagnosed cases in our cohort (Table 4). Because osteoporosis increases the risk of bone fractures, we believe the systematic chest CT detection of this morbidity should prompt the implementation of guideline-directed treatment for osteopenia and osteoporosis.[41]

We also found a high prevalence of emphysema in this study population (60%), mainly of mild to moderate degree. Although we defined emphysema as an associated comorbidity in the present work, we acknowledge that it is also a disease characteristic that defines a precise phenotype of the disease.[42] We observed no association with all-cause mortality as has been reported for more severe patients.[43,44] Zulueta et al. explored a large lung cancer screening cohort, finding that visually detected emphysema was associated with mortality.[45] Similar findings have been reported from several large population-based cohorts using software-based emphysema detection (−950 HU as the cut-off value).[46–48] Those findings are in conflict with the results of our study, perhaps due to differences in population type (population based or lung cancer screening cohorts vs. COPD cohort followed at university hospitals), differences in the prevalence of emphysema (Zulueta 30%, Han 27%, Oelsner 5%, Johannessen 40% vs. 62% of the present study) or method of emphysema detection (software based vs. visual based). However, an emphysema diagnosis is associated with subsequent risk of lung cancer and as such it could help clinicians reaffirm the strategy for secondary prevention over time.[49]

The prevalence of participants with ILA in the present investigation (9.2%) was similar to that reported in other COPD cohorts.[21] Currently, there is no defined strategy to implement the correct way to follow these patients, but identification of ILA should prompt a call to evaluate potential causes and imaging follow-up.

Liver density has emerged as a relevant CT-assessed comorbidity associated with metabolic disorders. In our study, the prevalence of CT-assessed steatosis (23.4%) was slightly lower than previously reported in COPD patients (ranging from 30% to 41%), but higher than the one reported in the general population (5%–20% prevalence).[27] Interestingly, non-alcoholic fatty liver disease was found to be independently related to the risk of developing ischaemic heart disease in COPD patients, regardless of classical risk factors.[50]

Finally, the presence of hiatus hernia is related to gastroesophageal reflux and this has been associated with exacerbations in the ECLIPSE study.[51] Its finding should help clinicians to look for gastroesophageal reflux disease symptoms and, if required, provide its appropriate treatment.

With regard to study limitations, the most important problem in our results is that of diagnosing an incidental disease to a person who may be undergoing the test for a different reason. This can lead to significant anxiety that may not affect individual's outcome and may lead to physicians ordering additional tests. However, most of the comorbidities described here directly impact the outcomes and many can be modified with early secondary prevention and specific treatment. A second limitation is that most of the patients studied were men and the findings need to be confirmed in larger groups of women with COPD. Third, only COPD patients with a baseline chest CT scan were included in our study as the CT had to be ordered for suspicion of some underlying problem. However, all the comorbidities were underdiagnosed clinically, suggesting that the diseases detected were not the product of that bias. We also acknowledge that the CT-investigated comorbidities were not systematically assessed at recruitment, but we believe this is 'real' under diagnosis in general practice. Fourth, the all-cause mortality was identified from medical records and family contacts, so the specific cause of death could not be clearly determined. Specific causes of death would have helped define which outcomes could be most helped with CT findings. Finally, only those patients without clinical or radiological signs of lung cancer were included in the study introducing an important selection bias.

In summary, using a systematic method to determine the presence of 10 comorbidities in clinically obtained chest CT increases their prevalence above that already clinically diagnosed. Visualization of the prevalence of these chest CT-assessed comorbidities and the strength of their association to risk of death can be expressed as a 'CT-comorbidome'. As many of the comorbidities are treatable, their systematic evaluation is of practical use for clinicians and patients alike. Whether this approach can result in better outcomes needs to be tested.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

Ana Ezponda: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); software (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Ciro Casanova:** Conceptualization (equal); project administration (equal); resources (equal); writing – review and editing (equal). **Miguel Divo:** Conceptualization (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal). **Marta Marín-Oto:** Data curation (equal); writing – review and editing (equal). **Carlos Cabrera:** Conceptualization (equal); resources (equal); writing – review and editing (equal). **Jose M. Marín:** Resources (equal); writing – review and editing. **Gorka Bastarrika:** Conceptualization (equal); methodology (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal). **Víctor Pinto-Plata:** Resources (equal); writing – review and editing. **Ángela**

Martin-Palmero: Visualization (equal); writing – review and editing (equal). **Francesca Polverino:** Validation (equal); writing – original draft (supporting); writing – review and editing (equal). **Bartolome R. Celli:** Conceptualization; investigation (equal); methodology (equal); supervision (equal); validation (equal); visualization (equal); writing – review and editing. **Juan P. de Torres:** Conceptualization; investigation (equal); methodology; supervision (equal); validation (equal); visualization (equal); writing-review and editing.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

HUMAN ETHICS APPROVAL DECLARATION

The study protocol was approved by the Institution's ethics committee (IRB approval no. 28/2012) and the patients signed the informed consent to participate in this study.

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SUPPORTING INFORMATION

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