

The Impact of Emphysema on Chronic Obstructive Pulmonary Diseases

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ABSTRACT

Emphysema is defined as an abnormal and permanent enlargement of the air spaces distal to the terminal bronchioles that is accompanied by destruction of the air space walls, with no obvious fibrosis (i.e. there is no fibrosis visible to the naked eye) and it is usually associated to tobacco smoking.

Although it is included in the pathological definition of chronic obstructive pulmonary disease (COPD), not all COPD patients have emphysema and its impact on the clinical presentation and the natural history of the disease is variable.

The present review will cover the prevalence of emphysema in COPD patients, its impact on the clinical presentation, association with comorbidities and the main outcomes of the disease: exacerbations, lung function decline and mortality. In this review, we will only evaluate the relationship of tobacco-related emphysema with COPD. (BRN Rev. 2017;3:235-46)

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EMPHYSEMA DEFINITION AND NONINVASIVE DETECTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease not only in its clinical but also in its pathological presentation. The pathological definition of COPD includes changes at the airway level (predominantly small airways: chronic bronchitis), lung parenchyma (emphysema) and the vascular compartment (vascular remodelling)¹. The contribution of each of these processes is highly variable, depending on the intensity, type of toxic inhalation (mainly tobacco) and individual's susceptibility.

Emphysema is defined as an abnormal and permanent enlargement of the air spaces distal to the terminal bronchioles that is

accompanied by destruction of the air space walls, with no obvious fibrosis (i.e., there is no fibrosis visible to the naked eye)¹. There are three pathological types of emphysema (Fig. 1): centrilobular (most commonly associated to tobacco), panacinar (usually associated to alpha-1-antitrypsin deficiency [AAT]) and paraseptal (that could occur associated with the previous types or alone, and that is usually associated to spontaneous pneumothorax)². Emphysema can contribute to airflow limitation (AL) through the destruction of alveolar walls, loss of airway tethering resulting in decreased elastic recoil and airway collapse.

Technological advances in software and computed tomography (CT) techniques currently allow a precise assessment of the presence, extent and distribution of emphysema³. The

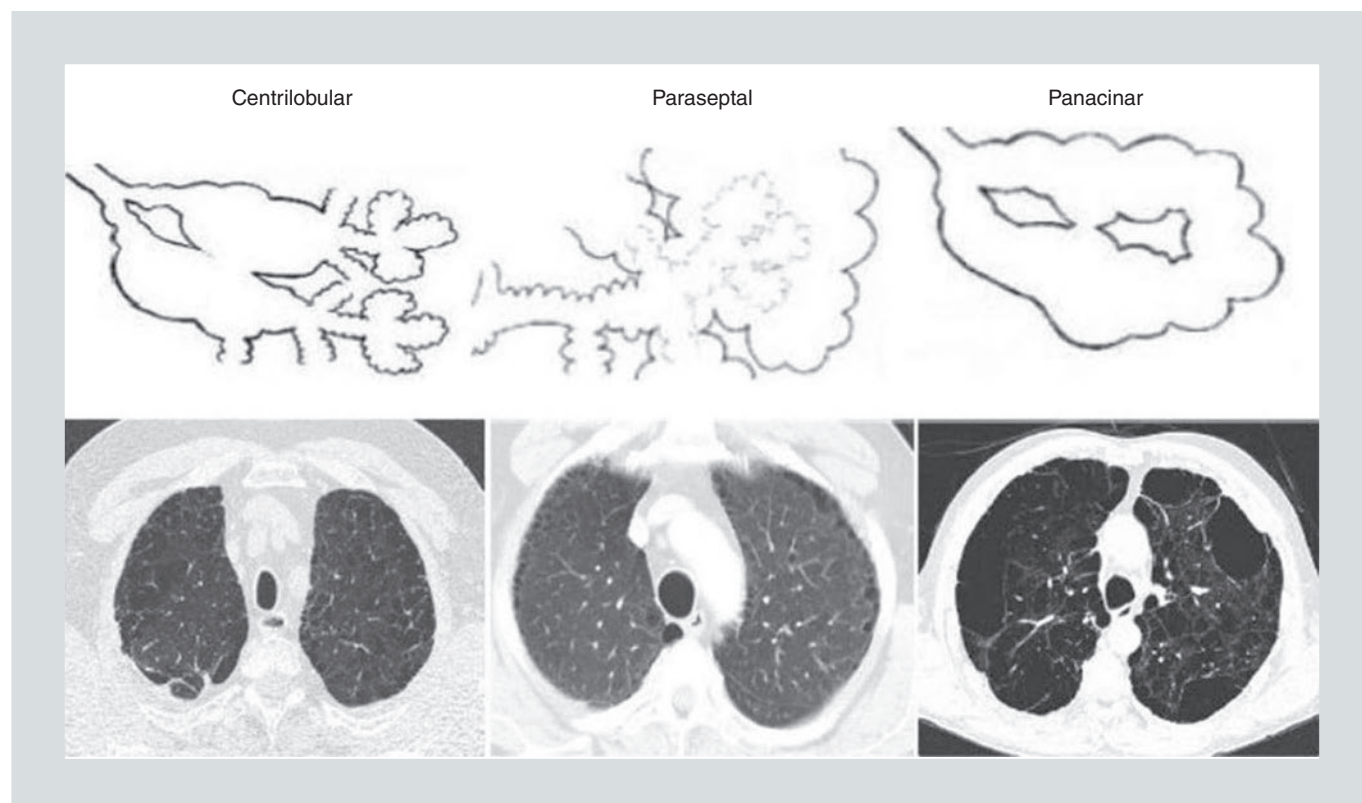


FIGURE 1. Visual and computed tomography (CT) description of the three types of emphysema.

presence and proportion of low attenuation areas (LAA) in CT scans (Fig. 2), correlate well with pathology⁴ and lung function⁵. Madani et al.⁴ found the strongest correlation with macroscopy with a threshold of -970 HU ($r = 0.543$, $p < 0.001$) and that with microscopy was observed at -960 and -970 HU, depending on the index considered ($r = 0.592$, $p < 0.001$ and $r = -0.546$, $p < 0.001$, respectively). For percentiles, 1st percentile showed the strongest correlation with both macroscopy ($r = -0.463$, $p < 0.001$) and microscopy ($r = -0.573$, $p < 0.001$ and $r = 0.523$, $p < 0.001$ for each microscopic measurement). This radiological technique has been used in COPD patients to determine if a patient is a candidate for lung volume reduction techniques⁶ or to monitor the response to augmentation therapy in those with severe AAT⁷. The National Emphysema Treatment Trial (NETT) classification of visual severity of emphysema, is the most widely used (Fig. 3).

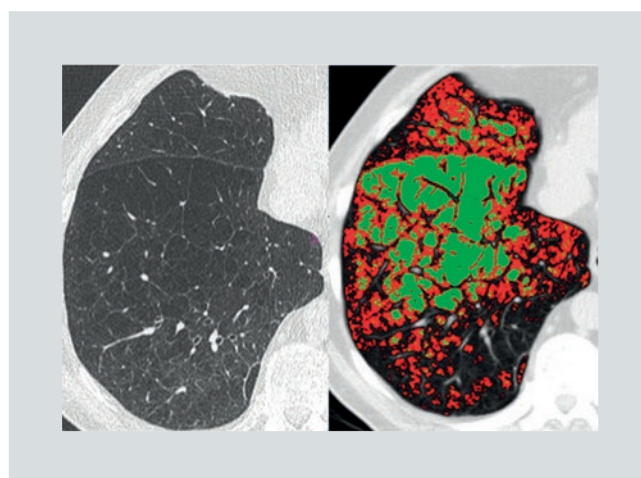


FIGURE 2. Low attenuation areas (LAA) detection in a chest computed tomography (CT) scan. Colours denote different grades of LAA (< -960 HU density, ranging from high (green) to less intense (red).

Prevalence of emphysema in COPD patients and its impact on symptoms

Several studies have explored the prevalence and distribution of emphysema in COPD patients. Nakano et al.⁸ studied a rather small sample of ($n = 73$) male COPD patients and

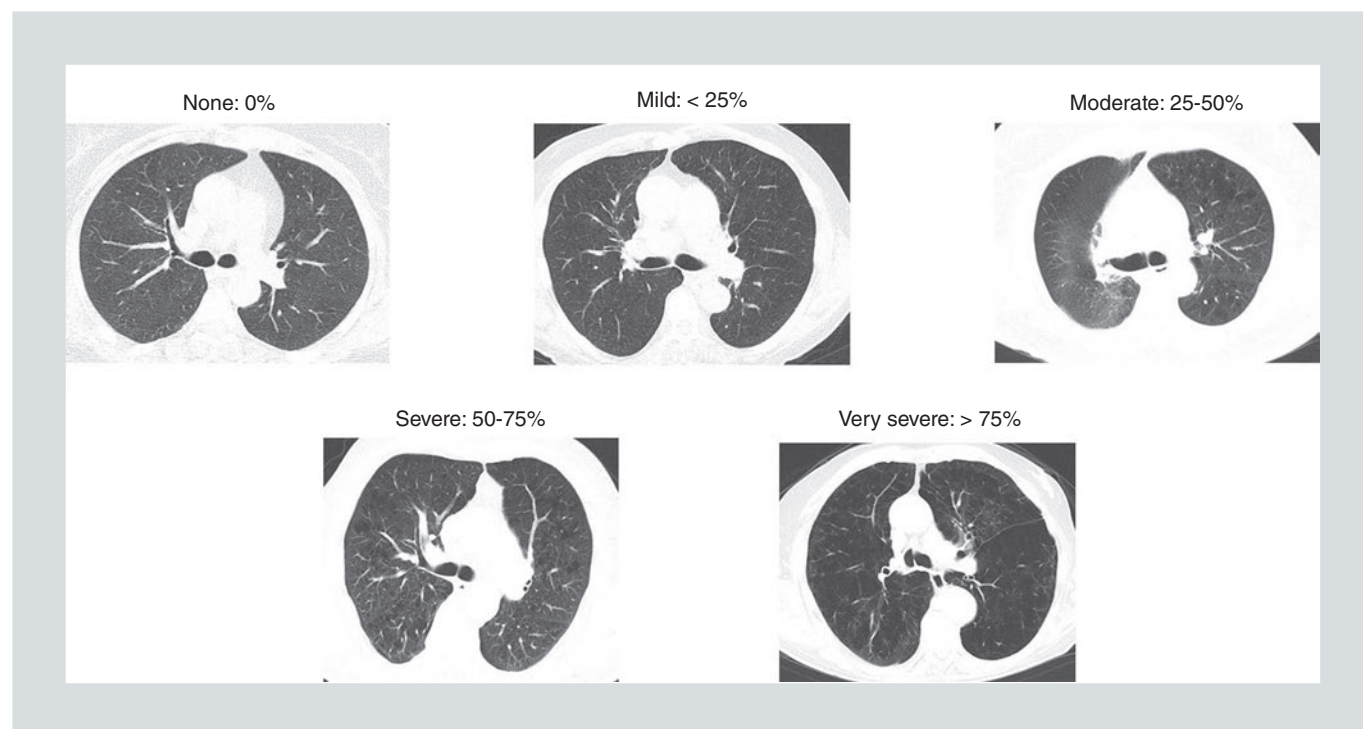


FIGURE 3. National emphysema treatment trial (NETT) classification of the extent of emphysema in computed tomography (CT) scans, expressed as different percentages of lung volume.

observed that LAA are more often distributed in the upper and inner parts of the lungs. They also reported that the contribution of the central distribution to pulmonary function tests may be greater than the peripheral distribution. Later, Mair et al.⁹ evaluated a larger population of COPD patients (this time also including females), confirming that emphysema was found predominantly in the upper/core zone and that this distribution related best to clinical features such as lower forced expiratory volume in the 1st second (FEV₁), body mass index (BMI) and higher body mass index (B), obstruction (O), dyspnoea (D) and exercise (E) (i.e., BODE) index and Medical Research Council (MRC) dyspnoea scale. Using multiple linear regression age, sex and emphysema severity were independently related to upper/lower distribution.

De Torres et al.¹⁰ investigated the impact of emphysema presence and distribution in a specific population of COPD patients with mild to moderate degree of AL. They found that the degree of emphysema in a population of 115 patients regularly followed in an outpatient clinic, was mild and mainly distributed in the upper and core regions. They concluded that, although the presence of emphysema has an impact on physiology, its severity and distribution seem to have little impact on other clinical parameters.

Recently, the Canadian Cohort Obstructive Lung Disease (CanCOLD) study from Canada¹¹ evaluated the presence of emphysema in a large population, including 408 healthy never smokers, 502 healthy ever-smokers and 451 COPD patients. They found that prevalence of emphysema was 11% in healthy never smokers, 30% in healthy ever smokers and 36%, 50% and 56% in patients with mild, moderate or

severe/very severe COPD, respectively. They noted that the presence of emphysema was independently associated with cough, chronic phlegm production, wheeze, MRC dyspnoea scale ≥ 2 , COPD Assessment Test (CAT) score ≥ 10 and an exacerbation frequency ≥ 2 in the first year of follow-up. Most of the patients (92%) had mild to moderate degree of AL.

Impact of emphysema on comorbidities

EMPHYSEMA AND CARDIOVASCULAR DISEASE

The presence of emphysema in COPD is usually associated not only with airway limitation but also with lung hyperinflation, which implies an increased volume over the tidal breathing range and increase in functional residual capacity (FRC) leading to high intrinsic positive end-expiratory pressure (PEEPi)¹². These physiological changes explain why COPD patients with emphysema usually complain of dyspnoea and exercise limitation¹. There is evidence that the cardiovascular (CV) impact of emphysema could be mediated via several different pathophysiological mechanisms:

- Lung hyperinflation at rest, can significantly affect heart size and function by causing intrathoracic hypovolemia and small end-diastolic dimensions of left and right chambers. These chambers could also be mechanically compressed causing end-diastolic stiffness¹³.
- During exercise, emphysematous patients develop “dynamic hyperinflation” further restraining the already poor cardiac function. Vassaux et al.¹⁴ proved that dynamic

hyperinflation is inversely associated with peak oxygen pulse (an indirect measure of cardiac stroke volume), while Come et al.¹⁵ showed that lung volume reduction surgery (LVRS) could significantly improve oxygen pulse (and exercise capacity) by deflating the lungs¹⁵.

- Finally, in many COPD patients, there is important skeletal muscle atrophy (sarcopenia) that occurs primarily in emphysematous patients. Such peripheral muscle depletion has been related by Teopompi et al.¹⁶ with poor cardiovascular response (CV) to exercise and to leg fatigue independently of the degree of airway obstruction.

EMPHYSEMA AND LUNG CANCER RISK

Radiologically detected emphysema has been recognized as an independent risk factor for lung cancer^{17,18}. The combination of COPD and emphysema in active or former smokers significantly multiplies this risk, making this group as a potential ideal target for lung cancer screening programs¹⁹. Several mechanisms have been described²⁰ to explain this lethal association:

1. Stimulation of the basal membrane-associated stem cells at the alveolar level that in an attempt to repair the damage produced by chronic inflammation and oxidative stress, may mutate to abnormal “malignant cells”.
2. Chronic retention of carcinogens leading to the generation of cancer.
3. Common genetic risk factors (cholinergic receptor nicotinic alpha subunit 3/5 (CHRNA3/5), hedgehog-interacting protein (HHIP), telomerase reverse transcriptase

(TERT), deoxyribonucleic acid (DNA) hypermethylation, micro ribonucleic acids (miRNAs)) that express as diseases running a parallel course.

In an effort to help identify those COPD patients at higher risk for lung cancer development, our group developed and validated the COPD Lung Cancer Screening Score (COPD-LUCSS)²¹. The COPD-LUCSS includes age, pack-years history, BMI and presence of radiological emphysema. It goes from 0-10 and a score ≥ 7 points increased the risk of developing a lung cancer 3 times compared with those with a score of 0-6 points. To simplify the identification of high-risk patients, the same authors also described the COPD-LUCSS diffusing capacity of carbon monoxide (DL_{CO}) replacing radiological emphysema by a $DL_{CO} < 60\%$ avoiding the need to have a baseline CT to determine the presence of emphysema²².

EMPHYSEMA: ASSOCIATION WITH MALNUTRITION AND OSTEOPOROSIS

Since the graphic description made by Netter in the Ciba Symposium pictorial book²³, the emphysematous COPD patient has been traditionally associated with a thin frail individual with low BMI and with loss of muscle mass, now well represented by a low free-fat mass index (FFMI). Several studies have demonstrated an inverse relationship between the extent of emphysema and the degree of malnutrition represented by BMI and specially FFMI²⁴. Although not well established for all patients, some data suggest that nutritional support in COPD patients who are malnourished, may have a positive impact on exercise capacity and quality of life of these patients²⁵.

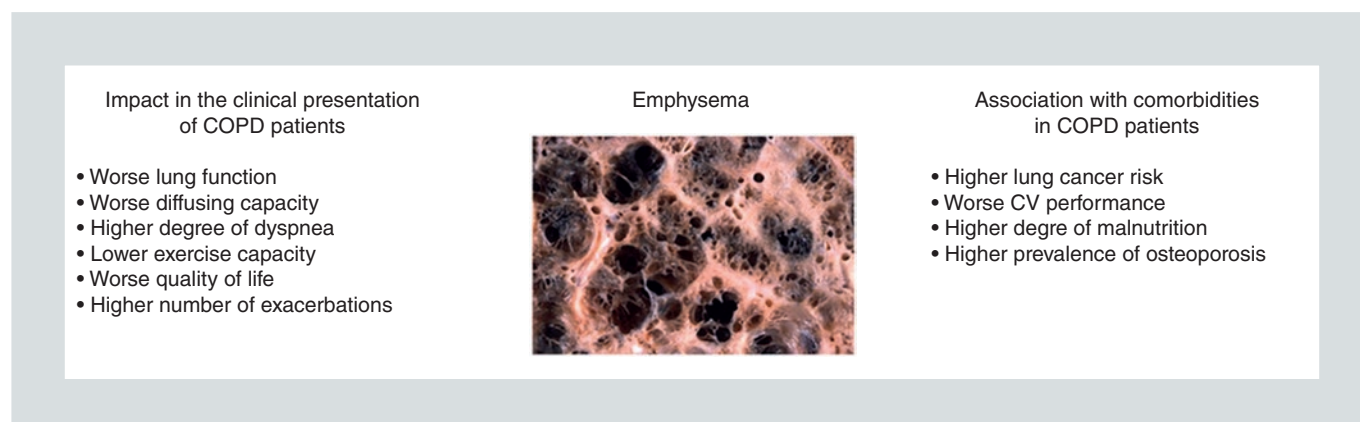


FIGURE 4. Impact of emphysema presence in the clinical presentation and the risk of associated comorbidities in chronic obstructive pulmonary disease (COPD) patients.

CV: cardiovascular

The relationship between emphysema and osteoporosis is scanty but increasing as more studies address it²⁶. Bon et al.²⁷ confirmed that the degree of emphysema in COPD patients is the most important factor associated with the presence of osteoporosis independently of other predictors such as age, gender, tobacco smoking and BMI. Several pathways have been proposed in trying to explain the association of these two matrix degradation processes at different locations of COPD patients, but more research is still needed to try to elucidate the nexus²⁸.

In summary, data suggest that emphysema presence, severity and distribution in COPD patients has an inverse relationship with the degree of airway limitation and diffusing capacity. It also has a negative impact on the clinical presentation of the disease mostly in patients with moderate to very severe airway limitation. The presence of emphysema in COPD patients puts them at higher risk of lung cancer, CV dysfunction, malnutrition and osteoporosis (Fig. 4).

INFLUENCE OF EMPHYSEMA IN THE NATURAL HISTORY OF PATIENTS WITH COPD

Recently, there have been important advances in the understanding of the natural history of COPD. This has been based, fundamentally, on observational studies of cohorts of patients with COPD^{29,30} and some population studies³¹, and it has led to important conceptual changes:

- The progression of COPD is heterogeneous²⁹⁻³¹.
- Most patients remain stable for long periods of time (5 to 8 years)²⁹⁻³²
- In a large number of patients, pulmonary developmental disorders, probably acquired in the first years of life, may lead to AL without an accelerated decline in lung function³³. In addition, the evolution of COPD may be different between spirometric parameters (FEV_1) and other pulmonary or extrapulmonary factors. In spite of the advances in the knowledge of the evolution of FEV_1 , the progression in other important parameters of

the disease remain poorly studied. We need a better characterization of the patients, to better describe the different natural histories of the phenotypes that coexist in COPD³⁴⁻³⁶.

EMPHYSEMA AND LUNG FUNCTION DECLINE

Several studies based on observational cohorts have shown that emphysema is one of the main factors associated with the decline of FEV₁.

However, in addition to being a causal factor, it could also be part of the disease process. Initially, the long-term longitudinal analysis of the BODE cohort showed that a lower BMI was associated with larger FEV₁ annual decline²⁹. Vestbo et al.³¹, in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) cohort, showed for the first time the importance of the emphysema estimated by CT in the decline of FEV₁. Patients who had > 10% LAA had a significant annual loss of FEV₁ with a decrease of 13 ml/yr. Although other factors (current smoker and bronchodilator reversibility) were higher in absolute numbers (ml/yr), probably emphysema was higher if adjusted by the initial baseline level of FEV₁.

Data from the ECLIPSE cohort with three years of follow-up were later confirmed in a smaller Japanese cohort (Hokaido)³⁰, but with five years of follow-up. In addition, the role of CT (% LAA or visual score) or percentage of carbon monoxide transfer factor (K_{co}) was maintained as an independent factor in the prediction of FEV₁ decline. Patients who lost more lung function versus those who did not lose had a % LAA of 25% and a K_{co} < 60% versus 10% LAA and K_{co} > 70%, respectively.

Recent studies have also shown that the rate of the decline in lung function is independently affected by the regional distribution or the severity of emphysema: more homogeneous distribution of emphysema contributed to an accelerated decline in FEV₁ independently of whole-lung emphysema severity³⁷.

At this time, only one group has evaluated the longitudinal evolution of hyperinflation through the inspiratory to total lung capacity IC/TLC ratio, observing that it was 0.65% per year and that it is higher in patients with more dyspnoea (modified MRC [mMRC]), a greater number of comorbidities (Charlson index) and worse FEV₁³⁸. In addition, in a new analysis, they observed that the progression of lung hyperinflation (estimated by a reserve volume (RV)/TLC ratio) was associated with frequent exacerbations and a faster FEV₁ decline³⁹.

Recently, the ECLIPSE cohort longitudinally evaluated the change in CT lung density over 3 years. The severity of objectively defined emphysema worsened over that time (mean decline -1.13 g/l [SE 0.06] per year). The annual decline in lung density was more rapid in women than in men and in current smokers than in former smokers. Circulating levels of the biomarkers surfactant protein D and soluble receptor for advanced glycation end-product (sRAGE) were significantly associated with both baseline lung density and its decline over time. These findings suggest that smoking cessation has the potential to limit further structural deterioration within the lung⁴⁰.

Interestingly, in that study the association between emphysema changes and FEV₁ decline was weak. This could be explained by the regional distribution of emphysema: the

lungs have a ventilation-perfusion ratio relatively high in the upper compared to the lower areas. Therefore, in the hypoventilated areas of the upper lobes, pulmonary emphysema causes lesser pulmonary dysfunction than when is located in the bases. In fact, previous studies have shown that the extent of emphysema presented higher correlations with DL_{CO} , AL and lung volumes when it is located in the basal portions of the lungs^{41,42}. These data could support the heterogeneity presentation of the disease with different natural histories.

EMPHYSEMA END EXACERBATIONS

It has been classically thought that patients with COPD and the emphysema phenotype have a lower frequency of exacerbations than those with the chronic bronchitis profile. However, the advances in imaging technology through the use of chest CT have allowed a better characterization of patients with emphysema and a more accurate analysis of the relationship with exacerbations.

Two large multicenter observational studies (ECLIPSE and Chronic Obstructive Pulmonary Disease gene [COPDgene]) have shown that emphysema is a risk factor for exacerbations regardless of the degree of airway limitation expressed by FEV_1 ^{43,44}. Furthermore, this association remained after compared with the thickness of the airway and showed an even stronger association in the large prospective Canadian Cohort of Obstructive Lung Disease (CanCOLD) where unlike previous studies the data were based on unselected individuals from a random sample from the general population¹¹.

Interestingly, in the COPDgene study, they observed that the relationship with the

exacerbations is not linear and it is necessary to reach an important threshold in the severity of emphysema in order to make evident this association: an emphysema percentage $\geq 35\%$ was associated with a significant increase in exacerbation frequency, with a 1.18-fold change for each 5% increase in emphysema. The influence of emphysema on exacerbation frequency at lower levels of emphysema, when adjusted for lung function and wall thickness, was less clear. In fact, decreased exacerbation frequency was seen for subjects with 10-35% emphysema⁴³.

Lung hyperinflation and gas trapping may be the main mechanisms that induce the presence of exacerbations^{45,46}. Although no studies or pharmacological trials have been designed to specifically evaluate this fact, it has been observed that patients with IC/TLC ratio < 0.25 or RV/TLC ratio $> 50\%$ have more exacerbations^{44,46}. In the NETT study, it was observed that LVRS reduces the frequency of COPD exacerbations and increases the time to first exacerbation⁴⁷. However, this effect was greatest in those subjects with the largest post-operative improvement in FEV_1 , but changes in lung volumes estimated by a slow vital capacity (VC) and FRC were excluded from the multivariable Cox regression model (to determine whether changes in physiologic variables were associated with exacerbations). The discrepancy could be related with the fact that the NETT study was not designed to evaluate exacerbations and this post-hoc analysis only included those exacerbations that required emergency room assistance or hospitalization⁴⁷.

Finally, we must take into account the issue that the relationship of exacerbations with emphysema could be bidirectional. Tanabe et al.⁴⁸ showed

that annual changes in CT emphysema parameters were greater in patients with a history of COPD exacerbations, although these data were not replicated in the ECLIPSE cohort⁴⁹.

EMPHYSEMA AND MORTALITY

About twenty years ago one of the main clinical features of the emphysema phenotype, such as “low weight”, was shown to be a predictor of general and respiratory mortality in patients with COPD, independent of FEV_1 ⁵⁰. This was confirmed by other studies and the risk cut-off point was estimated at a BMI threshold of < 20-21. Subsequently, another physiological surrogate marker of emphysema such as the lung hyperinflation expressed by the IC/TLC ratio (dubbed inspiratory fraction), also proved to be an independent and superior predictor than the FEV_1 . Its estimated risk threshold was an IC/TLC ratio < 0.25, with a three times higher mortality in patients with values below this cut-off point⁵¹.

More recently, the NETT study made possible the first solid analysis of the impact of CT-determined emphysema on survival of COPD patients⁵². In this cohort, with a significant amount of emphysema and lung hyperinflation, older age, lower BMI, oxygen consumption (in contrast to PaO_2), and greater lung hyperinflation were associated with an increased risk of death over time. Exercise capacity, quantified in a cardiopulmonary exercise test in contrast to a six-minute walking test (6MWT) distance, proved to be a powerful independent predictor of survival. Diffusing capacity DL_{CO} expressed as K_{CO} was also a good predictor of mortality but only in the univariable analysis⁵².

Another important finding from that study was the lack of association of the presence of upper lobe predominant emphysema and risk of mortality⁵², something that did happen with lower lobe predominance associated with the presence of centrilobular emphysema. Therefore, it could also be possible that lower-lobe emphysema may represent a phenotypic or pathobiologic variant of emphysema presented as centrilobular⁵³.

Subsequent studies^{54,55}, with smaller cohorts but longer follow-up time (4 versus 8 years) and with different AL severity observed a significant association of lung attenuation areas low attenuation area (% LAA) and the prognosis of the disease^{54,55}. Patient selection and emphysema evaluation criteria (% LAA) make comparisons between studies difficult.

Haruna et al.⁵⁴ demonstrated in a cohort of men with COPD that the ability of emphysema to predict mortality was independent of age, FEV_1 , and other predictors associated with the emphysema phenotype such as BMI, RV/TLC and the K_{CO} . However, important factors such as the BODE index and comorbidities were not included in the comparative analysis. Differences in survival of the worst LAA% quintile (> 30-40%) were observed only after three years of follow-up. However, unlike the study by Martinez et al.⁵³, in this case these authors did not find differences in prognosis according to the location of emphysema (lower versus upper lobes).

Johannessen et al.⁵⁵, have shown that the degree of emphysema predicts all-cause, respiratory and cardiovascular mortality in a population-based sample of subjects with and without COPD. Patients with a degree of emphysema

> 10 % (LAA) had three years shorter survival than patients with a degree of emphysema < 10%. Unfortunately, as in the previous study, this predictive power was not compared with other prognostic factors related to the phenotype emphysema such as the IC/TLC ratio, (K_{co}) or the BODE index. However, an independent predictive role of thick airway thickness was observed. In addition, the impact on survival of a relatively low degree of emphysema is of great relevance, since it can affect many patients with non-severe AL as it was observed in this study and replicated in the ECLIPSE cohort, where 2/3 of the patients evaluated had this emphysema severity⁵². This finding supports once again the importance of imaging studies for an adequate characterization of COPD patients.

The mechanisms by which emphysema may contribute to premature death include direct physiologic effects of losing lung parenchyma and vasculature. This loss has been related to lung-specific inflammatory markers, such as surfactant protein D and increased neutrophilic inflammatory infiltration^{56,57}. This parenchymal loss, will lead to a reduction in the area available for gas exchange, which may lead to hypoxaemia, poor exercise capacity, and reduced functional status. Loss of alveolar walls also contributes to untethering of airways, loss of radial traction forces, and reduction in airway calibre, which may contribute to more rapid FEV₁ decline and AL⁵⁸.

Other mechanisms linking emphysema to all-cause mortality include increased susceptibility to lung cancer³², pulmonary infections⁹, impaired cardiac function resulting in reduced left ventricular filling and stroke volume⁵⁹, endothelial and microvascular dysfunction of

the pulmonary and systemic capillary system and systemic inflammation⁶⁰.

It is now generally recognized that COPD is associated with systemic manifestations that impact on survival, such as skeletal muscle wasting, cachexia, osteoporosis, pulmonary hypertension, ischemic heart disease, and depression⁶¹. However, it is still unclear whether emphysema predisposes patients with COPD to such systemic manifestations and whether systemic manifestations contribute to the development of emphysema⁶², nor if patients with initial presentation as symptomatic emphysema without airway limitation then progress to spirometric COPD⁶³.

In summary, the degree of emphysema assessed by CT has an impact on the natural history of COPD. It is associated with rapid FEV₁ decline, increase of exacerbations and all-cause mortality in COPD patients from clinical studies as well as from the general population. This relationship is independent of the severity of AL measured by the FEV₁, and possibly not linear with the degree of emphysema itself (at least > 10%) according to the outcome (Fig. 5). These data provide evidence that the detection of emphysema on chest CT is of great value in order to adequately characterize COPD patients.

CONCLUSIONS AND MAIN MESSAGE

Determining the presence, type, distribution and severity of emphysema in COPD patients is important because it could greatly impact on their lung function severity and progression, symptoms severity, natural history and outcomes such as exacerbations and mortality.

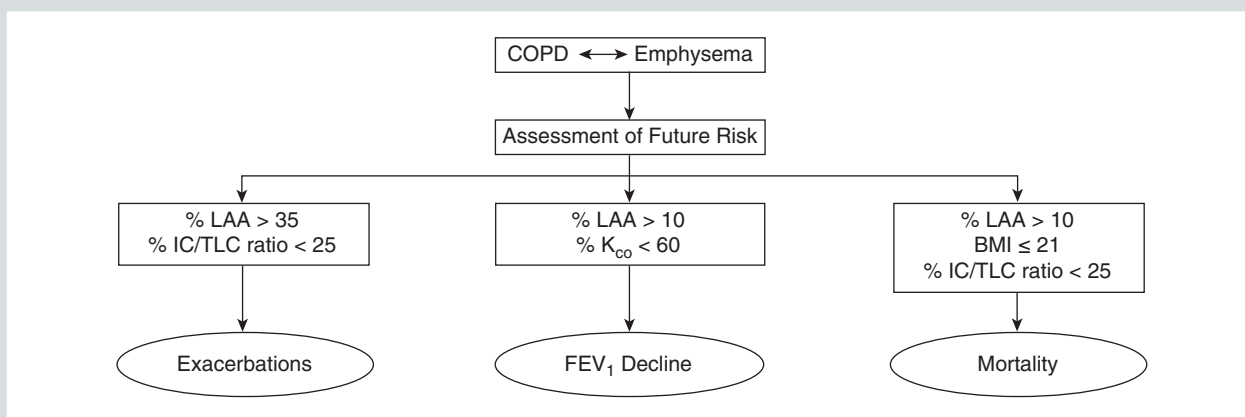


FIGURE 5. Parameters with their cut-off values associated with important outcomes in the natural history of chronic obstructive pulmonary disease (COPD) patients with the emphysema phenotype.

BMI: body mass index; FEV₁: forced expiratory volume in 1 second; IC/TLC: inspiratory capacity and lung total capacity; K_{co}: carbon monoxide transfer factor; LAA: low attenuation areas.

CONFLICT OF INTEREST

Dr. Juan P. de Torres and Dr. Ciro Casanova have nothing to disclose.

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