ORIGINAL ARTICLE

Characterization and Mortality Risk of Impaired Left Ventricular Filling in Chronic Obstructive Pulmonary Disease

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Abstract

Rationale: In chronic obstructive pulmonary disease (COPD), impaired left ventricular (LV) filling might be associated with coexisting heart failure with preserved ejection fraction (HFpEF) or due to reduced pulmonary venous return indicated by small LV size.

Objectives: We investigated the all-cause mortality associated with small LV or HFpEF and clinical features discriminating between both patterns of impaired LV filling in patients with COPD.

Methods: We performed transthoracic echocardiography (TTE) in patients with stable COPD from the COSYCONET (COPD and Systemic Consequences and Comorbidities Network) cohort to define small LV as LV end-diastolic diameter below the normal range and HFpEF features according to recommendations of the European Society of Cardiology. We assessed the ratio of early to late ventricular filling velocity (E/A), ratio of early mitral inflow velocity to annular early diastolic velocity (E/e′), serum N-terminal pro-brain natriuretic peptide, high-sensitivity troponin I, airflow limitation (FEV_1), lung hyperinflation (residual volume), and gas transfer capacity (D_{LCO}) and discriminated patients with small LV from those with HFpEF features or no relevant cardiac dysfunction as per TTE (normal^{TTE}). The primary outcome was all-cause mortality after 4.5 years.

Measurements and Main Results: In 1,752 patients with COPD, the frequency of small LV, HFpEF features, and normal^{TTE} was 8%, 16%, and 45%, respectively. Patients with small LV or HFpEF features had higher all-cause mortality rates than patients with normal^{TTE}: hazard ratio, 2.75 (95% confidence interval, 1.54–4.89) and 2.16 (95% confidence interval, 1.30–3.61), respectively. Small LV remained an independent predictor of all-cause mortality after adjusting for confounders including exacerbation frequency and measures of residual lung volume, D_{LCO}, or FEV_1. Compared with normal^{TTE}, patients with small LV had reduced LV filling, as indicated by lowered E/A. Yet, in contrast to patients with HFpEF features, patients with small LV had normal LV filling pressure (E/e′) and lower concentrations of N-terminal pro-brain natriuretic peptide and high-sensitivity troponin I.

Conclusions: In COPD, both small LV and HFpEF features are associated with increased all-cause mortality and represent two distinct patterns of impaired LV filling.

Clinical trial registered with www.clinicaltrials.gov (NCT01245933).

Keywords: ventricular underfilling; heart failure with preserved ejection fraction; COPD; lung hyperinflation; emphysema

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At a Glance Commentary

Scientific Knowledge on the Subject: In chronic obstructive pulmonary disease, impaired left ventricular (LV) filling might be associated with either coexisting heart failure with preserved ejection fraction or reduced pulmonary venous return, indicated by a smaller LV size. Differentiating between these two patterns is crucial, as their precise impact on mortality remains unclear and warrants further investigation.

What This Study Adds to the Field: Cardiac biomarkers and echocardiographic parameters help differentiate between disturbed LV filling from reduced venous return and coexisting heart failure with preserved ejection fraction in chronic obstructive pulmonary disease. Both patterns signal higher all-cause mortality but represent distinct, treatable traits.

Chronic obstructive pulmonary disease (COPD) and cardiovascular disease are among the leading causes of global mortality and disability (1). Both diseases coexist frequently, which confers poor disease outcomes and worsens survival (2, 3). A well-established instance is the interaction between COPD and cardiac dysfunction, namely heart failure, as both conditions share risk factors and clinical features, such as aging, acute hospitalization, and disease progression (4). Although heart failure with preserved ejection fraction (HFpEF) is believed to be a frequent cooccurring cardiac condition in COPD (5), left ventricular dysfunction might also arise as a disease-related cardiac manifestation in patients with COPD and hyperinflation. Imaging studies have indicated a close association of lung hyperinflation or emphysema with the reduction of end-diastolic left ventricular volume and the ensuing decline in cardiac output (6, 7). Likewise, airflow limitation and lung hyperinflation were linked to decreased left ventricular filling and cardiac chamber size, measured by echocardiography, in patients with COPD (8, 9). A further disease-related aspect is the reduction in pulmonary blood flow of emphysematous lung regions (10, 11) and the subsequent left ventricular underfilling (12). Reduced left ventricular filling in patients with COPD and hyperinflation is a treatable trait, as lung deflation with either pharmacological or bronchoscopic lung volume reduction improves cardiac function indicated by an increase in the left ventricle (LV) size (13–15).

We have previously reported that left ventricular diastolic dysfunction in patients with COPD is associated with exercise intolerance and physical inactivity, independent from lung function impairment (9, 16). However, data investigating the mortality risk in patients with COPD and impaired ventricular filling, either due to HFpEF or to COPD-related reduction of left ventricular filling, are still lacking. Furthermore, the identification of clinical features that distinguish HFpEF from COPD-related reduction of left ventricular filling is important and highly relevant for patient management (17).

Therefore, we aimed to investigate the mortality rate in patients with COPD-related reduction of left ventricular filling, indicated by small LV size, or in those with coexisting HFpEF compared with patients with COPD and normal cardiac function in a well-characterized COPD cohort. In addition, we sought to elucidate clinical features, echocardiographic measures, and cardiac biomarkers that distinguish COPD-related reduction of left ventricular filling from diastolic dysfunction associated with coexistent HFpEF. Some of the results of these studies have been previously reported in the form of an abstract (18).

Methods

Study Design

This analysis involves patients from the multicenter COSYCONET (COPD and Systemic Consequences and Comorbidities Network), a prospective longitudinal observational cohort study of patients with COPD. Patients were recruited at 31 German study centers, primarily after referrals from respiratory specialists (19). The main aim of the COSYCONET cohort is to investigate the impact of extrapulmonary disease manifestations, particularly cardiovascular comorbidities, on disease outcomes and all-cause mortality. The inclusion and exclusion criteria, as well as detailed study aims and methods, have been previously described (19). The study was approved by the ethics committee at the University of Marburg and is registered at ClinicalTrials.gov (NCT01245933). A written informed consent was obtained before enrollment.

Assessment of Lung Physiology, Cardiac Biomarkers, Anthropometric Measures, and Computed Tomography Imaging

Lung function testing, including spirometry, body plethysmography, and single-breath carbon monoxide lung uptake, was done as previously described (19). Furthermore, we measured serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) (MILLIPLEX; Merck Millipore) and high-sensitivity troponin I (hs-troponin I) (ARCHITECT STAT; Abbott Diagnostics), as previously described (20).

We used a whole-body bioelectrical impedance analysis (Nutribox analyzer; Pöcking, Germany) to calculate the skeletal muscle mass according to the equation provided by Janssen and colleagues (21) and the muscle mass index by dividing it by the body surface area. Pulmonary computed tomography (CT) was available for a subgroup of patients, and low-attenuation areas (LAA) were calculated as previously described (22).

Echocardiography and Stratification of the Study Population

We performed two-dimensional and Doppler echocardiography as recommended by the American Society of Echocardiography and the European Association of Cardiovascular Imaging (23, 24). Briefly, the main measures

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This article has a related editorial.

A data supplement for this article is available via the Supplements tab at the top of the online article.

of echocardiography were the left ventricular ejection fraction, left atrial diameter, left ventricular end-diastolic diameter (LVEDD), left ventricular mass index, left ventricular posterior wall diameter, interventricular septal diameter, tricuspid annular plane systolic excursion (TAPSE), the ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e′), and the ratio between early and late ventricular filling velocity (E/A). The evaluation of right ventricular function relied on the assessment of experienced examiners and was reported as dichotomous variable. Additional details on measures of echocardiography are previously described (8, 20, 25) and provided in the online supplement.

The stratification of the study groups and possibly confounding groups was performed in the following order: First, we identified heart failure with mid-range or reduced ejection fraction in patients with left ventricular ejection fraction $<$50% (26). Then, we defined right ventricular dysfunction (RVD) based on three criteria: TAPSE $<$17 mm, moderate to severe tricuspid value regurgitation, or impaired right ventricular function based on visual inspection (27, 28). Next, we defined HFpEF based on current guidelines (29). In detail, we identified patients who had objective structural features consistent with left ventricular diastolic dysfunction underlying HFpEF (23, 29) as follows: *1*) left ventricular hypertrophy defined by moderate to severely increased left ventricular mass index, posterior wall, or interventricular septal thickness; or *2*) moderate to severely increased left atrial diameter (27). In this subgroup of patients with structural features consistent with left ventricular dysfunction, we stratified those who also had NT-proBNP concentrations $>$220 pg/ml as having HFpEF features (29); otherwise, those who had NT-proBNP levels $\leq$ 220 pg/ml were stratified as having HFpEF risk. In addition to the aforementioned structural features, atrial fibrillation was also a criterion to stratify patients as HFpEF features (29). To avoid misclassifying patients with reduced venous return as HFpEF in the primary analysis, we did not consider parameters of diastolic dysfunction in stratifying the patients to HFpEF as recommended (23). Therefore, for the purpose of sensitivity analyses, we identified a subgroup of patients with more frank HFpEF, which included patients with HFpEF features who also had an E/e′ $>$ 9. Furthermore, in patients who did not have any of the previously indicated cardiac dysfunction patterns, we stratified patients who had LVEDD below the sex-specific normal range as small LV (i.e., LVEDD $<$42 mm in males and $<$39 mm in females) (23). Last, we stratified patients who did not demonstrate any of the above-indicated abnormalities as normal echocardiography (normal^{TTE}). Patients with moderate to severe left valvular heart disease were excluded from normal^{TTE} and small LV, as this might affect the left ventricular filling. For the same reason, patients with small left atrium, without small LV, were excluded from normal^{TTE}, as this might indicate early reduced LV filling. Details on measures and cutoff values of echocardiography used in patient stratification are provided in the online supplement. According to the aims of this analysis, the study population comprised patients with HFpEF features, small LV, and normal^{TTE}.

Statistical Analyses

To determine the statistical significance of the observed differences among the clinical variables between the study groups, we performed a one-way ANOVA, Kruskal-Wallis, or Fisher's exact test. For pairwise comparisons, *post hoc* analyses were performed using either Tukey's test or Dunn's test. To test for statistical dependence between two continuous variables, we used Pearson's test or, for skewed variables, Spearman's rank test.

Survival status during follow-up was ascertained as previously described (20). The primary outcome of this report was all-cause mortality after 4.5 years of follow-up. Accordingly, we used mixed-effects Cox models to demonstrate differences in survival time among the study groups. Independent predictors were cardiac dysfunction patterns of HFpEF features or small LV versus normal^{TTE} with further stepwise adjustment for age, sex, body mass index, smoking status, frequency of exacerbations, and one of the following lung function parameters: FEV_1, residual lung volume (RV), or D_{LCO}. The random intercept accounts for clustering by study centers. Hazard ratios demonstrate the relative rate of death in patients with either HFpEF features or small LV compared with patients with normal^{TTE}. Kaplan-Meier curves with the corresponding log-rank test were used to visualize survival probability between the study groups. Statistical analyses were performed using R (version 2022.12.0, RStudio; R Foundation). An α error of $<$5% was considered statistically significant.

Results

In 1,752 eligible patients, we first identified heart failure with mid-range or reduced ejection fraction and RVD in 3.6% and 3.5% of the patients, respectively (Figure 1). Then, we identified patients who demonstrated morphological features consistent with HFpEF and stratified those who also had elevated NT-proBNP as having HFpEF features (16%) and those with normal NT-proBNP as HFpEF risk (17%) (Figure 1). Furthermore, in patients who did not fulfill the criteria of the indicated cardiac dysfunction patterns, we identified patients with small LV, who represented 8% of the cohort population (Figure 1). Subsequently, patients with HFpEF features, small LV, and those who had normal echocardiography, as per the study definition, comprised the study population of this analysis (n = 1,209).

Patient demographics and pulmonary and cardiac characteristics according to study groups are shown in Table 1. Compared with patients with small LV or normal^{TTE}, patients with HFpEF features were older and had more frequent cardiovascular comorbidities. Furthermore, patients with small LV or HFpEF features had reduced exercise tolerance. In addition, patients with small LV had significantly lower body mass index, particularly lower skeletal muscle mass, than patients with HFpEF features or normal^{TTE}.

Lung Function in Patients with Small LV

A larger proportion of patients with small LV had severe COPD (Table 1). Accordingly, patients with small LV had more severe lung hyperinflation, as indicated by significantly higher residual lung volume, lower D_{LCO}, and larger attenuation areas on pulmonary CT than patients with HFpEF-features or normal^{TTE} (Table 1).

Diastolic Function and Cardiac Biomarkers in Patients with Small LV or HFpEF Features

We observed differences regarding echocardiographic functional parameters between the groups. Although patients with HFpEF features had higher left ventricular end-diastolic pressure, indicated by a higher

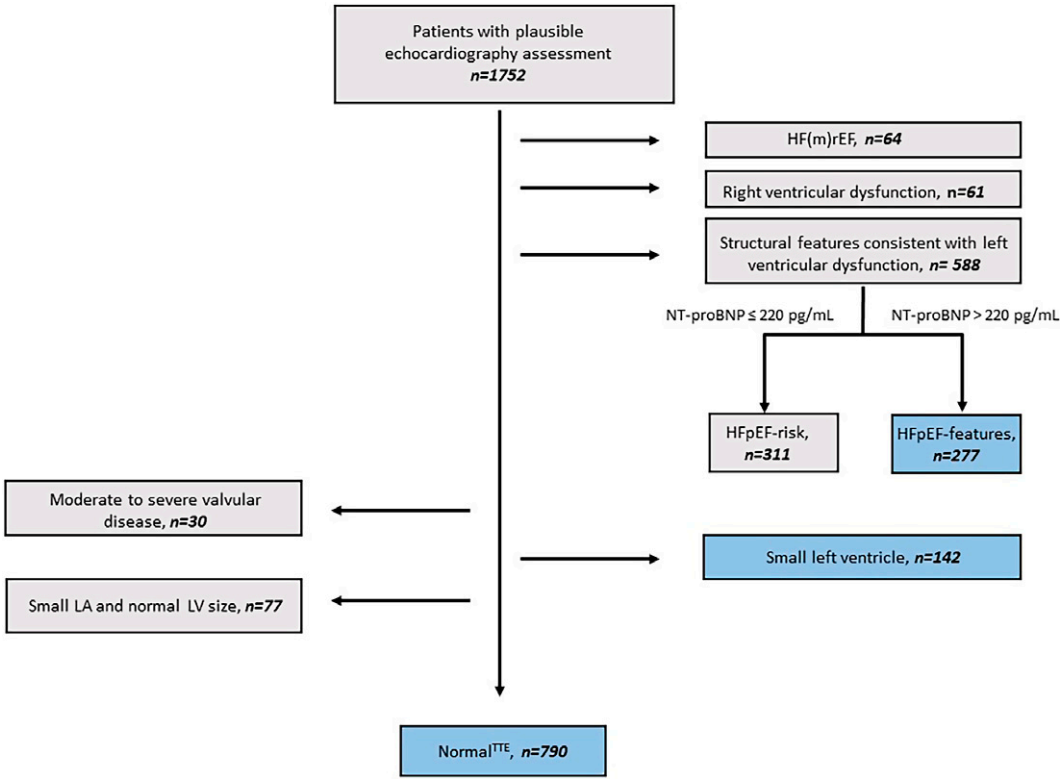

Figure 1. Study selection flowchart. The whole cohort: $N = 1{,}752$; patients with HF(m)rEF: $n = 64$; heart failure with preserved ejection fraction (HFpEF) features: $n = 277$; HFpEF risk: $n = 311$; right ventricular dysfunction: $n = 61$; small LV: $n = 142$. HF(m)rEF = heart failure with mid-range reduced ejection fraction; LA = left atrium; LV = left ventricle; normal^{TTE} = no cardiac dysfunction as per transthoracic echocardiography; NT-proBNP = N-terminal pro-brain natriuretic peptide.

E/e′ ratio (median, 9.1; interquartile range [IQR], 6.9–11.0) than patients with small LV (median, 7.7; IQR, 5.7–9.7) or normal^{TTE} (median, 7.8; IQR, 6.4–9.4; P values < 0.001), the E/e′ ratio was not increased in patients with small LV compared with those with normal^{TTE} ($P = 0.45$) (Table 1). Likewise, serum levels of both NT-proBNP and hs-troponin I were not higher in patients with small LV compared with normal^{TTE} but rather significantly higher in patients with HFpEF features (Table 1). However, patients with small LV demonstrated reduced left ventricular filling as indicated by lower E/A ratio (median, 0.81; IQR, 0.70–1.0) than patients with normal^{TTE} (median, 0.89; IQR, 0.73–1.1; $P = 0.02$), similar to patients with HFpEF features (Table 1). In addition, TAPSE was lower in patients with small LV compared with patients with normal^{TTE}. Noteworthy was that patients with small LV had a significantly lower LV mass index than those with HFpEF features or normal^{TTE}. The LV mass adjusted for age, sex, and height correlated well with the skeletal muscle mass across all the groups ($R = 0.53$; $P < 0.001$).

Impaired LV Filling and All-Cause Mortality in the COSYCONET Cohort

Out of 1,187 patients with available survival data who had normal^{TTE}, HFpEF features, or small LV, 82 patients died during a median follow-up time of 46 months (IQR, 23–55 months). Both patients with small LV or HFpEF features demonstrated a higher mortality rate than those with normal^{TTE} (Table 2 and Figure 2). Table 2 demonstrates the results of different mixed-effects Cox models. Small LV or HFpEF features remained independent predictors of all-cause mortality after adjustment for basic confounders, exacerbation frequency and either RV, D_{LCO}, or FEV_1 (Table 2). Although small LV characterizes a subgroup of patients with more severe COPD, small LV was a predictor of all-cause mortality independent from features of disease severity such as the Body-mass index, Obstruction, Dyspnea, and Exercise (BODE) score index or its single components or the skeletal muscle mass index (*see* Table E1 in the online supplement). In a further analysis, a subgroup of patients with HFpEF features who had E/e′ ratio > 9 also showed a higher mortality rate than normal^{TTE} (Table E2).

Using Kaplan-Meier analysis, we visualize that the mortality rate associated with small LV is independent from lung hyperinflation. Therefore, we stratified patients with normal^{TTE} and RV values :180% as normal^{TTE} with hyperinflation (Figure 3). Patients with small LV had a higher mortality rate than patients who had normal^{TTE} and hyperinflation ($n = 471$; hazard ratio, 2.09; 95% confidence interval, 1.11–3.97; $P = 0.02$) (Figure 3). Of note, mean predicted RV values were rather higher in patients with normal^{TTE} and hyperinflation than those with small LV (192 ± 41 vs. 183 ± 59). In addition, we also noticed that patients with small LV had lower LV mass index as well as lower skeletal muscle mass index than patients with normal^{TTE} and hyperinflation (mean [IQR] LV mass index, 66 [55–79] vs. 90 [77–104]; $P < 0.0001$; and mean [IQR]muscle mass index, 12.4 [7.5–25.6] vs. 13.2 [8.5–21]; $P = 0.04$).

Discussion

In this cohort of well-characterized patients with COPD, we report that patients with

Table 1. Baseline Clinical Characteristics of the Patients

	Normal^{TTE} ($n = 790$)	HFpEF Features ($n = 277$)	Small LV ($n = 142$)	*P* Value
Demographics				
Sex, % males	55	51	54	0.67
Age, yr	63 ± 8	68 ± 8	64 ± 8	<0.001*†
Body mass index, kg/m^2	26.7 ± 4.8	27.0 ± 5	24.4 ± 5	<0.001*‡
Muscle mass, kg	26.7 ± 7.4	26.4 ± 7.0	24.8 ± 7.6	0.019*‡
Muscle mass index, kg/m^2	17.6 (10.6–30.8)	16.0 (9.4–30.4)	12.4 (7.5–25.6)	0.005*‡
Current smokers, %	25	28	22	0.48
Pulmonary characteristics				
Severe COPD,§ %	35	34	57	<0.001
FEV_1, %	60 ± 21	59 ± 20	51 ± 22	<0.001*‡
RV, %	163 ± 51	157 ± 51	183 ± 59	<0.001*‡
$D_{L_{CO}}$, %	60 ± 22	60 ± 21	52 ± 21	0.002*‡
CT-LAA, %	16 (5.8–26.4)	12.1 (3.1–14.5)	30 (14–35.5)	0.017*‡
Exacerbation rate,‖ %	32	34	42	0.094
6-min-walk distance, m	438 ± 101	406 ± 105	411 ± 100	<0.001†‡
mMRC dyspnea scale :2, %	40	45	48	0.15
Cardiac characteristics				
Cardiovascular comorbidities, %				
CAD	12	27	9	<0.001
Hypertension	52	63	48	0.003
Diabetes mellitus	11	18	8	0.004
Hyperlipidemia	40	45	36	0.24
NT-proBNP, pg/ml	158 (27–335)	439 (314–694)	223 (51–371)	<0.001*†
hs-troponin I, ng/L	3.6 (2.2–6.4)	4.0 (2.6–7.4)	3.3 (2.2–4.8)	0.002*†‡
E/A ratio	0.89 (0.73–1.1)	0.83 (0.71–1.05)	0.81 (0.70–1.0)	0.021‡
E/e′ ratio	7.8 (6.4–9.4)	9.1 (6.9–11.0)	7.7 (5.7–9.7)	<0.01*†
e'_{septal}, cm/s	7.6 (6.2–9.1)	7.3 (5.9–9.0)	8.1 (6.3–10.0)	0.037*
$e'_{lateral}$, cm/s	9.8 (8.0–11.7)	9.0 (7.5–11.2)	9.1 (7.9–12.0)	0.15
a'_{septal}, cm/s	10.7 (9.2–12.0)	9.5 (8.0–11.6)	11.0 (9.2–13)	<0.001*†
$a'_{lateral}$, cm/s	11.6 (9.3–14.0)	11.0 (8.6–13.0)	13.0 (10.0–15.0)	<0.01*†
LV mass index	92 (78–105)	135 (113–153)	66 (55–79)	<0.001*†‡
TAPSE, cm	2.41 ± 0.39	2.34 ± 0.5	2.28 ± 0.37	<0.001†‡
Left atrial diameter, cm	3.5 ± 0.44	3.9 ± 0.84	3.1 ± 0.54	<0.001*†‡
ACE inhibitors, %	22	26	22	0.51
β blockers, %	17	40	11	<0.01*†
Statins, %	18	26	14	<0.01*†

Definition of abbreviations: a′ = late diastolic velocity obtained by tissue doppler imaging; ACE = angiotensin-converting enzyme; CAD = coronary artery disease; CT-LAA = lung low attenuation area per computed tomography; e′ = mitral annular early diastolic velocity; E/A = the ratio between early and late ventricular filling velocity; E/e′ = ratio between early mitral inflow velocity and mitral annular early diastolic velocity; HFpEF = heart failure with preserved ejection fraction; LV = left ventricle; mMRC = modified Medical Research Council; NT-proBNP = N-terminal pro-brain natriuretic peptide; RV = residual lung volume; TAPSE = tricuspid annular plane systolic excursion; TTE = transthoracic echocardiography.
Values are presented as mean ± SD or median (interquartile range). CT-LAA was available for $n = 84$, $n = 25$, and $n = 14$ patients with normal^{TTE}, HFpEF, and small LV, respectively. E/e′ was available for $n = 699$, $n = 169$, and $n = 85$ patients with normal^{TTE}, HFpEF, and small LV, respectively. E/A was available for $n = 906$, $n = 221$, and $n = 135$ patients with normal^{TTE}, HFpEF, and small LV, respectively.
**Post hoc* analysis $P < 0.05$ between small LV versus HFpEF.
†*Post hoc* analysis $P < 0.05$ between HFpEF versus normal^{TTE}.
‡*Post hoc* analysis $P < 0.05$ between small LV versus normal^{TTE}.
§Severe COPD indicates patients with Global Initiative for Chronic Obstructive Lung Disease stages III–IV.
‖Moderate-severe exacerbation within the previous 12 months to baseline study visit.

small LV size, an indicator of reduced LV filling, or patients with HFpEF features have an increased rate of all-cause mortality compared with patients with COPD and no relevant cardiac dysfunction. Moreover, patients with small LV demonstrate a disturbed left ventricular filling pattern that is distinct from HFpEF. Accordingly, patients with small LV have indicators of reduced LV filling, yet, in contrast to patients with HFpEF features, they have normal ventricular filling pressure and do not exhibit elevated markers of ventricular stress or cardiac injury, namely serum NT-proBNP and hs-troponin I.

In COPD, cardiac dysfunction is a multifaceted condition that is often believed to present as HFpEF. Nevertheless, impaired ventricular filling might also present as a disease-related cardiac manifestation in patients with hyperinflation or emphysema. Previous studies have already demonstrated impaired ventricular filling in patients with COPD compared with healthy control subjects, using either echocardiography (25, 30, 31) or magnetic resonance imaging (32). In addition, we have previously shown an association between reduced ventricular filling and COPD severity, using echocardiographic parameters of diastolic function (16). However, so far, studies investigating left ventricular dysfunction in patients with COPD have not distinguished COPD-related

Table 2. Mixed Effects Cox Models Demonstrate Survival Probabilities in Patients with Small Left Ventricle and Heart Failure with Preserved Ejection Fraction Features Compared with Normal Transthoracic Echocardiography

Exposure Variable	HR	95% CI	*P* Value
Model 1: unadjusted model			
HFpEF features	2.16	1.30–3.61	0.003
Small LV	2.75	1.54–4.89	0.001
Model 2: adjusted for basic confounders			
HFpEF features	1.63	0.95–2.79	0.077
Small LV	2.29	1.26–4.18	0.007
Model 3a: adjusted for basic confounders, exacerbations, and RV%			
HFpEF features	1.77	1.02–3.06	0.042
Small LV	2.26	1.23–4.16	0.009
Model 3b: adjusted for basic confounders, exacerbations, and D_{LCO}%			
HFpEF features	2.03	1.15–3.57	0.015
Small LV	2.12	1.12–4.03	0.020
Model 3c: adjusted for basic confounders, exacerbations, and FEV_1%			
HFpEF features	1.73	1.00–2.96	0.048
Small LV	1.88	1.03–3.45	0.040

Definition of abbreviations: CI = confidence interval; HFpEF = heart failure with preserved ejection fraction; HR = hazard ratio; LV = left ventricle; RV = residual lung volume.
Confounders: sex, age, body mass index, and smoking status versus former smoker.
Exacerbations were defined as moderate to severe exacerbation within the last 12 months.
Log-likelihood *P* values of all models was <0.001.

reduced ventricular filling from diastolic dysfunction associated with HFpEF. In previous work, Barr has highlighted the need for discriminating COPD-related reduction in ventricular filling from coexisting HFpEF and its consecutive role in treating impaired ventricular filling in patients with COPD (17). Moreover, knowledge about the effects of reduced ventricular filling on COPD outcomes is largely limited to its negative impacts on exercise capacity (9) and physical activity (16), whereas its impact on patient survival is still unclear. To our knowledge, this is the first study to report increased all-cause mortality in patients with COPD and reduced ventricular filling, indicated by small LV size, in a cohort of strictly stratified patients according to clearly defined patterns of cardiac dysfunction. Small LV was an independent predictor of all-cause mortality after adjustment for the main predictors of mortality in COPD, including the BODE index, smoking status, exacerbation frequency, and measures of lung function such as residual lung volume, gas transfer capacity, and FEV_1. A possible explanation of this later

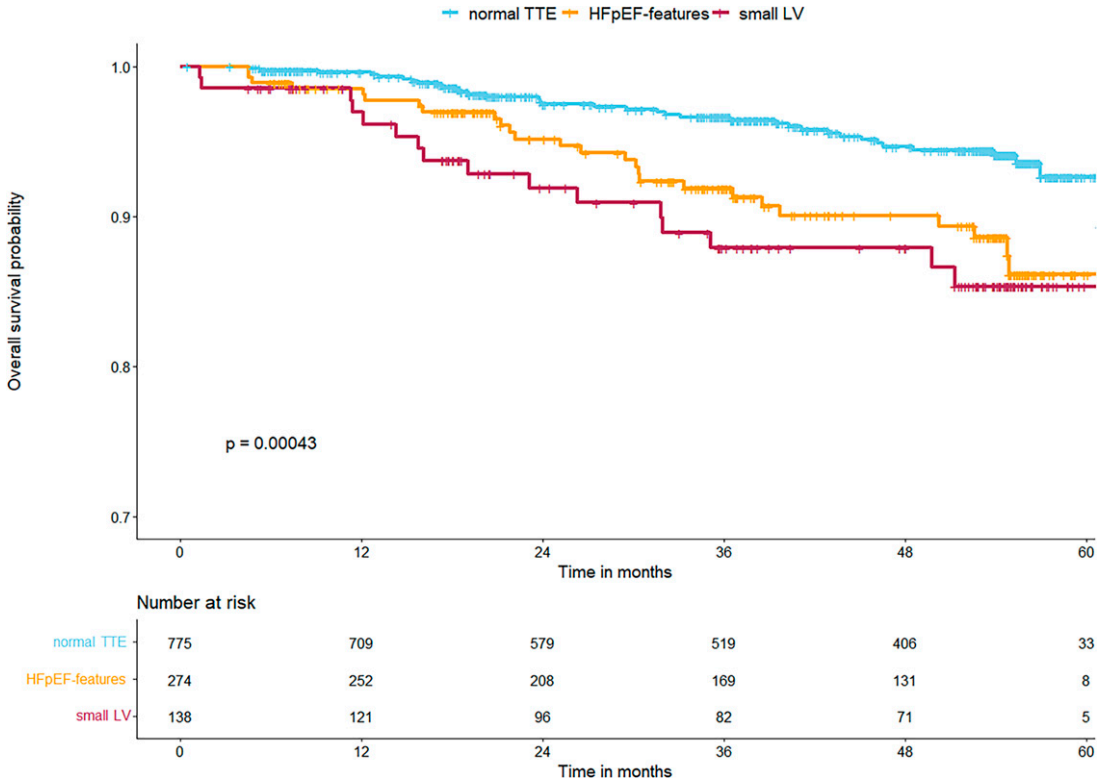

Figure 2. Kaplan-Meier curves demonstrate reduced survival probability of patients with small LV and HFpEF features compared with patients with normal TTE. *P* values are of the log-rank test. HFpEF = heart failure with preserved ejection fraction; LV = left ventricle; TTE = transthoracic echocardiography.

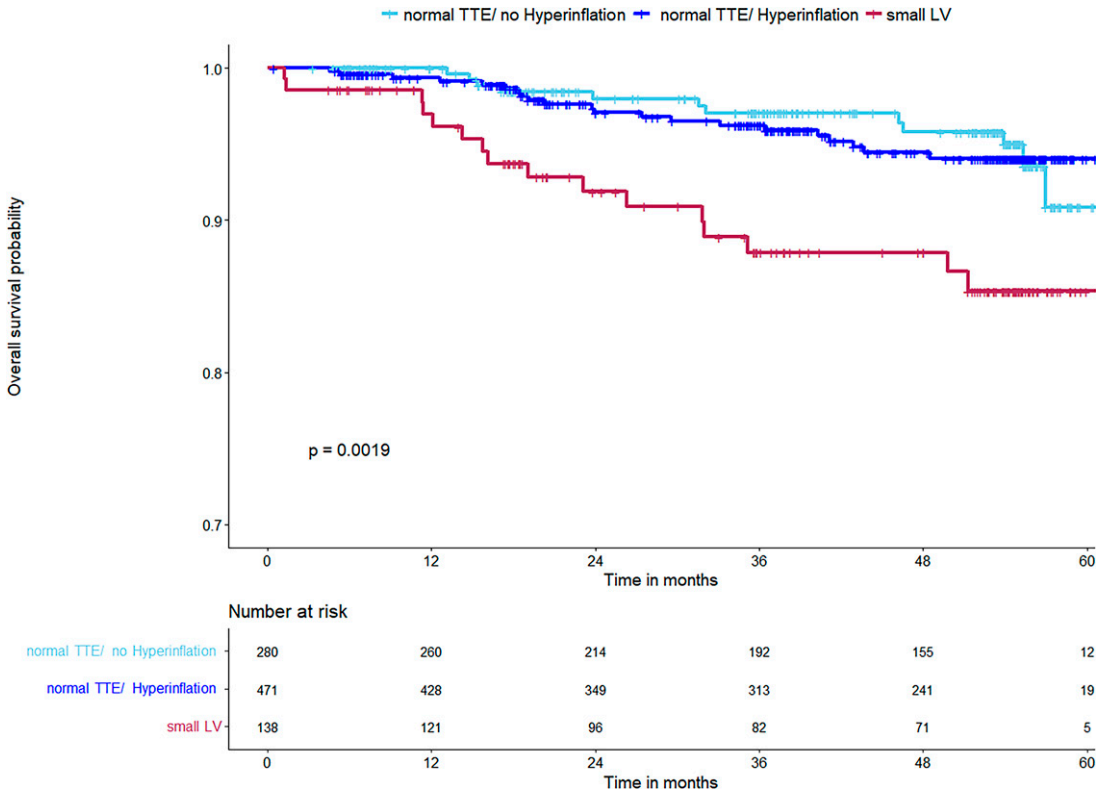

Figure 3. Kaplan-Meier curves demonstrate reduced survival probability of patients with small LV compared with patients without hyperinflation and normal transthoracic echocardiography (TTE) or patients with hyperinflation but normal TTE. *P* values are of the log-rank test. LV = left ventricle.

finding might be that many patients with small LV suffer from severe COPD and have worse lung function and emphysema. However, our finding that small LV is a predictor of mortality independent from lung function supports the notion that reduced ventricular filling is a clinical phenotype that confers worse prognosis through cardiopulmonary intermediates beyond lung function limitation.

The high frequency of patients with features of HFpEF in this COPD cohort can be mainly attributed to shared risk factors and etiologies, such as aging, smoking, and further cardiovascular risk factors like hypertension and dyslipidemia (4). However, COPD has also been shown to be an independent risk factor for some cardiovascular diseases (33, 34), including heart failure (34), and the diagnosis of COPD in patients with heart failure was associated with increased cardiovascular mortality and hospitalization (5). Nonetheless, cohort studies investigating the prevalence of HFpEF and other cardiac dysfunction patterns in patients with COPD based on objective assessments of cardiac structure, function, and biomarkers are scarce. In our cohort, almost one-third of the patients showed structural heart changes suggestive of HFpEF, such as LV hypertrophy or left atrial enlargement, of whom nearly half had more classical HFpEF features, with left ventricular stress indicated by elevated serum levels of NT-proBNP. A further key finding of this study is that patients with COPD and HFpEF features have a higher rate of all-cause mortality than patients with COPD and no cardiac dysfunction. As we report that having HFpEF features is a frequent comorbidity in patients with COPD, we suggest that HFpEF in COPD might be a treatable trait, and its management has the potential to decrease mortality in this subgroup of patients with COPD.

A hallmark of HFpEF is the increase in LV filling pressure caused by diastolic dysfunction, which is attributed to left ventricular stiffness often caused by ventricular hypertrophy (35). Likewise, reduced LV filling in patients with COPD and small LV could be accompanied by impaired diastolic function. However, it is pivotal not to misclassify patients with COPD and disturbed diastolic function due to reduced venous return, indicated by small LV, as HFpEF. In this context, the role of established measures of diastolic dysfunction and cardiac biomarkers appears to be key. Here, we report that patients with small LV did not differ from those with HFpEF features regarding impaired LV filling indicated by a lowered E/A ratio, yet patients with small LV had a normal E/e′ ratio, a parameter of LV filling pressure and a core indicator for HFpEF. Furthermore, serum levels of NT-proBNP, a marker of ventricular stress that strongly correlates with echocardiographic indices of ventricular filling pressure (36), were low in patients with small LV, similar to patients with COPD and no cardiac dysfunction. Therefore, we suggest that NT-proBNP might be an appropriate marker to distinguish reduced LV filling in COPD from coexisting HFpEF. Likewise, hs-troponin I, an indicator of myocardial injury, was significantly lower in patients with small LV than in those with HFpEF features. Furthermore, patients with small LV had lower TAPSE than patients with normal^{TTE},

despite the fact that patients of both groups had values within the normal range. An explanation of this finding might be that low TAPSE is associated not only with reduced right ventricular function but also with reduced volume (37), which has been previously reported in patients with emphysema (14, 15). These findings highlight that small LV is a distinct pattern of cardiac dysfunction in COPD, which, despite the lack of elevated cardiac markers, is associated with increased all-cause mortality.

The underlying mechanisms of reduced LV filling in patients with COPD have been studied before. Previous studies have linked reduced left ventricular size and filling to lung hyperinflation and emphysema (7, 9, 12). It also has been shown that the decrease in left heart size is a consequence of reduced venous return because of the regional loss of the low-pressured pulmonary capillary beds in emphysematous lung areas (6, 12, 38, 39). The findings of our study are consistent with these previous findings, as they demonstrate that patients with small LV size have more severe lung hyperinflation, reduced gas transfer, and a higher percentage of emphysema, as per CT imaging in a subgroup of our cohort. A further unexplored aspect of small LV size might be the decrease in LV mass. Interestingly, our data indicate that patients with small LV have decreased skeletal muscle mass, which correlated well with the decrease in LV mass, as has been previously reported in elderly subjects with sarcopenia and reduced LV mass (40, 41). Future studies are warranted to elucidate the role of cardiac sarcopenia in the pathogenesis of reduced LV filling in COPD.

We acknowledge the limitations of this study. First is the lack of cardiac magnetic resonance imaging, a gold standard for the assessment of LV size. However, we used well-established echocardiographic structural features in addition to cardiac biomarkers to stratify a large cohort of patients with COPD based on their cardiac dysfunction patterns. Second, pulmonary CT imaging to evaluate lung emphysema is not part of the study protocol of the COSYCONET cohort. Here, we used lung volumes to quantify lung hyperinflation and gas transfer capacity as a surrogate for the extent of emphysema. Furthermore, pulmonary CT scans were available in a subgroup of patients, and their results support our findings. Third, the criteria used to define HFpEF in our study, including the use of LA diameter instead of LA volume, were adapted to the available echocardiographic measures and did not include the functional measures of diastolic dysfunction to avoid misclassifying patients with reduced LV filling and small LV as HFpEF. However, our definition of HFpEF features was based on central criteria such as LV hypertrophy and LA enlargement in addition to NT-proBNP. In addition, a sensitivity analysis that considered echocardiographic functional parameters in defining elevated LV filling pressure has confirmed that patients with COPD with HFpEF have higher mortality rates than those with no cardiac dysfunction. Finally, because systolic pulmonary artery pressure was not reported as a continuous variable, we cannot exclude the possibility of incipient pulmonary hypertension in patients with small LV. To mitigate a possible confounding effect of pulmonary hypertension, individuals with obvious RVD were excluded from the analyses. Moreover, patients with small LV exhibited an average TAPSE within the normal range, and their NT-proBNP concentrations did not significantly differ from those in patients without cardiac dysfunction. Therefore, it appears improbable that there is significant pulmonary hypertension affecting the LV filling.

In conclusion, small LV and HFpEF features indicate two different patterns of impaired LV filling that are associated with increased all-cause mortality in patients with COPD. As both patterns of impaired LV filling represent two distinct treatable traits, a guideline-directed treatment of HFpEF and an intensified management of lung hyperinflation and emphysema in patients with small LV have the potential to reduce mortality in COPD. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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