Chest computed tomography-derived low fat-free mass index and mortality in COPD

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ABSTRACT Low fat-free mass index (FFMI) is an independent risk factor for mortality in chronic obstructive pulmonary disease (COPD) not typically measured during routine care. In the present study, we aimed to derive fat-free mass from the pectoralis muscle area (FFMPMA) and assess whether low FFMIPMA is associated with all-cause mortality in COPD cases. We used data from two independent COPD cohorts, ECLIPSE and COPDGene.

Two equal sized groups of COPD cases (n=759) from the ECLIPSE study were used to derive and validate an equation to calculate the FFMPMA measured using bioelectrical impedance from PMA. We then applied the equation in COPD cases (n=3121) from the COPDGene cohort, and assessed survival. Low FFMIPMA was defined, using the Schols classification (FFMI <16 in men, FFMI <15 in women) and the fifth percentile normative values of FFMI from the UK Biobank.

The final regression model included PMA, weight, sex and height, and had an adjusted R^2 of 0.92 with fat-free mass (FFM) as the outcome. In the test group, the correlation between FFMPMA and FFM remained high (Pearson correlation=0.97). In COPDGene, COPD cases with a low FFMIPMA had an increased risk of death (HR 1.6, p<0.001).

We demonstrated COPD cases with a low FFMIPMA have an increased risk of death.

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Introduction

Low fat-free mass index (FFMI) is an independent risk factor for mortality in chronic obstructive pulmonary disease (COPD), irrespective of lung function [1–3]. FFMI, obtained by dividing fat-free mass (FFM) by height squared (units: $kg \cdot m^{-2}$), is an indirect marker of muscle that includes skeletal and non-skeletal muscle mass, organs, connective tissue and bone [4]. However, it is not typically measured during routine care or in large epidemiological cohorts investigating COPD. FFM can be measured by using indirect techniques, such as air displacement plethysmography (ADP), bioelectrical impedance analysis (BIA), skin-fold anthropometry (SFA) or dual x-ray absorptiometry (DXA) [4, 5]. ADP is a reproducible measure of FFM, but assumes that the density of lean tissue is identical in all patients [6, 7]. The BIA and SFA are convenient, but are both criticised for underestimating or overestimating FFM, respectively, in comparison to the current research standard, DXA [5, 8]. The DXA technique is a more expensive method using specialised equipment involving radiation exposure and highly trained technicians, typically outside of COPD clinics [9].

Low FFMI has been defined, using different cut-points depending on the population. In COPD cases, a FFMI less than 16 $kg \cdot m^{-2}$ in males or 15 $kg \cdot m^{-2}$ in females is often used to define low FFMI [1, 10]. The European Working Group on Sarcopenia in Older People currently recommends using measures from age- and sex-stratified populations to define cut-points for low FFMI [11]. As FFMI decline accelerates with age and current cut-points may under-diagnose low FFMI in overweight and obese individuals [12, 13], it is important to take age and body mass index (BMI) into account, in addition to gender, when classifying low FFMI. Examples of this include reported reference values stratified by age, sex and BMI categories, based on data from 186 975 healthy individuals, aged 45 to 69 years of age, recruited as part of the UK Biobank [13].

Chest computed tomography (CT) scans are increasingly employed during routine care, and can be used to monitor muscle mass. In COPD, CT imaging of muscle groups, including the intercostal muscles and mid-thigh area, has been used to assess low muscle mass and predict adverse clinical outcomes [14, 15]. In patients with cancer, axial CT from the region of the third lumbar vertebra (L3) of the spine has been used to calculate the FFMI [16–18]. We previously demonstrated that pectoralis muscle area (PMA) is a reproducible measure of muscle mass that can be easily obtained from chest CT scans [19, 20]. Furthermore, low PMA has been associated with an increased risk of death [21] and muscle loss among cancer cases [22]. As low-dose CT for lung cancer screening has become part of the standard of care for high-risk current and former smokers [23, 24], PMA can be obtained without increasing cost or radiation exposure. However, the relationship between PMA and FFM has not been explored in detail among COPD cases. To do so would require a large cohort of COPD cases with both measured FFM and chest CT. Our goal was to derive FFM from PMA (FFM_{PMA}), and assess whether low $FFMI_{PMA}$ is associated with all-cause mortality in COPD cases. To achieve our objectives, we compared PMA to FFM, measured from BIA, and used the relationship to derive a formula to calculate FFM from PMA (FFM_{PMA}), measured in a large cohort of COPD cases from the Evaluation of COPD longitudinally to identify predictive surrogate endpoints (ECLIPSE) study. We then applied the formula in an independent cohort of COPD cases from COPDGene to examine the relationship between low $FFMI_{PMA}$ and all-cause mortality. We used $FFMI_{PMA}$ (as opposed to FFM_{PMA}) to assess survival, derived from the established cut-points for defining low FFMI [1, 10].

Materials and methods

Access to data was obtained and analyses were performed after obtaining approval from the Institutional Review Boards at all participating centres in ECLIPSE and COPDGene, including Brigham and Women's Hospital and University of Alabama at Birmingham. The ECLIPSE and COPDGene studies have been previously described in detail [25, 26]. Briefly, the ECLIPSE study (SCO104960, NCT00292552, www.eclipse-copd.com) recruited COPD patients and controls with a smoking history of ⩾10 pack-years, aged 45–75 years, from 46 centres across 12 countries [25]. The COPDGene Study

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(NCT00608764, www.copdgene.org) enrolled ever-smokers, both with and without COPD (Non-Hispanic White Americans and African Americans), aged 45–80, with at least 10 pack-years of lifetime smoking history from 21 US centres [26].

COPD was defined by the presence of Global Initiative for Chronic Obstructive Lung Disease (GOLD) lung function spirometry grades 2–4, with a post-bronchodilator FEV_1/FVC less than 0.7 and FEV_1 less than 80% predicted [27]. In ECLIPSE, FFM was derived from BIA, measured using the Bodystat 1500 (Bodystat Ltd, Isle of Man, UK). The measured resistance was converted to FFM, using the formula developed from the data of 1087 COPD cases by Rutten *et al.* [28]:

$$\text{FFM} = -11.81 + 0.245 \times \text{weight(kg)} + \frac{0.298 \times \text{height(cm)}^2}{\text{impedance}} + 0.148 \times \text{height(cm)} + 5.284 \text{ (if male)}$$

Quantitative assessments of the PMA were obtained from a single axial slice above the aortic arch by a trained analyst, using in-house software as previously described (supplementary figure S1) [19, 29]. Once the borders of the muscles were closed by manual tracing, a second filtering step was applied to remove all intra-muscular voxels, such as those representing adipose tissue that were outside of a tissue attenuation range of −50 to 90 Hounsfield units. The aggregate PMA (in cm^2) was calculated as the sum of the cross sectional area of right and left pectoralis major and minor muscles in that single slice. Quality control of the data involved two steps. All segmentations were visually inspected by pulmonologists with experience in lung imaging (A. Diaz and G. Washko). Segmentation failures were identified (*e.g.* malposition of the arm and anatomic distortion due to prior chest wall surgery) and excluded. In a second step, the distributions of PMA values for each muscle group (right, left, major and minor muscles) were examined, and the CT scans for individuals with muscle group values greater than 6SD from the median values were re-inspected and exclusions made, if supported by scan re-inspection. One COPD case in the ECLIPSE study and one in COPDGene had duplicate chest CTs, and in both cases the PMA from the first chest CT was arbitrarily selected for each duplicate, and the second measurement excluded. Analyses in ECLIPSE were further restricted to COPD cases who had a chest CT performed within 60 days of FFM measurements using BIA. A total of 98.0% of COPD cases in ECLIPSE with PMA measured on chest CT and phenotype data passed quality control and were included in the analyses. A total of 98.3% of the COPD cases in COPDGene with chest CT and phenotype data, including mortality information, passed quality control and were included in the analyses.

All statistical analyses were performed using the R software program. The ECLIPSE sample was randomly split into training and test groups, each comprising 759 COPD cases. The training group was used to develop a formula to predict FFM_{PMA}, and the test group was used to objectively test the performance of this formula. To test for differences in general characteristics between the training and test groups prior to model building, t-tests and Chi-squared tests were used. In the training group, manual stepwise multiple regression analysis was performed, with FFM as the dependent variable, taking weight, sex and height into consideration as independent variables ($p<0.05$). The adjusted R^2 correlation was used as a prediction model quality parameter. Variable selection was further assessed using automatic backwards and forwards stepwise multiple regression, based on the Akaike information criterion. In the test group, the Pearson correlation coefficient was used to assess the agreement between FFM from BIA and FFM derived from PMA. A Bland–Altman plot was used to check for systematic bias across the range of FFM values in the test group. FFMI was generated by dividing FFM by height squared in metres. $FFMI_{PMA}$ was used to differentiate FFMI derived from PMA on chest CT from FFMI that was measured using BIA throughout the study.

Survival modelling in COPDGene, using the September 2016 mortality dataset, was performed using Kaplan–Meier curves and Cox proportional hazards regression. Cox proportional hazards models included adjustment for the categorical variables sex, race, GOLD grade and number of comorbidities, as well as the continuous measures age and smoking duration (American Thoracic Society (ATS) pack-years). All covariates were collected at baseline. Race was based on self-report and GOLD grade on spirometry. Comorbidities were assessed as self-reported physician-diagnosed cancer, congestive heart failure, coronary artery disease, diabetes, hypertension, heart attack, stroke and gastroesophageal reflux. Low $FFMI_{PMA}$ was defined, using two criteria: the Schols classification and UK Biobank normative values. The Schols classification characterises male COPD cases with $FFMI_{PMA}$ <16 and female COPD cases with $FFMI_{PMA}$ <15, as having a low $FFMI_{PMA}$ [1]. The UK Biobank normative values were used to classify low $FFMI_{PMA}$, when $FFMI_{PMA}$ was less than the fifth percentile normative values for the appropriate age, sex and BMI categories in healthy individuals from the UK Biobank [13].

TABLE 1 Comparison of baseline characteristics between training and test groups of COPD cases in the ECLIPSE study

	Training	Test
Subjects n	759	759
Male sex %	65	64
Age years	64 (10)	64 (10)
Weight kg	75.3 (23.1)	74.2 (23)
Height m	1.69 (0.12)	1.69 (0.13)
BMI kg·m^{-2}	26.3 (6.4)	25.8 (6.9)
Current smoking %	35.8	35.4
FEV$_1$% pred	47.6 (26.1)	47.1 (22.9)
FEV$_1$/FVC	0.57 (0.23)	0.57 (0.22)

Data are presented as median (interquartile range) unless otherwise stated. No significant differences were observed between training and test groups ($p<0.05$) for any of the characteristics listed. COPD: chronic obstructive pulmonary disease; BMI: body mass index; FEV$_1$: forced expiratory volume in 1 s; FVC: forced vital capacity.

Results

To derive total body FFM from PMA, COPD cases from the ECLIPSE study were randomised into two groups of equal size (test and training). The test and training groups showed no significant differences in age, sex, weight, height, current smoking status or lung function measurements (table 1). The unadjusted R^2 correlation between PMA and FFM was 0.38 in the training group of COPD cases (table 2). The fully adjusted final model is presented in equation 1:

$$FFM_{PMA} = -15.9 + 0.09 \times PMA(cm^2) + 0.35 \times weight(kg) + 0.20 \times height(cm) + 7.47(\text{if male}) \quad (1)$$

This equation included PMA, weight, sex and height, and had an adjusted R^2 correlation of 0.92 among the total body FFM in the test group.

We then generated FFM$_{PMA}$ in the test group, using equation 1. In this subgroup, the FFM and FFM$_{PMA}$ were strongly related (R=0.973, 95% CI 0.969–0.976, $p<2.2\times10^{-16}$) (figure 1a). The correlation between FFM and FFM$_{PMA}$ was 0.935 (95% CI 0.922–0.945, $p<2.2\times10^{-16}$) and 0.967 (95% CI 0.958–0.974, $p<2.2\times10^{-16}$) between male and female COPD cases in the ECLIPSE test group, respectively (supplementary figure S2). The Bland–Altman plots (figure 1b and supplementary figure S2) further supported excellent agreement between total body FFM and FFM$_{PMA}$ across the range of values in the test group. The mean difference between FFM$_{PMA}$ and total body FFM in the test group was −0.28 kg

TABLE 2 Manual stepwise model building in the training group of ECLIPSE COPD cases to generate formula to convert PMA to FFM

Independent variable	Adjusted R^2	Beta	p-value
Model 1	0.38		
PMA cm^2		0.79	<0.0001
Model 2	0.79		
PMA cm^2		0.4	<0.0001
Weight kg		0.41	<0.0001
Model 3	0.90		
PMA cm^2		0.08	<0.0001
Weight kg		0.38	<0.0001
Sex (ref.: male)		9.5	<0.0001
Model 4	0.92		
PMA cm^2		0.09	<0.0001
Weight kg		0.35	<0.0001
Sex (ref.: male)		7.5	<0.0001
Height cm		0.20	<0.0001

COPD: chronic obstructive pulmonary disease; PMA: pectoralis muscle area; FFM: fat-free mass.

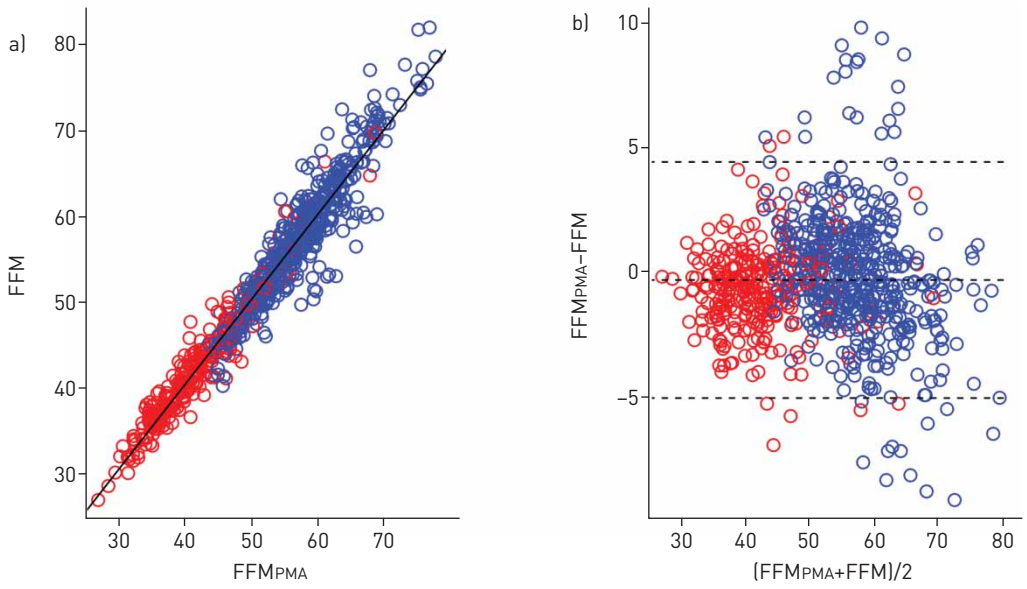

FIGURE 1 a) Relationship between fat-free mass derived from pectoralis muscle area (FFMPMA) and fat-free mass (FFM) in the test group comprised of 783 ECLIPSE chronic obstructive pulmonary disease cases. b) Bland–Altman plot comparing FFMPMA and FFM in the test group.

corresponding to −0.5% of FFM. The limits of agreement related to the mean difference between FFMPMA and FFM were ±4.7 kg.

Low FFMI in overweight and obese COPD cases

Equation 1 was then used to calculate FFMPMA in COPDGene. We divided FFMPMA by height squared to generate the index (FFMIPMA), in order to classify cases with a low FFMIPMA. In table 3, we noted that no COPD cases with a BMI greater than 25 were classified as having a low FFMIPMA, using the Schols classification criteria [1]. When we used the UK Biobank normative values, based on the fifth percentile values from age-, sex- and BMI-stratified groups, as reported by FRANSSEN *et al.* [13], 11% of the COPD cases who were overweight and 4.2% of COPD cases who were obese had a low FFMPMA. Furthermore, using the UK Biobank normative values, a significantly lower number of COPD cases with a low BMI had a low FFMIPMA (table 3, 92% *versus* 19.3%).

Relationship between FFMI derived from chest CT and survival in COPDGene

Next, we aimed to examine survival, stratified by low FFMIPMA. We began by exploring anthropometric and lung function characteristics between COPD cases in ECLIPSE and COPDGene. Overall, COPD cases in COPDGene had a higher number of females, African Americans and current smokers, higher body weight, higher FEV_1 % predicted, a lower FEV_1/FVC and less emphysema than COPD cases in ECLIPSE (table 4).

The median FFMIPMA derived from CT in COPDGene was slightly higher (median 18.4 $kg{\cdot}m^{-2}$, range 11.1–29.5 $kg{\cdot}m^{-2}$) than COPD cases in ECLIPSE (median 18.0 $kg{\cdot}m^{-2}$, range 11.5–28.1 $kg{\cdot}m^{-2}$). Initially,

TABLE 3 Criteria used to define low FFMI stratified by BMI category in COPD cases in COPDGene

BMI category	Schols classification		UK Biobank normative values	
	Normal	Low FFMIPMA	Normal	Low FFMIPMA
<18.5 $kg{\cdot}m^{-2}$	7 (8%)	81 (92%)	71 (81%)	17 (19%)
18.5–25 $kg{\cdot}m^{-2}$	668 (71%)	277 (29%)	720 (76%)	225 (24%)
25–30 $kg{\cdot}m^{-2}$	1028 (100%)	0 (0%)	915 (89%)	113 (11%)
>30 $kg{\cdot}m^{-2}$	1060 (100%)	0 (0%)	1015 (96%)	45 (4%)

Data are presented as n (% of BMI category). FFMI: fat-free mass index; BMI: body mass index; COPD: chronic obstructive pulmonary disease; FFMIPMA: fat-free mass index derived from pectoralis muscle area.

TABLE 4 Characteristics of COPD cases from ECLIPSE and COPDGene used in the current analyses

Characteristic of COPD cases	ECLIPSE	COPDGene	p-value
Subjects n	1518	3121	
Male sex %	64.3	55.5	<0.01
Age years	64 (10)	63.7 (12.8)	0.42
Weight kg	74.8 (23)	80 (25.9)	<0.01
Height m	1.7 (0.13)	1.7 (0.14)	0.1
BMI kg·m^{-2} %			<0.01
<18.5	4.9	2.8	
18.5–25	36.3	30.3	
25–30	36.6	32.9	
>30	22.3	34	
Race %			<0.01
Non-Hispanic White	97.5	80.3	
African American	1.8	19.7	
Other	<1	0	
Current Smoking %	35.6	39.5	0.07
FEV_1 % pred	47.4 (24.3)	51.3 (30)	<0.01
FEV_1/FVC	0.57 (0.22)	0.5 (0.22)	<0.01
% Emphysema	15.3 (17.4)	8.7 (18.2)	<0.01
FFMI$_{PMA}$	18 (3.3)	18.4 (3.6)	<0.01

Data are presented as median (interquartile range) unless otherwise stated. COPD: chronic obstructive pulmonary disease; BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; FFMI$_{PMA}$: fat-free mass index derived from pectoralis muscle area.

we used a FFMI$_{PMA}$ <16 kg·m^{-2} in male COPD cases and FFMI$_{PMA}$ <15 kg·m^{-2} in female COPD cases, to define low FFMI$_{PMA}$. In our analysis, among 3121 subjects with PMA data and longitudinal follow-up in COPDGene, there were 729 deaths with a median follow-up of 6.25 years. COPD cases with a low FFMI$_{PMA}$ were more likely to die than those with an FFMI$_{PMA}$ above this threshold (figure 2a). We further examined the relationship between all-cause mortality and low FFMI$_{PMA}$ in COPD cases, using Cox regression modelling, accounting for sex, age, race, smoking duration, GOLD category and number of comorbidities. When controlling for these additional covariates, a low FFMI$_{PMA}$ was still associated with a 60% increased risk of death (table 5 Model I: HR 1.6, 95% CI 1.2–1.9, p<0.001) in COPDGene. These results were also observed when we defined a low FFM$_{PMA}$, using the UK Biobank normative values (table 5 Model II: HR 1.5, 95% CI 1.2–1.8, p<0.001).

Discussion

We generated a formula to derive the FFM$_{PMA}$ and the FFMI$_{PMA}$, using the PMA obtained from chest CT scans of ever-smokers with COPD. We have shown that a low FFMI$_{PMA}$ is a significant predictor of all-cause mortality in COPD cases, independent of sex, age, race, smoking duration, GOLD grade and number of comorbidities. Our study has highlighted the need for further research that defines the thresholds for low FFMI in overweight and obese COPD cases; however, we believe that our methods will facilitate additional investigation of FFMI in COPD populations that might only have thoracic CT scans available to monitor body composition.

In the present report, we used a measure of muscle mass obtained from the trunk region to derive FFMI$_{PMA}$ in COPD cases, and demonstrated a strong correlation between the PMA and BIA-based assessment of FFM in unadjusted models and models including sex, height and weight. Improvement in the performance of the model with the inclusion of such anthropometrics is not surprising, given the sexually dimorphic nature of body composition. Differential wasting in COPD has been observed at both whole-body and extremity levels [30, 31]. The high performance of our equation to derive total body FFM from PMA in the test group suggests muscle wasting in COPD is more uniformly distributed than previously determined, or our benchmark BIA is insensitive to regional differences.

In this study, we demonstrated decreased survival associated with a low FFMI$_{PMA}$, derived from PMA measured on CT, after adjustment for lung function, categorised by GOLD stage. Although COPD is still primarily diagnosed based on airflow obstruction, the significant endpoints for patients, such as those affecting quality of life and disease progression, are often independent of the degree of airflow

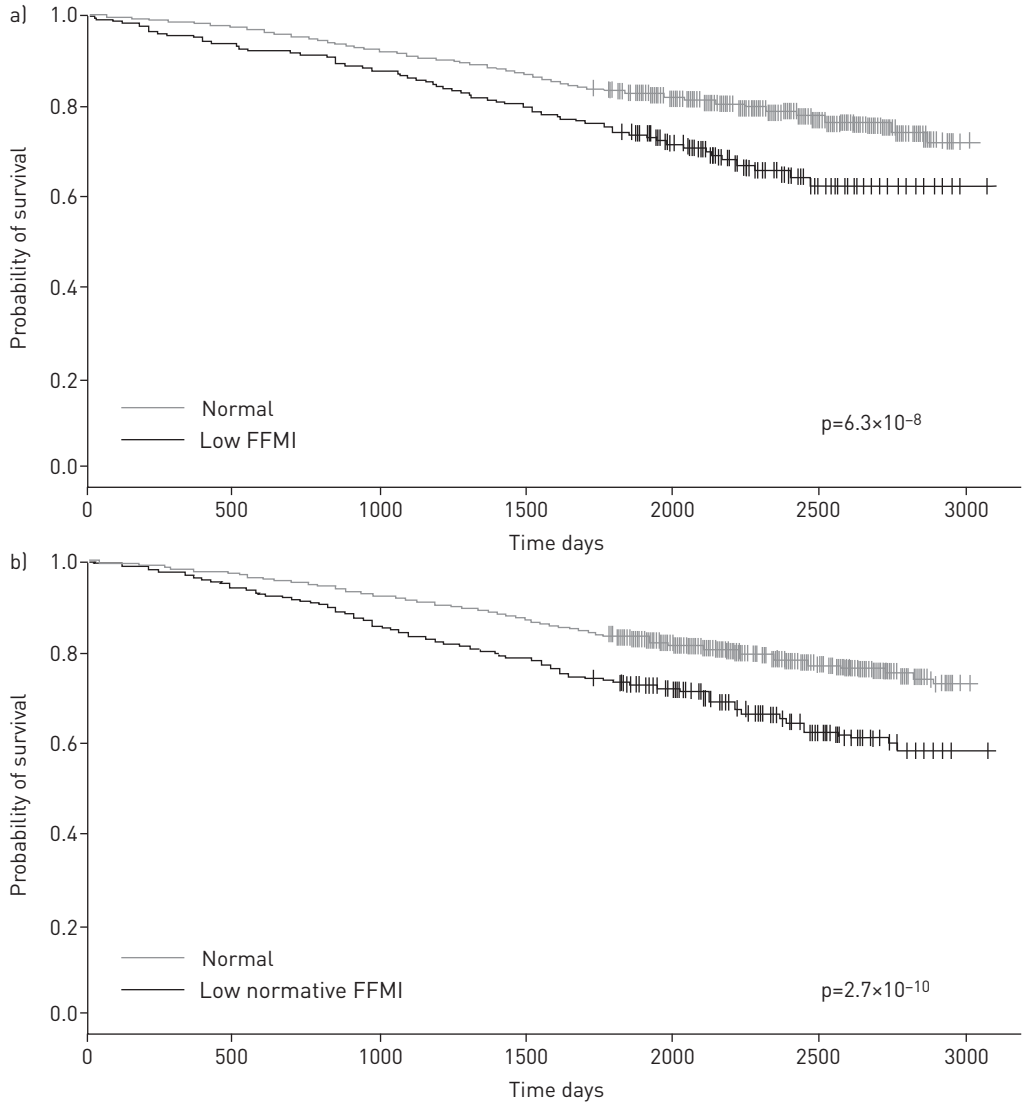

FIGURE 2 Kaplan–Meier survival stratified by low fat-free mass index (FFMI). a) Low fat-free mass index derived from pectoralis muscle area (FFMI$_{PMA}$) defined using Schols cut-points of FFMI$_{PMA}$ <16 kg·m^{-2} in men and FFMI$_{PMA}$ <15 kg·m^{-2} in women [1] b) Low FFMI$_{PMA}$ defined by fifth percentile of normative FFMI$_{PMA}$ stratified by sex, age and body mass index categories in the UK Biobank cohort [13].

obstruction [32]. The prognostic utility of FFMI is well supported, as several studies have demonstrated increased morbidity and mortality among COPD cases with a low FFMI [1, 2, 33]. Thus, assessing muscle function (including mass and strength) is encouraged in clinical practice. In fact, the identification of patients with low muscle mass is useful to tailor treatments that would improve muscle function, including exercise training, nutrition and hormone therapy [34]. Although our analysis does not allow us to have insight into the mechanisms that link low muscle mass to all-cause mortality, prior data in patients with COPD suggest that one of the potential mechanisms is systemic inflammation. COPD subjects with elevated levels of plasma fibrinogen, a blood biomarker for systemic inflammation, had low FFM [2], and a higher risk of death, compared to those with low fibrinogen levels [35]. Another possibility is that low muscle mass may reflect decreased physical activity, which in turn, is associated with increased all-cause mortality [36].

It is interesting that when the Schols criteria were used to classify low FFMI$_{PMA}$ in COPD cases, we observed no overweight COPD case in COPDGene with low FFMI$_{PMA}$. Other studies in COPD cases have also observed few COPD cases with low FFMI in overweight and obese cases using a similar cut-point [37, 38]. The converse is observed in populations with a lower BMI than that in the United States, such as in Asia, where a higher number of cases would have a low FFMI, based on the Schols cut-point; lower cut-points are recommended to define low muscle mass to diagnose sarcopenia [39]. As populations

TABLE 5 Relationship between risk of death from any cause and low FFMI in COPD cases from COPDGene

	HR (95% CI)	p-value
Model I		
Low $FFMI_{PMA}$	1.6 (1.2–1.9)	<0.001
Sex (ref.: male)	0.82 (0.69–0.97)	0.017
Age (ref.: 45–55 years)		
55–65 years	1.1 (0.88–1.5)	0.31
65–55 years	1.6 (1.3–2.1)	<0.001
>75 years	2.9 (2.2–3.9)	<0.001
Race (ref.: NHW)	1.2 (0.98–1.5)	0.08
log 10 (ATS pack-years smoking)	1.8 (1.3–2.6)	0.001
Final GOLD (ref.: GOLD 2)		
3	1.8 (1.5–2.2)	<0.001
4	4.8 (4.0–5.8)	<0.001
Self-reported comorbidities		
1–2	1.1 (0.9–1.3)	0.31
3 or more	1.5 (1.2–1.8)	<0.001
Model II		
Low normative $FFMI_{PMA}$	1.5 (1.2–1.8)	<0.001
Sex (ref.: male)	0.94 (0.81–1.1)	0.46
Age (ref.: 45–55 years)		
55–65 years	1.1 (0.88–1.5)	0.32
65–55 years	1.7 (1.3–2.2)	<0.001
>75 years	3.0 (2.2–4.0)	<0.001
Race (ref.: NHW)	1.2 (1.0–1.5)	0.049
log 10 (ATS pack-years smoking)	1.8 (1.3–2.6)	<0.001
Final GOLD (ref.: GOLD 2)		
3	1.8 (1.5–2.1)	<0.001
4	4.9 (4.1–5.9)	<0.001
Self-reported comorbidities		
1–2	1.1 (0.91–1.3)	0.39
3 or more	1.4 (1.2–1.8)	0.001

FFMI: fat-free mass index; COPD: chronic obstructive pulmonary disease; $FFMI_{PMA}$: fat-free mass index derived from pectoralis muscle area; NHW: Non-Hispanic White; ATS: American Thoracic Society; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

become more admixed, it will become more difficult to apply information on race groups to characterise individuals. Cut-points defined by using information such as BMI, age and gender, irrespective of race group are more relevant. Furthermore, obesity is a risk factor for COPD, and the prevalence of obesity continues to rise [40]. As current cut-points for low FFMI indicate decreased survival for those with a low FFMI, under-diagnosing low FFMI in an ever-increasing population of overweight and obese COPD cases is problematic. Cut-points for low FFMI that give consideration to BMI, age and gender will have greater utility over the long-term.

There are several limitations associated with the current investigation, which must be addressed. We used total body FFM from BIA to generate the equation to derive total body FFM from PMA. The gold standard research method to measure FFM in research is DXA, as BIA has been shown to underestimate FFM, and is sensitive to the patient's hydration status [41]. In our analysis, we employed a formula to convert BIA-derived total body FFM to a value that accounts for the underestimation of FFM from BIA in COPD cases [28]. We have not presented a method to derive FFM from DXA, but one to derive FFM from BIA, using PMA from chest CT. BIA is a validated technique to monitor FFM. For example, the European Society of Clinical Nutrition and Metabolism (ESPEN) [42], the European Respiratory Society [43] and the international consensus paper on cancer cachexia [44] all list BIA as a method by which FFMI can be monitored, an essential component to assess malnutrition, cachexia, sarcopenia and frailty. However, additional research focused on generating a formula to derive FFM, measured *via* DXA from PMA may refine the equation we present in the current study. Furthermore, we used PMA from chest CT and FFM from BIA at the baseline visit in ECLIPSE to generate the prediction formula, and not all participants had chest CT and BIA measured on the same day. To address this limitation, we restricted our analyses to include COPD cases from ECLIPSE, with chest CT and BIA within 60 days. In addition, for the Cox

regression analyses, self-reported comorbidities were used in our study and are subject to recall bias. Nonetheless, COPD cases with a low FFMI$_{PMA}$ had a similar increased risk of death survival (HR$_{Schols\ cut\text{-}point}$: 1.6, 95% CI 1.2–1.8) to other COPD cases in other studies that examined the relationship between low FFMI and all-cause mortality. For example, in a cohort of 1898 COPD cases, VESTBO *et al.* [2] reported an increased risk of death (HR 1.5, 95% CI 1.2–1.8) associated with a low FFMI.

Thus, we report a formula that can be used to establish an estimate of total body FFM in COPD cases, using information from chest CT, and assist in the characterisation of COPD patient prognosis. This formula can be used in COPD cases with chest CT, in order to expand research on muscle wasting, a marker of increased risk of all-cause mortality among COPD cases that requires further study. In summary, we have demonstrated that subjects with COPD and a low FFMI, derived from an easy-to-acquire PMA measurement on CT, have an increased risk of death.

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References

1 Schols AM, Broekhuizen R, Weling-Scheepers CA, *et al.* Body composition and mortality in chronic obstructive pulmonary disease. *Am J Clin Nutr* 2005; 82: 53–59.
2 Vestbo J, Prescott E, Almdal T, *et al.* Body mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: findings from the Copenhagen City Heart Study. *Am J Respir Crit Care Med* 2006; 173: 79–83.
3 Sanders KJC, Kneppers AEM, van de Bool C, *et al.* Cachexia in chronic obstructive pulmonary disease: new insights and therapeutic perspective. *J Cachexia Sarcopenia Muscle* 2016; 7: 5–22.
4 Prado CMM, Heymsfield SB. Lean tissue imaging: a new era for nutritional assessment and intervention. *JPEN J Parenter Enteral Nutr* 2014; 38: 940–953.
5 Steiner MC, Barton RL, Singh SJ, *et al.* Bedside methods *versus* dual energy X-ray absorptiometry for body composition measurement in COPD. *Eur Respir J* 2002; 19: 626–631.
6 Cooper C, Fielding R, Visser M, *et al.* Tools in the assessment of sarcopenia. *Calcif Tissue Int* 2013; 93: 201–210.
7 Fields DA, Goran MI, McCrory MA. Body-composition assessment via air-displacement plethysmography in adults and children: a review. *Am J Clin Nutr* 2002; 75: 453–467.
8 Ellegård LH, Ahlén M, Körner U, *et al.* Bioelectric impedance spectroscopy underestimates fat-free mass compared to dual energy X-ray absorptiometry in incurable cancer patients. *Eur J Clin Nutr* 2009; 63: 794–801.
9 Thibault R, Genton L, Pichard C. Body composition: why, when and for who? *Clin Nutr* 2012; 31: 435–447.
10 Evans WJ, Morley JE, Argilés J, *et al.* Cachexia: a new definition. *Clin Nutr* 2008; 27: 793–799.
11 Cruz-Jentoft AJ, Baeyens JP, Bauer JM, *et al.* Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010; 39: 412–423.
12 Kyle UG, Genton L, Hans D, *et al.* Age-related differences in fat-free mass, skeletal muscle, body cell mass and fat mass between 18 and 94 years. *Eur J Clin Nutr* 2001; 55: 663–672.
13 Franssen FME, Rutten EPA, Groenen MTJ, *et al.* New reference values for body composition by bioelectrical impedance analysis in the general population: results from the UK Biobank. *J Am Med Dir Assoc* 2014; 15: 448. e1–e6.
14 Marquis K, Debigaré R, Lacasse Y, *et al.* Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002; 166: 809–813.
15 Güerri R, Gayete A, Balcells E, *et al.* Mass of intercostal muscles associates with risk of multiple exacerbations in COPD. *Respir Med* 2010; 104: 378–388.
16 Mourtzakis M, Prado CM, Lieffers JR, *et al.* A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab* 2008; 33: 997–1006.
17 Thibault R, Pichard C. The evaluation of body composition: a useful tool for clinical practice. *Ann Nutr Metab* 2012; 60: 6–16.
18 Baracos VE, Reiman T, Mourtzakis M, *et al.* Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. *Am J Clin Nutr* 2010; 91: 1133S–1137S.
19 McDonald ML, Diaz AA, Ross JC, *et al.* Quantitative computed tomography measures of pectoralis muscle area and disease severity in chronic obstructive pulmonary disease. A cross-sectional study. *Ann Am Thorac Soc* 2014; 11: 326–334.
20 Diaz AA, Zhou L, Young TP, *et al.* Chest CT measures of muscle and adipose tissue in COPD: gender-based differences in content and in relationships with blood biomarkers. *Acad Radiol* 2014; 21: 1255–1261.

21 Kinsey CM, San José Estépar R, van der Velden J, *et al.* Lower pectoralis muscle area is associated with a worse overall survival in non-small cell lung cancer. *Cancer Epidemiol Biomarkers Prev* 2017; 26: 38–43.
22 Go S-I, Park MJ, Song H-N, *et al.* Prognostic impact of sarcopenia in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Cachexia Sarcopenia Muscle* 2016; 7: 567–576.
23 Wiener RS, Gould MK, Arenberg DA, *et al.* An official American Thoracic Society/American College of Chest Physicians policy statement: implementation of low-dose computed tomography lung cancer screening programs in clinical practice. *Am J Respir Crit Care Med* 2015; 192: 881–891.
24 Moyer VA, U.S. Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2014; 160: 330–338.
25 Vestbo J, Anderson W, Coxson HO, *et al.* Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). *Eur Respir J* 2008; 31: 869–873.
26 Regan EA, Hokanson JE, Murphy JR, *et al.* Genetic epidemiology of COPD (COPDGene) study design. *COPD* 2010; 7: 32–43.
27 Rabe KF, Hurd S, Anzueto A, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007; 176: 532–555.
28 Rutten EPA, Spruit MA, Wouters EFM. Critical view on diagnosing muscle wasting by single-frequency bio-electrical impedance in COPD. *Respir Med* 2010; 104: 91–98.
29 Diaz AA, Zhou L, Young TP, *et al.* Chest CT Measures of muscle and adipose tissue in COPD: gender-based differences in content and in relationships with blood biomarkers. *Acad Radiol* 2014; 21: 1255–1261.
30 Engelen MPKJ, Schols AMWJ, Does JD, *et al.* Skeletal muscle weakness is associated with wasting of extremity fat-free mass but not with airflow obstruction in patients with chronic obstructive pulmonary disease. *Am J Clin Nutr* 2000; 71: 733–738.
31 Engelen MP, Schols AM, Lamers RJ, *et al.* Different patterns of chronic tissue wasting among patients with chronic obstructive pulmonary disease. *Clin Nutr* 1999; 18: 275–280.
32 Vestbo J, Hurd SS, Agustí AG, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2013; 187: 347–365.
33 Mostert R, Goris A, Weling-Scheepers C, *et al.* Tissue depletion and health related quality of life in patients with chronic obstructive pulmonary disease. *Respir Med* 2000; 94: 859–867.
34 Maltais F, Decramer M, Casaburi R, *et al.* An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2014; 189: 15–62.
35 Miller BE, Tal-Singer R, Rennard SI, *et al.* Plasma fibrinogen qualification as a drug development tool in chronic obstructive pulmonary disease. Perspective of the chronic obstructive pulmonary disease biomarker qualification consortium. *Am J Respir Crit Care Med* 2016; 193: 607–613.
36 Vaes AW, Garcia-Aymerich J, Marott JL, *et al.* Changes in physical activity and all-cause mortality in COPD. *Eur Respir J* 2014; 44: 1199–1209.
37 Vanfleteren LEGW, Spruit MA, Groenen M, *et al.* Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; 187: 728–735.
38 Breyer MK, Spruit MA, Celis APM, *et al.* Highly elevated C-reactive protein levels in obese patients with COPD: a fat chance? *Clin Nutr* 2009; 28: 642–647.
39 Chen LK, Liu LK, Woo J, *et al.* Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. *J Am Med Dir Assoc* 2014; 15: 95–101.
40 Hanson C, Rutten EP, Wouters EFM, *et al.* Influence of diet and obesity on COPD development and outcomes. *Int J COPD* 2014; 9: 723–733.
41 Buchholz AC, Bartok C, Schoeller DA. The validity of bioelectrical impedance models in clinical populations. *Nutr Clin Pract* 2004; 19: 433–446.
42 Cederholm T, Barazzoni R, Austin P, *et al.* ESPEN guidelines on definitions and terminology of clinical nutrition. *Clin Nutr* 2017; 36: 49–64.
43 Schols AM, Ferreira IM, Franssen FM, *et al.* Nutritional assessment and therapy in COPD: a European Respiratory Society statement. *Eur Respir J* 2014; 44: 1504–1520.
44 Fearon K, Strasser F, Anker SD, *et al.* Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011; 12: 489–495.