Chest CT 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 current study, we aimed to derive FFM_{PMA} from the pectoralis muscle area (PMA) and assess whether low $FFMI_{PMA}$ is associated with all-cause mortality in COPD cases. To achieve our objectives, 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 FFM_{PMA} measured using bioelectrical impedance from PMA. Then in COPDGene, we applied the equation in COPD cases (n=3121) and assessed survival. Low $FFMI_{PMA}$ was defined using the Schols classification (FFMI<16 in men, FFMI<15 in women) and the 5th 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 FFM as the outcome. In the test group, the correlation between FFM_{PMA} with FFM remained

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high (Pearson correlation=0.97). In COPDGene, COPD cases with low $FFMI_{PMA}$ had increased risk of death (HR:1.6, P<0.001).

We demonstrated COPD cases with low $FFMI_{PMA}$ have increased risk of death.

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]. The FFMI, obtained by dividing fat-free mass (FFM) by height square (units: kg/m^2), is an indirect marker of muscle that includes skeletal and non-skeletal muscle mass, organs, connective tissue and bone[4]. It is not, however, measured during routine care or typically in large epidemiological cohorts investigating COPD. FFM can be measured using indirect techniques such as air displacement plethysmography (ADP), bioelectrical impedance (BIA), skin-fold anthropometry (SFA), 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]. BIA and SFA are convenient but criticized for underestimating or overestimating FFM, respectively, in comparison with the current research standard DXA[5, 8]. DXA is a more expensive method using specialized equipment involving radiation exposure and necessitating 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/m^2 in male or 15 kg/m^2 in female COPD cases 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 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 intercostal muscles and mid-thigh area, has been used to assess low muscle mass and to predict adverse clinical outcomes[14, 15]. In patients with cancer, axial CT from the third lumbar vertebra (L3) region of the spine has been used to calculate FFMI[16–18]. We previously demonstrated pectoralis muscle area (PMA) is a reproducible measure of muscle mass that can be easily obtained from chest CT scans[19, 20]. Further, low PMA has been associated with 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 the 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 FFM measured 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 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 with FFM_{PMA}) to assess survival due to the established cut-points for defining low FFMI [1, 10].

Materials and Methods

Access to data was obtained and analyses performed after obtaining approval from the Institutional Review Boards at all participating centers in ECLIPSE and COPDGene, including Brigham and Women's Hospital and University of Alabama at Birmingham. The ECLIPSE and COPDGene studies have been described in detail elsewhere [25, 26]. Briefly, ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) 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 centers across 12 countries(11). The COPDGene Study (NCT00608764, www.copdgene.org) enrolled ever smokers with and without COPD (Non-Hispanic Whites and African Americans), aged 45-80 with at least 10 pack-years of lifetime smoking history from 21 U.S. centers(14).

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 FEV1/FVC less than 0.7 and FEV_1 less than 80% predicted [27]. In ECLIPSE, the 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 using data from 1087 COPD cases by Rutten et al 2010[28]:

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

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 described previously [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 an 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 2 steps. All segmentations were visually inspected by pulmonologists with experience in lung imaging (AD, GW). Segmentation failures were identified (e.g. malposition of the arm, 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 exclusion made if supported by scan re-inspection. One COPD case in ECLIPSE 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 was further restricted to

COPD cases who had a chest CT within 60 days of FFM measured 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 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 program R. The ECLIPSE sample was randomly split into training and test groups each comprised of 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. T-tests and chi-square tests were used to test for differences in general characteristics between the training and test groups prior to model building. In the training group, manual stepwise multiple regression analysis was performed with FFM as the dependent variable considering weight, sex and height 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 Akaike Information Criterion (AIC). In the test group, the Pearson correlation coefficient was used to assess the agreement between FFM from BIA with 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 meters. $FFMI_{PMA}$ is used to differentiate FFMI derived from PMA on chest CT from FFMI measured using BIA throughout the manuscript.

Survival modeling 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 categorical variables sex, race, GOLD grade, number of comorbidities as well as the continuous measures of age and smoking duration (ATS pack-years). All covariates were collected at baseline. Race was based on self-report and GOLD grade by spirometry. Comorbidities were assessed by 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 characterizes male COPD cases with $FFMI_{PMA} <16$ and female COPD cases with $FFMI_{PMA} <15$ as having low $FFMI_{PMA}$[1]. UK Biobank normative values were used to classify low $FFMI_{PMA}$ when $FFMI_{PMA}$ was less than 5th percentile normative values for the appropriate age, sex and BMI categories in healthy individuals from the UK Biobank[13].

Results

To derive total body FFM from PMA, COPD cases from ECLIPSE were randomized into two equal sized test and training groups. The test and training groups did not differ significantly based on age, sex, weight, height, current smoking 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 depicted in equation 1:

$$FFM_{PMA} = -15.9 + 0.09 \times PMA(cm2) + 0.35 \times weight(kg) + 0.20 \times height(cm) + 7.47(if\ male) \quad [1]$$

This equation included PMA, weight, sex and height and had an adjusted R^2 correlation of 0.92 with 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% Confidence Interval (CI): 0.969-0.976, P<2.2×10^{-16}) (Figure 1a). The correlation between FFM and FFM_{PMA} was 0.935 (95% CI: 0.922-0.945, P<2.2×10^{-16}) and 0.967 (95% CI: 0.958-0.974, P<2.2×10^{-16}) between male and female COPD cases in the ECLIPSE test group, respectively (Supplementary Figure 2). The Bland-Altman plots (Figure 1b and Supplementary Figure 2) 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 corresponding to −0.5% of FFM. The limits of agreement related to the mean difference between FFM_{PMA} and FFM were ± 4.7 kg.

Low FFMI in overweight and obese COPD cases

We next used equation (1) to calculate FFM_{PMA} in COPDGene. We divided FFM_{PMA} by height squared to generate the index ($FFMI_{PMA}$) in order to classify cases who have low $FFMI_{PMA}$. In Table 3 we noted no COPD case with BMI greater than 25 was classified as having low $FFMI_{PMA}$ using the Schols classification criteria[1]. When we used the UK Biobank normative values based on the 5th percentile values from age, sex and BMI stratified groups reported by Franssen et al[13], 11% of COPD cases who were overweight and 4.2% of COPD cases who were obese had low FFM_{PMA}. Further, using the UK Biobank normative values, significantly fewer COPD cases with low BMI had low $FFMI_{PMA}$ (Table 3: 92% versus 19.3%).

Relationship between FFMI derived from chest CT and survival in COPDGene

Next, we aimed to examine the survival experience stratified by low $FFMI_{PMA}$. We began by exploring anthropometric and lung function characteristics between COPD cases in ECLIPSE and COPDGene. Overall, COPD cases from COPDGene had more females, African Americans and current smokers, weighed more, had higher FEV_1 percent predicted, a lower FEV_1/FVC and had less emphysema than COPD cases found in ECLIPSE (Table 4).

The median $FFMI_{PMA}$ derived from CT in COPDGene was slightly higher (median: 18.4 kg/m^2, range: 11.1 – 29.5) than COPD cases in ECLIPSE (median 18.0 kg/m^2, range: 11.5 – 28.1). Initially, 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 low $FFMI_{PMA}$ were more likely to die than those whose $FFMI_{PMA}$ was above this threshold (Figure 2a). We further examined the relationship between all-cause mortality and low $FFMI_{PMA}$ in COPD cases using Cox

regression modeling 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 have 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 research has highlighted the need for further research defining thresholds for low FFMI in overweight and obese COPD cases but we believe that our methods will permit additional investigation of FFMI in COPD populations who may only have a thoracic CT scan available for monitoring body composition.

In the current 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 and models which include sex, height and weight. Improvement in model performance with the inclusion of such anthropomorphics 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 may indicate muscle wasting in COPD is more uniformly distributed than previously determined or that our benchmark BIA is insensitive to these regional differences.

In this study, we demonstrated decreased survival associated with low $FFMI_{PMA}$ derived from PMA measured on CT when adjusting for lung function categorized 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 degree of airflow obstruction[32]. The prognostic utility of FFMI is well-supported, as several studies have demonstrated increased morbidity and mortality among COPD cases with 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 to improve muscle function including exercise training, nutrition, and hormone therapy[34]. Although our analysis does not allow us to have insight into the mechanisms linking low muscle mass and all-cause mortality, prior data in patients with COPD suggested that one of potential mechanisms is systemic inflammation. COPD subjects with elevated levels of plasma fibrinogen -a blood biomarker for systemic inflammation- had low FFM[2], and higher risk of death compared to those with low fibrinogen levels[35]. Another possibility is that low muscle mass might 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 this cut-point[37, 38]. The converse is observed in populations with lower BMI than in the United States, such as in Asia, where a higher number of cases would have low FFMI based on the Schols cut-point and lower cut-points are recommended to define low muscle mass to diagnose sarcopenia[39]. As populations become more admixed, information on race group will become harder to use to characterize individuals. Cut-points defined using information such as BMI, age and gender irrespective of race group are more relevant. Further, 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 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 to 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 for measuring FFM in research is DXA, as BIA has been show 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 underestimation of FFM from BIA in COPD cases[28]. We do not a present a method for deriving FFM from DXA, we present a method for deriving FFM from BIA using PMA from chest CT. BIA is a validated technique for monitoring for 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] list BIA as a method for monitoring FFMI, an essential component for assessing 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 manuscript. Further, we used PMA from chest CT and FFM from BIA at the baseline visit in ECLIPSE to generate the prediction formula and not every participant 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. Further for the cox regression analyses, self-reported comorbidities were used in our analyses and are subject to recall bias. Nonetheless, COPD cases with low $FFMI_{PMA}$ had similar increased risk of death survival ($HR_{Schols\ cut-point}$: 1.6, 95%CI: 1.2-1.8) to other COPD cases in other studies examining the relationship of low FFMI and all-cause mortality. For example, in a cohort of 1898 COPD cases, Vestbo et al. reported an increased risk of death (HR: 1.5, 95%CI: 1.2-1.8) associated with low FFMI[2].

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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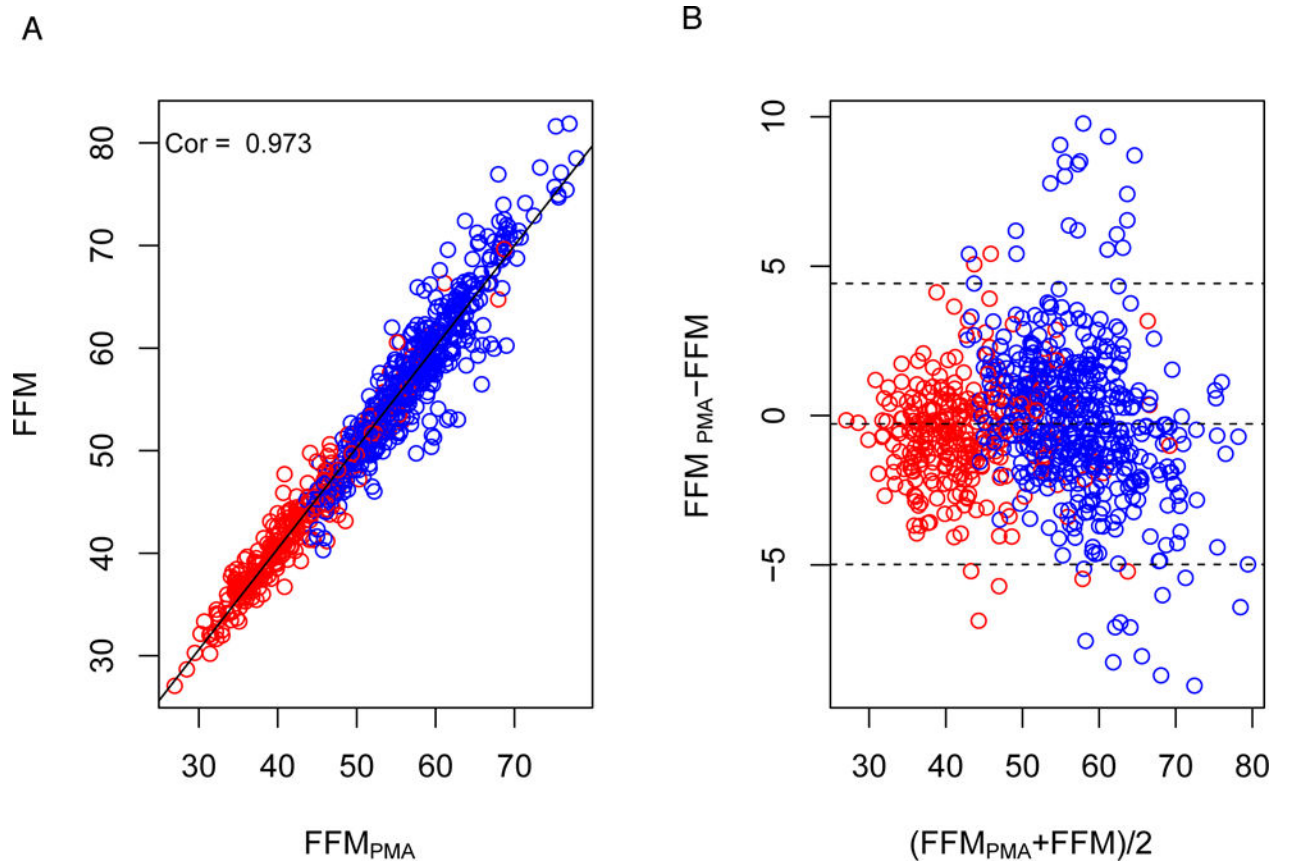
Figure 1.
A. Relationship between FFM_{PMA} and FFM in test group comprised of 783 ECLIPSE COPD cases. **B.** Bland-Altman plot comparing FFM_{PMA} and FFM in the test group. Abbreviations: FFMI – fat-free mass index, $FFMI_{PMA}$ – fat-free mass index derived from pectoralis muscle area, COPD – chronic obstructive pulmonary disease

A

B

Figure 2. Kaplan Meier Survival Stratified by Low FFMI

A. Low $FFMI_{PMA}$ defined using Schols cut-points of $FFMI_{PMA}$ <16 in men and $FFMI_{PMA}$ <15 in women[1] **B.** Low $FFMI_{PMA}$ defined by 5th percentile of normative $FFMI_{PMA}$ stratified by gender, age and BMI categories in the UK Biobank cohort[13]. Abbreviations: FFMI – fat-free mass index, $FFMI_{PMA}$ – fat-free mass index derived from pectoralis muscle area, COPD – chronic obstructive pulmonary disease
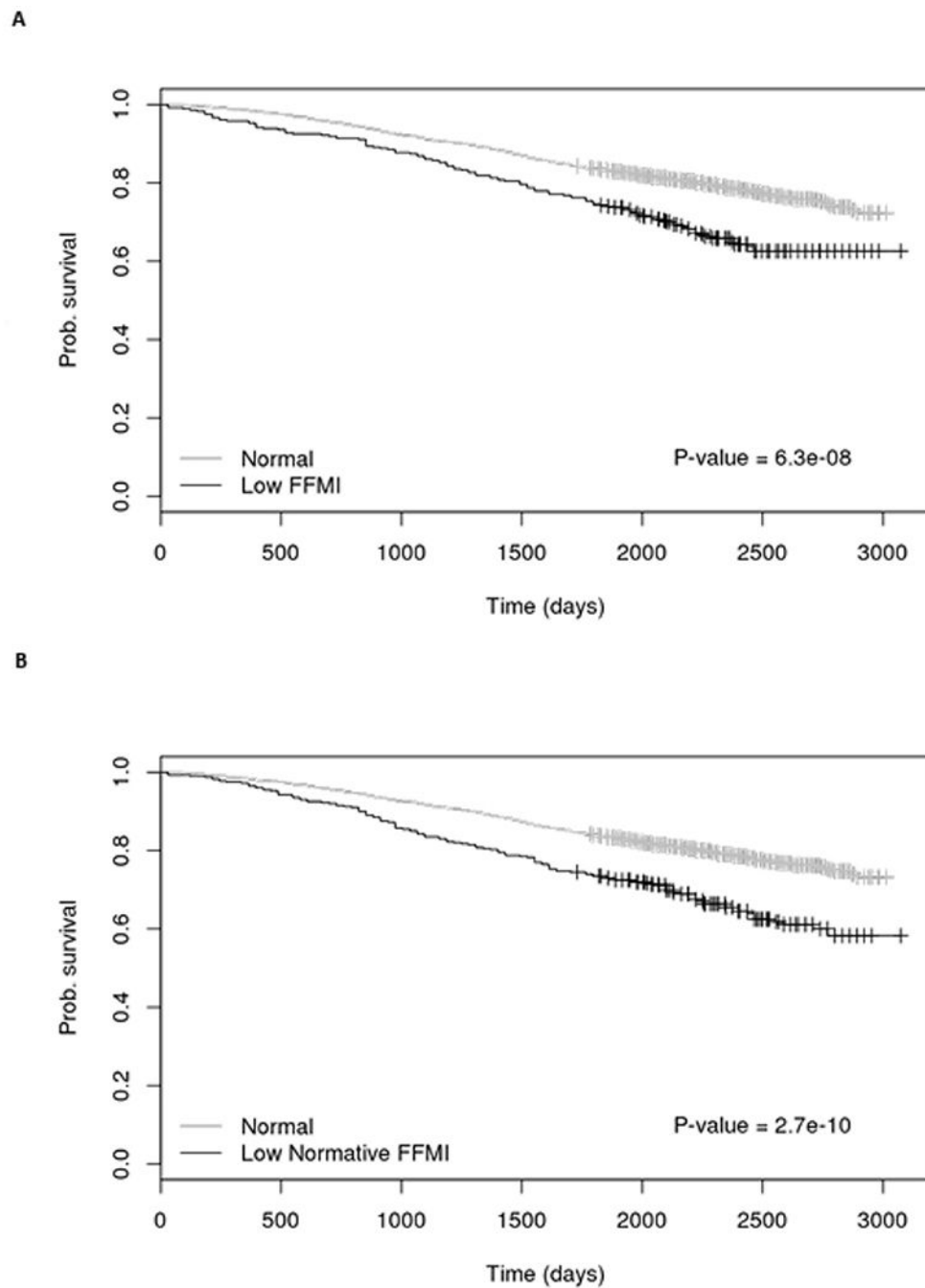
Table 1

Comparison of baseline characteristics between training and test groups of COPD cases in ECLIPSE. Unless otherwise denoted values are represented as median (interquartile range). Training and test groups did not differ significantly (P<0.05) for any characteristic listed in the table.

	Training	Test
N	759	759
Sex (% Male)	65	64
Age	64 (10)	64 (10)
Weight (kg)	75.3 (23.1)	74.2 (23)
Height (m)	1.69 (0.12)	1.69 (0.13)
BMI	26.3 (6.4)	25.8 (6.9)
Current Smoking (%)	35.8	35.4
FEV1 %	47.6 (26.1)	47.1 (22.9)
FEV1/FVC	0.57 (0.23)	0.57 (0.22)

Abbreviations: BMI – body mass index, FEV1pp – Forced Expiratory Volume in 1 second percent predicted, FEV1/FVC – Forced Expiratory Volume in 1 second / Forced Vital Capacity.

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

Abbreviation: PMA – pectoralis muscle area, FFM – fat-free mass.

Table 3

Criteria used to define low FFMI stratified by BMI category in COPD cases in COPDGene. Values denote N with percentage of BMI category in parentheses.

BMI Category	Schols Classification		UK Biobank Normative Values	
	Normal	Low FFMI$_{PMA}$	Normal	Low FFMI$_{PMA}$
<18.5	7 (8%)	81(92%)	71 (81%)	17 (19%)
18.5-25	668 (71%)	277 (29%)	720 (76%)	225 (24%)
25-30	1028 (100%)	0 (0%)	915 (89%)	113(11%)
>30	1060 (100%)	0 (0%)	1015 (96%)	45 (4%)

Abbreviations: N – number of individuals, BMI – body mass index, FFMI**PMA** – fat-free mass index derived from pectoralis muscle area, UK – United Kingdom.

Table 4

Characteristics of COPD cases from ECLIPSE and COPDGene used in the current analyses. Unless otherwise denoted values represent median with interquartile range in parentheses.

Characteristic of COPD cases		ECLIPSE	COPDGene	P
N		1518	3121	
Sex (% Male)		64.3	55.5	<0.01
Age		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 (%)	*<18.5*	4.9	2.8	
	18.5-25	36.3	30.3	<0.01
	25-30	36.6	32.9	
	>30	22.3	34	
Race (%)	*NHW*	97.5	80.3	
	AA	1.8	19.7	<0.01
	Other	<1	0	
Current Smoking (%)		35.6	39.5	0.07
FEV1pp		47.4 (24.3)	51.3 (30)	<0.01
FEV1/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

Abbreviations: BMI – body mass index, FEV1pp – Forced Expiratory Volume in 1 second percent predicted, FEV1/FVC – Forced Expiratory Volume in 1 second / Forced Vital Capacity.

Table 5

Relationship between risk of death from any cause with low FFMI in COPD cases from COPDGene.

Covariate		HR (95% CI)	P-value
Model I Low FFMI$_{PMA}$		1.6(1.2-1.9)	<0.001
Gender (ref - Male)		0.82 (0.69-0.97)	0.017
Age (ref 45-55 years)	55-65	1.1 (0.88-1.5)	0.31
	65-55	1.6 (1.3-2.1)	<0.001
	>75	2.9 (2.2-3.9)	<0.001
Race (ref NHW)		1.2 (0.98-1.5)	0.08
log10(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 Co-Morbidities	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
Gender (ref - Male)		0.94 (0.81-1.1)	0.46
Age (ref 45-55 years)	55-65	1.1 (0.88-1.5)	0.32
	65-55	1.7 (1.3-2.2)	<0.001
	>75	3.0 (2.2-4.0)	<0.001
Race (ref NHW)		1.2 (1.0-1.5)	0.049
log10(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 Co-Morbidities	1-2	1.1(0.91-1.3)	0.39
	3 or more	1.4 (1.2-1.8)	0.001

Abbreviations: FFMI$_{PMA}$- Fat-free mass index derived from pectoralis muscle area, GOLD – Global Initiative for Chronic Lung Disease, ATS – American Thoracic Society.