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Quantitative Assessment of Erector Spinae Muscles in Patients with COPD: Novel Chest CT-derived Index for Prognosis

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Abstract

Rationale: The loss of skeletal muscle mass and physical inactivity are important manifestations of chronic obstructive pulmonary disease (COPD), and both are closely related to poor prognoses in patients with COPD. Antigravity muscles are involved in maintaining normal posture and are prone to atrophy due to inactivity. The erector spinae muscle (ESM) group is one of the antigravity muscles and can be assessed via chest computed tomography (CT).

Objectives: We hypothesized that the cross-sectional area of ESM (ESM_{CSA}) in chest CT images may serve as a predictor of mortality in patients with COPD.

Methods: This study was a part of the prospective observational study undertaken at Kyoto University Hospital. ESM_{CSA} was measured in a single axial CT image at the level of the twelfth thoracic vertebrae in patients with COPD. The cross-sectional area of the pectoralis muscles (PM_{CSA}) was also measured. And then we evaluated the relationship between ESM_{CSA} and clinical parameters in patients with COPD including mortality. Age- and height-matched smoking control subjects were also evaluated.

Measurements and Main Results: In total, 130 male patients and twenty smoking control males were enrolled in this study. ESM_{CSA} was significantly lower in patients with COPD than in the smoking control subjects and was significantly correlated with disease severity. There was

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a significant but only moderate correlation between ESM_{CSA} and PM_{CSA}. ESM_{CSA} was significantly correlated with previously reported prognostic factors, such as body mass index (BMI), dyspnea (mMRC), $\%FEV_1$, inspiratory-to-total lung capacity ratio (IC/TLC), and emphysema severity (LAA%). Compared to PM_{CSA}, ESM_{CSA} was more strongly associated with mortality in patients with COPD. Among these known prognostic factors, the stepwise multivariate Cox proportional hazards analysis revealed that ESM_{CSA} was the strongest risk factor for mortality (Hazard Ratio (HR), 0.85; 95% confidence interval (CI), 0.79-0.92; $p<0.001$) and mMRC was an additional factor (HR, 2.35; 95% CI, 1.51-3.65; $p<0.001$).

Conclusions: ESM_{CSA} assessed via chest CT may be a valuable clinical parameter, as ESA_{CSA} correlates significantly with physiological parameters, symptoms and disease prognosis.

Abstract Word Count: 327

Chronic obstructive pulmonary disease (COPD) is a leading cause of death worldwide and is characterized by progressive airflow limitations and systemic inflammation (1). Weight loss is a common systemic manifestation of the disease and is considered a strong predictor of mortality in patients with COPD (2). However, skeletal muscle mass has attracted increasing amounts of attention because it reflects COPD severity more accurately than body mass index does (3) and because the loss of skeletal muscles is an excellent predictor of mortality (4). Loss of skeletal muscle mass may not be accompanied by a similar degree of adipose tissue loss (5). Therefore, the assessment of skeletal muscle mass is an important clinical assessments in patients with COPD.

Bioelectrical impedance analysis, dual-energy X-ray absorptiometry (DEXA), magnetic resonance imaging (MRI), and B-mode ultrasound are widely used to quantify both total and local skeletal muscle mass (5-8). The cross-sectional area (CSA) of skeletal muscles on single axial computed tomography (CT) imaging is also an alternative method for assessing local skeletal muscle mass (9-11). In these previous studies, several local muscles, such as the pectoralis muscles, intercostal muscles, abdominal muscles, or mid-thigh leg muscles were evaluated using CT images, with or without additional scans. However, it is possible that the loss of skeletal muscle mass occurs heterogeneously because of these specific roles and physiological activity in diseased patients.

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Antigravity muscles, or the muscles involved in maintaining normal posture via the opposition of gravity, reflect physical activity more than other muscle groups (8). In this study, we focused on the erector spinae muscles (ESMs), one of the major antigravity muscle groups that may be assessed via chest CT. Because chest CT is usually performed to diagnose and evaluate emphysema and to evaluate / exclude other critical pulmonary diseases, such as lung cancer and pulmonary fibrosis, these images may simultaneously be used to evaluate local skeletal muscle mass without requiring additional radiation exposure.

We hypothesized that the CSA of the ESMs (ESM_{CSA}) may serve as a predictor of mortality in patients with COPD.

Methods

Patients and Study Design

This study was a part of our prospective observational study and was performed at Kyoto University (12, 13). Male outpatients with stable COPD were enrolled in the study between March 2006 and April 2009. The entry criteria were the following: 1) a smoking history of twenty pack-years or more, 2) a diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (14), 3) a previous chest CT scan, and 4) no

COPD exacerbations within the past four weeks. The exclusion criteria were as follows: 1) alpha-1 anti-trypsin deficiency; 2) a combination of other respiratory diseases, such as bronchial asthma, interstitial pneumonia, or bronchiectasis; 3) a history of malignant neoplasms other than prostate cancer or endoscopically resected early cancer within the past five years; 4) abnormal shadows on chest CT scans, such as fibrosis; 5) a prior history of lobectomy; and 6) thoracic or upper lumber vertebrae degenerative disease or history of operation on the vertebrae.

The patients underwent both pulmonary function testing and chest CT scans (12, 13). Information regarding dyspnea severity (the modified British Medical Research Council scale (mMRC)), health-related quality of life (St. George's Respiratory Questionnaire (SGRQ)), and comorbidities was obtained via patient interviews in the outpatient clinic. Exacerbations (date and severity) were evaluated using patient diary entries. Comorbidity indices (Charlson index, COTE index) were calculated as reported (15, 16). Hospital records were examined to determine both the dates and causes of any deaths. When contact with a particular patient was lost, we attempted to contact them, their families, or the hospitals to which they were transferred via telephone or letter. All of the data at the entry point were reviewed and fixed retrospectively on January 2015 when the patients' survival statuses were fixed.

Age- and height-matched smoking male subjects were also enrolled as controls and

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evaluated via anthropometry, spirometry, and chest CT. The ethics committee of Kyoto University approved this study (approval No. E182), and all subjects provided written informed consent prior to participating.

Pulmonary Function Testing

Following the inhalation of bronchodilators (400 μg of salbutamol and 80 μg of ipratropium), pulmonary function testing and a chest CT scan were performed. Spirometry, lung volume subdivisions, and diffusion capacity (DL_{CO}) were measured using a Chestac-65V instrument (Chest MI, Inc., Tokyo, Japan). The predicted pulmonary function values were calculated based on the Japanese Respiratory Society guidelines (17).

CT Acquisition and Analysis

Chest CT scans (Aquilion 64; Toshiba, Tokyo, Japan) were obtained with the use of 0.5-mm collimation, a scan time of 500 milliseconds, 120 kilovolts peak (kVp), and auto exposure control. Routine calibration of the CT scanner was performed using air and water phantoms.

For the quantitative analysis of pulmonary emphysema, whole-lung CT images with 0.5-mm thicknesses were obtained using reconstruction kernel FC56. Using in-house software, the percentage of low attenuation area (LAA%) was calculated using a cut-off value of -960

Hounsfield Units (HUs), as described previously (12, 13). For the quantitative analysis of the ESMs, chest CT images reconstructed using the mediastinal setting (reconstruction kernel FC13) were utilized. Using a modified method described in a previous manuscript (18), the analysis was performed on a single axial chest CT image at the level of the lower margin of the 12th thoracic vertebrae using SINAPSE VINCENT (FUJIFILM Medical Co., Ltd., Tokyo, Japan). The details regarding the ESM_{CSA} measurement are described in the online supplement. Briefly, the left and right ESMs were subsequently identified and manually shaded (Figure 1A), the CSAs of both ESMs were calculated, and the ESM_{CSA} was presented as the sum of the right and left muscles. The CSA of the pectoralis muscles (PM_{CSA}) was also determined as described previously (Figure 1B) (9).

Statistical Analysis

The data pertaining to the continuous variables are expressed as the mean ± standard deviation (SD) unless otherwise specified. All statistical analyses were performed using SPSS software, version 18 (IBM Japan, Tokyo, Japan). A bivariate correlation analysis was performed between ESM_{CSA} and clinical parameters such as anthropometry, pulmonary function, and emphysema severity. An analysis of variance (ANOVA) and a post-hoc Tukey-Kramer test were performed to compare ESM_{CSA} values between groups. The relation of ESM_{CSA} categories and

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all-cause mortality was analyzed by Kaplan-Meier survival curves and log-rank tests. In these analyses, the determined cut-off values were based on the distribution of measurements obtained from smoking controls for categorization, such as the mean, mean-1SD, and mean-2SD.

Both univariate and multivariate Cox proportional hazards analyses were performed to investigate the relationship between the clinical parameters and mortality. A stepwise multivariate Cox proportional hazard analysis was performed to identify the parameter that correlated most significantly with mortality. The results of the Cox proportional hazard analysis are depicted as hazard ratios with 95% confidence intervals (CIs). P-values less than 0.05 were considered statistically significant.

Results

Patient Characteristics

The characteristics of the study subjects are provided in Table 1. In total, 154 patients with COPD were enrolled in this study. Twenty-four patients were excluded (four patients had interstitial pneumonia, 2 had asthma, 1 had bronchiectasis, 11 had abnormal shadows on chest CT scans, 5 had a history of malignancy within the past 5 years, and 1 underwent

lobectomy due to lung cancer); finally, 130 male patients were studied. The numbers of study subjects within each GOLD stage were as follows: stage I, 23 patients (17.7%); stage II, 61 patients (46.9%); stage III, 34 patients (26.2%); and stage IV, 12 patients (9.2%). Comorbidities are included in the online data supplement (Table E1). The characteristics of the twenty smoking control subjects are included in the online data supplement (Table E2). The weights of the patients with COPD were significantly lower than those of the smoking control subjects ($p<0.0001$).

Distribution of ESM_{CSA}

The ESM_{CSA} of the patients with COPD was significantly lower than that of the smoking control subjects (smoking controls vs. COPD patients; 39.20±6.98 vs. 29.77±6.97, $p<0.0001$). Among the patients with COPD, ESM_{CSA} was significantly decreased and correlated with disease severity (Figure 2). Even among the patients with GOLD stage I, ESM_{CSA} was significantly lower than the control subjects (31.3±7.2 vs. 39.2±7.0, $p<0.01$). The distribution of PM_{CSA} was similar to the distribution of the ESM_{CSA} (Figure E1 in the online data supplement).

Bivariate Correlation Analysis Comparing ESM_{CSA} and Clinical Parameters

The ESM_{CSA} of the patients with COPD correlated significantly with age ($r=-0.36$, $p<0.0001$),

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BMI (r=0.44, p<0.0001), mMRC (r=-0.36, p<0.0001), the Charlson comorbidity index (r=-0.21, p=0.02), and pulmonary function indices such as %FEV_1 (r=0.31, =0.0004), IC/TLC (r=029, p=0.0009), DL_{CO} (r=0.42, p=0.0002), and LAA% (r=-0.32, p=0.0002; Table 2). ESM_{CSA} also correlated significantly but not strongly with PM_{CSA} (r=0.49, p<0.0001; also see Figure E2 in the online data supplement). PM_{CSA} also correlated significantly with similar clinical parameters to ESM_{CSA} (Table E3 in the online data supplement).

Prognostic Survey

The median follow-up time as of January 2015 was 2541.5 days (range, 391-3136 days). Twenty-four of the 130 COPD patients died during the follow-up period. The causes of death were as follows: respiratory failure (n=7, 29.2%), lung cancer (n=3, 12.5%), malignancy other than lung cancer (n=3, 12.5%), sudden death (n=5, 20.8%), cardiovascular disease (n=3, 12.5%), and an unknown cause (n=3, 12.5%).

Kaplan-Meier survival curves based on the ESM_{CSA} subgroups using cut-off values based on the distributions of the smoking control subjects (with mean, mean-1SD, and mean-2SD values of 39, 35, 32 cm^2, respectively) are shown in Figure 3. The COPD patients with lower ESM_{CSA} values exhibited significantly worse survival (p<0.0001 by the log-rank test). The patients' characteristics based on the cut-off value of the ESM_{CSA} are included in the online

data supplement (Table E4).

Cox Proportional Hazards Analyses

The relationship between all-cause mortality and clinical parameters, including ESM_{CSA} was analyzed via a univariate Cox proportional hazards analysis. Older age (p=0.03), lower BMI (p=0.003), higher mMRC (p<0.0001), lower $\%FEV_1$ (p=0.007), lower IC/TLC (p<0.0001), lower DL_{CO} (p<0.0001), higher LAA% (p=0.0004), lower PM_{CSA} (p=0.0004), and lower ESM_{CSA} (p<0.0001) significantly correlated with all-cause mortality (Table 3). The comorbidity indices (Charlson index and COTE index) did not correlate with all-cause mortality.

Multivariate Cox proportional hazard analyses were performed to compare the contribution of these indices (Table 4). Four different models were analyzed. In model 1, we included established parameters, such as dyspnea (mMRC), pulmonary functions ($\%FEV_1$, IC/TLC, DL_{CO}), with ESM_{CSA} as explanatory variables. We included PM_{CSA} instead of ESM_{CSA} in model 2. We included BMI instead of ESM_{CSA} or PM_{CSA} in model 3 because BMI is a classically reported surrogate marker of COPD mortality. In addition, we included LAA% instead of ESM_{CSA}, PM_{CSA} or BMI in model 4 because we previously reported that LAA% is a better predictor for mortality than BMI (19). In model 1, both ESM_{CSA} (Hazard Ratio (HR), 0.86; 95% confidence interval (CI), 0.78-0.93; p=0.0002) and mMRC (HR, 2.28; 95% CI, 1.29-4.19; p=0.005) correlated

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significantly with all-cause mortality. In model 2 and 3, only mMRC and in model 4, mMRC (HR, 2.10; 95% CI, 1.25-3.66; p=0.005) and IC/TLC (HR, 0.93; 95% CI, 0.86-1.00; p=0.04) correlated significantly with all-cause mortality. A stepwise Cox proportional hazard analysis demonstrated that ESM_{CSA} (HR, 0.85; 95% CI, 0.79-0.92; p<0.001) was the most significant risk factor for all-cause mortality, and mMRC (HR, 2.35; 95% CI, 1.51-3.65; p<0.001) was also a significant factor (Table 5).

Finally, we conducted a preliminary analysis measuring the daily step counts of 32 COPD patients. ESM_{CSA} correlated significantly with the daily step count (Figure E3 in the online data supplement).

Discussion

This study was the first to demonstrate the clinical utility of quantitatively analyzing ESMs using chest CT images in patients with COPD. ESM_{CSA} is associated with severe airflow limitations, respiratory symptoms, and emphysema severity. We have also uncovered the evidence that ESM_{CSA} is the greatest risk factor for all-cause mortality among both established and reported prognostic predictors, such as $\%FEV_1$, BMI, LAA%, IC/TLC, COTE index, and mMRC.

The loss of skeletal muscle mass is induced by various mechanisms, such as smoking, systemic inflammation, inactivity, malnutrition, and enhanced energy expenditure (20-22). Recent studies have revealed that skeletal muscle mass is considered a useful prognostic index in the context of COPD (4), and even a local assessment of lower limb muscle mass is sufficiently useful for predicting mortality or frailty of diseases (10, 23, 24). In the present study, we focused on the ESMs as antigravity muscles and also evaluated the pectoralis muscles (PMs) as respiratory muscles (9). There was a significant but only moderate correlation between these muscle groups (r=0.61 among all study subjects, and r=0.48 among patients with COPD; Figure E2 in the data supplement). Both ESM_{CSA} and PM_{CSA} correlated significantly with BMI, mMRC, pulmonary function, and emphysema severity, but in our preliminary analysis of 32 patients with COPD, ESM_{CSA} correlated more strongly with physical activity as measured via pedometry than PM_{CSA} (Figure E3 in the online data supplement). Although the physical activity levels of all subjects were not directly assessed in the present study, this observation implies that ESM_{CSA} is a comprehensive parameter because ESM_{CSA} reflected both physical activity and physiological severity indexes of COPD. Since physical activity is reportedly the best predictor of the prognosis for patients with COPD (25-27), ESM_{CSA} will be a stronger risk factor for mortality in patients with COPD as a consequence.

The measurement of ESM_{CSA} has several advantages, compared with reports pertaining

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to the skeletal muscles, such as the PMs (9), mid-thigh muscles (23). PM_{CSA} may be affected by the position of the upper extremities during scanning. Other skeletal muscles, such as the mid-thigh muscles and psoas muscles, require additional scans and X-ray exposure for analysis.

The most important finding in the present study is that among other established prognostic predictors such as lung function, BMI, LAA% and mMRC, ESM_{CSA} was found to be the strongest risk factor for all-cause mortality (Table 3, 4, 5). For BMI, in particular, since an index of skeletal muscle mass is reported as a better prognostic factor than BMI (4), our finding that ESM_{CSA} is better than BMI is quite consistent. And for dyspnea, a previous study by our colleagues indicated that dyspnea is a strong predictor for all-cause mortality (28). However, the characteristics of patients enrolled in this study were different, as they were younger in age; additionally, some of the participants were female and exhibited lower FEV_1 values. Despite these differences, this study also demonstrated and confirmed that mMRC is a significant risk factor for all-cause mortality (Tables 3, 4, 5). Although we did not have patients with mMRC 4 (Figure E4 in the online data supplement), this does not appear to have been a disadvantage of our investigation. Patients with the most severe dyspnea, mMRC 4, may also exhibit more severe ESM loss due to nearly bed-bound conditions. In another one of our previous studies, LAA%, age, and BMI were independent predictors of all-cause mortality (19). The present cohort included older patients, excluded females, and was characterized by higher

FEV_1, higher LAA% and lower DL_{CO}/VA values. Although the previous investigation may have included more non-emphysematous patients, the present study found and confirmed that LAA% is a risk factor for all-cause mortality in the present study (Table 3).

Compared with other previous studies that have evaluated prognostic predictors, such as IC/TLC, RV/TLC, and comorbidities in patients with COPD, our results are mostly consistent except for comorbidities (29, 30). The comorbidity indices (Charlson index and COTE index) did not correlate with mortality in the present study. The subjects enrolled in the present study exhibited lower comorbidity indices perhaps because only patients with fewer comorbidities were recruited and because differences existed in the prevalence of comorbidities (such as cardiovascular disease) between patients in East Asia (including Japan) and those in Europe (1). Despite these differences, the validity of the prognostic factors described in previous reports was confirmed in the present study (Tables 3, 4, 5). We also observed a consistent trend involving specific causes of death (Figure E5 in the online data supplement) with recent findings by Sin et al (31). Based on these observations, we have concluded that ESM_{CSA} may be universally applicable as a risk measure of all-cause mortality in patients with COPD.

There are several limitations of this study. First, the sample size was small, and female patients were excluded, and there was no replication cohort. However, the validity of the reported prognostic factors was also confirmed in this study population, which supports the

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consistency of the present findings. Second, a standard method for measuring the ESM_{CSA} has not yet been established. ESM_{CSA} was analyzed via manual shading of a specific muscle area after the application of a density mask between -50 to 90 HU in this study. Automated programs to measure ESM_{CSA} are necessary to allow a more objective and precise analysis. We chose a single slice at the level of the twelfth thoracic vertebrae to analyze ESM_{CSA} according to a previous report (18). We conducted additional analyses of ESM_{CSA} using three consecutive slices and found that the CSA of the single slice correlated strongly with the average of the three slices ($r=0.98$, $p<0.0001$). Because our intent was to develop a measure that may be applied to existing clinically acquired imaging data, we are confident in the sufficient utility and validity of the single-slice image analysis. Third, to qualify the mechanisms of ESM loss, the physical activity levels of all study subjects were not directly evaluated. However, from our preliminary analysis and other reports, ESM_{CSA} was thought to be a comprehensive parameter reflecting both physical activity and physiological parameters. An objective evaluation of physical activity levels may allow detailed discussions regarding the relationship between ESM_{CSA} and physical activity levels.

The quantitative analysis of ESMs has a good potential for application in clinical settings. Because pulmonary comorbidities, such as interstitial pneumonia (32) or lung cancer (33), are important in patients with COPD, chest CT is of growing importance and is often performed

even in large-scale investigations such as the COPDGene (34) and ECLIPSE studies (35). In this situation, developing and validating an additional utility of chest CT is crucial and beneficial. Moreover, there is no need for the use of additional instruments, such as a pedometer or a tri-axial accelerometer just to assess physical activity. Furthermore, it is possible to evaluate longitudinal changes of ESA_{CSA} in these patients and observe precursory phenomenon of disease worsening. Therefore, the quantitative analysis of ESMs in chest CT images would enable clinicians and researchers to explore a significant objective index of the disease severity or condition in individual patients.

In conclusion, ESM_{CSA} obtained from a single axial chest CT image is correlated with the clinical parameters of COPD and may be the strongest risk factor for all-cause mortality in patients with COPD. Without extra radiation exposure, ESM analysis via existing chest CTs will provide an additional and important objective index reflecting the disease severity and future prognosis in patients with COPD.

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Figure Legends

Figure 1. Representative CT images used to measure the cross-sectional area of skeletal muscles. The erector spinae muscles (A) and the pectoralis muscles (B) are in green.

Figure 2. The cross-sectional area of the erector spinae muscles (ESM_{CSA}) analyzed via chest CT in both smoking control subjects and patients with chronic obstructive pulmonary disease (COPD). The open circles correspond to the smoking control subjects. The closed circles correspond to the patients with COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage. ESM_{CSA} was significantly different between the groups ($p<0.0001$) as determined by ANOVA. The smoking control subjects exhibited significantly higher values compared with the patients with COPD as determined by the Tukey-Kramer analysis. The patients with GOLD stage IV COPD exhibited significantly lower values compared with the patients with stage I ($p<0.05$) and stage II ($p<0.01$) disease as determined by the Tukey-Kramer analysis. The horizontal bars indicate the mean values. *: $p<0.0001$, †: $p<0.01$, ‡: $p<0.05$.

Figure 3. Kaplan-Meier survival curves stratified by the cross-sectional area of the erector spinae muscles (ESM_{CSA}) (n=130). The cut-off values correspond to the means, mean-1SDs, and mean-2SDs determined in the smoking control subjects (39, 32, and 25 cm^2, respectively). The COPD patients with lower ESM_{CSA} values exhibited significantly worse survival rates ($p<0.0001$ by the log-rank test).

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Table 1. Patient characteristics (n=130)

Variable	
Sex, M/F	130/0
Age, years	71.6±8.4 (46-89)
Height, cm	164.4±6.1 (150.0-180.0)
Weight, kg	57.8±8.7 (41.0-94.0)
BMI, kg/m^2	21.4±2.9 (14.7-29.0)
Smoking status, former/current	106/24
Smoking history, pack-years	70.0±38.5 (20-220)
mMRC, 0/1/2/3/4	34/55/28/13/0
GOLD stage, I/II/III/IV	23/61/34/12
LTOT, n (%)	6 (4.6)
Prior exacerbation*, y/n	29/101
Charlson index	1.6±0.9 (1-5)
COTE index	0.3±0.6 (0-3)
SGRQ total score, unit	28.9±15.5 (1.6-7.8)
SGRQ activity score, unit	40.2±22.3 (0-92.5)

FEV_1, L	1.60±0.67 (0.5-3.42)
FEV_1, % predicted	57.6±20.3 (18.7-100.1)
FVC, L	3.31 ± 0.82 (1.68-5.56)
FEV_1/FVC, %	47.2±12.7 (22.4-68.8)
VC, L	3.27±0.75 (1.37-5.23)
IC/TLC, %	37.4±7.4 (18.0-54.9)
RV/TLC, %	42.4±8.3 (25.5-70.4)
DL_{CO}, mL/min/mmHg	12.4±4.77 (2.66-23.0)
LAA% (<-960HU), %	33.2±8.9 (10.2-53.9)
PM_{CSA}, cm^2	25.91±7.41 (13.50-44.52)
ESM_{CSA}, cm^2	29.77±6.97 (12.88-46.29)

The continuous variables are presented as the mean±SD (ranges). Definitions of the abbreviations: BMI = body mass index, mMRC = modified British Medical Research Council scale, GOLD = Global Initiative for Chronic Obstructive Lung Disease, LTOT = long-term oxygen therapy, SGRQ = St. George's Respiratory Questionnaire, LAA% = percentage of the lung field occupied by low attenuation areas, PM_{CSA} = cross-sectional area of the pectoralis muscles, ESM_{CSA} = cross-sectional area of the erector spinae muscles. *Moderate-to-severe exacerbation within a year before enrollment.

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Table 2. A bivariate analysis of the cross-sectional area of the erector spinae muscles

Variable	r	p value
Age, years	-0.36	<0.0001
Height, cm	0.28	0.002
Weight, kg	0.54	<0.0001
BMI, kg/m^2	0.44	<0.0001
Smoking history, pack-years	0.06	0.5
mMRC, unit	-0.36	<0.0001
Prior exacerbation, n*	-0.10	0.2
Charlson index, unit	-0.21	0.02
COTE index, unit	-0.15	0.08
SGRQ total score, unit	-0.35	<0.0001
SGRQ activity score, unit	-0.32	0.0003
FEV_1, L	0.40	<0.0001
FEV_1, % predicted	0.31	0.0004
FVC, L	0.36	<0.0001
VC, L	0.41	<0.0001

IC/TLC, %	0.29	0.0009
RV/TLC, %	-0.27	0.002
DL_{CO}, mL/min/mmHg	0.42	<0.0001
$PaO_{2,}$ mmHg	0.09	0.3
LAA% (<-960HU), %	-0.32	0.0002
PM_{CSA}, cm^2	0.49	<0.0001

Definitions of the abbreviations: BMI = body mass index, mMRC = modified British Medical Research Council scale, SGRQ = St. George's Respiratory Questionnaire, LAA% = percentage of the lung field occupied by low attenuation areas, PM_{CSA} = cross-sectional area of the pectoralis muscles. *Moderate-to-severe exacerbation within a year before enrollment.

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Table 3. A univariate Cox proportional hazards analysis of all-cause mortality

Variable	HR	95% CI	p value
Age, years	1.06	1.00-1.12	0.03
BMI, kg/m^2	0.80	0.69-0.93	0.003
Smoking history, pack-years	1.00	0.98-1.01	0.4
mMRC, unit	2.89	1.88-4.53	<0.0001
Exacerbation*, n	1.23	0.95-1.49	0.1
Charlson index	1.36	0.84-2.03	0.2
COTE index	0.98	0.47-1.74	1.0
SGRQ total score, unit	1.03	1.01-1.06	0.01
SGRQ activity score, unit	1.03	1.01-1.05	0.01
FEV_1, L	0.31	0.13-0.64	0.001
FEV_1, % predicted	0.97	0.95-0.99	0.007
FVC, L	0.36	0.19-0.63	0.0003
FVC % predicted	0.97	0.95-0.99	0.005
VC, L	0.31	0.17-0.54	<0.0001
VC, % predicted	0.97	0.95-0.99	0.001

IC/TLC, %	0.89	0.84-0.94	<0.0001
RV/TLC, %	1.08	1.4-1.12	0.0003
DL_{CO}, mL/min/mmHg	0.82	0.74-0.90	<0.0001
$PaO_{2,}$, mmHg	0.98	0.94-1.03	0.5
LAA% (<-960HU), %	1.09	1.04-1.15	0.0004
PM_{CSA}, cm^2	0.89	0.83-0.95	0.0004
ESM_{CSA}, cm^2	0.84	0.79-0.90	<0.0001

Definitions of the abbreviations: HR = hazard ratio, CI = confidence interval, BMI = body mass index, mMRC = modified British Medical Research Council scale, SGRQ = St. George's Respiratory Questionnaire, LAA% = percentage of the lung field occupied by low attenuation areas, PM_{CSA} = cross-sectional area of the pectoralis muscles, ESM_{CSA} = cross-sectional area of the erector spinae muscles. *Moderate-to-severe exacerbation within two years after enrollment.

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Table 4. A multivariate Cox proportional hazards analysis of all-cause mortality

	Model 1			Model 2			Model 3			Model 4		
Variable	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
Age, years	1.01	0.96-1.07	0.7	1.02	0.97-1.09	0.4	1.03	0.98-1.10	0.3	1.03	0.97-1.09	0.3
mMRC, unit	2.28	1.29-4.19	0.005	2.03	1.20-3.54	0.008	2.20	1.29-3.90	0.004	2.10	1.25-3.66	0.005
FEV_1, % predicted	1.02	0.99-1.05	0.2	1.02	0.99-1.05	0.3	1.02	0.98-1.05	0.3	1.01	0.98-1.05	0.4
IC/TLC, %	0.93	0.86-1.00	0.07	0.92	0.86-1.00	0.04	0.94	0.86-1.02	0.1	0.93	0.86-1.00	0.04
DL_{CO}, mL/min/mmHg	0.99	0.86-1.13	0.8	0.93	0.82-1.06	0.3	0.92	0.81-1.04	0.2	0.91	0.79-1.04	0.2
ESM_{CSA}, cm^2	0.86	0.78-0.93	0.0002		—			—			—	
PM_{CSA}, cm^2		—*		0.96	0.89-1.03	0.3		—			—	
BMI, kg/m^2		—			—		0.93	0.81-1.04	0.4		—	
LAA% (<-960HU), %		—			—			—		1.00	0.93-1.08	0.96

Definitions of the abbreviations: HR = hazard ratio, CI = confidence interval, mMRC = modified British Medical Research Council scale, ESM_{CSA} = cross-sectional area of the erector spinae muscles, PM_{CSA} = cross-sectional area of the pectoralis muscles, LAA% = percentage of the lung field occupied by low attenuation areas. *Variables not included in the model.

Table 5. A stepwise multivariate Cox proportional hazards analysis of all-cause mortality

Variable	HR	95% CI	p value
ESM_{CSA}, cm^2	0.85	0.79-0.92	<0.001
mMRC, unit	2.35	1.51-3.65	<0.001
Age, years			0.4
BMI, kg/m^2			0.4
LAA% (<-960HU), %			0.8
DL_{CO}, mL/min/mmHg			0.7
IC/TLC, %			0.2
FEV_1, % predicted			0.6

Definitions of the abbreviations: HR = hazard ratio, CI = confidence interval, mMRC = modified British Medical Research Council scale, ESM_{CSA} = cross-sectional area of the erector spinae muscles, BMI = body mass index.

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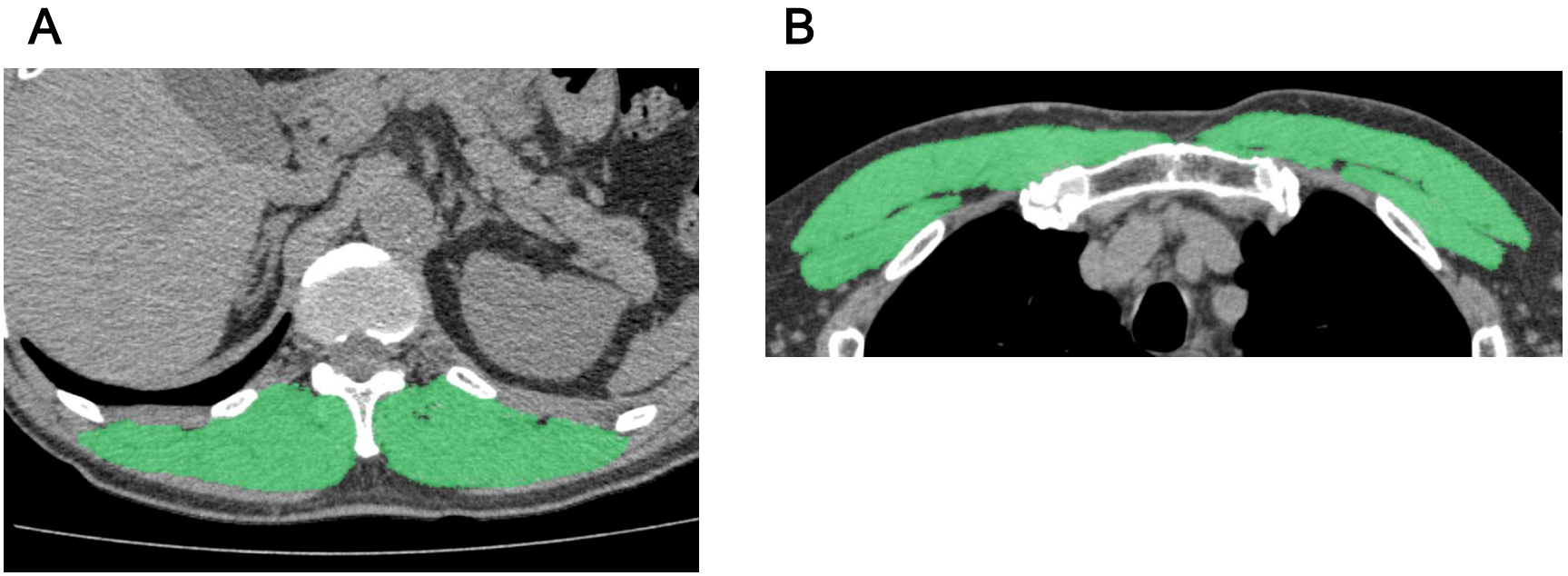
Figure 1



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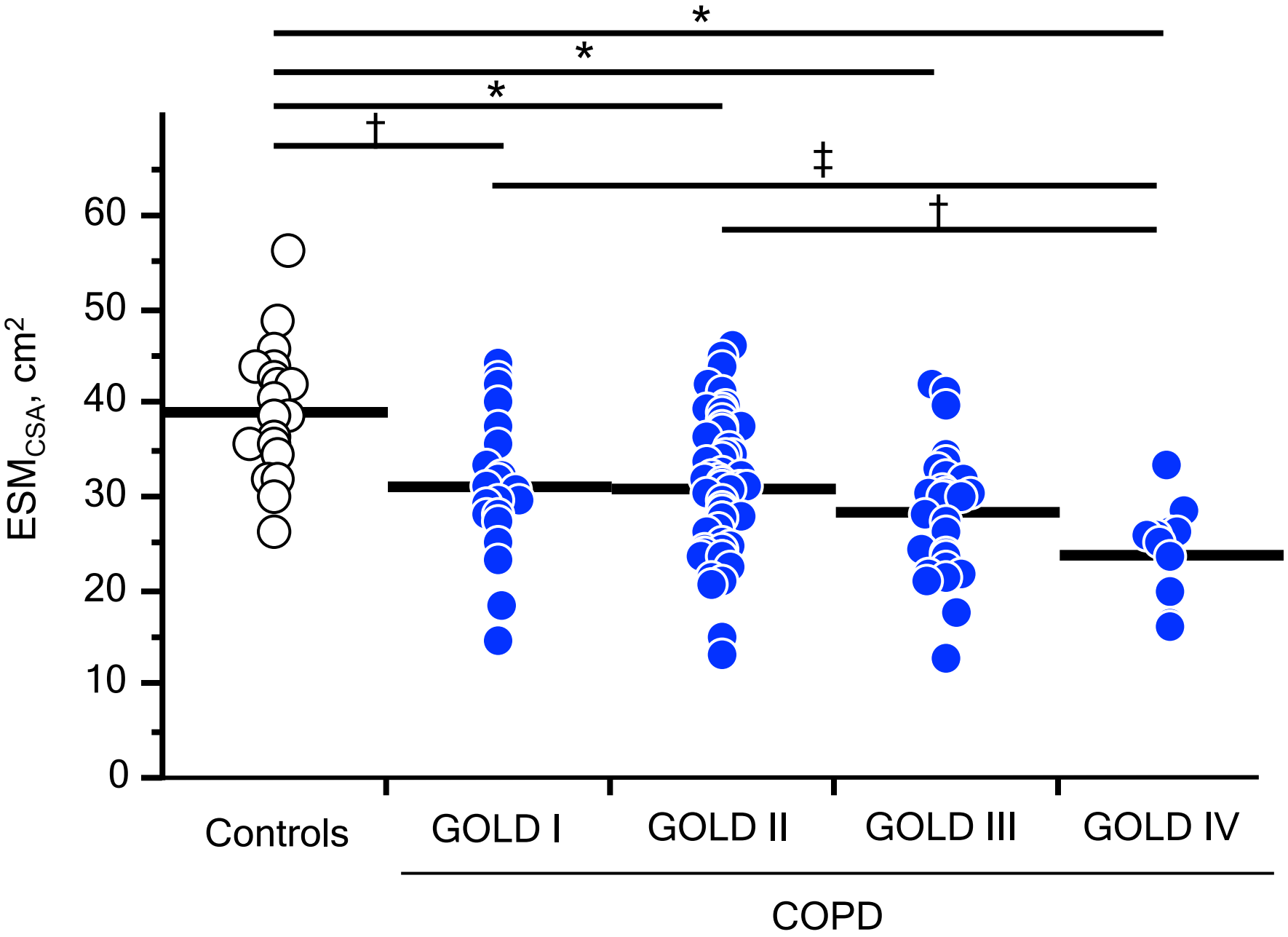

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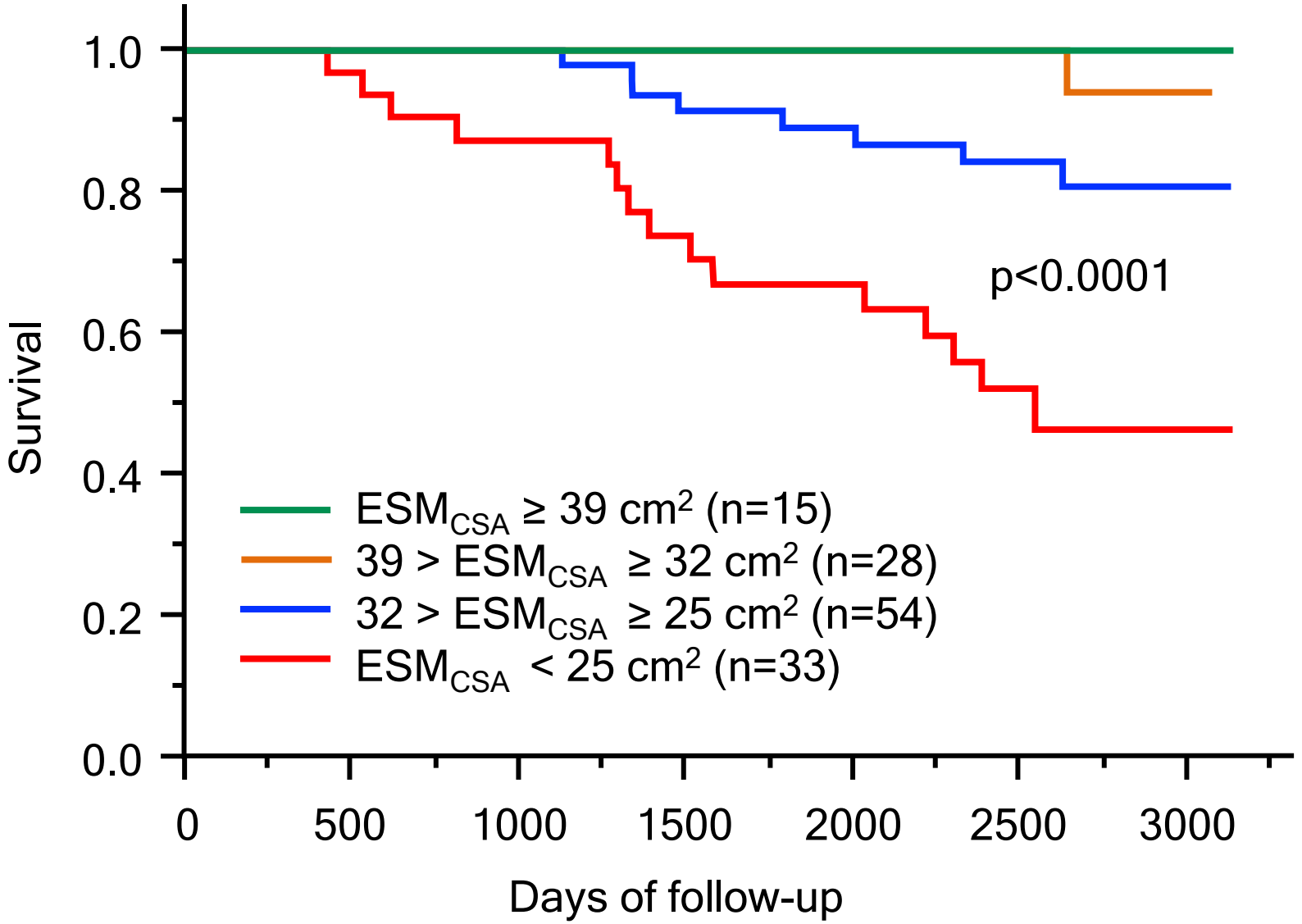
Figure 3



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Online Data Supplement

Quantitative Assessment of Erector Spinae Muscles in Patients with COPD: Novel Chest CT-derived Index for Prognosis

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Methods

Quantitative analysis of the ESMs

Chest CT images were reconstructed using the mediastinal setting (reconstruction kernel FC13). Using a modified method described in previous manuscripts (E1, E2), the analysis was performed on a single axial chest CT image at the level of the lower margin of the 12th thoracic vertebrae using SINAPSE VINCENT (FUJIFILM Medical Co., Ltd., Tokyo, Japan). ESM_{CSA} was measured by K.T. or S.S. (pulmonary physicians) and averaged. The left and right muscles were subsequently identified using a predefined attenuation range of -50 and 90 HUs and were manually shaded. The CSAs of both ESMs were calculated, and the ESM_{CSA} was presented as the sum of the right and left muscles. The intra- and inter-observer reliabilities were determined in twenty patients with COPD and twenty smoking control subjects by K.T. and S.S. (pulmonary physicians). The intraclass correlation coefficient (ICC) of the intra-observer agreement was 0.994 and ICC of the inter-observer reliability was 0.992.

Preliminary analysis

Thirty-two male outpatients with stable COPD were enrolled in this analysis between November 2011 and August 2012. The relationship between the cross-sectional areas of the skeletal muscles (ESM_{CSA} or PM_{CSA}) and daily physical activity was evaluated. To evaluate daily physical activity, the number of daily steps was measured using a pedometer (EX-300; Yamasa Tokei Keiki Co, Ltd., Tokyo, Japan). The participants were instructed to carry the pedometer in their pocket continuously for 14 consecutive days, except during bathing, sleeping, and water-based activities. The data collected during inclement weather were excluded. The average daily step count was calculated and used as a variable.

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E2. McDonald ML, Diaz AA, Ross JC, San Jose Estepar R, Zhou L, Regan EA, Eckbo E, Muralidhar N, Come CE, Cho MH, Hersh CP, Lange C, Wouters E, Casaburi RH, Coxson HO, Macnee W, Rennard SI, Lomas DA, Agusti A, Celli BR, Black-Shinn JL, Kinney GL, Lutz SM, Hokanson JE, Silverman EK, Washko GR. 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.

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Figure Legends

Figure E1. The cross-sectional area of the pectoralis muscles (PM_{CSA}) analyzed via chest CT in both smoking control subjects and patients with chronic obstructive pulmonary disease (COPD).

The open circles correspond to the smoking control subjects. The closed circles correspond to the patients with COPD according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage. PM_{CSA} was significantly different between the groups ($p<0.0001$) as determined by ANOVA. The smoking control subjects exhibited significantly higher values compared with the patients with COPD, as determined by the Tukey-Kramer analysis. The patients with GOLD stage IV COPD exhibited significantly lower values compared with the patients with stage I ($p<0.05$) and stage II ($p<0.05$) disease, as determined by the Tukey-Kramer analysis. The horizontal bars indicate mean values. *: $p<0.0001$, †: $p<0.05$.

Figure E2. Relationship between the cross-sectional areas of the erector spinae muscles (ESM_{CSA}) and the pectoralis muscles (PM_{CSA}) in both smoking control patients and patients with chronic obstructive pulmonary disease (COPD).

ESM_{CSA} and PM_{CSA} significantly but moderately correlated with each other ($p<0.0001$, $r=0.61$).

Figure E3. Relationship between the cross-sectional area (CSA) of the skeletal muscles and physical activity as measured using a pedometer (steps/day).

The CSAs of the erector spinae muscles (ESM_{CSA}) (A) and the pectoralis muscles (PM_{CSA}) (B) each correlated significantly with the daily step count.

Figure E4. Kaplan-Meier survival curves according to the modified British Medical Research

Council scale (mMRC).

The COPD patients with higher mMRC values exhibited significantly worse survival rates ($p<0.0001$ by the log-rank test).

Figure E5. Causes of death according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages.

Death from respiratory failure or sudden death is indicated in blue, and death from malignancy is indicated in red. Other causes and unknown causes are indicated in white. Of the 130 patients enrolled in this study, two of the twenty-three patients with GOLD stage I, twelve of the sixty-one patients with GOLD stage II, three of the thirty-four patients with GOLD stage III, and seven of the twelve patients with GOLD stage IV died during the follow-up period. Both of the two patients with GOLD stage I died of malignancy. Six (50%) of the twelve patients with GOLD stage II died of either respiratory failure or sudden death, and two (16.7%) died of malignancy. One (33.3%) of the three patients with GOLD stage III died of either respiratory failure or sudden death, and one (33.3%) died of malignancy. Five (71.4%) of the seven patients with GOLD stage IV died of either respiratory failure or sudden death, and one (14.2%) died of malignancy.

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TABLES

Table E1. Comorbidities

Comorbidities	n (%)	Comorbidities	n (%)
Cardiovascular disease		Renal disease	
Hypertension	38 (29.2)	Severe renal disease	1 (0.8)
Myocardial infarction	6 (4.6)	Mild renal disease	1 (0.8)
ASO	6 (4.6)	Connective tissue disease	
Aortic aneurysm	4 (3.1)	Rheumatic arthritis	4 (3.1)
Angina pectoris	3 (2.3)	Sjogren syndrome	1 (0.8)
Atrial fibrillation	3 (2.3)	Respiratory disease	
Other arrhythmia	3 (2.3)	Sleep apnea syndrome	1 (0.8)
Congestive heart failure	2 (1.5)	Allergic disease	
Others	3 (2.3)	Allergic rhinitis	1 (0.8)
Cerebrovascular disease		Urological disorder	
Cerebral infarction	5 (3.8)	BPH	18 (13.8)
TIA	1 (0.8)	Renal stone	2 (1.5)
Coagulopathy		Orthopedic disorder	
ATIII deficiency	1 (0.8)	Osteoarthritis	7 (5.4)
Metabolic disease		Osteoporosis	5 (3.8)
Diabetes	16 (12.3)	Sciatic neuralgia	2 (1.5)
Hyperlipidemia	16 (12.3)	Others	2 (1.5)
Hyperuricemia	5 (3.8)	Dermatological disorder	
Hypothyroidism	3 (2.3)	Seborrheic keratosis	2 (1.5)
Hyperthyroidism	1 (0.8)	Others	2 (1.5)

Neoplasms		Otological disorder	
Prostate cancer	4 (3.1)	Chronic otitis media	3 (2.3)
Gastric cancer	2 (1.5)	Sinusitis	2 (1.5)
Colorectal cancer	1 (0.8)	BPPV	2 (1.5)
Colorectal adenoma	4 (3.1)	Neurological disorder	
Other benign tumor	3 (2.3)	Essential tremor	2 (1.5)
Liver disease		Psychological disorder	
Chronic hepatitis	3 (2.3)	Depression	2 (1.5)
Gastrointestinal disorder		Others	2 (1.5)
Ulcerative disease	9 (6.9)	Ocular disorder	
GERD	8 (6.2)	Glaucoma	5 (3.8)
Chronic gastritis	2 (1.5)	Cataract	2 (1.5)
Others	3 (2.3)	Others	4 (3.1)

Definitions of the abbreviations: ASO = arteriosclerosis obliterans, TIA = transient ischemic attack, GERD = gastroesophageal reflux disease, BPH = benign prostatic hyperplasia, BPPV = benign paroxysmal positional vertigo.

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Table E2. Characteristics of the smoking control subjects

Variable	Smoking controls	COPD	p-value
Sex, M/F	20/0	130/0	
Age, years	69.7±5.9 (61-80)	71.6±8.4 (46-89)	0.3
Height, cm	164.9±5.7 (153.9-178.6)	164.4±6.1 (150.0-180.0)	0.8
Weight, kg	66.7±9.1 (44.5-81.0)	57.8±8.7 (41.0-94.0)	<0.0001
BMI, kg/m^2	24.5±2.6 (18.1-29.2)	21.4±2.9 (14.7-29.0)	<0.0001
Smoking status, former/current	15/5	106/24	0.5
Smoking history, pack-years	42.1±32.3 (0.45-126)	70.0±38.5 (20-220)	0.003
FEV_1, L	2.79±0.53 (1.72-3.92)	1.60±0.67 (0.5-3.42)	<0.0001
FEV_1, % predicted	98.8±11.4 (81.0-125.5)	57.6±20.3 (18.7-100.1)	<0.0001
FVC, L	3.54±0.70(2.31-5.34)	3.31±0.82 (1.68-5.56)	0.3

FEV_1/FVC, %	79.0±4.2 (71.1-86.4)	47.2±12.7 (22.4-68.8)	<0.0001
VC, L	3.58±0.70 (2.25-5.18)	3.27±0.75 (1.37-5.23)	0.09
LAA% (<-960HU), %	19.5±6.9 (9.0-34.4)	33.2±8.9 (10.2-53.9)	<0.0001
PM_{CSA}, cm^2	39.04±10.50 (20.15-57.57)	25.91±7.41 (13.50-44.52)	<0.0001
ESM_{CSA}, cm^2	39.20±6.98 (26.21-56.39)	29.77±6.97 (12.88-46.29)	<0.0001

The continuous variables are presented as the mean±SD (ranges). Definitions of the abbreviations: BMI = body mass index, LAA% = percentage of the lung field occupied by low attenuation areas, PM_{CSA} = cross-sectional area of the pectoralis muscles, ESM_{CSA} = cross-sectional area of the erector spinae muscles.

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Table E3. A bivariate analysis of the cross-sectional area of the pectoralis muscles

Variable	r	p-value
Age, years	-0.28	0.001
Height, cm	0.08	0.4
Weight, kg	0.44	<0.0001
BMI, kg/m^2	0.45	<0.0001
Smoking history, pack-years	0.1	0.2
mMRC, unit	-0.29	0.0007
Prior exacerbation, n*	-0.09	0.3
Charlson index, unit	-0.18	0.05
COTE index, unit	-0.12	0.2
SGRQ total score, unit	-0.33	0.0002
SGRQ activity score, unit	-0.32	0.0003
FEV_1, L	0.30	0.0005
FEV_1, % predicted	0.26	0.003
FVC, L	0.19	0.03
VC, L	0.26	0.003
IC/TLC, %	0.31	0.0003
RV/TLC, %	-0.29	0.0007

DL_{CO}, mL/min/mmHg	0.50	<0.0001
$PaO_{2,}$ mmHg	0.22	0.01
LAA% (<-960HU), %	-0.46	<0.0001
ESM_{CSA}, cm^2	0.49	<0.0001

Definitions of the abbreviations: BMI = body mass index, mMRC = modified British Medical Research Council scale, SGRQ = St. George's Respiratory Questionnaire, LAA% = percentage of the lung field occupied by low attenuation areas, ESM_{CSA} = cross-sectional area of the erector spinae muscles. *Moderate-to-severe exacerbation within a year before enrollment.

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Table E4. Characteristics of the subjects according to the cross-sectional areas of the erector spinae muscles using the cut-off value

Variable	$ESM_{CSA} \geq 39\ cm^2$	$39 > ESM_{CSA} \geq 32\ cm^2$	$32 > ESM_{CSA} \geq 25\ cm^2$	$ESM_{CSA} < 25\ cm^2$	p-value
Sex, M/F	15/0	28/0	54/0	33/0	
Age, years	67.5±8.7	69.2±8.7	71.4±8.0	75.8±7.3	0.003
Height, cm	166.2±6.3	166.8±6.6	164.2±5.4	162.0±6.0	0.01
Weight, kg	67.2±10.5	60.1±8.0	57.3±6.8	52.6±7.3	<0.0001
BMI, kg/m^2	24.2±2.5	21.6±2.6	21.3±2.6	20.1±2.8	<0.0001
Smoking history, pack-years	68.8±26.2	78.6±42.2	68.4±39.4	65.9±39.0	0.6
mMRC, 0/1/2/3/4	6/8/1/0/0	10/13/5/0/0	15/21/10/8/0	3/13/12/5/0	0.006
GOLD stage, I/II/III/IV	4/8/3/0	5/16/6/1	11/23/14/6	3/14/11/5	0.4
Prior exacerbation*, y/n	4/11	3/25	11/43	11/22	0.2
Charlson index	1.5±0.6	1.4±0.6	1.6±0.8	1.8±1.2	0.2

COTE index	0.3±0.5	0.1±0.4	0.4±0.7	0.4±0.7	0.4
SGRQ total score, unit	19.2±10.6	24.2 ± 13.6	26.6 ± 18.2	34.7±12.2	0.01
SGRQ activity score, unit	28.9±17.7	36.0±23.7	36.7±23.5	52.2±19.2	0.006
FEV_1, L	1.96±0.74	1.80±0.72	1.61±0.63	1.22±0.46	0.0004
FEV_1, % predicted	66.3±19.6	61.0±19.5	58.8±20.8	48.8±18.1	0.02
FVC, L	3.65±0.92	3.55±0.82	3.36±0.78	2.89±0.72	0.003
IC/TLC, %	40.0±8.2	39.7±7.3	37.1±7.3	34.8±6.4	0.03
DL_{CO}, mL/min/mmHg	13.46±4.50	14.62±4.38	12.71±4.90	9.70±3.79	0.0003
LAA% (<-960HU), %	30.5±7.2	30.9±9.2	32.3±8.5	37.7±8.5	0.005
PM_{CSA}, cm^2	32.49±6.44	27.27±8.13	26.20±6.30	21.30±6.14	<0.0001
ESM_{CSA}, cm^2	41.94±2.13	34.73±2.13	29.20±1.92	20.95±3.53	<0.0001

Definitions of the abbreviations: BMI = body mass index, mMRC = modified British Medical Research Council scale, GOLD = Global Initiative for

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Chronic Obstructive Lung Disease, SGRQ = St. George's Respiratory Questionnaire, LAA% = percentage of the lung field occupied by low attenuation areas, PM_{CSA} = cross-sectional area of the pectoralis muscles, ESM_{CSA} = cross-sectional area of the erector spinae muscles. *Moderate-to-severe exacerbation within a year before enrollment.

Support Table. A multivariate Cox proportional hazards analysis of all-cause mortality

	Model 1			Model 2		
Variable	HR	95% CI	p value	HR	95% CI	p value
Age, years	1.01	0.96-1.08	0.7	1.03	0.97-1.09	0.3
mMRC, unit	2.31	1.27-4.38	0.005	2.11	1.22-3.78	0.008
FEV_1, % predicted	1.02	0.99-1.05	0.2	1.02	0.99-1.05	0.3
IC/TLC, %	0.93	0.85-1.02	0.1	0.93	0.86-1.01	0.1
DL_{CO}, mL/min/mmHg	0.99	0.86-1.14	0.9	0.94	0.82-1.07	0.3
BMI, kg/m^2	0.99	0.82-1.18	0.9	0.95	0.79-1.15	0.6
ESM_{CSA}, cm^2	0.86	0.78-0.93	0.0002		—	
PM_{CSA}, cm^2		—		0.97	0.89-1.04	0.4

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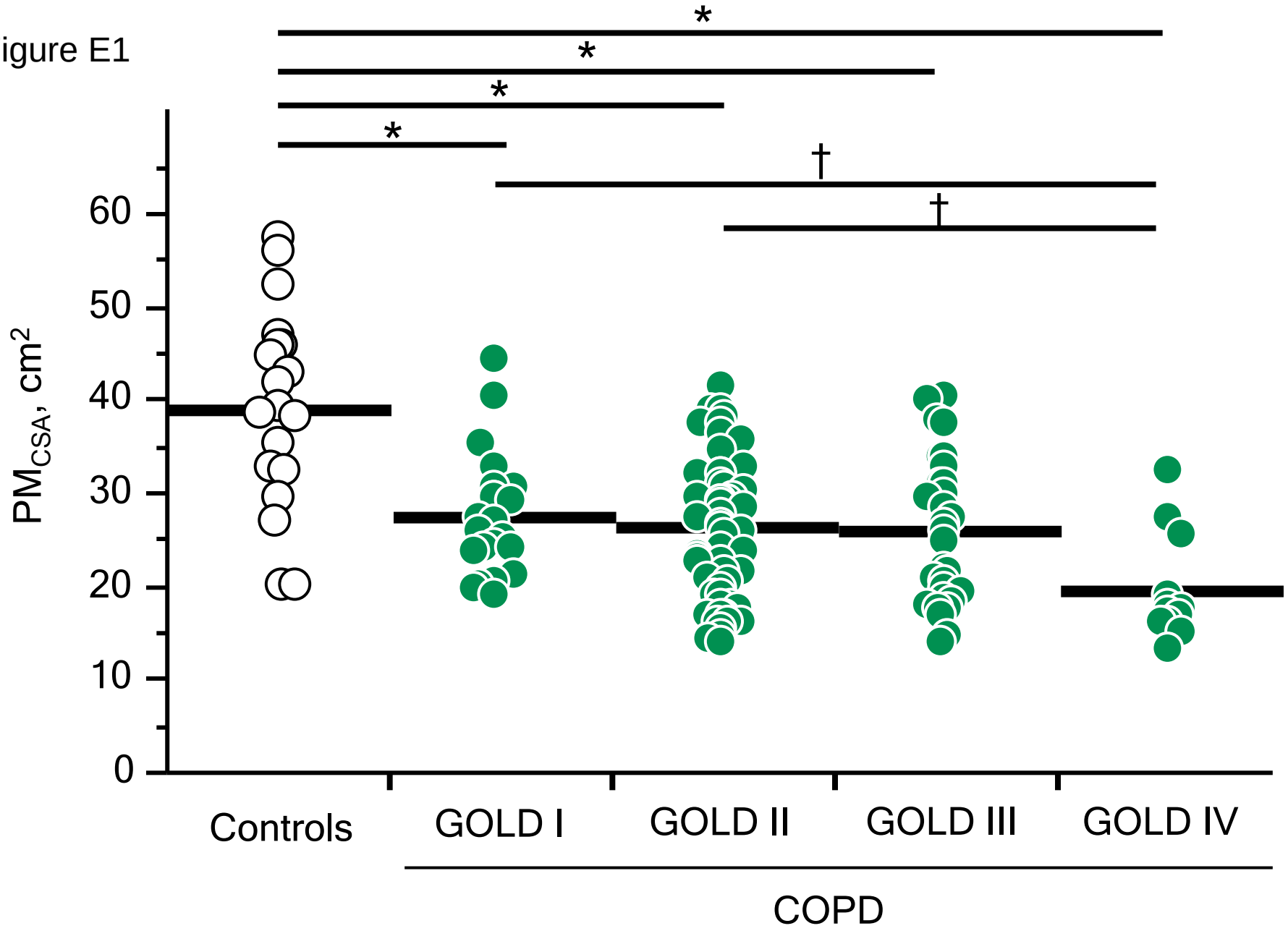
Figure E1



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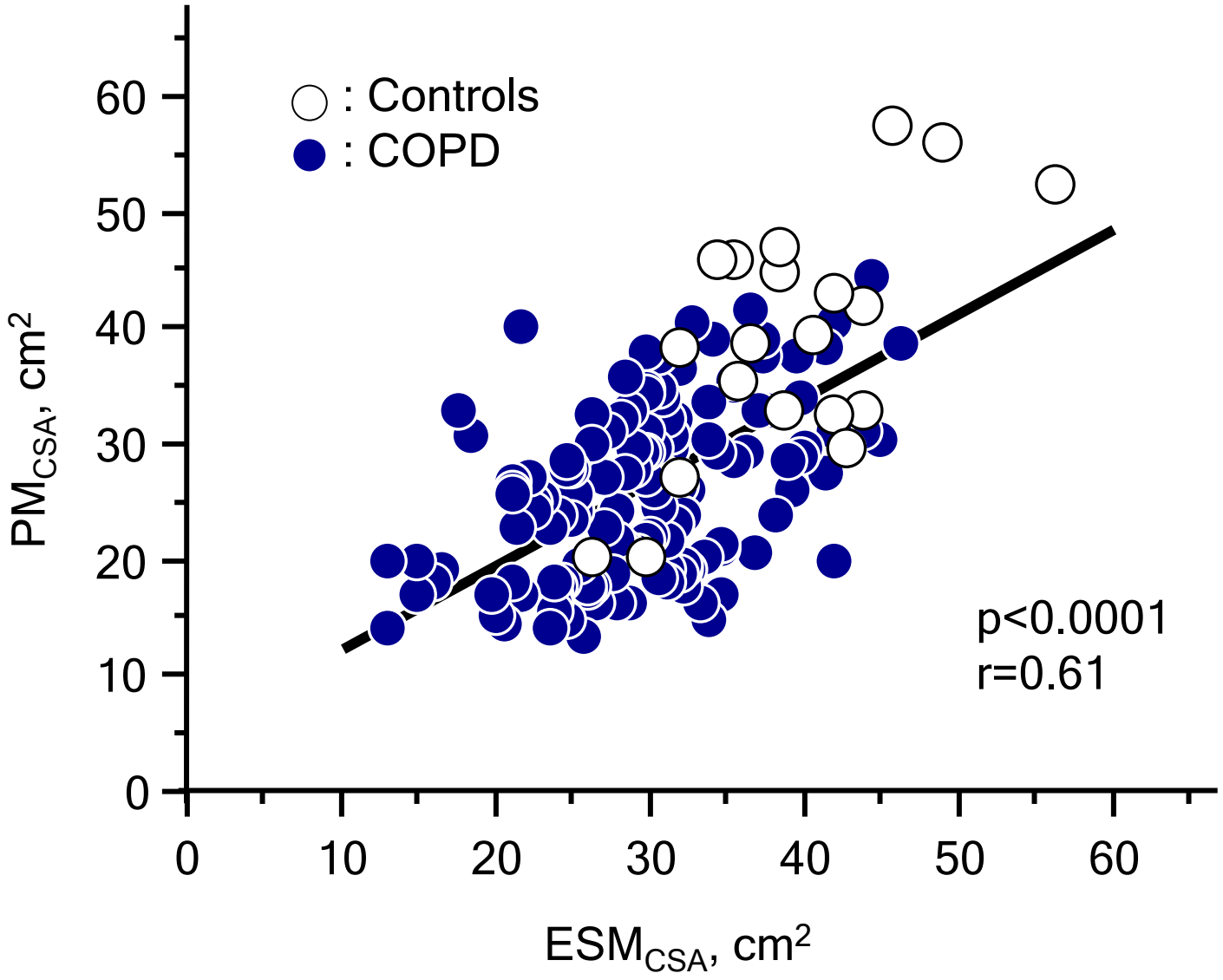

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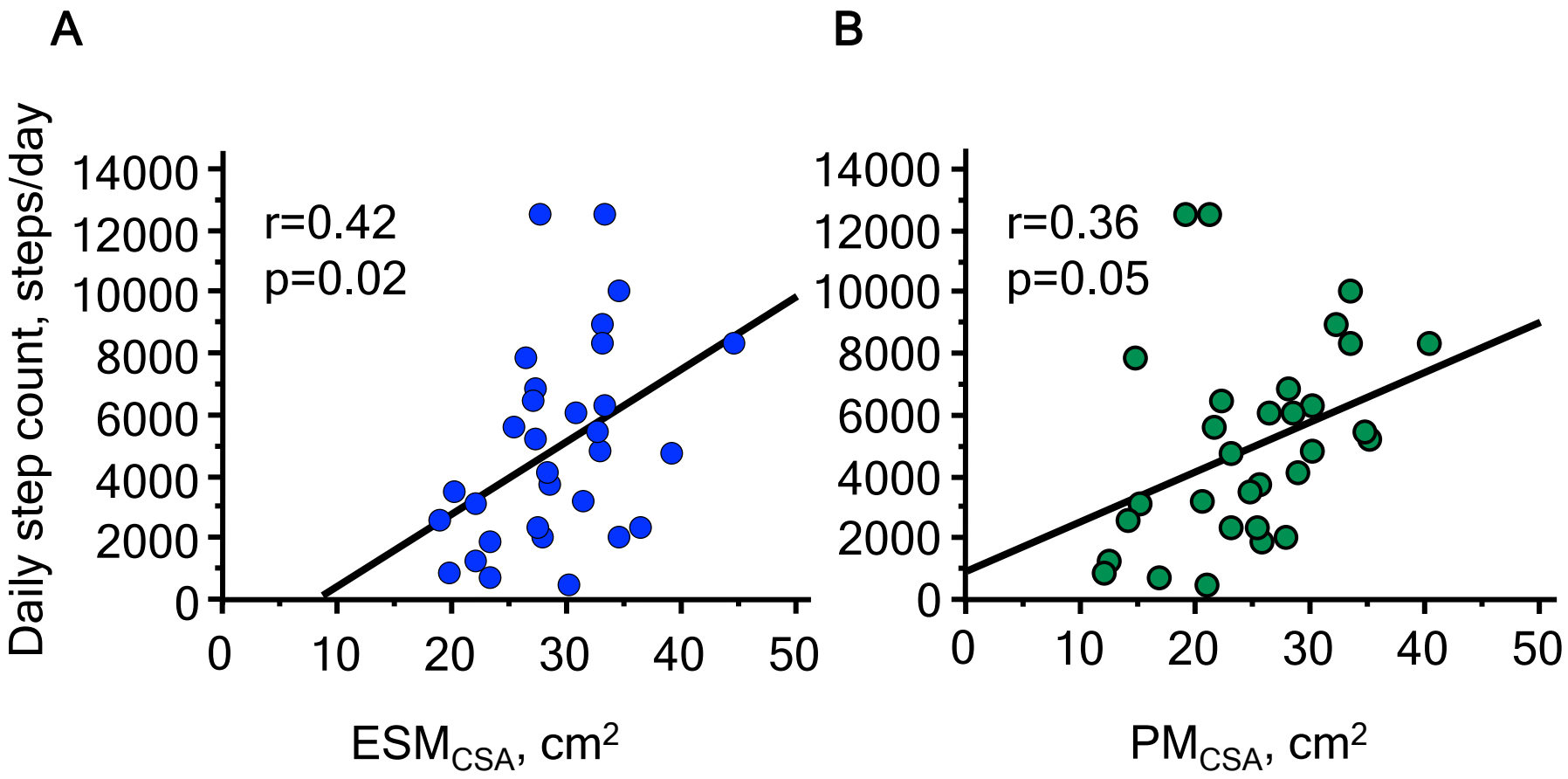
Figure E3



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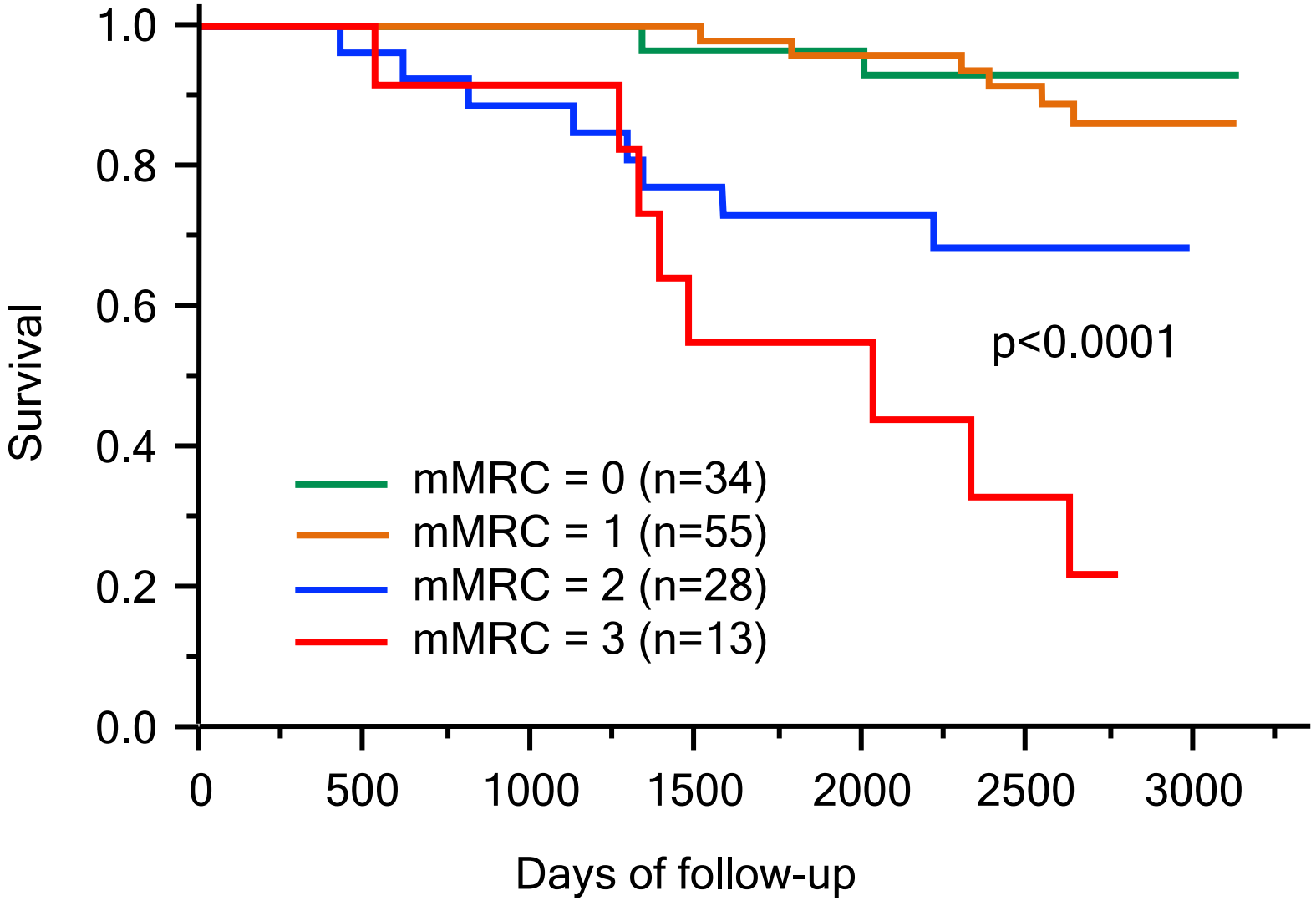

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Figure E5