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Antigravity muscle density on computed tomography and health-related independence in normal weight patients with chronic obstructive pulmonary disease

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Abstract

Background Low body mass index (BMI) is a prognostic factor, and skeletal muscle adiposity may affect mortality irrespective of BMI in patients with chronic obstructive pulmonary disease (COPD). However, the association between muscle adiposity and healthy life expectancy in normal-weight patients remains unestablished.

Objective To examine whether lower chest computed tomography (CT)-assessed erector spinae muscle density (ESMD), which represents antigravity muscle adiposity, is associated with subsequent loss of health-related independence in normal-weight patients with COPD.

Methods The ESMD lower limit of normal (LLN) was determined in 194 healthy subjects undergoing lung cancer screening CT. In a prospective cohort of patients with COPD undergoing baseline inspiratory/expiratory CT, the onset of loss of health-related independence, requiring long-term nursing facility or home nursing/medical care, was recorded over 5 years.

Results Smokers with COPD ($n=199$) were divided into 4 groups on the basis of BMI and the ESMD–LLN: underweight ($n=22$), normal-weight with ($n=40$) and without ($n=81$) low ESMD, and overweight ($n=56$). Greater airway wall thickening was associated with BMI-independent low ESMD. A multivariable Cox proportional hazards model including only normal-weight patients with COPD ($n=121$) indicated that low ESMD was independently associated with a higher loss-of-independence rate after adjusting for FEV_1, COPD assessment test score, and a smaller cross-sectional area of erector spinae muscles (hazard ratio [95% confidence interval] = 3.21 [1.30–7.89]).

Conclusion Low antigravity muscle density could reflect airway wall thickening and shorten healthy life expectancy in normal-weight patients with COPD.

Keywords Chronic obstructive pulmonary disease, Computed tomography, Healthy life expectancy, Skeletal muscle, Airway wall thickness

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of physical dysfunction and frailty, resulting in shorter healthy life expectancy and higher mortality, particularly in the ageing population [1, 2]. COPD is characterized by airflow limitation induced by airway disease and emphysema as well as various extrapulmonary comorbidities, such as weight loss and sarcopenia. While severe emphysema with a low body mass index (BMI) and skeletal muscle loss is considered to indicate an advanced disease stage leading to poor prognosis [3], low skeletal muscle quantity is also observed in a portion of normal-weight patients with COPD and may worsen their prognosis [4, 5, 6]. However, prognostic factors in normal-weight patients with COPD are not fully understood. Given differential impacts of free fat mass on clinical outcomes among underweight, normal-weight, and overweight patients with COPD [5], it is important to examine the associations between skeletal muscle abnormality and clinical outcomes, such as loss of health-related independence, specifically in normal-weight patients with COPD, in addition to those in underweight patients.

Chest computed tomography (CT) is commonly employed to screen for lung cancer and to evaluate airway tree morphology and emphysema [7]. Chest CT also allows the quantity and quality of antigravity muscles, such as the erector spinae muscles (ESMs), to be measured. Low muscle quantity, assessed as smaller cross-sectional areas of ESM (ESMAs) on CT, is associated with poor prognosis in smokers with and without COPD [8, 9, 10]. A lower density of skeletal muscle on CT reflects intramuscular adiposity [11] and is associated with low exercise capacity, impaired physical activity, and increased mortality independent of BMI in smokers with COPD [12, 13]. Moreover, the clinical impact of low ESM density (ESMD) has been proposed in patients with various lung conditions, such as lung transplant recipients and patients with asthma [14, 15]. These findings led us to hypothesize that lower ESMD is associated with shorter healthy life expectancy in normal-weight patients with COPD.

To test this hypothesis, in this study, we determined the lower limit of normal (LLN) of ESMD in healthy subjects with a lung cancer screening CT dataset. Using prospective longitudinal COPD cohort data, the aim of this study was to examine whether more severe lung pathophysiology is associated with low ESMD in patients with COPD and whether low ESMD is associated with a greater risk of losing health-related independence over 5 years in normal-weight patients.

Methods

Study subjects and clinical examinations

In this study, we used two datasets, including a retrospective cohort of healthy subjects who participated in the Lung Cancer Screening Program at Takeda Hospital in Japan (the Takeda cohort) and a prospective observational COPD cohort at Kyoto University Hospital and Terada Respiratory Clinic (the Kyoto–Himeji cohort). The details for each cohort are described in the supplemental material. Briefly, the Takeda cohort was used to determine the LLN of the ESMA and ESMD on CT. Asymptomatic never smokers without a history of lung disease who underwent lung cancer screening CT and spirometry at Takeda Hospital between 2016 and 2020 were consecutively included in the analyses [16, 17]. Subjects whose forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) was < 0.7 or whose FEV_1/FVC was < LLN were excluded. In the Kyoto-Himeji COPD cohort, smokers with COPD aged ≥ 40 years were prospectively enrolled and underwent inspiratory/expiratory and spirometry at Kyoto University Hospital and Terada Clinic between 2018 and 2020 [18, 19, 20]. In this study, the follow-up period was extended to 5 years. The diagnosis of COPD was based on an FEV_1/FVC < 0.7 on postbronchodilator spirometry. Reference values on spirometry for Japanese subjects were calculated by using the LMS method [21]. Overweight, normal weight, and underweight status were defined as BMI ≥ 25 kg/m^2, ≥ 18.5 kg/m^2, and < 18.5 kg/m^2, respectively.

Evaluation of health-related independence, symptoms, and physical activity

A long-term care insurance system (LTCI) in Japan provides healthcare and social support to seniors, and the use of this system is officially certified by the government. In accordance with a previous report [20], in this study, health-related independence was defined as healthy self-reliant conditions not requiring either long-term hospital care [2] or new certification for LTCI service needs, including home nursing/medical care [22]. The date of loss of health-related independence was recorded over 5 years, and data as of May 2024 were used in this study. Symptoms were evaluated via the modified Medical Research Council (mMRC) scale and the COPD assessment test (CAT) [23, 24]. Daily physical activity was evaluated via the Life-Space Assessment questionnaire, and its score < 60 was considered to indicate physical inactivity with social isolation [25, 26].

CT acquisition

In the Takeda cohort, full-inspiratory CT images with a 0.5 mm slice thickness were obtained using an Aquilion Prime scanner (Canon Medical Systems, Otawara, Japan). In the Kyoto-Himeji cohort, full-inspiratory and

end-tidal-expiratory CT images with a 1.0-mm slice thickness were obtained via an Aquilion Precision scanner at Kyoto University Hospital and an Aquilion Lightning scanner at the Terada Clinic with the same scanning conditions (Canon Medical Systems, Otawara, Japan).

CT quantification of ESM density and area

A custom-made Python script was used for the CT analyses. The left and right ESM were visually identified on a single axial slice at the level of the lower margin of the 12th thoracic vertebra. Their edges were manually segmented using a CT value ranging between − 50 and 90 Hounsfield Units (HU) [8, 9]. Regions surrounded by manually determined edges were considered as ESM. ESMA was calculated as the sum of the areas of the right and left ESM regions, and ESMD was calculated as the mean CT value in the segmented ESM regions [12, 14, 27]. The normality of distributions of CT values in the ESM regions were assessed based on visual inspection of their histograms.

CT analysis of the airway and lung parenchyma

A SYNAPSE® VINCENT volume analyser (FUJIFILM, Tokyo, Japan) and a custom-made Python script were used for CT analyses. Following lung segmentation, the percentage of lungs occupied by emphysema regions, defined as voxels <-950 on inspiratory CT, was calculated (LAV%) [7, 18, 19]. Nonrigid registration of inspiratory and expiratory CT images was performed to calculate the percentage of lungs occupied by nonemphysematous air-trapping regions representing small airway dysfunction (SAD%). The nonemphysematous air-trapping regions are those ≥ − 950 HU on inspiratory CT and < − 856 HU on registered expiratory CT [28, 29]. Following segmentation of the airway tree via the SYNAPSE® VINCENT volume analyser, the segmented tree was processed for extraction of the luminal centreline to count all airway branches as the total airway count (TAC) [17, 30]. The wall area (WA) was measured at the 5 segmental airways (RB1, RB4, RB10, LB1, and LB10) and averaged [16].

Statistical analysis

Data are expressed as the mean ± standard deviation (SD) unless otherwise described. In the Takeda cohort (healthy subjects), the LLNs of ESMD and ESMA for males and females were calculated as the mean− 1.645 × SD. Group comparisons were made using Student's *t* test and Tukey's multiple comparison test. Associations between continuous variables were assessed using Pearson's correlation coefficient after confirming normality. In the Kyoto–Himeji cohort, multivariable linear regression models were constructed to determine whether WA, LAV%, SAD%, and TAC were associated with ESMD or ESMA. The models included age, sex, height, BMI, smoking status, pack-years, institution, and comorbidities (hypertension, diabetes, heart disease) as covariates. To compare the rate of loss of health-related independence over 5 years between groups, Kaplan–Meier survival curves with log-rank tests and Cox proportional hazard models were used. Cox proportional hazard models for only normal-weight patients with COPD included group (normal weight with and without low ESMD or normal weight with and without low ESMA), age, sex, height, smoking status, pack-years, institution, comorbidities, and FEV_1 as independent variables. Annual changes in each measure of lung function could be considered linear on the basis of scatter plots. Linear mixed effect models were used to calculate annual changes in lung function, body weight, and Life-Space Assessment Questionnaire scores over 5 years, with random-effects intercepts and slopes for each patient and fixed cohort effects. Statistical analyses were performed using R statistical software version 4.0.1. A P value < 0.05 was considered to indicate statistical significance.

Results

Study populations and determination of LLNs for ESM density/area

As previously reported [20], of 221 patients with COPD initially included in the Kyoto–Himeji cohort, 199 patients who completed CAT and Life-Space Assessment Questionnaire were included in this study. In addition, 194 asymptomatic smokers without a history of concomitant lung diseases in the Takeda cohort were included as healthy control participants. The patients' characteristics are summarized in Table 1. The distributions of ESMD and ESMA are shown in Figure S1. CT values in the segmented ESM regions were considered normally distributed for all cases in the two cohorts. The LLNs for ESMD and ESMA were 38.8 HU and 28.6 cm^2 in males and 33.4 HU and 21.5 cm^2 in females, respectively. There was no correlation between ESMD and ESMA in the control participants or patients with COPD (Figure S2).

Associations of pulmonary indices with ESM density/area in patients with COPD

As shown in Table 2, univariable and multivariable models were constructed to explore the physiological and structural factors associated with ESMD < LLN (low ESMD) and ESMA < LLN (low ESMA) in patients with COPD. A lower FEV_1 was associated with low ESMD and ESMA in both multivariable models. In the univariable models, greater wall area was associated with low ESMD but not low ESMA, whereas greater LAV% and SAD% were associated with low ESMA but not low ESMD. According to the multivariable models, greater wall area tended to be associated with low ESMD (estimate [95%

Table 1 Basic characteristics of the two cohorts

	Takeda cohort (Healthy)	Kyoto-Hime-ji cohort (COPD)
N	194	199
COPD, n (%)	0 (0.0%)	100 (100.0%)
Age, years	51.3 (8.4)	72.7 (8.2)
Sex, Female, n (%)	97 (50.0%)	13 (6.5%)
Height, cm	164.2 (8.6)	164.9 (7.0)
BMI, kg/m^2	22.5 (3.0)	23.2 (3.7)
Current smoker, n (%)	0 (0.0%)	50 (25.1%)
Pack-years	0	59.9 (30.5)
FEV1, L	2.90 (0.63)	1.67 (0.67)
FEV_1 percent predicted, %	101.0 (10.1)	63.2 (22.4)
FVC, L	3.58 (0.78)	3.10 (0.91)
FVC percent predicted, %	100.3 (10.1)	89.6 (22.1)
FEV_1/FVC	0.81 (0.05)	0.53 (0.12)
Wall area, mm^2	21.4 (3.2)	28.1 (4.8)
LAV%, %	1.8 (2.0)	15.3 (12.6)
LLN for ESMD, HU	Male 38.8, Female 33.4	
LLN for ESMA, cm^2	Male 28.6, Female 21.5	
ESMD < LLN, %		80 (40.2%)
ESMA < LLN, %		59 (29.6%)

The data are expressed as the means (standard deviations, SDs) and percentages

BMI, body mass index; COPD, chronic obstructive pulmonary disease; ESMA, cross-sectional erector spinae muscle area; ESMD, erector spinae muscle density; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroid; LAV, low attenuation volume; LLN, lower limits of normal; SAD, small airway dysfunction; TAC, total airway count

confidence interval] = 1.07 (1.00–1.15) per +1 mm^2, $p = 0.055$).

Clinical features in normal-weight patients with COPD with and without low ESM density

As shown in Figs. 1 and 199 patients with COPD were divided into 22 underweight, 121 normal-weight, and 56 overweight patients. The prevalence of low ESMA was greater in underweight patients than in normal-weight patients or overweight patients (68%, 30%, and 14%, respectively). This trend was not observed for the prevalence of ESMD < LLN in underweight, normal-weight, and overweight patients (45, 33, and 54%, respectively). The comparisons of clinical characteristics between patients with and without low ESMD and ESMA in normal-weight patients, underweight patients, and overweight patients are summarized in Table 3 and S1.

Loss of health-related independence over 5 years in normal-weight patients with COPD

During the median [interquartile range] follow-up of 54 [42–60] months, the loss of health-related independence was observed in 46 patients with COPD, which consisted of 13 underweight, 24 normal-weight, and 9 overweight patients. As shown in Fig. 2, the health-related independence rate in underweight patients was lower than that in normal-weight patients or overweight patients (log-rank test $p < 0.001$). When focusing on normal-weight patients with COPD ($n = 121$), the loss of health-related independence was observed in 15 (38%) of 40 patients with low ESMD and in 9 (11%) of 81 patients with normal ESMD. The maintenance rate of health-related independence was lower in those with low ESMD than in those without low ESMD (log-rank test $p < 0.001$). A lower health-related independence rate was also observed in normal-weight patients with low ESMA (log-rank test $p = 0.02$). Furthermore, as shown in Table 4, in the Cox proportional hazards model including only normal-weight patients with COPD, low ESMD was associated with a greater risk of losing health-related independence (hazard ratio [95% confidence interval] = 4.84 [1.16, 20.13], $p = 0.04$) after adjusting for age, sex, height, current smoking, pack-years, institution, comorbidities, FEV_1 and CAT. In the model including both low ESMD and ESMA, low ESMD was independently associated with a greater risk of losing health-related independence. As shown in Figure S3,

Table 2 Exploration of factors associated with low ESMD in patients with COPD

	ESMD < LLN		ESMA < LLN	
	Unadjusted	Adjusted	Unadjusted	Adjusted
FEV1, +1 L	0.69 (0.44–1.06)	0.52 (0.31–0.91) *	0.31 (0.18–0.54) **	0.43 (0.22–0.84) *
Wall area, + 1 mm^2	1.08 (1.02–1.15) *	1.07 (1.00-1.15)	1.02 (0.96–1.09)	1.04 (0.95–1.13)
LAV%, + 10%	0.98 (0.78–1.23)	1.25 (0.93–1.67)	1.57 (1.23–2.01) **	1.02 (0.72–1.46)
SAD%, + 10%	1.13 (0.89–1.45)	1.29 (0.98–1.70)	1.48 (1.12–1.95) **	1.14 (0.80–1.62)
TAC, + 10	1.01 (0.97–1.05)	1.00 (0.96–1.04)	0.95 (0.91-1.00) *	0.95 (0.90-1.00) *

Univariable and multivariable logistic regression models were constructed to obtain the unadjusted and adjusted odds ratio, respectively. The multivariable models included age, sex, height, body mass index (BMI), smoking status, pack-years, institutes, and comorbidities (hypertension, diabetes, and heart disease) as covariates. ESMA, cross-sectional erector spinae muscle area; ESMD, erector spinae muscle density; FEV_1, forced expiratory volume in 1 s; LAV, low Attenuation volume; LLN, lower limits of normal; SAD, small airway dysfunction; TAC, total airway count. * indicates $p < 0.05$, ** indicates $p < 0.01$

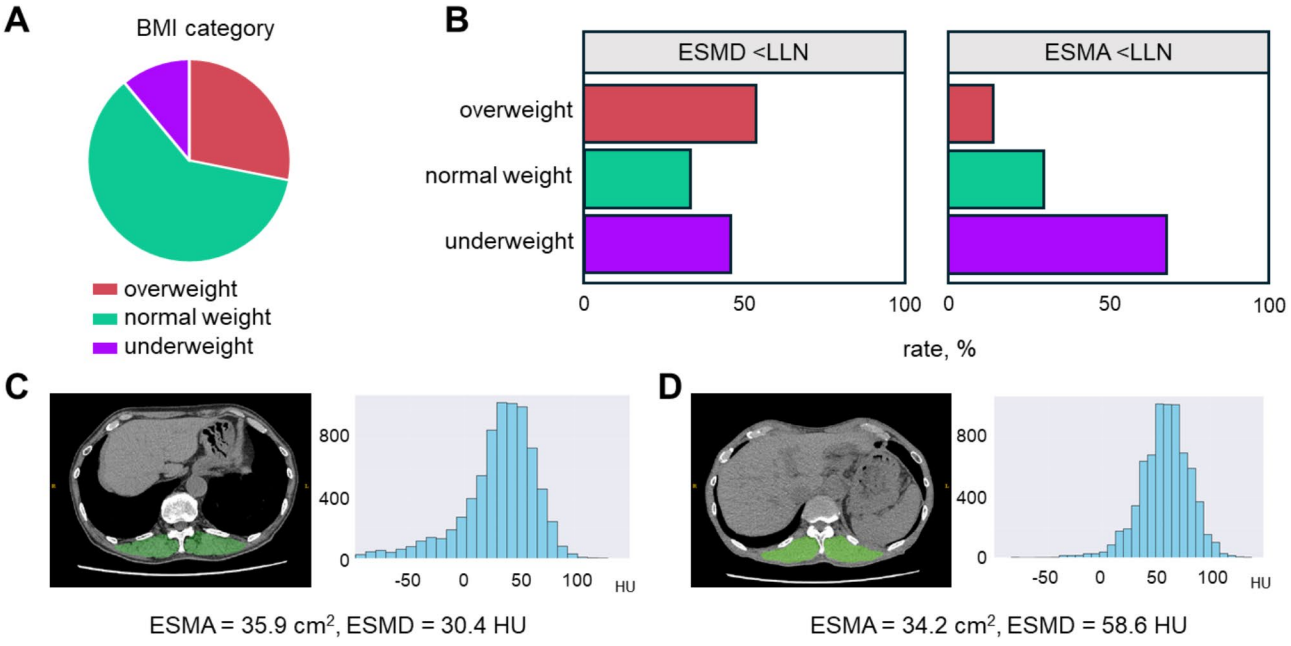

Fig. 1 Body mass index categories and erector spinae muscle abnormality in patients with COPD. **A**. Distribution of overweight, normal-weight, and underweight patients with COPD in the Kyoto–Himeji cohort. Overweight: body mass index (BMI) ≥ 25 kg/m2; normal weight: BMI ≥ 18.5 kg/m2; underweight: BMI < 18.5 kg/m2. **B**.: The prevalence of erector spinae muscle (ESM) abnormalities, such as low ESM area (ESMA) and density (ESMD) among patients with COPD stratified by BMI. **C**, **D**. Representative normal-weight patients with low and normal ESMD despite similar ESMA

Table 3 Characteristics of patients with and without low ESMD among underweight, normal-weight, or overweight patients with COPD in the Kyoto–Himeji cohort

	Underweight		Normal weight		Overweight	
	Low ESMD	Normal ESMD	Low ESMD	Normal ESMD	Low ESMD	Normal ESMD
n	10	12	40	81	30	26
Age, years	77.0 (9.9)	79.8 (5.3)	74.9 (8.0) **	70.4 (7.5)	74.3 (6.9) *	69.7 (8.8)
Sex, Female, n (%)	2 (20.0%)	2 (16.7%)	2 (5.0%)	5 (6.2%)	1 (3.3%)	1 (3.9%)
Height, cm	159.3 (8.5)	159.3 (8.1)	165.2 (7.3)	166.0 (6.4)	164.7 (7.5)	165.2 (6.0)
BMI, kg/m^2	17.5 (0.7)	16.3 (1.7)	22.5 (1.7)	22.3 (1.9)	27.8 (2.6)	27.0 (1.3)
Current smoker, n (%)	5 (50.0%)	4 (33.3%)	9 (22.5%)	20 (24.7%)	6 (20.0%)	6 (23.1%)
Pack-years	55.7 (26.7)	55.6 (18.9)	58.0 (28.0)	59.5 (31.3)	70.5 (34.4)	55.5 (32.7)
Hypertension, n (%)	4 (40.0%)	3 (25.0%)	27 (67.5%)	42 (51.9%)	20 (66.7%)	16 (61.5%)
Diabetes, n (%)	0 (0.0%)	0 (0.0%)	4 (10.0%)	13 (16.1%)	0 (0.0%) **	7 (26.9%)
Heart disease, n (%)	1 (10.0%)	1 (9.1%)	7 (18.0%)	13 (16.5%)	7 (23.3%)	7 (26.9%)
mMRC ≥ 2, n (%)	3 (30.0%) *	10 (83.3%)	9 (22.5%)	14 (17.3%)	6 (20.0%)	6 (23.1%)
CAT ≥ 10, n (%)	9 (90.0%)	9 (75.0%)	22 (55.0%)	36 (44.4%)	14 (46.7%)	12 (46.2%)
Life space assessment < 60, n (%)	3 (30.0%)	6 (54.6%)	8 (20.0%)	9 (11.1%)	5 (16.7%)	1 (3.9%)
Exacerbation ≥ 2, %	0 (0.0%)	1 (8.3%)	3 (7.5%)	4 (4.9%)	0 (0.0%)	2 (7.7%)
Inhaled corticosteroid, %	3 (30.0%)	5 (41.7%)	18 (45.0%)	33 (40.7%)	17 (56.6%)	17 (65.4%)
FEV_1%predicted, %	49.7 (19.5)	37.7 (5.1)	59.3 (20.2)	66.2 (23.8)	68.8 (17.6)	70.0 (21.0)
FVC %predicted, %	77.5 (22.0)	68.0 (21.4)	88.4 (22.6)	93.8 (21.7)	91.3 (18.5)	90.7 (21.0)
FEV_1/FVC	0.48 (0.09)	0.42 (0.10)	0.52 (0.11)	0.53 (0.12)	0.57 (0.09)	0.59 (0.10)
LAV%, %	25.8 (14.6)	27.6 (12.9)	16.9 (11.6)	15.3 (12.0)	9.3 (9.2)	10.2 (11.7)
SAD%, %	31.2 (9.2)	40.1 (12.1)	32.6 (9.2) **	27.3 (10.9)	23.4 (12.0)	21.1 (11.4)
Wall area, mm^2	29.1 (4.1) *	25.7 (2.6)	28.2 (5.1)	27.7 (4.2)	30.4 (4.7)	27.2 (6.1)
TAC	329.6 (70.7) **	251.6 (48.0)	298.1 (66.3)	313.7 (79.9)	315.2 (62.2)	306.2 (64.2)

The data are expressed as the means (standard deviations, SDs) and %

Heart disease is defined as the presence of chronic heart failure or ischemic heart disease

BMI, body mass index; CAT, COPD assessment test; ESMD, erector spinae muscle density; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; LAV, low attenuation volume; mMRC, modified medical research council; SAD, small airway dysfunction; TAC, total airway count. * indicates $p < 0.05$, ** indicates $p < 0.01$

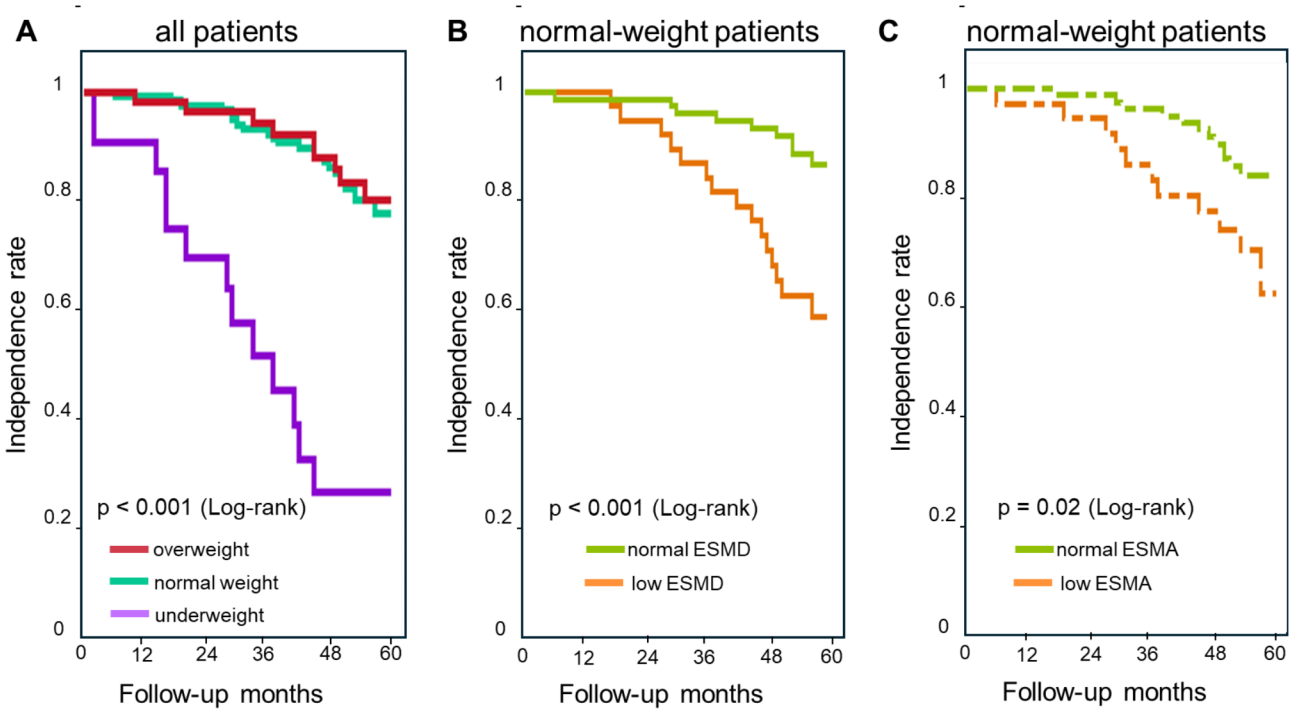

Fig. 2 Loss of health-related independence over five years in patients categorized according to body mass index and erector spinae muscle density. (**A**) All patients with COPD were categorized into underweight, normal-weight, and overweight patients. (**B**) Normal-weight patients were divided into those with low and normal ESMD. (**C**) Normal-weight patients were divided into those with low and normal ESMA. The median follow-up period was 48 months. Loss of health-related independence was defined as either (1) living in a long-term care facility, (2) needing nursing care under a government certificate, or (3) experiencing acute death due to rapid deterioration

Table 4 Cox proportional hazard analysis for loss of independence over 5 years in normal-weight patients with COPD with erector spinae muscle abnormalities

	Model 1	Model 2	Model 2
Age, +1 year	1.08 (1.01–1.16) *	1.11 (1.03–1.19) **	1.08 (1.01–1.16) *
Sex, Female	0.57 (0.08–4.33)	1.03 (0.15–6.94)	0.72 (0.10–5.44)
Height, + 1 m	0.95 (0.87–1.03)	0.97 (0.89–1.05)	0.95 (0.87–1.03)
Current smoker, yes	1.22 (0.44–3.42)	1.78 (0.63–5.03)	1.40 (0.49–4.05)
Pack-years, +1	1.01 (1.00-1.02)	1.01 (1.00-1.03)	1.01 (1.00-1.03)
Institutes, university	0.94 (0.34–2.63)	0.69 (0.23–2.10)	0.69 (0.22–2.13)
Comorbidities, yes	0.92 (0.33–2.54)	1.31 (0.47–3.69)	1.25 (0.43–3.60)
CAT ≥ 10, yes	0.81 (0.34–1.94)	0.93 (0.40–2.16)	0.85 (0.36-2.00)
FEV1, +1 L	0.40 (0.16–0.99) *	0.47 (0.20–1.06)	0.42 (0.16–1.01)
ESMD < LLN, yes	3.15 (1.31–7.61) *		3.21 (1.30–7.89) *
ESMA < LLN, yes		2.40 (0.92–6.25)	2.43 (0.90–6.57)

Values indicate odds ratio (95% confidence interval). All the models were constructed with age, sex, height, smoking status, pack-years, institution, comorbidities (hypertension, diabetes, and heart disease), COPD assessment score (CAT) ≥ 10 and FEV_1 as the independent variables. ESMA, cross-sectional erector spinae muscle area; ESMD, erector spinae muscle density; FEV_1, forced expiratory volume in 1 s. * indicates $p < 0.05$, ** indicates $p < 0.01$

the longitudinal changes in FEV1, body weight, or Life-Space Assessment Questionnaire did not differ between normal-weight patients with and without low ESMD. As shown in Figure S4, the health-related independence rate did not differ between underweight and overweight patients with and without low ESMD.

Discussion

This study showed that the prevalence of ESMD < LLN (low ESMD) was 33% in normal-weight patients with COPD and further showed that in addition to underweight patients, normal-weight patients with the low ESMD carried a greater risk of loss of health-related independence over 5 years. Moreover, the association between the low ESMD and the subsequent loss of health-related independence in normal-weight patients

was significant even after adjustment for demographics, FEV_1, and ESMA. Although previous studies have shown the associations of lower skeletal muscle quantity and adiposity with mortality independent of BMI [8, 13], to our knowledge, this is the first study to show that a lower density of antigravity muscles was associated with a shorter healthy life expectancy in normal-weight patients with COPD, independent of the cross-sectional areas of the antigravity muscles.

Healthy life expectancy is considered the average number of years that a person can expect to live at a certain level of health and maintain independence [31, 32]. In this study, the onset of loss of independence was determined by using records for the start of residency in long-term care medical facilities [2] or new certification for Japanese LTCI services, including home nursing/medical care [22]. Eligibility for the LTCI services is rigorously assessed by authorized government staff via a multi-item questionnaire regarding activities of daily living [33, 34]. Once certified by the government, subjects can receive in-home services and services at facilities, including nursing homes and long-term care health facilities under the LTCI system. Indeed, epidemiological studies have used the new certification of the LTCI care as an outcome for dependency in elderly subjects [22, 35]. Moreover, adverse outcomes, defined as either mortality, ≥ 1 inpatient stay, the need for home health care, or nursing facility use, are associated with frailty in patients with COPD [2]. Taken together, we believe that the use of health-related independence as clinical outcomes in this study is relevant in COPD management toward extension of healthy life expectancy.

The observed associations between low ESMD and future risk of loss of independence in normal-weight patients were significant even after adjusting for CAT ≥ 10 and ESMA. The rate of CAT ≥ 10 did not differ between normal-weight patients with and without low ESMD. These findings suggest that low ESMD provides additional clinical information that symptom assessment questionnaires such as CAT could not detect.

Notably, there was no significant association between ESMD and ESMA in this study. In a previous study, skeletal muscle density is associated with physical activity whereas skeletal muscle area is associated with total energy expenditure in patients with COPD [12]. We speculate that muscle adiposity is not always accompanied by a loss of skeletal muscle quantity and that ESMD may reflect different pathophysiological features than ESMA and complementarily affect clinical outcomes. This concept is in line with a previous report on patients with severe respiratory failure, in which the prognostic impacts differed according to skeletal muscle density and area [36].

A lower FEV_1 was significantly associated with low ESMD, and a greater airway wall of central airway tended to be associated with low ESMD after adjustment for BMI in patients with COPD. These findings are consistent with previous studies showing that lower CT density in respiratory muscles, such as the diaphragm, intercostals, and latissimus dorsi, is associated with lower FEV_1 in patients with COPD [37, 38]. Moreover, LAV% on inspiratory CT and SAD% on registered inspiratory/expiratory CT were not associated with low ESMD in this study. Therefore, the observed association between low FEV_1 and low ESMD can be attributed to central airway remodelling. A previous study revealed direct deposition of fat to the walls of airways in overweight subjects with and without asthma [39]. Increased epicardial fat is associated with central airway wall thickening in patients with COPD [40]. In an obese mouse model, adipose tissue can induce the expression of macrophage-inducible C-type lectin, leading to the activation of the TGF-β pathway and fibrosis [41]. Whether these factors are associated with the observed associations between increased wall area of the airways and lower ESMD in patients with COPD should be further investigated in future studies.

This study quantified ESMA and ESMD on chest CT, although the psoas muscles at the third or fourth lumber level are commonly evaluated as antigravity muscles [42]. We believe that the measurement of ESM has an advantage over that of the psoas muscle for patients with lung diseases because ESMs can be evaluated on regular clinical chest CT scans, whereas the psoas muscles are not always included in chest CT scan and its measurement requires an additional abdominal CT scan that causes radiation exposure.

Due to the cross-sectional nature of this study, it is difficult to evaluate whether maintenance of ESMD over time has clinical benefits in patients with COPD. In previous studies, a decline in ESMA over three years is associated with future exacerbations and mortality in patients with COPD [43]. In patients who underwent lung transplantation, maintenance of ESMD for over one year after transplantation was associated with long-term survival [14]. Further studies are needed to examine whether longitudinal changes in ESMD are associated with the subsequent loss of independence in patients with COPD.

In this study, the significant association between low ESMD and loss of independence was found in normal-weight patients with COPD, but not in underweight or overweight patients with COPD. These findings are in line with a previous report on the differential effects of free fat mass on exercise capacity between different BMI categories in patients with COPD [5] and may reflect the complexity of the relationship between body weight, muscle density, and loss of independence in patients with COPD. It should also be noted that underweight patients

with low and normal ESMD were very old (mean age, 77.0 and 79. 8 years, respectively) in this study. These older ages might have affected the higher rate of loss of independence in underweight patients than in normal-weight and overweight patients. Moreover, older age makes it difficult to evaluate the impact of ESMD on loss of independence in underweight patients because loss of health-related independence occurs even in the general elderly population aged around 80 years. This should be investigated using a cohort of underweight patients with COPD at younger age in future studies.

There are several limitations in this study. First, the sample size was relatively small. In particular, the number of underweight and overweight patients was small. This might have affected the absence of significant differences in the rate of health-related independence between underweight patients with and without low ESMD and between overweight patients with and without low ESMD in this study. Second, the data in this study were based on monoracial data. The applicability of the present findings to normal-weight patients with COPD from other races with different BMI distributions needs to be further investigated. Third, the age demographics of the subjects differed between the healthy cohort and the COPD cohort. Finally, because the CT values of skeletal muscle may be attenuated by soft tissues such as subcutaneous fat, ESMD values, particularly in overweight patients, should be interpreted with caution.

Conclusion

This study revealed that in addition to underweight patients with COPD, normal-weight patients with COPD and low ESM density also had a greater risk for loss of health-related independence over 5 years. These findings confirm the importance of quantitative CT assessment of ESMD and suggest that maintenance and restoration of the quality of antigravity muscles might be a therapeutic target to improve clinical outcomes.

Supplementary Information

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Supplementary Material 1

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Author contributions
ST and NT analysed and interpreted the CT data and wrote the manuscript. TM, YS, KT, HS, TO, KM, IM, AS and SS contributed to the conception and interpretation of the data. RS contributed to the interpretation of CT data. TH contributed to the editing of the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All components of this study were performed in accordance with the Declaration of Helsinki. The use of the Takeda cohort was approved by the ethics committees of Kyoto University Hospital and Takeda Hospital (approval no. R2751-2 and no. 2019, respectively), and written informed consent was waived because of the retrospective analysis of the data. The Kyoto-Himeji cohort was approved by the ethics committees of Kyoto University Hospital (approval no. C1311), and written informed consent was obtained from each patient. This cohort was registered with the University Hospital Medical Information Network (UMIN000028387, registration date August 1st, 2017).

Consent for publication
Consent was obtained directly from the patients.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

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