


The Cross-Sectional Area of Erector Spinae Muscles Obtained from Chest CT Is an Independent Predictor of Death in COPD

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Background: Skeletal muscle loss usually predicts poor clinical outcomes in patients with chronic obstructive pulmonary disease (COPD). However, the prognostic value of erector spinae muscle (ESM) in COPD remains unclear.

Methods: The cross-sectional area of ESM (ESMCSA) was retrospectively measured on a single-slice axial image obtained from chest computed tomography of COPD patients. The clinical characteristics and 5-year all-cause mortality of these patients were recorded.

Results: The ESMCSA of COPD patients in the non-survivor group was significantly lower than that in the survivor group ($P < 0.001$). Decreased ESMCSA was significantly correlated with pulmonary function decline ($P < 0.001$). The threshold of ESMCSA to predict the 5-year all-cause mortality of COPD was 23.42cm^2 , and Kaplan–Meier survival curves showed that the 5-year cumulative survival rate of COPD patients was significantly decreased when ESMCSA was less than 23.42cm^2 ($P < 0.001$). Multivariate Cox regression analyses showed that ESMCSA was an independent predictor for 5-year all-cause mortality in COPD patients ($P = 0.018$). Based on the ESMCSA, age, percentage of predicted diffusing lung capacity for carbon monoxide, partial pressure of oxygen as well as carbon dioxide in the arterial blood, a nomogram prediction model for 5-year survival probability in COPD was established. The concordance indexes for the nomogram in the training and validation cohorts were 0.852 and 0.890, respectively. The calibration curve of the nomogram model was close to the ideal curve, and its clinical decision curve showed a good clinical application value.

Conclusion: ESMCSA is a significant predictor for 5-year all-cause mortality in COPD patients, and the nomogram model based on ESMCSA has a certain reference value for predicting COPD prognosis.

Keywords: chronic obstructive pulmonary disease, erector spinae muscle, mortality, computed tomography, nomogram model

Introduction

Chronic obstructive pulmonary disease (COPD) is an important public health problem due to its high morbidity and mortality. It accounted for 212.3 million prevalent cases, 3.3 million deaths and 74.4 million disability adjusted life years worldwide in 2019.¹ COPD is usually associated with several comorbidities, such as lung cancer,² bronchiectasis,³ sleep apnea hypopnea syndrome,⁴ cardiovascular diseases² and osteoporosis,² which may increase the risk of hospitalization, mortality and healthcare costs.

Skeletal muscle loss is another frequent comorbidity in patients with COPD and is associated with adverse clinical outcomes, including higher mortality, frequent readmissions and decreased life quality.⁵ The assessment tools for skeletal muscle loss include body mass index (BMI), muscle function, muscle strength and muscle mass.^{6,7} It has been demonstrated that patients with sarcopenia usually experience varying degrees of weakness and malnutrition, and their BMI can reflect these conditions to some extent. However, BMI cannot discriminate between the relative proportions of skeletal muscle and other tissues; it may represent an insensitive and non-specific method for diagnosing skeletal muscle



loss.⁸ Muscle function can be determined by gait speed, and muscle strength can be quantified using hand grip strength.⁹ Muscle mass can be measured using a bioelectrical impedance analysis device, magnetic resonance imaging, B-mode ultrasound or dual-energy X-ray absorptiometry.^{10–13} However, these examinations have not yet been widely used for quantifying the severity of skeletal muscle loss in COPD patients in the clinical settings.

Chest computed tomography (CT) is a routine examination for the patients with COPD, thus measuring the cross-sectional area of skeletal muscles via a single-slice axial CT scan provides an alternative method for assessing skeletal muscle mass. The cross-sectional area of pectoralis muscle (PMCSA) obtained from chest CT is a reliable indicator for measuring body composition and can serve as a useful clinical surrogate for assessing skeletal muscle loss.¹⁴ Several studies have discussed the correlation between PMCSA and COPD prognosis.¹⁵ For example, PMCSA is significantly associated with COPD-related traits, including spirometric measures, dyspnea as well as 6-minute-walk distance,¹⁶ and accelerated loss of PMCSA are significantly associated with COPD exacerbations.¹⁷

Beyond pectoralis muscle evaluation on chest CT, emerging researches have focused on the erector spinae muscle (ESM) - a key antigravity muscle group essential for postural maintenance and physical activity.^{10,18} Given that physical activity is an independent prognostic factor for COPD,¹⁹ quantitative measurement of cross-sectional area of ESM (ESMCSA) via CT imaging is increasingly recognized as a potential biomarker for predicting COPD prognosis.²⁰ Although a few studies have explored the relationship between ESMCSA and mortality in the patients with COPD, the findings are conflicting. For example, it has been reported that there were no correlations between ESMCSA and mortality.²¹ Meanwhile, other studies have shown that the patients with COPD with lower ESMCSA values exhibited significantly worse survival rates.^{22,23} These contradictory outcomes may be constrained by the sample size and racial composition. Therefore, the present study aimed to explore whether ESMCSA was an independent predictor of death in COPD, and further to establish a nomogram model based on ESMCSA to predict the 5-year survival probability in patients with COPD.

Methods

Subjects

This was a single-center retrospective cohort study of COPD patients who received inpatient treatments at the Department of Respiratory and Critical Care Medicine, the Second Affiliated Hospital of Xi'an Jiaotong University, from January 1, 2014, to December 31, 2018. COPD was defined as post-bronchodilator forced expiratory volume in the first second (FEV₁)/forced vital capacity (FVC) less than 0.70. Only the first admission was recorded for patients with multiple admissions during the study period. This study excluded the patients aged <40 years or ≥80 years. Patients with asthma, bronchiectasis, active tuberculosis, malignancy, thoracic vertebral degenerative disease or vertebral surgery, scoliosis, kyphosis, chronic liver disease and end-stage renal disease were all excluded. The survival status of the patients was retrospectively followed up for 5 years after discharge from the hospital, and 506 patients were finally enrolled in the study (Figure 1). All patients or their family members provided informed consent approved by the Research Committee of Human Investigation of the Second Affiliated Hospital of Xi'an Jiaotong University.

Chest CT Examination

All enrolled patients underwent chest CT scans either within one week prior to the hospitalization or during their hospital stay. For quantitative analysis of the ESMCSA, a single-slice axial image at the lower margin of the 12th thoracic vertebra from the chest CT was used. ESM was identified on this transverse plane and manually selected based on the attenuation range of skeletal muscle values. Then, the cross-sectional area of ESM was manually shaded, and ESMCSA is presented as the sum of the left and right cross-sectional areas of ESM (Figure 2A).

Pulmonary Function and Blood Gas Analysis

Pulmonary function tests were performed when the patients were stable enough to use the spirometer maneuver before leaving the hospital. Reversibility assessment was conducted in COPD patients with a short-acting beta-2 agonist. The arterial blood samples were collected immediately and analyzed when the COPD patients were admitted to the hospital.

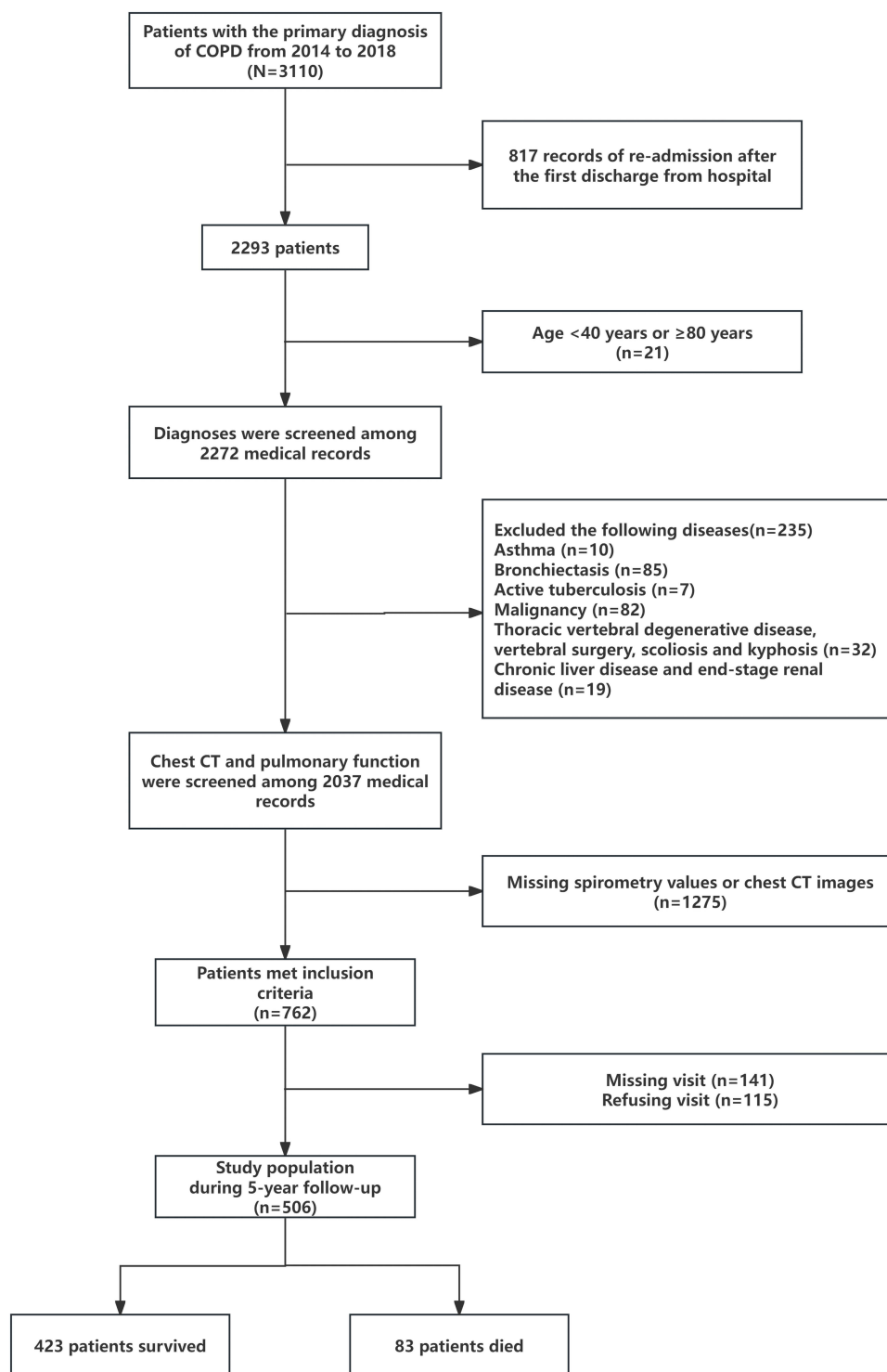


Figure 1 Flow chart of the cohort in the present research.

Clinical and Biochemical Examinations

The demographic and clinical information of all the participants were recorded in detail. Routine blood tests and biochemical parameters were determined at the beginning of hospitalization, and all these parameters were collected in this study.

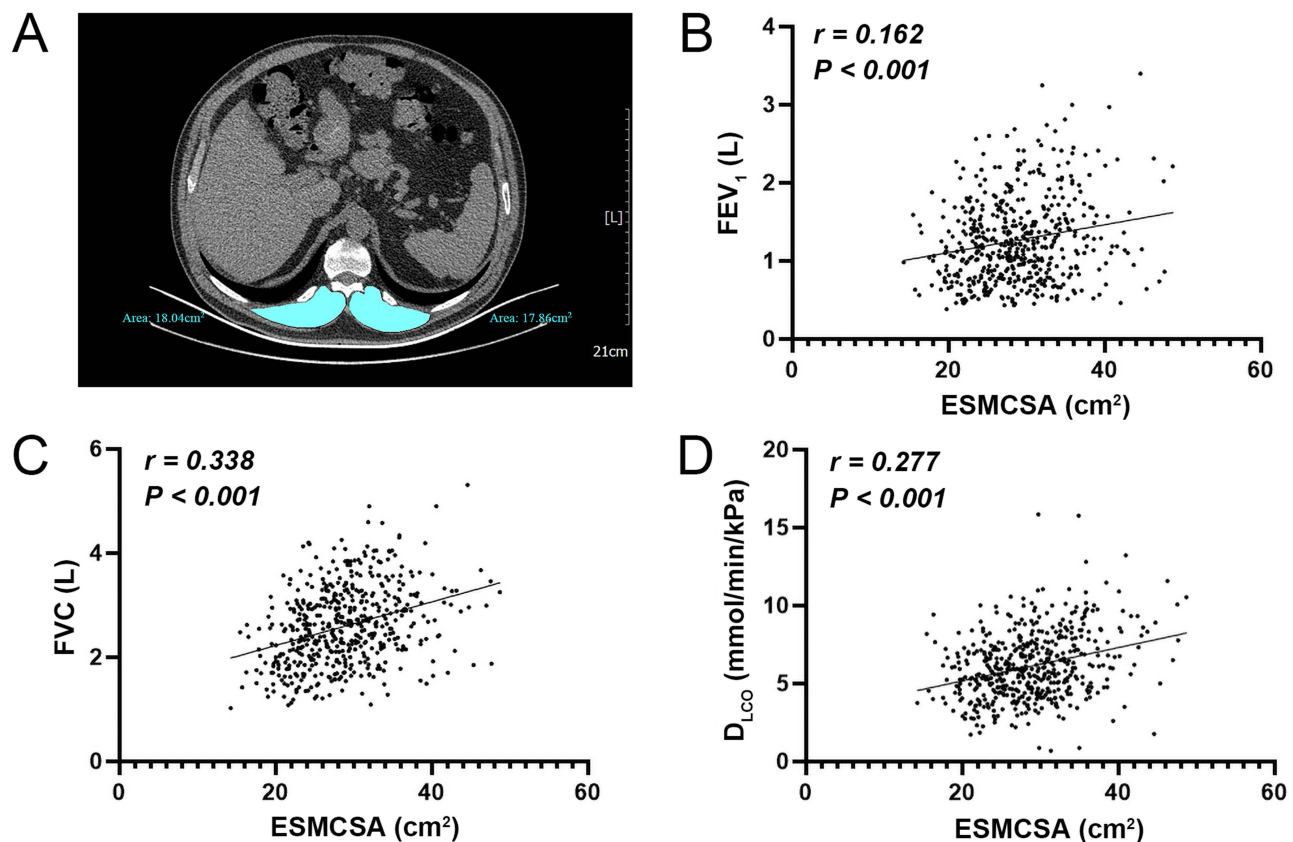


Figure 2 The correlations between ESMCSA and pulmonary function parameters. A representative axial computed tomographic image used to measure the ESMCSA of COPD patient (A). The correlations between ESMCSA and FEV₁ (B), FVC (C) as well as D_{LCO} (D) were determined by Spearman analysis.

Abbreviations: ESMCSA, cross-sectional area of erector spinae muscles; FEV₁, forced expiratory volume in the first second; FVC, forced vital capacity; D_{LCO}, diffusing lung capacity for carbon monoxide.

Statistical Analysis

All data were examined using the Kolmogorov–Smirnov test for normal distribution. Normally distributed data are presented as mean \pm standard deviation (SD), and non-normally distributed data are presented as median (interquartile range). Categorical variables are presented as percentages. The differences between the two groups were examined using Student's *t* test or Mann Whitney *U*-test. Correlations between ESMCSA and pulmonary function parameters were determined by Spearman analysis.

The diagnostic performance of ESMCSA for predicting 5-year all-cause in COPD patients was evaluated through receiver operating characteristic (ROC) curve analysis, and the optimal threshold of ESMCSA was determined by maximizing Youden's index. The 5-year cumulative survival rates were further analyzed using Kaplan–Meier survival curves based on this cutoff of ESMCSA. Univariate and multivariate Cox proportional hazards analyses were used to identify the clinical parameters which significantly correlated with the 5-year all-cause mortality of COPD patients. A nomogram model was established based on the independent risk factors from multivariate Cox proportional hazards analysis. The study population was randomly divided into the training cohort (355 cases) and validation cohort (151 cases) at a ratio of 7:3, and the evaluation and validation were confirmed using the concordance index (C-index), calibration curve and decision curve analysis (DCA). In all statistical analyses, a two-tailed *P* value < 0.05 was considered significant. All statistical analyses were performed with the SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA) and R version 4.3.2 (<http://www.r-project.org>).

Results

Characteristics of the Study Population

The baseline characteristics of the study population are shown in Table 1. Non-survivors were older and had a lower BMI than the survivors (both $P < 0.05$). The smoking index and comorbidity incidences of diabetes, hypertension and coronary heart disease were not significantly different between the non-survivor and survivor groups ($P > 0.05$). Compared with survivors, the value of ESMCSA was significantly decreased in the non-survivors ($26.45 \pm 5.18 \text{ cm}^2$ vs $29.26 \pm 6.04 \text{ cm}^2$,

Table 1 Clinical and Physiological Characteristics of the Study Patients

Characteristic	Total	Survivors	Non-survivors	P-value
Total number of patients	506	423	83	
Age (year)	66.00(60.00–71.00)	66.00(59.00–71.00)	68.00(63.00–74.00)	0.003
Male (%)	77.5	76.4	83.1	0.177
Body mass index (kg/m^2)	23.78 ± 3.99	24.05 ± 3.87	22.38 ± 4.33	< 0.001
Smoking index (pack-year)	20.00(0.00–40.00)	20.00(0.00–40.00)	30.00(0.00–43.75)	0.059
Smoking status				
Never (%)	35.2	36.5	27.8	
Former (%)	33.4	34.7	26.4	
Current (%)	31.4	28.8	45.8	
Comorbidity				
Diabetes (%)	7.9	7.5	9.7	0.523
Hypertension (%)	28.4	27.5	33.3	0.311
Coronary heart disease (%)	17.0	16.8	18.1	0.801
ESMCSA (cm^2)	28.80 ± 5.99	29.26 ± 6.04	26.45 ± 5.18	< 0.001
FEV ₁ (L)	1.18(0.84–1.57)	1.21(0.88–1.59)	0.99(0.71–1.47)	0.002
FEV ₁ (%predicted)	47.40(34.00–65.10)	48.80(35.80–65.40)	37.70(27.10–62.90)	0.004
FVC (L)	2.60 ± 0.75	2.62 ± 0.76	2.46 ± 0.69	0.075
FVC (% predicted)	81.42 ± 21.47	82.18 ± 20.85	77.53 ± 24.17	0.071
FEV ₁ /FVC (%)	47.16(38.16–58.48)	48.25(40.25–58.91)	40.98(32.62–58.23)	0.003
RV (L)	2.19(1.86–2.64)	2.18(1.87–2.63)	2.26(1.77–2.81)	0.563
RV (% predicted)	100.15(85.58–113.50)	100.20(86.40–113.30)	97.10(76.40–118.30)	0.430
TLC (L)	5.03(4.27–5.77)	5.04(4.27–5.79)	4.97(4.26–5.63)	0.284
TLC (% predicted)	86.83 ± 14.09	87.60 ± 13.94	82.94 ± 14.28	0.006
RV/TLC (%)	$45.66(39.19–51.23)$	$45.18(39.14–50.07)$	$46.21(39.21–54.44)$	0.165
D _{LCO} (mmol/min/kPa)	5.95(4.59–7.40)	6.16(4.78–7.59)	4.63(3.56–5.95)	< 0.001
D _{LCO} (% predicted)	78.98 ± 25.21	81.81 ± 24.44	64.58 ± 24.29	< 0.001
pH	7.43 ± 0.03	7.43 ± 0.03	7.43 ± 0.03	0.891
PaO ₂ (mmHg)	71.45 ± 11.27	72.32 ± 10.77	67.05 ± 12.72	< 0.001
PaCO ₂ (mmHg)	39.00(35.70–42.60)	38.80(35.60–42.00)	40.40(36.70–47.80)	< 0.001
PO ₂ (A-a) (mmHg)	26.30(19.68–32.63)	26.00(19.60–32.40)	27.70(20.40–33.30)	0.241
Leukocyte count ($\times 10^9/\text{L}$)	6.51(5.17–8.27)	6.42(5.11–8.33)	6.60(5.30–8.16)	0.917
Hemoglobin (g/L)	138.00(127.75–147.00)	138.00(128.00–147.00)	137.00(123.00–146.00)	0.465
Platelet count ($\times 10^9/\text{L}$)	187.00(146.00–227.25)	187.00(149.00–229.00)	180.00(141.00–221.00)	0.484
Neutrophil count ($\times 10^9/\text{L}$)	4.24(3.14–5.99)	4.24(3.09–5.85)	4.31(3.29–6.38)	0.285
Albumin (g/L)	39.18 ± 4.06	39.38 ± 3.99	38.14 ± 4.28	0.064
Globulin (g/L)	25.01 ± 4.24	24.98 ± 4.09	25.17 ± 4.96	0.718
ALT (IU/L)	16.00(12.00–24.00)	16.00(12.00–25.00)	15.00(10.00–21.00)	0.587
AST (IU/L)	18.00(16.00–23.00)	18.00(16.00–23.00)	18.00(15.00–23.00)	0.567
Creatinine ($\mu\text{mol}/\text{L}$)	66.64(56.90–77.65)	67.30(57.33–77.74)	64.53(54.80–74.37)	0.165

Note: Data are expressed as mean \pm standard deviation or median (interquartile range) or percentage.

Abbreviations: ESMCSA, cross-sectional area of erector spinae muscles; FEV₁, forced expiratory volume in the first second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; D_{LCO}, diffusing lung capacity for carbon monoxide; PaO₂, partial pressure of oxygen in arterial blood; PaCO₂, partial pressure of carbon dioxide in arterial blood; PO₂(A-a), alveolar-arterial oxygen gradient; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

$P < 0.001$). Pulmonary ventilation and diffusion function of COPD patients in the non-survivor group were worse than those in the survivor group. Moreover, the partial pressure of oxygen in arterial blood (PaO_2) was significantly decreased, and the partial pressure of carbon dioxide in arterial blood (PaCO_2) was notably increased in the non-survivors compared with the survivors (both $P < 0.001$). However, the alveolar-arterial oxygen gradient [$\text{PO}_2(\text{A-a})$] did not differ between the two groups ($P = 0.241$). The differences in leukocyte count, hemoglobin, platelet count, neutrophil count, albumin and other biochemical parameters between the non-survivors and survivors were not significant (all $P > 0.05$).

ESMCSA Was Associated with Pulmonary Function and COPD Prognosis

Bivariate correlation analysis showed that ESMCSA was significantly positively correlated with FEV_1 ($r = 0.162$, $P < 0.001$), FVC ($r = 0.338$, $P < 0.001$) and D_{LCO} ($r = 0.277$, $P < 0.001$), and the results are shown in the Figure 2B–D. ROC was used to evaluate the diagnostic value of ESMCSA for 5-year all-cause mortality of COPD patients, and the cut-off value of ESMCSA was 23.42cm^2 with an area under the ROC curve (AUC) as 0.64 (95% CI 0.57–0.70, $P < 0.001$, Figure 3A). The study population was further divided into two groups according to the ESMCSA threshold, and the clinical and physiological characteristics are shown in the supplementary material (Table S1). The 5-year all-cause mortality was significantly increased when the value of ESMCSA was $< 23.42\text{cm}^2$ in patients with COPD (27.6% vs 13.7%, $P = 0.001$). Kaplan–Meier survival curves showed that the 5-year cumulative survival rate for COPD patients was significantly decreased when ESMCSA was $< 23.42\text{cm}^2$ (Log rank test $\chi^2 = 12.62$, $P < 0.0001$, Figure 3B). The study population were further divided into four groups according to ESMCSA values (mean, mean-1SD and mean-2SD), and Kaplan–Meier survival curves showed that the lower ESMCSA values corresponded with the worse survival in patients with COPD ($P < 0.001$, Figure S1).

Factors Associated with 5-year All-Cause Mortality in COPD Patients

The relationships between clinical parameters and 5-year all-cause mortality were evaluated using univariate and multivariate Cox proportional hazards analyses, and the results are presented in the Table 2. In the univariate Cox proportional hazards analysis, ESMCSA was an independent predictor for 5-year all-cause mortality of COPD patients (HR=2.25, 95% CI 1.42–3.56, $P = 0.001$). In addition, age, BMI, $\text{FEV}_1\%$, $\text{D}_{\text{LCO}}\%$, $\text{TLC}\%$, PaO_2 and PaCO_2 were significant predictors for 5-year all-cause of COPD patients (all $P < 0.05$). The multivariate Cox proportional hazards

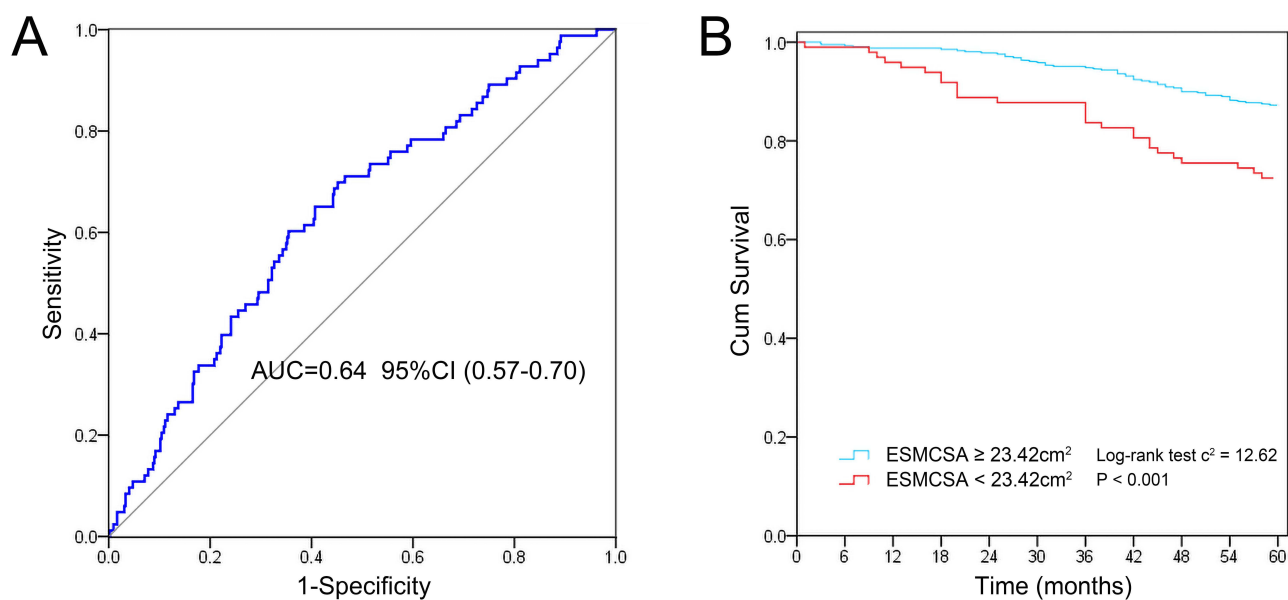


Figure 3 The values of ESMCSA for 5-year all-cause mortality of COPD patients. (A) Receiver operating characteristic curve for ESMCSA of the study patients, and the cut-off value was 23.42cm^2 . (B) Kaplan–Meier survival curves of COPD patients according to the cut-off value of ESMCSA, and the COPD patients with $\text{ESMCSA} < 23.42\text{cm}^2$ showed significantly worse survival rates.

Abbreviation: ESMCSA, cross-sectional area of erector spinae muscles.

Table 2 Univariate and Multivariate Associations with 5-year All-Cause Mortality of COPD Patients

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (per increase of 1-year)	1.05(1.02–1.08)	0.003	1.04(1.01–1.07)	0.015
Sex (female vs male)	0.67(0.38–1.20)	0.177		
BMI (per increase of 1 point)	0.90(0.85–0.96)	<0.001	0.94(0.88–1.00)	0.055
Smoking index (pack-year)	1.01(1.00–1.01)	0.090		
ESMCSA (cm ²) (≥23.42 vs <23.42)	2.25(1.42–3.56)	0.001	1.83(1.11–3.01)	0.018
FEV ₁ (% predicted)	0.99(0.98–1.00)	0.031	1.00(0.99–1.01)	0.892
FVC (% predicted)	0.99(0.98–1.00)	0.056		
D _{LCO} (% predicted) (≥80 vs <80%)	3.30(1.96–5.56)	<0.001	2.35(1.34–4.14)	0.003
RV (% predicted)	1.00(0.99–1.00)	0.250		
TLC (% predicted)	0.98(0.96–0.99)	0.003	0.99(0.97–1.01)	0.270
pH (≥7.40 vs <7.40)	1.46(0.87–2.43)	0.149		
PaO ₂ (≥60 vs <60 mmHg)	2.99(1.87–4.77)	<0.001	2.05(1.24–3.37)	0.005
PaCO ₂ (≥50 vs <50 mmHg)	3.27(1.81–5.91)	<0.001	2.81(1.46–5.40)	0.002
Hypertension (yes vs no)	1.32(0.81–2.16)	0.262		
Diabetes (yes vs no)	1.29(0.59–2.81)	0.523		
Coronary heart disease (yes vs no)	1.09(0.60–1.98)	0.784		
Leukocyte count (per increase of 1 × 10 ⁹ /L)	1.02(0.94–1.10)	0.637		
Hemoglobin (per increase of 1g/L)	1.00(0.99–1.01)	0.564		
Platelet count (per increase of 1 × 10 ⁹ /L)	1.00(0.99–1.00)	0.777		
Neutrophil count (per increase of 1 × 10 ⁹ /L)	1.06(0.98–1.14)	0.139		
Albumin (g/L)	1.01(0.96–1.07)	0.071		
Creatinine (μmol/L)	0.99(0.98–1.01)	0.192		

Abbreviations: HR, relative risk; CI, confidence interval; BMI, body mass index; ESMCSA, cross-sectional area of erector spinae muscles; FEV₁, forced expiratory volume in the first second; FVC, forced vital capacity; D_{LCO}, diffusing lung capacity for carbon monoxide; RV, residual volume; TLC, total lung capacity; PaO₂, partial pressure of oxygen in arterial blood; PaCO₂, partial pressure of carbon dioxide in arterial blood.

analysis further demonstrated that ESMCSA was still a significant predictor for 5-year all-cause mortality of COPD patients (HR=1.83, 95% CI 1.11–3.01, P=0.018). Moreover, older age (P=0.015), lower D_{LCO}% (P=0.003), lower PaO₂ (P=0.005) and higher PaCO₂ (P=0.002) were significantly correlated with 5-year all-cause mortality in COPD patients. However, FEV₁%, TLC% and BMI had no significant effects on the 5-year all-cause mortality of COPD patients (all P>0.05).

Clinical Prediction Nomogram Model

Five significant independent risk factors (age, D_{LCO}%, ESMCSA, PaO₂ and PaCO₂) for predicting 5-year all-cause mortality in the multivariate Cox proportional hazards analysis were included to establish a clinical prediction nomogram model (Figure 4), and this model showed an excellent discrimination, whose C-index in the training cohort and validation cohort was 0.852 and 0.890, respectively. The goodness-of-fit of this model was evaluated using the Hosmer–Lemeshow test and yielded non-significant values in the training cohort (P=0.415) and the validation cohort (P=0.880). The calibration curve for the nomogram model confirmed a high degree of agreement between the anticipated and observed survival probabilities (Figure 5A and B). The DCA showed that the nomogram provided a greater net benefit with a wider range of threshold probabilities in both the training and validation cohorts (Figure 5C and D).

Discussion

Our present study demonstrated that ESMCSA is an independent factor for 5-year all-cause mortality of COPD patients, and it is feasible to establish a clinical prediction nomogram model for predicting the 5-year survival probability of COPD based on ESMCSA and some associated parameters.

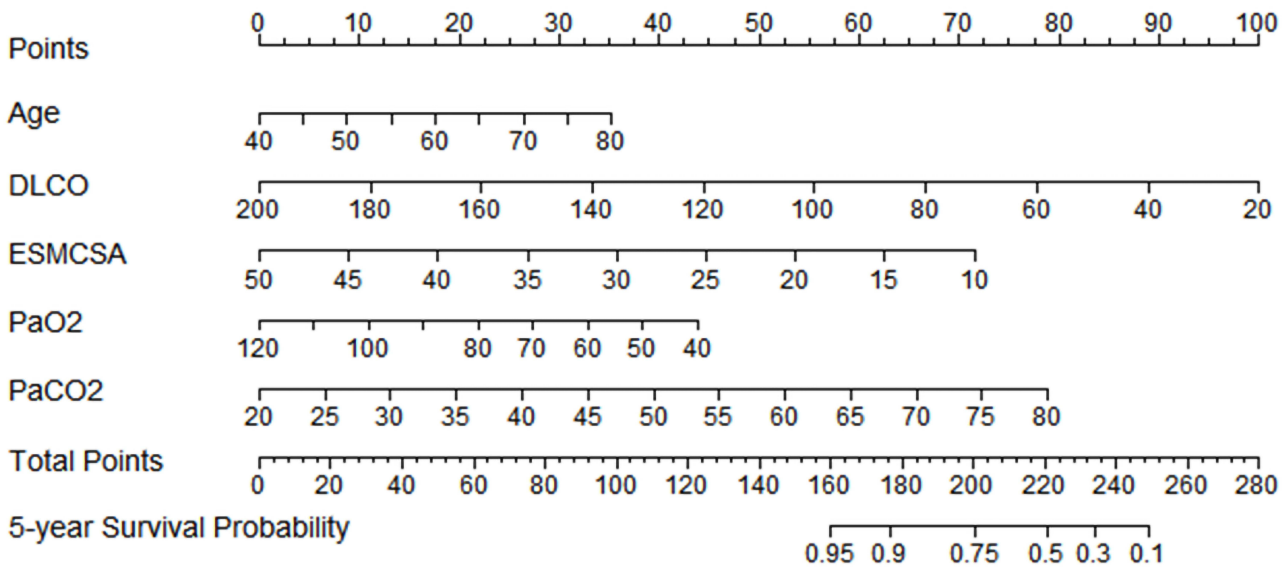


Figure 4 Nomogram in patients with COPD. The nomogram prediction model for 5-year survival probability in COPD was established based on age, D_{LCO} %, ESMCSA, PaO_2 and $PaCO_2$.

Abbreviations: D_{LCO} , diffusing lung capacity for carbon monoxide; ESMCSA, cross-sectional area of erector spinae muscles; PaO_2 , partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of carbon dioxide in arterial blood.

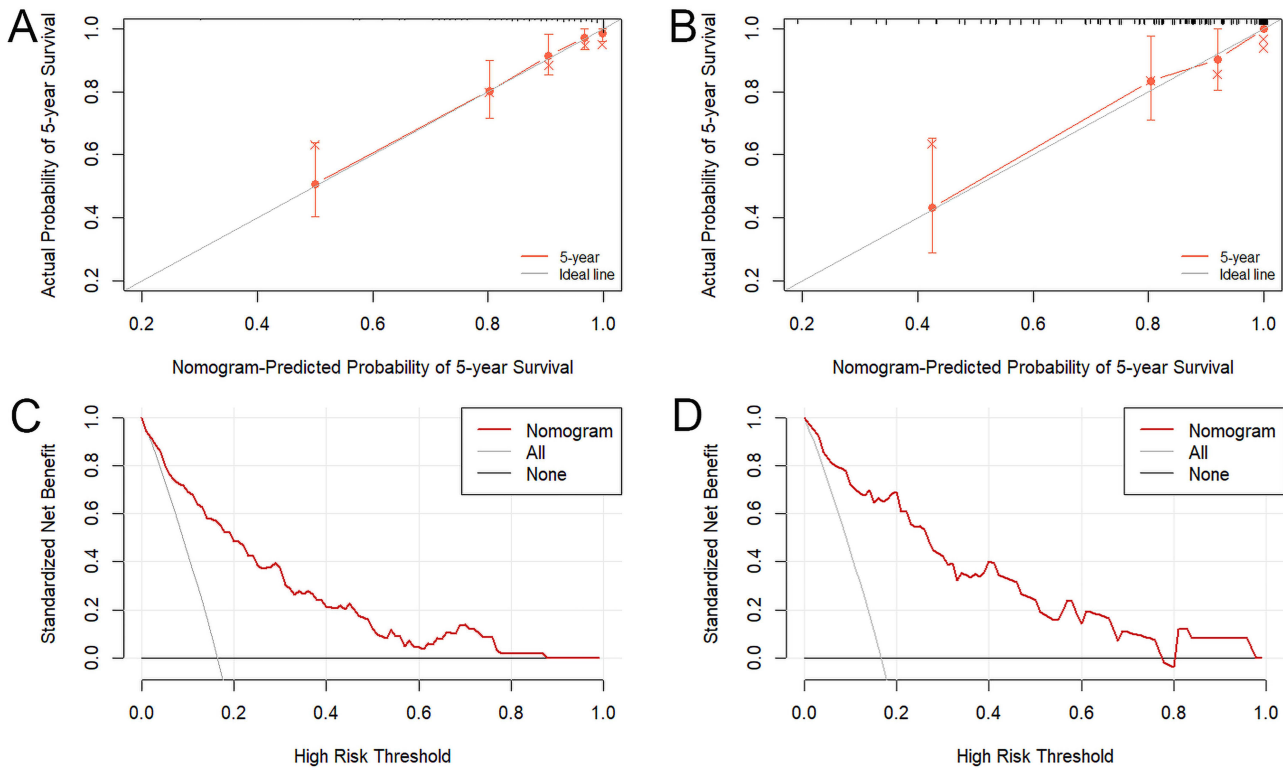


Figure 5 Validation of the nomogram model. Calibration curves of the prediction nomogram in the training cohort (A) and validation cohort (B). The 45° straight line represents an ideal model, a close distance between the calibration curve of the nomogram model and ideal curve indicates high accuracy. The calibration curve affirmed the accuracy of the model in aligning predicted probabilities with actual outcomes by the Hosmer–Lemeshow test, and the predicted and real results were not significantly different. Decision curve analysis for the nomogram in the training cohort (C) and validation cohort (D), demonstrated clinical applicability of the model.

Skeletal muscle dysfunction is a common complication of COPD, which can be used to predict all-cause mortality of COPD patients. Low skeletal muscle mass, including total muscle mass measured by fat-free mass index (FFMI) and peripheral muscle mass measured by appendicular skeletal muscle index (ASMI), is associated with re-hospitalization

due to the acute exacerbation and high mortality risk in the patients with COPD.^{6,24} Compared with other skeletal muscles, ESM has less age-related atrophy and better representation of physical activity levels, and can be little affected by body position and posture.^{10,18} In addition, obtaining ESMCSA values does not increase additional radiation exposure compared to other skeletal muscles, as chest CT is a routine examination for patients with COPD. Therefore, we hypothesized that the ESMCSA could be used to predict COPD prognosis in the clinical settings. Our present study found that ESMCSA was significantly decreased in the non-survivors, indicating that ESMCSA may be a predictor of COPD mortality. Our data further demonstrated that decreased ESMCSA was significantly correlated with pulmonary function decline. For instance, it was positively correlated with FEV₁, FVC and D_{LCO}, which is consistent with the previous findings,^{21,23} suggesting that decreased ESM mass may contribute to impaired pulmonary function.

ROC analysis showed that the ESMCSA threshold for 5-year all-cause mortality in COPD patients was 23.42cm², suggesting that COPD patients with ESMCSA less than 23.42cm² require heightened surveillance due to their high mortality risk profile. However, the AUC of ESMCSA is less than the standard acceptable value, which may be related with the small number of non-survivors in the present study. Further Kaplan–Meier survival curves showed that the 5-year cumulative survival rates declined in proportion to decreased ESMCSA values, indicating that ESMCSA is a potential biomarker for predicting the 5-year all-cause mortality in patients with COPD.

Multivariate Cox proportional hazards analysis showed that ESMCSA was an independent predictor for 5-year all-cause mortality in COPD patients. This may be related with skeletal muscle dysfunction leading to exercise capacity impairment or exercise intolerance, which in turn results in a more pronounced loss of muscle mass. Our study also found that BMI was not an independent factor for 5-year all-cause mortality of COPD, which may be related to the fact that BMI cannot differentiate between muscle mass and fat. For instance, some COPD patients may have lost considerable lean body mass, but their BMI are normal due to the extra fat stores.²⁵ It has been proven that COPD is an age-related disease,²⁶ and our study also showed that aging could increase the mortality risk of COPD.

It has been reported that FEV₁ is associated with hospitalization time, mechanical ventilation needs and intensive medical care for acute exacerbations of COPD, but not significantly correlated with the mortality.²⁷ Our present study has also demonstrated that FEV₁ is not an independent predictor of mortality in COPD patients, which is consistent with previous findings.^{28,29} The limited predictive value of FEV₁ for COPD prognosis may stem from critical study limitations, including the small sample size and collection of pulmonary function data during post-exacerbation period rather than stable stage. Similar to previous studies reported,^{30–32} we also found that age, D_{LCO}%, PaO₂ as well as PaCO₂ were notable indicators for all-cause mortality in COPD patients.

For a more realistic approach to clinical practice, we attempted to establish a nomogram model based on the ESMCSA and other significant parameters in the multivariate Cox proportional hazards analysis. Finally, a clinical prediction nomogram model has been established based on age, D_{LCO}%, ESMCSA, PaO₂ and PaCO₂. The C-index and calibration curve demonstrated that the present prediction nomogram model had considerable discriminative and calibration capabilities. DCA further showed that this nomogram model displayed large positive net gains within a wide range of threshold probabilities. Therefore, this nomogram model has demonstrated that ESMCSA can serve as a parameter for predicting the 5-year survival probability of COPD patients, and has significant application value for risk stratification. While prior studies have shown ethnic variability in the prognostic utility of ESMCSA in COPD,^{21,23} our findings derived exclusively from Chinese COPD patients warrant cautious interpretation. The generalizability of the established ESMCSA threshold to other ethnic populations requires external validation through multi-center cohort studies with diverse racial representations.

Several limitations of our study should be mentioned. First, the small number of non-survivors may limit the generalizability of the findings. Multi-center and prospective studies involving larger numbers of patients are needed to confirm the present results. Second, the treatment information within five years after discharge from the hospital had some impacts on the 5-year all-cause mortality of COPD patients, but these data were missing in our study. Third, a standard method for measuring the ESMCSA has not yet been established. We currently use a single-layer chest axial CT image at the lower edge level of the 12th thoracic vertebra and manually select the left and right ESM based on the attenuation range of skeletal muscle values to evaluate the ESMCSA. Therefore, it is necessary to establish an automated program for measuring the ESMCSA to provide a more objective and precise result. Finally, all COPD patients

underwent pulmonary function tests immediately after achieving clinical convalescence from acute exacerbation, but these measurements may not reflect the true baseline pulmonary function status of the patients. To address this limitation, our ongoing research will collect the pulmonary function data of stable COPD patients and evaluate their prognostic values in multidimensional risk stratification models.

In conclusion, ESMCSA obtained from a single-slice axial chest CT image is a significant predictor for 5-year all-cause mortality in COPD patients. The clinical prediction nomogram model based on ESMCSA, age, $D_{LCO}\%$, PaO_2 and $PaCO_2$ may provide reference values for predicting the survival period of COPD patients.

Data Sharing Statement

The datasets and analyses of this study are available from the corresponding author upon reasonable request.

Ethical Approval

The study adhered to the ethical principles outlined in the declaration of Helsinki. All patients or their family members provided informed consent, which was approved by the Research Committee of Human Investigation of the Second Affiliated Hospital of Xi'an Jiaotong University.

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Disclosure

The authors declare that there are no conflicts of interest on this work.

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