Low Skeletal Muscle Area at the T12 Paravertebral Level as a Prognostic Marker for Community-Acquired Pneumonia

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Rationale and Objectives: This study aimed to investigate whether the dorsal skeletal muscle area at 12th thoracic level (T12SMA) could be used as a predictor of in-hospital mortality and long-term survival among patients with community-acquired pneumonia (CAP).

Materials and Methods: A retrospective study was conducted on 1701 CAP patients who underwent chest computed tomography (CT) examinations at the First Hospital of Qinhuangdao. The primary outcome was in-hospital mortality. The T12SMA was analyzed. Multivariate regression logistic models were constructed to identify the prognostic markers of hospital mortality. Cox regression logistic models were constructed to identify the risk factors of long-term survival.

Results: The multiple logistic regression analysis showed that T12SMA [odds ratio (OR) = 0.946; p = 0.007], CURB-65 (OR = 1.521; p = 0.008), creatinine (OR = 1.003; p = 0.001), albumin (OR = 0.908; p = 0.001) and intensive care unit (ICU) (OR = 2.715; p = 0.007) were independent risk factors for predicting the in-hospital mortality. The cox regression logistic analysis showed that T12SMA (OR = 0.968; p = 0.000), age (OR= 1.036; p = 0.000), sex (OR= 1.435; p = 0.002), CURB-65 (OR = 1.311; p = 0.000), albumin (OR = 0.952; p = 0.000), creatinine (OR = 1.002; p = 0.000) and ICU (OR = 1.606; p = 0.001) were prognostic markers of long-term survival.

Conclusion: T12SMA, CURB-65, creatinine, albumin and ICU were independent risk factors for in-hospital mortality among patients with CAP. And low T12SMA affected the in-hospital mortality and long-term survival of patients with CAP.

Key Words: Community-acquired pneumonia; Computed tomography; Skeletal muscle area.

Abbreviations: CAP community-acquired pneumonia, CT computed tomography, SMA skeletal muscle area, T12SMA dorsal skeletal muscle area at T12 vertebral level, ICU intensive care unit, T12SMD dorsal skeletal muscle density at T12 vertebral level, BMI body mass index, CRP C-reactive protein

INTRODUCTION

Community-acquired pneumonia (CAP) is a very common respiratory disease and an important cause of mortality and morbidity worldwide (1–3). CAP patients may have different outcomes varying from rapid recovery to death. Therefore, it is crucial to evaluate the severity of CAP before starting treatment. Commonly, CURB-65 is used to evaluate the severity of CAP, which has been recommended by several CAP guidelines (4,5). Sarcopenia, which is defined as age-associated loss of muscle mass and strength, is also associated with a worse prognostic index of pneumonia (6). In addition, this syndrome is a risk factor for dysphagia (7), which has been associated with hospital readmission for aspiration and non-aspiration pneumonia (8).

In 2018, the European Working Group on Sarcopenia in Older People (EWGSOP) revised the diagnostic criteria for sarcopenia (9). The EWGSOP recommends the area measurement on a single cross-section computed tomography (CT) image at the level of the third lumbar (L3) vertebra as an alternative tool, since this area accurately represents the

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whole-body muscle. Thus, this method may serve as an alternative tool for assessing muscle quantity. A study showed that sarcopenia, which was defined by L3 skeletal muscle area (SMA) using a single transverse CT slice, was highly prevalent among patients with respiratory failure requiring mechanical ventilation (10). However, abdominal CT is not a routine examination for patients with CAP. Chest CT scanning is a conventional assessment for patients with CAP. The examination of the twelfth thoracic (T12) vertebra on CT images may serve as an alternative strategy when L3 is unavailable (11). Moreover, the decline in paravertebral muscle size and attenuation at T12 on CT images had been reported to be associated with in-hospital mortality and long-term survival in elderly patients undergoing chronic obstructive pulmonary disease (COPD) (12). The relationship between the dorsal skeletal muscle area at T12 vertebral level (T12SMA) and the mortality of CAP remains unclear.

This study retrospectively investigated clinical parameters, including T12SMA, dorsal skeletal muscle density at T12 vertebral level (T12SMD), and other risk factors, to evaluate whether these parameters might serve as prognostic markers for in-hospital mortality with CAP. It also explored whether the level of T12SMA at admission might be a predictor of long-term survival among patients with CAP.

METHOD AND MATERIALS

This study was approved by the ethics committee of the First Hospital of Qinhuangdao.

Population Cohort and Design

This retrospective study included patients hospitalized due to CAP at the First Hospital of Qinhuangdao between January 2015 and December 2018. The inclusion criteria were the following: 1) all patients were diagnosed with CAP, 2) patients over 18 years of age. The exclusion criteria were: 1) no adequate imaging within 7days after admission; 2) clinical data about CURB-65 missing; 3) clinical data about albumin, glucose, creatinine and body mass index(BMI) missing. They were divided into two groups based on their survival when discharged from the hospital. All enrolled patients were followed up until October 31, 2020.

Definition of CAP

The definition of CAP was done according to the 2016 CAP clinical practice guidelines by the Chinese Thoracic Society (4).

Data Collection

Initial data after admission were extracted from the Hospital Information System. Demographic variables included age and sex. Physical examination included mental status, respiratory rate, blood pressure, temperature, pulse, height and weight. Laboratory data included urea, glucose, albumin, creatinine and C-reactive protein (CRP). The scores of CURB-65 [confusion, urea>7mmol/L, respiratory rate≥30/min, blood pressure (systolic blood pressure<90mmHg or diastolic blood pressure≤60 mmHg) and age ≥65 years] was calculated (13). The primary outcome was in-hospital mortality.

Measurement of T12SMA and T12SMD

Patients underwent plain CT using a 64-row multidetector CT (GE Healthcare, Milwaukee, WI, USA) with 1-mm slice thickness in the supine position at admission or within 7days after admission. The electronically stored CT images were collected from Picture Archiving and Communication Systems (PACS, IMPAX6.3.1.4095, AGFA HealthCare NV, Belgium). T12SMA was defined as any muscle within the region posterior to the T12 spine and ribs and no more lateral than the lateral-most edges of the erector spinal muscles (Fig 1). The skeletal muscle boundaries were segmented manually. The cross-sectional muscle area and radiodensity were semi-automated thresholding using Slice-O-matic software, version 4.3 (Tomovision, Montreal, QC, Canada). Skeletal muscle was identified and quantified by use of Hounsfield unit (HU) thresholds (−29 to +150) (14). All imaging analyses were conducted in the cross-sectional area at the level of T12 vertebral. T12SMA was recorded as the sum of bilateral dorsal SMA, while T12SMD was recorded as the mean of bilateral dorsal muscle group radiodensity (Fig 1). Muscle segmentations were performed by an experienced operator, with

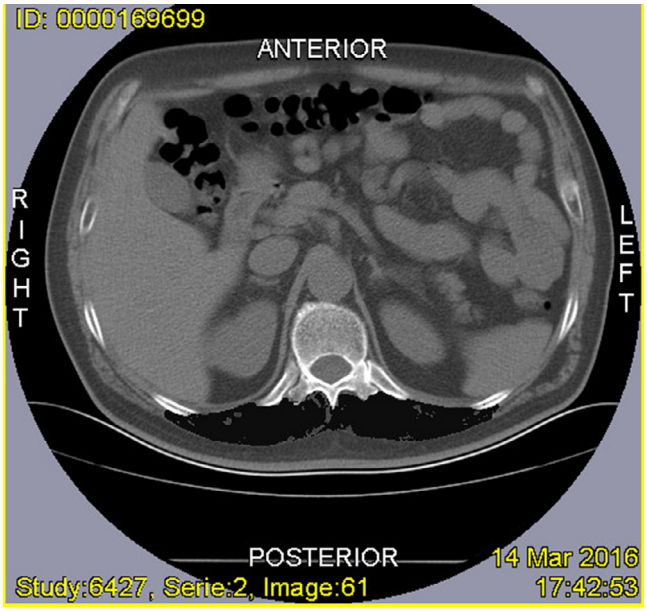

Figure 1. Example of the dorsal skeletal muscle area at T12 vertebral level (T12SMA). Delineation of T12SMA, using a threshold of -29 to +150 HU. The paravertebral skeletal muscle area was 42.33cm^2, the dorsal skeletal muscle density mean was 39.37 HU.

an audit of all images and segmentations by a musculoskeletal radiologist.

Statistical Analysis

Statistical analyses were performed using SPSS 23.0 (IBM, NY, USA). All demographic and clinical characteristics were described between the two groups based on the status at discharge (surviving or deceased) and compared using chi-square test or Student's t-test. Multivariate regression logistic models were constructed to identify the prognostic markers of hospital mortality. The selected variables were subjected to forward conditional stepwise regression. $p<0.05$ was considered to be statistically significant.

To emphasize the prognostic role of T12SMA in hospital mortality, the receiver operating characteristic (ROC) curve was used to analyze the accuracy, sensitivity, specificity, and area under the ROC. The Youden index was obtained by the ROC analysis, and the maximum tangent point was selected to establish the cutoff value. Cox regression logistic models were constructed to identify the prognostic markers of long-term survival. $p<0.05$ was considered to be statistically significant.

RESULTS

A total of 2808 CAP patients were analyzed. One thousand one hundred and seven patients were additionally excluded due to missing clinical data. Eventually, this study enrolled 1701(61%) patients (995 males and 706 females), aged 65.39±17.17 years (Table 1). Of the 1701 patients, 70 died at discharge. The demographic and clinical characteristics and details of patient samples in the two groups are shown in (Table 1). In the univariate analyses, the variables, such as age (65.39±17.17, p = 0.000), BMI (23.47±4.25, p = 0.000), CURB-65(1.11±0.99, p = 0.000), glucose (7.54±3.96, p = 0.000), albumin (35.47±5.55, p = 0.000), creatinine (86.42±92.53) and CRP (53.23±64.24, p = 0.003) had significant differences between the groups. T12SMA was lower in the deceased group (26.65±8.96) than in the surviving group (34.67±10.51, p = 0.005). Further, 246 patients (14.5%) were admitted to the intensive care unit (ICU) during hospitalization, and the frequency of ICU had significant differences between the groups (p = 0.000).

Multivariate analyses were performed using the significant risk factors determined in the univariate analysis. As shown in (Table 2, multiple logistic regression analysis showed that T12SMA [odds ratio (OR) = 0.946; 95% confidence interval (CI), 0.909 − 0.985, p = 0.007], CURB-65 (OR = 1.521; 95% CI, 1.115 − 2.076, p = 0.008), creatinine (OR = 1.003; 95% CI, 1.001 − 1.005, p = 0.001), albumin (OR = 0.908; 95% CI, 0.857 − 0.964, p = 0.001) and ICU (OR=2.715; 95% CI, 1.314 − 5.608, p = 0.007) were independent risk predictors for the in-hospital mortality.

The area under the ROC curve (AUC) for the prognostic role of T12SMA in hospital mortality was 0.728 (p = 0.000). The optimal cutoff value of T12SMA to predict survival was 30.67 cm^2 (Fig 2).

As shown in (Table 3), the variables in the cox regression logistic models were T12SMA (OR = 0.968; 95% CI, 0.955

TABLE 1. Clinical Characteristics of Patients in the Two Groups

Variable	All Patients (n = 1701)	Surviving (n = 1631)	Deceased (n = 70)	t or χ^2	p
Sex (males/females)	995/706	951/680	44/26	0.572	0.449
Age	65.39±17.17	64.94±17.17	75.93±13.05	-5.28	0.000
BMI(kg/m^2)	23.47±4.25	23.56±4.23	21.57±4.27	3.84	0.000
Confusion [n(%)]	139(8.2)	117 (7.2)	22 (31.4)	52.62	0.000
Temperature (°C)	36.7±8.24	37.14±8.41	36.82±0.81	0.31	0.756
Respiratory rate≥30/min[n(%)]	68(4.0)	62(3.8)	6(8.6)	3.98	0.046
Pulse (/min)	87.65±17.44	87.05±16.88	101.0±24.07	-6.65	0.000
SBP (mmHg)	130.83±23.21	131.06±22.66	124.86±33.19	2.19	0.028
DBP (mmHg)	77.99±13.38	78.17±12.89	73.5±21.3	2.87	0.004
Urea (mmol/L)	7.02±5.78	6.76±5.39	12.99±9.93	-9.03	0.000
CURB-65	1.11±0.99	1.06±0.96	2.19±1.08	-9.55	0.000
Glucose (mmol/L)	7.54±3.96	7.46±3.85	9.39±5.71	-4.00	0.000
Albumin (g/L)	35.47±5.55	35.67±5.48	30.68±4.81	7.5	0.000
Creatinine (μmol/L)	86.42±92.53	83.53±86.06	152.1±176.9	-6.14	0.000
T12SMA (cm^2)	34.34±10.56	34.67±10.51	26.65±8.96	6.287	0.000
T12SMD (HU)	38.47±10.25	38.71±10.23	32.71±9.03	4.827	0.000
ICU [n(%)]	246(14.5)	207 (12.7)	39 (55.7)	100.428	0.000
CRP(mg/L)	53.23±64.24	52.16±63.7	79.47±72.46	-2.962	0.003

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; T12SMA, dorsal skeletal muscle area at the T12 vertebral level; T12SMD, dorsal skeletal muscle density at the T12 vertebral level; ICU, intensive care unit; CRP, C-reactive protein. p <0.05 was considered statistically significant.

TABLE 2. Logistic Regression Analysis of the Risk Factors for in-Hospital Mortality

	B	SE	Wald	*p*	OR	95% CI	
T12SMA	-0.055	0.020	7.351	0.007	0.946	0.909	0.985
CURB-65	0.419	0.159	6.989	0.008	1.521	1.115	2.076
Creatinine	0.003	0.001	10.182	0.001	1.003	1.001	1.005
Albumin	-0.096	0.030	10.226	0.001	0.908	0.857	0.964
ICU	0.999	0.370	7.278	0.007	2.715	1.314	5.608

Multiple logistic regression analysis, in-hospital mortality was considered as the dependent variables in a multiple logistic regression analysis with sex, age, BMI, CURB-65, T12SMA, T12SMD, creatinine, albumin, glucose, ICU and CRP as independent variables. Abbreviations: T12SMA, dorsal skeletal muscle area at the T12 vertebral level; ICU, intensive care unit.

– 0.982, p = 0.000), age(OR = 1.036; 95% CI, 1.025 – 1.046, p = 0.000), sex(OR = 1.435; 95% CI, 1.137 – 1.810, p = 0.002), CURB-65 (OR = 1.311; 95% CI, 1.154 – 1.489, p = 0.000), albumin (OR = 0.952; 95% CI, 0.933 – 0.972, p = 0.000), creatinine (OR = 1.002; 95% CI, 1.001 – 1.002, p = 0.000) and ICU(OR = 1.606; 95% CI, 1.223 – 2.108, p = 0.001). They were independent risk factors for predicting the long-term survival.

DISCUSSION

The incidence of CAP was 7.13 per 1000 person-years in China (15) and CAP was among the top 10 causes of death worldwide (16). In this study, we showed that T12SMA, CURB-65, creatinine, albumin and ICU were independent risk factors for in-hospital mortality among patients with CAP. Low T12SMA affected the in-hospital mortality and long-term survival of patients with CAP. As a surrogate of L3 SMA, T12SMA was used to measure the skeletal muscle mass of patients with CAP in this study. As reported, the low skeletal muscle mass prognosticated high mortality in the acute episode and long-term survival chronic rehabilitation stage with different lung diseases that included COPD, cancer and COVID-19 pneumonia (12,17,18). Muscle mass may affect the occurrence of pneumonia through different mechanisms. Weakened muscle strengths and low body muscle mass were risk factors for the onset of pneumonia, which suggested malnutrition (19,20). T12SMA was associated with the serum albumin level and BMI at admission in our study (supplementary Table). Muscle mass was maintained by protein homeostasis (21). Serum albumin concentrations were associated with reduced muscle mass in relatively healthy, well-nourished, elderly men and women (22). Meanwhile, the decline of skeletal muscle mass was closely correlated with inflammatory proteins. The lower the level of skeletal muscle mass, the more severe was the inflammatory response (23). Similar to the above study, we found that T12SMA was associated with the inflammation biomarker CRP (supplementary Table). Therefore, the level of skeletal muscle mass reflected the degree of inflammatory response. In addition, inflammation caused the production of pro-inflammatory cytokines and induced muscle weakness (24). Pro-inflammatory cytokines induced muscle proteolysis by a twostep process, consisting of myofibrillar protein cleavage by calpains and/or caspase-3, followed by further degradation by the ubiquitin-proteasome system (24,25). What's more, paravertebral muscle is a major muscle of respiration along with the diaphragm and intercostal muscles. Low T12SMA suggested a loss of respiratory muscle mass, which was a risk factor for the onset of pneumonia (19). Our findings suggest that the quantitative assessment of the paravertebral muscle on CT may aid risk assessment in patients with CAP.

Sarcopenia was defined as the progressive decline of skeletal muscle area, strength and function. Generally bioelectrical impedance analysis (BIA) and dual-energy X-ray absorption (DXA) have been used to measure the muscle mass and grip strength devices and a gait speed test have been used to measure function (26,27). Although we do not measure sarcopenia as previously defined by others, CT-derived muscle

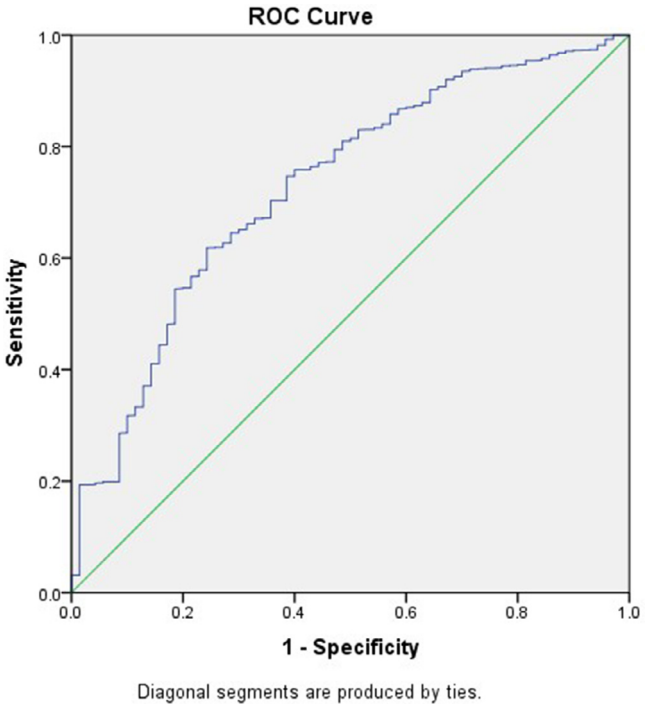

Figure 2. ROC curve of T12SMA to predict the hospital mortality of patients [AUC = 0.728, p = 0.000, 95%CI (0.668~0.789)].

TABLE 3. Cox Regression Analysis of the Risk Factors for Long-Term Survival

Variables	B	SE	Wald	*p*	OR	95% CI	
T12SMA	-0.032	0.007	19.676	0.000	0.968	0.955	0.982
Age	0.035	0.005	45.969	0.000	1.036	1.025	1.046
Sex	0.361	0.119	9.258	0.002	1.435	1.137	1.810
CURB-65	0.271	0.065	17.372	0.000	1.311	1.154	1.489
Albumin	-0.049	0.010	21.876	0.000	0.952	0.933	0.972
Creatinine	0.002	0.000	18.167	0.000	1.002	1.001	1.002
ICU	0.473	0.139	11.617	0.001	1.606	1.223	2.108

Cox regression analysis, long-term survival was considered as the dependent variables in a cox regression analysis with age, sex, BMI, CURB-65, T12SMA, T12SMD, creatinine, albumin, glucose and ICU as independent variables. Abbreviations: T12SMA, dorsal skeletal muscle area at the T12 vertebral level; ICU, intensive care unit.

measurements likely reflect multiple factors that influence in-hospital and long-time outcomes (28). Muscles could serve as a surrogate prognosticator and improve the assessment of patients' overall physical fitness (29), while overcoming drawbacks of other risk assessment tools. For example, BMI is a commonly recorded known risk factor but fails to discriminate between fat mass and lean body mass (30). This suggests that skeletal muscle size may be more sensitive than BMI as a measure of wasting and weakness. Also, tests such as stair-climbing or the 6-min walk test require additional patient effort and cooperation (31,32) while muscle quantification relies on already available objective data, given that CT scans of the thorax are commonly obtained in patients with CAP.

Further, CURB-65 is a classical tool for evaluating the severity of CAP. A previous meta-analysis showed that the AUC area under the curve (AUC) of CURB-65 was about 0.8 for predicting 30-day mortality in hospitalized CAP patients (33). Similarly, our study showed that CURB-65 was significantly elevated in the deceased group and was an independent risk factor for predicting the in-hospital mortality. Albumin is a protein made by the liver that plays many important roles. Numerous studies confirmed that serum albumin correlated with short-term and long-term mortality of CAP (34,35). In line with previous studies, albumin level was also an independent predictor of in-hospital mortality and long-term survival of CAP in our study.

This study had several limitations. First, this was a single-center retrospective study. A certain number of patients were eliminated due to unavailable imaging or clinical data elements, resulted in a 39% exclusion rate. Especially very critically ill patients who could not undergo CT often had a bad outcome rapidly. Thus, larger studies with data from other hospitals or regions are required to assess the role of the paravertebral muscle mass in CAP risk prediction. Second, confounding factors, such as arterial blood gas analysis, pathogens of infection were not evaluated in our study. Finally, muscle is just one body composition metric that can be derived from CT examinations. Future studies could explore the role of fat, edema and bone density in this context. Prospective data collection would also allow the inclusion of important factors such as respiratory function measurement and exercise testing.

CONCLUSION

The T12SMA was an independent predictive factor for in-hospital mortality and long-term survival in adult patients with CAP. Skeletal muscle mass loss was a crucial problem in CAP and hence should not be neglected. This study presented an alternative method for measuring the skeletal muscle mass when the CT scans were available, especially for critically ill patients whose body composition like BMI could not be acquired. Finally, these findings allow us to evaluate CT-derived muscle measurement in the prediction of CAP or other infections.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.acra.2021.12.026.