Analysis of Association between CT-assessed Body Composition and Survival Composition of Patients with Sepsis in EICU

Tian Yun Xu
First Affiliated Hospital of Anhui Medical University
He Zhang
First Affiliated Hospital of Anhui Medical University
Jie Zhi Li
First Affiliated Hospital of Anhui Medical University
Nan Wang (523601821@qq.com)
the Fourth Affiliated Hospital of Anhui medical univeisity https://orcid.org/0000-0002-0257-1865

Research article

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Abstract

Background: The prevalence of sepsis among patients in the intensive care unit is high. Thus, the evaluation of prognosis in these patients is paramount. This study aimed to appraise the role of the abdominal composition quantified from computed tomography (CT) scan in predicting a 90-day mortality rate among patients with sepsis in the emergency intensive care unit (EICU).

Method: Through Cox regression analysis, the skeletal muscle density (SMD, skeletal muscle area (SMA), and subcutaneous adipose tissue area (SAT) assessed by the CT abdomen were associated with the 90-day mortality rate, with adjustment to the acute physiology and chronic health assessment (APACHE II) score, sequential organ failure assessment (SOFA) score, and BMI. Linear regression was performed to analyze other clinical factors.

Result: The Cox regression analyses showed that compared with the non-survival group at 90-day, patients with a higher SMD (HR per 10 HU = 0.619; 95% CI = 0.450 - 0.853; p = 0.003), SMA (HR per 10 cm^2 = 0.870; 95% CI = 0.781 - 0.969; p = 0.011), and SAT (HR per 10 cm^2 = 0.954; 95% CI = 0.912 - 0.999; P = 0.047) were significantly associated with a lower 90-day mortality rate. These significant correlations persisted after adjusting for the BMI, APACHE II, and SOFA scores. Further analysis revealed gender differences in the SMD and skeletal muscle index (SMI) between the survival and the non-survival group.

Conclusion: The content of body composition assessed by an abdominal CT scan is highly associated with the 90-day mortality of patients with sepsis in the EICU, of which the SMD, SMA, and SAT represent valuable prognostic factors.

Introduction

Sepsis is associated with life-threatening organ dysfunction as a result of imbalances in the host response to an infection [1], which is a common clinical challenge faced by the emergency and critical care clinician. Sepsis contributes to a huge burden to the society and economy, with the mortality rate exceeding 25%. Given the prevalence and impactful of this disorder, in 2016, the American Society of Intensive Medicine and the European Society of Intensive Medicine have jointly issued the 3rd international consensus on the definition and diagnostic criteria of sepsis [2].

Muscular atrophy is a serious sequela of critical illnesses. Low muscle density has been associated with poor prognosis [3]. In particular, muscle loss is related to higher hospitalization and mortality among patients in the ICU. Furthermore, patients who have survived following discharge from the ICU may also experience functional changes that affect their quality of life. Therefore, the concept of sarcopenia has been introduced in 2010 by the European Working Group on Sarcopenia in Older People [4], which is defined as a syndrome characterized by a progressive and comprehensive loss of skeletal muscle mass and strength.

In recent years, studies have shown that skeletal muscle acts as an endocrine organ of cytokines and peptides that plays a key role in the inflammatory process [5]. Also, skeletal muscle content is of great significance to the nutritional status and prognostic risk assessment of ICU patients with sepsis. Given that the systemic inflammatory response represents a risk factor for muscle loss, this warrants further study to define the relationship between skeletal muscle content and survival rate in the presence of inflammatory response [6],to analyze whether skeletal muscle loss is related to mortality.To date, there is no research examining the influence of body composition on the prognostic evaluation of ICU patients with sepsis. Therefore, this study aimed to evaluate the association between body composition and 90-day mortality among these patients.

Methods

Patients and data

This was a single-center, retrospective analysis of the abdominal body composition of critically ill patients with sepsis admitted to the EICU of Anhui Medical University from January 2015 to December 2018. Patient inclusion criteria for the study were 18 years of age or older, hospitalization in the EICU for at least 4 days, and at least one abdominal CT examination within 24 hours before or 4 days after admitting to the EICU. Patients were excluded if they were pregnant or diagnosed with chronic neuromuscular diseases.

Data including patient age, gender, weight, height, BMI, skeletal muscle density and area, visceral fat area and density, subcutaneous fat area and density, intermuscular fat area and density, the worst scores on APACHE II and SOFA within 24 hours of admission, laboratory indicators, 90-day survival rate, ventilation time, EICU length of stay (EICU-LOS), hospital length of stay, continuous renal replacement therapy (CRRT), Charlson comorbidity index (CCI) [7], and the nutrition risk in critically ill (NUTRIC) score [8] were collected. The survival prognostic information of patients discharged from the hospital before 30 days was followed up by telephone.

CT scan analysis

High accuracy for the analysis of the body composition of a single-slice abdominal CT scan at the level of the third lumbar vertebra (L3) has been previously demonstrated [9]. Based on the evaluation of magnetic resonance imaging (MRI), the skeletal muscle area at this level is closely related to the volume of skeletal muscle in the whole body [3]. In our study, patients' abdominal CT images were analyzed by experienced radiologists using the Mimics version 17 software (Fig. 1) [10]. Patients were excluded from the study if the quality of the CT images were low or the muscle integrity was damaged due to factors such as trauma or artifacts. The vertebral bone markers at the L3 level were used to ensure the reproducibility and consistency of measurements.

Varying ranges of HU value (Hounsfield) were used to define body compositions, with the HU of muscle ranging − 29 to + 150, HU of intermuscular fatty tissue and subcutaneous fat tissue ranging − 190 to -30, and HU of visceral fatty tissue ranging − 150 to -50 [3, 11]. SMD was evaluated by the average radiation muscle attenuation of the entire muscle at the L3 level, and the HU scale was a radioactivity scale that described the tissue density in CT scans [12]. By analyzing the bone density scale, a higher HU value indicated a higher skeletal muscle density and a lesser fat infiltration [13]. Given that the body composition content corresponded to the nutritional status and survival prognosis of patients with sepsis in the EICU, this was analyzed according to the primary endpoint of our study, which was the 90-day mortality rate. The secondary endpoints included ventilation time, length of hospital stay, norepinephrine dose, CRRT time, CCI score, and gender differences (Fig. 1).

Statistical analysis

A normality test was performed for all the continuous variables. To compare the survival and non-survival groups, the independent sample *t*-test was used for the normally distributed data, whereas the Mann-Whitney U test was used to analyze non-normally distributed variables. Fisher's exact test and Chi2 test were used to analyze categorical variables. Following univariate analyses, BMI was added to the model to adjust for the severity of the disease (model 2), and then the APACHE II and SOFA scores were added to the second adjustment model (model 3). The 'age' included in the APACHE II was therefore not separately included in the adjustment model. Logistic regression and linear regression were used to explore the relationship between skeletal muscle area (SMA), skeletal muscle density (SMD), subcutaneous adipose tissue area (SAT), and the ventilation time, hospital stay, norepinephrine dose, CRRT duration, and CCI score. Kaplan-Meier chart was used to analyze the relationship between skeletal muscle index and 90-day mortality (divided into two groups according to the median) stratified by gender, and the log-rank test was performed to compare the survival curves between the two groups.

SPSS Statistics 23.0 is used for all the statistical analysis, and values were expressed as mean ± standard deviation (SD) or median and quartile. All data were two-sided. A P-value of < 0.05 was considered statistically significant.

Results

Patients selection

During the study period, A total of 1898 patients were included in the study, 460 patients met the clinical criteria for sepsis but only 128 patients fulfilled our study criteria for the abdominal CT scans. The quality of CT images was suboptimal in the subcutaneous fatty tissue in 4 patients, and another patient had surgery on the abdominal muscles. Therefore, a total of 123 patients with complete clinical data were included in our study (fig.2).

Patient characteristics

Table 1 reflects the patient's comorbidities and main infections, Table 2 contains the characteristics of 90-day survivors and non-survivors, Table 3 contains univariate analysis and adjusted models, Table 4 contains the correlation between skeletal muscle density, area, and subcutaneous fat tissue area with secondary results, and Table 5 shows the relationship between SMD and SMI of different genders and 90-

day mortality. The basic demographics of patients were outlined in Table 1. Overall, the 90-day mortality rate was 35.8%. When compared with the survival group, patients in the non-survival group were significantly older (67±16 vs 57±16 years, p = 0.001), had higher APACHE II scores (21±5 vs 17±5, p <0.001), and higher SOFA scores [10 (8-13) vs 8 (7-11) cm^2, p = 0.005] (Table 2). Upon admission to the ICU, the average SMD of all patients was 30.21 HU, the average SMA was 124.61 cm^2, and the average SAT was 112.85 cm^2. The non-survival group had a lower SMD (26.7±9.3 vs 32.2± 9.3 HU, p = 0.003), lower SMA (114.8±27.4 vs 130.1±30.9 cm^2; p = 0.007), and also lower SAT (96.1±65.4 vs. 122.2±71.6 cm^2, p = 0.043) when compared with the survival group.

Table 1. Demographics of patients included in the study.

Characteristics	Overall patients (n = 123)	
Comorbidities	Total	(%)
AKI/CKD	33	26.8
cerebrovascular disease	32	26
diabetes	30	24.3
heart failure	25	20.3
connective tissue disease	15	12.2
gastroduodenal ulcer	14	11.3
tumor	14	11.3
Others	20	16.2
Focus of infection	Total	(%)
Respiratory	39	31.7
Hepatobiliary	25	20.3
Urinary tract	11	8.9
Others	48	39

AKI acute kidney injury,CKD chronic kidney diseases

Table 2. Comparisons of patient demographics between the survival and the non-survival groups.

	Survivors (79)		Non-survivors (44)		P value
	M/medium/n	SD/IQR/%	M/medium/n	SD/IQR/%	
Age	56.61	.30	67.07	16.23	0.001
male，n	48	61%	34	77%	0.074
BMI	21.60	20.45-22.60	21.23	20.06-22.17	0.317
APACHE II	16.59		21.36	5.08	
SOFA	8	7-11	10	8-13	0.005
NUTRIC	4	2-5	5	5-7	
PCT	7.54	3.36-38.84	7.795	3.89-30.73	0.858
Charlson comorbidity index	3	2	6	2	
Length of hospital stay before ICU admission, days	0	0-1	1	0-2	0.391
Time from ICU admission to CT scan, days	1	1-3	2	1-4	0.285
SMD (HU)	32.15	9.26	26.74	9.25	0.002
SMA (cm^2)	130.09		114.76		0.007
SMI cm^2/m^2	46.65	8.9	41.63		0.004
IMAT (HU)	-59.26	5.28	-57.21	6.53	0.075
IMAT (cm^2)	13.10	6.44	14.91	7.62	0.166
SAT (HU)	-85.44	13.95	-80.25		0.074
SAT (cm^2)	122.21	71.56	96.06	65.42	0.043
VAT (HU)	-82.85		-85.20	-93.13, -73.3	0.897
VAT (cm^2)	93.30	63.54	91.27	80.40	0.878
Length of ventilation	6	0-10	10	4-16	0.002
ICU length of stay	8	5-15	10	6-16	0.301
Hospital length of stay	22	15-31	15	11-23	0.005
NA (mg)	12	0-54	80	12-410	
CRRT，n	11	14%	15	34%	0.012

BMI body mass index,APACHE Ⅱ Acute physiology and chronic health evaluation Ⅱ, SOFA sequential organ failure assessment,PCT procalcitonin,CCI Charlson comorbidity index, SMD skeletal muscle density,SMA skeletal muscle area,IMAT intermuscular adipose tissue,SAT subcutaneous adipose tissue,VAT visceral adipose tissue,SMI SMA/height2,NA noradrenaline,CRRT continuous renal replacement therapy

COX regression analysis (Table 3) demonstrated that higher SMD was associated with a lower 90-day mortality (hazard ratio, HR per 10 HU = 0.619; 95% CI = 0.450 - 0.853; p = 0.003). After adjusting for the confounding factors (SOFA and APACHE II), this significant association had persisted (HR per 10 HU=0.722; 95% CI=0.524-0.997; p=0.048).

Table 3. Cox regression analyses: an association between SMD, SMA, or SAT and 90-day mortality.

90-day mortality	Univariable N = 123			Model 2 N=123			Model 3 N=123		
	HR	95%	P	HR	95%	P	HR	95%	P
SMDhu (per 10)	0.619	0.450-0.853	0.003	0.613	0.442-0.851	0.003	0.722	0.524-0.997	0.048
SMAcm^2 (per 10)	0.870	0.781-0.969	0.011	0.860	0.768-0.963	0.009	0.889	0.797-0.992	0.036
SATcm^2 (per 10)	0.954	0.912-0.999	0.047	0.952	0.907-0.999	0.046	0.952	0.914-0.992	0.020

Model 2 adjusts BMI; Model 3 adjusts SOFA, APACHE II.

Similarly, higher SMA was significantly associated with lower 90-day mortality (HR per 10 cm^2 = 0.870; 95% CI =0.781 - 0.969; p = 0.011), and remained significant after adjusting for the confounding factors (HR per 10 cm^2 = 0.889; 95% CI = 0.797 - 0.992; p = 0.036).

Furthermore, higher SAT was also significantly correlated with a lower 90-day mortality rate (HR per 10 cm^2 = 0.954; 95% CI = 0.912-0.999; p = 0.047), which again, remained significant after adjusting for the confounding factors SOFA and APACHE II (HR per 10 cm^2 = 0.952; 95% CI = 0.914-0.992; p = 0.02).

Analyses of secondary endpoints

Higher SMD, SMA, and SAT were associated with lower CCI scores (Table 4). After adjusting for the APACHE II and SOFA scores, this correlation remained significant. The amount of norepinephrine was related to the SAT but this correlation was non-significant after adjusting for the confounding variables. There were significant gender differences in the SMD and skeletal muscle index (SMI) between the survival and the non-survival group, where the SMD and SMI were higher among the male survivors while this phenomenon was not observed in female patients (Table 4, Table 5 and fig.3).

Table 4. Logistic and linear regression analyses: an association between SMD, SMA, or SAT and secondary outcomes.

	Univariable			Adjusts APACHE II and SOFA		
	OR/B	95% Cl	P value	OR/B	95% Cl	P value
Length of ventilation						
SMD per10HU	-1.133	-2.867 to 0.601	0.198	-0.727	-2.332 to 0.878	0.372
SMA per10cm^2	-0.088	-0.637 to 0.460	0.751	-0.001	-0.507 to 0.505	0.997
SAT per10cm^2	-0.013	-0.251 to 0.225	0.917	0.038	-0.181 to 0.257	0.734
Hospital length of stay						
SMD per10HU	-0.038	-2.792 to 2.716	0.978	0.134	-2.670 to 2.938	0.925
SMAper10cm^2	0.196	-0.669 to 1.061	0.655	0.258	-0.622 to 1.137	0.563
SAT per10cm^2	0.085	-0.290 to 0.460	0.654	0.073	-0.309 to 0.454	0.706
NA (mg)						
SMD per10HU	-18.219	-56.121 to 19.682	0.343	-11.437	-46.868 to 23.998	0.524
SMAper10cm^2	-2.317	-14.269 to 9.636	0.702	-1.137	-12.287 to 10.012	0.840
SAT per10cm^2	-5.634	-10.720 to -0.547	0.030	-4.509	-9.270 to 0.252	0.063
CRRT, n						
SMD per10HU	0.319	0.868-2.181	0.174	0.330	0.880-2.201	0.158
SMA per10cm^2	0.111	0.970-1.286	0.125	0.113	0.968-1.294	0.129
SAT per10cm^2	0.056	0.995-1.125	0.071	0.062	1.000-1.133	0.051
CCI						
SMD per10HU	-0.559	-0.948 to -0.169	0.005	-0.459	-0.827 to -0.093	0.015
SMA per10cm^2	-0.016	-0.283 to -0.037	0.011	-0.137	-0.253 to -0.021	0.021
SAT per10cm^2	-0.061	-0.015 to -0.008	0.025	-0.055	-0.105 to -0.005	0.032

Table 5. The comparison of body composition between the survival and the non-survival groups of different genders.

Body Composition	Survivors (79)	Non-survivors (44)	P-value
	Male		
Number	48	34	
SMD(HU)	35.908.50	26.809.60	
SMI cm^2/m^2	50.268.05	43.199.37	
SATcm^2	106.2268.01	79.2458.34	0.064
	Female		
Number	31	10	
SMD(HU)	26.347.24	26.498.40	0.958
SMI cm^2/m^2	41.057.24	36.316.21	0.071
SATcm^2	146.9570.88	153.2457.15	0.800

Discussion

Our study has demonstrated that the lower body compositions including the SMA, SMD, and SAT of EICU patients with sepsis are significantly associated with a poorer 90-day overall survival, which is consistent with previous studies and indicating that the severity of skeletal muscle loss is an important predictor of patient prognosis [14-16]. Specifically, among critically ill patients, our findings were consistent with the study by Wilhelmus et al., confirming that the density and area of skeletal muscle play an important role in evaluating the survival prognosis [3]. EICU patients often suffer from malnutrition and systemic inflammation, which contributes to a decline in their immune function leading to an imbalance in response to infection and sepsis [19]. Coupled with significant skeletal muscle loss, these factors will lead to higher hospitalization and mortality rates [17,18]. At present, varying cut-off values have been used to define abdominal skeletal sarcopenia, and the optimal cut-off value for predicting patient survival through sarcopenia remains unknown [20]. Nevertheless, the prognostic significance of sarcopenia based on Martin et al.'s definition is currently widely used in cancer patients [21-23].

This study revealed that higher subcutaneous adipose tissue was associated significantly with a lower 90-day mortality rate among EICU patients with sepsis. Interestingly, other studies have observed a lower hospital mortality rate in severely ill patients who were otherwise overweight and obesity [24], while a large observational cohort study of 154308 patients has provided more solid evidence for this phenomenon of obesity paradox [25]. Some authors believe that adipose tissue may play an important role in the immune system of EICU patients under physiological stress [17]. Another explanation for this obesity paradox may be that when patients are exposed to intense inflammation and metabolic stress, adipose tissue may act as a nutritional reserve that gives survival advantage. Furthermore, specific hormones in obesity have also been shown to play a role in influencing mortality [26]. Bornstein and colleagues reported a positive correlation between the leptin concentration and the survival rate of patients with sepsis, suggesting the role of leptin in the adaptive response to critical illness [26,27].

A large number of randomized controlled trials have shown that norepinephrine shares the same clinical efficacy as other vasoactive drugs but it has fewer complications such as cardiac arrhythmias [28]. In our study, a linear relationship between the area of subcutaneous adipose tissue and the amount of norepinephrine was demonstrated. When the confounding variables have been adjusted, this relationship disappeared, indicating the association of the amount of norepinephrine to the severity of the disease.

The Charlson Comorbidity Index (CCI) is currently one of the most commonly used tools in comorbidity assessment [7,29]. This study demonstrated a significant association between CCI and body composition. The study by Gong et al. highlighted the important role of CCI in assessing skeletal muscle mass and physical function, which correlated a higher the CCI score with a lower muscle area, providing essential information and evidence for the diagnosis of sarcopenia [7].

It is generally recognized that the body compositions and the metabolisms of fat and protein differ between men and women [30-32], but few have explored the relationship between body composition of different genders and in patients with sepsis in critical settings. Here, we analyzed and compared the differences in body composition of different genders between the survival and the non-survival groups of patients with sepsis in EICU, and found that in men, the skeletal muscle index and skeletal muscle density of the survival group were significantly higher. In women, no such difference was observed. Further studies are warranted to delineate the pathophysiological pathways that may explain the influence of gender differences in skeletal muscle and survival prognosis in critically ill patients with sepsis. In preclinical models and healthy participants, gender-based differences in the fiber type composition of skeletal muscle, function, and muscle fatigue sensitivity have been widely reported [33,34]. Also, the study by Choi et al. has shown that compared with females, male patients with advanced cancer and muscle wasting were significantly associated with mortality [35].

Our study represented the first analysis associating body composition with survival outcomes of patients with sepsis in EICU. This was a retrospective study carried out in a tertiary hospital in China with no variability in races [36] of the included patients. However, selection bias was apparent, which included only those patients with sepsis who had undergone abdominal CT scans. Patients' Also, nutritional supports of these patients were not explored.

Conclusions

The body composition assessed by the abdominal CT scan is significantly associated with the 90-day survival prognosis of EICU patients with sepsis, which is independent of BMI, SOFA, and APACHE II scores, especially among male patients. Therefore, body composition should be measured and incorporated into the overall assessment of the nutritional status and prognosis in clinical practice.

Abbreviations

AKI: acute kidney injury; CKD: chronic kidney diseases; BMI: body mass index; APACHE II: Acute physiology and chronic health evaluation II; SOFA: sequential organ failure assessment; PCT procalcitonin; CCI: Charlson comorbidity index; SMD: skeletal muscle density; SMA: skeletal muscle area; IMAT: intermuscular adipose tissue; SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue; SMI: SMA/height2; NA: noradrenaline; CRRT: continuous renal replacement therapy

Declarations

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None

Authors' contributions

YX analyzed the data and wrote the paper.HZ and JL collected the date.NW checked the integrity of the data and the accuracy of the data analysis.All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

The study was approved by the ethics committee of the First Affiliated Hospital, Anhui Medical University (No.Quick-PJ2020-16-08). Informed consent was waived because the study was retrospective in design. The study was performed in accordance to the Helsinki Declaration.All patients'records were anonymized and de-identified prior to analysis.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Figures

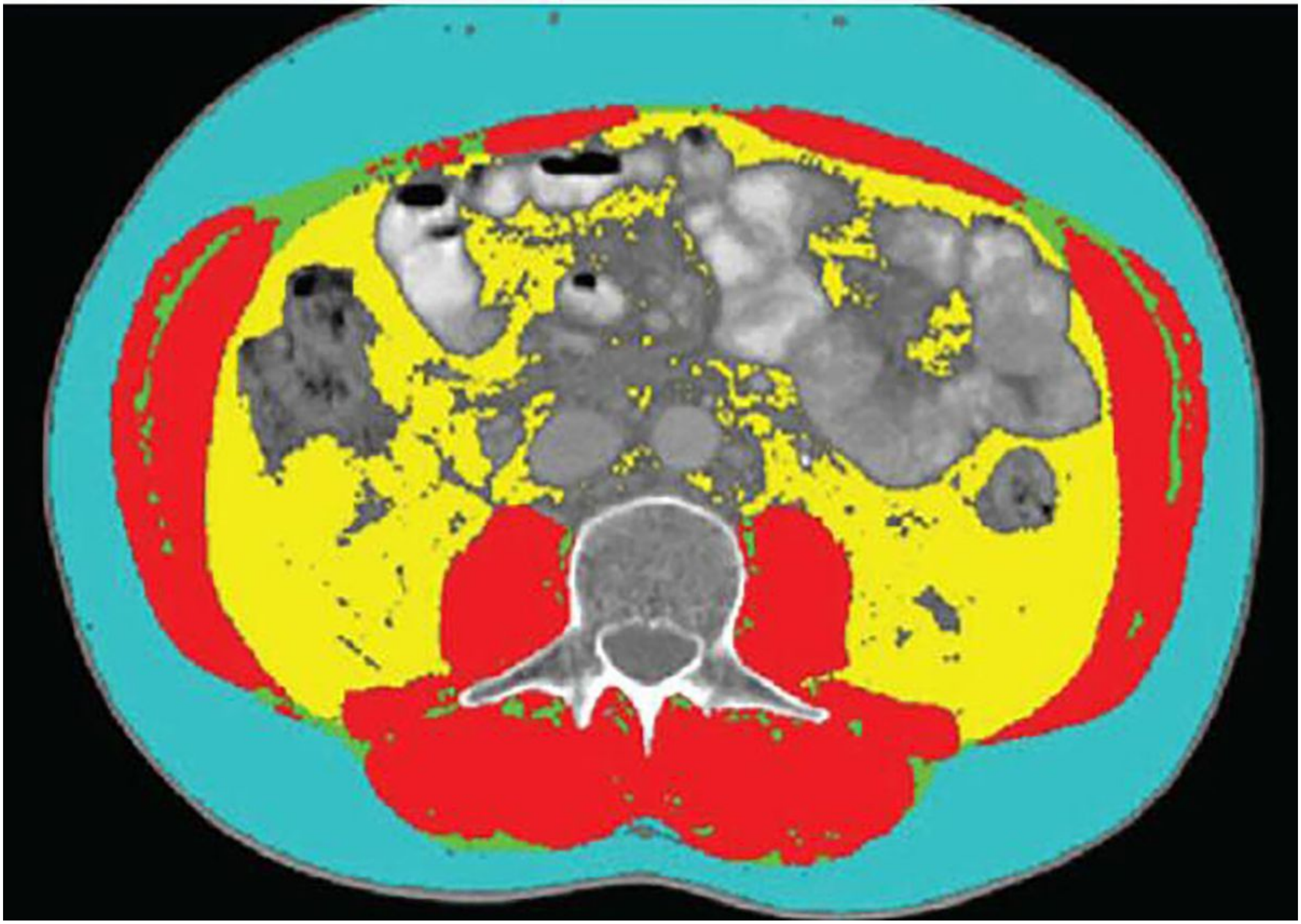

Figure 1

An Example of a CT slice at the L3 level to determine the body composition. SMD(red),VAT(yellow),SAT(bule),IMAT(green).

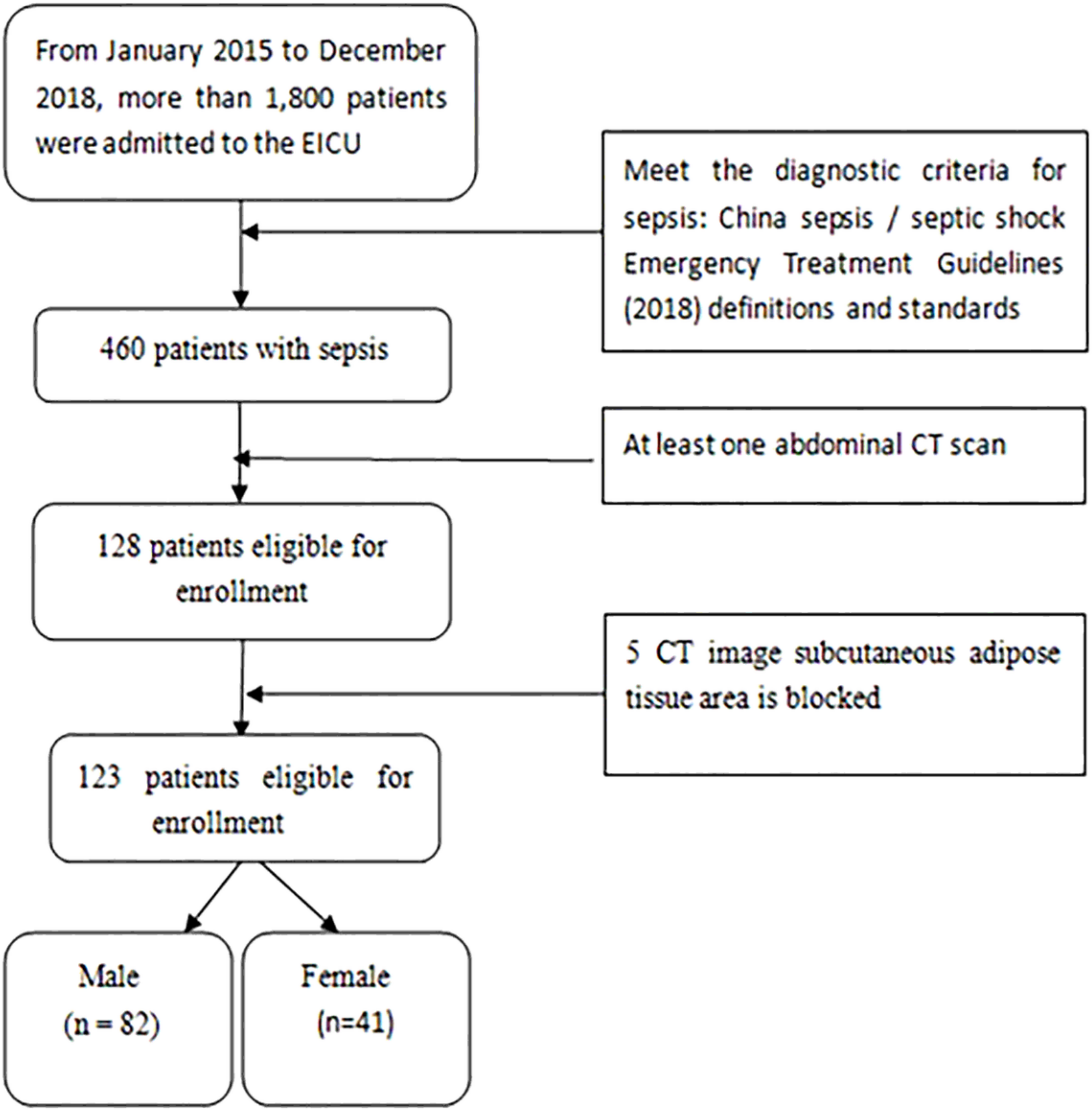

Figure 2

Flow chart of patient selection for the study.

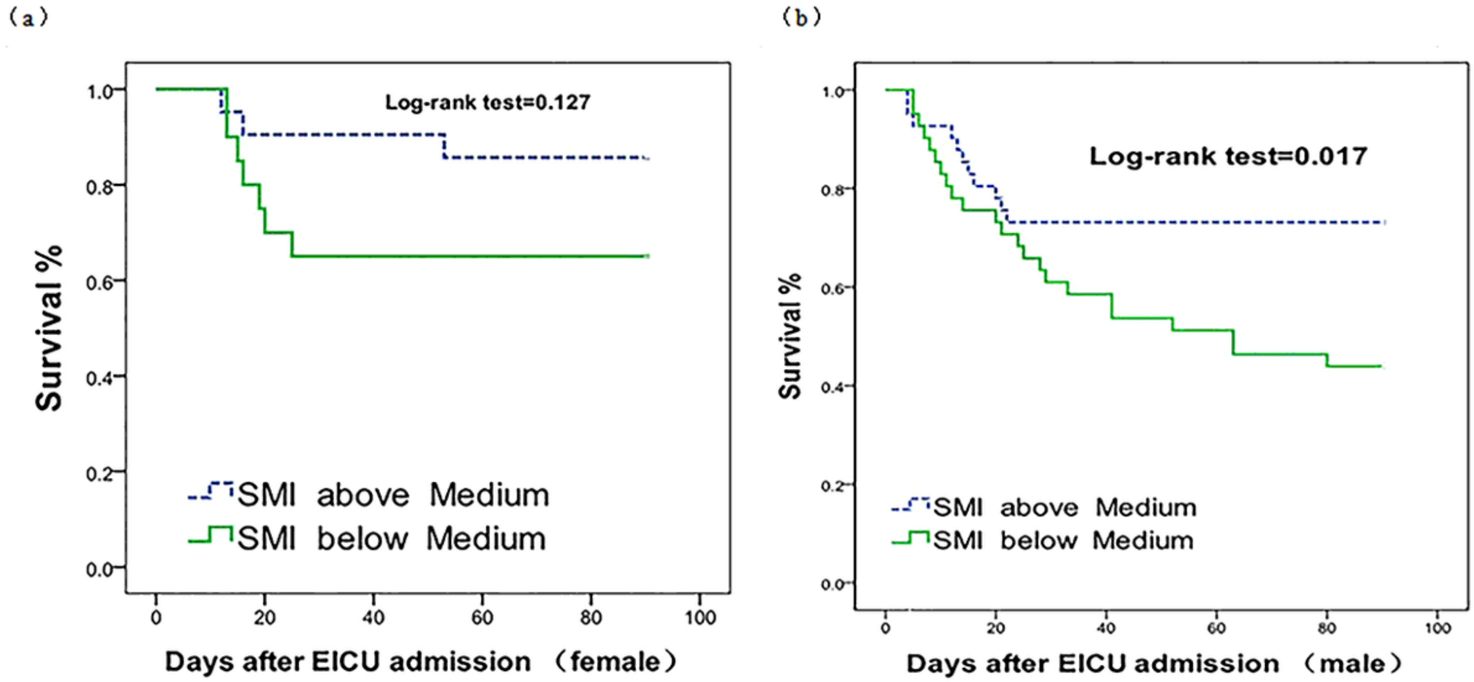

Figure 3

Kaplan-Meier Charts illustrated the association between the SMI and the mortality rate of different genders.