Adipose Tissue is a Predictor of 30-days Mortality in Patients with Bloodstream Infection Caused by Carbapenem-Resistant Klebsiella Pneumoniae

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Research article

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Abstract

Background: Prevalence of CRKP bloodstream infection with high mortality has attached physicians' attention. High-VAT and high-SAT were confirmed by previous studies that closely related to increased pneumonia severity, more complications, and higher mortality in COVID-19. Thus, we speculate that CT-quantified body composition may also be connected to all-cause mortality and bacterial clearance in patients with CRKP bloodstream infection.

Methods: We investigated the associations of CT-quantified body composition with CRKP bloodstream infectious patients. All of the CT images were obtained at the level of the L3/4 spinal level. The prognostic value of the body composition was analyzed using the Cox regression model, and precise clinical nomograms were established.

Results: Factors associated with 30-day all-in hospital mortality included TAT [adjusted odds ratio (OR)=1.028, 95% confidence interval (CI), 1.004–1.053; p = 0.028], age [OR=1.031, 95% CI, 1.001–1.062; p = 0.046] and SOFA score [OR=1.137, 95% CI 1.047–1.235; p = 0.002]**.** Compared with low-VAT, patients with high-VAT show a strikingly poor prognosis in both 30-day mortality (P=0.0449, Figure 2A) and all-cause mortality (P=0.0048, Figure 2C). The results of TAT were similar with VAT.

Conclusions: Our study suggests that CT-derived composition could be a credible and effective alternative to assess the prognosis of patients with BSIs owing to CRKP. CT-quantified total adipose tissue, age and SOFA scores were independently associated with 30-day all-cause mortality in these severe infectious patients, while skeletal muscle did not have obvious statistical significance.

1. Introduction

Currently, with the growing use of carbapenem drugs, the emergence of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is rapidly increasing, posing a severe threat to vulnerable patients and augmenting the burden on the public health system[1–3]. Furthermore, the mortality of CRKP bloodstream infection patients was ranging from 33.0–52.8% in 28- or 30-day all-cause mortality, unfortunately, higher mortality rates in developing countries, arousing global attention[4, 5]. Therefore, it is crucial to identify the prognostic factors of 30-day or all-cause mortality in the early time and take effective and targeted intervention measures to reduce mortality due to bloodstream infection (BSI) caused by CRKP[6]. According to previous literature, overweight and obesity were found associated with influenza A and Coronavirus Disease 19 (COVID-19) complications, severity, and mortality[7–9]. Traditional index, such as body mass index (BMI), however, is insufficient for reflecting the distinguishing between fat and muscle mass, or visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and skeletal muscle (SM). Abdominopelvic computed tomography (CT) imaging is not only a routine examination that assists clinical management with diagnosis of critically ill patients but also a more accurate method to differentiate body composition. Moreover, CT-defined body composition is widely confirmed for accurately reflecting on different types of adipose tissue as well as muscle mass.

High-VAT and high-SAT were confirmed by previous studies that closely related to increased pneumonia severity, more complications, and higher mortality in COVID-19[10, 11]. Thus, we speculate that CT-quantified body composition may also be connected to all-cause mortality and bacterial clearance in patients with CRKP bloodstream infection. Besides, some of these seriously infected patients were a lack in weight on admission or during treatment periods, CT-defined body components provided an alternative for the clinical physician to acquire and access the nutritional status of the extremely severe infectious patients and develop a personalized treatment plan for patients.

Therefore, the primary aim of our study was to explore the relationship between CT-quantified body composition (VAT, SAT and SM) and 30-days mortality in patients with BSIs owing to CRKP. Additionally, the independent risk factors in these patients were analyzed. Furthermore, we tried to construct the 30-day mortality nomogram to predict 15-day or 30-day survival probability based on the prognostic factors derived from multivariate Cox regression analysis.

2. Methods

2.1. Study Population and Design

There was a single-center retrospective cohort study, approved by the ethics committee of the First Affiliated Hospital of Wenzhou Medical University, one of the largest health care centers in the southern province of Zhejiang, China. Patients, both suffering from CRKP infection in the bloodstream firstly in the hospital judged by clinical and microbiological data and having abdominopelvic computed tomography imaging from 2016 January 1st to 2020 June 1st, were eligible for the study. Patients who were not the first time cultivated CRKP in our hospital, less than 16 years old, or refused further treatment were excluded. Carbapenem-resistant *Klebsiella pneumoniae* was defined as minimum inhibitory concentration (MIC) ≥ 4 mg/L to both imipenem and meropenem according to Clinical and Laboratory Standards Institute guidelines[12].

2.2 Variables and definitions

Patients' baseline data, including demographic characteristics, presence of comorbid conditions, acute complications, Sequential Organ Failure Assessment (SOFA) Score, exposure to invasive interventions, surgery within 1 month before onset, renal replacement therapy, bacterial specimen type, Pitt bacteremia score, and details on therapy were reviewed and obtained from electronic medical records. The observational onset of our research was defined as the date of microbiology specimen collection in the first cultivated CRKP. The date: SOFA score, body temperature, and inflammation indicators of blood were recorded within 48 hours of start pointing. Antibiotic treatment, exposure to tracheostomy and mechanical ventilation, renal replacement therapy and acute complications (respiratory failure, kidney failure and shock) maintained for more than 48 hours were considered for analysis. The average Chinese weight,66 kg for males and 57 kg for females, was an alternative to some of these seriously infected patients on account of lacking weight records. Based on the recommended medication and antimicrobial susceptibility test of *Klebsiella pneumoniae*, antibiotic treatment options were divided into polymyxin B-

based (PMB-based) or tigecycline-based (TGC-based) combination therapy or others[13]. Early appropriate antibiotic therapy was the regard of administering 48 hours or less by the prescribing physicians after the first culture of CRKP and including at least two active drugs[14–16].

2.3 Body Composition

Area-based quantification of adipose tissue and muscle mass compartments were performed on the L3/4 spinal level using LifeX software[17]. Two experienced radiologists drew the eligible CT planar. Patients all underwent multidetector-CT scans with quantification of Body Composition within 7 days before cultivated CRKP in the hospital. If the patient has undergone multiple abdominal CT examinations, the time point closest to the starting point of our experiment was chosen. The manually determined specific regions of interest (ROI) includes VAT (the fascial plane of the abdominal muscle wall, using standard Hounsfield Unit (HU) ranges − 190 to -30, Fig. 1) area expressed in mm^2 and SM (the skeletal muscle using HU ranges 40 to 100, Fig. 1) area expressed in mm^2, the subcutaneous adipose tissue(SAT) area was defined as the subtraction between total adipose tissue (TAT) area and VAT area[18]. All CT examinations were performed using the scanners: Brilliance-64, Philips Medical Systems, Eindhoven, The Netherlands; 128-MDCT scanner Somatom Definition, Siemens Health- care Sector, Forchheim, Germany.

2.4. Statistical analyses

R software, GraphPad Prism and Stats were conducted for statistical analyses. The 15-day and 30-day survival nomograms were constructed based on the prognostic factors derived from multivariate Cox regression analysis to predict 15-day and 30-day survival possibilities. Continuous variables were exhibited for means, medians, range and standard deviation (SD) and compared using an independent t-test or Wilcoxon test;Spearman's correlation coefficient was used for variable correlation; Chi-square test was used to analyze categorical variables; log-rank survival analysis was employed to determine the effect of various variables on patients 30-day survival. The optimal cut-off value for VAT and TAT were calculated by X-tile program (constructed by Yale University, New Haven, CT, USA). All statistical tests were two-sided and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Participators Characteristics

Of the 72 eligible patients, both suffered from CRKP bloodstream infection and had abdominopelvic computed tomography were recruited from the First Affiliated Hospital of Wenzhou Medical University, a 4100-bed general teaching hospital, Other infectious patients were excluded from the analysis for having incomplete information, or no CT-based body composition quantification, or having cultivated CRKP before entering our hospital, or below 16 years old. Abdominopelvic CT examination was routinely implemented for these severe infectious patients with some complex or critical complications according to doctors' experience. As of discharge time, 27 patients died during 30 days follow-up, and the average survival time were 24.14 days. Additional baseline clinicopathological parameters were presented in

Table 1. As for the association of adipose fat and muscle tissue with 30-day mortality, we observed that TAT and VAT were dependently related to 30-day mortality according to Table 1, furthermore, high-TAT was closely associated with worse clinical outcome, after adjusting for comorbid conditions and other differences in baseline characteristics. (Table 2).

Table 1
Demographic and clinical characteristics of patient's univariate analysis of risk factors associated with survival.

	No.(%) or mean (SD)			
Demographic data	Survival	Non-survival	All	P value
	n = 45	n = 27	n = 72	
Age (year)	60.18(13.20)	70.30(13.83)	63.97(14.22)	0.003
Male	35(77.8%)	25(92.6%)	60(83.30%)	0.190
Surgery	16(35.6%)	6(22.2%)	22(30.6%)	0.234
Co-morbidities				
Cardiovascular disease	1(2.2%)	5(18.5%)	6(8.3%)	0.025
Chronical obstructive pulmonary disease	0(0.0%)	1(3.7%)	1(1.4%)	0.375
Chronic kedney disease	3(6.7%)	5(18.5%)	8(11.1%)	0.142
Diabetes mellitus	5(11.1%)	10(37.0%)	15(20.8%)	0.009
Central Nervous System Disease	5(11.1%)	5(18.5%)	10(13.9%)	0.486
Cancer	7(15.6%)	3(11.1%)	10(13.9%)	0.733
Charlson comorbidity index	1.29(1.71)	2.22(2.08)	1.64(1.89)	0.042
Acute complications				
Shock	12(26.7%)	12(44.4%)	24(33.3%)	0.121
Acute respiratory failure	12(26.7%)	9(33.3%)	21(29.2%)	0.574
Acute renal failure	6(13.3%)	8(29.6%)	14(19.4%)	0.091
Tracheal intubation status	12(26.7%)	10(37.0%)	22(30.6%)	0.355
Creatinine	86.47(108.87)	123.59(134.35)	100.39(119.51)	0.204
CRP	71.33(29.92)	79.96(38.54)	74.57(33.42)	0.292
PCT	6.09(15.67)	11.14(15.13)	7.98(14.94)	0.166
SOFA score, points	5.89(3.93)	9.70(4.45)	7.32(4.50)	0.000
Pitt bacteremia score, points	3.29(2.74)	5.15(3.29)	3.99(3.07)	0.017
Body compositions				
Skeletal muscle	5.22(2.65)	5.97(3.30)	5.50(2.91)	0.294

	No.(%) or mean (SD)			
Visceral adipose tissue	11.03(5.90)	15.37(8.39)	12.66(7.20)	0.012
Subcutaneous adipose tissue	11.67(6.80)	14.93(12.00)	12.89(9.16)	0.145
Total adipose tissue	22.70(11.07)	30.30(16.56)	25.55(13.79)	0.022
Cultivated bacteria site				
Catheter related infections	7(15.6%)	3(11.1%)	10(13.9%)	0.733
Hydrothorax or ascites	4(8.9%)	2(7.4%)	6(8.3%)	1.000
Pulmonary	17(37.8%)	18(66.7%)	35(48.6%)	0.018
Abdominal	13(28.9%)	7(25.9%)	20(27.8%)	0.786
Urinary	15(33.3%)	5(18.5%)	20(27.8%)	0.174
Skin and Soft Tissue	4(8.9%)	5(18.5%)	9(12.5%)	0.281
Combined viral infection	4(8.9%)	2(7.4%)	6(8.3%)	1.000
Combined fungal infection	20(44.4%)	16(59.3%)	36(50.0%)	0.224
Details of antibiotics				
Early appropriate therapy	28(62.2%)	14(51.9%)	42(58.3%)	0.388
PMB-based therapy	10(22.2%)	8(29.6%)	18(25.0%)	0.482
TGC-based therapy	23(51.1%)	9(33.3%)	32(44.4%)	0.142
Risk factors	**Univariate analysis**	**Multivariate analysis**		
	P value	**Odds ratio**	**95% CI**	**P value**
SOFA score	.058	1.137	1.047,1.235	0.002
Age	.098	1.031	1.001,1.062	0.046
Total adipose tissue	.039	1.028	1.004,1.053	0.024

Table 2. Comparison between survival and non-survival using COX regression analysis.

Risk factors	Univariate analysis	Multivariate analysis		
	P value	Odds ratio	95% CI	P value
SOFA score	.058	1.137	1.047,1.235	0.002
Age	.098	1.031	1.001,1.062	0.046
Total adipose tissue	.039	1.028	1.004,1.053	0.024

3.2 Associations of Body Composition with survival

As for the association of adipose fat and muscle tissue with 30-day mortality, we observed that TAT and VAT were dependently related to 30-day mortality while SM had no difference according to Table 1, Furthermore, high-TAT was closely associated with worse clinical outcome, after adjusting for comorbid conditions and other differences in baseline characteristics. (Table 2). Compared with low-VAT, patients with high-VAT show a strikingly poor prognosis in both 30-day mortality (P = 0.0449, Fig. 2A) and all-cause mortality (P = 0.0048, Fig. 2C). The results of TAT were similar with VAT (Fig. 2B and Fig. 2D).

3.3 Prognostic score for survival

In the multivariable analysis (Table 2), factors associated with 30-day all-in hospital mortality included TAT [adjusted odds ratio (OR) = 1.028, 95% confidence interval (CI), 1.004–1.053; p = 0.028], age [OR = 1.031, 95% CI, 1.001–1.062; p = 0.046] and SOFA score [OR = 1.137, 95% CI 1.047–1.235; p = 0.002]

An OS nomogram was constructed to predict 15-, 30- and 45- day survival of CRKP bloodstream infectious patients (Fig. 3). Total scores were summations of each variable based on the intersection of the vertical line. As shown in Fig. 3, VAT, TAT, age and SOFA score contributed the most risk points (ranged, 0-100), whereas the other clinical information contributed much less. The Harrell's C-index of the nomogram was 0.79. By using a nomogram, we could precisely convert each patient clinical index to the corresponding point, and then evaluate the likelihood of survival. HR values for therapy progression derived from Cox models suggested that patients with TAT high are more likely to benefit from CRKP bloodstream infection. The combination of body composition, age and SOFA showed a good ability to predict survival.

4. Discussion

The evaluation of body composition by abdominal CT imaging in BSI patients ascribed to CRKP have not previously been reported. So far, to our knowledge, it was the first study to assess the correlation between CT-defined body composition and CRKP bloodstream infectious patients. Based on the Cox regression and nomogram of 15-day and 30-day mortality in BSI of CRKP, the main finding of our study was that

high-TAT and SOFA sores were associated with worse clinical outcomes, while skeletal muscle did not have obvious statistical significance.

Prevalence and high mortality among patients suffered from CRKP bloodstream infection have attached physicians' attention, especially these individuals with important morbidities. Hence, it was necessary for us to early identify the risk prognostic factors leading to the death of these patients and take targeted and effective intervention methods to reduce mortality. CT-quantified subcutaneous and visceral adipose tissue were doubtfully identified as an extremely significant risk factor for COVID-19 patients with more severe complication and higher mortality based on the present proof-of studies[10, 19]. In addition, CT-derived compositions would be a credible and effective alternative to assess patient's whether they had overweight or obese, especially for these severely infected patients lacking body weight to calculate BMI.

Univariate analysis showed that CRKP bloodstream infectious patients who had higher visceral adipose tissue and total adipose tissue were more likely to die, while skeletal muscle had not predictive meaning, which was similar to the results of CT-defined body components on the prognosis of COVID-19[11, 20]. It is generally acknowledged that more fat area is prone to develop metabolic diseases characterized by carbohydrate, lipid, and protein metabolic disturbances, resulting in insulin resistance, hyperglycemia, hyperlipidemia, hypoalbuminemia as well as their complications[21]. Meanwhile, as we did in the univariate analysis of the death group and the survival group, patients with cardiovascular disease or diabetes mellitus had a worse prognosis[22, 23]. Worse, these metabolic-related morbidities often co-exist in a single individual, playing a significant role in the mortality of CRKP bloodstream infectious patients. In addition, excessive adipose tissue, especially visceral adipose tissue, was strongly associated with systemic inflammatory status and the delay of the immune response in the pathophysiological pathways, recently highlighted in COVID-19. Patients with impaired immune response were likely to develop metabolic disorders, while patients with metabolic dysfunctions were more easily in a chronic low-grade inflammatory status[24]. Therefore, combined obesity-related metabolic morbidities and adipose tissue-mediated immune dysfunction had an extremely critical impact on the survival of severe infectious patients with BSIs attributed to CRKP. Meanwhile, possibly excessive adipose tissue including VAT and SAT served as reservoirs for microorganisms such as Mycobacterium tuberculosis, HIV, influenza A virus, coronavirus according to previous researches[24, 25]. Additionally, a higher expression of angiotensin-converting enzyme 2(ACE2) was expressed in adipose tissue and other organs like the kidney, which were susceptible to suffer from infection.

Our research results demonstrated that high total adipose tissue is independently associated with worse clinical outcomes, after adjusting for comorbid conditions and other differences in baseline characteristics. According to an in *vitro* analysis of the two different human adipose tissues (VAT and SAT), VAT was likely implicated in the production of more proinflammatory cytokines, such as interleukin-6(IL-6), interleukin-8(IL-8), tumor necrosis factor- α (TNF-α), monocyte chemoattractant protein-1(MCP-1) [26]. Nevertheless, in our study based on the data analysis, VAT did not provide an important survival benefit in CRKP bloodstream infectious patients like COVID-19 in previously published studies[11, 20, 27]. We speculated that one of the reasons was attributed to Chinese people having a low BMI (lesser visceral

adiposity) than European and American country individuals, so that VAT was not a particularly large proportion. Hence, further high-quality relative researches in this area are extremely crucial to verify this result in the future.

Besides, based upon the multivariable analysis, the SOFA score, served to monitor daily organ dysfunction, and age were also significant indicators of the risk factors for these severe difficult-to-treat infections. SOFA score was considered as an effective and applicable prediction in hospital all-cause mortality among infectious patients caused by multidrug-resistant enterobacteria[28]. The higher of SOFA score, the more organ (respiratory, renal, neurological, renal and cardiovascular) dysfunction, which was not conducive to the patient's recovery and contributed to the increase of mortality[29].

There were several important limitations in our work that must be acknowledged. One of our shortcomings was that the sample size was relatively small which might have limited the power of the research. Additionally, advanced age or multiple severe comorbidities potentially leads to worse clinical outcomes and increased the risk of all-cause mortality among some of these patients. It was impossible to calculate the body surface area due to the lack of body weight that could not compare the density of muscle, visceral fat, and subcutaneous fat with the prognosis of infected patients. In spite of the above limitations, this was the first article to explore the relationship between CT-qualified components and mortality among patients who suffered from CRKP bloodstream infection. Although our study has some shortcomings, our results provided physicians with some clinical significance for the body components and prognosis of patients with CRKP bloodstream infection. In addition, the nomogram of 15-day and 30-day mortality in BSI of CRKP can assist clinicians to judge the prognosis of these crucial infectious individuals and take some effective interventions to increase the survival in the early time. Further high-quality prospective researches in this area are extremely needed in the future.

5. Conclusion

Our study suggests that CT-derived composition could be a credible and effective alternative to assess the prognosis of patients with BSIs owing to CRKP. CT-quantified total adipose tissue, age and SOFA scores were independently associated with 30-day all-cause mortality in these severe infectious patients, while skeletal muscle did not have obvious statistical significance.

Declarations

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Conflicts of interest

The authors declare that they have no competing interests.

Availability of data and materials

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

Code availability

Not applicable

Ethics approval

This study was approved by the Institutional Review Board of The First Affiliated Hospital of Wenzhou Medical University(921993).

Consent to participate

Not applicable

Consent for publication

The requirement for written informed consent was waived because all patient information was anonymized and de-identified during data recording.

Authors' contributions

Weiyang Cai and Jianzhong Ye conceived and designed the study. Piaopiao Ying, Jiajing Chen and Yinchai Ye performed in data collection. Weiyang Cai, Piaopiao Ying and Jiajing Chen analyzed the data. Piaopiao Ying, Jianzhong Ye, Yinchai Ye and Weiyang Cai wrote the manuscript.

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Figures

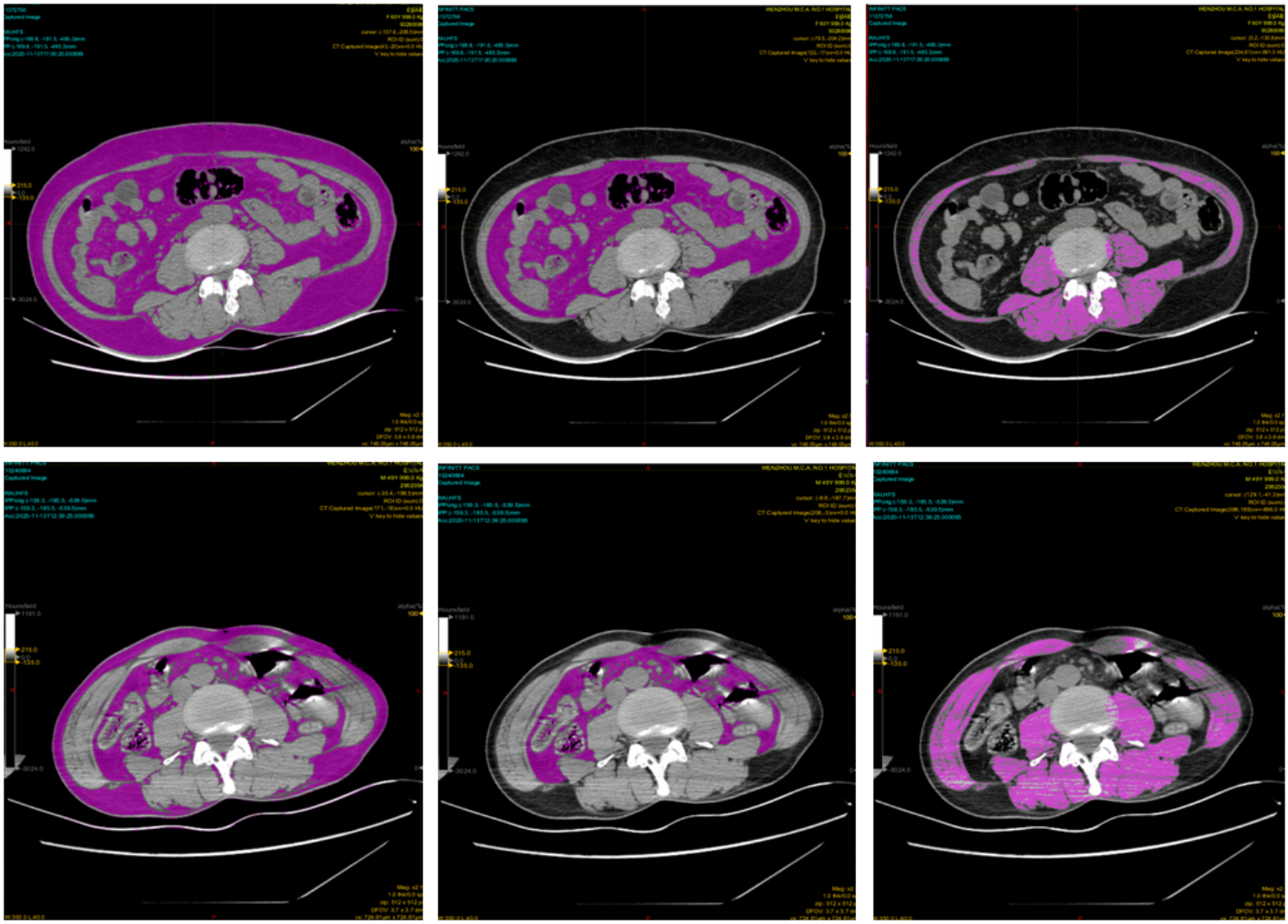

Figure 1

Example of a computed tomography (CT)-scan with the area-based, densitometric quantification of adipose tissue (threshold: −190 to −30 HU) measured at spinal level L3/4: regions of interest (ROI) containing total adipose tissue (TAT) (the right) and visceral adipose tissue (VAT) (the middle); and an example of the densitometric quantification of skeletal muscle (SM), dorsal and psoas muscles (threshold: 40 to 100 HU) (the left).

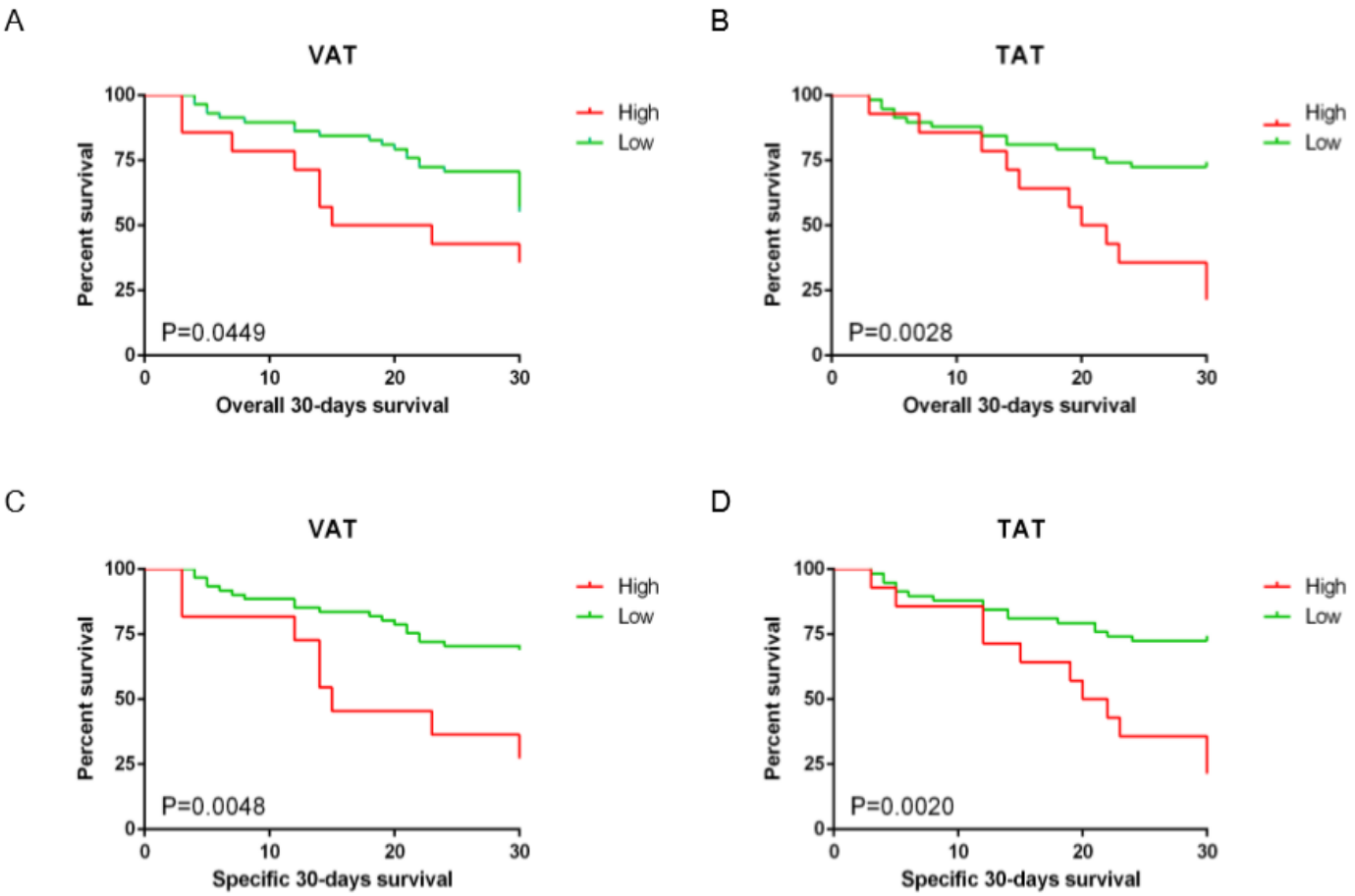

Figure 2

Outcomes of CRKP infection patients based on CT Body Composition. 30-day all-cause mortality based on visceral adipose tissue (A) and total adipose tissue (B). Specific 30-day all-cause mortality based on visceral adipose tissue (C) and total adipose tissue (D).

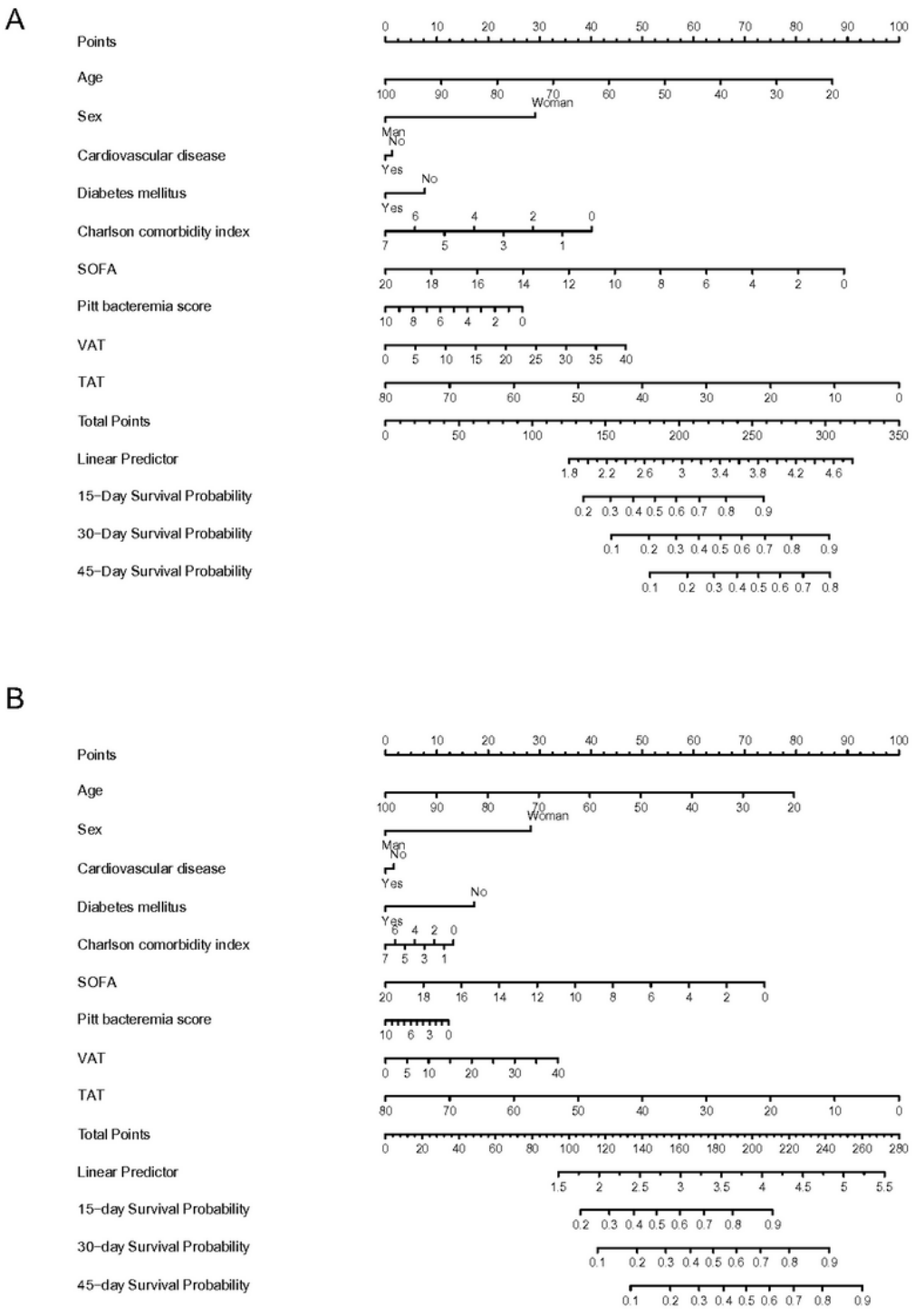

Figure 3

The nomogram to predict the all-cause (A) and specific-cause (B) mortality of CRKP bloodstream infectious patients.