Adipose tissue is a predictor of 30-days mortality in patients with bloodstream infection caused by carbapenem-resistant *Klebsiella pneumoniae*

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Abstract

**Background:** Prevalence of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) bloodstream infection with high mortality has attached physicians’ attention. High visceral adipose tissue (VAT) and high subcutaneous adipose tissue (SAT) were confirmed by previous studies that were 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 (BSI).

**Methods:** We investigated the associations of CT-quantified body composition with the mortality of CRKP bloodstream infectious patients. All 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:** 72 eligible patients both suffered from CRKP bloodstream infection and performed abdominopelvic CT were included. Factors associated with 30-day all-in hospital mortality included total adipose tissue (TAT) [adjusted hazard ratio (HR) = 1.028, 95% confidence interval (CI), 1.003–1.053; \( P = 0.025 \)], age [HR = 1.030, 95% CI, 1.000–1.061; \( P = 0.047 \)] and SOFA scores [HR = 1.138, 95% CI 1.049–1.263; \( P = 0.002 \)]. Compared with low-VAT, patients with high-VAT show a strikingly poor prognosis in both 30-day all-cause mortality (\( P = 0.0108, \) Fig. 2A) and 30-day CRKP BSI mortality (\( P = 0.0049, \) Fig. 2C). The results of TAT were similar to VAT.

**Conclusions:** Our study suggested that CT-derived body composition could be a credible and effective alternative to assess the prognosis of patients with BSI owing to CRKP. CT-quantified TAT, 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.
Keywords: adipose tissue, carbapenem-resistant klebsiella pneumoniae, bloodstream infection, 30-day mortality, nomogram

Background
Currently, the emergence of carbapenem-resistant klebsiella pneumoniae (CRKP) is rapidly increasing with the growing usage of carbapenems, 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 ranged from 33.0 to 52.8% in 28- or 30-day all-cause mortality, 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 CRKP bloodstream infection (BSI) [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 distinctions 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 the 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 are closely related to increased pneumonia severity, more complications, and higher mortality in COVID-19 [10, 11], and a pioneering study had revealed the association of visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT) and infections caused by Mycobacterium avium [7]. Thus, we speculated that CT-quantified body composition may also be connected with all-cause mortality and bacterial clearance in patients with CRKP BSI. Besides, it is not suitable for severely infected patients to weigh them with the conventional methods so that data on the weight of those who were missing during their hospitalization. CT-defined body components provided an alternative for clinical physicians to acquire and assess the nutritional status of extremely severe infectious patients and develop a personalized treatment plan for them.

Therefore, the primary aim of our study was to explore the relationship between CT-quantified body composition (VAT, SAT, and SM) and 30-day mortality in patients with BSI 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 14-day or 30-day survival probability based on the prognostic factors derived from multivariate Cox regression analysis.

Methods
Study population and design
This study was a single-center retrospective cohort research, 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 suffered from CRKP BSI supported by clinical symptoms and etiological evidence during their hospitalization and performed abdominopelvic computed tomography imaging from 2016 January 1st to 2020 June 1st, were eligible for the study. CRKP BSI were nosocomial infections and was first detected during hospitalization in our hospital. Meanwhile, Abdominopelvic CT examinations were performed in these infectious patients due to abdominal trauma, enteric or urinary tract infection, severe sepsis, multiple organ dysfunction syndromes, etc. Patients who did not detect CRKP BSI for the first time in our hospital, less than 16 years old, or refused further treatment were excluded. CRKP was defined as minimum inhibitory concentration (MIC) ≥ 4 mg/L to both imipenem and meropenem according to Clinical and Laboratory Standards Institute guidelines [12].

Variables and definitions
Patients’ baseline data, including demographic characteristics, presence of comorbid conditions, acute complications (shock, acute respiratory failure, acute renal failure), Sequential Organ Failure Assessment (SOFA) Scores, exposure to invasive intervention surgery, renal replacement therapy, infection site, combined viral and fungal infection, Pitt bacteremia scores, 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 scores, body temperature, and inflammation indicators of blood were recorded within 48 h before positive blood culture with CRKP infection. 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 h were considered for analysis. Surgery was defined as invasive procedures which could be found in the surgical record in the electronic medical records within 1 month before and after the CRKP BSI. Cultivated fungal, detection of 1,3-β-D-glucan or galactomannan antigen-positive, combined with the patient’s symptoms, signs, and antifungal drug treatment was referred to as fungal infection. Equally, the related viral nucleic acid tests and the clinical conditions of infectious patients were treated as viral infections. The average Chinese weight, 66 kg for males and 57 kg for females, was an alternative to some of these seriously infected patients in case 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 (aminoglycosides, Fosfomycin, carbapenem, etc.) [13]. Early appropriate antibiotic therapy was the regard of administered 48 h or less by the prescribing physicians after the first culture of CRKP and included at least two in-vitro active drugs [14–16].

**Body composition**

Area-based quantifications of adipose tissue and muscle mass compartments were performed on the L3/4 spinal level using a semiautomatic software tool (Syngo Volume tool, Siemens Healthcare, Munich, Berlin, Germany) [17]. Two experienced radiologists drew the eligible CT planar. Records of multidetector-CT scans with quantification of body composition were retrieved 7 days before or after positive blood culture with CRKP. 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 region of interest (ROI) includes VAT (the fascial plane of the abdominal muscle wall, using standard Hounsfield Unit (HU) range –190 to −30, Fig. 1) area expressed in mm², TAT (whole abdominal circumference, using HU range −190 to −30), SM (sum of M. psoas major, M. erector

*Fig. 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: region of interest (ROI) containing total adipose tissue (TAT) (A1 and B1) and visceral adipose tissue (VAT) (B1 and B2), and an example of the densitometric quantification of skeletal muscle (SM), dorsal and psoas muscles (threshold: 40 to 100 HU) (C1 and C2)
spinae, M. quadratus lumborum, M. latissimus dorsi, M. transversus abdominis, M. obliquus internus abdominis and externus abdominis, and M. rectus abdominis, measured by limiting the attenuation threshold between 40 and 100 HU, Fig. 1 area expressed in mm², 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 scanners: Brilliance-64, Philips Medical Systems, Eindhoven, The Netherlands; 128-MDCT scanner Somatom Definition, Siemens Health-care Sector, Forchheim, Germany.

Statistical analyses
R software, GraphPad Prism, and Stats were conducted for statistical analyses. The 14-day and 30-day survival nomograms were constructed based on the prognostic factors derived from multivariate Cox regression analysis to predict 14-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 values for VAT and TAT were calculated by the X-tile program (constructed by Yale University, New Haven, CT, USA). The cut-off of high TAT and VAT were 36.95 mm² and 18.96 mm², respectively. All statistical tests were two-sided and P < 0.05 was considered statistically significant.

Results
Participators characteristics
A total of 90 eligible patients, both suffered from CRKP bloodstream infection and had abdominopelvic computed tomography within 7 days were recruited from the First Affiliated Hospital of Wenzhou Medical University, a 4100-bed general teaching hospital; of these, 2 were excluded from the analysis due to incomplete information, 6 were excluded owing to cultivated CRKP before entering our hospital, 3 were excluded because of only 1 day of hospitalization, 7 were excluded for failed abdominopelvic CT image. 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 was 24.14 days. Additional baseline clinicopathological parameters were presented in Table 1.

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 differences (Table 1). Furthermore, high-TAT was closely associated with worse clinical outcomes, after adjusting for comorbid conditions and other differences in baseline characteristics (Table 2). Compared with low-VAT, patients with high-VAT showed a strikingly poor prognosis in both 30-day all-cause mortality (P = 0.0108, Fig. 2A) and 30-day CRKP BSI mortality (P = 0.0049, Fig. 2C). The results of TAT were similar to VAT (Fig. 2B, D).

Prognostic scores for survival
In the multivariable analysis (Table 2), factors associated with 30-day all-in hospital mortality included total adipose tissue (TAT) [adjusted hazard ratio (HR) = 1.028, 95% confidence interval (CI), 1.003–1.053; P = 0.025], age [HR = 1.030, 95% CI, 1.000–1.061; P = 0.047] and SOFA scores [HR = 1.138, 95% CI 1.049–1.263; P = 0.002].

A nomogram was constructed to predict 14- and 30-day survival of patients with CRKP bloodstream infectious (Fig. 3). Total scores were summations of each variable based on the intersection of the vertical lines. As shown in Fig. 3, VAT, TAT, age, and SOFA scores contributed the most risk points (ranged 0–100), whereas the other clinical information contributed much less. By using a nomogram, we could precisely convert each patient’s 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 lower TAT are more likely to survive from CRKP bloodstream infection. The combination of body composition, age, and SOFA showed a good ability to predict survival.

Discussion
The evaluation of body composition by abdominal CT imaging in CRKP BSI patients has not previously been reported. So far, to our knowledge, it was the first study to assess the correlation between CT-defined body composition and survival of CRKP BSI patients. Based on the Cox regression and nomogram of 14-day and 30-day mortality in the included patients, the main finding of our study was that high-TAT, age, and SOFA scores were associated with worse clinical outcomes, while skeletal muscle did not have obvious statistical significance.

Prevalence and high mortality among patients suffering 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 identified as an extremely significant risk factor for COVID-19 patients with more severe complications and higher mortality based on the present proof-of-studies [10, 19].

Table 1 Demographic and clinical characteristics of CRKP bloodstream infectious patient’s univariate analysis of risk factors associated with survival

| Demographic data | No. (%) or mean (SD) | Survival | Non-survival | All | P value |
|------------------|-----------------------|----------|--------------|-----|---------|
| Demographic data |                       | 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 |
| Creatinine, umol/L | 86.47 (108.87)  | 123.59 (134.35) | 100.39 (119.51) | 0.204 |
| CRP, mg/L        | 71.33 (29.92)         | 79.96 (38.54) | 74.57 (33.42) | 0.292 |
| PCT, ng/ml       | 6.09 (15.67)          | 11.14 (15.13) | 7.98 (14.94)  | 0.166 |
| SOFA score, points | 5.84 (3.90)      | 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 |
| Cardiovascular disease | 1 (2.2%)     | 5 (18.5%)   | 6 (8.3%)    | 0.025 |
| Chronic obstructive pulmonary disease | 0 (0.0%)     | 1 (3.7%)    | 1 (1.4%)    | 0.375 |
| Chronic kidney 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 |
| Body compositions |                       |           |             |      |         |
| Skeletal muscle   | 5.22 (2.65)          | 5.97 (3.30)  | 5.50 (2.91)  | 0.294 |
| 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 |
| Infection type    |                       |           |             |      |         |
| 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 | 22 (48.9%)           | 9 (33.3%)   | 31 (43.1%)  | 0.197 |
| Other antibiotics therapy | 13 (28.9%) | 10 (37.0%)  | 23 (31.9%)  | 0.473 |

CRP C-reactive protein, PCT procalcitonin, SOFA sequential organ failure assessment, PMB-based therapy polymyxin B-based therapy, TGC-based therapy tigecycline-based (TGC-based) combination therapy
addition, CT-derived body composition would be a credible and effective alternative to assess patients’ nutritional status, especially for those severely infected patients lacking body weight to calculate BMI.

Univariate analysis showed that CRKP BSI patients who had higher visceral adipose tissue and total adipose tissue were more likely to die, while skeletal muscle had no 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,

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

| Risk factors       | Univariate analysis | Multivariate analysis |
|--------------------|---------------------|----------------------|
|                    | P value             | Adjusted HR | 95% CI | P value |
| SOFA score         | 0.001               | 1.138       | 1.049,1.263 | 0.002 |
| Age                | 0.004               | 1.030       | 1.000,1.061 | 0.047 |
| Total adipose tissue | 0.031          | 1.028       | 1.003,1.053 | 0.025 |

SOFA, sequential organ failure assessment.

Cox regression was used for estimating the impact of these demographic and clinical characteristics on CRKP bloodstream infectious patient’s mortality outcomes for confounding variables based on P < 0.1 in univariate analysis.

![Fig. 2](image-url) 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). All-cause mortality based on visceral adipose tissue (C) and total adipose tissue (D).
Fig 3 The nomogram to predict the 30-day all-cause mortality (A) and 30-day mortality owing to CRKP BSI (B) of CRKP bloodstream infectious patients.
patients with cardiovascular disease or diabetes mellitus had a worse prognosis [22, 23]. Unfortunately, these metabolic-related morbidities often co-exist in a single individual, playing a significant role in the mortality of CRKP BSI 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 morbidity 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 research [24, 25].

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

There were several limitations in our work that must be acknowledged. One of our shortcomings was that the sample size was relatively small, which might limit the power of the research. Additionally, advanced age or multiple severe comorbidities potentially leads to worse clinical outcomes and increased risk of all-cause mortality among some of these patients. It was impossible to calculate the body surface area due to the lack of bodyweight that could not compare the density of muscle, visceral fat, and subcutaneous fat with the prognosis of infected patients. Besides, considering that CT scan is an expensive tool and has side effects, it may find obstacles that in clinical practices for CRKP BSI patients, there’s no need to perform abdominopelvic CT as a diagnostic tool. 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 clinical significance for the association between body components and prognosis of patients with CRKP bloodstream infection. In addition, the nomogram of 14-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 survival at an early time. Further high-quality prospective researches in this area are extremely needed in the future.

Conclusion
Our study suggested that CT-derived body composition could be a credible and effective alternative to assess the prognosis of patients with BSI 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.

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Authors’ contributions
WC, JY and PY conceived and designed the study. PY, JC, and YY analyzed the data. PY, JY, YY, and WC wrote the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials
The dataset used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
This study was approved by the Ethics Committee in Clinical Research of The First Affiliated Hospital of Wenzhou Medical University (KY2021-R096). Due to it was a retrospective study, which collected information on past diagnosis and treatment from electronic medical records, the ethics committee approved the waiver of informed consent on participate section.
Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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