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The impact of body mass index on survival of medical patients with sepsis: a prospective cohort study in a university hospital in China

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Abstract

Objective To evaluate the impact of body mass index (BMI) on survival of a Chinese cohort of medical patients with sepsis.

Design A single-center prospective cohort study conducted from May 2015 to April 2017.

Setting A tertiary care university hospital in China.

Participants 178 patients with sepsis admitted to the medical intensive care unit (ICU) were included.

Main outcome measures The primary outcome was 90-day mortality. The secondary outcomes were in-hospital mortality, length of ICU stay, and length of hospital stay.

Results The median age (interquartile range) was 78 (66-84) years and the majority of patients (77.0%) were older than 65 years. The 90-day mortality was 47.2%. The in-hospital mortality was 41.6%, and the length of ICU stay and hospital stay were 12 (5-22) and 15 (9-28) days, respectively. Compared with in-hospital survivors, non-survivors had significantly lower BMI and PaO_2/FiO_2 (both $p < 0.05$), and higher lactate, bilirubin, INR, sequential organ failure assessment (SOFA) score, and APACHE II score (all $p < 0.05$). Those with healthcare-acquired infections, hypotension, oliguria, septic shock, and intubation were also at increased risk of death (all $p < 0.05$). Cox proportional hazard regression analysis identified that sequential organ failure assessment (SOFA) score (HR = 1.229, $p < 0.001$), APACHE II score (HR = 1.050, $p < 0.001$) and BMI (HR = 0.940, $p = 0.029$) were all independent predictors of the 90-day mortality. Patients were divided into four groups based on

BMI (underweight, normal, overweight, and obese). Differences in survival among the four groups were demonstrated by Kaplan-Meier survival analysis (p = 0.008), with the underweight patients showing a lower survival rate.

Conclusions SOFA score, APACHE II score and BMI were independent factors associated with survival in a Chinese cohort of medical patients with sepsis, while underweight patients were at higher risk of death.

Key words: Sepsis; Septic shock; Body mass index; Critical care; Mortality

Strengths and limitations of this study

Our prospective observational cohort study was focused on medical patients with sepsis.

The clinical characteristics and clinical outcomes of medical patients with sepsis were analysed in a university hospital in China.

The impact of BMI on survival of medical patients with sepsis was evaluated.

Our analyses were limited by the use of weight ascertained at ICU admission, rather than the patient's true outpatient weight.

Introduction

Sepsis is a major cause of morbidity and mortality worldwide [1]. Of these patients, half are treated in the intensive care unit (ICU) [2]. In a national population-based study of sepsis in Spain, medical diagnostic categories were the majority of patients who developed sepsis, while only 26% of surgical patients developed sepsis [3]. Many studies have analyzed the characteristics and clinical outcomes of surgical patients with sepsis but few of these have focused on medical patients.

Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify whether adults are underweight, overweight and obese [4]. Several studies have examined the effects of BMI on mortality with conflicting conclusions. Lower mortality in the obese has been observed in some studies [5-9], but some researchers believe that the true paradox may lie in the variations in sepsis interventions, such as the administration of resuscitation fluids and antimicrobial therapy [6]. In other studies, morbidly obese and underweight patients have been shown to be associated with higher mortality [10,11]. Thus, the impact of BMI on survival of patients with sepsis is still controversial.

As the relationship between BMI and clinical outcomes of sepsis is complex, which may be related partly to differences in patient characteristics, we therefore set out to evaluate prospectively the impact of BMI on survival in a cohort of medical patients with sepsis admitted to the medical ICU in a university hospital.

Patients and Methods

Design

This was a prospective cohort study, which was conducted in the medical ICU of a university-affiliated urban teaching hospital from May 2015 to April 2017.

Subjects

Hospitalized patients admitted to the medical ICU with sepsis acquired in the community or in a hospital were eligible for the study if they met any of the following criteria of severe sepsis [12]: (1) sepsis-induced hypotension, (2) lactate above upper laboratory level limits, (3) urine output <0.5 mL Kg^{-1} h^{-1} for more than 2 h despite adequate fluid resuscitation, (4) acute lung injury with Pao_2/Fio_2<250 in the absence of pneumonia as infection source, (5) acute lung injury with Pao_2/Fio_2 <200 in the presence of pneumonia as infection source, (6) creatinine >2.0 mg/dL (176.8 μmol/L), (7) bilirubin >2mg/dL (34.2 μmol/L), (8) platelet count <100,000 μL, and (9) coagulopathy (international normalized ratio >1.5).

Patients were excluded from the study if they met one of the following criteria: (1) the patient had sepsis that required surgical treatment, or was caused by a surgical procedure related infection, (2) age <18 years, (3) the patient had a positive HIV antibody titer or had known/suspected tuberculosis at baseline, (4) expected lifespan <3 months due to severe pre-existing comorbidities, (5) active Do Not Resuscitate or Do Not Intubate order, and (6) pregnant.

All patients accepted treatment according to the international guidelines for management of sepsis and septic shock [12,13]. We collected the following

demographic and clinical data: patient's gender, age, weight, height, primary site of infection, community-acquired or hospital-acquired infection, hypotension, lactate level, oliguria, PaO_2/FiO_2, serum creatinine, total bilirubin, platelets, international normalized ratio (INR), Glasgow coma scale, SOFA score, acute physiology and chronic health evaluation (APACHE) II score, septic shock, non-invasive ventilation, intubation, positive blood culture, length of ICU stay, and length of hospital stay. Those who survived to discharge were followed for at least 90 days.

BMI is defined as the weight in kilograms divided by the square of the height in meters (kg/m^2). Using the World Health Organization (WHO) criteria for designation of BMI [4], patients were classified as underweight (BMI < 18.50 kg/m^2), normal weight (BMI = 18.50 to 24.99 kg/m^2), overweight (BMI = 25.0 to 29.99 kg/m^2), and obese (BMI ≧ 30.0 kg/m^2).

Outcomes

The primary outcome was 90-day mortality, while the secondary outcomes were in-hospital mortality, length of ICU stay, and length of hospital stay.

Statistical analysis

Continuous variables were expressed as median (interquartile range) and categorical variables as numbers (%). Clinical data were compared among the in-hospital survivors and non-survivors. Continuous variables were compared using the non-parametric Mann–Whitney U test, and categorical variables were compared using the Chi squared test. Cox proportional hazard regression analysis was undertaken to assess the factors associated with 90-day mortality. The variables

significantly associated with 90-day non-survival in the univariate analysis were used in the Cox proportional hazard regression analysis.

Patients were divided into four groups based on BMI (underweight, normal, overweight, and obese). Clinical data were compared between the four groups, where continuous variables were compared using the non-parametric Kruskal-Wallis H test, and categorical variables were compared using the Chi squared test. Kaplan-Meier survival curves were constructed to show the survival probabilities at day-90 according to BMI classification, and compared using the log rank test.

All analyses were conducted using SPSS, version 22.0 (IBM, Armonk, NY, USA). A p value <0.05 was considered significant.

Results

In total, 178 medical patients with sepsis were included in this study, with male patients accounting for 65.2% (n=116). The median age (interquartile range) was 78 (66-84) years, and most patients were at least 65 years old (137/178 cases, 77.0%). The most common primary site of infection was the lung (131 cases, 73.6%), followed by abdomen (15 cases, 8.4%), urinary tract (13 cases, 7.3%), gastrointestinal tract (12 cases, 6.7%) and other sites (7 cases, 3.9%). Septic shock patients accounted for 33.1% (59 cases). Blood culture was positive in 38 patients (21.3%). The 90-day mortality was 47.2% (84/178 cases), and the in-hospital mortality was 41.6% (74/178 cases). The length of ICU stay and the length of hospital stay were 12 (5-22) and 15 (9-28) days, respectively.

Compared with in-hospital survivors, non-survivors had significantly lower BMI and PaO_2/FiO_2 (both $p < 0.05$), higher lactate, bilirubin, INR, SOFA score and APACHE II score (all $p < 0.05$). Meanwhile, more patients died with healthcare-acquired infections, hypotension, oliguria, septic shock, and intubation (all $p < 0.05$) (table 1).

Cox proportional hazard regression analysis was conducted and the independent factors for 90-day death were identified as SOFA score (HR = 1.220, $p < 0.001$), APACHE II score (HR = 1.050, $p < 0.001$) and BMI (HR = 0.940, $p = 0.029$) (table 2).

Patients were divided into four groups based on BMI (underweight, normal, overweight, and obese). The percentage of males (72.7%, 71.4%, 55.6%, and 18.2%, $p = 0.002$), chronic obstructive pulmonary disease (24.2%, 21.4%, 0, and 27.3%, p=0.017), hypotension (57.6%, 34.7%, 25.0%, and 9.1%, $p = 0.007$), septic shock (57.6%, 30.6%, 25.0%, and 9.1%, $p = 0.004$), in-hospital mortality (60.6%, 41.8%, 30.6%, and 18.2%, $p = 0.027$) and 90-day mortality (66.7%, 48.0%, 36.1%, and 18.2%, $p = 0.015$) were statistically different among the four groups (table 3).

Kaplan-Meier survival curves were constructed to show the survival probabilities at day-90 according to BMI classification and these were compared using the log rank test, which also showed that higher BMI was associated with better prognosis (p=0.008) (figure 1).

Discussion

This prospective observational cohort study was focused on medical patients with sepsis admitted to the ICU, and the results showed that SOFA score, APACHE II score and BMI were identified as independent factors for 90-day mortality by Cox regression analysis. Mortality increased with increasing SOFA and APACHE II score, which was consistent with previous studies[14-16]. However, BMI was also found to be an independent predictor of survival, where 90-day mortality decreased with an increase in BMI. While studies examining the risk factors associated with outcomes in sepsis reached inconsistent conclusions on the association of BMI with mortality, our results confirmed a protective effect of higher BMI on mortality in patients with sepsis caused by medical conditions.

Globally, the prevalence of obesity has reached epidemic proportions, especially in developed countries. BMI is still a useful proxy of overall health because it is highly correlated with body surface area, which is commonly used as a surrogate measure in obesity classification. Even though it is widely accepted that obesity is a risk factor for diabetes mellitus, hypertension, and cardiovascular diseases, the present study and several other studies have indicated that overweight and obese patients with sepsis tend to experience lower mortality. This has been called the "obesity paradox" [5-9,17]. Although some researchers have expressed doubt that the true paradox may lie in the variations in sepsis interventions [6,18], a meta-analysis concluded that individuals who are considered overweight or obese have a reduced adjusted mortality when admitted to the ICU with sepsis or septic shock [8]. Recently another meta-analysis also concluded that being overweight was associated with lower

mortality (OR 0.87, 95% CI 0.77-0.97, p = 0.02) compared with obese (OR 0.89, 95% CI 0.72-1.10, p = 0.29) and morbidly obese (OR 0.64, 95% CI 0.38-1.08, p = 0.09) patients who did not exhibit significantly reduced mortality compared with normal weight patients [19]. In a large and nationally representative sample of over 1,000 hospitals in the US, obesity was found to be significantly associated with a 16% decrease in the odds of dying among sepsis patients who were hospitalized [20].

Underweight patients with sepsis may be more common in developing countries than developed countries. In the present study, the percentages of underweight, normal weight, overweight and obese patients were 18.4%, 55.3%, 20.1%, and 6.1%, respectively, while those with sepsis in a study in Canada and the US represented 6.8%, 35.3%, 28.3%, and 29.0% [6]. Being underweight was found to be one of the independent risk factors of mortality in a study on the correlation between surgical site infection and mortality [10]. Furthermore, Lee et al [11] also reported that being underweight was associated with mortality in patients with severe sepsis and septic shock.

Consequently, previous studies on sepsis have shown that overweight and obese patients have a decreased risk for mortality, and underweight patients may have a higher mortality. However, BMI has not been shown to be an independent factor for clinical outcomes by multivariable analyses. In our cohort of medical patients with sepsis, which mainly included the elderly and less obese patients, BMI was identified as an independent factor for survival. The mechanism of the correlation between BMI and mortality of sepsis is unclear. There are several potential reasons that could

explain this. First, higher BMI resulted in more fat reserves, and patients could have a greater capacity to cope with the inflammatory response during sepsis and sepsis-associated acute lung injury [21-23]. Furthermore, they may be able to tolerate extensive weight loss and dysfunction associated with critical illness [24]. Secondly, a higher BMI can lead to an increased level of lipoproteins. High-density lipoproteins may not only bind and inactivate lipopolysaccharide (LPS) or other harmful bacterial products released during sepsis [25], but also modulate adhesion molecule expression, upregulate endothelial nitric oxide synthase, and counteract oxidative stress [26]. Thirdly, higher BMI can lead to increased adipose tissue deposition. Adipose tissue is increasingly being considered as a functional endocrine organ and associated with increased renin-angiotensin system activity [27]. It appears to have protective hemodynamic effects during sepsis and may decrease the need for fluid or vasopressor support [18,28]. This may be the reason why the percentages of patients with hypotension and with septic shock in the four groups decreased as BMI increased in the present study.

It should be noted that in the majority of our patients (73.6%) sepsis was associated with pulmonary infection, a much higher percentage as compared to other studies. Ranieri et al [29] reported that the primary sites of infection in adults with septic shock were lung (43.9%), abdomen (30.0%), urinary tract (12.3%), skin (5.5%) and other sites (8.3%). Scheer et al [30] found that the most common primary site of infection was different between medical and surgical patients. In medical patients, lung was the most common primary site (42.0%-56.7%), while it was abdomen

(48.4%-64.4%) in surgical patients.

There were several limitations to our study. Firstly, the BMI of our patients ranged from 12.11 to 32.46. Morbidly obese patients were not included in the study, although morbidly obese patients are not common in this country. Secondly, the present study used weight ascertained at ICU admission, rather than the patient's true outpatient weight. This practice may misclassify the BMI category in as many as 21.9% of patients due to lack of fluid balance adjustment [31]. Lastly, although 178 patients were included in this prospective study, it was still difficult to avoid sample-related bias, because a large proportion of our patients were older than 65 years.

Conclusions

To our knowledge, this is the first prospective cohort study that focused on medical patients with sepsis, showing that SOFA score, APACHE II score and BMI were independent predictors of survival, and more importantly, underweight patients were at higher risk of death.

Acknowledgements

Not applicable.

Authors' contributions

QTZ, YCS, YAZ designsed the study. QTZ, YCS, NS, YAZ, and QBM coordinated the study. MW, JZ, YLD, SL, and HXG were responsible for patient screening,

enrollment, and follow-up. QTZ, MW, and YCS analyzed the data. QTZ drafted the manuscript. YCS critically revised the manuscript. All authors had full access to all study data, read and approved the final version of the manuscript.

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None.

Competing interests

None declared.

Ethics approval and consent to participate

The study protocol was approved (approval number M2015021) by the ethics committee of Peking University Third Hospital, Beijing, China. All patients or their legally authorized representatives provided written informed consent to participate in the study.

Data sharing statement

No additional data are available.

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Table 1.Comparison of demographics and clinical data between groups defined by clinical outcome in 178 patients with sepsis

Characteristics	Survivors (n=104)	Non survivors (n=74)	p value
Age (year)	78.0 (60.0-84.0)	78.0 (69.0-84.0)	0.291
Males	67 (64.4)	49 (66.2)	0.805
Body mass index (kg/m^2)	23.2 (20.4-26.1)	21.7 (18.4-24.2)	0.006
Comorbidities			
COPD	23 (22.1)	9 (12.2)	0.088
Diabetes mellitus	26 (25.0)	21 (28.4)	0.614
Hypertension	47 (45.2)	31 (41.9)	0.662
Cerebrovascular disease	30 (28.8)	15 (20.3)	0.194
Neoplasm	18 (17.3)	12 (16.2)	0.848
Liver disease	5 (4.8)	4 (5.4)	1.000
Heart failure	20 (19.2)	14 (18.9)	0.958
Chronic renal failure	18 (17.3)	11 (14.9)	0.664
Smoking (pack years)	0 (0-30.0)	0 (0-16.3)	0.509
Primary site of infection			
Lung	77 (74.0)	54 (73.0)	0.874
Abdomen	10 (9.6)	5 (6.8)	0.499
Urinary tract	7 (6.7)	6 (8.1)	0.728
Gastrointestinal tract	7 (6.7)	5 (6.8)	1.000

Other site	3 (2.9)	4 (5.4)	0.452
Community-acquired infection	85 (81.7)	50 (67.6)	0.030
Hypotension	22 (21.2)	41 (55.4)	<0.001
Lactate level (mmol/L)	1.8 (1.0-3.4)	2.7 (1.5-5.7)	0.001
Oliguria	8 (7.7)	16 (21.6)	0.007
PaO_2/FiO_2(mmHg)	198.5 (119.3-287.5)	152.5 (99.6-210.3)	0.006
Serum Creatinine (μmol/L)	97.0 (68.3-176.3)	108.5 (64.0-194.3)	0.868
Total bilirubin (μmol/mL)	13.1 (9.9-22.3)	18.0 (12.5-32.8)	0.015
Platelets ($\times 10^9$/L)	161.0 (95.8-232.5)	123.0 (75.0-204.3)	0.067
INR	1.2 (1.0-1.4)	1.3 (1.1-1.6)	0.015
Glasgow coma scale	15.0 (10.0-15.0)	13.0 (10.0-15.0)	0.117
SOFA score	5.0 (4.0-7.0)	9.0 (7.0-11.0)	<0.001
APACHE II score	16.0 (12.0-22.0)	21.0 (17.0-30.0)	<0.001
Septic shock	21 (20.2)	38 (51.4)	<0.001
Non-invasive ventilation	28 (26.9)	24 (32.4)	0.426
Intubated	36 (34.6)	43 (58.1)	0.002
Positive blood culture	19 (18.3)	19 (25.7)	0.235
Length of ICU stay (days)	12.0 (6.0-22.0)	12.0 (3.0-25.0)	0.521
Length of hospital stay (days)	18.0 (10.0-30.0)	13.0 (3.0-25.0)	0.009

Data are presented as n (%) or median (interquartile range) unless stated otherwise. COPD: Chronic obstructive pulmonary disease; INR: International normalized ratio; SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation.

Table 2. Risk factors for 90-day mortality of patients with sepsis or septic shock by Cox regression analysis

Variables	Hazard ratio (95% Confidence interval)	p value
Body mass index (kg/m^2)	0.940 (0.889-0.994)	0.029
Hypotension	0.781 (0.229-2.670)	0.694
Lactate level (mmol/L)	1.018 (0.943-1.098)	0.648
Oliguria	1.288 (0.715-2.321)	0.399
PaO_2/FiO_2(mmHg)	1.000 (0.997-1.002)	0.933
Septic shock	1.075 (0.320-3.615)	0.907
SOFA score	1.229 (1.123-1.345)	<0.001
APACHE Ⅱ score	1.050 (1.022-1.080)	<0.001
Intubated	1.511 (0.931-2.452)	0.095

SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation.

Table 3. Comparison of demographics and clinical data among groups defined by body mass index in patients with sepsis

Characteristics	Underweight (n=33)	Normal (n=98)	Overweight (n=36)	Obese (n=11)	p value
Age (years)	79.0 (69.0-86.0)	78.0 (67.0-84.0)	73.0 (57.0-83.0)	77.0 (71.0-86.0)	0.162
Males	24 (72.7)	70 (71.4)	20 (55.6)	2 (18.2)	0.002
Comorbidities					
COPD	8(24.2)	21 (21.4)	0	3 (27.3)	0.017
Diabetes mellitus	8 (24.2)	25 (25.5)	9 (25.0)	5 (45.5)	0.530
Hypertension	14 (42.4)	38 (38.8)	19 (52.8)	7 (63.6)	0.265
Cerebrovascular disease	10 (30.3)	24 (24.5)	11 (30.6)	0	0.193
Neoplasm	7 (21.2)	14 (14.3)	8 (22.2)	1 (9.1)	0.547
Liver disease	2 (6.1)	5 (5.1)	2 (5.6)	0	0.879
Heart failure	8 (24.2)	17 (17.3)	5 (13.9)	4 (36.4)	0.319
Chronic renal failure	5 (15.2)	14 (14.3)	7 (19.4)	3 (27.3)	0.669
Smoking (pack-years)	0 (0-20.5)	0 (0-30.0)	0 (0-3.0)	0 (0-30.0)	0.561
Primary site of infection					
Lung	27 (81.8)	69 (70.4)	27 (75.0)	8 (72.7)	0.637
Abdomen	2 (6.1)	9 (9.2)	3 (8.3)	1 (9.1)	0.956
Urinary tract	1 (3.0)	9 (9.2)	2 (5.6)	1 (9.1)	0.656
Gastrointestinal tract	2 (6.1)	6 (6.1)	3 (8.3)	1 (9.1)	0.955
Other site	1 (3.0)	5 (5.1)	1 (2.8)	0	0.800

Community-acquired infection	25 (75.8)	76 (77.6)	26 (72.2)	8 (72.7)	0.925
Hypotension	19 (57.6)	34 (34.7)	9 (25.0)	1 (9.1)	0.007
Lactate level (mmol/L)	2.4 (1.6-7.2)	2.1 (1.0-4.3)	1.6 (1.2-3.3)	1.9 (0.6-2.9)	0.201
Oliguria	8 (24.2)	13 (13.3)	3 (8.3)	0	0.121
PaO_2/FiO_2 (mmHg)	180.0(113.5-251.0)	164.5(102.3-240.5)	188.0(140.5-268.5)	215.0(153.0-300.0)	0.340
Serum Creatinine (μmol/L)	89.0 (57.0-127.0)	118.5 (72.5-190.5)	91.0 (60.0-212.5)	86.0 (56.0-112.0)	0.136
Total bilirubin (μmol/mL)	18.0 (10.1-33.1)	14.4 (10.1-28.4)	17.2 (12.2-26.3)	15.2 (11.3-20.0)	0.819
Platelets ($\times 10^9$/L)	139.0 (75.0-213.0)	147.0 (86.0-209.8)	182.5 (128.3-253.8)	115.0 (49.0-144.0)	0.056
INR	1.3 (1.1-1.6)	1.2 (1.0-1.5)	1.2 (1.1-1.3)	1.1 (1.0-1.2)	0.269
Glasgow coma scale	13.0 (10.0-15.0)	15.0 (12.0-15.0)	15.0 (11.0-15.0)	13.0 (10.0-15.0)	0.761
SOFA score	8.0 (5.0-11.0)	7.0 (5.0-9.0)	6.0 (4.0-8.0)	5.0 (5.0-8.0)	0.382
APACHEⅡ score	18.0 (16.0-24.0)	19.0 (13.0-25.0)	18.0 (13.0-22.0)	14.0 (9.0-17.0)	0.060
Septic shock	19 (57.6)	30 (30.6)	9 (25.0)	1(9.1)	0.004
Non-invasive ventilation	7 (21.2)	30 (30.6)	10 (27.8)	5 (45.5)	0.466
Intubated	19 (57.6)	43 (43.9)	13 (36.1)	4 (36.4)	0.305
Positive blood culture	7 (21.2)	24 (24.5)	4 (11.1)	3 (27.3)	0.383
Length of ICU stay (days)	10.0 (4.0-25.0)	13.0 (7.0-25.0)	11.0 (4.0-19.0)	9.0(6.0-13.0)	0.461
Length of hospital stay (days)	13.0 (4.0-29.0)	16.0 (10.0-28.0)	16.0 (8.0-32.0)	13.0(8.0-20.0)	0.813
In-hospital mortality	20 (60.6)	41 (41.8)	11 (30.6)	2 (18.2)	0.027
90-day mortality	22 (66.7)	47 (48.0)	13 (36.1)	2 (18.2)	0.015

Data are presented as n (%) or median (interquartile range). COPD: Chronic obstructive pulmonary disease; INR: International normalized ratio; SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation.

Fig 1. Kaplan-Meier survival plot for 90-day survival of underweight, normal weight, overweight, and obese patients with sepsis.

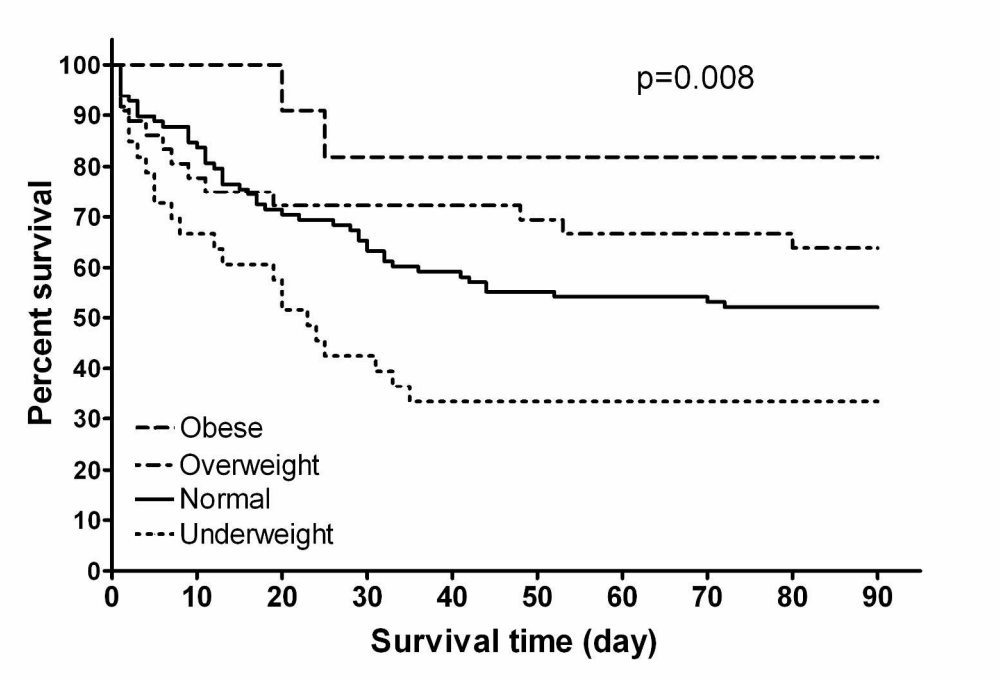

Fig 1. Kaplan-Meier survival plot for 90-day survival of underweight, normal weight, overweight, and obese patients with sepsis.

246x167mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5,6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6,7*
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6,7
		(*b*) Describe any methods used to examine subgroups and interactions	6,7
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8,18-22
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The impact of body mass index on survival of medical patients with sepsis: a prospective cohort study in a university hospital in China

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The impact of body mass index on survival of medical patients with sepsis: a prospective cohort study in a university hospital in China

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Abstract

Objective To evaluate the impact of body mass index (BMI) on survival of a Chinese cohort of medical patients with sepsis.

Design A single-center prospective cohort study conducted from May 2015 to April 2017.

Setting A tertiary care university hospital in China.

Participants 178 patients with sepsis admitted to the medical ICU were included.

Main outcome measures The primary outcome was 90-day mortality. The secondary outcomes were in-hospital mortality, length of ICU stay, and length of hospital stay.

Results The median age (interquartile range) of the patients was 78 (66-84) years. The 90-day mortality was 47.2%. The in-hospital mortality was 41.6%, and the length of ICU stay and hospital stay were 12 (5-22) and 15 (9-28) days, respectively. Cox proportional hazard regression analysis identified that sequential organ failure assessment (SOFA) score (HR = 1.229, $p < 0.001$), APACHE II score (HR = 1.050, $p < 0.001$) and BMI (HR = 0.940, $p = 0.029$) were all independent predictors of the 90-day mortality. Patients were divided into four groups based on BMI [underweight 33 (18.5%), normal 98 (55.1%), overweight 36 (20.2%), and obese 11 (6.2%)]. The percentage of males (72.7%, 71.4%, 55.6%, and 18.2%, $p = 0.002$), chronic obstructive pulmonary disease (24.2%, 21.4%, 0, and 27.3%, $p = 0.017$), hypotension (57.6%, 34.7%, 25.0%, and 9.1%, $p = 0.007$), septic shock (57.6%, 30.6%, 25.0%, and 9.1%, $p = 0.004$), in-hospital mortality (60.6%, 41.8%, 30.6%, and 18.2%, $p = 0.027$) and 90-day mortality (66.7%, 48.0%, 36.1%, and 18.2%, $p = 0.015$) were

statistically different among the four groups. Differences in survival among the four groups were demonstrated by Kaplan-Meier survival analysis (p = 0.008).

Conclusions BMI was an independent factor associated with survival in a Chinese cohort of medical patients with sepsis, patients with lower BMI having a higher risk of death.

Key words: Sepsis; Septic shock; Body mass index; Critical care; Mortality

Strengths and limitations of this study

- Our prospective observational cohort study was focused on medical patients with sepsis and conducted at a university hospital in China.
- The impact of BMI on 90-day survival of medical patients with sepsis was evaluated by Cox proportional hazard regression analysis and Kaplan-Meier survival analysis.
- Our analyses were limited by the use of weight ascertained at ICU admission, rather than the patient's true outpatient weight.

Introduction

Sepsis is a major cause of morbidity and mortality worldwide [1]. Of these patients, half are treated in the intensive care unit (ICU) [2]. In a national population-based study of sepsis in Spain, medical diagnostic categories were the majority of causes in patients who developed sepsis, while only 26% of surgical patients developed sepsis [3].

Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify whether adults are underweight, overweight and obese [4]. Several studies have examined the effects of BMI on mortality with conflicting conclusions. Lower mortality in the obese has been observed in some studies [5-9], but some researchers believe that the true paradox may lie in the variations in sepsis interventions, such as the administration of resuscitation fluids and antimicrobial therapy [6]. In other studies, morbidly obese and underweight patients have been shown to be associated with higher mortality [10,11]. Thus, the impact of BMI on survival of patients with sepsis is still controversial [12, 13].

As the relationship between BMI and clinical outcomes of sepsis is complex, which may be related partly to differences in patient characteristics, we therefore set out to evaluate prospectively the impact of BMI on survival in a cohort of medical patients with sepsis admitted to the medical ICU in a university hospital.

Patients and Methods

Design

This was a prospective cohort study, which was conducted in the medical ICU of a university-affiliated urban teaching hospital in China from May 2015 to April 2017.

Subjects

Sepsis was defined as the presence (probable or documented) of infection together with systemic manifestations of infection[14]. Hospitalized patients admitted to the medical ICU with sepsis acquired in the community or in a hospital were eligible for the study if they met any of the following criteria of severe sepsis [14]: (1) sepsis-induced hypotension, (2) lactate above upper laboratory level limits (1.5mmol/L in this study), (3) urine output <0.5 mL Kg^{-1} h^{-1} for more than 2 h despite adequate fluid resuscitation, (4) acute lung injury with Pao_2/Fio_2<250 in the absence of pneumonia as infection source, (5) acute lung injury with Pao_2/Fio_2 <200 in the presence of pneumonia as infection source, (6) creatinine >2.0 mg/dL (176.8 μmol/L), (7) bilirubin >2mg/dL (34.2 μmol/L), (8) platelet count <100,000 μL, and (9) coagulopathy (international normalized ratio >1.5).

Patients were excluded from the study if they met one of the following criteria: (1) the patient had sepsis that required surgical treatment, or was caused by a surgical procedure related infection, (2) age <18 years, (3) the patient had a positive HIV antibody titer or had known/suspected tuberculosis at baseline, (4) expected lifespan <3 months due to severe pre-existing comorbidities, (5) active Do Not Resuscitate or Do Not Intubate order, and (6) pregnant.

All patients accepted treatment according to the international guidelines for management of sepsis and septic shock [14,15]. We collected the following

demographic and clinical data: patient's gender, age, weight, height, primary site of infection, community-acquired or hospital-acquired infection, hypotension, lactate level, oliguria, PaO_2/FiO_2, serum creatinine, total bilirubin, platelets, international normalized ratio (INR), Glasgow coma scale, SOFA score, acute physiology and chronic health evaluation (APACHE) II score, septic shock, non-invasive ventilation, intubation, positive blood culture, length of ICU stay, and length of hospital stay. Those who survived to discharge were followed for at least 90 days.

BMI is defined as the weight in kilograms divided by the square of the height in meters (kg/m^2). Using the World Health Organization (WHO) criteria for designation of BMI [4], patients were classified as underweight (BMI < 18.50 kg/m^2), normal weight (BMI = 18.50 to 24.99 kg/m^2), overweight (BMI = 25.0 to 29.99 kg/m^2), and obese (BMI ≧ 30.0 kg/m^2).

Outcomes

The primary outcome was 90-day mortality, while the secondary outcomes were in-hospital mortality, length of ICU stay, and length of hospital stay.

Statistical analysis

Continuous variables were expressed as median (interquartile range) and categorical variables as numbers (%). Clinical data were compared among the in-hospital survivors and non-survivors. Continuous variables were compared using the non-parametric Mann–Whitney U test, and categorical variables were compared using the Chi squared test. Cox proportional hazard regression analysis was undertaken to assess the factors associated with 90-day mortality. The variables

significantly associated with 90-day non-survival in the univariate analysis were used in the Cox proportional hazard regression analysis.

Patients were divided into four groups based on BMI (underweight, normal, overweight, and obese). Clinical data were compared between the four groups, where continuous variables were compared using the non-parametric Kruskal-Wallis H test, and categorical variables were compared using the Chi squared test. Kaplan-Meier survival curves were constructed to show the survival probabilities at day-90 according to BMI classification, and compared using the log rank test.

All analyses were conducted using SPSS, version 22.0 (IBM, Armonk, NY, USA). A p value <0.05 was considered significant.

Patient involvement

No patients were involved in developing the hypothesis, the specific aims or the research questions, nor were they involved in the design or implementation of this study. No patients were involved in the interpretation of study results or write up of the manuscript. There are no plans to involve patients in the dissemination of results.

Results

Figure 1 shows the patient-selection process. In total, 178 medical patients with sepsis were included in this study, with male patients accounting for 65.2% (n=116). The median age (interquartile range) was 78 (66-84) years, and most patients were at least 65 years old (137/178 cases, 77.0%). The most common primary site of infection was the lung (131 cases, 73.6%), followed by abdomen (15 cases, 8.4%), urinary tract

(13 cases, 7.3%), gastrointestinal tract (12 cases, 6.7%) and other sites (7 cases, 3.9%). Septic shock patients accounted for 33.1% (59 cases). Blood culture was positive in 38 patients (21.3%). The 90-day mortality was 47.2% (84/178 cases), and the in-hospital mortality was 41.6% (74/178 cases). The length of ICU stay and the length of hospital stay were 12 (5-22) and 15 (9-28) days, respectively.

Compared with in-hospital survivors, non-survivors had significantly lower BMI and PaO_2/FiO_2 (both $p < 0.05$), higher lactate, bilirubin, INR, SOFA score and APACHE II score (all $p < 0.05$). Meanwhile, more patients died with healthcare-acquired infections, hypotension, oliguria, septic shock, and intubation (all $p < 0.05$) (table 1).

Cox proportional hazard regression analysis was conducted and the independent factors for 90-day death were identified as SOFA score (HR = 1.220, $p < 0.001$), APACHE II score (HR = 1.050, $p < 0.001$) and BMI (HR = 0.940, $p = 0.029$) (table 2).

Patients were divided into four groups based on BMI [underweight 33 (18.5%), normal 98 (55.1%), overweight 36 (20.2%), and obese 11 (6.2%)] . The percentage of males (72.7%, 71.4%, 55.6%, and 18.2%, $p = 0.002$), chronic obstructive pulmonary disease (24.2%, 21.4%, 0, and 27.3%, p=0.017), hypotension (57.6%, 34.7%, 25.0%, and 9.1%, $p = 0.007$), septic shock (57.6%, 30.6%, 25.0%, and 9.1%, $p = 0.004$), in-hospital mortality (60.6%, 41.8%, 30.6%, and 18.2%, $p = 0.027$) and 90-day mortality (66.7%, 48.0%, 36.1%, and 18.2%, $p = 0.015$) were statistically different among the four groups (table 3).

Kaplan-Meier survival curves were constructed to show the survival probabilities at day-90 according to BMI classification and these were compared using the log rank test, which also showed that higher BMI was associated with better prognosis (p=0.008) (figure 2).

Discussion

This prospective observational cohort study was focused on medical patients with sepsis admitted to the ICU, and the results showed that, besides SOFA score and APACHE II score, BMI was identified as an independent factor for 90-day mortality by Cox regression analysis. The association of SOFA and APACHE II score with mortality in this cohort was consistent with previous studies[16-18]. However, BMI was also found to be an independent predictor of survival, where 90-day mortality decreased with an increase in BMI. While studies examining the risk factors associated with outcomes in sepsis reached inconsistent conclusions on the association of BMI with mortality, our results confirmed that BMI was an independent predictor of mortality in patients with sepsis caused by medical conditions.

Globally, the prevalence of obesity has reached epidemic proportions, especially in developed countries [19]. BMI is still a useful proxy of overall health because it is highly correlated with body surface area, which is commonly used as a surrogate measure in obesity classification. Even though it is widely accepted that obesity is a risk factor for diabetes mellitus, hypertension, and cardiovascular diseases, the present

study and several other studies have indicated that overweight and obese patients with sepsis tend to experience lower mortality. This has been called the "obesity paradox" [5-9,20]. Although some researchers have expressed doubt that the true paradox may lie in the variations in sepsis interventions [6,21], a meta-analysis concluded that individuals who are considered overweight or obese have a reduced adjusted mortality when admitted to the ICU with sepsis or septic shock [8]. Recently another meta-analysis also concluded that being overweight was associated with lower mortality (OR 0.87, 95% CI 0.77-0.97, p = 0.02) compared with obese (OR 0.89, 95% CI 0.72-1.10, p = 0.29) and morbidly obese (OR 0.64, 95% CI 0.38-1.08, p = 0.09) patients who did not exhibit significantly reduced mortality compared with normal weight patients [12]. In a large and nationally representative sample of over 1,000 hospitals in the US, obesity was found to be significantly associated with a 16% decrease in the odds of dying among sepsis patients who were hospitalized [22].

Underweight patients with sepsis may be more common in developing countries than developed countries. In the present study, the percentages of underweight, normal weight, overweight and obese patients were 18.4%, 55.3%, 20.1%, and 6.1%, respectively, while those with sepsis in a study in Canada and the US represented 6.8%, 35.3%, 28.3%, and 29.0% [6]. Being underweight was found to be one of the independent risk factors of mortality in a study on the correlation between surgical site infection and mortality [10]. Furthermore, Lee et al [11] also reported that being underweight was associated with mortality in patients with severe sepsis and septic shock.

Consequently, previous studies on sepsis have shown that overweight and obese patients have a decreased risk for mortality[5-9,20,22], and underweight patients may have a higher mortality[10,11]. However, BMI has not been shown to be an independent factor for clinical outcomes by multivariable analyses. In our cohort of medical patients with sepsis, which mainly included the elderly and less obese patients, BMI was identified as an independent factor for survival. The mechanism of the correlation between BMI and mortality of sepsis is unclear. There are several potential reasons that could explain this. First, higher BMI resulted in more fat reserves, and patients could have a greater capacity to cope with the inflammatory response during sepsis and sepsis-associated acute lung injury [23-25]. Furthermore, they may be able to tolerate extensive weight loss and dysfunction associated with critical illness [26]. Secondly, a higher BMI can lead to an increased level of lipoproteins. High-density lipoproteins may not only bind and inactivate lipopolysaccharide (LPS) or other harmful bacterial products released during sepsis [27], but also modulate adhesion molecule expression, upregulate endothelial nitric oxide synthase, and counteract oxidative stress [28]. Thirdly, higher BMI can lead to increased adipose tissue deposition. Adipose tissue is increasingly being considered as a functional endocrine organ and associated with increased renin-angiotensin system activity [29]. It appears to have protective hemodynamic effects during sepsis and may decrease the need for fluid or vasopressor support [21,30].

In general, sex has not been found to be an independent predictor for survival in patients with sepsis, which is the same as the results of our current study. But in some

special population, for example in liver cirrhosis patients with bloodstream infection, male sex may be an independent risk factor for mortality[31].

As the relationship between BMI and clinical outcomes of sepsis may be related partly to differences in patient characteristics, we therefore set out to evaluate the impact of BMI on survival in a cohort of medical patients with sepsis, which is different from surgical septic patients. Ranieri et al [32] reported that the primary sites of infection in adults with septic shock were lung (43.9%), abdomen (30.0%), urinary tract (12.3%), skin (5.5%) and other sites (8.3%). Scheer et al [33] found that the most common primary site of infection was different between medical and surgical patients. In medical patients, lung was the most common primary site (42.0%-56.7%), while it was abdomen (48.4%-64.4%) in surgical patients. It should be noted that in the majority of our patients (73.6%) sepsis was associated with pulmonary infection, a much higher percentage as compared to other studies. He et al[34] reported that pulmonary-sepsis showed worse outcome than abdominal-sepsis, and pulmonary infection is a risk factor for one-year mortality and quality of life after sepsis.

There were several limitations to our study. Firstly, the BMI of our patients ranged from 12.11 to 32.46. There was no morbidly obese patient in the current study. In fact, morbidly obese people are rare in this country. Secondly, the present study used weight ascertained at ICU admission, rather than the patient's true outpatient weight. This practice may misclassify the BMI category in as many as 21.9% of patients due to lack of fluid balance adjustment [35]. Thirdly, BMI was used to determine the nutritional status of patients in this study. BMI is a simple index and

widely used in clinical practice, but other indices such as percent body fat might better reflect body composition[36]. Lastly, it was a single-center study with 178 participants, and a large proportion of our patients were older than 65 years, which may have led to a sample-related bias.

Conclusions

To our knowledge, this is the first prospective cohort study that focused on medical patients with sepsis, showing that BMI was an independent predictor of survival, patients with lower BMI having a higher risk of death.

Acknowledgements

Not applicable.

Authors' contributions

QTZ, YCS, YAZ designed the study. QTZ, YCS, NS, YAZ, and QBM coordinated the study. MW, JZ, YLD, SL, and HXG were responsible for patient screening, enrollment, and follow-up. QTZ, MW, and YCS analyzed the data. QTZ drafted the manuscript. YCS critically revised the manuscript. All authors had full access to all study data, read and approved the final version of the manuscript.

Funding

None.

Competing interests

None declared.

Ethics approval and consent to participate

The study protocol was approved (approval number M2015021) by the ethics committee of Peking University Third Hospital, Beijing, China. All patients or their legally authorized representatives provided written informed consent to participate in the study.

Data sharing statement

The authors declare that all data supporting the findings of this study are available within the article.

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Table 1.Comparison of demographics and clinical data between groups defined by clinical outcome in 178 patients with sepsis

Characteristics	Survivors (n=104)	Non survivors (n=74)	p value
Age (year)	78.0 (60.0-84.0)	78.0 (69.0-84.0)	0.291
Males	67 (64.4)	49 (66.2)	0.805
Body mass index (kg/m^2)	23.2 (20.4-26.1)	21.7 (18.4-24.2)	0.006
Comorbidities			
COPD	23 (22.1)	9 (12.2)	0.088
Diabetes mellitus	26 (25.0)	21 (28.4)	0.614
Hypertension	47 (45.2)	31 (41.9)	0.662
Cerebrovascular disease	30 (28.8)	15 (20.3)	0.194
Neoplasm	18 (17.3)	12 (16.2)	0.848
Liver disease	5 (4.8)	4 (5.4)	1.000
Heart failure	20 (19.2)	14 (18.9)	0.958
Chronic renal failure	18 (17.3)	11 (14.9)	0.664
Smoking (pack years)	0 (0-30.0)	0 (0-16.3)	0.509
Primary site of infection			
Lung	77 (74.0)	54 (73.0)	0.874
Abdomen	10 (9.6)	5 (6.8)	0.499
Urinary tract	7 (6.7)	6 (8.1)	0.728
Gastrointestinal tract	7 (6.7)	5 (6.8)	1.000

Other site	3 (2.9)	4 (5.4)	0.452
Community-acquired infection	85 (81.7)	50 (67.6)	0.030
Hypotension	22 (21.2)	41 (55.4)	<0.001
Lactate level (mmol/L)	1.8 (1.0-3.4)	2.7 (1.5-5.7)	0.001
Oliguria	8 (7.7)	16 (21.6)	0.007
PaO_2/FiO_2(mmHg)	198.5 (119.3-287.5)	152.5 (99.6-210.3)	0.006
Serum Creatinine (μmol/L)	97.0 (68.3-176.3)	108.5 (64.0-194.3)	0.868
Total bilirubin (μmol/mL)	13.1 (9.9-22.3)	18.0 (12.5-32.8)	0.015
Platelets ($\times 10^9$/L)	161.0 (95.8-232.5)	123.0 (75.0-204.3)	0.067
INR	1.2 (1.0-1.4)	1.3 (1.1-1.6)	0.015
Glasgow coma scale	15.0 (10.0-15.0)	13.0 (10.0-15.0)	0.117
SOFA score	5.0 (4.0-7.0)	9.0 (7.0-11.0)	<0.001
APACHE II score	16.0 (12.0-22.0)	21.0 (17.0-30.0)	<0.001
Septic shock	21 (20.2)	38 (51.4)	<0.001
Non-invasive ventilation	28 (26.9)	24 (32.4)	0.426
Intubated	36 (34.6)	43 (58.1)	0.002
Positive blood culture	19 (18.3)	19 (25.7)	0.235
Length of ICU stay (days)	12.0 (6.0-22.0)	12.0 (3.0-25.0)	0.521
Length of hospital stay (days)	18.0 (10.0-30.0)	13.0 (3.0-25.0)	0.009

Data are presented as n (%) or median (interquartile range) unless stated otherwise. COPD: Chronic obstructive pulmonary disease; INR: International normalized ratio; SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation.

Table 2. Risk factors for 90-day mortality of patients with sepsis or septic shock by Cox regression analysis

Variables	Hazard ratio (95% Confidence interval)	p value
Body mass index (kg/m^2)	0.940 (0.889-0.994)	0.029
Hypotension	0.781 (0.229-2.670)	0.694
Lactate level (mmol/L)	1.018 (0.943-1.098)	0.648
Oliguria	1.288 (0.715-2.321)	0.399
PaO_2/FiO_2(mmHg)	1.000 (0.997-1.002)	0.933
Septic shock	1.075 (0.320-3.615)	0.907
SOFA score	1.229 (1.123-1.345)	<0.001
APACHE Ⅱ score	1.050 (1.022-1.080)	<0.001
Intubated	1.511 (0.931-2.452)	0.095

SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation.

Table 3. Comparison of demographics and clinical data among groups defined by body mass index in patients with sepsis

Characteristics	Underweight (n=33)	Normal (n=98)	Overweight (n=36)	Obese (n=11)	p value
Age (years)	79.0 (69.0-86.0)	78.0 (67.0-84.0)	73.0 (57.0-83.0)	77.0 (71.0-86.0)	0.162
Males	24 (72.7)	70 (71.4)	20 (55.6)	2 (18.2)	0.002
Comorbidities					
COPD	8(24.2)	21 (21.4)	0	3 (27.3)	0.017
Diabetes mellitus	8 (24.2)	25 (25.5)	9 (25.0)	5 (45.5)	0.530
Hypertension	14 (42.4)	38 (38.8)	19 (52.8)	7 (63.6)	0.265
Cerebrovascular disease	10 (30.3)	24 (24.5)	11 (30.6)	0	0.193
Neoplasm	7 (21.2)	14 (14.3)	8 (22.2)	1 (9.1)	0.547
Liver disease	2 (6.1)	5 (5.1)	2 (5.6)	0	0.879
Heart failure	8 (24.2)	17 (17.3)	5 (13.9)	4 (36.4)	0.319
Chronic renal failure	5 (15.2)	14 (14.3)	7 (19.4)	3 (27.3)	0.669
Smoking (pack-years)	0 (0-20.5)	0 (0-30.0)	0 (0-3.0)	0 (0-30.0)	0.561
Primary site of infection					
Lung	27 (81.8)	69 (70.4)	27 (75.0)	8 (72.7)	0.637
Abdomen	2 (6.1)	9 (9.2)	3 (8.3)	1 (9.1)	0.956
Urinary tract	1 (3.0)	9 (9.2)	2 (5.6)	1 (9.1)	0.656
Gastrointestinal tract	2 (6.1)	6 (6.1)	3 (8.3)	1 (9.1)	0.955
Other site	1 (3.0)	5 (5.1)	1 (2.8)	0	0.800

Community-acquired infection	25 (75.8)	76 (77.6)	26 (72.2)	8 (72.7)	0.925
Hypotension	19 (57.6)	34 (34.7)	9 (25.0)	1 (9.1)	0.007
Lactate level (mmol/L)	2.4 (1.6-7.2)	2.1 (1.0-4.3)	1.6 (1.2-3.3)	1.9 (0.6-2.9)	0.201
Oliguria	8 (24.2)	13 (13.3)	3 (8.3)	0	0.121
PaO_2/FiO_2 (mmHg)	180.0(113.5-251.0)	164.5(102.3-240.5)	188.0(140.5-268.5)	215.0(153.0-300.0)	0.340
Serum Creatinine (μmol/L)	89.0 (57.0-127.0)	118.5 (72.5-190.5)	91.0 (60.0-212.5)	86.0 (56.0-112.0)	0.136
Total bilirubin (μmol/mL)	18.0 (10.1-33.1)	14.4 (10.1-28.4)	17.2 (12.2-26.3)	15.2 (11.3-20.0)	0.819
Platelets ($\times 10^9$/L)	139.0 (75.0-213.0)	147.0 (86.0-209.8)	182.5 (128.3-253.8)	115.0 (49.0-144.0)	0.056
INR	1.3 (1.1-1.6)	1.2 (1.0-1.5)	1.2 (1.1-1.3)	1.1 (1.0-1.2)	0.269
Glasgow coma scale	13.0 (10.0-15.0)	15.0 (12.0-15.0)	15.0 (11.0-15.0)	13.0 (10.0-15.0)	0.761
SOFA score	8.0 (5.0-11.0)	7.0 (5.0-9.0)	6.0 (4.0-8.0)	5.0 (5.0-8.0)	0.382
APACHEⅡ score	18.0 (16.0-24.0)	19.0 (13.0-25.0)	18.0 (13.0-22.0)	14.0 (9.0-17.0)	0.060
Septic shock	19 (57.6)	30 (30.6)	9 (25.0)	1(9.1)	0.004
Non-invasive ventilation	7 (21.2)	30 (30.6)	10 (27.8)	5 (45.5)	0.466
Intubated	19 (57.6)	43 (43.9)	13 (36.1)	4 (36.4)	0.305
Positive blood culture	7 (21.2)	24 (24.5)	4 (11.1)	3 (27.3)	0.383
Length of ICU stay (days)	10.0 (4.0-25.0)	13.0 (7.0-25.0)	11.0 (4.0-19.0)	9.0(6.0-13.0)	0.461
Length of hospital stay (days)	13.0 (4.0-29.0)	16.0 (10.0-28.0)	16.0 (8.0-32.0)	13.0(8.0-20.0)	0.813
In-hospital mortality	20 (60.6)	41 (41.8)	11 (30.6)	2 (18.2)	0.027
90-day mortality	22 (66.7)	47 (48.0)	13 (36.1)	2 (18.2)	0.015

Data are presented as n (%) or median (interquartile range). COPD: Chronic obstructive pulmonary disease; INR: International normalized ratio; SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation.

Fig 1. Patient selection.

Fig 2. Kaplan-Meier survival plot for 90-day survival of underweight, normal weight, overweight, and obese patients with sepsis.

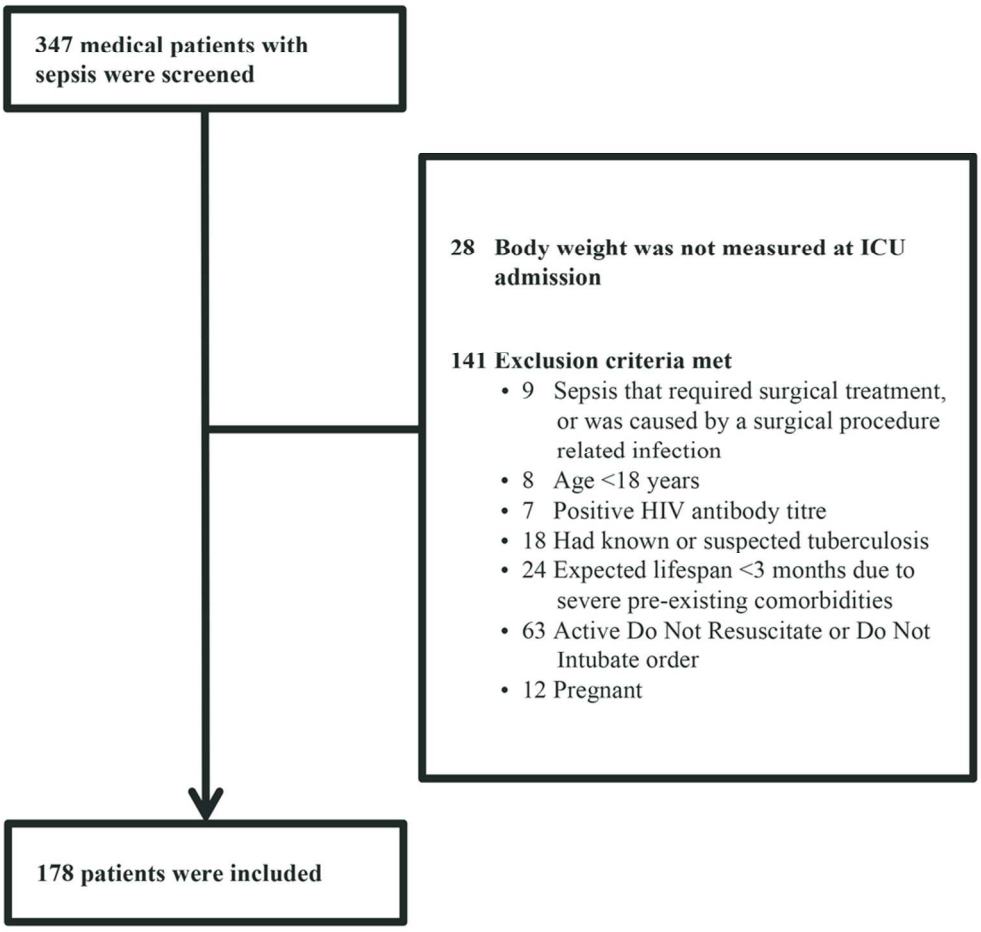

Fig 1. Patient selection.

90x90mm (300 x 300 DPI)

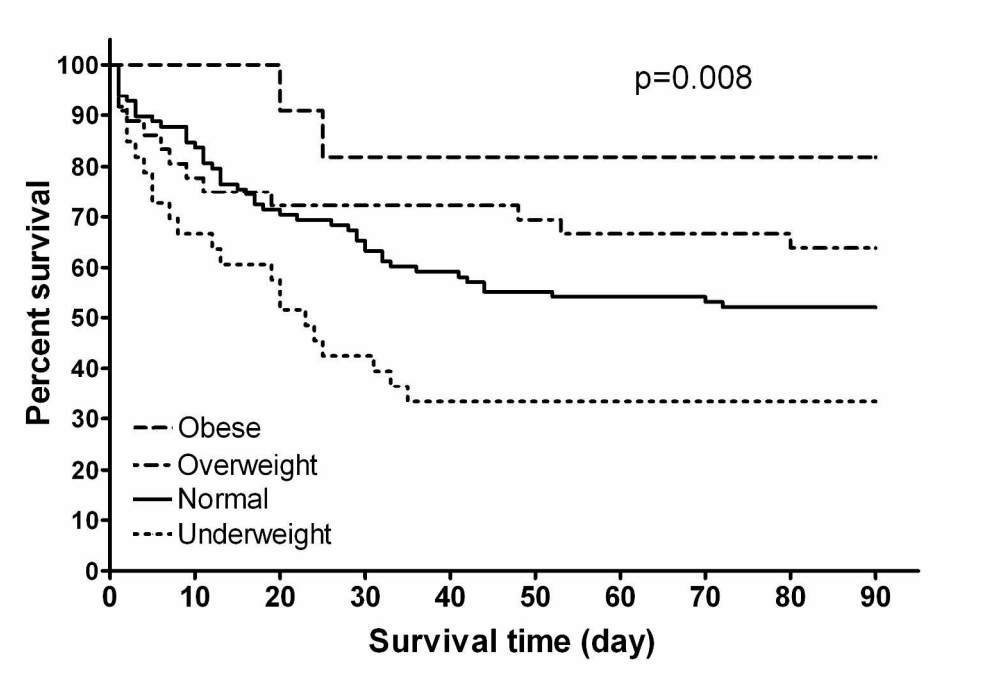

Fig 2. Kaplan-Meier survival plot for 90-day survival of underweight, normal weight, overweight, and obese patients with sepsis.

246x167mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6,7*
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6,7
		(*b*) Describe any methods used to examine subgroups and interactions	6,7
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7,8
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,8
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8,19-23
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12,13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The impact of body mass index on survival of medical patients with sepsis: a prospective cohort study in a university hospital in China

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The impact of body mass index on survival of medical patients with sepsis: a prospective cohort study in a university hospital in China

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Abstract

Objective To evaluate the impact of body mass index (BMI) on survival of a Chinese cohort of medical patients with sepsis.

Design A single-center prospective cohort study conducted from May 2015 to April 2017.

Setting A tertiary care university hospital in China.

Participants 178 patients with sepsis admitted to the medical intensive care unit (ICU) were included.

Main outcome measures The primary outcome was 90-day mortality. The secondary outcomes were in-hospital mortality, length of ICU stay, and length of hospital stay.

Results The median age (interquartile range) was 78 (66-84) years and the majority of patients (77.0%) were older than 65 years. The 90-day mortality was 47.2%. The in-hospital mortality was 41.6%, and the length of ICU stay and hospital stay were 12 (5-22) and 15 (9-28) days, respectively. Cox proportional hazard regression analysis identified that sequential organ failure assessment (SOFA) score (HR = 1.229, $p < 0.001$), APACHE II score (HR = 1.050, $p < 0.001$) and BMI (HR = 0.940, $p = 0.029$) were all independently associated with the 90-day mortality. Patients were divided into four groups based on BMI [underweight 33 (18.5%), normal 98 (55.1%), overweight 36 (20.2%), and obese 11 (6.2%)]. The 90-day mortality (66.7%, 48.0%, 36.1%, and 18.2%, $p = 0.015$) and in-hospital mortality (60.6%, 41.8%, 30.6%, and 18.2%, $p = 0.027$) were statistically different among the four groups. Differences in survival among the four groups were demonstrated by Kaplan-Meier survival analysis

(p = 0.008), with the underweight patients showing a lower survival rate.

Conclusions BMI was an independent factor associated with survival in a Chinese cohort of medical patients with sepsis, patients with lower BMI having a higher risk of death.

Key words: Sepsis; Septic shock; Body mass index; Critical care; Mortality

Strengths and limitations of this study

Our prospective observational cohort study was focused on medical patients with sepsis and conducted at a university hospital in China.

The impact of BMI on 90-day survival of medical patients with sepsis was evaluated by Cox proportional hazard regression analysis and Kaplan-Meier survival analysis.

Our analyses were limited by the use of weight ascertained at ICU admission, rather than the patient's true outpatient weight.

Introduction

Sepsis is a major cause of morbidity and mortality worldwide [1]. Of these patients, half are treated in the intensive care unit (ICU) [2]. In a national population-based study of sepsis in Spain, medical diagnostic categories were the majority of causes in patients who developed sepsis, while surgical diagnoses were identified in only 26% of cases [3].

Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify whether adults are underweight, overweight and obese [4]. Several studies have examined the effects of BMI on mortality with conflicting conclusions. Lower mortality in the obese has been observed in some studies [5-9], but some researchers believe that the true paradox may lie in the variations in sepsis interventions, such as the administration of resuscitation fluids and antimicrobial therapy [6]. In other studies, morbidly obese and underweight patients have been shown to be associated with higher mortality [10,11]. Thus, the impact of BMI on survival of patients with sepsis is still controversial [12, 13].

As the relationship between BMI and clinical outcomes of sepsis is complex, we therefore set out to evaluate prospectively the impact of BMI on survival in a cohort of medical patients with sepsis admitted to the medical ICU in a university hospital.

Patients and Methods

Design

This was a prospective cohort study, which was conducted in the medical ICU of

a university-affiliated urban teaching hospital in China from May 2015 to April 2017.

Subjects

Sepsis was defined as the presence (probable or documented) of infection together with systemic manifestations of infection[14]. Hospitalized patients admitted to the medical ICU with sepsis acquired in the community or in a hospital were eligible for the study if they met any of the following criteria of severe sepsis [14]: (1) sepsis-induced hypotension, (2) lactate above upper laboratory level limits (1.5mmol/L in this study), (3) urine output <0.5 mL Kg^{-1} h^{-1} for more than 2 h despite adequate fluid resuscitation, (4) acute lung injury with Pao_2/Fio_2<250 in the absence of pneumonia as infection source, (5) acute lung injury with Pao_2/Fio_2 <200 in the presence of pneumonia as infection source, (6) creatinine >2.0 mg/dL (176.8 μmol/L), (7) bilirubin >2mg/dL (34.2 μmol/L), (8) platelet count <100,000 μL, and (9) coagulopathy (international normalized ratio >1.5).

Patients were excluded from the study if they met one of the following criteria: (1) the patient had sepsis that required surgical treatment, or was caused by a surgical procedure related infection, (2) age <18 years, (3) the patient had a positive HIV antibody titer or had known/suspected tuberculosis at baseline, (4) expected lifespan <3 months due to severe pre-existing comorbidities, (5) active Do Not Resuscitate or Do Not Intubate order, and (6) pregnant.

All patients accepted treatment according to the international guidelines for management of sepsis and septic shock [14,15]. We collected the following demographic and clinical data: patient's gender, age, weight, height, primary site of

infection, community-acquired or hospital-acquired infection, blood pressure, lactate level, urine output, PaO_2/FiO_2, serum creatinine, total bilirubin, platelets, international normalized ratio (INR), Glasgow coma scale, SOFA score, acute physiology and chronic health evaluation (APACHE) II score, non-invasive ventilation, intubation, positive blood culture, length of ICU stay, and length of hospital stay. Those who survived to discharge were followed for at least 90 days.

BMI is defined as the weight in kilograms divided by the square of the height in meters (kg/m^2). Using the World Health Organization (WHO) criteria for designation of BMI [4], patients were classified as underweight (BMI < 18.50 kg/m^2), normal weight (BMI = 18.50 to 24.99 kg/m^2), overweight (BMI = 25.0 to 29.99 kg/m^2), and obese (BMI ≧ 30.0 kg/m^2).

Outcomes

The primary outcome was 90-day mortality, while the secondary outcomes were in-hospital mortality, length of ICU stay, and length of hospital stay.

Statistical analysis

Continuous variables were expressed as median (interquartile range) and categorical variables as numbers (%). Clinical data were compared between the in-hospital survivors and non-survivors. Continuous variables were compared using the non-parametric Mann–Whitney U test, and categorical variables were compared using the Chi squared test. Cox proportional hazard regression analysis was undertaken to assess the factors associated with 90-day mortality. The variables significantly associated with 90-day non-survival in the univariate analysis were used

in the Cox proportional hazard regression analysis.

Patients were divided into four groups based on BMI (underweight, normal, overweight, and obese). Clinical data were compared among the four groups, where continuous variables were compared using the non-parametric Kruskal-Wallis H test, and categorical variables were compared using the Chi squared test. Kaplan-Meier survival curves were constructed to show the survival probabilities at day-90 according to BMI classification, and compared using the log rank test.

All analyses were conducted using SPSS, version 22.0 (IBM, Armonk, NY, USA). A p value <0.05 was considered significant.

Patient involvement

No patients were involved in developing the hypothesis, the specific aims or the research questions, nor were they involved in the design or implementation of this study. No patients were involved in the interpretation of study results or write-up of the manuscript. There are no plans to involve patients in the dissemination of results.

Results

Figure 1 shows the patient-selection process. In total, 178 medical patients with sepsis were included in this study, with male patients accounting for 65.2% (n=116). The median age (interquartile range) was 78 (66-84) years, and most patients were at least 65 years old (137/178 cases, 77.0%). The most common primary site of infection was the lung (131 cases, 73.6%), followed by abdomen (15 cases, 8.4%), urinary tract (13 cases, 7.3%), gastrointestinal tract (12 cases, 6.7%) and other sites (7 cases, 3.9%).

Septic shock patients accounted for 33.1% (59 cases). Blood culture was positive in 38 patients (21.3%). The 90-day mortality was 47.2% (84/178 cases), and the in-hospital mortality was 41.6% (74/178 cases). The length of ICU stay and the length of hospital stay were 12 (5-22) and 15 (9-28) days, respectively.

Compared with in-hospital survivors, non-survivors had significantly lower BMI and PaO_2/FiO_2 (both $p < 0.05$), higher lactate, bilirubin, INR, SOFA score and APACHE II score (all $p < 0.05$). Meanwhile, more patients died with healthcare-acquired infections, hypotension, oliguria, septic shock, and intubation (all $p < 0.05$) (table 1).

Cox proportional hazard regression analysis was conducted and the independent factors for 90-day death were identified as SOFA score (HR = 1.220, $p < 0.001$), APACHE II score (HR = 1.050, $p < 0.001$) and BMI (HR = 0.940, $p = 0.029$) (table 2).

Patients were divided into four groups based on BMI [underweight 33 (18.5%), normal 98 (55.1%), overweight 36 (20.2%), and obese 11 (6.2%)] . The percentage of males (72.7%, 71.4%, 55.6%, and 18.2%, $p = 0.002$), chronic obstructive pulmonary disease (24.2%, 21.4%, 0, and 27.3%, p=0.017), hypotension (57.6%, 34.7%, 25.0%, and 9.1%, $p = 0.007$), septic shock (57.6%, 30.6%, 25.0%, and 9.1%, $p = 0.004$), in-hospital mortality (60.6%, 41.8%, 30.6%, and 18.2%, $p = 0.027$) and 90-day mortality (66.7%, 48.0%, 36.1%, and 18.2%, $p = 0.015$) were statistically different among the four groups (table 3).

Kaplan-Meier survival curves were constructed to show the survival probabilities

at day-90 according to BMI classification and these were compared using the log rank test, which also showed that higher BMI was associated with better prognosis (p=0.008) (figure 2).

Discussion

This prospective observational cohort study was focused on medical patients with sepsis admitted to the ICU, and the results showed that besides SOFA score and APACHE II score, BMI was identified as an independent factor for 90-day mortality by Cox regression analysis. The association of SOFA and APACHE II score with mortality in this cohort was consistent with previous studies[16-18]. However, BMI was also found to be independently associated with survival, where 90-day mortality decreased with an increase in BMI. While studies examining the risk factors associated with outcomes in sepsis reached inconsistent conclusions on the association of BMI with mortality, our results confirmed that BMI was independently associated with mortality in patients with sepsis caused by medical conditions.

Globally, the prevalence of obesity has reached epidemic proportions, especially in developed countries [19]. BMI is still a useful proxy of overall health because it is highly correlated with body surface area, which is commonly used as a surrogate measure in obesity classification. Even though it is widely accepted that obesity is a risk factor for diabetes mellitus, hypertension, and cardiovascular diseases, the present study and several other studies have indicated that overweight and obese patients with sepsis tend to experience lower mortality. This has been called the “obesity paradox”

[5-9,20]. Although some researchers have expressed doubt that the true paradox may lie in the variations in sepsis interventions [6,21], a meta-analysis concluded that individuals who were overweight or obese had a reduced adjusted mortality when admitted to the ICU with sepsis or septic shock [8]. Recently another meta-analysis also concluded that being overweight was associated with lower mortality (OR 0.87, 95% CI 0.77-0.97, p = 0.02) compared with obese (OR 0.89, 95% CI 0.72-1.10, p = 0.29) and morbidly obese (OR 0.64, 95% CI 0.38-1.08, p = 0.09) patients who did not exhibit significantly reduced mortality compared with normal weight patients [12]. In a large and nationally representative sample of over 1,000 hospitals in the US, obesity was found to be significantly associated with a 16% decrease in the odds of dying among sepsis patients who were hospitalized [22].

Underweight patients with sepsis may be more common in developing countries than in developed countries. In the present study, the percentages of underweight, normal weight, overweight and obese patients were 18.4%, 55.3%, 20.1%, and 6.1%, respectively, while those with sepsis in a study in Canada and the US represented 6.8%, 35.3%, 28.3%, and 29.0% [6]. Being underweight was found to be one of the independent risk factors of mortality in a study on the correlation between surgical site infection and mortality [10]. Furthermore, Lee et al [11] also reported that being underweight was associated with mortality in patients with severe sepsis and septic shock. However, BMI has not been shown to be an independent factor for clinical outcomes by multivariable analyses. In our cohort of medical patients with sepsis, which mainly included elderly and less obese patients, BMI was identified as an

independent factor for survival, patients with lower BMI having a higher risk of death. Thus, our findings would be helpful for evaluating the clinical outcomes of medical patients with sepsis, although validation in further large sample, multi-center studies is still needed.

The mechanism of the correlation between BMI and mortality of sepsis is unclear. There are several potential reasons that could explain this. First, higher BMI resulted in more fat reserves, and patients could have a greater capacity to cope with the inflammatory response during sepsis and sepsis-associated acute lung injury [23-25]. Furthermore, they may be able to tolerate extensive weight loss and dysfunction associated with critical illness [26]. Secondly, a higher BMI can lead to an increased level of lipoproteins. High-density lipoproteins may not only bind and inactivate lipopolysaccharide (LPS) or other harmful bacterial products released during sepsis [27], but also modulate adhesion molecule expression, upregulate endothelial nitric oxide synthase, and counteract oxidative stress [28]. Thirdly, higher BMI can lead to increased adipose tissue deposition. Adipose tissue is increasingly being considered as a functional endocrine organ and associated with increased renin-angiotensin system activity [29]. It appears to have protective hemodynamic effects during sepsis and may decrease the need for fluid or vasopressor support [21,30].

In general, sex has not been found to be an independent predictor for survival in patients with sepsis, which is the same as the results of our current study. But in some special populations, for example in liver cirrhosis patients with bloodstream infection, male sex may be an independent risk factor for mortality[31].

As the relationship between BMI and clinical outcomes of sepsis may be related partly to differences in patient characteristics, we therefore set out to evaluate the impact of BMI on survival in a cohort of medical patients with sepsis, which is different from surgical septic patients. Ranieri et al [32] reported that the primary sites of infection in adults with septic shock were lung (43.9%), abdomen (30.0%), urinary tract (12.3%), skin (5.5%) and other sites (8.3%). Scheer et al [33] found that the most common primary site of infection was different between medical and surgical patients. In medical patients, lung was the most common primary site (42.0%-56.7%), while it was abdomen (48.4%-64.4%) in surgical patients. It should be noted that in the majority of our patients (73.6%) sepsis was associated with pulmonary infection, a much higher percentage as compared to other studies. He et al[34] reported that pulmonary-sepsis showed worse outcome than abdominal-sepsis, and pulmonary infection was a risk factor for one-year mortality and quality of life after sepsis.

There were several limitations to our study. Firstly, the BMI of our patients ranged from 12.11 to 32.46. There was no morbidly obese patient in the current study. In fact, morbidly obese people are rare in this country. Ten severe thinness patients with BMI less than 16.0 were included in the present study, which maybe a small danger that low BMIs represent a sample related bias. But the 90-day mortality and in-hospital mortality of severe thinness patients were 70.0% and 60.0%, respectively, which were not different from those of all 33 underweight patients (66.7% and 60.6%, respectively). Secondly, the present study used weight ascertained at ICU admission, rather than the patient's true outpatient weight. This practice may misclassify the BMI

category in as many as 21.9% of patients due to lack of fluid balance adjustment [35]. Thirdly, BMI was used to determine the nutritional status of patients in this study. BMI is a simple index and widely used in clinical practice, but other indices such as percent body fat might better reflect body composition[36]. Lastly, it was a single-center study with 178 participants, and a large proportion of our patients were older than 65 years, which may have led to a sample-related bias.

Conclusions

To our knowledge, this is the first prospective cohort study that focused on medical patients with sepsis, showing that BMI was independently associated with survival, patients with lower BMI having a higher risk of death.

Acknowledgements

Not applicable.

Authors' contributions

QTZ, YCS, YAZ designed the study. QTZ, YCS, NS, YAZ, and QBM coordinated the study. MW, JZ, YLD, SL, and HXG were responsible for patient screening, enrollment, and follow-up. QTZ, MW, and YCS analyzed the data. QTZ drafted the manuscript. YCS critically revised the manuscript. All authors had full access to all study data, read and approved the final version of the manuscript.

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None.

Competing interests

None declared.

Ethics approval and consent to participate

The study protocol was approved (approval number M2015021) by the ethics committee of Peking University Third Hospital, Beijing, China. All patients or their legally authorized representatives provided written informed consent to participate in the study.

Data sharing statement

The authors declare that all data supporting the findings of this study are available within the article.

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Table 1.Comparison of demographics and clinical data between groups defined by in-hospital clinical outcome in 178 patients with sepsis

Characteristics	Survivors (n=104)	Non survivors (n=74)	p value
Age (year)	78.0 (60.0-84.0)	78.0 (69.0-84.0)	0.291
Males	67 (64.4)	49 (66.2)	0.805
Body mass index (kg/m^2)	23.2 (20.4-26.1)	21.7 (18.4-24.2)	0.006
Comorbidities			
COPD	23 (22.1)	9 (12.2)	0.088
Diabetes mellitus	26 (25.0)	21 (28.4)	0.614
Hypertension	47 (45.2)	31 (41.9)	0.662
Cerebrovascular disease	30 (28.8)	15 (20.3)	0.194
Neoplasm	18 (17.3)	12 (16.2)	0.848
Liver disease	5 (4.8)	4 (5.4)	1.000
Heart failure	20 (19.2)	14 (18.9)	0.958
Chronic renal failure	18 (17.3)	11 (14.9)	0.664
Smoking (pack years)	0 (0-30.0)	0 (0-16.3)	0.509
Primary site of infection			
Lung	77 (74.0)	54 (73.0)	0.874
Abdomen	10 (9.6)	5 (6.8)	0.499
Urinary tract	7 (6.7)	6 (8.1)	0.728
Gastrointestinal tract	7 (6.7)	5 (6.8)	1.000

Other site	3 (2.9)	4 (5.4)	0.452
Community-acquired infection	85 (81.7)	50 (67.6)	0.030
Hypotension	22 (21.2)	41 (55.4)	<0.001
Lactate level (mmol/L)	1.8 (1.0-3.4)	2.7 (1.5-5.7)	0.001
Oliguria	8 (7.7)	16 (21.6)	0.007
PaO_2/FiO_2(mmHg)	198.5 (119.3-287.5)	152.5 (99.6-210.3)	0.006
Serum Creatinine (μmol/L)	97.0 (68.3-176.3)	108.5 (64.0-194.3)	0.868
Total bilirubin (μmol/mL)	13.1 (9.9-22.3)	18.0 (12.5-32.8)	0.015
Platelets ($\times 10^9$/L)	161.0 (95.8-232.5)	123.0 (75.0-204.3)	0.067
INR	1.2 (1.0-1.4)	1.3 (1.1-1.6)	0.015
Glasgow coma scale	15.0 (10.0-15.0)	13.0 (10.0-15.0)	0.117
SOFA score	5.0 (4.0-7.0)	9.0 (7.0-11.0)	<0.001
APACHE II score	16.0 (12.0-22.0)	21.0 (17.0-30.0)	<0.001
Septic shock	21 (20.2)	38 (51.4)	<0.001
Non-invasive ventilation	28 (26.9)	24 (32.4)	0.426
Intubated	36 (34.6)	43 (58.1)	0.002
Positive blood culture	19 (18.3)	19 (25.7)	0.235
Length of ICU stay (days)	12.0 (6.0-22.0)	12.0 (3.0-25.0)	0.521
Length of hospital stay (days)	18.0 (10.0-30.0)	13.0 (3.0-25.0)	0.009

Data are presented as n (%) or median (interquartile range) unless stated otherwise. COPD: Chronic obstructive pulmonary disease; INR: International normalized ratio; SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation.

Table 2. Risk factors for 90-day mortality of patients with sepsis or septic shock by Cox regression analysis

Variables	Hazard ratio (95% Confidence interval)	p value
Body mass index (kg/m^2)	0.940 (0.889-0.994)	0.029
Hypotension	0.781 (0.229-2.670)	0.694
Lactate level (mmol/L)	1.018 (0.943-1.098)	0.648
Oliguria	1.288 (0.715-2.321)	0.399
PaO_2/FiO_2(mmHg)	1.000 (0.997-1.002)	0.933
Septic shock	1.075 (0.320-3.615)	0.907
SOFA score	1.229 (1.123-1.345)	<0.001
APACHE Ⅱ score	1.050 (1.022-1.080)	<0.001
Intubated	1.511 (0.931-2.452)	0.095

SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation. The variables significantly associated with 90-day non-survival in the univariate analysis were used in the Cox proportional hazard regression analysis.

Table 3. Comparison of demographics and clinical data among groups defined by body mass index in patients with sepsis

Characteristics	Underweight (n=33)	Normal (n=98)	Overweight (n=36)	Obese (n=11)	p value
Age (years)	79.0 (69.0-86.0)	78.0 (67.0-84.0)	73.0 (57.0-83.0)	77.0 (71.0-86.0)	0.162
Males	24 (72.7)	70 (71.4)	20 (55.6)	2 (18.2)	0.002
Comorbidities					
COPD	8(24.2)	21 (21.4)	0	3 (27.3)	0.017
Diabetes mellitus	8 (24.2)	25 (25.5)	9 (25.0)	5 (45.5)	0.530
Hypertension	14 (42.4)	38 (38.8)	19 (52.8)	7 (63.6)	0.265
Cerebrovascular disease	10 (30.3)	24 (24.5)	11 (30.6)	0	0.193
Neoplasm	7 (21.2)	14 (14.3)	8 (22.2)	1 (9.1)	0.547
Liver disease	2 (6.1)	5 (5.1)	2 (5.6)	0	0.879
Heart failure	8 (24.2)	17 (17.3)	5 (13.9)	4 (36.4)	0.319
Chronic renal failure	5 (15.2)	14 (14.3)	7 (19.4)	3 (27.3)	0.669
Smoking (pack-years)	0 (0-20.5)	0 (0-30.0)	0 (0-3.0)	0 (0-30.0)	0.561
Primary site of infection					
Lung	27 (81.8)	69 (70.4)	27 (75.0)	8 (72.7)	0.637
Abdomen	2 (6.1)	9 (9.2)	3 (8.3)	1 (9.1)	0.956
Urinary tract	1 (3.0)	9 (9.2)	2 (5.6)	1 (9.1)	0.656
Gastrointestinal tract	2 (6.1)	6 (6.1)	3 (8.3)	1 (9.1)	0.955
Other site	1 (3.0)	5 (5.1)	1 (2.8)	0	0.800

Community-acquired infection	25 (75.8)	76 (77.6)	26 (72.2)	8 (72.7)	0.925
Hypotension	19 (57.6)	34 (34.7)	9 (25.0)	1 (9.1)	0.007
Lactate level (mmol/L)	2.4 (1.6-7.2)	2.1 (1.0-4.3)	1.6 (1.2-3.3)	1.9 (0.6-2.9)	0.201
Oliguria	8 (24.2)	13 (13.3)	3 (8.3)	0	0.121
PaO_2/FiO_2 (mmHg)	180.0(113.5-251.0)	164.5(102.3-240.5)	188.0(140.5-268.5)	215.0(153.0-300.0)	0.340
Serum Creatinine (μmol/L)	89.0 (57.0-127.0)	118.5 (72.5-190.5)	91.0 (60.0-212.5)	86.0 (56.0-112.0)	0.136
Total bilirubin (μmol/mL)	18.0 (10.1-33.1)	14.4 (10.1-28.4)	17.2 (12.2-26.3)	15.2 (11.3-20.0)	0.819
Platelets ($\times 10^9$/L)	139.0 (75.0-213.0)	147.0 (86.0-209.8)	182.5 (128.3-253.8)	115.0 (49.0-144.0)	0.056
INR	1.3 (1.1-1.6)	1.2 (1.0-1.5)	1.2 (1.1-1.3)	1.1 (1.0-1.2)	0.269
Glasgow coma scale	13.0 (10.0-15.0)	15.0 (12.0-15.0)	15.0 (11.0-15.0)	13.0 (10.0-15.0)	0.761
SOFA score	8.0 (5.0-11.0)	7.0 (5.0-9.0)	6.0 (4.0-8.0)	5.0 (5.0-8.0)	0.382
APACHEⅡ score	18.0 (16.0-24.0)	19.0 (13.0-25.0)	18.0 (13.0-22.0)	14.0 (9.0-17.0)	0.060
Septic shock	19 (57.6)	30 (30.6)	9 (25.0)	1(9.1)	0.004
Non-invasive ventilation	7 (21.2)	30 (30.6)	10 (27.8)	5 (45.5)	0.466
Intubated	19 (57.6)	43 (43.9)	13 (36.1)	4 (36.4)	0.305
Positive blood culture	7 (21.2)	24 (24.5)	4 (11.1)	3 (27.3)	0.383
Length of ICU stay (days)	10.0 (4.0-25.0)	13.0 (7.0-25.0)	11.0 (4.0-19.0)	9.0(6.0-13.0)	0.461
Length of hospital stay (days)	13.0 (4.0-29.0)	16.0 (10.0-28.0)	16.0 (8.0-32.0)	13.0(8.0-20.0)	0.813
In-hospital mortality	20 (60.6)	41 (41.8)	11 (30.6)	2 (18.2)	0.027
90-day mortality	22 (66.7)	47 (48.0)	13 (36.1)	2 (18.2)	0.015

Data are presented as n (%) or median (interquartile range). COPD: Chronic obstructive pulmonary disease; INR: International normalized ratio; SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation.

Fig 1. Patient selection.

Fig 2. Kaplan-Meier survival plot for 90-day survival of underweight, normal weight, overweight, and obese patients with sepsis.

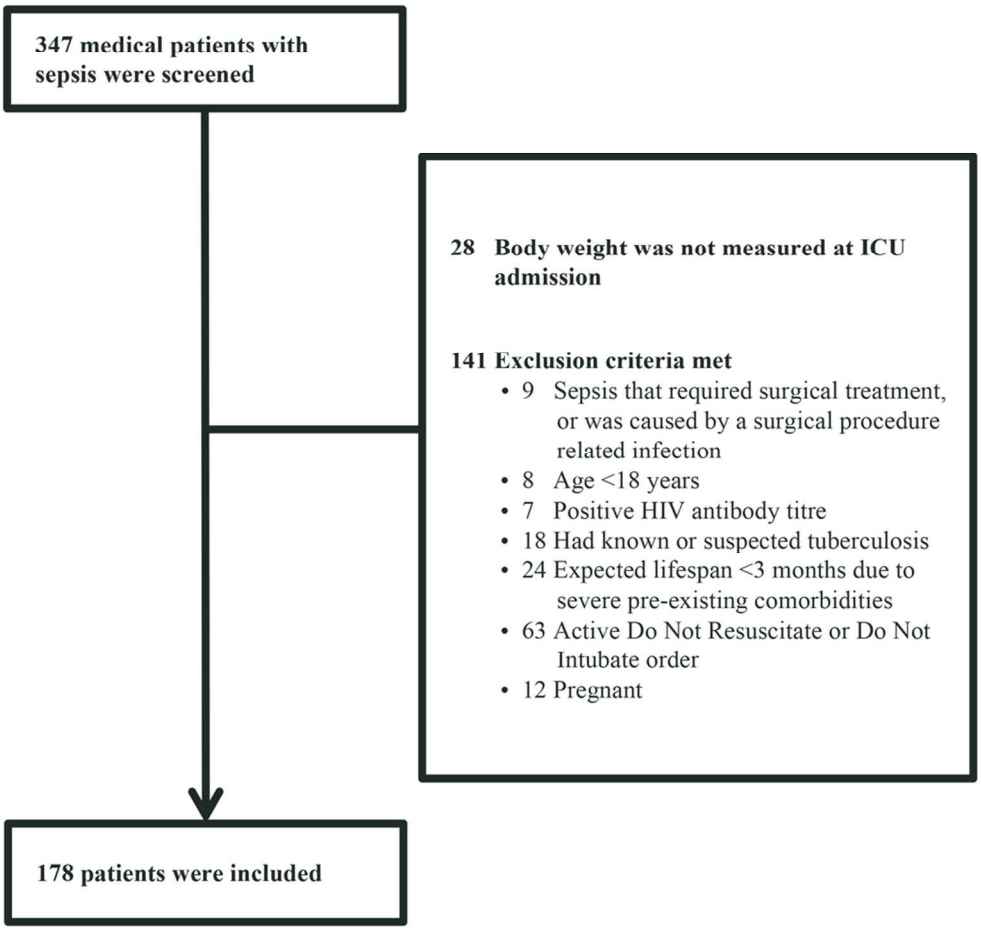

Fig 1. Patient selection.

90x90mm (300 x 300 DPI)

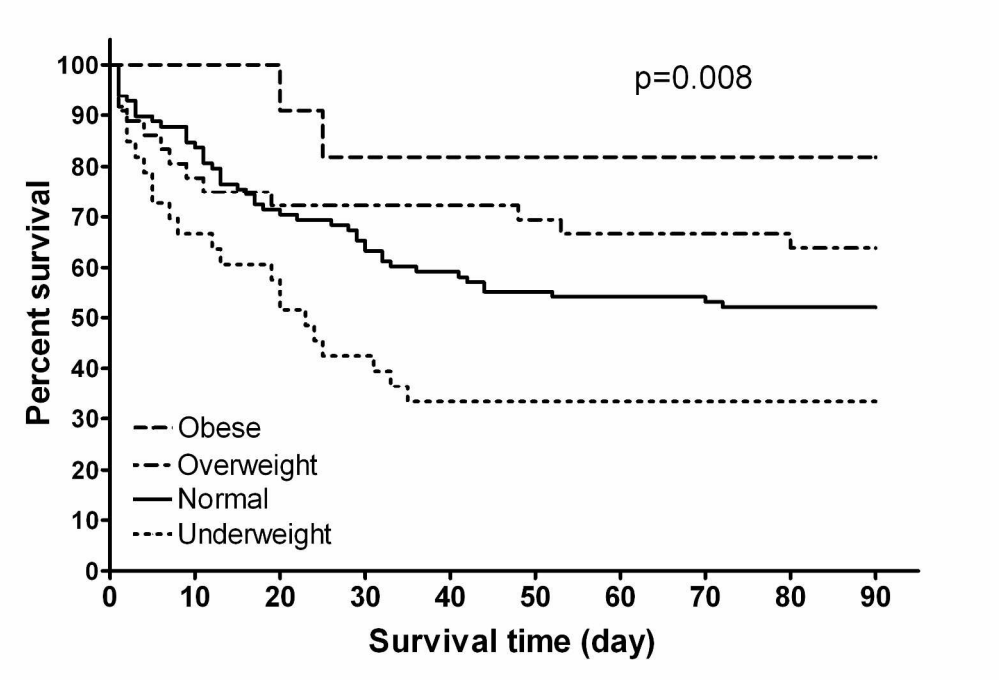

Fig 2. Kaplan-Meier survival plot for 90-day survival of underweight, normal weight, overweight, and obese patients with sepsis.

246x167mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4, 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4, 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6,7
		(*b*) Describe any methods used to examine subgroups and interactions	6,7
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7,8
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,8
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8,9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8,19-25
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12,13
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13, 14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The impact of body mass index on survival of medical patients with sepsis: a prospective cohort study in a university hospital in China

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The impact of body mass index on survival of medical patients with sepsis: a prospective cohort study in a university hospital in China

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Abstract

Objective To evaluate the impact of body mass index (BMI) on survival of a Chinese cohort of medical patients with sepsis.

Design A single-center prospective cohort study conducted from May 2015 to April 2017.

Setting A tertiary care university hospital in China.

Participants A total of 178 patients with sepsis admitted to the medical intensive care unit (ICU) were included.

Main outcome measures The primary outcome was 90-day mortality while the secondary outcomes were in-hospital mortality, length of ICU stay, and length of hospital stay.

Results The median age (interquartile range) was 78 (66-84) years old and 77.0% patients were older than 65 years. The 90-day mortality was 47.2%. The in-hospital mortality was 41.6%, and the length of ICU stay and hospital stay were 12 (5-22) and 15 (9-28) days, respectively. Cox proportional hazard regression analysis identified that sequential organ failure assessment (SOFA) score (HR = 1.229, $p < 0.001$), APACHE II score (HR = 1.050, $p < 0.001$) and BMI (HR = 0.940, $p = 0.029$) were all independently associated with the 90-day mortality. Patients were divided into four groups based on BMI [underweight 33 (18.5%), normal 98 (55.1%), overweight 36 (20.2%), and obese 11 (6.2%)]. The 90-day mortality (66.7%, 48.0%, 36.1%, and 18.2%, $p = 0.015$) and in-hospital mortality (60.6%, 41.8%, 30.6%, and 18.2%, $p = 0.027$) were statistically different among the four groups. Differences in survival

among the four groups were demonstrated by Kaplan-Meier survival analysis (p = 0.008), with the underweight patients showing a lower survival rate.

Conclusions BMI was an independent factor associated with 90-day survival in a Chinese cohort of medical patients with sepsis, with patients having a lower BMI at a higher risk of death.

Key words: Sepsis; Septic shock; Body mass index; Critical care; Mortality

Strengths and limitations of this study

This prospective observational cohort study focused on medical patients with sepsis and was conducted at a university hospital in China.

The impact of BMI on 90-day survival of medical patients with sepsis was evaluated by Cox proportional hazard regression analysis and Kaplan-Meier survival analysis.

Our analyses were limited by the use of weight ascertained at ICU admission rather than the patient's baseline outpatient body weight.

Introduction

Sepsis is a major cause of morbidity and mortality worldwide [1]. Of these patients, half are treated in the intensive care unit (ICU) [2]. In a national population-based study of sepsis in Spain, medical diagnostic categories made up the majority of causes of sepsis, while surgical diagnoses were identified in only 26% of cases [3].

Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify whether adults are underweight, overweight and obese [4]. Several studies have examined the effects of BMI on mortality with conflicting conclusions. Lower mortality in the obese has been observed in some studies [5-9], but some researchers believe that the true paradox may lie in the variations in sepsis interventions, such as the administration of resuscitation fluids and antimicrobial therapy [6]. In other studies, morbidly obese and underweight patients have been shown to be associated with higher mortality [10,11]. Thus, the impact of BMI on survival of patients with sepsis is still controversial [12, 13].

As the relationship between BMI and clinical outcomes of sepsis is complex, we therefore set out to evaluate prospectively the impact of BMI on survival in a cohort of medical patients with sepsis admitted to the medical ICU in a university hospital.

Patients and Methods

Design

This was a prospective cohort study, which was conducted in the medical ICU of

a university-affiliated urban teaching hospital in China from May 2015 to April 2017.

Subjects

Sepsis was defined as the presence (probable or documented) of infection together with systemic manifestations of infection[14]. Hospitalized patients admitted to the medical ICU with sepsis acquired in the community or in a hospital were eligible for the study if they met any of the following criteria of severe sepsis [14]: (1) sepsis-induced hypotension, (2) lactate above upper laboratory level limits (1.5mmol/L in this study), (3) urine output <0.5 mL Kg^{-1} h^{-1} for more than 2 h despite adequate fluid resuscitation, (4) acute lung injury with Pao_2/Fio_2<250 in the absence of pneumonia as infection source, (5) acute lung injury with Pao_2/Fio_2 <200 in the presence of pneumonia as infection source, (6) creatinine >2.0 mg/dL (176.8 μmol/L), (7) bilirubin >2mg/dL (34.2 μmol/L), (8) platelet count <100,000 μL, and (9) coagulopathy (international normalized ratio >1.5).

Patients were excluded from the study if they met one of the following criteria: (1) the patient had sepsis that required surgical treatment, or was caused by a surgical procedure related infection, (2) age <18 years, (3) the patient had a positive HIV antibody titer or had known/suspected tuberculosis at baseline, (4) expected lifespan <3 months due to severe pre-existing comorbidities, (5) active Do Not Resuscitate or Do Not Intubate order, and (6) pregnant.

All patients accepted treatment according to the international guidelines for management of sepsis and septic shock [14,15]. We collected the following demographic and clinical data: patient's gender, age, weight, height, primary site of

infection, community-acquired or hospital-acquired infection, blood pressure, lactate level, urine output, PaO_2/FiO_2, serum creatinine, total bilirubin, platelets, international normalized ratio (INR), Glasgow coma scale, SOFA score, acute physiology and chronic health evaluation (APACHE) II score, non-invasive ventilation, intubation, positive blood culture, length of ICU stay, and length of hospital stay. Those who survived to discharge were followed for at least 90 days.

BMI is defined as the weight in kilograms divided by the square of the height in meters (kg/m^2). Using the World Health Organization (WHO) criteria for designation of BMI [4], patients were classified as underweight (BMI < 18.50 kg/m^2), normal weight (BMI = 18.50 to 24.99 kg/m^2), overweight (BMI = 25.0 to 29.99 kg/m^2), and obese (BMI ≧ 30.0 kg/m^2).

Outcomes

The primary outcome was 90-day mortality, while the secondary outcomes were in-hospital mortality, length of ICU stay, and length of hospital stay.

Statistical analysis

Continuous variables were expressed as median (interquartile range) and categorical variables as numbers (%). Clinical data were compared between the in-hospital survivors and non-survivors. Continuous variables were compared using the non-parametric Mann–Whitney U test, and categorical variables were compared using the Chi squared test. Cox proportional hazard regression analysis was undertaken to assess the factors associated with 90-day mortality. The variables significantly associated with 90-day non-survival in the univariate analysis were used

in the Cox proportional hazard regression analysis.

Patients were divided into four groups based on BMI (underweight, normal, overweight, and obese). Clinical data were compared among the four groups, where continuous variables were compared using the non-parametric Kruskal-Wallis H test, and categorical variables were compared using the Chi squared test. Kaplan-Meier survival curves were constructed to show the survival probabilities at day-90 according to BMI classification, and compared using the log rank test.

All analyses were conducted using SPSS, version 22.0 (IBM, Armonk, NY, USA). A p value <0.05 was considered significant.

Patient involvement

No patients were involved in developing the hypothesis, the specific aims or the research questions, nor were they involved in the design or implementation of this study. No patients were involved in the interpretation of study results or write-up of the manuscript. There are no plans to involve patients in the dissemination of results.

Results

Figure 1 shows the patient-selection process. In total, 178 medical patients with sepsis were included in this study, with male patients accounting for 65.2% (n=116). The median age (interquartile range) was 78 (66-84) years, and most patients were at least 65 years old (137/178, 77.0%). The most common primary site of infection was the lung (131 cases, 73.6%), followed by abdomen (15 cases, 8.4%), urinary tract (13 cases, 7.3%), gastrointestinal tract (12 cases, 6.7%) and other sites (7 cases, 3.9%).

Septic shock patients accounted for 33.1% (59 cases). Blood culture was positive in 38 patients (21.3%). The 90-day mortality was 47.2% (84/178 cases), and the in-hospital mortality was 41.6% (74/178 cases). The length of ICU stay and the length of hospital stay were 12 (5-22) and 15 (9-28) days, respectively.

Compared with in-hospital survivors, non-survivors had significantly lower BMI and PaO_2/FiO_2 (both $p < 0.05$), higher lactate, bilirubin, INR, SOFA score and APACHE II score (all $p < 0.05$). Meanwhile, more patients died with healthcare-acquired infections, hypotension, oliguria, septic shock, and intubation (all $p < 0.05$) (table 1).

Cox proportional hazard regression analysis was conducted and the independent factors for 90-day death were identified as SOFA score (HR = 1.220, $p < 0.001$), APACHE II score (HR = 1.050, $p < 0.001$) and BMI (HR = 0.940, $p = 0.029$) (table 2).

Patients were divided into four groups based on BMI [underweight 33 (18.5%), normal 98 (55.1%), overweight 36 (20.2%), and obese 11 (6.2%)] . The percentage of males (72.7%, 71.4%, 55.6%, and 18.2%, $p = 0.002$), chronic obstructive pulmonary disease (24.2%, 21.4%, 0, and 27.3%, p=0.017), hypotension (57.6%, 34.7%, 25.0%, and 9.1%, $p = 0.007$), septic shock (57.6%, 30.6%, 25.0%, and 9.1%, $p = 0.004$), in-hospital mortality (60.6%, 41.8%, 30.6%, and 18.2%, $p = 0.027$) and 90-day mortality (66.7%, 48.0%, 36.1%, and 18.2%, $p = 0.015$) were statistically different among the four groups (table 3).

Kaplan-Meier survival curves were constructed to show the survival probabilities

at day-90 according to BMI classification and these were compared using the log rank test, which also showed that higher BMI was associated with better prognosis (p=0.008) (figure 2).

Discussion

This prospective observational cohort study focused on medical patients with sepsis admitted to the ICU, and the results showed that besides SOFA score and APACHE II score, BMI was identified as an independent factor for 90-day mortality by Cox regression analysis. The association of SOFA and APACHE II score with mortality in this cohort was consistent with previous studies[16-18]. This study adds the finding that BMI was independently associated with survival, where 90-day mortality decreased with an increase in BMI. While studies examining the risk factors associated with outcomes in sepsis reached inconsistent conclusions on the association of BMI with mortality, our results confirmed that BMI was independently associated with mortality in patients with sepsis caused by medical conditions.

Globally, the prevalence of obesity has reached epidemic proportions, especially in developed countries [19]. BMI is still a useful proxy of overall health because it is highly correlated with body surface area, which is commonly used as a surrogate measure in obesity classification. Even though it is widely accepted that obesity is a risk factor for diabetes mellitus, hypertension, and cardiovascular diseases, the present study and several other studies have indicated that overweight and obese patients with sepsis tend to experience lower mortality. This has been called the “obesity paradox”

[5-9,20]. Although some researchers have expressed doubt that the true paradox may lie in the variations in sepsis interventions [6,21], a meta-analysis concluded that individuals who were overweight or obese had a reduced adjusted mortality when admitted to the ICU with sepsis or septic shock [8]. Recently another meta-analysis also concluded that being overweight was associated with lower mortality (OR 0.87, 95% CI 0.77-0.97, p = 0.02) compared with obese (OR 0.89, 95% CI 0.72-1.10, p = 0.29) and morbidly obese (OR 0.64, 95% CI 0.38-1.08, p = 0.09) patients who did not exhibit significantly reduced mortality compared with normal weight patients [12]. In a large and nationally representative sample of over 1,000 hospitals in the US, obesity was found to be significantly associated with a 16% decrease in the odds of dying among sepsis patients who were hospitalized [22].

Underweight patients with sepsis may be more common in developing countries than in developed countries. In the present study, the percentages of underweight, normal weight, overweight and obese patients were 18.4%, 55.3%, 20.1%, and 6.1%, respectively, while those with sepsis in a study in Canada and the US represented 6.8%, 35.3%, 28.3%, and 29.0% [6]. Being underweight was found to be one of the independent risk factors of mortality in a study on the correlation between surgical site infection and mortality [10]. Furthermore, Lee et al [11] also reported that being underweight was associated with mortality in patients with severe sepsis and septic shock. However, BMI has not been shown to be an independent factor for clinical outcomes by multivariable analyses. In our cohort of medical patients with sepsis, which mainly included elderly and less obese patients, BMI was identified as an

independent factor for survival, patients with lower BMI having a higher risk of death. Thus, our findings would be helpful for evaluating the clinical outcomes of medical patients with sepsis, although validation in future large sample, multi-center studies is still needed.

The mechanism of the correlation between BMI and mortality of sepsis is unclear. There are several potential reasons that could explain this. First, higher BMI resulted in more fat reserves, and patients could have a greater capacity to cope with the inflammatory response during sepsis and sepsis-associated acute lung injury [23-25]. Furthermore, they may be able to tolerate extensive weight loss and dysfunction associated with critical illness [26]. Secondly, a higher BMI can lead to an increased level of lipoproteins. High-density lipoproteins may not only bind and inactivate lipopolysaccharide (LPS) or other harmful bacterial products released during sepsis [27], but also modulate adhesion molecule expression, upregulate endothelial nitric oxide synthase, and counteract oxidative stress [28]. Thirdly, higher BMI can lead to increased adipose tissue deposition. Adipose tissue is increasingly being considered as a functional endocrine organ and associated with increased renin-angiotensin system activity [29]. It appears to have protective hemodynamic effects during sepsis and may decrease the need for fluid or vasopressor support [21,30].

In general, sex has not been found to be an independent predictor for survival in patients with sepsis, which is the same as the results of our current study. But in some special populations, for example in liver cirrhosis patients with bloodstream infection, male sex may be an independent risk factor for mortality[31].

As the relationship between BMI and clinical outcomes of sepsis may be related partly to differences in patient characteristics, we therefore set out to evaluate the impact of BMI on survival in a cohort of medical patients with sepsis, which is different from surgical septic patients. Ranieri et al [32] reported that the primary sites of infection in adults with septic shock were lung (43.9%), abdomen (30.0%), urinary tract (12.3%), skin (5.5%) and other sites (8.3%). Scheer et al [33] found that the most common primary site of infection was different between medical and surgical patients. In medical patients, the lung was the most common primary site (42.0%-56.7%), while it was abdomen (48.4%-64.4%) in surgical patients. It should be noted that in the majority of our patients (73.6%), sepsis was associated with pulmonary infection, a much higher percentage as compared to other studies. He et al[34] reported that pulmonary-sepsis showed worse outcome than abdominal-sepsis, and pulmonary infection was a risk factor for one-year mortality and quality of life after sepsis.

There were several limitations to our study. Firstly, the BMI of our patients ranged from 12.11 to 32.46. There was no morbidly obese patient in the current study. In fact, morbidly obese people are rare in this country. 10 severely underweight patients with BMI less than 16.0 were included in the present study, which introduces possible sample bias in patients in the low BMI category. However, the 90-day and in-hospital mortality of these 10 severely underweight patients were 70.0% and 60.0% respectively, not significantly different from that of all 33 underweight patients (66.7% and 60.6%, respectively). Secondly, the present study used weight ascertained at ICU admission, rather than the patient's baseline outpatient body weight. This

practice may misclassify the BMI category in as many as 21.9% of patients due to lack of fluid balance adjustment [35]. Thirdly, BMI was used to determine the nutritional status of patients in this study. BMI is a simple index and widely used in clinical practice, but other indices such as percent body fat might better reflect body composition[36]. Lastly, it was a single-center study with 178 participants, and a large proportion of our patients were older than 65 years, which may have led to a sample-related bias.

Conclusions

To our knowledge, this is the first prospective cohort study that focused on medical patients with sepsis, showing that BMI was independently associated with 90-day survival, with patients having a lower BMI at a higher risk of death.

Acknowledgements

Not applicable.

Authors' contributions

QTZ, YCS, YAZ designed the study. QTZ, YCS, NS, YAZ, and QBM coordinated the study. MW, JZ, YLD, SL, and HXG were responsible for patient screening, enrollment, and follow-up. QTZ, MW, and YCS analyzed the data. QTZ drafted the manuscript. YCS critically revised the manuscript. All authors had full access to all study data, read and approved the final version of the manuscript.

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None.

Competing interests

None declared.

Ethics approval and consent to participate

The study protocol was approved (approval number M2015021) by the ethics committee of Peking University Third Hospital, Beijing, China. All patients or their legally authorized representatives provided written informed consent to participate in the study.

Data sharing statement

The authors declare that all data supporting the findings of this study are available within the article.

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Table 1.Comparison of demographics and clinical data between groups defined by in-hospital clinical outcome in 178 patients with sepsis

Characteristics	Survivors (n=104)	Non survivors (n=74)	p value
Age (year)	78.0 (60.0-84.0)	78.0 (69.0-84.0)	0.291
Males	67 (64.4)	49 (66.2)	0.805
Body mass index (kg/m^2)	23.2 (20.4-26.1)	21.7 (18.4-24.2)	0.006
Comorbidities			
COPD	23 (22.1)	9 (12.2)	0.088
Diabetes mellitus	26 (25.0)	21 (28.4)	0.614
Hypertension	47 (45.2)	31 (41.9)	0.662
Cerebrovascular disease	30 (28.8)	15 (20.3)	0.194
Neoplasm	18 (17.3)	12 (16.2)	0.848
Liver disease	5 (4.8)	4 (5.4)	1.000
Heart failure	20 (19.2)	14 (18.9)	0.958
Chronic renal failure	18 (17.3)	11 (14.9)	0.664
Smoking (pack years)	0 (0-30.0)	0 (0-16.3)	0.509
Primary site of infection			
Lung	77 (74.0)	54 (73.0)	0.874
Abdomen	10 (9.6)	5 (6.8)	0.499
Urinary tract	7 (6.7)	6 (8.1)	0.728
Gastrointestinal tract	7 (6.7)	5 (6.8)	1.000

Other site	3 (2.9)	4 (5.4)	0.452
Community-acquired infection	85 (81.7)	50 (67.6)	0.030
Hypotension	22 (21.2)	41 (55.4)	<0.001
Lactate level (mmol/L)	1.8 (1.0-3.4)	2.7 (1.5-5.7)	0.001
Oliguria	8 (7.7)	16 (21.6)	0.007
PaO_2/FiO_2(mmHg)	198.5 (119.3-287.5)	152.5 (99.6-210.3)	0.006
Serum Creatinine (μmol/L)	97.0 (68.3-176.3)	108.5 (64.0-194.3)	0.868
Total bilirubin (μmol/mL)	13.1 (9.9-22.3)	18.0 (12.5-32.8)	0.015
Platelets ($\times 10^9$/L)	161.0 (95.8-232.5)	123.0 (75.0-204.3)	0.067
INR	1.2 (1.0-1.4)	1.3 (1.1-1.6)	0.015
Glasgow coma scale	15.0 (10.0-15.0)	13.0 (10.0-15.0)	0.117
SOFA score	5.0 (4.0-7.0)	9.0 (7.0-11.0)	<0.001
APACHE II score	16.0 (12.0-22.0)	21.0 (17.0-30.0)	<0.001
Septic shock	21 (20.2)	38 (51.4)	<0.001
Non-invasive ventilation	28 (26.9)	24 (32.4)	0.426
Intubated	36 (34.6)	43 (58.1)	0.002
Positive blood culture	19 (18.3)	19 (25.7)	0.235
Length of ICU stay (days)	12.0 (6.0-22.0)	12.0 (3.0-25.0)	0.521
Length of hospital stay (days)	18.0 (10.0-30.0)	13.0 (3.0-25.0)	0.009

Data are presented as n (%) or median (interquartile range) unless stated otherwise. COPD: Chronic obstructive pulmonary disease; INR: International normalized ratio; SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation.

Table 2. Risk factors for 90-day mortality of patients with sepsis or septic shock by Cox regression analysis

Variables	Hazard ratio (95% Confidence interval)	p value
Body mass index (kg/m^2)	0.940 (0.889-0.994)	0.029
Hypotension	0.781 (0.229-2.670)	0.694
Lactate level (mmol/L)	1.018 (0.943-1.098)	0.648
Oliguria	1.288 (0.715-2.321)	0.399
PaO_2/FiO_2(mmHg)	1.000 (0.997-1.002)	0.933
Septic shock	1.075 (0.320-3.615)	0.907
SOFA score	1.229 (1.123-1.345)	<0.001
APACHE Ⅱ score	1.050 (1.022-1.080)	<0.001
Intubated	1.511 (0.931-2.452)	0.095

SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation. The variables significantly associated with 90-day non-survival in the univariate analysis were used in the Cox proportional hazard regression analysis.

414 **Table 3. Comparison of demographics and clinical data among groups defined by body mass**

415 **index in patients with sepsis**

Characteristics	Underweight (n=33)	Normal (n=98)	Overweight (n=36)	Obese (n=11)	p value
Age (years)	79.0 (69.0-86.0)	78.0 (67.0-84.0)	73.0 (57.0-83.0)	77.0 (71.0-86.0)	0.162
Males	24 (72.7)	70 (71.4)	20 (55.6)	2 (18.2)	0.002
Comorbidities					
COPD	8(24.2)	21 (21.4)	0	3 (27.3)	0.017
Diabetes mellitus	8 (24.2)	25 (25.5)	9 (25.0)	5 (45.5)	0.530
Hypertension	14 (42.4)	38 (38.8)	19 (52.8)	7 (63.6)	0.265
Cerebrovascular disease	10 (30.3)	24 (24.5)	11 (30.6)	0	0.193
Neoplasm	7 (21.2)	14 (14.3)	8 (22.2)	1 (9.1)	0.547
Liver disease	2 (6.1)	5 (5.1)	2 (5.6)	0	0.879
Heart failure	8 (24.2)	17 (17.3)	5 (13.9)	4 (36.4)	0.319
Chronic renal failure	5 (15.2)	14 (14.3)	7 (19.4)	3 (27.3)	0.669
Smoking (pack-years)	0 (0-20.5)	0 (0-30.0)	0 (0-3.0)	0 (0-30.0)	0.561
Primary site of infection					
Lung	27 (81.8)	69 (70.4)	27 (75.0)	8 (72.7)	0.637
Abdomen	2 (6.1)	9 (9.2)	3 (8.3)	1 (9.1)	0.956
Urinary tract	1 (3.0)	9 (9.2)	2 (5.6)	1 (9.1)	0.656
Gastrointestinal tract	2 (6.1)	6 (6.1)	3 (8.3)	1 (9.1)	0.955
Other site	1 (3.0)	5 (5.1)	1 (2.8)	0	0.800

Community-acquired infection	25 (75.8)	76 (77.6)	26 (72.2)	8 (72.7)	0.925
Hypotension	19 (57.6)	34 (34.7)	9 (25.0)	1 (9.1)	0.007
Lactate level (mmol/L)	2.4 (1.6-7.2)	2.1 (1.0-4.3)	1.6 (1.2-3.3)	1.9 (0.6-2.9)	0.201
Oliguria	8 (24.2)	13 (13.3)	3 (8.3)	0	0.121
PaO_2/FiO_2 (mmHg)	180.0(113.5-251.0)	164.5(102.3-240.5)	188.0(140.5-268.5)	215.0(153.0-300.0)	0.340
Serum Creatinine (μmol/L)	89.0 (57.0-127.0)	118.5 (72.5-190.5)	91.0 (60.0-212.5)	86.0 (56.0-112.0)	0.136
Total bilirubin (μmol/mL)	18.0 (10.1-33.1)	14.4 (10.1-28.4)	17.2 (12.2-26.3)	15.2 (11.3-20.0)	0.819
Platelets ($\times 10^9$/L)	139.0 (75.0-213.0)	147.0 (86.0-209.8)	182.5 (128.3-253.8)	115.0 (49.0-144.0)	0.056
INR	1.3 (1.1-1.6)	1.2 (1.0-1.5)	1.2 (1.1-1.3)	1.1 (1.0-1.2)	0.269
Glasgow coma scale	13.0 (10.0-15.0)	15.0 (12.0-15.0)	15.0 (11.0-15.0)	13.0 (10.0-15.0)	0.761
SOFA score	8.0 (5.0-11.0)	7.0 (5.0-9.0)	6.0 (4.0-8.0)	5.0 (5.0-8.0)	0.382
APACHEⅡ score	18.0 (16.0-24.0)	19.0 (13.0-25.0)	18.0 (13.0-22.0)	14.0 (9.0-17.0)	0.060
Septic shock	19 (57.6)	30 (30.6)	9 (25.0)	1(9.1)	0.004
Non-invasive ventilation	7 (21.2)	30 (30.6)	10 (27.8)	5 (45.5)	0.466
Intubated	19 (57.6)	43 (43.9)	13 (36.1)	4 (36.4)	0.305
Positive blood culture	7 (21.2)	24 (24.5)	4 (11.1)	3 (27.3)	0.383
Length of ICU stay (days)	10.0 (4.0-25.0)	13.0 (7.0-25.0)	11.0 (4.0-19.0)	9.0(6.0-13.0)	0.461
Length of hospital stay (days)	13.0 (4.0-29.0)	16.0 (10.0-28.0)	16.0 (8.0-32.0)	13.0(8.0-20.0)	0.813
In-hospital mortality	20 (60.6)	41 (41.8)	11 (30.6)	2 (18.2)	0.027
90-day mortality	22 (66.7)	47 (48.0)	13 (36.1)	2 (18.2)	0.015

Data are presented as n (%) or median (interquartile range). COPD: Chronic obstructive pulmonary disease; INR: International normalized ratio; SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation.

Fig 1. Patient selection.

Fig 2. Kaplan-Meier survival plot for 90-day survival of underweight, normal weight, overweight, and obese patients with sepsis.

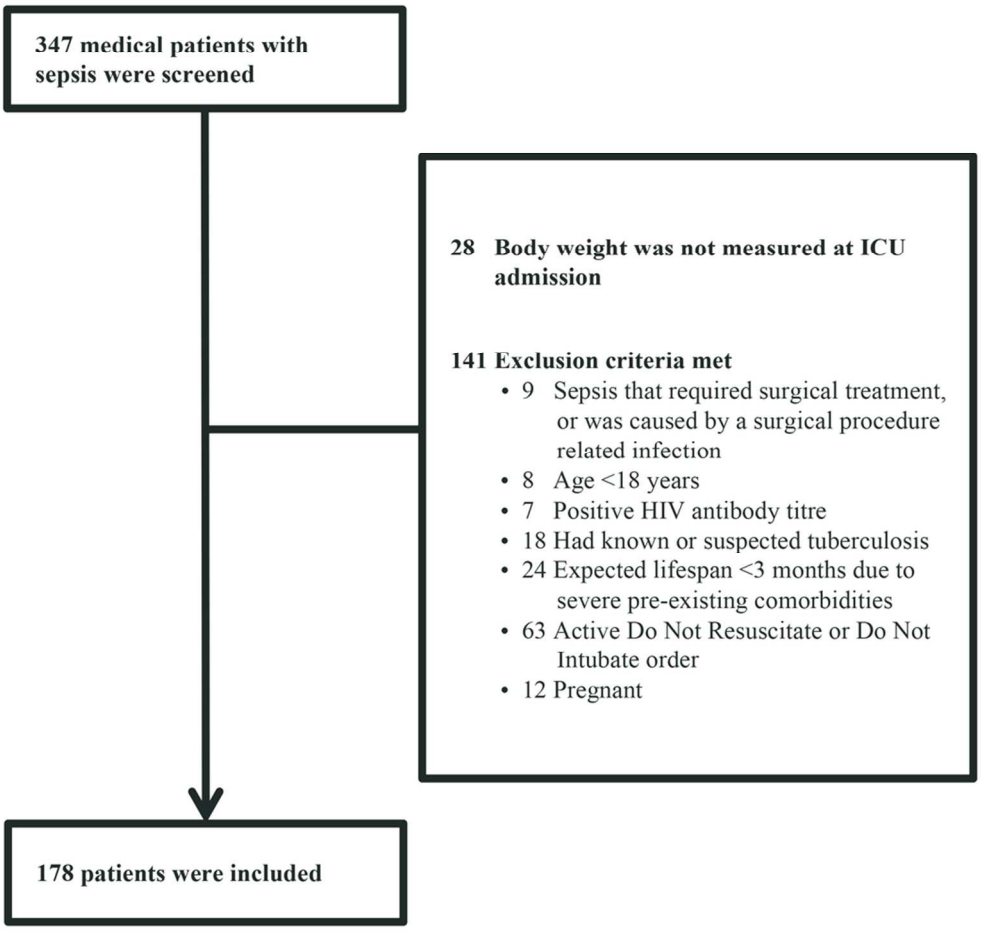

Fig 1. Patient selection.

90x90mm (300 x 300 DPI)

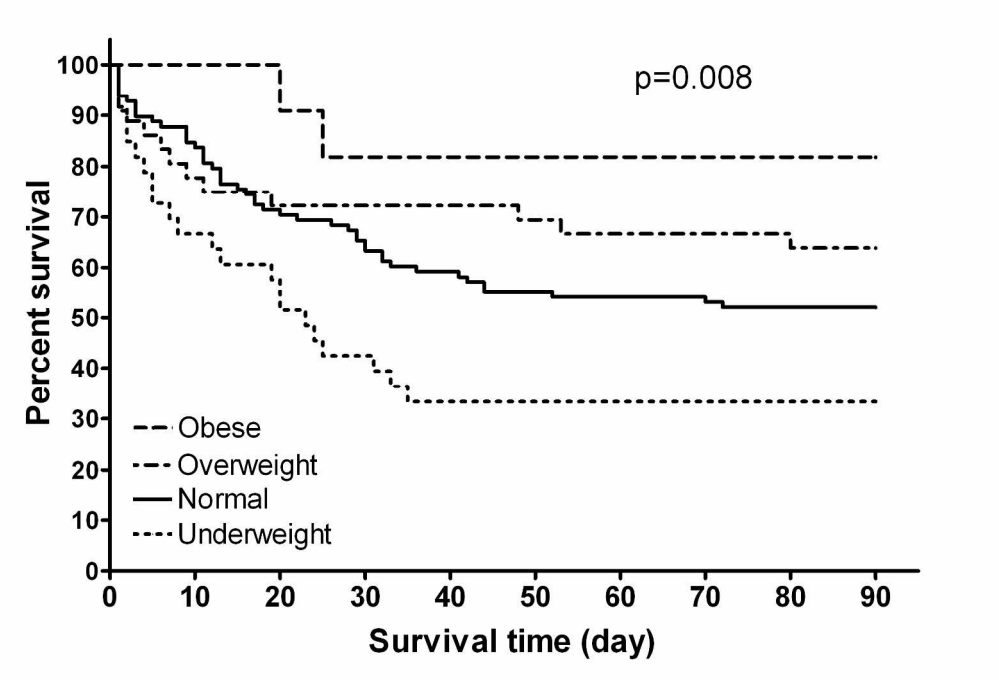

Fig 2. Kaplan-Meier survival plot for 90-day survival of underweight, normal weight, overweight, and obese patients with sepsis.

246x167mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4, 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4, 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6,7*
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6,7
		(*b*) Describe any methods used to examine subgroups and interactions	6,7
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7,8
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,8
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8,9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8,19-25
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12,13
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.