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Increased body mass index linked to greater short- and long-term survival in sepsis patients: A retrospective analysis of a large clinical database

Shuhe Li[a,1], Xiaoguang Hu[a,1], Jinghong Xu[a,b], Fa Huang[a,b], Zilu Guo[c], Li Tong[a], Ka Yin Lui[a], Lu Cao[d], Yanping Zhu[a], Jiyou Yao[e], Xiaobin Lin[f], Xiangdong Guan[a], Changjie Cai[a,*]

[a] Department of Critical Care Medicine, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, 510080, China
[b] Guangdong Provincial Key Laboratory of Organ Donation and Transplant Immunology, Guangzhou, 510080, China
[c] Department of Statistics, William March Rice University, 6100 Main St., Houston, TX 77005, USA
[d] Department of Extracorporeal Circulation, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, 510080, China
[e] Department of Hepatobiliary Surgery, Guangzhou First People's Hospital, Guangzhou 510180, China
[f] Department of Pharmacology, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, 510080, China

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ABSTRACT

Objectives: We investigated the impact of obesity (proxied as body mass index (BMI)), on short- and long-term mortality in sepsis patients.
Methods: We conducted a retrospective analysis with adult sepsis ICU patients in a US medical institution from 2001 to 2012 in the MIMIC-III database. The WHO BMI categories were used. Multivariate logistic regression assessed the relationships between BMI and 30-day and 1-year mortality.
Results: In total, 5563 patients were enrolled. Obese patients tended to be younger ($P < 0.001$), to be female ($P < 0.001$), to acquire worse SOFA scores ($P < 0.001$), and to receive more aggressive treatment compared with their normal weight counterparts. Obese patients had notably longer mechanical ventilation periods and ICU and hospital lengths of stay (LOSs). In the final model, overweight and obese patients had lower 30-day (OR 0.77, 95% CI 0.66–0.91; OR 0.65, 95% CI 0.56–0.77, respectively) and 1-year (OR 0.83, 95% CI 0.71–0.96; OR 0.70, 95% CI 0.60–0.81, respectively) mortality risks than normal weight patients. In contrast, underweight patients had worse 30-day and 1-year outcomes compared with normal weight patients ($P = 0.01$, $P < 0.001$, respectively). In morbidly obese, severe sepsis and septic shock patients, obesity remained protective.
Conclusions: Obesity was correlated with short- and long-term survival advantages in sepsis patients.

Introduction

Sepsis, a syndrome of lethal pathophysiological and biochemical dysfunction induced by an uncontrolled response to infection, is a predominant cause of death in ICUs and a global healthcare challenge (Singer et al., 2016). In US hospitals, sepsis is among the most costly conditions (Torio and Andrews, 2006), accounting for 35% of all hospitalizations that culminated in death (Rhee et al., 2017). A recent meta-analysis estimated a global prevalence of 5.3 million potential deaths attributed to sepsis annually (Fleischmann et al., 2016). Despite the intense investigations and countless clinical trials on sepsis, the biological mechanisms, effective diagnostic approaches and optimal bedside management strategies have yet to be identified (Coopersmith et al., 2018). Hence, prognostic factors for sepsis might be crucially involved in assisting clinicians in identifying patients at high risk and making wiser medical judgements.

Obesity is a substantial global public burden due to our growing preference for energy-dense food and a sedentary lifestyle, and the prevalence has tripled worldwide from 1975 to 2016. Although

* Corresponding author at: Department of Critical Care Medicine, The First Affiliated Hospital of Sun Yat-Sen University, No.58, Zhongshan 2nd Road, Yuexiu District, Guangzhou, Guangdong Province, 510080, China
E-mail addresses: lish7@mail2.sysu.edu.cn (, huxiaog@mail2.sysu.edu.cn (X. Hu), xujh38@mail2.sysu.edu.cn (J. Xu), huangf56@mail2.sysu.edu.cn (F. Huang), zg12@rice.edu (Z. Guo), tongli2@mail2.sysu.edu.cn (L. Tong), lvjiax@mail2.sysu.edu.cn (K.Y. Lui), caolu3@mail2.sysu.edu.cn (L. Cao), zhuyp8@mail2.sysu.edu.cn (Y. Zhu), yaojy23@mail2.sysu.edu.cn (J. Yao), linxb6@mail2.sysu.edu.cn (X. Lin), carlg@163.com (X. Guan), caichjie@mail.sysu.edu.cn (C. Cai).
[1] Shuhe Li and Xiaoguang Hu contributed equally to this work.

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obesity is a strong contributor to increased all-cause mortality and multiple chronic comorbidities (e.g., myocardial infarction, stroke, endometrial cancers), there is a peculiar phenomenon termed the "obesity paradox" first characterized in patients with acute decompensated heart failure (Fonarow et al., 2007). This suggests that obesity might also have a protective effect against specific diseases (e.g., chronic kidney diseases (Kalantar-Zadeh et al., 2005) and HIV/AIDS (Chlebowski et al., 1995)), yet whether this effect exists with regard to sepsis has remained controversial thus far (Trivedi et al., 2015).

While there is a body of literature evaluating the impact of obesity on non-selected critically ill patients within the previous version of the database used in this study (Abhyankar et al., 2012), there is still a paucity of studies on the abovementioned paradoxical phenomenon in the unique setting of sepsis. Therefore, we aimed to assess the association between obesity (high BMI) and the risks of short- and long-term mortality in sepsis patients, utilizing the real-world data obtained from the latest Multiparameter Intelligent Monitoring in Intensive Care (MIMIC-III) database (Johnson et al., 2016).

Methods

Database

We employed the open-access free critical care database MIMIC-III for this study; this database contains anonymized health-related information for over forty thousand patients admitted to ICUs at the Beth Israel Deaconess Medical Centre in the US from 2001 to 2012. The up-to-date version 1.4 of MIMIC-III was used. The authors were obliged to complete the training course to obtain access to the database.

Study population

All patients with a diagnosis relevant to sepsis within the database were initially screened, including those with sepsis, severe sepsis and septic shock (ICD9 codes: 99591, 99592, 78552, respectively). The following inclusion criteria were applied: (1) age above 18 years and (2) at least one weight value. For the patients lacking height records, their heights were generated as the average height plus or minus a random number within the range of standard deviation based on the statistics of the US population for different sexes and ages (Fryar et al., 2016). The final participants were divided into four groups according to the World Health Organization (WHO) BMI classifications: underweight (BMI $< 18.5\ kg/m^2$), normal weight (BMI: 18.5 to $<25\ kg/m^2$), overweight (BMI: 25 to $<30\ kg/m^2$), and obese (BMI $\geq 30\ kg/m^2$). Additionally, an individual ICU admission was considered a statistical unit rather than a particular patient because the BMI values varied between different admissions even for one patient.

Data extraction

We executed the data extraction with structure query language (SQL) in PostgreSQL (v9.6; PostgreSQL Global Development Group). We extracted the following variables: baseline features (e.g., age, sex, ethnicity), vital signs and degrees of organ failure 24 h after ICU admission (e.g., heart rate, mean arterial pressure, Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score II (SAPS-II)), and intervention-associated information (e.g., the presence of surgery, mechanical ventilation). BMI was calculated as weight (in kilograms)/height (in metres)^2. If a variable, for instance, heart rate, was measured more than once in the inclusion period, we took the average of the highest and lowest values.

Outcomes

The primary outcomes were the 30-day and 1-year mortality rates after ICU admission. The secondary outcomes included in-hospital mortality, ICU length of stay (LOS) and hospital LOS and the total ventilation duration.

Statistical analysis

Initially, univariate analysis was conducted to compare all the study variables. Continuous variables are described as the means and standard deviations and were compared with pairwise Student's t-tests and one-way ANOVA across groups. Categorical variables are presented as numbers and percentages and were compared by Pearson's chi-square test or Fisher's exact test as appropriate. We carried out the survival analysis using the log-rank test and 30-day and 1-year Kaplan–Meier curves. The multivariate logistic regression model was constructed as follows: variables with P-values < 0.15 in the univariate test or with clinical importance were included in the model. We assessed multicollinearity for independent variables by the variance inflation factor (VIF) with an upper limit of 2.

Additionally, we implemented several post hoc analyses. First, we removed individuals with imputed heights and reran the entire analysis to check whether our method of dealing with missing height records distorted the conclusion. Second, we performed stratification analyses based on age, SOFA scores and ICU types to determine their confounding influences. Moreover, the subtype of BMI "morbidly obese", defined as BMI $\geq 40\ kg/m^2$, was studied due to the distinctive pathophysiology and higher all-cause mortality in morbidly obese individuals compared to the obese population with BMIs in the range of 30–40 kg/m^2 (Fontaine et al., 2003). Finally, we examined the subgroups of patients diagnosed with "severe sepsis" or "septic shock" to determine whether the conclusions persisted despite the smaller population size with worse physiologic states.

All statistical analyses were performed using SPSS software (v22.0; IBM, Armonk, NY); a two-sided $P < 0.05$ was considered statistically significant.

Results

Population and baseline characteristics

The MIMIC-III database contained 6137 ICU admission records for 4680 specific individuals, of whom there were 6 patients aged less than 18 years (all infants). A total of 566 records were excluded due to a lack of weight values. Finally, we included 5563 (90.6%) subjects as our study population (Figure 1).

The baseline characteristics of the patients are presented in Table 1. Obese patients tended to be younger (64.2 ± 14.8 vs. 67.6 ± 17.5 years, $P < 0.001$) and female (48.8% vs. 40.8%, $P < 0.001$) compared with normal weight patients. Coronary care unit (CCU) was a more frequent choice for heavier patients to receive medical care, probably owing to their susceptibilities to cardiovascular diseases ($P < 0.05$). Overweight and obese patients had dramatically higher blood glucose levels than the normal weight patients ($P < 0.01$, $P < 0.001$, respectively), corresponding with the high prevalence of diabetes mellitus comorbid with obesity. Additionally, obese participants had worse SOFA scores than their normal weight counterparts (7.1 ± 4.0 vs. 6.6 ± 3.7, $P < 0.001$).

Univariate analysis of clinical outcomes

Clinical outcomes are shown in Table 2. As might be expected, obese patients were more likely to receive aggressive

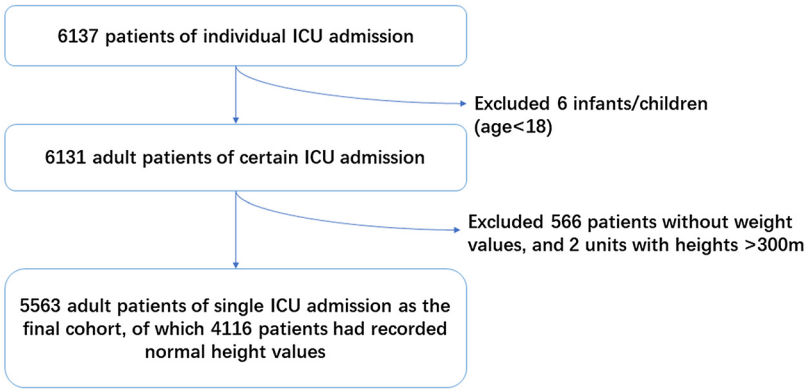

Figure 1. Flowchart of study cohort selection.

methods of care delivery: they had significantly higher incidences of surgery (94.0% v 90.7%, $P < 0.05$), mechanical ventilation (58.3% v 48.0%, $P < 0.001$), and vasopressor administration (55.7% v 51.0%, $P < 0.01$), and they had a comparably high rate of renal replacement therapy (33.1% v 31.6%, $P = 0.35$) compared with the normal weight population. Furthermore, obese patients were predisposed to experience a prolonged period of respiratory support (199.5 ± 257.1 vs. 169.7 ± 221.5 h, $P < 0.05$) and longer ICU and hospital LOS compared with the normal weight cohort (Figure 2) (8.2 ± 10.7 vs. 6.4 ± 9.3 days, $P < 0.001$; 20.5 ± 23.9 vs. 16.9 ± 21.9 days, $P < 0.001$ individually).

Table 1
Univariate analysis of baseline characteristics in 5563 sepsis patients by BMI category.

Variables	Overall	Underweight	Normal weight	Overweight	Obese	P-value
Baseline characteristics						
n (%)	5563	274(4.9)	1726(31.0)	1653(29.7)	1910(34.3)	
Age (years), n (%)	66.3(16.2)	66.2(18.5)	67.6(17.5)	67.4(15.9)	64.2(14.8)[a]	<0.001
Female, n (%)	2444(43.9)	128(46.7)	704(40.8)	679(41.1)	933(48.8)[a]	<0.001
Race, n (%)						<0.001
White	4113(73.9)	192(70.1)	1246(72.2)	1248(75.5)[c]	1427(74.7)	0.06
Hispanic or Latino	184(3.3)	6(2.2)	61(3.5)	56(3.4)	61(3.2)	0.69
Black	572(10.3)	46(16.8)[b]	175(10.1)	158(9.6)	193(10.1)	0.003
Asian	175(3.1)	19(6.9)	97(5.6)	45(2.7)[a]	14(0.7)[a]	<0.001
Other	519(9.3)	11(4.0)[c]	147(8.5)	146(8.8)	215(11.3)[b]	<0.001
Marital status, n (%)						<0.001
Married	2546(45.8)	94(34.3)[a]	813(47.1)	791(47.9)	848(44.4)	<0.001
Single/divorced/separated/unknown	2152(38.7)	142(51.8)[a]	623(36.1)	628(38.0)	759(39.7)[c]	<0.001
Widowed	865(15.5)	38(13.9)	290(16.8)	234(14.2)[c]	303(15.9)	0.16
Admission type, n (%)						0.11
Elective	211(3.8)	4(1.5)	62(3.6)	73(4.4)	72(3.8)	0.11
Emergency/urgent	5352(96.2)	270(98.5)	1664(96.4)	1580(95.6)	1838(96.2)	0.11
Insurance type, n (%)						0.001
Medicare/Medicaid	4023(72.3)	219(79.9)[c]	1274(73.8)	1205(72.9)	1325(69.4)[b]	<0.001
Private	1410(25.3)	49(17.9)[c]	408(23.6)	407(24.6)	546(28.6)[a]	<0.001
Other	130(2.3)	6(2.2)	44(2.5)	41(2.5)	39(2.0)	0.74
ICU type, n (%)						0.05
CCU	504(9.1)	20(7.3)	130(7.5)	174(10.5)[b]	180(9.4)[c]	0.01
CSRU	214(3.8)	6(2.2)	59(3.4)	69(4.2)	80(4.2)	0.26
MICU	3724(66.9)	188(68.6)	1198(69.4)	1086(65.7)[c]	1252(65.5)[c]	0.05
SICU	754(13.6)	46(16.8)	222(12.9)	214(12.9)	272(14.2)	0.22
TSICU	367(6.6)	14(5.1)	117(6.8)	110(6.7)	126(6.6)	0.78
Vital signs within 24 h after ICU admission						
Heart rate (bpm)	91.8(17.3)	92.7(16.9)	91.8(17.4)	91.7(17.5)	91.8(17.1)	0.84
MAP (mmHg)	72.4(10.2)	73.0(10.0)	71.9(9.9)	72.4(10.3)	72.7(10.4)	0.10
Temperature (°C)	36.8(0.8)	36.7(0.8)	36.8(0.8)	36.8(0.8)	36.9(0.8)[a]	<0.001
Respiratory rate (bpm)	21.0(4.6)	20.6(5.2)	21.0(4.7)	21.2(4.6)	21.0(4.5)	0.48
SpO2 (%)	96.7(3.3)	97.2(2.7)	96.8(3.3)	96.6(3.6)	96.6(3.1)	0.04
Blood glucose (mg/dL)	142.8(50.9)	131.6(43.3)	135.1(46.0)	142.1(48.9)[b]	151.8(55.9)[a]	<0.001
Severity of organ dysfunction						
SOFA	6.9(3.9)	6.5(3.4)	6.6(3.7)	6.9(3.9)	7.1(4.0)[a]	<0.001
SAPS II	45.4(16.2)	46.5(16.4)	45.5(15.8)	45.9(16.5)	44.6(16.3)	0.07
SIRS	3.2(0.9)	3.2(0.9)	3.3(0.8)	3.2(0.9)	3.2(0.8)	0.06
qSOFA	2.0(0.6)	2.0(0.7)	2.1(0.6)	2.0(0.6)	2.0(0.6)[c]	0.02

Abbreviations: BMI: body mass index, Medicare/Medicaid: insurances intended for patients with elder ages, low incomes or chronic complications provided by state or federal programs, CCU: coronary care unit, CSRU: cardiac surgery recovery unit, MICU: medical intensive care unit, SICU: surgical intensive care unit, TSICU: thoracic surgery intensive care unit, MAP: mean arterial pressure, SpO2: peripheral capillary oxygen saturation, SOFA: sequential organ failure assessment, SAPS II: simplified acute physiology score II, SIRS: systemic inflammation response syndrome, qSOFA: quick- sequential organ failure assessment.

[a] $P < 0.001$.

[b] $P < 0.01$.

[c] $P < 0.05$ compared with normal weight category.

Table 2
Univariate analysis of clinical outcomes in 5563 patients by BMI category.

Variables	Overall	Underweight	Normal weight	Overweight	Obese	P-value
Surgery, n (%)	5134(92.3)	246(89.8)	1566(90.7)	1527(92.4)	1795(94.0)[c]	0.001
Dialysis, n (%)	1783(32.1)	71(25.9)	546(31.6)	534(32.3)	632(33.1)	0.12
Ventilation, n (%)	2924(52.6)	133(48.5)	828(48.0)	850(51.4)[c]	1113(58.3)[a]	<0.001
Ventilation duration (hours)	182.8(241.5)	143.8(169.7)	169.7(221.5)	179.7(247.1)	199.5(257.1)[c]	0.003
Vasopressor, n (%)	2969(53.4)	133(48.5)	881(51.0)	891(53.9)	1064(55.7)[b]	0.01
ICU LOS (days)	7.1(9.9)	5.7(6.7)	6.4(9.3)	6.9(9.8)	8.2(10.7)[a]	<0.001
Hospital LOS (days)	18.2(21.6)	15.3(13.4)	16.9(21.9)	17.5(19.1)	20.5(23.9)[a]	<0.001
In-hospital mortality, n (%)	1818(32.7)	100(36.5)	588(34.1)	547(33.1)	583(30.5)[c]	0.06
30-day mortality, n (%)	1761(31.7)	117(42.7)[c]	602(34.9)	517(31.3)[c]	525(27.5)[a]	<0.001
1-year mortality, n (%)	2972(53.4)	185(67.5)[a]	979(56.7)	888(53.7)	920(48.2)[a]	<0.001

Abbreviations: BMI: body mass index, LOS: length of stay.
[a] $P < 0.001$.
[b] $P < 0.01$.
[c] $P < 0.05$ compared with normal weight category.

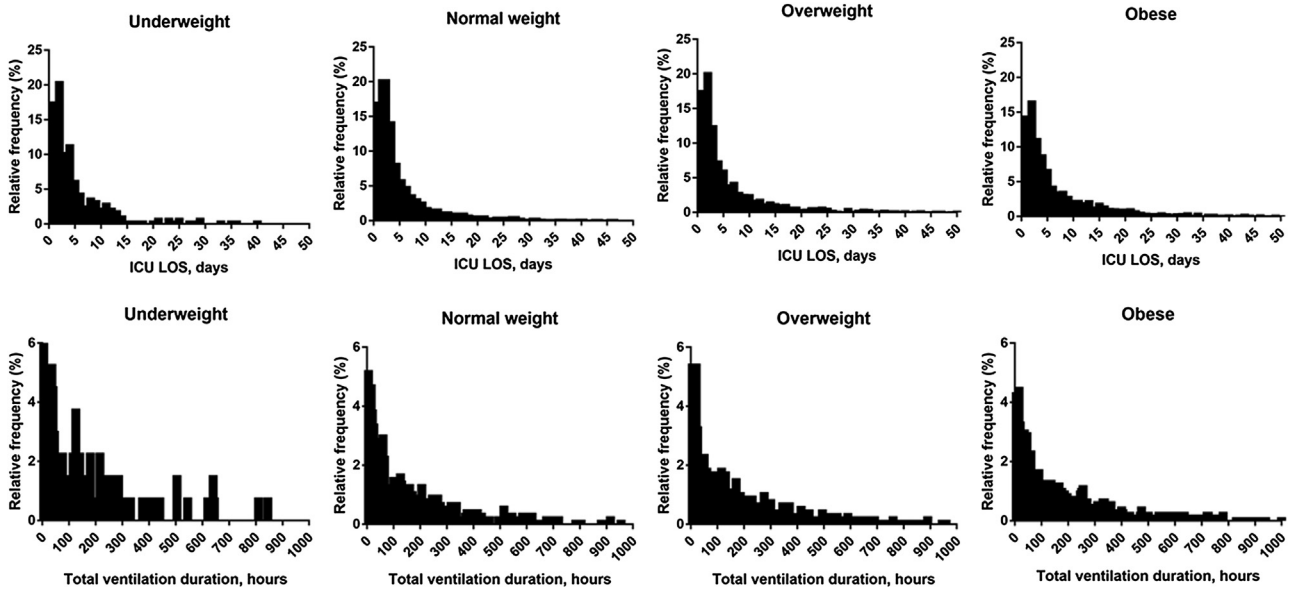

Figure 2. Histogram presenting the distribution of ICU LOS and total ventilation duration by BMI category.
Abbreviations: LOS: length of stay, BMI: body mass index. Obese patients were likely to experience prolonged period of ICU LOS ($P < 0.001$) and mechanical ventilation duration ($P < 0.05$) compared with normal cohort.

Survival analysis and multivariate logistic regression model

Kaplan–Meier survival curves at 30 days and 1 year are shown in Figure 3, indicating the notable survival advantage in the obese group compared with their normal weight counterparts (log-rank test $P < 0.001$).

The multivariate logistic regression model showed a similar trend in the relationship between BMI and mortality risk as that in the univariate analyses (Table 3). After adjusting for all clinical covariates listed, BMI remained a significant factor for 30-day and 1-year mortality ($P < 0.001$ for each). Overweight and obese patients had mortality risk reductions of 23.0% and 35.0% compared with their normal weight counterparts at the end of 30 days (OR 0.77, 95% CI 0.66–0.91, $P = 0.002$; OR 0.65, 95% CI 0.56–0.77, $P < 0.001$, respectively) and 17.0% and 30.0% lower risks at 1 year (OR 0.83, 95% CI 0.71–0.96, $P = 0.01$; OR 0.70, 95% CI 0.60–0.81, $P < 0.001$, respectively). In contrast, the underweight group had mortality risks that were 46.0% and 75.0% higher than those of the normal weight group at 30 days and 1 year, respectively (OR 1.46, 95% CI 1.09–1.96, $P = 0.01$; OR 1.75, 95% CI 1.30–2.36, $P < 0.001$ individually). In addition, the findings for in-hospital mortality were analogous to those above, and overweight and obese patients had significantly better survival than those who were normal weight (OR 0.85, 95% CI 0.72–1.00, $P < 0.05$; OR 0.73, 95% CI 0.62–0.86, $P < 0.001$).

Regarding the predictors associated with worse prognosis, older age, first encountered ICU type, lower MAP (<70 mmHg), higher SOFA and SAPS-II scores and the need for mechanical ventilation were the responsible determinants at both time points ($P < 0.05$ for first ICU type encountered specifically; $P < 0.001$ for all the other factors). The mortality risks of patients admitted to the surgical intensive care unit (SICU) and thoracic surgery intensive care unit (TSICU) firstly were lower than those initially treated in the CCU, even at the end of 1 year ($P = 0.003$ for each), because the SICU and TSICU are designated for less critically ill patients undergoing elective surgery. Sex was not included in the model until 1 year ($P = 0.003$), mainly due to the widely recognized long-term survival benefit associated with female sex.

Post-hoc analyses

The results had no marked differences in the post hoc analyses. After the removal of patients with height values that were manually generated later, we had 4116 subjects, and the cohort had

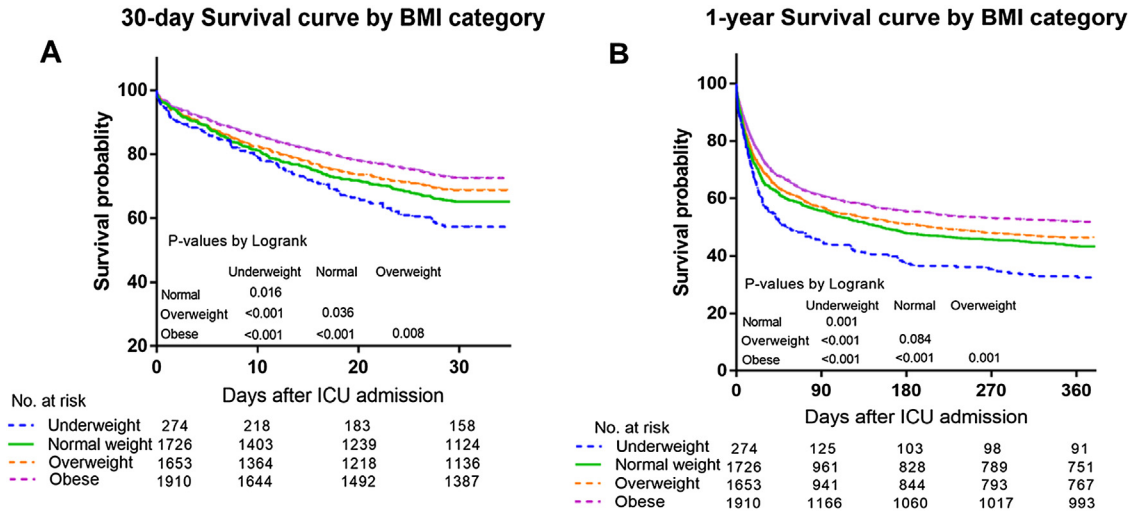

Figure 3. Kaplan–Meier curves of 30-day and 1-year mortality by BMI category.
Abbreviations: BMI: body mass index. Fig. 3(A) and 3(B) represents 30-day and 1-year Kaplan–Meier curves respectively. The numbers at risk refer to the patients' number at the beginning of the time periods. The survival probability is cut at 0.4, 0.2 in 30-day and 1-year survival curves respectively for exhibition purpose.

characteristics that strongly resembled those of the final cohort. Nevertheless, the results in the final regression model remained the same, indicating that our method of dealing with missing height records did not introduce selection bias.

Moreover, age, SOFA levels and ICU types were used for stratification and examined separately. We noticed that in different ranges of age (41–60; 61–79; ≥80 years), BMI was still significantly associated with 1-year mortality (all $P < 0.01$); additionally, obesity remained beneficial in patients aged above 61 years ($P < 0.05$) (Figure 4(A)). With respect to the extent of organ failure, the marked advantages of obesity were the greatest in the group with moderately severe organ dysfunction at 1 month (SOFA score range: 2 to 16, $P < 0.05$) (Figure 4(B)), perhaps because the effect of obesity was not overshadowed by the "either too good or too ill"

Table 3
The multivariate logistics regression models for 30-day and 1-year mortality.

Variables	30-day OR (95% CI)	P	1-year OR (95% CI)	P
BMI category (ref. Normal weight)		<0.001		<0.001
Underweight	1.46 (1.09–1.96)	0.01	1.75 (1.30–2.36)	<0.001
Overweight	0.77 (0.66–0.91)	0.002	0.83 (0.71–0.96)	0.01
Obese	0.65 (0.56–0.77)	<0.001	0.70 (0.60–0.81)	<0.001
Gender (ref. female)	-	0.17	1.20 (1.07–1.35)	0.003
Age (ref. ≤ 40 years)		<0.001		<0.001
41–60 years	1.41 (1.01–1.96)	0.04	1.42 (1.09–1.84)	0.01
61–79 years	1.62 (1.16–2.27)	0.004	1.65 (1.27–2.15)	<0.001
≥80 years	2.07 (1.45–2.95)	<0.001	2.12 (1.59–2.82)	<0.001
Marriage status (ref. Married)		0.04		0.90
Single/divorced/separated/unknown	1.12 (0.97–1.30)	0.11	–	0.91
Widowed	1.26 (1.04–1.51)	0.02	–	0.70
Race (ref. White)		0.08		0.49
Other	–	0.008	–	0.26
Asian	–	0.52	–	0.15
Black	–	0.22	–	0.64
Hispanic or Latino	–	0.81	–	0.84
Admission type (ref. Elective)	1.54 (1.05–2.25)	0.03	–	0.18
Insurance type (ref. Medicare/Medicaid)		0.23		0.08
Private	–	0.71	–	0.07
Other	–	0.11	–	0.32
Admission ICU type (ref. CCU)		0.003		0.02
CSRU	0.72 (0.48–1.06)	0.10	0.79 (0.55–1.14)	0.21
MICU	0.90 (0.72–1.13)	0.38	0.77 (0.62–0.95)	0.02
SICU	0.64 (0.49–0.85)	0.002	0.68 (0.53–0.88)	0.003
TSICU	0.72 (0.52–1.00)	<0.05	0.64 (0.47–0.86)	0.003
MAP (ref. ≥ 70 mmHg)	1.48 (1.30–1.68)	<0.001	1.48 (1.31–1.67)	<0.001
SOFA (<2; 2–3; 4–5; 6–8; 9–11; 12–16; >16)	1.25 (1.17–1.33)	<0.001	1.11 (1.05–1.18)	<0.001
SAPS-II (<20; 21–30; 31–40; 41–50; 51–60; >60)	1.60 (1.49–1.71)	<0.001	1.60 (1.50–1.71)	<0.001
Surgery	–	0.24	–	0.18
Ventilation	1.52 (1.32–1.76)	<0.001	1.30 (1.14–1.48)	<0.001
Dialysis	–	0.14	–	0.14
Vasopressor	–	0.52	–	0.10

Abbreviations: OR: odds ratio, CI: confidence interval, BMI: body mass index, CCU: coronary care unit, CSRU: cardiac surgery recovery unit, MICU: medical intensive care unit, SICU: surgical intensive care unit, TSICU: thoracic surgery intensive care unit, MAP: mean arterial pressure, SOFA: sequential organ failure assessment, SAPS II: simplified acute physiology score II.
– Not included in the logistics regression model.

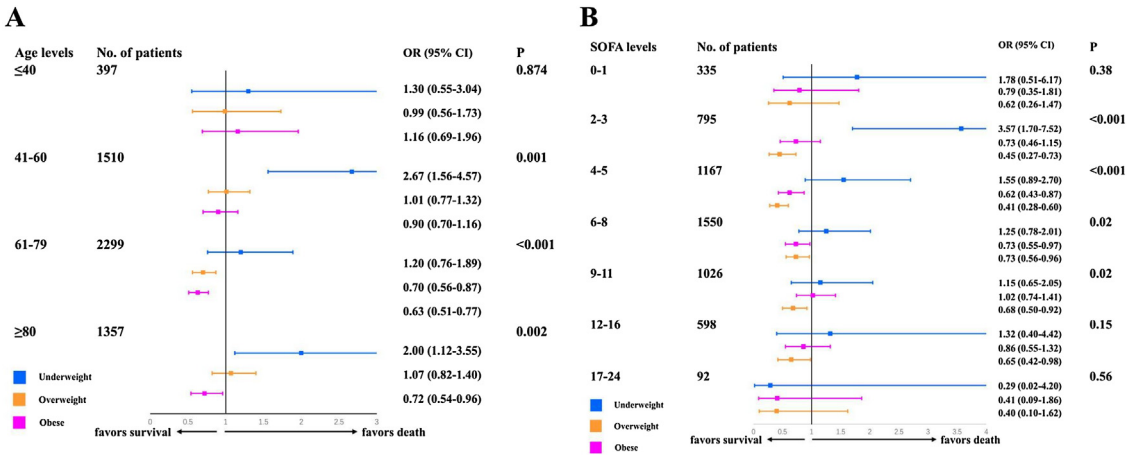

Figure 4. Forest plots depicting the ORs of mortality risks on the stratification of age and SOFA levels by BMI category.
Abbreviations: BMI: body mass index, OR: odds ratio, CI: confidence interval. Fig. 4(A) shows ORs of 1-year mortality stratified by age levels, and 4(B) demonstrates ORs of 30-day mortality on the stratification of SOFA levels. Squares represent ORs with 95% CIs demonstrated as horizontal bars, and blue, orange and purple colors stand for underweight, overweight and obese groups. Normal weight category acts as the reference group.

physiologic states in this group. Additionally, in individual ICU departments apart from the CSRU, obese cohorts were associated with significantly better survival (Table 4), which might be explained by the inadequate detection power due to the rather small population in the CSRU (n = 214).

It was strongly suggested that the subgroup of morbidly obese patients, with BMIs >40 kg/m^2, also had a considerable survival advantage. They tended to be young and female and to have mildly lower SAPS-II scores, extended ventilation duration and LOS, and relatively lower 30-day and 1-year mortality compared to those with BMIs ranging from 30 to 40 kg/m^2. Nonetheless, as confirmed by the regression model, the 30-day and 1-year mortality rates of the morbidly obese cohort were 31.0% and 29.0%, respectively, which were lower than those of their normal counterparts (OR 0.69, 95% CI 0.54–0.89, P = 0.004; OR 0.71, 95% CI 0.57–0.90, P = 0.004).

Eventually, we analysed the subgroups of severe sepsis (n = 2177) and septic shock patients (n = 998). Our models indicated that obese patients still had crucial survival benefits at 30 days in both the severe sepsis and septic shock subsets (P < 0.001, P = 0.005 separately), although the advantages became insignificant at the end of 1 year.

Discussion

In this retrospective analysis, we found that the 30-day and 1-year mortality rates were likely to be lower in overweight, obese and even morbidly obese patients after adjusting for confounding factors compared to their normal weight counterparts. Conversely, a BMI below 18.5 kg/m^2 was predictive of a relatively higher mortality risk.

The results regarding the impact of obesity on sepsis patients' outcomes have been ambiguous so far (Trivedi et al., 2015). In contrast with our findings, a secondary study of a prospective, multi-centre SOAP cohort (Sakr et al., 2008) claimed that BMI was not an independent predictor of SAPS-II adjusted ORs for hospital mortality in sepsis (n = 1083) or septic shock (n = 431) patients. In addition, obese patients were found to be more prone to having more comorbidities, including ICU-acquired infections, respiratory and cardiovascular failure, and a greater need for mechanical ventilation, which was in accordance with the greater need for respiratory support and longer ventilation duration in our obese cohort. Additionally, a retrospective observational study conducted in two American centres by Gaulton et al. (2014), which identified 1835 presumed sepsis patients by a sepsis-specific antibiotic algorithm, indicated that obese patients had an insignificantly increased adjusted OR for 28-day mortality compared to non-obese patients (defined as BMIs between 18.5 and 30 kg/m^2), and no significant difference was noted in mortality across WHO BMI classifications either. However, obesity appeared to be associated with decreased ORs at longer time points from sepsis onset, suggesting a potential late survival advantage. Furthermore, Chalkias et al. (2013) reported that increased sagittal abdominal diameter (SAD), rather than BMI, was significantly correlated with increased morbidity and mortality in a severe sepsis cohort, indicating that BMI might be inadequately representative of obesity.

Nonetheless, in partial alignment with the large global audit ICON (Sakr et al., 2015), which included more than ten thousand patients in 730 ICUs, a sub-analysis of sepsis patients (n = 2696) suggested that a lower adjusted HR for 60-day in-hospital mortality was associated with being overweight, although obese or morbidly obese patients did not experience the same benefits. However, the summed proportion of obese and morbidly obese participants was relatively small compared with that in our cohort (19.1% v 34.3%), which might explain the insufficient power to

Table 4
Odds ratios of 1-year mortality in individual ICU departments by BMI category.

ICU departments	Overall	Underweight	Normal weight	Overweight	Obese	P-value
CCU	504	1.53 (0.52–4.50)	Reference	0.88 (0.55–1.42)	0.44 (0.28–0.70)	<0.001
CSRU	214	1.47 (0.25–8.70)		1.14 (0.56–2.32)	0.74 (0.37–1.45)	0.54
MICU	3724	1.59 (1.15–2.21)		0.88 (0.75–1.04)	0.79 (0.67–0.92)	<0.001
SICU	754	2.20 (1.10–4.41)		0.80 (0.55–1.17)	0.68 (0.48–0.98)	0.003
TSICU	367	0.70 (0.23–2.11)		0.81 (0.48–1.36)	0.46 (0.27–0.76)	0.02

Abbreviations: BMI: body mass index, OR: odds ratio, CI: confidence interval, CCU: coronary care unit, CSRU: cardiac surgery recovery unit, MICU: medical intensive care unit, SICU: surgical intensive care unit, TSICU: thoracic surgery intensive care unit. ORs with 95% CIs are presented. Normal weight category acts as the reference group.

detect favourable survival in people with greater BMIs. A retrospective study (Kuperman et al., 2013) including 792 sepsis patients demonstrated that increased BMI was related to decreased unadjusted OR but the relationship became statistically insignificant in the regression model; however, diabetes remained a beneficial predictor even after adjusting for covariates, suggesting a possible rationale for the protective effect of obesity. Furthermore, a meta-analysis conducted by Pepper et al. (2016) containing 6 studies reported pooled adjusted OR reductions in mortality for both overweight and obese subjects compared to normal weight subjects, whereas in the morbidly obese cohort, there was an inconsequential survival advantage, which was predominantly in agreement with the results of this study.

Whether the obesity paradox phenomenon exists has been unclear because the underlying mechanism is still poorly understood. Fundamentally, it has been intensely debated whether it is a real phenomenon or a consequence of selection bias because obese patients tend to be younger and female and to have less severe organ dysfunction at the time of ICU admission, as noted in our study and other studies (Hogue et al., 2009), although the obese cohort in this study had worse SOFA scores. Nevertheless, the survival benefits for overweight, obese and even morbidly obese subjects remained appreciable in our final regression model after modification by confounding predictors including age, sex, and extent of organ failure. The trend towards improved survival in obese patients still existed in the subsets of patients above 61 years old and those with SOFA scores ranging from 2 to 16 in the stratification analysis. Second, in reference to obesity-associated comorbidities, hypertension (Uretsky et al., 2007) and insulin resistance (Kuperman et al., 2013) might also be potential protectors that improve survival after sepsis onset. This is possibly due either to the sympathetic nervous or endocrine changes that induce a positive response to sepsis, or the medications being administered. For instance, in sepsis animal models, the oral medication rosiglitazone used to treat diabetes was reported to have increased the serum levels of adiponectin, thus resulting in a better prognosis (Uji et al., 2009). Third, in an episode of an extremely acute catabolic reaction, i.e., sepsis, increased levels of energic fuel and nutritional reserves (Niedziela et al., 2014) might be crucial for improving sepsis outcomes in patients with high body weights. In addition, adipokines and inflammatory factors released by adipocytes, particularly leptin and interleukin-10, could mitigate the deleterious immune response, hereby contributing to improved survival during acute critical illness (Hauner, 2010). Eventually, discrepancies in care delivery and pharmacologic management could also affect mortality. Obese patients are likely to receive more attention from nursing staff (Nasraway et al., 2002) and be treated earlier and more aggressively (O'Brien et al., 2012) due to their tendency towards complications and flawed physiologic reserves, as seen in the obese cohort in our study, which exhibited higher incidences of surgery, respiratory support, renal replacement therapy and vasopressor usages. Compared to leaner patients, obese septic shock patients were found to be less resuscitated due to their heavier body weight (Wacharasint et al., 2013), and a restrictive fluid strategy would reduce the burden from heart or lung injuries (Stewart et al., 2009). Additionally, antithrombotic medications such as heparin are more likely to be prescribed to obese patients (O'Brien et al., 2006), which might be beneficial on the haemodynamics of sepsis.

Furthermore, our findings suggested that there was a trend towards extended periods of ventilation, longer ICU and hospital LOS in obese patients, as prior studies have reported (Papadimitriou-Olivgeris et al., 2016; Sakr et al., 2015). This finding is mainly attributed to higher risks of nosocomial infection and respiratory complications (Sakr et al., 2008) that are associated with obesity. Obese patients are inclined to have lower tidal volumes, elevated airway resistance, impeded gas exchange (Littleton, 2012), and even excess oxygen demand by respiratory muscles (Burki and Baker, 1984). Respiratory failure in septic patients is frequently manifested as acute respiratory distress syndrome (ARDS), and Gong et al. (2010) indicated that patients with higher BMIs had greater risks of developing ARDS and prolonged LOS; however, a recent meta-analysis (Ni et al., 2017) showed decreased unadjusted ORs for mortality in obese and morbidly obese patients with ARDS. Nevertheless, the optimization of ventilation strategies remains a challenge, especially for obese sepsis patients.

Last, in subsets of patients with severe sepsis or septic shock, BMI was still an important predictor in the model, while the survival advantage of obesity existed at specific time points. Obese severe sepsis patients have been reported to have favourable survival (Prescott et al., 2014) (Gaulton et al., 2015), although the concept has been discarded in the currently applicable international definitions (Sepsis-3) (Singer et al., 2016). With respect to septic shock, the literature has suggested that a positive relationship exists between obesity and survival (Wurzinger et al., 2010) (Wacharasint et al., 2013) (Arabi et al., 2013), and compared to normal weight subjects, obese patients tend to develop pneumonia less often, receive less fluid volume per kilogram, and have a reduced need for vasopressors (Wacharasint et al., 2013) (Arabi et al., 2013).

The limitations of our study are as follows: first, it is a retrospective, single-centre analysis, so that like other observational studies, we cannot exclude the influence of residual confounding factors that may have affected the results to some extent. Second, due to the nature of the MIMIC database, the proportion of missing data in some indexes was as high as 28%, which might result in selection bias; however, the method of dealing with missing height records has been shown to be unbiased, and we did not include baseline variables with more than 5% of the total values missing in our final regression model. Third, because of the defects of our study design, we lacked information on patients' previous comorbidities, infection details (e.g., pathogens, source of infection), processes of care such as fluid and antibiotic management strategies, source infection control, and the use of prophylaxis against thrombosis. Inequality in these factors between obese and non-obese patients may have biased our conclusion towards being positive. Fourth, the new definition Sepsis-3 was not used in this study because the data collection period of MIMIC-III was before its release. Moreover, despite the large population in the database, the subpopulations in our study (e.g., the morbidly obese or septic shock groups) were relatively small, which may affect the credibility of our results in post hoc analyses.

Conclusions

In this retrospective single-centre sepsis cohort, we observed short- and long-term survival advantages in obese patients after excluding the confounding effects of baseline characteristics and discovered a trend towards a prolonged period of mechanical ventilation, an increased ICU and hospital LOS, suggesting that there are more challenging respiratory conditions in the obese septic population. Future well-designed studies are warranted to evaluate the impacts on sepsis of abdominal or truncal obesity, specific medical care and to determine the potential mechanism underlying the phenomenon.

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Conflict of interest

None of the authors has any economic or other competing interests to be declared.

Authors' contributions

SL and XH participated in the study conception and design, statistical analysis, data interpretation, drafting and revisions of the manuscript. ZG participated in the data acquisition and revisions of data analysis and interpretation. JX, FH, LT, KL, LC, YZ, JY participated in study conception and design, data interpretation and revisions of the manuscript. CC participated in study conception and design, data interpretation and revisions of the manuscript, also supervised the whole study. SL and XH contributed equally to the article and should be regarded as co-first authors.

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