

BMJ Open Association between obesity and 1-year mortality in septic patients: a retrospective cohort study

Li Zhang ,¹ Lingna Fang,² Hang Lihua,¹ Chong Li³

To cite: Zhang L, Fang L, Lihua H, *et al.* Association between obesity and 1-year mortality in septic patients: a retrospective cohort study. *BMJ Open* 2023;**13**:e066526. doi:10.1136/bmjopen-2022-066526

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-066526>).

Received 20 July 2022
Accepted 29 January 2023



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Department of Anesthesiology, The First People's Hospital of Kunshan Affiliated with Jiangsu University, Kunshan, Jiangsu, People's Republic of China

²Department of Endocrinology, The First People's Hospital of Kunshan Affiliated with Jiangsu University, Kunshan, China

³Department of Osteoporosis, The First People's Hospital of Kunshan Affiliated with Jiangsu University, Kunshan, Jiangsu, People's Republic of China

Correspondence to
Professor Chong Li;
sdzl7182@163.com

ABSTRACT

Objective Sepsis is a major contributor of intensive care units (ICUs) patient mortality. Prior investigations claimed that obesity enhances overall survival (OS) of septic patients. However, the reported results were inconsistent. This study examined the association between obesity and the 1-year mortality of septic patients.

Design A retrospective cohort study.

Setting The Medical Information Mart for Intensive Care III database.

Participants 3145 septic patients were separated into three distinct cohorts, based on their WHO body mass index (BMI) status.

Outcomes Our primary endpoint was the 1-year mortality from the date of ICU hospitalization.

Result 1334 (42.4%) died within 1 year. The 1-year mortality rate was low in obese patients (38.8%), compared with normal (46.9%) and overweight (42.1%) patients. Crude assessment revealed that obese patients experienced reduced 1-year mortality, relative to normal weight patients (HR 0.79, 95% CI 0.69 to 0.9, $p < 0.001$). However, once adjusted for baseline variables and comorbidities, no correlation was found between obesity and the 1-year mortality (HR 0.93, 95% CI 0.81 to 1.06, $p = 0.28$) of septic patients. There was an association among diabetic (HR 0.72, 95% CI 0.56 to 0.93, $p = 0.012$) and hypertensive (HR 0.73, 95% CI 0.58 to 0.92, $p = 0.008$) patients, and among males (HR 0.71, 95% CI 0.59 to 0.86, $p < 0.001$), with obese individuals experiencing the lowest mortality rate. Given these evidences, the interactions between BMI and mortality in diabetic ($p = 0.031$) and hypertensive ($p = 0.035$) patients were significant.

Conclusion In our study, obese diabetic and hypertensive patients associated to less sepsis-related mortality risk, compared with normal weight patients. Further researches were need to validated.

INTRODUCTION

Sepsis is a widespread and life-threatening condition.¹ However, the heterogeneity associated with sepsis and septic shock prevents the collection of reproducible mortality-related data, which generally ranges between 15% and 56%.¹⁻⁶ Hence, a closer inspection of patient characteristics that enable strong survival outcomes in septic patients may allow establishment of new and effective approaches of managing sepsis.

STRENGTHS AND LIMITATION OF THIS STUDY

- ⇒ Large septic patients in Medical Information Mart for Intensive Care III.
- ⇒ Univariable analysis shown demographic, comorbidities, vital signs and lab tests associated with mortality.
- ⇒ Cox regression was used to calculate the adjusted HR of obesity and 1-year mortality association.
- ⇒ The research was retrospective and was based out of data from a single centre, there may be some unintentional biases that influenced the results.

Over 25% of adult intensive care units (ICUs) patients in the USA are overweight or obese.^{7 8} Emerging evidences suggested the presence of an obesity paradox, whereby obesity markedly reduces mortality in terminally ill patients^{9 10} like those with persistent cardiac disease, renal insufficiency and sepsis.^{6 11-13} The underlying mechanism behind this is yet undetermined. However, some speculate involvement of enhanced metabolic reserve,^{14 15} stimulation of the renin-angiotensin axis¹⁶ and release of adipose tissue-based immunomodulatory mediators like leptin and soluble-tumour necrosis factor receptor-2.¹⁷

Currently, there is limited information on the link between sepsis and obesity. More importantly, the reported studies are limited by small sample size, and failure to compensate for possible confounders like severity of illness, comorbidities, infection location^{6 18} or recent weight loss. Notably, any weight measurement following fluid resuscitation can produce false estimate elevations. Similarly, late-stage weight measurements, such as those obtained later during hospitalisation, can also produce false lows, particularly, if the patient experienced weight loss owing to an extended hospital stay or sepsis catabolism. To prevent possible fluid resuscitation-mediated weight gain or septic catabolism-mediated weight loss, we

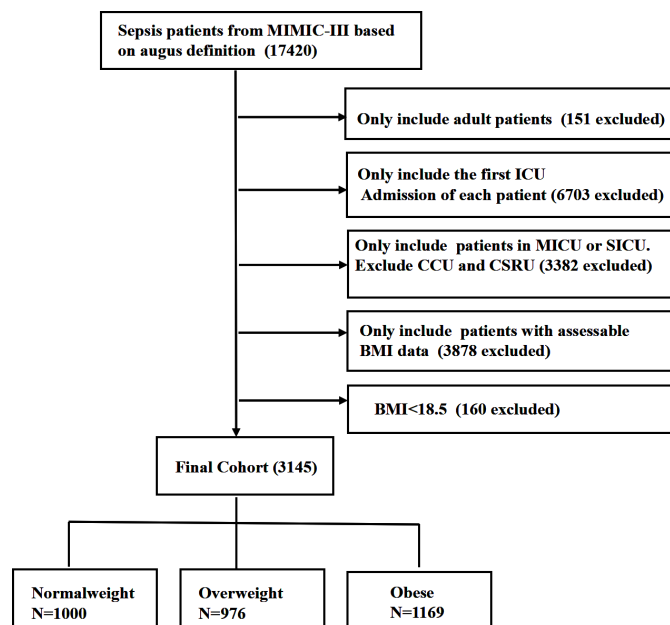


Figure 1 Flow chart of patient selection. Study cohort. Illustration of exclusion and inclusion criteria as utilised to select the final cohort of 3145 patients. BMI, body mass index; ICU, intensive care unit; CCU, cardiac care unit; CSRU, cardiac surgery recovery room; SICU, surgical intensive care unit; MIMIC, Medical Information Mart for Intensive Care III.

measured the initial body mass index (BMI) data using dry body weight.

Given the aforementioned challenges, the true relationship between obesity and overall survival (OS) following sepsis remains unknown. This warrants additional research involving large sample population and extensive analyses. To obtain better septic patient prognosis, it is crucial to uncover any potential link between obesity and septic patient OS. In case obesity truly protects against sepsis-related death, then an extensive analysis of the underlying signalling is necessary to identify sepsis aetiology and develop efficacious therapies. Alternately, in case obesity further complicates sepsis-related conditions, including death, then researchers may need to explore novel approaches to treat this subgroup of septic patients. Therefore, here, we rigorously analysed a large clinical data repository to identify the relationship, if any, between BMI and septic patient OS, after adjusting for possible confounders. Hypertensive¹⁹ and insulin resistant²⁰ patients may also act as potential protectors, improving survival after the onset of sepsis. When analysing a person's risk for obesity, it is important to take into account the sex and gender differences in adipose tissue.²¹ Therefore, we performed a subgroup analysis based on gender, diabetes and hypertension.

METHODS

Study approval and design

This investigation followed the guidelines of the STrengthening the Reporting of OBServational studies in

Epidemiology statement. The research design was a retrospective, longitudinal, single-centre, retrospective examination of adult patients diagnosed with sepsis.

DATABASE

This research received approval from the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Centre (BIDMC) review boards. In addition, the informed consent requirement was waived due to the retrospective nature of the investigation. Medical Information Mart for Intensive Care III (MIMIC-III) provided physiological data of 38 605 ICU patients, who were admitted to the ICUs of BIDMC, a tertiary care university hospital in Boston, Massachusetts, USA between the years 2002 and 2011.

Patient and public involvement

Neither patients nor the public were directly involved in this.

The sample cohort

The initial patient selection identified all hospitalised patients with a sepsis diagnosis within the aforementioned time period. Among these patients, the following were chosen for analysis: (1) age >18 years (2) admitted to the medical ICUs and SICU (3) first ICU admission (4) available BMI information. The following patients were eliminated from analysis: (1) those with missing height or weight information and (2) BMI <18.5 kg/m².

Following a review of 38 605 MIMIC-III adult admissions, we discovered sepsis in 17 420 patients using the Angus methodology.²² We finally select 3145 patients for analysis. Overall, our study population (figure 1) consisted of 1000 normal weight (BMI 18.5 to <25 kg/m²), 976 overweight (BMI 25 to <29.9 kg/m²) and 1169 obese (BMI ≥30 kg/m²) patients.

Data retrieval

The structure query language (SQL) in PostgreSQL (V.9.6; PostgreSQL Global Development Group) was used to retrieve data. The following parameters were recorded and analysed: baseline profiles (eg, age, sex), vital signs, severity of organ failure 24 hours post-ICU admission (eg, maximum heart rate, minimum arterial pressure, minimum temperature, Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score (SAPS)), intervention-related data (eg, sedative, vasopressor, mechanical ventilation) and laboratory results (eg, haemoglobin, pH, partial pressure of oxygen (PO₂)). BMI was computed as weight (in kilograms)/height (in metres).²

Outcomes

Our primary endpoint was the 1-year mortality from the date of ICU hospitalisation. The US Social Security Death Index provided information regarding patient deaths following discharge.

Statistical analysis

All study variables were assessed using univariate analysis. Continuous data, assessed via pairwise Student's *t*-tests and one-way ANOVA, are provided as means±SD and medians (IQR). Categorical data, examined using Pearson's χ^2 or Fisher's exact test, where necessary, are provided as numbers and percentages. Variables that were significant (*p* values <0.1) in univariate analysis or were deemed clinically relevant were entered into multivariate analysis. We explored the multicollinearity for independent data using the variance inflation factor, with an upper limit of 2 (online supplemental table S1). Missing data are processed using multiple interpolations. Data missing values are given in online supplemental table S2. Lastly, a subgroup analysis was carried out to identify any potential differences among individual subgroups and interaction tests were also performed.

All analyses were performed using R Statistical Software (<http://www.R-project.org>, The R Foundation). A two-sided *p*<0.05 was set as the significance threshold.

Covariates

On admission, all demographic and admission data, including age, gender, weight, height and disease severity, were recorded using the SAPS, SOFA and Elixhauser comorbidity scores.^{23–25}

Comorbidities

We identified the following comorbidities using the documented international classification of disease-9 (ICD-9) codes: diabetes, hypertension, chronic obstructive pulmonary disease (COPD), persistent renal disease, liver disease, coronary artery disease (CAD), congestive heart failure (CHF), atrial fibrillation (AFIB), stroke and malignant tumour.

RESULTS

Baseline characteristics of sepsis cases

Table 1 lists the patient baseline profiles of 3145 septic adults, based on their matched BMI statuses. The mean age was 65.3±16.6 years and 53.2% were male. Obese patients exhibited younger age (62.9±15.3 vs 67.5±17.3) and there were more obese females (51.8% vs 45.2%) than normal weight patients. Among obese patients, common comorbidities such as diabetes, hypertension, CHF, renal disease and liver disease were markedly elevated, compared with normal weight patients. Similarly, the SOFA scores within 24 hours of ICU admission were also considerably elevated in obese (6.0 (4.0, 9.0) vs 5.0 (3.0, 8.0)) vs normal weight patients.

Outcome

Table 2 summarises the patient prognoses of all study participants. In total, 772 (24.5%) and 1334 (42.4%) patients died within 28 days and a year after ICU admission, respectively. Moreover, 272 normal weight (27.2%), 244 overweight (25%), and 256 obese (21.9%) patients

died within 28 days after ICU admission. In addition, 469 normal weight (46.9%), 411 overweight (42.1%) and 454 obese (38.8%) patients died within 1 year after admission. Lastly, the median ICU stay duration of obese patients was longer (5.1 days (IQR 2.2–12.0)) than normal weight patients.

Obesity and the 1-year mortality rate

Figure 2 illustrates the univariate analysis of the BMI-stratified 1-year mortality rate of patients with sepsis. Our analyses revealed a marked relationship between patient variables (ie, age, BMI, diabetes, hypertension, CAD, CHF, AFIB, malignant cancer, stroke, chronic obstructive pulmonary disease, renal disease, liver disease, vital signs within 24 hours of ICU admission, SOFA and SAPS) and 1-year mortality. We adjusted for potential confounding factors in subsequent analyses.

Considering BMI as a continuous variable, we observed a marked correlated between BMI and 1-year mortality (HR 0.99, 95% CI 0.98 to 0.99, *p*<0.001). Following additional age and sex adjustment, the relationship altered (HR 0.99, 95% CI 0.99 to 1, *p*=0.148).

Based on crude analysis, obese patients exhibited reduced 1-year mortality, relative to normal weight patients (HR 0.79, 95% CI 0.69 to 0.9, *p*<0.001). Following adjustments for baseline demographics and comorbidities, the relationship was no longer significant (HR 0.93, 95% CI 0.81 to 1.06, *p*=0.28 for 1-year mortality) (table 3).

Subgroup analyses and interaction analysis

Subgroup analyses (figure 3) based on gender, diabetes and hypertension revealed that male, overweight (adjusted HR 0.8, 95% CI 0.68 to 0.96, *p*=0.014), and obese (adjusted HR 0.71, 95% CI 0.59 to 0.86, *p*<0.001) patients were strongly correlated with the 1-year mortality. We further assessed subgroups of diabetic (*n*=1022) and hypertensive (*n*=1301) patients, and revealed that, among these patient populations (diabetic (adjusted HR 0.72, 95% CI 0.56 to 0.93, *p*=0.012) and hypertensive (adjusted HR 0.73, 95% CI 0.58 to 0.92, *p*=0.008)), obesity was strongly related to enhanced OS. Furthermore, a strong interaction existed between BMI and mortality among diabetics (*p*=0.031) and hypertensive (*p*=0.035) patients.

DISCUSSION

This study identified 17420 patients with sepsis. Among them, we selected 3145, based on our inclusion and exclusion criteria, and 1334 (42.4%) patients died within 1 year following the initial ICU admission. Table 1 summarises the cohort demographics, based on BMI status. Among all participants, 37.2% were obese and 31.0% were overweight. The 1-year mortality was reduced in overweight and obese patients, relative to normal-weight patients. When normal weight (BMI 18.5–24.9 kg/m²) was employed as a reference in Cox regression analysis, the obese patient 1-year mortality risk was 0.93 (95% CI 0.81 to 1.06, *p*=0.28). Diabetic (adjusted HR 0.72, 95% CI 0.56

Table 1 Baseline of the cohort

Variable	Body mass index (kg/m ²) n (%)				P value
	Total (n=3145)	Normal weight (18.5 to <25) (n=1000)	Overweight (25 to <29.9) (n=976)	Obese (>= 30) (n=1169)	
BMI (kg/m ²)	29.6±8.4	22.4±1.7	27.4±1.4	37.6±8.7	<0.001
Age (years)	65.3±16.6	67.5±17.3	65.9±17.0	62.9±15.3	<0.001
Gender, n (%)					<0.001
Female	1471 (46.8)	452 (45.2)	414 (42.4)	605 (51.8)	
Male	1674 (53.2)	548 (54.8)	562 (57.6)	564 (48.2)	
SAPS score	20.5±5.5	20.5±5.5	20.3±5.5	20.5±5.6	0.6
Elixhauser comorbidity score	0.4±1.6	0.3±1.4	0.4±1.7	0.4±1.7	0.337
SOFA score, Median (IQR)	6.0 (3.0, 8.0)	5.0 (3.0, 8.0)	6.0 (4.0, 8.0)	6.0 (4.0, 9.0)	0.006
Comorbidity					
Diabetes, n (%)					<0.001
No	2123 (67.5)	782 (78.2)	695 (71.2)	646 (55.3)	
Yes	1022 (32.5)	218 (21.8)	281 (28.8)	523 (44.7)	
Hypertension, n (%)					0.002
No	1844 (58.6)	622 (62.2)	580 (59.4)	642 (54.9)	
Yes	1301 (41.4)	378 (37.8)	396 (40.6)	527 (45.1)	
CHF, n (%)					0.061
No	2051 (65.2)	670 (67)	649 (66.5)	732 (62.6)	
Yes	1094 (34.8)	330 (33)	327 (33.5)	437 (37.4)	
AFIB, n (%)					0.576
No	2241 (71.3)	724 (72.4)	686 (70.3)	831 (71.1)	
Yes	904 (28.7)	276 (27.6)	290 (29.7)	338 (28.9)	
Renal disease, n (%)					0.011
No	2619 (83.3)	862 (86.2)	798 (81.8)	959 (82)	
Yes	526 (16.7)	138 (13.8)	178 (18.2)	210 (18)	
Liver disease, n (%)					0.007
No	2775 (88.2)	905 (90.5)	863 (88.4)	1007 (86.1)	
Yes	370 (11.8)	95 (9.5)	113 (11.6)	162 (13.9)	
Metastatic cancer, n (%)					<0.001
No	2374 (75.5)	713 (71.3)	715 (73.3)	946 (80.9)	
Yes	771 (24.5)	287 (28.7)	261 (26.7)	223 (19.1)	
Stroke, n (%)					0.849
No	2881 (91.6)	913 (91.3)	893 (91.5)	1075 (92)	
Yes	264 (8.4)	87 (8.7)	83 (8.5)	94 (8)	
COPD, n (%)					0.124
No	2639 (83.9)	834 (83.4)	838 (85.9)	967 (82.7)	
Yes	506 (16.1)	166 (16.6)	138 (14.1)	202 (17.3)	
CAD, n (%)					0.276
No	2662 (84.6)	859 (85.9)	813 (83.3)	990 (84.7)	
Yes	483 (15.4)	141 (14.1)	163 (16.7)	179 (15.3)	
Vital signs					
MAP min (mm Hg)	55.7 (48.0, 63.0)	55.3 (48.0, 63.0)	56.0 (48.0, 64.0)	55.0 (48.0, 63.0)	0.542
Heart rate min	74.0 (64.0, 86.0)	75.0 (64.0, 86.0)	73.0 (63.0, 85.0)	74.5 (64.0, 85.0)	0.519
Laboratory tests					
PO2 min	75.0 (53.0, 103.0)	73.0 (52.0, 108.0)	77.0 (53.5, 109.5)	75.0 (54.0, 97.0)	0.171
pH min	7.3 (7.2, 7.4)	7.3 (7.2, 7.4)	7.3 (7.2, 7.4)	7.3 (7.2, 7.4)	< 0.001
Haemoglobin min	9.8 (8.7, 11.2)	9.8 (8.7, 11.2)	9.7 (8.6, 11.2)	9.9 (8.7, 11.4)	0.337
Creatinine max, Median (IQR)	1.3 (0.9, 2.3)	1.1 (0.7, 2.0)	1.3 (0.9, 2.3)	1.5 (0.9, 2.6)	<0.001

Continued

Table 1 Continued

Variable	Body mass index (kg/m ²) n (%)				P value
	Total (n=3145)	Normal weight (18.5 to <25) (n=1000)	Overweight (25 to <29.9) (n=976)	Obese (>= 30) (n=1169)	
Lactate max, Median (IQR)	2.0 (1.3, 3.5)	2.0 (1.3, 3.4)	2.0 (1.3, 3.5)	2.0 (1.3, 3.5)	0.838
Interventions					
Mechanical ventilation use, n (%)					<0.001
No	1458 (46.4)	488 (48.8)	488 (50)	482 (41.2)	
Yes	1687 (53.6)	512 (51.2)	488 (50)	687 (58.8)	
Vasopressor use, n (%)					0.657
No	2004 (63.7)	628 (62.8)	620 (63.5)	756 (64.7)	
Yes	1141 (36.3)	372 (37.2)	356 (36.5)	413 (35.3)	
Sedative use, n (%)					0.001
No	1699 (54.0)	573 (57.3)	543 (55.6)	583 (49.9)	
Yes	1446 (46.0)	427 (42.7)	433 (44.4)	586 (50.1)	

For all continuous covariates, the mean values and SD are reported.
 AFIB, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; MAP, minimum arterial pressure; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

to 0.93, $p=0.012$) and hypertensive (adjusted HR 0.73, 95% CI 0.58 to 0.92, $p=0.008$) patients were significantly related to the 1-year mortality in subgroup analysis. We also observed a marked interactive effect between BMI/diabetes/hypertension and the 1-year mortality. Based on our analyses, obese diabetic, hypertensive and male patients were at a reduced mortality risk at 1-year post-ICU admission, relative to normal weight patients (both unadjusted and adjusted analyses).

Several prior studies investigated the association between BMI and sepsis-related mortality. However, the conclusion remains inconclusive.^{18 26-29} In a majority of studies, BMI was shown to be negatively correlated with sepsis-related mortality, and obesity greatly reduced the mortality risk of septic patients.^{6 18 27-29} Nevertheless, a retrospective observational investigation suggested that obese participants displayed a non-significant increase in mortality risk in adjusted 28-day mortality, relative to non-obese septic controls.²⁶ A prospective study¹⁸ reported

enhanced OS of morbidly obese patients (87%), relative to normal (84%) or underweight (78%) patients. However, this pattern did not reach significance, which corroborated with our results. One investigation revealed that augmented sagittal abdominal diameter, and not BMI, was markedly related to mortality among patients with sepsis. This indicated that BMI may ineffectively represent obesity.³⁰ Another study investigated the association between BMI, muscle mass and OS in 10 140 Parkinson's disease patients. The aforementioned study concluded that patients with elevated BMI and enhanced or normal muscle mass experience the best OS.³¹ BMI poorly represents adiposity, and may not precisely reflect the fat status, muscle to fat ratio, or overall body composition.³² In the future, we recommended prospective investigations quantifying adipose tissue either at or before sepsis detection using anthropometric indexes of enhanced adiposity (eg, waist circumference, waist-to-hip ratio, percentage of visceral vs total body fat)³³; or body

Table 2 One-year mortality in different BMI patients with sepsis

Outcome	BMI (kg/m ²) n (%)				P value
	Total (n=3145)	Normal weight (18.5 to <25) (n=1000)	Overweight (25 to <29.9) (n=976)	Obese (>= 30) (n=1169)	
Time in ICU (days)	4.3 (2.0, 9.9)	3.9 (1.9, 8.7)	3.9 (2.0, 9.0)	5.1 (2.2, 12.0)	<0.001
28-day mortality, n (%)					0.016
No	2373 (75.5)	728 (72.8)	732 (75)	913 (78.1)	
Yes	772 (24.5)	272 (27.2)	244 (25)	256 (21.9)	
1-year mortality, n (%)					<0.001
No	1811 (57.6)	531 (53.1)	565 (57.9)	715 (61.2)	
Yes	1334 (42.4)	469 (46.9)	411 (42.1)	454 (38.8)	
4-year mortality, n (%)					<0.001
No	1434 (45.6)	404 (40.4)	441 (45.2)	589 (50.4)	
Yes	1711 (54.4)	596 (59.6)	535 (54.8)	580 (49.6)	

BMI, body mass index; ICU, intensive care unit.

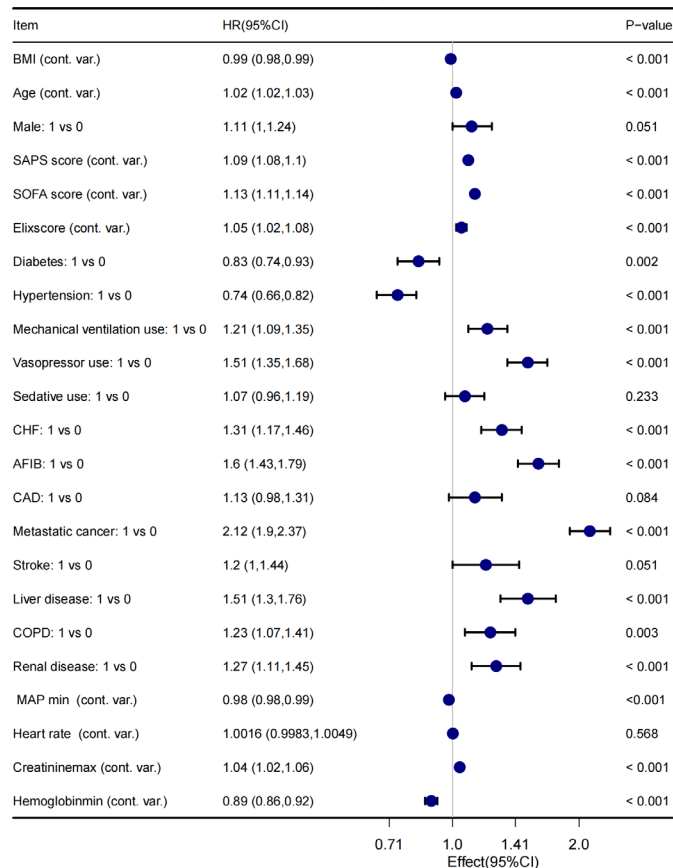


Figure 2 Univariable Cox analysis figure baseline of the cohort. Forest plot show the hazard ratio of univariate analysis.

composition evaluations via CT or dual-energy X-ray absorptiometry.

We discovered gender differences in obesity and 1-year mortality; it is important to consider the clinical implications of this. One implication is the identification of at-risk populations. The average age of the women in this cohort was 66.2 years, implying that the majority were postmenopausal. In general, oestrogen has a protective effect on females. Because of the natural decrease in endogenous estradiol during menopause, postmenopausal women gain visceral fat mass, decreases muscle mass. This may account for the gender differences in the results.

Adipose tissue was traditionally thought of as a storage site for lipids but is now recognised as an endocrine organ secreting signalling molecules and hormones that regulate metabolic homeostasis. Adipocytokines are released by adipose tissue, which is made up of adipose cells and other immune cells. Adipocytokines that cause inflammation include 'TNF- α ', 'interleukin-6' and 'resistin', etc. The most representative adipocytokine that inhibits inflammation is 'adiponectin'.³⁴

Our analysis revealed a marked association between BMI and diabetes. Hypertensive¹⁹ and insulin resistant²⁰ patients were also reported to experience enhanced septic patient OS, which corroborates well with our findings. This is likely due to alterations within the

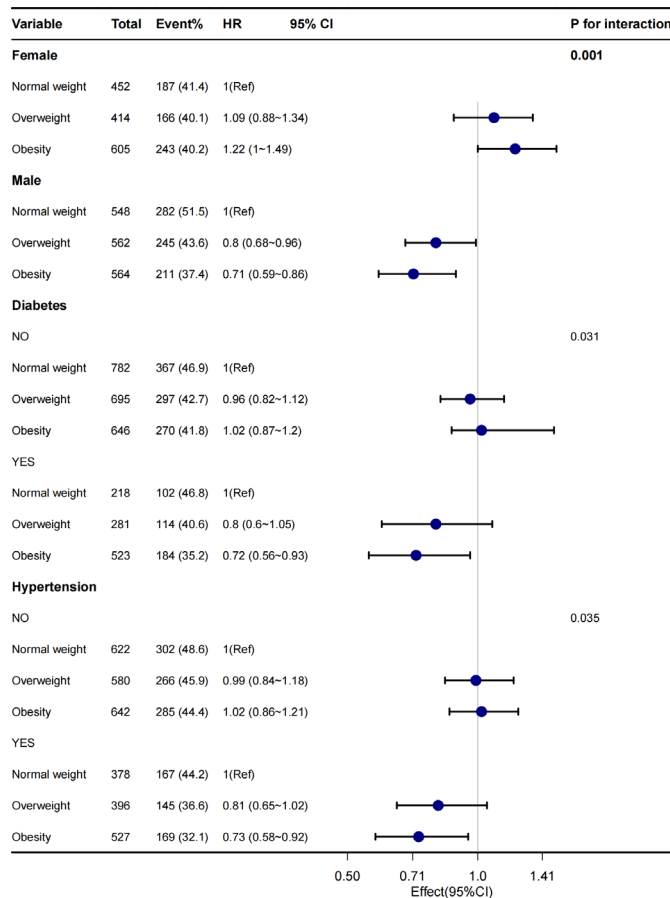


Figure 3 The association between BMI and 1-year mortality in subgroups. BMI, body mass index.

sympathetic nervous or endocrine system, which trigger a beneficial response in septic patients, or in the medications delivered to septic patients. Diabetes mellitus is strongly correlated with enhanced infectious disease-related mortality,³⁵ yet, in another cohort,³⁶ diabetes is strongly related to diminished mortality risk. Based on a retrospective investigation²⁰ involving 792 patients with sepsis, obesity and morbid obesity were highly protective against patient death. Moreover, this protection may be due to the simultaneous presence of comorbid insulin resistance and diabetes, which is in agreement with our study. In another retrospective study, a U-shaped relationship was observed between BMI and all-cause mortality in type 2 diabetic patients, who carried the lowest mortality risk among all overweight patients.³⁷ Among hypertensive CAD patients, overweight or obesity offered more protection against patient death or development of nonfatal myocardial infarction or stroke.¹⁹ It is well known that obese hypertensive patients tend to exhibit an elevated cardiac output, excess blood volume, and reduced systemic vascular resistance, relative to normal weight patients.³⁸⁻⁴⁰ Since systemic resistance represents the hypertensive cardiovascular disease status, the relatively reduced values in obese patients may translate to an enhanced prognosis within this patient population. There may be multiple reasons behind the observed obesity

Table 3 Multivariable Cox analysis

Variable	Total	Event%	Non-adjusted		Adjust I		Adjust II	
			HR 95% CI	P value	HR 95% CI	P value	HR 95% CI	P value
BMI	3145	1334 (42.4)	0.99 (0.98 to 0.99)	<0.001	0.99 (0.99 to 1)	0.148	1 (0.99 to 1.01)	0.772
Normal weight	1000	469 (46.9)	1(Ref)		1(Ref)		1(Ref)	
Overweight	976	411 (42.1)	0.88 (0.77 to 1)	0.058	0.89 (0.78 to 1.02)	0.09	0.94 (0.82 to 1.07)	0.328
Obesity	1169	454 (38.8)	0.79 (0.69 to 0.9)	<0.001	0.83 (0.72 to 0.94)	0.004	0.93 (0.81 to 1.06)	0.28
Trend test	3145	1334 (42.4)	0.89 (0.83 to 0.95)	<0.001	0.91 (0.85 to 0.97)	0.004	0.96 (0.9 to 1.03)	0.275

Adjusted I for age, gender and SOFA.
 Adjusted II for age, gender, SAPS, SOFA, elixscore, diabetes, hypertension, coronary artery disease, congestive heart failure, atrial fibrillation, malignancy cancer, stroke, chronic obstructive pulmonary disease, renal disease, liver disease, MAP, creatinine, haemoglobin.
 BMI, body mass index; MAP, minimum arterial pressure; SAPS, Simplified Acute Physiology Score ; SOFA, Sequential Organ Failure Assessment.

paradox. First, obese patients tend to experience more frequent diabetes check-ups, which may result in the early detection and better management of the disease, thereby producing enhanced outcomes. As has been reported in prior investigations,^{41 42} the mean age of obese participants was considerably younger than the normal-weight category in our study. Therefore, overweight individuals may possess a metabolic reserve that protects them from adverse or undesirable outcomes.

We also made adjustments for the age, gender, disease, severity, vital signs and comorbidities variables to determine whether these factors affect patient outcome. Based on our analyses, overweight/obese patients experienced better OS, however, it did not reach significance. Another explanation may be that patients with type 2 diabetes, owing to their obesity-related metabolic stress, may have enhanced prognosis and reduced complications and comorbidity risk,⁴³ relative to a low BMI genetic susceptibility-induced type 1 diabetic.⁴⁴ Additional investigations are needed to delineate between the effects of type 1 and type 2 diabetes mellitus. Diabetic and hypertensive patients, with poor control or advanced underlying disease, may lose weight unintentionally and experience reduced or normal BMI. This can enhance mortality risk by incorrectly suggesting that augmented BMI protects against patient death in diabetic and hypertensive patients.

Our work has the following limitations: First, the research was retrospective. Therefore, unlike other observational investigations, there may be some unintentional biases that influenced the results. Second, the MIMIC database used in this study had missing information, which in some indexes was as high as 28%. This may have introduced potential selection bias. We have included in this manuscript our method of dealing with missing height records, which we confirmed was unbiased. Also, when conducting the final regression analysis, any baseline variables with over 5% of missing values were excluded from analysis. Third, our findings invoke discussion and hypotheses regarding the topic of BMI and mortality link, but do not imply causality. It is possible that some confounding factors remained in our quantitative data, particularly, due to the exclusion of smoking status⁴² and diabetes type in our multivariate analysis.

Lastly, we measured adiposity using BMI. Hence, there was no direct assessment of body composition, such as, visceral fat or fat distribution.

CONCLUSIONS

In conclusion, according to our analysis, men and obese patients with diabetes and hypertension have a reduced risk of sepsis-related mortality compared with normal weight patients. This essential information is highly beneficial to septic patient intervention and clinical prognosis. Combining the findings of BMI and mortality risk, recommendations for body weight management should be individualised for different patients. Our conclusion requires further validation in a prospective investigation.

Contributors LZ and LF were equally responsible for the writing of the manuscript. LZ conducted the statistical analyses. CL and HL participated in the study design and conduct and assisted in the writing of the manuscript. LZ act as guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval After successfully completing the National Institutes of Health Protecting Human Research Participants training course, We obtained approval to use MIMIC-III data for research (Certification Number: 38807989).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data for this study were obtained from MIMIC III, which was approved by Massachusetts Institute of Technology (No. 0403000206) and Beth Israel Deaconess Medical Center (2001-P-001699/14).

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is

properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Li Zhang <http://orcid.org/0000-0002-6738-8930>

REFERENCES

- Rhee C, Dantes R, Epstein L, et al. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014. *JAMA* 2017;318:1241-9.
- Kaukonen K-M, Bailey M, Suzuki S, et al. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. *JAMA* 2014;311:1308-16.
- Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med* 2013;369:840-51.
- Gaieski DF, Edwards JM, Kallan MJ, et al. Benchmarking the incidence and mortality of severe sepsis in the United States. *Crit Care Med* 2013;41:1167-74.
- Shankar-Hari M, Harrison DA, Rubenfeld GD, et al. Epidemiology of sepsis and septic shock in critical care units: comparison between sepsis-2 and sepsis-3 populations using a national critical care database. *Br J Anaesth* 2017;119:626-36.
- Pepper DJ, Demirkale CY, Sun J, et al. Does obesity protect against death in sepsis? A retrospective cohort study of 55,038 adult patients. *Crit Care Med* 2019;47:643-50.
- Hogue CW, Stearns JD, Colantuoni E, et al. The impact of obesity on outcomes after critical illness: a meta-analysis. *Intensive Care Med* 2009;35:1152-70.
- Akinnusi ME, Pineda LA, El Solh AA. Effect of obesity on intensive care morbidity and mortality: a meta-analysis. *Crit Care Med* 2008;36:151-8.
- Karampela I, Chrysanthopoulou E, Christodoulatos GS, et al. Is there an obesity paradox in critical illness? epidemiologic and metabolic considerations. *Curr Obes Rep* 2020;9:231-44.
- Endalifer ML, Diress G. Epidemiology, predisposing factors, biomarkers, and prevention mechanism of obesity: A systematic review. *J Obes* 2020;2020:6134362.
- Mewes C, Böhnke C, Alexander T, et al. Favorable 90-day mortality in obese Caucasian patients with septic shock according to the sepsis-3 definition. *J Clin Med* 2019;9:46.
- Mei X, Hu S, Mi L, et al. Body mass index and all-cause mortality in patients with percutaneous coronary intervention: a dose-response meta-analysis of obesity paradox. *Obes Rev* 2021;22:e13107.
- Park J, Ahmadi S-F, Streja E, et al. Obesity paradox in end-stage kidney disease patients. *Prog Cardiovasc Dis* 2014;56:415-25.
- Ng PY, Eikermann M. The obesity conundrum in sepsis. *BMC Anesthesiol* 2017;17:147.
- Marques MB, Langouche L. Endocrine, metabolic, and morphologic alterations of adipose tissue during critical illness. *Crit Care Med* 2013;41:317-25.
- Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab* 2004;89:2548-56.
- Winkler G, Kiss S, Keszthelyi L, et al. Expression of tumor necrosis factor (TNF)-alpha protein in the subcutaneous and visceral adipose tissue in correlation with adipocyte cell volume, serum TNF-alpha, soluble serum TNF-receptor-2 concentrations and C-peptide level. *Eur J Endocrinol* 2003;149:129-35.
- Dossett LA, Dageforde LA, Swenson BR, et al. Obesity and site-specific nosocomial infection risk in the intensive care unit. *Surg Infect (Larchmt)* 2009;10:137-42.
- Uretsky S, Messerli FH, Bangalore S, et al. Obesity paradox in patients with hypertension and coronary artery disease. *Am J Med* 2007;120:863-70.
- Kuperman EF, Showalter JW, Lehman EB, et al. The impact of obesity on sepsis mortality: a retrospective review. *BMC Infect Dis* 2013;13:377.
- Chang E, Varghese M, Singer K. Gender and sex differences in adipose tissue. *Curr Diab Rep* 2018;18:69.
- Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001;29:1303-10.
- Vincent JL, Moreno R, Takala J, et al. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. on behalf of the Working group on sepsis-related problems of the European Society of intensive care medicine. *Intensive Care Med* 1996;22:707-10.
- van Walraven C, Austin PC, Jennings A, et al. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. *Med Care* 2009;47:626-33.
- Le Gall JR, Loirat P, Alperovitch A, et al. A simplified acute physiology score for ICU patients. *Crit Care Med* 1984;12:975-7.
- Gaulton TG, Weiner MG, Morales KH, et al. The effect of obesity on clinical outcomes in presumed sepsis: a retrospective cohort study. *Intern Emerg Med* 2014;9:213-21.
- Li Q, Tong Y, Liu S, et al. Association between body mass index and short-term mortality in patients with intra-abdominal infections: a retrospective, single-centre cohort study using the medical information Mart for intensive care database. *BMJ Open* 2021;11:e046623.
- Li S, Hu X, Xu J, et al. Increased body mass index linked to greater short- and long-term survival in sepsis patients: a retrospective analysis of a large clinical database. *Int J Infect Dis* 2019;87:109-16.
- Wurzinger B, Dünser MW, Wohlmuth C, et al. The association between body-mass index and patient outcome in septic shock: a retrospective cohort study. *Wien Klin Wochenschr* 2010;122:31-6.
- Chalkias A, Nitsotolis T, Papalexandrou A, et al. Sagittal abdominal diameter may effectively predict future complications and increased mortality in intensive care unit patients with severe sepsis. *J Crit Care* 2013;28:964-9.
- Ramkumar N, Pappas LM, Beddhu S. Effect of body size and body composition on survival in peritoneal dialysis patients. *Perit Dial Int* 2005;25:461-9.
- Christopher KB. The body mass index paradox. *Crit Care Med* 2015;43:2693-4.
- Pichard C, Kyle UG, Morabia A, et al. Nutritional assessment: lean body mass depletion at hospital admission is associated with an increased length of stay. *Am J Clin Nutr* 2004;79:613-8.
- Maximus PS, Al Achkar Z, Hamid PF, et al. Adipocytokines: are they the theory of everything? *Cytokine* 2020;133.
- Zoppini G, Fedeli U, Schievano E, et al. Mortality from infectious diseases in diabetes. *Nutr Metab Cardiovasc Dis* 2018;28:444-50.
- Lin C-C, Li C-I, Liu C-S, et al. Obesity paradox in associations between body mass index and diabetes-related hospitalization and mortality in patients with type 2 diabetes: retrospective cohort studies. *Diabetes Metab* 2019;45:564-72.
- Salehidooost R, Mansouri A, Amini M, et al. Body mass index and the all-cause mortality rate in patients with type 2 diabetes mellitus. *Acta Diabetol* 2018;55:569-77.
- Barrett-Connor E, Khaw KT. Is hypertension more benign when associated with obesity? *Circulation* 1985;72:53-60.
- Messerli FH. Cardiovascular adaptations to obesity and arterial hypertension: detrimental or beneficial? *Int J Cardiol* 1983;3:94-7.
- Messerli FH, Sundgaard-Riise K, Reisin E, et al. Disparate cardiovascular effects of obesity and arterial hypertension. *Am J Med* 1983;74:808-12.
- Costanzo P, Cleland JGF, Pellicori P, et al. The obesity paradox in type 2 diabetes mellitus: relationship of body mass index to prognosis: a cohort study. *Ann Intern Med* 2015;162:610-8.
- Tobias DK, Pan A, Jackson CL, et al. Body-Mass index and mortality among adults with incident type 2 diabetes. *N Engl J Med* 2014;370:233-44.
- Perry JRB, Voight BF, Yengo L, et al. Stratifying type 2 diabetes cases by BMI identifies genetic risk variants in Lama1 and enrichment for risk variants in lean compared to obese cases. *PLoS Genet* 2012;8:e1002741.
- Wing RR, Lang W, Wadden TA, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care* 2011;34:1481-6.