

# Abdominal Obesity and Short-term Mortality in Critically Ill Patients with Sepsis: A Retrospective Cohort Study Based on the MIMIC-IV Database

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## Research

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# Abstract

**Purpose:** Multiple studies have demonstrated an obesity paradox such that obese septic patients have a lower mortality rate and a relatively favorable prognosis. However, less is known on the association between abdominal obesity and short-term mortality in patients with sepsis. We conducted this study to determine whether the obesity-related survival benefit remains among abdominal obese patients.

**Methods:** A retrospective cohort study was conducted using data derived from the Medical Information Mart for Intensive Care IV database. Septic patients ( $\geq 18$  years) with or without abdominal obesity of first intensive care units (ICU) admission in the database were enrolled. The primary outcome was mortality within 28 days of ICU admission and multivariable logistic regression analyses were employed to assess any association between abdominal obesity and the outcome variable.

**Results:** A total of 21534 patients were enrolled finally, the crude 28-day mortality benefit after ICU admission was not observed in patients with abdominal obesity (15.8% vs. 15.3%,  $p=0.32$ ). In the extended multivariable logistic models, the odds ratio (OR) of abdominal obesity was significantly inverted after incorporating metabolic variables into the logistic model (OR range 1.094-2.872,  $p = 0.02$ ). The subgroup analysis showed interaction effects in impaired fasting blood glucose/diabetes and metabolic syndrome subgroups ( $P = 0.001$  and  $<0.001$ , respectively). In the subgroups of blood pressure, high-density lipoprotein cholesterol, and triglyceride level, no interaction was detected in the association between abdominal obesity and mortality. After propensity score matching, 6523 pairs of patients were selected. The mortality significantly higher in the abdominal obesity group (17.0% vs. 14.8%,  $p = 0.015$ ). Notably, the non-abdominal obese patients were weaned off vasopressors and mechanical ventilation more quickly than those in the abdominal obesity group (vasopressor-free days on day 28 of 27.0 vs. 26.8,  $p < 0.001$ ; ventilation-free days on day 28 of 26.7 vs. 25.6,  $p < 0.001$ ).

**Conclusion:** Abdominal obesity was associated with increased risk of adjusted sepsis-related mortality within 28 days after ICU admission and was partially mediated through metabolic syndrome components.

## Introduction

Sepsis is a dysregulated response of the host to infection, which can lead to tissue damage, organ dysfunction, and death[1]. The estimated annual incidence is 70-240 per 100,000 and increasing at a rate of 1.5% each year worldwide[2, 3]. According to the latest global statistics, total incidence exceeding 48.9 million cases and accounts for 11 million deaths each year[4]. Despite the increasing appreciation for pathogenesis, the main management of sepsis relies on supportive treatment. Sepsis is a refractory disease that has continued to rise the number of deaths over the past decade[2-4].

Globally, with the improvement of living conditions, obese people comprise a significant and increasing proportion of the worldwide population. Over the past four decades, the prevalence of obesity has increased dramatically in developed countries as well as in developing countries[5-7]. As obesity rises in

the general population, approximately 34% of adult patients in critical care units were overweight and 15–20% were obesity[8, 9]. World Health Organization (WHO) defines overweight and obesity as abnormal or excessive fat accumulation that may endanger physical health, which is measured by body mass index (BMI)[10]. Obesity is associated with an increased risk of metabolic, cardiovascular, chronic inflammatory diseases and other malignant disorders, and shorten life expectancy, emerging as the fourth leading cause of mortality around the world[11, 12]. Recently, there is a growing number of observational studies supported that critically ill patients who are overweight or mildly obese may exhibit a decreased mortality[13-15]. Nevertheless, the mechanism of this survival benefit, called “obesity paradox” is unclear, the potential accompanied hazards of obesity cannot be neglected.

Obesity is often accompanied by metabolic disturbances such as dyslipidemia, hyperglycemia, hypertension and impaired fasting glucose[10, 16]. According to the third Adult Treatment Panel (ATPIII) criteria that individuals with abnormalities at least three of the five components [elevated waist circumference (WC), elevated blood pressure, high triglyceride (TG), low high-density lipoprotein cholesterol (HDL-C), and impaired fasting blood glucose (FBG)/diabetes] could be defined as metabolic syndrome (MetS)[17]. Some epidemiologic surveys suggest that WC-defined abdominal obesity, one of the characteristics of the MetS, predicts a worse prognosis in various concomitant diseases than BMI-defined obesity[18, 19]. Recently, a large retrospective cohort study found that abdominal obesity is associated with increased future risk of sepsis-related mortality over 10 years[20]. It is not yet known whether the MetS overall or its individual components are stronger predictors for risk of sepsis-related mortality than BMI.

The specific aims of this retrospective analysis were two-fold. Firstly, to evaluate whether the abdominal obese patients admitted to the ICU for sepsis derived an obesity-related survival benefit in a large dataset. Secondly, if the survival benefit does not exist, to determine whether this benefit reoccurs after adjusting for MetS components which contain FBG/diabetes, plasma TG, blood pressure and serum HDL-C levels.

## **Materials And Methods**

### **Study design**

This retrospective cohort study was performed based on an online international database-Medical Information Mart for Intensive Care IV (MIMIC-IV)[21]. The MIMIC-IV contains comprehensive and high-quality data profiles of patients admitted to ICUs at the Beth Israel Deaconess Medical Center between 2008 and 2019 (inclusive). One author (ZL) obtained permission for the database (certification number 42669087) and was responsible for data extraction.

### **Inclusion and exclusion criteria**

Adult patients in the MIMIC-IV who fulfilled the definition of Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) were eligible for inclusion. The Sepsis-3 criteria implies patients with documented or suspected infection and a concurrent increase in Sequential Organ Failure Assessment

(SOFA) by greater than or equal to 2 points were considered to have sepsis[22]. Infection was identified from the International Classification of Diseases 10th Edition (ICD-10) code in the MIMIC-IV. Patients younger than 18 years old were excluded. For patients with multiple ICU admissions, only the first ICU stay was included in analysis.

## **Data extraction**

Baseline characteristics within the first 24h after ICU admission were collected from the database, including demographic characteristics, comorbidities, laboratory outcomes, and disease severity scores. Laboratory variables including white blood cell (WBC) count, hemoglobin, platelet counts, HDL-C, TG, lactate, hemoglobinA1c (HbA1c), glutamic oxalacetic transaminase (AST), glutamic pyruvic transaminase (ALT), total bilirubin (TB) and albumin. If a variable was recorded more than once within the first 24 h, we adopted the value associated with the greatest severity of illness. The application of renal replacement therapy (RRT), use of mechanical ventilation (MV), and administration of vasopressors, antihypertensive drugs, hypoglycemic agents and lipid-lowering agents, were also recorded. Due to the missing information of WC throughout this database, the records of abdominal palpation showed diagnosis of 'obese' were considered abdominal obesity group, with the remaining patients making up the non-abdominal obesity group. The patients had no abdominal palpation records were not included. The source codes for all analyses can be found at <https://github.com/MIT-LCP/mimic-code.git>

## **Outcomes and covariates**

The main independent variable examined in present study was abdominal obesity at admission, which was categorized based the abdominal palpation outcomes. Covariates were metabolic components included FBG/diabetes, plasma TG, blood pressure, serum HDL-C levels and MetS, as well as demographic characteristics, comorbidities, laboratory outcomes, disease severity scores and clinical treatment measures. The primary outcome in the present study was 28-day mortality after ICU admission. Secondary outcomes included in-hospital mortality, 60-day mortality and 90-day mortality, lengths of stay in ICU and in hospital, the number of ventilator-free and vasopressor-free days within 28 days after ICU admission, and reduction in serum lactate (calculated as the difference between the maximum serum lactate level within 24 hour and 72 hour).

## **Subgroup analysis**

Subgroup analysis was performed to investigate the interaction between prognosis of patients with sepsis and abdominal obesity, as well as metabolic conditions. Stratification was performed according to the metabolic status after ICU admission, which contains FBG/diabetes (FBG  $\geq$  or  $<$ 100mg/dL), blood pressure ( $\geq$  or  $<$ 130/85mmHg), serum HDL-C levels ( $\geq$  or  $<$  40mg/dL for male, and  $\geq$  or  $<$  50mg/dL for female), plasma TG ( $\geq$  or  $<$ 150mg/dL) and metabolic score ( $\geq$  or  $<$  3).

## **Propensity score matching**

A propensity score matching (PSM) method based on a multivariable logistic regression model was applied to balance the bias of potential confounding factors and generate comparable study cohorts[23]. The covariate balancing propensity score estimation was conducted considering baseline characteristics, including gender, age, comorbidities, disease severity scores [SOFA score, Charlson Comorbidity Index (CCI), SAPS II score] and laboratory tests. A one-to-one nearest neighbor matching algorithm was carried out with a 0.05 caliper width. This strategy resulted in 6523 pairs in each group and applied to further analyses.

## **Statistical analysis**

In this retrospective study, the implausible/extreme values of continuous variables (less than 5%) were replaced by the mean or median values. Missing data for the remaining variables (less than 50% of values missing) were handled by means of multiple imputation[24]. Additionally, we set dummy variables for categorical variables with missing information.

Continuous data with a normal distribution were presented as the means (SD) and were analyzed with independent-samples t tests. Nonnormally distributed continuous variables were expressed as median and interquartile ranges (IQRs), which were tested by the Mann-Whitney U test. Categorical variables were described as percentages and were compared via the chi-square test or Fisher's exact test. The Kaplan-Meier method was applied to compare lengths of stay.

Multivariate logistic regression was used to evaluate the relationship between abdominal obesity and the primary outcome. Baseline variables considered significant by the researchers from a clinical perspective were included in our multivariate regression models. Multicollinearity was tested by the variable inflation factor (VIF) method, with a  $VIF \geq 5$  was regarded as an indication of multicollinearity. The goodness-of-fit to the multivariate regression model was tested using the Hosmer-Lemeshow Test. SPSS (IBM SPSS 26.0, SPSS Inc) was used for statistical analyses. Subgroup analysis and graphing were conducted using R software version 4.1.0 (R Foundation for Statistical Computing, Auckland, New Zealand).

# **Results**

## **Sepsis Cases**

Among 76540 adult encounters admitted to ICUs at the Beth Israel Deaconess Medical Center between 2008 and 2019, we identified 53150 first ICU stays, including 21615 patients with sepsis according to the Sepsis-3 criteria. Of these, 33 had no abdominal palpation records, 48 had extreme values of weight. Complete data for 21534 sepsis encounters were available for analysis. Among the study cohort, abdominal palpation of 7080 patients showed a diagnosis of 'obese' (Figure 1).

## **Baseline characteristics**

The baseline characteristics of the abdominal obesity and non-abdominal obesity groups are summarized in Table 1. Patients in the abdominal obesity associated more comorbidities, including hypertension, diabetes, coronary heart disease (CHD), congestive heart failure (CHF), chronic kidney disease (CKD), atrial fibrillation (AFIB). Statistical differences in SOFA score [3 (2–5) vs. 3(2–4)] and SAPS II score [39(31-49) vs. 37(29-47)] were detected between the abdominal obesity group and the non-abdominal obesity group on admission. Furthermore, components of MetS, except for WC and blood pressure, were significantly different between the groups (all P <0.05). A larger percentage of the abdominal obesity patients received MV (72.4% vs. 59.3%), vasopressor treatment (61.5% vs. 51.5%) and RRT use (11.5% vs. 6.3%) during their ICU stay. Additional baseline information is presented in Additional file (Table S1)

**Table 1** Comparisons of the baseline characteristics and prognoses between patients with and without abdominal obesity.

Variables	All patients (n=21534)	Non- abdominal obesity (n=14454)	Abdominal obesity (n=7080)	p	Missing data (%)
Age	68(56-79)	68(55-80)	67(57-76)	0.273	0.0
Gender(male),n(%)	12428(57.7%)	8789(60.8%)	3639(51.4%)	<0.001	0.0
Emergency, n(%)	17185(79.8%)	11489(79.5%)	5696(80.5%)	0.097	0.0
Comorbidities, n(%)					
Diabetes	6491(30.1%)	3506(24.3%)	2985(42.2%)	<0.001	0.0
Hypertension	6556(30.4%)	4106(28.4%)	2450(34.6%)	<0.001	0.0
COPD	1858(8.6%)	1010(7.0%)	848(12.0%)	<0.001	0.0
CHF	4899(22.8%)	2969(20.5%)	1930(27.3%)	<0.001	0.0
CHD	6913(32.1%)	4469(30.9%)	2444(34.5%)	<0.001	0.0
AFIB	6589(30.6%)	4117(28.5%)	2472(34.9%)	<0.001	0.0
Renal	3578(16.6%)	2189(15.1%)	1389(19.6%)	<0.001	0.0
Liver	1335(6.2%)	888(6.1%)	447(6.3%)	0.627	0.0
Malignancy	3127(14.9%)	2284(15.8%)	933(13.2%)	<0.001	0.0
Laboratory tests					
WBC(K/uL)	13.2(9.5-17.9)	12.8(9.1-17.5)	13.9(10.1-18.8)	<0.001	1.1
Hemoglobin(g/dL)	11.0(9.7-12.3)	10.9(9.7-12.3)	11.1(9.7-12.4)	0.001	1.4
Platelet(K/uL)	177(126-244)	173(122-239)	187(134-253)	<0.001	1.6
Plasma glucose(mg/dL)	118(97-155)	114(96-148)	127(102-172)	<0.001	0.1
HbA1c(%)	5.9(5.5-6.7)	6.0(5.6-6.5)	6.3(5.8-7.0)	<0.001	58.3
HDL-c(mg/dL)	42(32-53)	43(33-55)	40(31-50)	<0.001	67.8
LDL-c(mg/dL)	85(62-112)	85(63-112)	84(61-112)	0.104	69.1
TG(mg/dL)	122(85-180)	115(81-166)	135(93-209)	<0.001	59.0
TC(mg/dL)	161(130-195)	162(131-195)	158(128-195)	0.067	66.3
TB(mg/dL)	0.7(0.4-1.5)	0.7(0.4-1.5)	0.7(0.4-1.4)	0.252	34.2
AST(IU/L)	54(29-149)	54(29-146)	56(30-156)	<0.001	7.2

ALT(IU/L)	42(23-110)	41(22-110)	42(24-110)	0.029	7.2
Creatinine(mg/dL)	1.0(0.7-1.5)	1.0(0.7-1.4)	1.1(0.8-1.7)	<0.001	0.8
BUN(mg/dL)	21(14-35)	20(14-34)	23(16-37)	<0.001	0.9
Albumin(g/dL)	3.1(2.6-3.5)	3.1(2.6-3.5)	3.1(2.6-3.5)	0.573	76.3
Lactate(mmol/L)	1.9(1.3-2.8)	1.9(1.3-2.8)	1.9(1.3-2.9)	0.951	17.9
Blood culture, n(%)				<0.001	0.0
Positive	2580(12.0%)	1572(10.9%)	1008(14.2%)		
Negative	12477(57.9%)	8188(56.6%)	4289(60.6%)		
Untested	6477(30.1%)	4694(32.5%)	1783(25.2%)		
Severity of illness					
SOFA	3(2-4)	3(2-4)	3(2-5)	<0.001	0.0
CCI	5(4-7)	5(3-7)	5(4-7)	<0.001	0.0
SAPS II	38(29-48)	37(29-47)	39(31-49)	<0.001	0.0
Interventions, n(%)					
Oxygen inhalation	18607(86.4%)	12260(84.8%)	6347(89.6%)	<0.001	0.0
MV use	13687(63.6%)	8564(59.3%)	5123(72.4%)	<0.001	0.0
Vasopressor use	11803(54.8%)	7448(51.5%)	4355(61.5%)	<0.001	0.0
RRT use	1722(8.0%)	911(6.3%)	811(11.5%)	<0.001	0.0
Drug use, n(%)					
Lipid-lowering agents	7506(34.9%)	4671(32.3%)	2835(40.0%)	<0.001	0.0
Aspirin	10652(49.5%)	6839(47.3%)	3813(53.9%)	<0.001	0.0
Hypoglycemic agents	12613(58.6%)	7688(53.2%)	4925(69.6%)	<0.001	0.0
Antihypertensive agents	16620(77.2%)	10574(73.2%)	6046(85.4%)	<0.001	0.0
MetS disorders					
Impaired FBG/diabetes	8473(39.3%)	4868(33.7%)	3605(50.9%)	<0.001	0.0
Elevated blood pressure	7371(34.6%)	4844(33.9%)	2527(36.1%)	0.002	0.0
Hypertriglyceridemia	3108(14.4%)	1784(12.3%)	1324(18.7%)	<0.001	0.0
Low HDL-c	3721(17.3%)	2330(16.1%)	1391(19.6%)	<0.001	0.0
MetS (any 3 of the MetS	3450(16.0%)	912(6.3%)	2538(35.8%)	<0.001	0.0

disorders)					
Primary outcome					
28day mortality, n(%)	3322(15.4%)	2205(15.3%)	1117(15.8%)	0.320	NA
Secondary outcomes					
Hospital mortality, n(%)	3258(15.1%)	2150(14.9%)	1108(15.6%)	0.136	NA
60day mortality, n(%)	3460(16.1%)	2283(15.8%)	1177(16.6%)	0.120	NA
90day mortality, n(%)	3474(16.1%)	2289(15.8%)	1185(16.7%)	0.091	NA
ICU LOS(day)	2.8(1.4-5.8)	2.3(1.3-4.7)	3.9(2.0-8.4)	<0.001	NA
Hospital LOS(day)	8.0(5.0-14.0)	7.4(4.6-12.7)	9.7(5.8-16.7)	<0.001	NA
MV free in 28day	26.7(23.3-27.6)	27.0(24.5-27.7)	25.6(21.1-27.4)	<0.001	NA
Vasopressor free in 28day	27.1(25.3-27.7)	27.2(25.7-27.8)	26.8(24.2-27.7)	<0.001	NA
Lactate reduction	1.0(0.1-2.8)	1.1(0.2-2.9)	0.9(0.1-2.7)	0.232	NA

COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; CHD, coronary heart disease; AFIB, atrial fibrillation; WBC, white blood cell; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglyceride; TC, total cholesterol; TB, total bilirubin; BUN, blood urea nitrogen; HbA1c, hemoglobinA1c; SOFA, Sequential Organ Failure Assessment; CCI, Charlson Comorbidity Index; SAPS II, Simplified Acute Physiology Score II; MV, mechanical ventilation; RRT, renal replacement therapy; MetS, metabolic syndrome; FBG, fasting blood glucose; LOS, length of stay

### Association between abdominal obesity and 28-day mortality

In total, 3322 patients (15.4%) of the study population died within 28 days after ICU admission, whereas the 28-day mortality rate (15.8% versus 15.3%,  $P=0.320$ ) among patients with abdominal obesity and those without abdominal obesity showed no statistically significant difference (Table 1). Baseline characteristics which were significant variables on univariate analysis were entered in multivariate regression models, and the 28-day mortality between the two groups was not significantly different (OR range 0.980-1.863,  $p=0.067$ ). Notably, after incorporating metabolic indicators into the multivariate logistic regression analysis model, abdominal obesity was an independent risk factor of 28-day mortality in critically ill patients (OR range 1.094-2.872,  $p=0.020$ ). Similar results were observed after including pharmaceutical therapies and clinical interventions as covariates (OR range 1.056-2.914,  $p=0.030$ ) (Table 2). The results of VIF test showed that there was no co-linearity between the selected variables (Additional file: Table S8). After PSM, the two groups of patients had significant differences in 28-day mortality ( $P = 0.015$ ) (Table 3).

**Table 2** Association between abdominal obesity and 28-day mortality using an extended model method

	OR of abdominal obesity	95% CI	p
Model 1	1.041	0.962-1.125	0.320
Model 2	0.962	0.884-1.046	0.364
Model 3	1.351	0.980-1.863	0.067
Model 4	1.773	1.094-2.872	0.020
Model 5	1.754	1.056-2.914	0.030

Adjusted covariates: Model 1 = abdominal obesity. Model 2 = Model 1 + (SOFA score, SAPS II score, comorbidities including hypertension, CHF, chronic kidney disease, atrial AFIB, CHD and malignancy). Model 3 = Model 2 + (gender, age, Laboratory examination results including WBC count, lactate level, HbA1c, albumin, total bilirubin, blood culture on ICU admission). Model 4 = Model 3 + (MetS components including impaired FBG/diabetes, elevated blood pressure, low-HDL-C, hypertriglyceridemia). Model 5 = Model 4 + (pharmaceutical therapies including hypoglycemic agents, lipid-lowering agents, antihypertensive drugs, vasopressors and clinical interventions including MV, RRT, oxygen inhalation).

### Secondary Outcomes with propensity score-matched cohorts

No significant differences were found in terms of in-hospital mortality, 60-day mortality and 90-day mortality between the two groups before PSM (Table 1). Although there appeared to be a subtle decrease in cumulative 90-day mortality of patients without abdominal obesity, this difference was not statistically significant (Log rank test;  $P=0.307$ ) (Figure 2). Results for the secondary outcomes after PSM showed statistically significant differences between the study groups. Compared with the non-abdominal obesity group, the median lengths of ICU stay (3.9 vs. 2.2 day;  $p < 0.001$ ) and hospital stay (9.8 vs. 7.2 day;  $p < 0.001$ ) were longer for abdominal obesity individuals. Patients in abdominal obesity group had longer durations of MV (MV free days on day 28 of 25.6 vs. 26.7,  $p < 0.001$ ) and vasopressor use (vasopressor free days on day 28 of 26.8 vs. 27.0,  $p < 0.001$ ) than patients in non-abdominal obesity group. With respect to lactate, statistical difference of reduction in serum lactate between day 1 and day 3 was not observed among the groups (0.9 vs. 1.0mmol/L;  $p = 0.457$ ). Table 3 shows the detailed results.

### Table 3 Clinical outcomes analysis with propensity score matched cohorts

Clinical outcomes	Non-Abdominal obesity	Abdominal obesity	p
<b>Primary outcome</b>			
28-day mortality n (%)	968(14.8%)	1107(17.0%)	0.015
<b>Secondary outcomes</b>			
Hospital mortality, n (%)	966(14.8%)	1073(16.4%)	0.025
60-day mortality n (%)	1038(15.9%)	1112(17.0%)	0.040
90-day mortality n (%)	1056(16.2%)	1125(17.2%)	0.035
ICU LOS (days)	2.2(1.3-4.1)	3.9(2.0-8.5)	<0.001
Hospital LOS (days)	7.2(4.3-12.4)	9.8(5.8-16.9)	<0.001
Ventilation-free days in 28 days	26.7(24.1-27.5)	25.6(21.1-27.4)	<0.001
Vasopressor-free days in 28 days	27.0(25.6-27.7)	26.8(24.2-27.7)	<0.001
Serum lactate reduction	1.0(0.1-2.8)	0.9(0.1-2.7)	0.457

LOS, length of stay

### Subgroup and Sensitivity analyses

Subgroup analysis was performed according to patients with impaired FBG/diabetes, elevated blood pressure, low HDL-C level, hypertriglyceridemia and MetS (Figure 3). The OR of abdominal obesity was significant in the impaired FBG/diabetes [positive: OR 0.857, 95% confidence interval (CI) 0.763–0.964,  $p = 0.004$ ; negative: OR 1.084, 95% CI 0.963–1.220,  $p = 0.090$ ], hypertriglyceridemia ( $\geq 150\text{mg/dL}$ : OR 1.280, 95% CI 1.032–1.588,  $p = 0.004$ ;  $< 150\text{mg/dL}$ : OR 1.053, 95% CI 0.898–1.234,  $p = 0.074$ ) and MetS (positive: OR 1.597, 95% CI 1.261–2.023,  $p < 0.001$ ; negative: OR 0.959, 95% CI 0.871–1.058,  $p = 0.561$ ) subgroups, and significant interactions were observed in impaired FBG/diabetes ( $p$  value for interaction, 0.001) and MetS subgroups ( $p$  value for interaction,  $<0.001$ ). However, estimates of the association between abdominal obesity and 28-day mortality after being stratified by glucose, and a significant inverse association (OR=0.857, 95% CI 0.763–0.964) was observed in patients with impaired FBG/diabetes.

Among the BMI categories, underweight was significantly associated with higher 28day-mortality (Additional file: Table S2). Given that, nutritional status may actually matter more to patients than the impact of obesity itself. To test the robustness of our findings, patients with low BMI( $<18.5$ ) and low albumin levels ( $<2.1\text{g/dL}$ ), as surrogate markers for malnutrition[25], were excluded for sensitivity analyses. The results remained stable after adjustment for confounding factors (Additional file: Table S6 and Table S7).

## Discussion

In the present study, we preliminarily assessed association between BMI and mortality of sepsis patients extracted from MIMIC-IV database. The results suggest that overweight ( $25 < \text{BMI} < 29.9$ ) patients had a remarkably lower mortality compared to patients with normal/low BMI (Additional file: Table S2). Our findings corroborate some previous studies and support the hypothesis of a protective effect of overweight against death from sepsis[26]. However, when we regrouped patients according to abdominal obesity, various changes were observed, the obesity-related survival benefit was no longer existed. Individuals with abdominal obesity are predisposed to longer MV duration, longer ICU stay, and more treatment measures. In addition, after excluding confounders like gender, age, comorbidities, disease severity scores, laboratory tests, treatment measures, especially MetS components, abdominal obesity is found to be one of risk predictors of mortality in critically ill patients. Similar effects have been reported in animal models of sepsis[27]. In contrast to the normal weight group, obese mice had higher mortality rates, wider ranges of coexisting illnesses and disease severity. Some studies have speculated that such association might be the result of visceral adipose tissue which secretes high levels of pro-inflammatory cytokines, leading to a state of chronic inflammation and an modified immune response to infection[28]. This conjecture was similar to that demonstrated in a study by Gurunathan et al[29]. In the retrospective analysis, they found that abdominal obesity was probably superior to other adiposity indices in predicting major septic complications as well as in 30-day mortality following elective surgery. A subsequent large prospective cohort study reached a similar conclusion that WC was associated with an increased future risk of sepsis-related mortality. By systematic long term follow-up of 0.5 million adults, they reported that abdominal obesity was an independent risk factor of mortality related to sepsis[20]. We consider these investigations to be complementary since our study assessed short-term prognoses and does not preclude the possibility of long-term potential adverse outcomes of abdominal obesity in sepsis.

On reviewing all the aforementioned outcomes, we speculated that the risk of death and other poor prognosis were confounded by metabolic disorders [impaired FBG ( $\geq 100\text{mg/dL}$ ) or diabetes, high blood pressure ( $\geq 130/85\text{mmHg}$ ), low serum HDL-C ( $< 40\text{mg/dL}$  for male, and  $< 50\text{mg/dL}$  for female), hypertriglyceridemia ( $\geq 150\text{mg/dL}$ )]. It is well established that MetS is associated with increased mortality in cardiovascular diseases, cancer, and non-alcoholic fatty liver disease[30]. There seems no strong reason to suspect that MetS can increase mortality in severely sick patients. We additionally performed subgroup analysis to detect the interaction between MetS parameters and the association of abdominal obesity with short-term mortality risk, and significant interactions between impaired FBG/diabetes, MetS and abdominal obesity were detected. Intriguingly, in the FBG/diabetes subgroup, hyperglycemia in abdominal obese individuals appears to have a mild protective effect on short-term mortality (OR=0.857, 95% CI 0.763–0.964). There appeared to be good agreement between the results of our current work and previous research by Brunkhorst et al. The trial has reported that intensive intravenous insulin infusion in strict glycemic control did not significantly improve the prognosis, but increased the risk of hypoglycemic complications[31]. Hence, our results here support this recommendation that serum glucose levels should be maintained at relatively high levels ( $< 10\text{ mmol/L}$ ) [32]. Notably, although statistically significant interaction was not met between the subgroup of TG levels, we noticed that the association between abdominal obesity and 28-day mortality was still significant in

the subgroup with high TG levels( $\geq 150\text{mg/dL}$ ), which offered a possibility that the reduction in circulating TG may contribute to reduce the risk of short-term mortality in these patients.

In this retrospective observational study, we also grouped patients by BMI to analyze the cumulative mortality among patients. Compared with normal-weight individuals, the rate of 90-day mortality was significantly lower among patients with higher BMI (overweight), and underweight was associated with increased mortality (Additional file: Figure S3). This finding was in agreement with those in the previous studies[33]. Then we regrouped patients based on the records of abdominal palpation, the results of cumulative 90-day mortality did not show a significant difference between abdominal obesity and non-abdominal obesity groups, obesity-related survival benefit was no longer available. Li et al. have previously suggested that abdominal obesity is associated with increased future risk of sepsis-related mortality over 10 years in a large population-based research[20]. In this present study, the follow up period may have been too short to show a significant difference.

Notably, the effect of nutritional status regarding the implications of obesity in critical illness outcomes cannot be ignored. Nutritional status may actually matter more to patients than the impact of obesity itself as underweight patients exhibited remarkably higher mortality compared to normal weight population (Additional file: Table S2). Based on this, BMI and serum albumin levels were chosen as surrogate markers of malnutrition in this study to carry out subgroup analyses[25]. In subgroups of these two markers, no interaction was detected (Additional file: Figure S2). Abdominal obesity seems to be a better predictor of short-term mortality than BMI in patients with sepsis.

In this study, there were significant differences in disease severity between the two groups. The initial disease severity may also influence the length of stay and mortality rates. Accordingly, we detected the interaction between abdominal obesity and disease severities. These data show that when severity of illness is accounted for-using SAPS II score ( $>34$ ) and SOFA score ( $>10$ ) on hospital presentation-no interaction was detected (Additional file: Figure S2). which suggested the possibility that these differences are due to obesity itself.

One strength of this investigation is that it assesses the effects of abdominal obesity and mortality rates in patients with sepsis, instead of relying solely on BMI. Our study provides tentative evidence and add valuable information to the existing literature on the short-term outcomes of critically ill patients with abdominal obesity. Additional strength of this study is that, given that abdominal obesity is one of the characteristics of the MetS, we explored the influence of metabolic parameters when assessing the risk of death in patients with sepsis. Furthermore, our results are representative of more recent clinical data of sepsis patients compared with other large database study that predates our study period, and detailed electronic clinical data was applied to identify SOFA/Sepsis 3 definitions rather than using administrative codes for sepsis.

Our study also has several limitations. First, despite WC is a relatively easy to access parameter, the measurements are not routinely documented during hospital admittance in MIMIC-IV database. Therefore, we could classify abdominal obesity only according to abdominal palpation recordings of

physicians. The examination of abdomen records showed a diagnosis of 'obese' was defined abdominal obesity, which may bear a certain level of subjectivity and potential false negative rate. Second, our study was a retrospective cohort study based on public electronic healthcare records, the data generated during routine clinical care and records. There are several challenges in obtaining the laboratory results, such as serum glucose had been tested multiple times in a day, we extracted the first morning values as the FBG, indeed, we could not confirm whether the patients were fasting or had eaten before blood sampling. In addition, Due to the time drift, it is not certain whether the abdominal obesity triggered the use of medications and interventions or if it had already been in place. These factors can be difficult to adjust for in a retrospective observational study. Finally, due to the retrospective nature of the study, one point cannot be ignored is the differences in baseline characteristics of comorbidities, especially regarding cardiovascular diseases including hypertension, coronary artery disease and heart failure. Despite a PSM model has been introduced to minimize the bias, a few statistically significant differences were still present between cohorts. These discrepancies may be explained by the fact that both overweight and obesity have been previously reported as risk factors for these comorbidities. Detailed explanation was not included in the information available from the MIMIC-IV databases-thereby becoming another potential limitation of our analyses. We fully realize that observational study and unknown bias may affect the study results. Careful, multifaceted and rigorous statistical approaches are required to produce valid, reliable, and actionable results. A randomized controlled study comparing the prognosis of abdominal obesity and non-abdominal obesity and the underlying causes are needed in the future.

## Conclusion

In conclusion, our retrospective analysis suggests that obesity-related survival benefit was not present in the abdominal obese patients with sepsis. In contrast, abdominal obesity group was associated with a higher risk of 28-day mortality after adjustment for MetS parameters. FBG/diabetes and serum TG may have subtle effect on 28-day ICU mortality but MetS can dramatically increase the mortality of abdominal obese patients.

## Abbreviations

MIMIC-IV: Medical Information Mart for Intensive Care IV; ICU: intensive care units; OR: odds ratio; CI: confidence interval; FBG: fasting blood glucose; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride; HbA1c: hemoglobinA1c; PSM: propensity score matching; MetS: metabolic syndrome; WC: waist circumference; BMI: body mass index; SOFA: Sequential Organ Failure Assessment; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; CHD, coronary heart disease; CKD, chronic kidney disease; AFIB, atrial fibrillation; WBC, white blood cell; LDL, low density lipoprotein; TC, total cholesterol; TB, total bilirubin; BUN, blood urea nitrogen; CCI, Charlson Comorbidity Index; SAPS II, Simplified Acute Physiology Score II; MV, mechanical ventilation; RRT, renal replacement therapy

## Declarations

## Acknowledgments

Not applicable

## Authors' contributions

Zhou Lv and Minglu Gu contributed equally to this work. Lai Jiang and Yanfei Mao conceptualized the research aims, planned the analyses and guided the literature review, Dr Jiang and Dr Mao are designated conjointly as corresponding authors. Zhou Lv extracted the data from the MIMIC-IV database. Miao Zhou participated in processing the data and doing the statistical analysis. Zhou Lv and Minglu Gu wrote the first draft of the paper and the other authors provided comments and approved the final manuscript. All the authors gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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## Availability of data and materials

The datasets presented in the current study are available in the MIMIC IV database (<https://physionet.org/content/mimiciv/1.0/>).

## Ethics approval and consent to participate

The establishment of this database was approved by the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA) and consent was obtained for the original data collection. Therefore, the ethical approval statement and the need for informed consent were waived for this manuscript.

## Consent for publication

Not applicable

## Competing interests

The authors of this article have no conflict of interest.

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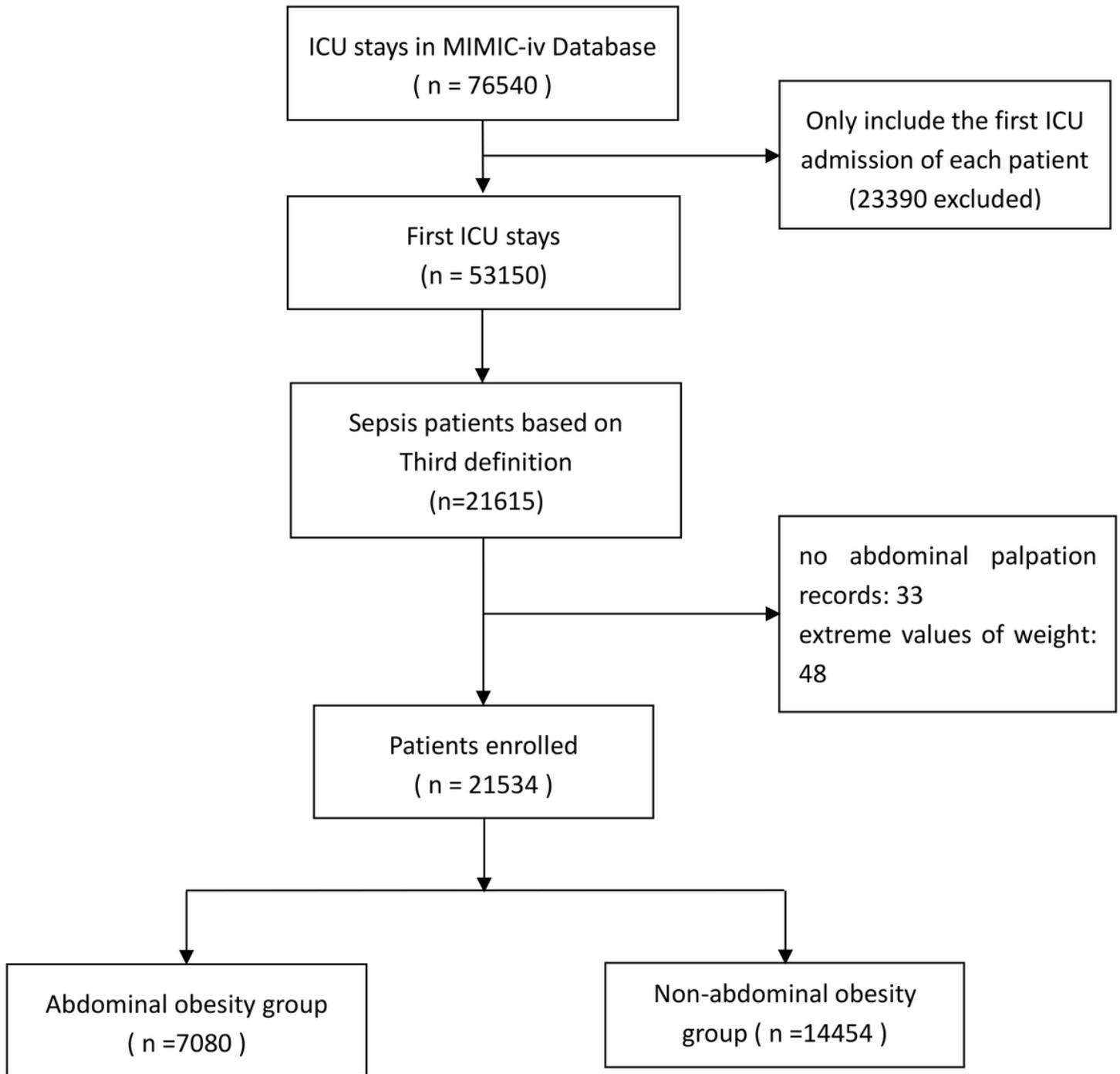
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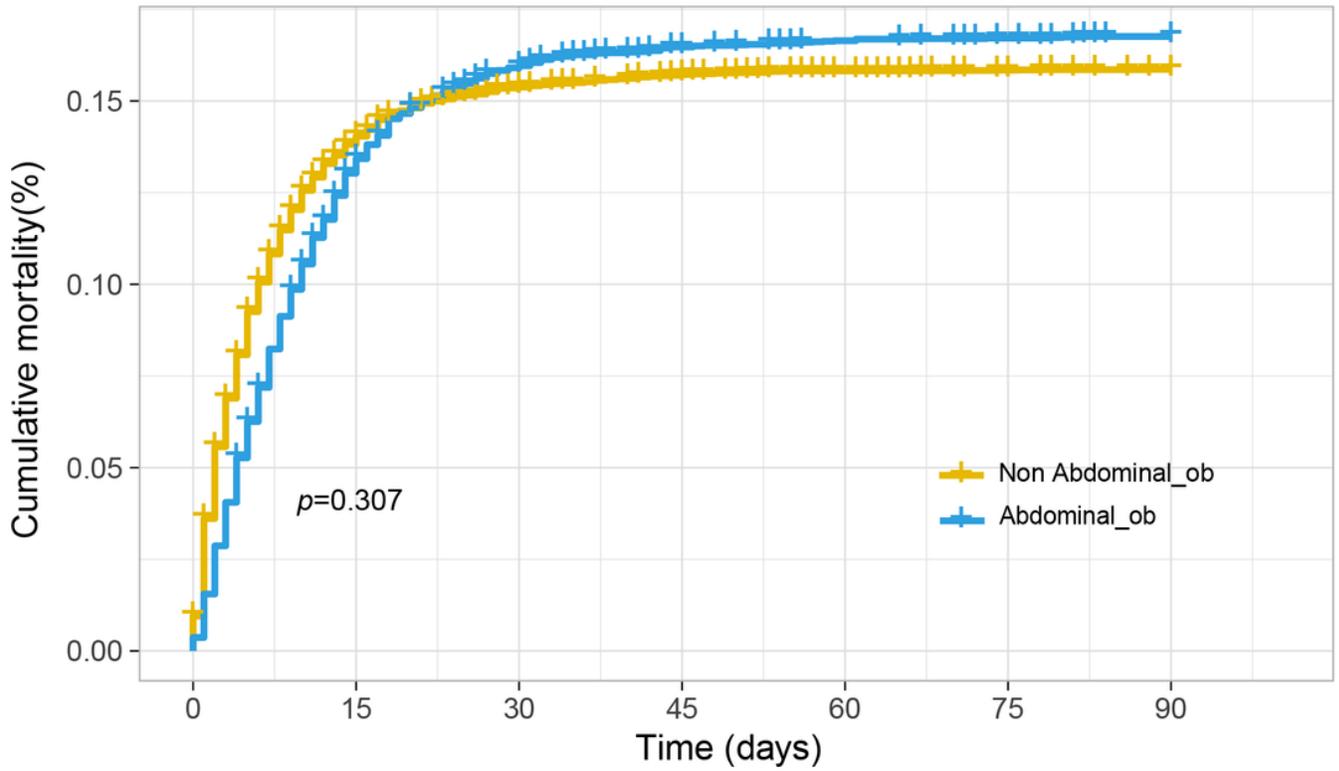
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## Figures



**Figure 1**

Flow chart of the study participants. Abbreviations: ICU, intensive care unit; MIMIC, Medical Information Mart for Intensive Care IV.

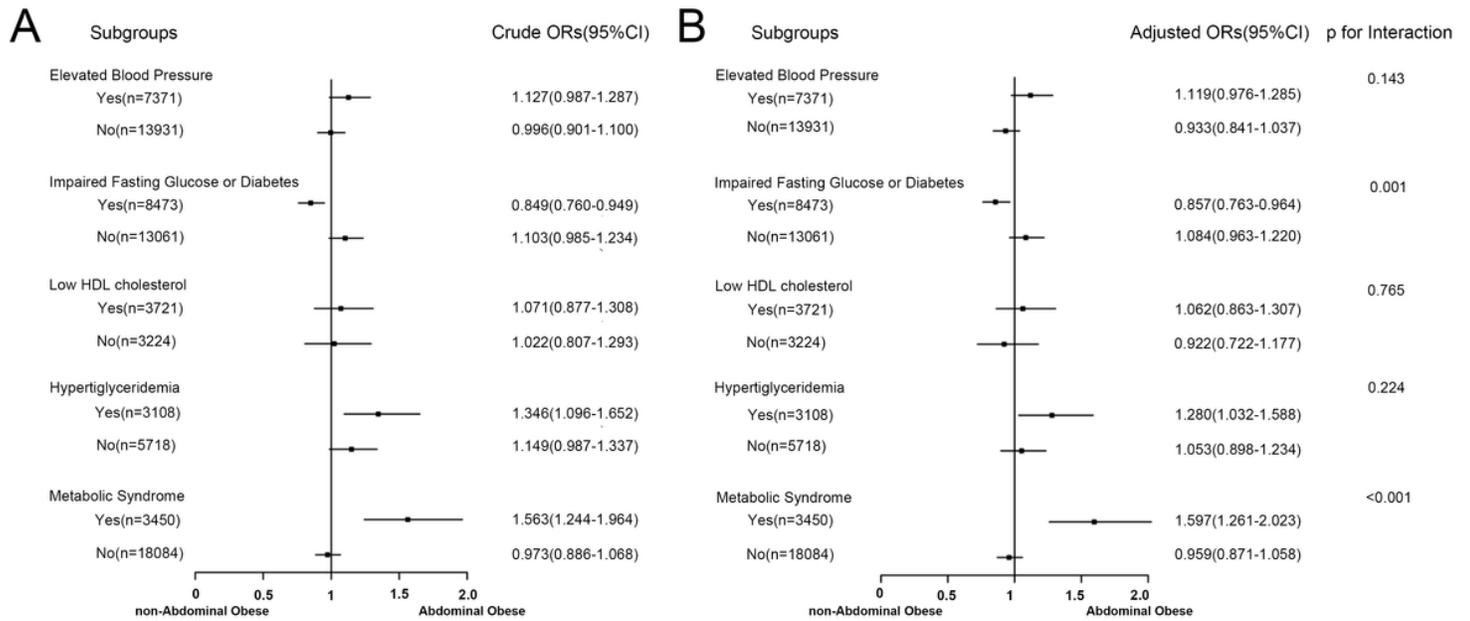


Number at risk

Non Abdominal_ob	14454	12417	12165	12087	12032	12007	11990
Abdominal_ob	7080	6142	5931	5874	5853	5840	5826
	0	15	30	45	60	75	90

Figure 2

Cumulative 90-day mortality among 21534 patients with sepsis grouped by abdominal obesity.



**Figure 3**

Subgroup analysis of the association between abdominal obesity and 28-day mortality. Abbreviations: OR, odd ratios; CI, confidence interval; HDL, high density lipoprotein.

## Supplementary Files

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