Documentation of Body Mass Index is Associated with an Improvement of Mortality in Sepsis: Analysis of MIMIC-III Database

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Research

Keywords: body mass index, sepsis, mortality

Posted Date: September 20th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-895726/v1

Abstract

Purpose: While improving outcomes in septic patients is currently becoming one of the hot research topics, the contribution of a body mass index (BMI) medical record to altering outcomes among septic patients in intensive care units (ICU) has not been examined. This study was designed to examine the association of BMI record with mortality specifically in ICU septic patients.

Methods: The MIMIC-III database was employed to identify septic patients who had or had not measured height and weight to calculate BMI. Propensity score analysis was used to minimize confounders. The comparative risks of outcomes were further adjusted in the matched cohort with the use of a Cox proportional-hazards regression model. Kaplan-Meier survivor curve was plotted for outcomes in the propensity-score-matched cohort.

Results: Among 10418 eligible septic patients, 4157 patients who had measured height and weight (BMI group) and 4157 patients who had not measured height and weight (No-BMI group) had similar propensity score. Significant benefit in terms of hospital mortality was observed among BMI group, compared to No-BMI group (19.24% vs. 24.44%, p<0.001). 30-day mortality (20.30% vs. 26.36%, p<0.001) and 1 year mortality (38.66% vs. 44.17%, p<0.001) was significantly higher in No-BMI group.

Conclusions: In a general population of critically ill patients with sepsis, documentation of BMI is associated with an improvement of mortality

Introduction

Sepsis is a life-threatening organ dysfunction caused by a maladjusted host response to infection. Despite advances in anti-infective therapy and organ function support techniques, the fatality rate of sepsis is still as high as 30–70%[1, 2]. Sepsis has become the main cause of death in non-cardiac patients in ICU[3, 4]. Improving outcomes of septic patients is currently becoming one of the hot research topics. In these studies, an interesting idea emerges. Researchers found that patients with sepsis who were overweight or obese had better outcomes[5–8]. The phenomenon was known as obesity paradox, which means that overweight and obesity may be somewhat protective while running a higher risk of chronic disease and mortality than normal-weight individuals[9]. The exact mechanism of obesity paradox remains unclear. When reviewing the literature, we found that most of these studies were supported by retrospective data and randomized controlled trial data is sparse. It means that data quality and data missingness for unknown reasons would not be ignored. This study was designed to compare the prognostic difference between two groups (A. With BMI record, B. Without BMI record) in ICU patients with sepsis and prove that findings based on a group of selected populations is controversial.

Method

Database

The study used Medical Information Mart for Intensive Care III (MIMIC-III) database, which is a large, freely available database comprising de-identified health-related data associated with over forty thousand patients who stayed in critical care units of the Beth Israel Deaconess Medical Center between 2001 and 2012. The latest version of MIMIC-III was MIMIC-III v1.4, which comprises over 58,000 hospital admissions. The database, although de-identified, contains detailed information regarding the clinical care of patients. All these data were collected during routine clinical care and data collection was not visible to caregivers, which mean there was no interference with their workflow[10]. The access to the database was approved after completion of the National Institutes of Health (NIH) web-based training course named “Protecting Human Research Participants” by the author Yuting Wang (ID: 7188960). Informed consent was waived because this was a study of the clinical database.

Selection Of Population

The inclusion criteria were first ICU admission of patients over 16 years old with a diagnosis of sepsis based on the Angus criteria of sepsis[11]. Data from subsequent admissions were excluded if patients were admitted to ICU more than once (Fig. 1).

Variables

The following clinical information was collected: age, gender, care unit type, weight, height, comorbidities defined by Elixhauser et al[12] combined in a composite score by van Walraven et al[13], hereafter referred to as the Elixhauser-van Walraven Comorbidity Index (EVCI),the use of mechanical ventilation, vasopressor and dialysis in the first 24 hours of ICU admission, death from any causes during the hospital stay, after a follow-up 30 days and a follow-up 1 year, length of stay in ICU. The severity of illness was represented by SAPS-II and SOFA scores. According to the analysis in the calculation of the simplified acute physiology score (SAPS-II) and the sequential organ failure assessment (SOFA) score. ICU values were defined as the most abnormal laboratory result in the first 24 hours of ICU admission. BMI was calculated as the weight (in kilograms) divided by the square of the height (in meters). All BMIs are presented in Kg/m^2.

Study Cohort

The patients who had height and weight documentation less than 24h before their ICU admission or during their ICU stay were categorized as the BMI group, while the remaining patients making up the no BMI group (Fig. 1).

Statistics

The propensity score match method was applied to identify a cohort of patients with similar baseline characteristics. The propensity score was estimated with the use of a multivariable logistic regression model with BMI status as the dependent variable and all the baseline characteristics outlined in Table 1 as covariates. A 1:1 matching protocol without replacement was used with a caliper width equal to 0.02 of the standard deviation of the logit of the propensity score. Standardized differences were estimated for all the baseline covariates before and after matching to assess prematch imbalance and postmatch balance. Standardized differences of less than 5% for a given covariate indicate a relatively small imbalance. In the matched cohort, paired comparisons were performed with the use of McNemar's test for binary variables and a paired Student's t-test or paired-sample test for continuous variables. The comparative risks of outcomes were further adjusted for in the matched cohort with the use of a Cox proportional-hazards regression model that was stratified on the matched pair to preserve the benefit of matching. Kaplan-Meier survivor curve was plotted for outcomes in the propensity-score-matched cohort.

Table 1
Comparison of the basic clinical characteristics between the original cohort and the adjusted (weighted) cohort

Covariate	Original cohort			Matched cohort		
	BMI	No-BMI	P-value	BMI	No-BMI	P-value
N	4347	6071		4157	4157	
Gender (male, %)	54.36	51.62	0.006	53.36	53.47	0.947
Age (≥ 65, %)	56.02	58.91	0.003	56.94	56.60	0.757
Care Unit (MICU, %)	49.76	55.44	< 0.001	51.34	51.60	0.809
Comorbidity_index	8.69(7.69)	8.29(7.42)	0.008	8.48(7.62)	8.64(7.55)	0.347
SOFA	5.99(3.62)	5.29(3.50)	< 0.001	5.78(3.47)	5.82(3.72)	0.489
SAPS-II	42.37 (14.69)	41.37 (15.20)	< 0.001	42.15 (14.68)	42.17 (15.63)	0.957
Severe sepsis(%)	25.47	23.85	0.059	25.21	25.11	0.919
Septic shock(%)	17.09	15.85	0.090	17.01	17.06	0.953
Interventions						
Mechanical ventilation use (1st 24 h) (%)	61.08	51.74	< 0.001	59.30	59.23	0.947
Vasopressor use (1st 24 h) (%)	41.68	29.95	< 0.001	39.04	39.62	0.590
Dialysis use (1st 24 h) (%)	5.48	4.28	0.005	4.93	5.05	0.801
Length of stay in ICU (day)	8.43 (9.68)	6.79 (8.77)	< 0.001	8.20 (9.51)	7.32 (9.23)	< 0.001
In-hospital mortality (%)	19.60	23.01	< 0.001	19.24	24.44	< 0.001
30-day mortality (%)	20.43	25.54	< 0.001	20.30	26.36	< 0.001
1 year mortality (%)	38.81	43.53	< 0.001	38.66	44.17	< 0.001

Results

The study identified 10418 patients who met the inclusion criteria, of whom 4347 had documentation of height and weight, and 6071 had no documentation. Before propensity-score matching, there were differences between the two groups in several of the baseline variables (Table 1). With the use of propensity-score matching, 4157 patients who had documentation of height and weight (BMI group) were matched with 4157 patients who had no documentation (No-BMI group). After matching, the standardized differences were less than 5% for all variables, indicating only small differences between the two groups (Table 1).

BMI group was associated with significantly lower risks of in-hospital death (19.24% vs. 22.44%; hazard ratio, 0.752; 95% confidence interval [CI], 0.685 to 0.827; $P < 0.001$), 30-day mortality (20.30% vs. 26.36%; hazard ratio, 0.789; 95% CI, 0.717 to 0.867; $p < 0.001$) and 1 year mortality (38.66% vs. 44.17%; hazard ratio, 0.859; 95% CI, 0.802 to 0.921; $p < 0.001$) (Table 2 and Fig. 2).

Table 2
Risk of primary outcomes in the propensity-score-matched cohort

Outcome	No. of patients with event	Event rate (%)	Hazard ratio (95% CI)	P-value
In-hospital mortality				
BMI	800	19.24	0.752(0.685–0.827)	< 0.001
No-BMI	1016	24.44	Reference	
30-day mortality				
BMI	844	20.30	0.789(0.717–0.867)	< 0.001
No-BMI	1086	26.36	Reference	
1 year mortality				
BMI	1607	38.66	0.859(0.802–0.921)	< 0.001
No-BMI	1820	44.17	Reference	

Discussion

When using the propensity score match method to balance variables, effectively control confounding bias, the missing data turn out to be of great significance. In this study, it turns out to be that septic patients with BMI documentation were associated with significantly lower risks of death. If samples with default are simply excluded as in other retrospective studies, the accuracy of the results will be questioned. Patients without documentation of height and weight were associated with significantly higher risks of death. These group of patients are often ignored or excluded in retrospective studies. As the saying goes, “the dead can’t talk”, there may be a survivor bias caused by the silent data in those retrospective research results. Thus, obesity paradox proved by a group of selected populations who obviously have better outcomes is arguable. Obese patients have a greater prevalence of comorbid conditions that may affect outcomes, and they are faced with a new set of care challenges in ICU, for example, airway management, pharmacology, and nutrition management. So, clinicians quite often assume that obese patients in ICU may be faced with poorer outcomes and pay more attention to them. Therefore, it is too early to conclude that obesity paradox exists in patients with sepsis.

Moreover, in those retrospective studies on the obesity paradox, BMI was used as the standard for defining and diagnosing obesity. There is a sense in which obesity paradox seems to be “BMI paradox” from this aspect. BMI only used the ratio of height to weight to reflect the degree of obesity. It could not truly reveal the distribution and accumulation degree of adipose tissue in obese patients, which may be one of the important reasons for the "obesity paradox" in sepsis. With the in-depth study of the anatomical distribution, tissue structure, and biological function of adipose tissue, visceral obesity is closely related to the risk of death in patients with sepsis. Pisitsak et al. retrospectively analyzed 257 septic patients who had undergone abdominal CT, measured the Visceral Adipose Tissue (VAT) and Subcutaneous Adipose Tissue (SAT) area, and calculated the ratio. It was found that the increased VAT/SAT ratio increased the risk of death in septic patients, and there was no significant correlation with BMI. Furthermore, patients with VAT/SAT > 1.21 had longer mechanical ventilation time, renal replacement treatment time and ICU stay time. They also found that the ratio of pro-inflammatory cytokine IL-8 to anti-inflammatory cytokine IL-10 was also higher in septic patients with high VAT/SAT, which indicated that VAT accumulation is a high-risk factor for poor prognosis in septic patients, and VAT increase in obese patients may lead to increased inflammatory response in the body[14]. Other indices such as waist circumference[15], waist-to-hip ratio[15], and body fat ratio[16], could also truly reflect the degree of obesity and truly reveal the distribution and accumulation degree of adipose tissue in obese patients, which may be more suitable for studying “obesity paradox” than BMI.

Obesity is a highly heterogeneous group of diseases[17–19], obesity paradox in sepsis hides an "inaccuracy" in obesity classification. Some researchers[5, 20] remind that the obesity paradox in critically ill patients is not a phenomenon that fits all cases. The obesity paradox in critical patients should be specifically interpreted in a variety of conditions. The pathophysiological mechanism of obesity should be deeply explored in basic research and clinical trials, to provide new ideas for revealing the pathogenesis of sepsis conforming to clinical characteristics, which are of great clinical transformation value. It is too early to tell that obesity paradox exists in septic patients especially drawn from retrospective study in which missing data are deleted roughly.

Some limitations need to be acknowledged in this study. The study was a non-randomized, observational study, due to the retrospective nature of the study, hence suffers from potential selection and ascertainable bias despite robust propensity-score matching. The variables which were not captured in this study may affect the outcomes. Furthermore, as most of the studies, this study uses BMI to assess critical patients’ body shape or composition while critically ill patients may be reported an incorrect BMI due to immobilization. BMI does not assess body composition, which may misclassify critically ill patients. For example, aggressive fluid resuscitation could elevate BMI, thereby misclassify sicker patients as obese. While some chronically ill patients may be reported an artificially low BMI, which is resulted from substantial muscle wasting and a relatively high ratio of adipose tissue to lean muscle mass. A better index to assess body composition and predict the mortality of critically ill patients need to be explored.

Conclusions

In conclusion, the missing data contain a lot. In a general population of critically ill patients with sepsis, documentation of BMI is associated with an improvement of mortality. The obesity paradox is arguable in a cohort of septic patients. Scientific methods are needed to gain a clear insight into this paradox.

Declarations

- **Ethics approval and consent to participate**

Informed consent was waived because this was a study of clinical database. The access to the database was approved after completion of the National Institutes of Health (NIH) web-based training course named “Protecting Human Research Participants” by the author Yuting Wang (ID: 7188960)

- **Consent for publication**

Not applicable

- **Availability of data and material**

Please contact author for data requests

- **Funding**

There is no financial support used for the study.

• **Authors' contributions**

Yuting Wang carried out the concepts, design, definition of intellectual content and conceived the idea for the article and manuscript editing. Xiaoming Lin and Xiangyu Hong performed data acquisition and statistical analysis the author approved the final manuscript. Ting Huang, Rongcheng Xie, Xuefeng Lin and Lianfang Zhang carried out literature search and manuscript preparation. Jiefei Ma carried out manuscript review and polish. All authors read and approved the final manuscript.

- **Acknowledgements**

Not applicable

- **Conflict of interest statement**

All authors declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in the manuscript entitled “Documentation of body mass index is associated with an improvement of mortality in sepsis: analysis of MIMIC-III database”.

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Figures

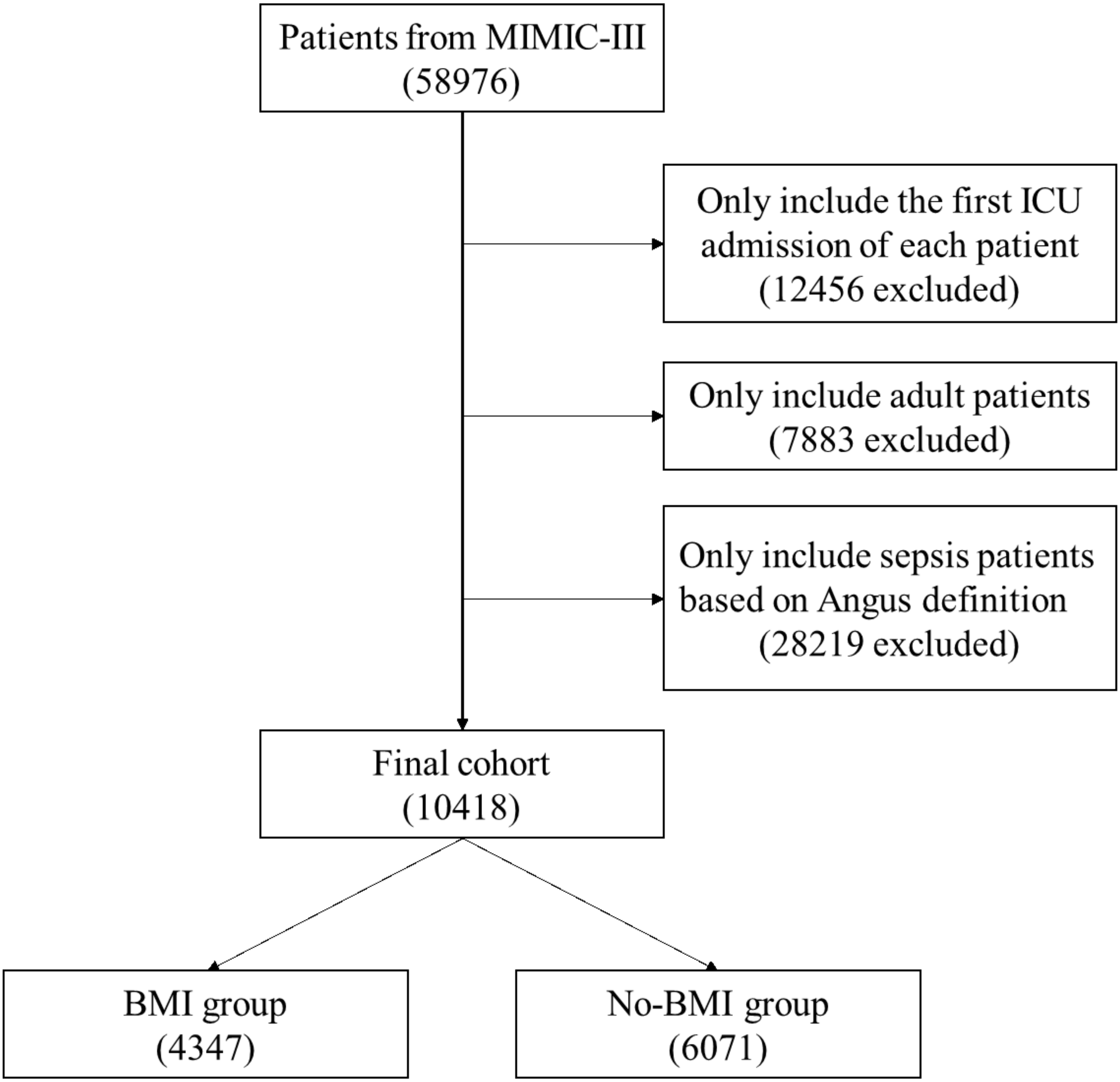

Figure 1

Study cohort. Illustration of inclusion and exclusion criteria as utilized to select the final cohort of 10418 patients

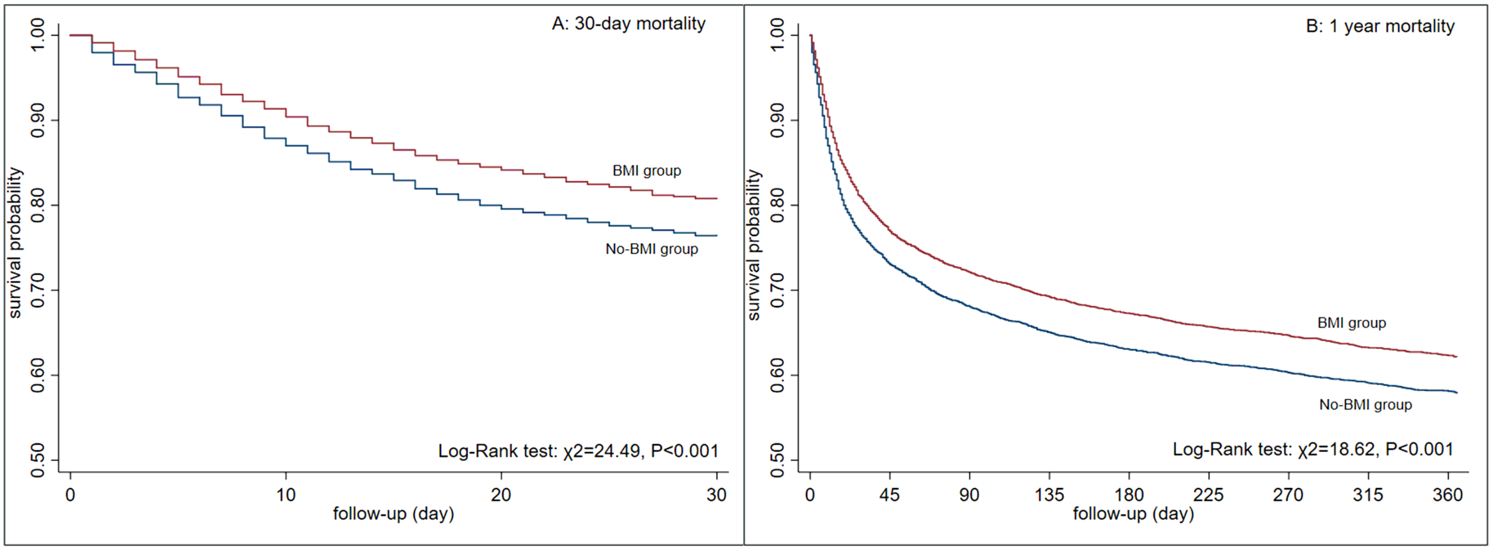

Figure 2

Kaplan-Meier survivor curve of outcomes in the propensity-score-matched cohort