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Association between low body mass index and increased 28-day mortality of severe sepsis in Japanese cohorts

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Current research regarding the association between body mass index (BMI) and altered clinical outcomes of sepsis in Asian populations is insufficient. We investigated the association between BMI and clinical outcomes using two Japanese cohorts of severe sepsis (derivation cohort, Chiba University Hospital, n = 614; validation cohort, multicenter cohort, n = 1561). Participants were categorized into the underweight (BMI < 18.5) and non-underweight (BMI ≥ 18.5) groups. The primary outcome was 28-day mortality. Univariate analysis of the derivation cohort indicated increased 28-day mortality

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trend in the underweight group compared to the non-underweight group (underweight 24.4% [20/82 cases] vs. non-underweight 16.0% [85/532 cases]; $p = 0.060$). In the primary analysis, multivariate analysis adjusted for baseline imbalance revealed that patients in the underweight group had a significantly increased 28-day mortality compared to those in the non-underweight group ($p = 0.031$, adjusted odds ratio [OR] 1.91, 95% confidence interval [CI] 1.06–3.46). In a repeated analysis using a multicenter validation cohort (underweight n = 343, non-underweight n = 1218), patients in the underweight group had a significantly increased 28-day mortality compared to those in the non-underweight group ($p = 0.045$, OR 1.40, 95% CI 1.00–1.97). In conclusion, patients with a BMI < 18.5 had a significantly increased 28-day mortality compared to those with a BMI ≥ 18.5 in Japanese cohorts with severe sepsis.

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection[1]; the excessive spillover of humoral mediators, including interleukin (IL)-6, into the systemic circulation is a well-known component of the dysregulated response[2]. Body mass index (BMI), which is a measure of body fat, is associated with an altered inflammatory response[3]. BMI is a non-invasively measurable physical characteristic and clinically practical variable; therefore, greater understanding of the relationship between BMI and altered clinical outcomes may contribute to improvements in basic sepsis care[4].

A recent systematic review found eight studies investigating whether BMI was associated with altered outcome of sepsis; however, all studies were conducted in either Europe or North America[5]. The systematic review concluded that patients with an increased BMI improved survival following sepsis[4,6]. By contrast, patients with a low BMI significantly increased blood IL-6 levels compared to those with a high BMI in North America[3]. However, studies regarding BMI in sepsis in Asian populations are limited; after the publication of the systematic review, a single-center study of sepsis with a small sample size in China reported that patients with a low BMI had increased mortality[7]. Non-obese patients were more common in Asian countries than in Europe and North America[8–10].

Thus, we tested the hypothesis that patients with a lower BMI have worse clinical outcomes through an altered inflammatory response using large Japanese cohorts of severe sepsis. The primary outcome was 28-day mortality, and blood IL-6 levels were measured in the derivation cohort.

Methods

Study setting and patients.
This observational study deployed the following severe sepsis cohorts. The methods were conducted in accordance with the Declaration of Helsinki and relevant guidelines.

Derivation cohort: a single-center cohort.
Patients admitted to the intensive care unit (ICU) at Chiba University Hospital, Japan, between October 2012 and May 2019 were retrospectively screened, and patients with severe sepsis were assessed for eligibility[11]. Patients who had missing data regarding BMI and mortality were excluded.

Validation cohort: multicenter cohorts.
The validation cohort consisted of Japanese Association for Acute Medicine Sepsis Registry (JAAMSR) and Focused Outcomes Research in Emergency Care in Acute Respiratory Distress Syndrome, Sepsis, and Trauma (FORECAST) cohorts. These two cohorts were multicenter, prospective, observational studies conducted by the Japanese Association for Acute Medicine (JAAM) without an overlapping duration for patient enrollment. JAAMSR recruited patients with severe sepsis from 15 ICUs in Japan between June 2010 and May 2011. FORECAST, which followed JAAMSR and was conducted by the JAAM, enrolled study participants with severe sepsis from 59 ICUs in Japan between January 2016 and March 2017. We made the decision to combine the two cohorts with the aim of strengthening the robustness. Because our institution had participated in FORECAST, the population that overlapped with the derivation cohort was removed from the validation cohort.

Data collection and definition.
We chose our normal BMI range in accordance with the World Health Organization (WHO) classification (18.5 ≤ BMI < 25.0). The WHO classification has two high BMI categories (25.0 ≤ BMI < 30.0 and BMI ≥ 30.0). However, due to the small sample size of the highest BMI category (BMI ≥ 30.0, 7.3% in the derivation cohort), we combined the two high BMI categories. We first screened for differences in mortality between the abnormal BMI (underweight, BMI < 18.5 or overweight, BMI ≥ 25.0) and normal (18.5 ≤ BMI < 25.0) groups in the derivation cohort. Significant discovery results were tested for replication and generalizability in a multicenter validation cohort.

Blood IL-6 levels in the derivation cohort were rapidly measured after blood sample collections on days 1, 2, and 3 at the clinical laboratory in Chiba University Hospital using rapid measurement systems (IL-6, Roche Diagnostics, Tokyo, Japan)[12]. Raw data were converted into a logarithmic scale for analysis.

Severe sepsis and septic shock were defined according to the Sepsis-2 criteria[11]. All patients received treatment according to the international guidelines for the management of severe sepsis and septic shock[13,14].

Statistical analysis.
Data are presented as medians (quartiles). Categorical data were analyzed using the Pearson's chi-square test. The Mann–Whitney U test or Kruskal–Wallis test was used for unpaired comparisons depending on the number of groups.

	Underweight (BMI < 18.5) (n = 82)	Non-underweight (BMI ≥ 18.5) (n = 532)	p value
Age, yr	70 (57–77)	69 (61–76)	0.62
Male sex, n (%)	51 (62.2)	355 (66.7)	0.41
Body mass index	17.3 (16.0–17.8)	23.3 (20.9–26.3)	< 0.0001
Site of infection, n (%)			0.33
Lung	39 (47.6)	207 (38.9)	
Intra-abdominal	24 (29.3)	162 (30.5)	
Urinary tract	8 (9.8)	44 (8.3)	
Skin and soft tissue	4 (4.9)	56 (10.5)	
Others	7 (8.5)	63 (11.8)	
Comorbidity, n (%)			
Diabetes mellitus	12 (14.6)	152 (28.6)	0.008
Stroke	5 (6.1)	17 (3.2)	0.18
Malignancy	29 (35.4)	153 (28.8)	0.22
Heart failure	10 (12.2)	48 (9.0)	0.36
Chronic kidney disease	8 (9.8)	40 (7.5)	0.48
Liver disease	7 (8.5)	33 (6.2)	0.42
Chronic lung disease	8 (9.8)	25 (4.7)	0.059
Septic shock, n (%)	41 (50.0)	252 (47.4)	0.65
SOFA score	11 (9–14)	12 (9–15)	0.38
APACHE II score	29 (24–36)	29 (23–36)	0.72
Mechanical ventilation, n (%)	38 (46.3)	226 (42.5)	0.51
Catecholamine, n (%)	51 (62.2)	329 (61.8)	0.95
Laboratory data on day 1			
White blood cell ($\times 10^3/mm^3$)	8.5 (3.4–14.0)	11.5 (5.9–17.0)	0.012
Creatinine (mg/dL)	1.3 (0.7–2.2)	1.4 (0.9–2.6)	0.10
Lactate (mmol/L)	2.5 (1.5–5.7)	2.4 (1.4–4.8)	0.49

Table 1. Baseline characteristics in the derivation cohort. Data are presented as median (quartile). *BMI* body mass index, *SOFA* sequential organ failure assessment, *APACHE* acute physiology and chronic health evaluation.

Multivariate logistic regression was used to analyze 28-day mortality by the BMI category. We selected this approach to adjust for potential baseline imbalances, including age, sex, the Sequential Organ Failure Assessment (SOFA) score, and site of infection. We compared blood IL-6 levels measured on days 1, 2 and 3 between the BMI categories using a generalized estimating equation.

Statistical significance was determined by a two-tailed *p* value < 0.05. Data were analyzed using SPSS software version 24.0 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA).

Ethical approval and consent to participate. The institutional review board at Chiba University Graduate School of Medicine approved this study and waived the need for written informed consent from subjects or their legal surrogates.

Results
Baseline patient characteristics. Of the 785 patients treated during the study period, 614 were included in this analysis (Supplementary Fig. S1 online). Participants were categorized by BMI into the following groups: underweight (n = 82), normal weight (n = 350), and overweight (n = 182). No significant differences were observed in baseline characteristics, except increased probability of diabetes mellitus, higher white blood cell counts, and serum creatinine levels in the overweight group (Supplementary Table S1 online).

Primary outcome in the derivation cohort. The 28-day mortality rate was 24.4%, 15.7%, and 16.5% in the underweight, normal, and overweight groups, respectively. According to the screening analysis, we chose the potential threshold of BMI 18.5 and further analyzed between the underweight (BMI < 18.5) and non-underweight (BMI ≥ 18.5) groups (Table 1). Univariate analysis revealed a non-significant trend of increased 28-day mortality in the underweight group (24.4%) compared to the non-underweight group (16.0%) (*p* = 0.060).

Multivariate logistic regression analysis to adjust for potential baseline imbalances including age, male sex, the SOFA score, and site of infection indicated that patients with severe sepsis in the underweight group had a significantly increased 28-day mortality compared to those in the non-underweight group (*p* = 0.031, adjusted odds ratio [OR] 1.91, 95% confidence interval [CI] 1.06–3.46) (Table 2A).

Variable	Odds ratio	95% CI	p value
A. Derivation cohort			
Age-per year	1.02	1.00–1.04	0.008
Male sex	0.82	0.50–1.34	0.43
SOFA	1.18	1.11–1.25	< 0.0001
Site of infection			
Lung	1.00	Reference	
Intra-abdominal	0.45	0.26–0.80	0.006
Urinary tract	0.50	0.20–1.26	0.14
Skin and soft tissue	0.48	0.19–1.22	0.12
Others	1.04	0.52–2.09	0.89
Underweight (BMI < 18.5)	1.91	1.06–3.46	0.031
B. Validation cohort			
Age-per year	1.02	1.01–1.03	< 0.0001
Male sex	1.07	0.79–1.44	0.64
SOFA	1.22	1.17–1.27	< 0.0001
Site of infection			
Lung	1.00	Reference	
Intra-abdominal	0.72	0.50–1.05	0.092
Urinary tract	0.45	0.28–0.74	0.002
Skin and soft tissue	0.84	0.51–1.40	0.51
Others	1.27	0.83–1.94	0.26
Type of cohort			
JAAMSR	1.00	Reference	
FORECAST	0.72	0.54–0.96	0.26
Underweight (BMI < 18.5)	1.40	1.00–1.97	0.045
C. Combined cohorts			
Age-per year	1.02	1.01–1.03	< 0.0001
Male sex	1.00	0.78–1.29	0.64
SOFA	1.20	1.16–1.24	< 0.0001
Site of infection			
Lung	1.00	Reference	
Intra-abdominal	0.61	0.45–0.84	0.002
Urinary tract	0.45	0.29–0.69	< 0.0001
Skin and soft tissue	0.73	0.47–1.13	0.16
Others	1.19	0.83–1.70	0.34
Type of cohort			
JAAMSR	1.00	Reference	
Single center cohort	0.42	0.30–0.59	< 0.0001
FORECAST	0.77	0.58–1.03	0.083
Underweight (BMI < 18.5)	1.50	1.12–2.00	0.006

Table 2. Multivariate logistic regression analysis of 28-day mortality. *CI* confidence interval, *SOFA* sequential organ failure assessment, *BMI* body mass index.

Primary outcome in the validation cohort. To validate the increased mortality of the underweight group, we deployed a validation cohort enrolling 1561 patients (underweight n = 343, non-underweight n = 1218) (Supplementary Fig. S2 online). There were significant differences in age, site of infection, proportion of patients with diabetes mellitus and chronic lung disease, white blood cell count, and serum creatinine levels according to BMI classifications (Supplementary Table S2 online). A repeated multivariate analysis indicated that patients with severe sepsis in the underweight group had a significantly increased 28-day mortality compared to those in the non-underweight group (p = 0.045, adjusted OR 1.40, 95% CI 1.00–1.97) (Table 2B). To rule out the bias due to the comorbidities, we performed another logistic regression model using Charlson co-morbidities index with the data set of FORECAST study. As a result, the underweight group showed consistent worse outcome after correction with comorbidities.

Primary outcome in the combined cohorts. To investigate the accuracy of the findings in the derivation and validation cohorts, we combined the two cohorts enrolling 2175 patients (underweight n = 425, non-underweight n = 1750). There were significant differences in age, site of infection, proportion of patients with
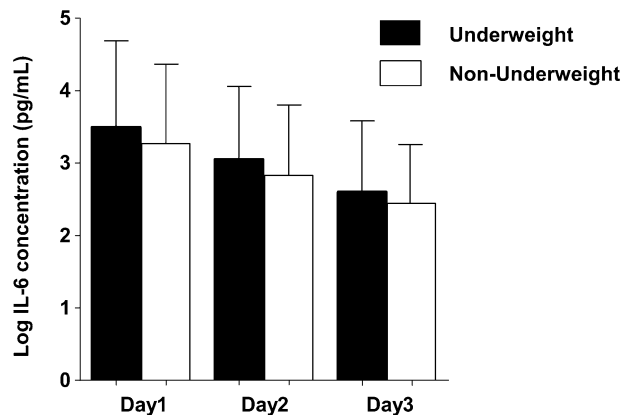
Figure 1. Comparison of blood IL-6 levels between the underweight (BMI < 18.5) and non-underweight (BMI ≥ 18.5) group at days 1, 2, and 3. There was a non-significant trend of increased blood IL-6 levels in the underweight group compared to the non-underweight group in a generalized estimating equation using log-converted serum IL-6 concentration at days 1, 2, and 3 ($p = 0.088$, adjusted OR 1.24, 95% CI 0.96–1.60). *IL* interleukin, *BMI* body mass index.

diabetes mellitus, stroke, and chronic lung disease, white blood cell count, and serum creatinine levels between the underweight and non-underweight group (Supplementary Fig. S3 online). The underweight group remained a significant predictor for 28-day mortality in the logistic regression model ($p = 0.006$, adjusted OR 1.50, 95% CI 1.12–2.00) (Table 2C).

IL-6 analysis in the derivation cohort. Data regarding blood IL-6 levels were available for 413 of the 614 study subjects. There was a non-significant trend of increased blood IL-6 levels in the underweight group compared to the non-underweight group, as determined through a generalized estimating equation using log-converted blood IL-6 levels from days 1, 2, and 3 ($p = 0.088$, adjusted OR 1.24, 95% CI 0.96–1.60) (Fig. 1). To evaluate the predictive accuracy of the logistic regression model after adjustment with blood IL-6 levels, we performed another analysis predicting 28-day mortality. While the underweight group showed a consistent significance as an independent predictor for 28-day mortality with either of IL-6 levels, only IL-6 levels at day3, but not IL-6 levels at day1 and day2, was a significant variable for predicting the outcome during sepsis (Supplementary Table S4 online).

Discussion

The present study of severe sepsis, using two large Japanese cohorts, found that patients with a BMI < 18.5 had an increased 28-day mortality. There was a trend of increased blood IL-6 levels in patients with a BMI < 18.5 during the initial 3 days.

Over the years, whether BMI was associated with altered mortality of patients with severe sepsis has been rarely reported in Asian population; we only found one single-center study with a small sample size (sepsis n = 178) conducted in a Chinese population. In the Chinese study, patients with a BMI < 18.5 had the highest 90-day mortality (66.7%) compared to the other subgroups with BMI ≥ 18.5 (18.2–48.0%)[7]. In accordance with these findings, the present study that enrolled 2175 patients with severe sepsis in total verified the increased mortality in patients with a BMI < 18.5. While the recent meta-analysis of BMI studies in Europe, North America, and Australia highlighted the benefit of obesity in sepsis[15], two sepsis studies in North America revealed patients with a low BMI had increased mortality, which were in line with the results of this study[16,17]. Notably, the underweight group only accounted for 4.9–6% of the North American study, whereas our two cohorts included more than three times (19%) the percentage of patients with low BMI[16,17]. Therefore, our study is potentially more robust with regard to the conclusions derived from the data.

Differences in physical characteristics between the Asian and Western population, including body fat and muscle mass, have been widely recognized[8,9]. As such, the average BMI of 22.1 in the present study was lower than the BMI reported in previous European and North American studies (range 25.1–26.1)[18,19] but similar to the median BMI of 22.5 that was previously reported in critically ill Japanese patients[20]. A single-center Japanese study including all critically ill patients (n = 1,616, sepsis fraction unknown) revealed that patients with a BMI < 18.5 had a significantly increased mortality compared to those with a BMI ≥ 18.5[20], thus supporting the use of the BMI < 18.5 threshold for distinguishing low BMI groups in Asian populations[10].

Plausible mechanisms postulated by bench studies could strengthen the relationship between low BMI populations and worse outcomes following sepsis. Lipoproteins and adipose tissue have a protective effect on the survival of sepsis patients through binding pathogen lipids and sequestering lipopolysaccharide (LPS), which could decrease systemic inflammation[21,22]. As proof of these interactions, our study highlighted the trend of higher blood IL-6 levels in patients with a lower BMI. An elevation of blood IL-6 levels, used for classifying severity of sepsis[23–25], reinforces the plausibility of poor outcomes in patients with a low BMI. Furthermore, in accordance

with our results, Wacharasint et al. also found that in Canadian population, patients with a BMI < 25 had worse outcomes and higher blood IL-6 levels[3].

This study has limitations that need to be addressed. First, we analyzed data retrospectively. Second, we used BMI as a surrogate value to assess the percentage of body fat, but this might not be accurate for the evaluation of metabolic status without more detailed information. Therefore, adding other measurements, such as muscle volume or lipid markers, would be greatly beneficial to further understand the effect of metabolism on clinical outcomes following sepsis.

Conclusions
In Japanese cohorts of severe sepsis, patients with a BMI < 18.5 had a significantly increased 28-day mortality compared to those with a BMI ≥ 18.5.

Data availability
The datasets used and analyzed during our study are available from the corresponding author upon reasonable request.

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Author contributions

T.O., S.K., T.S., and T.N., study concept and design, acquisition of data, statistical analysis and interpretation of data, drafting the manuscript, and critical revision of the manuscript for important intellectual content. All other authors, acquisition of data and interpretation of data, and revising the article critically for important intellectual content. All authors read and approved the final manuscript.

Competing interests

Additional information

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