

Body Mass Index and Ventilator Dependence in Critically Ill Subjects in Japan: A Cohort Study Using a Nationwide Database

Jun Fujinaga, Etsushi Suzuki, Hiromasa Irie, and Mutsuo Onodera

BACKGROUND: Body mass index (BMI) can be an important indicator for health outcomes among critically ill patients. However, the association between BMI and ventilator dependence at ICU discharge among these patients remains unknown. We aimed to evaluate the association between BMI at ICU admission and ventilator dependence at the time of ICU discharge. As secondary outcomes, we used ICU mortality, hospital mortality, and implementation of tracheostomy during ICU stay. **METHODS:** This is a retrospective cohort study. The data were derived from The Japanese Intensive Care Patient Database, a nationwide ICU database in Japan. We included all patients in the registry who were ≥ 16 y old, received mechanical ventilation, and were admitted to an ICU between April 2018 and March 2019. On the basis of their BMI at ICU admission, subjects were classified as underweight ($< 18.5 \text{ kg/m}^2$); normal weight ($\geq 18.5 \text{ kg/m}^2$ to $< 23 \text{ kg/m}^2$); overweight ($\geq 23 \text{ kg/m}^2$ to $< 27.5 \text{ kg/m}^2$); or obese ($\geq 27.5 \text{ kg/m}^2$). **RESULTS:** Among 11,801 analyzed subjects, 388 (3.3%) subjects were ventilator-dependent at ICU discharge. Compared with normal-weight subjects, the risk for ventilator dependence at ICU discharge increased among underweight subjects even after adjusting for potential confounders and inter-ICU variance in 2-level multivariable logistic regression analysis (odds ratio 1.46 [95% CI 1.18–1.79]). Although obesity was also associated with a higher risk of ventilator dependence, the association was less clear (odds ratio 1.10 [95% CI 0.99–1.22]). The risk of ICU mortality, hospital mortality, and implementation of tracheostomy also increased in underweight subjects. **CONCLUSIONS:** Critically ill underweight subjects had a higher risk of ventilator dependence at ICU discharge compared to normal-weight subjects, even after adjusting for potential confounders and inter-ICU variance. The association between BMI and ventilator dependence should be examined using information on subjects' nutritional status and frailty in further studies. **Key words:** body mass index; critical illness; underweight; obesity; mechanical ventilation; ventilator dependence. [Respir Care 0;0(0):1–●. © 0 Daedalus Enterprises]

Introduction

Body mass index (BMI) is associated with various health outcomes in the general population.^{1,2} For example, obesity is a risk factor for malnutrition, and obese people have higher risks for diabetes mellitus, cardiovascular disease, and mortality.^{1–3} BMI can be also an important indicator of health outcomes among critically ill patients. In these patients, being underweight is associated with inadequate nutritional status, impaired functional status, and increased mortality.⁴ Obesity is also associated with adverse events, including longer duration of mechanical ventilation and hospital length of stay, along with other morbidities.^{4,5} However, some studies have reported that obesity is associated with a lower risk of mortality among critically ill

subjects,^{6,7} and the effect of obesity on health outcomes is still unknown.

In examining the trajectory of obese patients, weaning failure or ventilator dependence is a significant issue,⁸ and its predictive factors have been extensively studied.^{9–12} Being underweight or overweight/obese would be important, predictive factors because they may indicate malnutrition or reduced respiratory system compliance, which can lead to ventilator dependence.¹³ Despite their significance, the associations between being underweight or obese/overweight and ventilator dependence during the acute phase of critical illness remain unknown. Accordingly, we aimed to evaluate the associations between BMI at ICU admission and ventilator dependence at the time of ICU discharge using a nationwide database in Japan.

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Methods**Study Design and Subjects**

The data in this study were derived from The Japanese Intensive Care Patient Database, which was established by the Japanese Society of Intensive Care Medicine to construct a high-quality ICU database as a national registry. The details of the registry are described elsewhere.¹⁴ Approval for this study was obtained from the institutional ethics committee at Kurashiki Central Hospital (No. 3356), and the need for informed consent was waived.

We included all patients in the registry who were ≥ 16 y old, received mechanical ventilation, and were admitted to an ICU between April 1, 2018, and March 31, 2019. We excluded patients who had already undergone tracheostomy before ICU admission, and whose data for height or weight were lacking. Patients whose BMI was $< 10 \text{ kg/m}^2$ or $> 50 \text{ kg/m}^2$ were excluded to ensure the accuracy of data entry. We also excluded patients who were discharged from the ICU on the same day of admission, were admitted for ICU procedures (eg, central venous catheter insertion or cardioversion), or were transferred from other hospitals.

Variables

We collected data that included subject demographics (ie, age, sex, height, weight, chronic organ insufficiency), admitting diagnoses, SOFA (Sepsis related Organ Failure Assessment) scores,¹⁵ elective or emergency surgery, implementation of tracheostomy during ICU stay, the day of tracheostomy, treatment during ICU stay, ICU and hospital length of stay, ICU mortality, and hospital mortality. Chronic organ insufficiency was defined on the basis of the Acute Physiology and Chronic Health Evaluation (APACHE) II and III, and the

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QUICK LOOK**Current knowledge**

Body mass index (BMI) can be an important indicator of health outcomes among critically ill patients. Being underweight or overweight/obese can be important predictive factors because they lead to malnutrition or reduced respiratory system compliance, respectively. However, the association between BMI and ventilator dependence at ICU discharge among these patients remains unknown.

What this paper contributes to our knowledge

This retrospective cohort study aimed to evaluate the association between BMI at ICU admission and ventilator dependence at the time of ICU discharge. Underweight critically ill subjects receiving mechanical ventilation had a higher risk of ventilator dependence at ICU discharge, even after adjusting for potential confounders and inter-ICU variance, compared to subjects who were normal weight.

Simplified Acute Physiology Score (SAPS) II.¹⁴ We also obtained the time of ICU discharge and the time of discontinuation of mechanical ventilation. If these times were the same, the subject was considered to have been receiving mechanical ventilation after ICU discharge. For subjects with multiple ICU admissions during the same hospitalization, we collected the data similarly as the first ICU admission.

BMI at ICU admission was calculated as the ratio of weight (kg) to squared height (m^2), and study subjects were classified according to the recommendation for the Asian population from the World Health Organization: underweight ($< 18.5 \text{ kg/m}^2$); normal weight ($\geq 18.5 \text{ kg/m}^2$ to $< 23 \text{ kg/m}^2$); overweight ($\geq 23 \text{ kg/m}^2$ to $< 27.5 \text{ kg/m}^2$); and obese ($\geq 27.5 \text{ kg/m}^2$).¹⁶

Our primary outcome of interest was ventilator dependence at ICU discharge, which was defined as tracheostomy placement during ICU stay and receiving mechanical ventilation at the last ICU discharge. As secondary outcomes, we used ICU mortality, hospital mortality, and implementation of tracheostomy during ICU stay.

Statistical Analysis

We performed descriptive analysis for subject characteristics and outcomes according to BMI categories. To compare the characteristics between the categories, we used the chi-square test for categorical variables and the Kruskal-Wallis test for the continuous variables.

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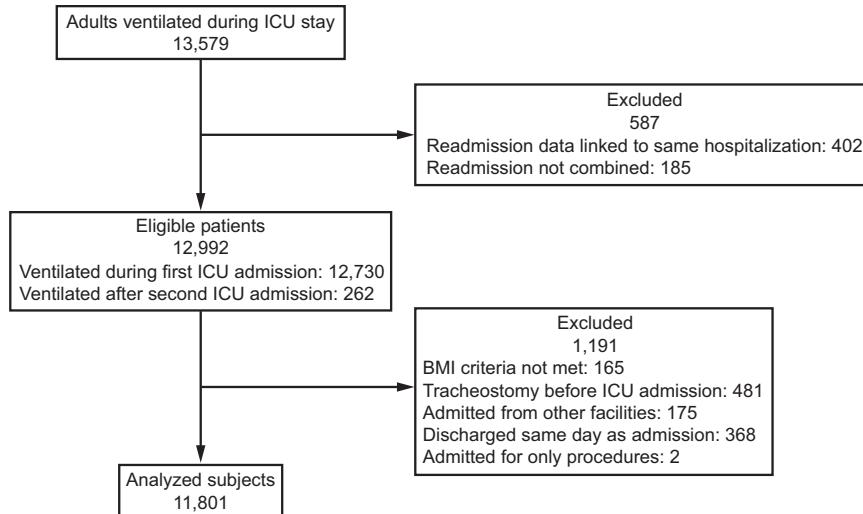


Fig. 1. Flow chart. BMI = body mass index.

The structure of our data was a 2-level hierarchy with subjects at level 1 nested within ICUs at level 2. To account for this data structure, we performed 2-level multivariable logistic regression analysis, adjusting for both subject-level and ICU-level variables as fixed effects and allowing for heterogeneity between ICUs. We first estimated an empty model (ie, model 1), which only included each ICU as a random intercept and allowed us to detect variances in the number of ventilator-dependent subjects between ICUs. An ICU-level random effect of the intercept was assumed to be normally distributed with a mean of zero. Thereafter we estimated model 2 to assess the association between BMI categories and ventilator dependence using subject-level and ICU-level variables.

As subject-level variables, we adjusted for age, sex, comorbidities, treatment during ICU stay (venovenous or venoarterial extracorporeal membrane oxygenation and continuous or intermittent renal replacement therapy), SOFA score, elective or emergency surgery, and admitting diagnoses. As ICU-level variables, we adjusted for the type of hospital (ie, academic or nonacademic), its number of beds, and the number of ICU beds. We used Markov chain Monte Carlo methods to obtain odds ratios and their 95% CIs for ventilator dependence at ICU discharge, ICU mortality, hospital mortality, and implementation of tracheostomy during ICU stay. In Markov chain Monte Carlo, the first 2,500 simulations were discarded as burn-in, and the remaining 10,000 were obtained. We used normal priors for the fixed effects and noninformative uniform priors for the variance of each ICU in the mixed-effects model. With regard to ICU-level variance, we calculated the median odds ratios.^{17,18}

We conducted 2 sensitivity analyses. First, we analyzed only who survived to ICU discharge. Second, we excluded subjects whose BMI was $> 40 \text{ kg/m}^2$. We also conducted a

stratified analysis by age groups ($< 65 \text{ y}$ and $\geq 65 \text{ y}$). All analyses were performed with Stata 16.1 (StataCorp, College Station, Texas). We considered a P value of $< .05$ (2-tailed) as statistically significant.

Results

We identified 13,579 records of eligible patients in 46 ICUs. Of the datasets from 587 readmissions, 402 were linked to datasets from the same hospitalization; others were excluded. After eliminating patients who met exclusion criteria, we included a total of 11,801 subjects for analysis (Fig. 1). The characteristics of subjects and participating ICUs are shown in Table 1 and Table 2. A total of 388 (3.3%) subjects underwent tracheostomy during their ICU stay and received mechanical ventilation at ICU discharge. Additional data and the risks of ventilator dependence in each ICU are shown in the supplementary materials (available at <http://www.rcjournal.com>).

Table 3 shows the results of the 2-level logistic regression models. After we examined the ICU-level variance in ventilator dependence with no explanatory variables (model 1), we modeled subject- and ICU-level variables simultaneously (model 2). In model 1, the median odds ratio was 1.95 (95% CI 1.62–2.46), which indicates that the ICU-level variance of the risk of ventilator dependence at ICU discharge is high. The median odds ratio in model 1 indicates that, if we select a subject in an ICU with a higher probability of ventilator dependence, the subject's odds of ventilator dependence is 1.95 times higher than that of a subject in an ICU with a lower probability of ventilator dependence. Even after adjusting ICU-level variables, being underweight was associated with ventilator dependence at ICU discharge (odds ratio 1.46 [95% CI 1.18–1.79]). The association between obesity and ventilator dependence was less clear. Sensitivity analyses

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Table 1. Subject Characteristics by Body Mass Index

	Total	Body Mass Index Category, kg/m ²				<i>P</i>
		Underweight (< 18.5)	Normal (≥ 18.5 to < 23)	Overweight (≥ 23 to < 27.5)	Obese (≥ 27.5)	
Subjects	11,801 (100)	1,596 (13.5)	4,962 (42.0)	3,834 (32.5)	1,409 (11.9)	
Body mass index, kg/m ²	22.4 (20.0–25.1)	17.2 (16.1–17.9)	21.0 (19.9–22.0)	24.7 (23.9–25.9)	29.6 (28.4–32.0)	
Male	7,459 (63.2)	822 (51.5)	3,057 (61.6)	2,688 (70.1)	892 (63.3)	< .001
Age, y	70 (60–78)	72 (62–79)	71 (62–78)	70 (60–77)	65 (52–74)	< .001
SOFA score	6 (4–9)	6 (4–9)	6 (4–9)	6 (5–9)	7 (5–9)	< .001
Underlying condition						
Heart failure	185 (1.6)	32 (2)	71 (1.4)	59 (1.5)	23 (1.6)	.45
Respiratory failure	151 (1.3)	56 (3.5)	58 (1.2)	27 (0.7)	10 (0.7)	< .001
Liver failure	64 (0.5)	5 (0.3)	23 (0.5)	23 (0.6)	13 (0.9)	.11
Liver cirrhosis	136 (1.2)	8 (0.5)	49 (1)	55 (1.4)	24 (1.7)	.004
Malignancies	409 (3.5)	74 (4.6)	196 (4)	95 (2.5)	44 (3.1)	< .001
Immunosuppressive state	655 (5.6)	163 (10.2)	298 (6)	143 (3.7)	51 (3.6)	< .001
Dialysis	702 (6)	111 (7)	356 (7.2)	173 (4.5)	62 (4.4)	< .001
Disease group						
Cardiovascular	6,168 (52.3)	635 (39.8)	2,562 (51.6)	2,213 (57.7)	758 (53.8)	< .001
Pulmonary	1,300 (11)	296 (18.6)	549 (11.1)	325 (8.5)	130 (9.2)	
Gastrointestinal/liver/other	2,633 (22.3)	468 (29.3)	1,126 (22.7)	743 (19.4)	296 (21)	
Neurogenic	1,276 (10.8)	164 (1.3)	548 (11)	392 (10.2)	172 (12.2)	
Trauma	424 (3.6)	33 (2.1)	177 (3.6)	161 (4.2)	53 (3.8)	
Emergency admission	6,099 (51.7)	962 (6.3)	2,503 (5.4)	1,851 (48.3)	783 (55.6)	< .001
Admission classification						
Non-operative	3,415 (28.9)	596 (37.3)	1,372 (27.7)	1,012 (26.4)	435 (3.9)	< .001
Emergency surgery	2,579 (21.9)	356 (22.3)	1,086 (21.9)	801 (2.9)	336 (23.9)	
Elective surgery	5,807 (49.2)	644 (4.4)	2,504 (5.5)	2,021 (52.7)	638 (45.3)	
Cardiac arrest before ICU admission	705 (6.0)	116 (7.3)	304 (6.1)	201 (5.2)	84 (6.0)	.035
ICU treatment						
IABP	574 (4.9)	42 (2.6)	207 (4.2)	231 (6)	94 (6.7)	< .001
Venoarterial ECMO	278 (2.4)	25 (1.6)	94 (1.9)	108 (2.8)	51 (3.6)	< .001
Venovenous ECMO	55 (0.5)	7 (0.4)	21 (0.4)	14 (0.4)	13 (0.9)	.060
IRRT or CRRT	1,647 (14)	240 (15)	722 (14.6)	484 (12.6)	201 (14.3)	.032
Ventilator dependence at ICU discharge	388 (3.3)	82 (5.1)	159 (3.2)	94 (2.5)	53 (3.8)	< .001
ICU mortality	883 (7.5)	161 (10.1)	335 (6.8)	266 (6.9)	121 (8.6)	< .001
Hospital mortality	1,620 (13.7)	343 (21.5)	664 (13.4)	413 (10.8)	200 (14.2)	< .001
Tracheostomy during ICU stay	797 (6.8)	157 (9.8)	336 (6.8)	206 (5.4)	98 (7.0)	< .001

Data are presented as *n* (%) or median (interquartile range).

SOFA = Sequential Organ Failure Assessment

AIDS = Acquired immunodeficiency syndrome

IABP = intra-aortic balloon pump

ECMO = extracorporeal membrane oxygenation

IRRT = intermittent renal replacement therapy

CRRT = continuous renal replacement therapy

Table 2. Characteristics of 46 Participating ICUs in Japan: 2018–2019

	Total	University Hospital	Non-academic
Facilities	46	22 (47.8)	24 (52.2)
ICU beds	10 (6–14)	12 (6–16)	9 (7–12)
Hospital beds	678 (550–978)	738.5 (644–1,025)	56.5 (471–708)
Subjects	11,801	5,692 (48.2)	6,109 (51.8)
Ventilator dependence	388	186 (3.3)	202 (3.3)

Data are presented as *n* (%) or median (interquartile range).

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Table 3. Ventilator Dependence Among Critically Ill Subjects in Japan: 2018–2019

	Model 1	Model 2
Fixed effects		
Subject-level variables		
Body mass index, kg/m ²		
< 18.5	1.46 (1.18–1.79)	
≥ 18.5 to < 23	Ref.	
≥ 23 to < 27.5	0.87 (0.73–1.03)	
≥ 27.5	1.10 (0.99–1.23)	
Age, y	1.01 (1.00–1.01)	
Male	1.05 (0.90–1.22)	
SOFA score	1.06 (1.03–1.08)	
Underlying condition		
Heart failure	1.87 (1.50–2.33)	
Respiratory failure	2.06 (1.61–2.65)	
Liver cirrhosis	1.27 (1.02–1.59)	
Immunosuppressive state	1.16 (0.90–1.44)	
Dialysis	0.57 (0.46–0.68)	
Malignancies	1.58 (1.34–1.83)	
ICU therapy		
Venoarterial ECMO	2.90 (2.42–3.54)	
Venovenous ECMO	4.31 (3.85–4.81)	
IRRT or CRRT	2.76 (2.46–3.13)	
Preceding cardiac arrest	2.29 (2.04–2.62)	
Disease group, n (%)		
Gastrointestinal/liver/other	Ref.	
Cardiovascular	0.50 (0.42–0.61)	
Pulmonary	3.60 (3.08–4.22)	
Neurogenic	4.37 (3.54–5.25)	
Trauma	3.72 (3.41–4.09)	
Emergency surgery	1.14 (0.92–1.40)	
ICU-level variable		
Hospital type		
Academic hospital	Ref.	
Non-academic		
≤ 299 beds	1.03 (0.86–1.23)	
300–599 beds	0.58 (0.51–0.66)	
600–999 beds	1.18 (0.88–1.64)	
≥ 1,000 beds	0.53 (0.43–0.66)	
Number of ICU beds		
≤ 9	Ref.	
10–15	0.63 (0.48–0.83)	
≥ 16	0.47 (0.39–0.58)	
Random effects		
Median odds ratio	1.95 (1.62–2.46)	1.64 (1.37–2.02)
Hospital level variance (SD)	0.49 (0.16)	0.27 (0.11)

Data are presented as odds ratios (95% CI).

SOFA score = Sequential Organ Failure Assessment score

ECMO = Extracorporeal membrane oxygenation

IRRT = intermittent renal replacement therapy

CRRT = continuous renal replacement therapy

ICU mortality, hospital mortality, and implementation of tracheostomy were associated with being underweight (see the supplementary materials at <http://www.rcjournal.com>). Being overweight was associated with reduced risks of hospital mortality and implementation of tracheostomy. In the age-stratified analysis, ventilator dependence increased in underweight, overweight, and obese subjects < 65 y old (see the supplementary materials at <http://www.rcjournal.com>). By contrast, in subjects ≥ 65 y, being overweight was associated with a reduced risk of ventilator dependence compared to other BMI categories.

Discussion

Using data from a nationwide database, we examined the association between BMI and ventilator dependence at ICU discharge in Japan. Compared with normal-weight critically ill subjects, the risk for ventilator dependence at ICU discharge increased among underweight counterparts, even after adjusting for potential confounders and inter-ICU variance. Although obesity was also associated with a higher risk of ventilator dependence, the association was less clear.

One of the possible explanations to interpret our findings is frailty. Underweight or unintentional weight loss is an important indicator of frailty, which often leads to worse health outcomes in critically ill patients.¹⁹ A previous study showed a U-shaped association between BMI and physical frailty,²⁰ and frailty could explain the association between being underweight or obese/overweight and health outcomes. The next possible explanation is low skeletal muscle mass in underweight subjects. Respiratory and skeletal muscle mass, including the diaphragm, have a significant role in the respiratory system.²¹ In patients who are underweight, however, skeletal muscle may be reduced compared to those who are normal weight.²² Low skeletal muscle mass is reported to be associated with lower pulmonary function and diaphragm dysfunction,^{23,24} which can be associated with prolonged ventilation.²⁵ In addition to inspiratory muscles (eg, diaphragm), expiratory muscles (eg, those of abdominal wall and rib cage) play significant roles in critically ill ventilated patients.²⁶ As another possible mechanism, previous studies have reported that obese subjects have a higher risk of pulmonary complications and infection.^{27,28} This could explain the increased risk of ventilator dependence among obese subjects in this study.

In the age-stratified analysis, we noted a U-shaped pattern between ventilator dependence and BMI categories in subjects < 65 y old. By contrast, in overweight subjects ≥ 65 y old, there was a reduced risk of ventilator dependence compared to other BMI categories. Being overweight or obese could have a protective effect as a fuel source during highly catabolic states, and it might be an indicator of the absence of illness-induced malnutrition and better exposure to adequate health care.²⁹ However, we should interpret the association

showed a similar association between subjects' BMI and the risk of ventilator dependence (see the supplementary materials at <http://www.rcjournal.com>).

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between BMI and ventilator dependence in older patients carefully because they may represent a selected population who, in general, are less likely to receive mechanical ventilation due to their advanced age.³⁰ Although we excluded these patients from the current analysis, it should be noted that there were few subjects < 50 y old in our study population.

A recent systematic review reported that subjects whose BMI was 30–39.9 kg/m² had a lower risk of hospital mortality compared to subjects with normal weight (ie, 18.5–24.9 kg/m²).⁵ In our study, however, no association was found between obesity and hospital mortality, and we observed that overweight subjects had a lower risk of hospital mortality. This difference may be explained by the subjects' nutritional status because obese subjects with malnutrition were reported to have worse outcomes than obese subjects without malnutrition.³¹

Consistent with previous studies, being underweight was associated with ICU and hospital mortality.^{4,32} We also found a positive association between being underweight and the implementation of tracheostomy, which has not been previously reported. Since prolonged mechanically ventilated patients often need tracheostomy,³³ we interpret *a posteriori* that frailty plays a role in the association between being underweight and the need for tracheostomy.

This study has some strengths. We used Japanese Intensive Care Patient Database composed of data from ICUs from various types of hospitals across Japan. While the details of data quality management in the database have been described elsewhere, a specific committee maintains the quality of data collection to ensure validity and credibility.¹⁴ We thus believe that our study subjects represent critically ill patients receiving mechanical ventilation in Japan. Second, we categorized study subjects' BMI into 4 categories according to the recommendation for the Asian population from the World Health Organization's expert consultation.¹⁶ Previous studies have reported that this criterion was associated with mortality or cardiovascular disease in the Asian population.^{34,35} Third, multilevel analyses were utilized to account for hierarchical data structure. The median odds ratio of model 2 was 1.64 (95% CI 1.37–2.02), which indicates a large variance of the risk of ventilator dependence at ICU discharge between ICUs. The variance derives from a variety of characteristics of each facility including medical resources, such as the number of ICU beds or availability of a step-down unit for weaning from the ventilator. There was also no information about the patient-to-intensivist ratio, the patient-to-respiratory therapist ratio, or surgical versus medical populations in each ICU. These differences in medical resources may affect ICU discharge criteria and the status of respiratory support at ICU discharge, which could explain the variance of the risk of ventilator dependence across the ICUs in this study. It would be important to properly consider the inter-ICU variation in future studies.

There are some limitations to this study. First, the database does not contain information on patients' frailty, malnutrition, or skeletal muscle mass. Therefore, there is some concern that BMI is insufficient as a measure of these variables because it does not distinguish fat mass from lean mass. Although we adjusted for some variables that are closely related with frailty or malnutrition (eg, underlying diseases), relevant information for dysphagia was unavailable. Thus, the present findings can only partly be explained by frailty or malnutrition. Second, the database contains only a few obese patients, especially those with a BMI > 40 kg/m², so we cannot fully examine the association in more morbidly obese subjects. Considering the low prevalence of morbid obesity in the Asian population,³⁶ our findings would be fairly generalizable to the Asian population. Third, almost all of our study population consisted of Asians, and we used the WHO classification suitable for the Asian population, which we believe provides an overall pattern that could be extrapolated to the non-Asian population. However, we should note that the cutoff points of BMI categories cannot be readily applicable to non-Asian populations. Fourth, the association between obesity and lower mortality has been described as an "obesity paradox" in some previous studies,^{7,32,37} which can arise from selection bias.²⁹ To account for this problem, future studies need to consider the trajectories of subjects before admission to ICUs.

Conclusions

Being underweight while receiving mechanical ventilation was associated with a higher risk of ventilator dependence at the time of ICU discharge, even after adjusting for potential confounders and inter-ICU variance. The risk of ICU mortality, hospital mortality, and tracheostomy placement also increased in underweight subjects. The association between BMI and ventilator dependence should be examined in further studies using information about subjects' nutritional status and frailty.

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