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Research Article

Relationship between body mass index and risk of delirium in an intensive care unit

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A R T I C L E I N F O

Keywords:
Body mass index
Delirium
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Intensive care unit
Obesity
Overweight
Underweight

A B S T R A C T

Objective: Delirium in the intensive care unit (ICU) is a common and critical condition that leads to poor prognosis in older patients, but the association between body mass index (BMI) and the incidence of delirium remains unclear.
Methods: We retrospectively analyzed 5,622 patients admitted to the ICU of a tertiary referral hospital between 2013 and 2022. We collected sociodemographic data, vital signs, laboratory results, and delirium scale scores. We subdivided the patients into four categories: underweight (<18.5 kg/m^2), normal weight (18.5–22.9 kg/m^2), overweight (23–24.9 kg/m^2), and obese (>25 kg/m^2). The primary outcome was the incidence of delirium according to the BMI categories. We performed multivariable logistic regression analysis, adjusted for sex, age, past smoking and alcohol history, benzodiazepine use, and laboratory abnormalities.
Results: Among the 5,622 patients in the ICU (mean age, 72.9 years; male, 60.1%; mean BMI, 24.2 kg/m$^{2)}$, the incidence of delirium was 19.0% (1,069 patients). The mean modified incidence of delirium was higher among underweight patients (odds ratio [OR]=1.51, confidence interval [CI]=1.07–2.12, $p = 0.02$) than among normal-weight patients. Overweight and obese status were not independently associated with delirium (OR=0.90, CI=0.70–1.17, $p = 0.43$; OR= 0.97; CI=0.77–1.21, $p = 0.78$, respectively). The area under the receiver-operating characteristic curve of the multivariable logistic regression model was 0.71 (95% CI=0.69–0.73).
Conclusions: Underweight status is an independent risk factor for delirium in the ICU. Additional caution is required when evaluating underweight patients for delirium. Obese or overweight status are not associated with delirium, providing evidence for the obesity paradox.

1. Introduction

Delirium, characterized by sudden fluctuations in consciousness and cognitive function, is a major health issue, especially in critically ill patients. The prevalence of delirium in the intensive care unit (ICU) varies from 20% to 80%, and it is associated with poor prognoses such as increased risk of mortality, extended hospital stays, and cognitive impairment (McNicoll et al., 2003; Thomason et al., 2005; Krewulak et al., 2018). Delirium is reported to be one of the six causes of hospitalization-related injuries in patients aged >65 years (Girard et al., 2008). However, delirium may not be well identified because the symptoms may not be evident or may fluctuate throughout the day. Clinicians commonly miss or misdiagnose delirium; in previous studies, rates of misdiagnosis have ranged from 32% to 67% (Aldemir et al., 2001). Many studies have been conducted to identify risk factors for the diagnosis and prevention of delirium, and are still in progress (Zaal et al., 2015; Bramley et al., 2021; Peng et al., 2022).

Body mass index (BMI) is an important assessment tool for evaluating health problems in older people. BMI, which is simply calculated using the height and weight, is easy to measure and is widely used in studies on mortality, quality of life, and daily functions in the older population (Da Cunha & Sichieri, 2007; Naruishi et al., 2018). Being

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

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underweight has been consistently associated with poor quality of life and high mortality in older people, whereas studies on the prognosis of obese or overweight older patients have shown mixed results (Janssen et al., 2005; Winter et al., 2014). Since delirium is prevalent in older people, BMI could also be considered a useful marker when evaluating the risk of delirium in this population.

The role of BMI as a marker of malnutrition is well known, and its association with sarcopenia in older people has been well-documented (Bellelli et al., 2018; James & François, 1994). Considering that malnutrition, sarcopenia, and muscle mass loss increase the risk of delirium (Olofsson et al., 2007; Zucchelli et al., 2022), it can be hypothesized that low BMI and underweight are associated with delirium. The nutritional requirements of the brain may not be met in presence of feeding difficulties, inflammation, alterations in muscle performance, and metabolic imbalances. Malnutritional and other alterations in inflammatory and metabolic systems may contribute to the development of delirium (Bellelli et al., 2018; Rosted et al., 2018). Few studies have addressed this topic, and have focused on postoperative delirium after specific types of surgery, with relatively few participants (Chung et al., 2015; Juliebø et al., 2009; Scholz et al., 2016). The association between BMI and delirium has been suggested in few studies (Albanese et al., 2022; Kong et al., 2022; Deng et al., 2022), but to our knowledge, no studies have been conducted in the ICU.

In this study, we subdivided patients into BMI categories of underweight, normal, overweight, and obese groups to investigate the effect of BMI on delirium in the ICU. We hypothesized that being underweight would have a significant effect on the development of delirium. We also examined the effects of overweight and obese status on delirium.

2. Methods

2.1. Study design and participants

This longitudinal observational study included patients admitted to the ICU at Gangnam Severance Hospital, a tertiary referral hospital in Seoul, South Korea, between January 2013 and April 2022. The records of 12,442 patients were examined, and the exclusion criteria were as follows: (1) no records of evaluation data or absent data at the scheduled time of evaluation, (2) age <50 years, and (3) any missing data on BMI at ICU admission. After exclusion, 5622 patients—1069 with delirium and 4553 without delirium—were analyzed (Fig. 1). All patient data, including sex, age, weight/height, APACHE II scores, blood pressure, benzodiazepine use, delirium severity score, delirium subtypes, medical history (smoking and alcohol history), and laboratory results (Hb, Na, K, BUN, Cr, bilirubin, albumin, liver function, and arterial blood gas analysis [ABGA]) were obtained from the electronic medical records (EMRs) (Aldemir et al., 2001; Dubois et al., 2001; Girard et al., 2008).

2.2. BMI and categorization

BMI was calculated as weight divided by the square of the height (kg/m^2), and the patients were categorized according to World Health Organization [WHO] and Asia-Pacific guidelines: underweight (<18.5 kg/m^2), normal weight (18.5–22.9 kg/m^2), overweight (23–24.9 kg/m^2), and obese (>25 kg/m^2) (Pan & Yeh, 2008).

2.3. Delirium assessment

This study was part of the ICU Distress and Delirium Management project, which was conducted in the ICU at Gangnam Severance Hospital in 2012 to manage and monitor delirium (Oh et al., 2015). The nurses and a trained psychiatrist conducted rounds every day in the ICU to assess patients and identify delirious patients following the protocol. The nurses assessed the delirium using the Richmond Agitation–Sedation Scale (RASS) and the Confusion Assessment Method for the ICU (CAM-ICU). Patients who were sedated (RASS score = −4 or −5) were excluded. A psychiatrist then reviewed the charts and CAM-ICU results, and evaluated the patients, and the diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Patients aged >50 years were assessed daily from admission until discharge. The results were recorded in the EMR.

At our hospital, when a patient is found in a state of delirium (CAM-ICU: positive), the delirium severity and subtype are assessed by a psychiatrist using the Korean version of the Delirium Rating Scale (K-DRS) and the Delirium Motor Subtype Scale (DMSS), respectively (Kim et al., 2018; Lee et al., 2011). The K-DRS is a demonstrably effective tool for evaluating the severity of delirium in patients (Lee et al., 2011), and it is also a reliable tool for identifying hyperactive, hypoactive, and mixed subtypes of delirium [27]. Ethical approval was obtained from the institutional review board of the Gangnam Severance Hospital, Yonsei

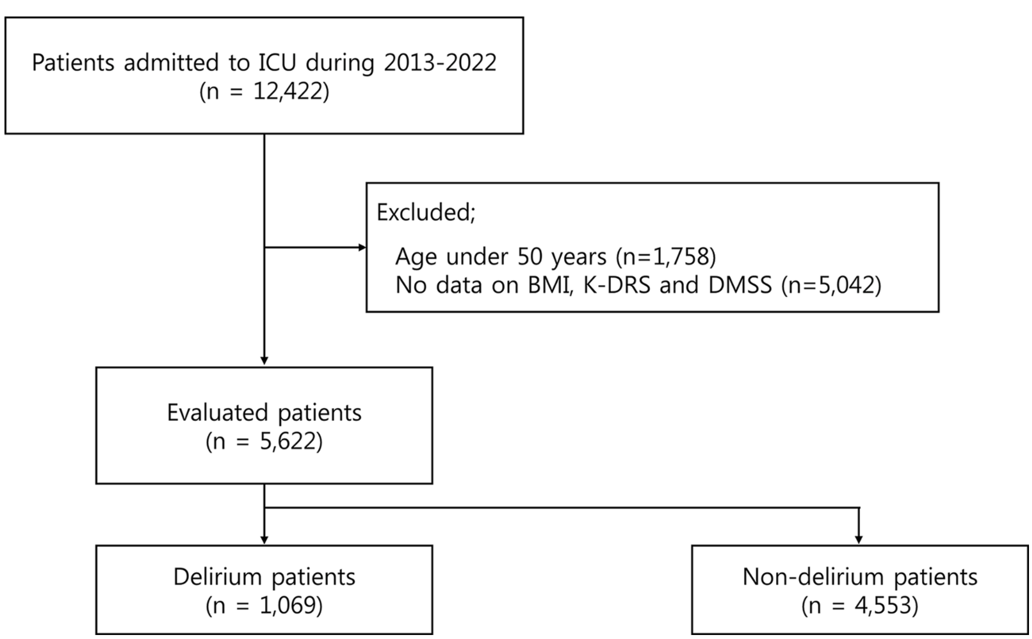

Fig. 1. Flowchart of patient selection based on the inclusion and exclusion criteria.

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2.4. Statistical analysis

Continuous variables were presented as means ± standard deviations and categorical variables were presented as absolute numbers with percentages. Student's *t*-test was used to compare continuous variables, and chi-square test was used to compare categorical variables. Since the number of participants was big enough to exceed the size limit of 40, the normality test was not performed (Khalid et al., 2022). Two-tailed p-values <0.05 were considered statistically significant. Odds ratios (ORs) with 95% confidence intervals (CIs) were determined using multivariable logistic regression analysis, and the variability inflation factor was calculated to verify multicollinearity. The area under the receiver-operating characteristic (AUROC) curve was calculated to determine model performance. All statistical analyses were performed using the Statistical Package for the Social Sciences, version 25 (IBM, Armonk, NY, USA).

3. Results

3.1. Characteristics of the study participants

The sociodemographic characteristics of the participants are presented in Table 1. The mean age of the participants was 72.94 ± 11.63 years, and there were more men (60.1%) than women in our sample. The mean BMI was 24.22 ± 13.12, and the mean APACHE II score was 24.22 ± 13.12; 34.8% were smokers and 34.8% had a history of consuming alcoholic drinks. Among all the patients, 19% developed delirium during their ICU stay. Among the patients with delirium, the mean K-DRS score was 15.49 ± 7.00, the mean number of days to delirium onset was 6.03 days, and the hypoactive subtype was the most common subtype (50.1%). The additional patient characteristics are shown in Table 1.

3.2. Comparison between groups

The results of the comparison between the delirium and non-delirium patient groups are shown in Table 2. The patients in the delirium group were older ($p < 0.001$) and had significantly higher APACHE II scores ($p < 0.001$) than those in the non-delirium group. Benzodiazepines were prescribed more frequently ($p < 0.001$) in patients with delirium than in those without delirium, and abnormal laboratory findings such as anemia ($p < 0.001$), azotemia ($p = 0.013$), hypoalbuminemia ($p < 0.001$), hyperbilirubinemia ($p < 0.001$), elevated LFT ($p < 0.001$), and metabolic acidosis ($p < 0.001$) were significantly more frequent among patients with delirium. The delirium group had a higher mean BMI ($p < 0.001$). The two groups did not differ in the proportions of normal-weight patients ($p = 0.78$), but the proportion of underweight patients was higher ($p < 0.001$) and the proportions of overweight ($p = 0.0013$) and obese patients ($p < 0.001$) were lower in the delirium group ($p < 0.001$).

Table 1
Baseline characteristics of the participants.

	Total participants ($n = 5622$)
Age, years	72.94 ± 11.63
Male sex, n (%)	3378 (60.1)
BMI, kg/m^2	19.27 ± 8.55
Tobacco use, n (%)	1950 (34.8)
Alcohol use, n (%)	1951 (34.8)
APACHE II score	24.22 ± 13.12
Delirium, n (%)	1069 (19.0)
K-DRS	15.49 ± 7.00
Delirium onset, days	6.03 ± 6.80
DMSS type, n (%)	
Hyperactive subtype	295 (27.9)
Hypoactive subtype	529 (50.1)
Mixed motor subtype	233 (22.0)
No motor subtype	12 (0.0)

BMI, body mass index; APHACHE, Acute Physiology and Chronic Health Evaluation; K-DRS, Korean version of the Delirium Rating Scale; DMSS, Delirium Motor Subtype Scale.

Table 2
Comparison of demographic characteristics between delirious and non-delirious patients.

	Delirium ($N = 1069$)	Non-delirium ($N = 4553$)	p-value
Age, years	76.94 ± 11.29	72 ± 11.51	<0.001
Male sex, n (%)	622 (58.2)	2756 (60.5)	0.1691
BMI, kg/m^2	24.55 ± 18.3	24.14 ± 11.57	<0.001
BMI categories, n (%)			
Normal	416 (38.9)	1695 (37.2)	0.78
Underweight	122 (11.4)	332 (7.3)	<0.001
Overweight	205 (19.2)	1036 (22.8)	0.0013
Obese	326 (30.5)	1490 (32.7)	<0.001
Tobacco use, n (%)	365 (34.2)	1585 (34.9)	0.7014
Alcohol use, n (%)	350 (32.8)	1601 (35.3)	0.1419
APACHE II score	23.15 ± 8.43	18.33 ± 8.32	<0.001
Hypotension, n (%)	94 (8.8)	361 (7.9)	0.3842
Hypertension, n (%)	294 (27.5)	1178 (25.9)	0.2929
Benzodiazepine use, n (%)	444 (41.5)	1431 (31.4)	<0.001
Anemia, n (%)	822 (78.7)	3142 (71.1)	<0.001
Azotemia, n (%)	14 (1.3)	25 (0.6)	0.0127
Hyponatremia, n (%)	134 (12.5)	616 (13.5)	0.4176
Hypoalbuminemia, n (%)	517 (48.4)	1858 (40.8)	<0.001
Hyperbilirubinemia, n (%)	18 (1.7)	25 (0.6)	<0.001
Elevated LFT, n (%)	527 (49.3%)	1911 (42.0)	<0.001
Metabolic acidosis, n (%)	355 (35.9)	1194 (28.6)	<0.001

BMI, body mass index; APHACHE, Acute Physiology and Chronic Health Evaluation; LFT, liver function test.

3.3. Multivariable logistic regression analysis

In the multivariable logistic regression (Table 3), underweight status (OR = 1.51, 95% CI = 1.08–2.12) was independently associated with the development of delirium in the ICU, whereas overweight (OR = 0.90, 95% CI = 0.70–1.17) and obese status were not (OR = 0.97, 95% CI = 0.77–1.21). Older age (OR = 1.04, 95% CI = 1.03–1.05), high APACHE II score (OR = 1.05, 95% CI = 1.04–1.06), hypertension (OR = 1.25, 95% CI = 1.01–1.54), benzodiazepine use (OR = 1.36, 95% CI = 1.11–1.65), hypoalbuminemia (OR = 1.33, 95% CI = 1.09–1.62), and elevated LFT (OR = 1.28, 95% CI = 1.06–1.56) were also associated

Table 3
Results for multiple logistic regression analysis.

	Odds ratio	95% CI	p-value
Age, years	1.039	(1.030 - 1.049)	<0.001
Male sex, n (%)	0.907	(0.727 - 1.131)	0.383
Normal weight	1		
Underweight	1.509	(1.076 - 2.116)	0.017
Overweight	0.903	(0.699 - 1.168)	0.437
Obese	0.969	(0.774 - 1.214)	0.785
Tobacco use	1.152	(0.905 - 1.469)	0.252
Alcohol use	1.035	(0.812 - 1.320)	0.781
APACHE II score	1.052	(1.040 - 1.064)	<0.001
Hypotension	1.085	(0.754 - 1.563)	0.659
Hypertension	1.246	(1.011 - 1.537)	0.040
Benzodiazepine use	1.356	(1.114 - 1.653)	0.003
Anemia	0.941	(0.742 - 1.194)	0.615
Azotemia	2.187	(0.853 - 5.613)	0.104
Hyponatremia	1.008	(0.748 - 1.359)	0.959
Hypoalbuminemia	1.328	(1.092 - 1.617)	0.005
Hyperbilirubinemia	1.358	(0.414 - 4.456)	0.614
Elevated LFT	1.283	(1.059 - 1.556)	0.011
Metabolic acidosis	1.101	(0.902 - 1.345)	0.347

CI, confidence interval; APHACHE, Acute Physiology and Chronic Health Evaluation; LFT, liver function test.

with an increased risk of developing delirium. The AUROC of the multiple logistic analysis model was 0.71 (95% CI, 0.69–0.73) (Fig. 2). In comparison, according to BMI categories, the mean K-DRS score was the highest for the underweight group, but the difference was not statistically significant. Moreover, the days to onset of delirium and DMSS type did not significantly differ among the BMI categories (Table 4).

4. Discussion

This observational, longitudinal study investigated the association between BMI and delirium in 5622 patients admitted to the ICU in a tertiary university hospital. We found that underweight status was an independent risk factor for delirium, whereas overweight and obese status were not. Similar to our findings, in previous studies, underweight status was associated with postoperative delirium after hip fracture surgery, gastrointestinal surgery, and total knee arthroplasty (Chung et al., 2015; Juliebø et al., 2009; Scholz et al., 2016). Among all patients, 19.0% developed delirium (1069 patients), and being underweight was independently associated with a 1.51-fold higher risk of developing delirium during ICU stay (95% CI = 1.08–2.12).

The mechanisms underlying the association between underweight status and delirium are unclear, and the etiology may be multifactorial, such as feeding difficulties, inflammation, alterations in muscle performance, and metabolic imbalances. Low BMI is a useful marker of malnutrition, sarcopenia, frailty, and/or underlying subclinical pathology (Bellelli et al., 2018; Cohen-Mansfield & Perach, 2011a; James & François, 1994). Malnutrition is associated with delirium, and nutritional supplementation has been found to reduce the incidence of delirium and shorten hospital stay (Lundström et al., 2007; Olofsson et al., 2007). Delirium is more common in patients with sarcopenia than in those without sarcopenia (Bellelli et al., 2018). The inflammatory stimulation of sarcopenic patients may lead to the activation of brain microglia and overproduction of inflammatory modulators and cytokines, leading to neurocognitive changes that are known to cause delirium (Cunningham & Maclullich, 2013). A cascade of adenosine triphosphate depletion and production of reactive oxygen and nitrogen,

Table 4
Delirium scores according to BMI categories.

	Normal (N = 416)	Underweight (N = 122)	Overweight (N = 205)	Obesity (N = 326)	p-value
K-DRS	15.8 ± 6.96	16.31 ± 7.19	14.58 ± 6.57	15.37 ± 7.19	0.099
Delirium onset, days	6.03 ± 6.8	5.48 ± 6.13	6.3 ± 6.8	6.6 ± 6.81	0.156
DMSS type, n (%)					0.746
Hyperactive subtype	120 (29.3)	29 (24.0)	53 (26.1)	93 (28.7)	
Hypoactive subtype	202 (49.4)	62 (51.2)	99 (48.8)	166 (51.2)	
Mixed motor subtype	87 (21.3)	30 (24.8)	51 (25.1)	65 (20.1)	
No motor subtype	7 (0.0)	1 (0.0)	2 (0.0)	2 (0.0)	

K-DRS, Korean version of the Delirium Rating Scale; DMSS, Delirium Motor Subtype Scale.

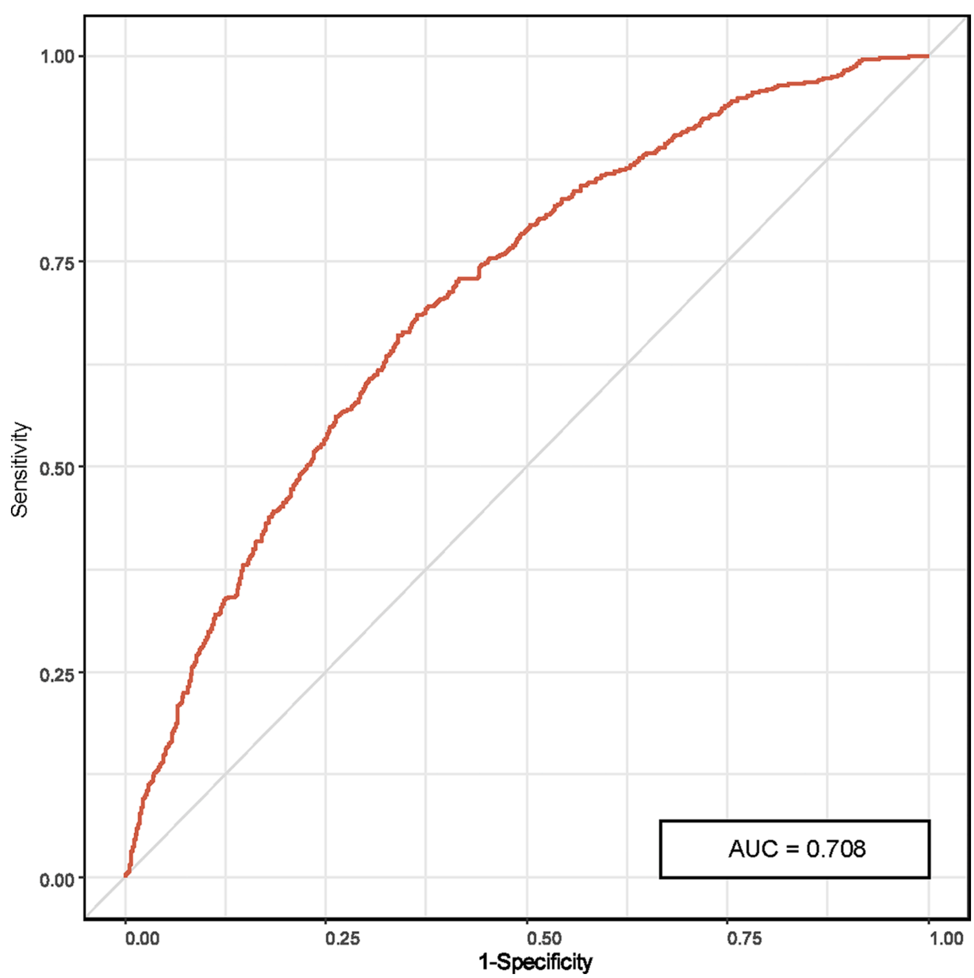

Fig. 2. Outcome of receiver-operating characteristic (ROC) curve analysis.

resulting in oxidative stress in patients with compromised nutritional status may lead to inadequate brain perfusion (Bobyn et al., 2005), all of which may contribute to the development of delirium.

Moreover, in a previous study of two million people over two decades, being underweight in middle age and old age was associated with increased risk of dementia (Qizilbash et al., 2015). Considering that dementia and delirium share similar clinical and pathogenic features (Simone & Tan, 2011), the negative effects of being underweight on dementia may also have important implications.

Meanwhile, in our study, obesity or overweight did not show any association with delirium. The few studies on the association between obesity or overweight and delirium have shown mixed results. One study suggested that high BMI (>30) was a risk factor for postoperative delirium after lung transplantation (Sher et al., 2017), whereas another study conducted in China showed the protective effects of high BMI against postoperative delirium (Deng et al., 2022). Obesity may increase the risk of postoperative complications (Sher et al., 2017); however, it is concurrently associated with a long survival time after surgery (Tjeertes et al., 2015). Contrary to the general expectation that obesity or overweight has negative effects, in many studies, high BMI does not have harmful effects on mortality, general health, or even cognitive function in older patients (Janssen et al., 2005; Kim et al., 2016; Tjeertes et al., 2015; Winter et al., 2014). However, this so-called "obesity paradox" (Tjeertes et al., 2015) remains controversial, and research on this topic is still underway. Our finding that obesity and overweight did not significantly effect delirium in older patients may be understood under this "obesity paradox." The low incidence of osteoporosis in overweight patients, due to increased weight-bearing bone formation, may prevent falls and potential trauma (Cohen-Mansfield & Perach, 2011b; Potter et al., 1995). Obesity can also provide energy reserves in times of stress and illness and may prolong the period of pre-death weight loss (Cohen-Mansfield & Perach, 2011b; Morley, 2001). Furthermore, the level of serum urate, an antioxidant, which is positively correlated with BMI, may help prevent the development of neurodegenerative diseases (Euser et al., 2009). In a meta-analysis of the risk of dementia in overweight/obese patients, mid-life obesity was associated with an increased risk of later dementia, whereas late-life obesity showed the opposite result (Pedditzi et al., 2016). High BMI may have a long-term and chronic effect on cognitive function, especially given that high BMI is also associated with low volumes of gray and white matter (Nepal et al., 2014; Pedditzi et al., 2016); however, regarding the acute effect, overweight/obesity may even have a protective effect against cognitive decline (Kim et al., 2016; Pedditzi et al., 2016), which could provide a clue for interpreting the results of our study.

The strength of this study lies in the fact that, to our knowledge, it is the first to examine the effect of BMI on delirium in patients admitted to the ICU. BMI was subdivided into four categories according to the WHO criteria, and the extent to which each category increased the risk of delirium was examined. Resultantly, underweight status was an independent risk factor for delirium in ICU patients, while overweight and obese status did not show significant associations. Hence, the risk of delirium must be cautiously examined in underweight patients. Being underweight not only causes many health problems in older people but also increases the risk of delirium, especially in the ICU; therefore, it is important to manage the weight of older patients. Considering that delirium in ICU patients is associated with poor prognosis, such as high mortality and long hospital stay, our findings could be helpful in clinical practice, especially for critically ill patients. The inclusion of low BMI in the delirium prediction model should be considered, and a practical approach to managing underweight, such as providing supportive nutritional care, should also be considered. Moreover, our results support the "obesity paradox," which is a controversial issue. However, the association between weight and delirium and the underlying mechanisms remain to be elucidated.

However, this study had some limitations. Due to the retrospective design of the study, the risk of bias in data selection cannot be denied. Moreover, our study was conducted at a single center in an Asian country; therefore, our findings must be generalized to the situations in other countries with caution. However, our results may be helpful for populations in Asian settings, considering we included a large population of 5622 ICU patients.

5. Conclusion

We found an increased risk of delirium in the ICU-admitted patients who were underweight, but not in those who were obese or overweight. Our findings conformed with those of previous studies, but contradicted the assumption that obese people have a high risk of delirium. However, little is known about the mechanisms underlying this association; therefore, further research on this topic is required.

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CRediT authorship contribution statement

Yujin Ko: Conceptualization, Methodology, Visualization, Investigation, Formal analysis, Writing – original draft. **Hesun Erin Kim:** Data curation, Formal analysis, Investigation. **Jin Young Park:** Data curation, Supervision. **Jae-Jin Kim:** Data curation, Supervision. **Jaehwa Cho:** Data curation, Supervision. **Jooyoung Oh:** Conceptualization, Methodology, Investigation, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare no actual or potential conflicts of interest related to this study.

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None.

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