Body mass index, blood glucose, and mortality in patients with ischemic stroke in the intensive care unit: A retrospective cohort study

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Background: Excessive BMI was associated with lower mortality after stroke. However, some believed that excessive BMI can lead to a poor prognosis because of some physiological mechanism, such as glucose metabolism disorder. Therefore, this study aims to discuss the association between mortality, BMI, and blood glucose.

Materials and methods: This was a retrospective observational study and all data were extracted from the Medical Information Mart for Intensive Care III database. The exposure was BMI classified into the normal weight group and the excessive weight group. The outcome concluded 30-day, 90-day, and 1-year mortality. The association between two groups and mortality was elucidated by Cox regression models, propensity score matching (PSM) and inverse probability of treatment weighting (IPTW). The underlying effect of blood glucose on the "obesity paradox" was analyzed by causal mediation analysis.

Results: According to Cox regression models, a significant beneficial effect of excessive BMI in terms of mortality was observed: 30-day mortality (HR 0.57, 95% CI 0.35–0.90, P = 0.017), 90-day mortality (HR 0.53, 95% CI 0.36–0.78, P = 0.001), and 1-year mortality (HR 0.65, 95% CI 0.46–0.91, P = 0.013). After PSM and IPTW, we got a similar conclusion. The causal mediation analysis showed that the protective effect of excessive BMI on 30-day mortality reduced with the increase of blood glucose.

Conclusion: For ischemic stroke patients in the Intensive Care Unit, those with excessive BMI are associated with both lower short-term mortality and lower long-term mortality, while the protective effect on 30-day mortality weakened accompanied by the increase of blood glucose.

KEYWORDS

body mass index, glucose, mortality, ischemic stroke, intensive care unit
Introduction

Stroke is a multifactorial and global pandemic disease, with the second leading cause of death and the third leading cause of disability, which imposes enormous medical, economic, and social burdens (Campbell and Khatri, 2020). As reported, the three most dominant risk factors for stroke are hypertension, high body mass index, and high blood glucose, in which the high BMI is the fastest-growing risk factor (Feigin et al., 2021). Although excessive BMI were associated with the higher morbidity, it can also link to the lower mortality after onset, which is called obesity paradox. Obesity paradox has been observed in atrial fibrillation (Proietti et al., 2017), heart failure (Oreopoulos et al., 2008), coronary artery disease (Uretsky et al., 2007), acute myocardial infarction (Colombo et al., 2015), end-stage kidney (Ahmadi et al., 2015).

In stroke patients, the obesity paradox had been demonstrated in a recent review that included 25 studies with about 300,000 cases (Bagheri et al., 2015). But there are still some articles holding different opinions (Ryu et al., 2011; Dehlendorff et al., 2014). All previous articles discussed the protective effect of excessive BMI in the total stroke population, but lack of research for critically ill stroke patients. However, critically ill patients tend to be at greater risk of death and need to be handled more carefully. Besides, in the clinical work of the intensive care unit (ICU), a normal weight is often not considered as a risk factor and cannot attract special attention. Therefore, it is meaningful to conduct a separate analysis to directly show the relationship between excessive BMI and mortality for ischemic stroke patients in the ICU.

Evidence suggested that hyperglycemia was not only an independent risk factor for stroke but also contributed to a worse prognosis in stroke patients regardless of diabetes (Masrur et al., 2015; Zhu et al., 2017). Unfortunately, when the body suffers from an acute illness, it can cause a transient increase in blood glucose, even in those without glucose metabolism disorder before, which is known as stress hyperglycemia. Besides, insulin resistance was proposed to be one of the causes of stress hyperglycemia (Ettertor et al., 2010). Due to this, obesity, associated with insulin resistance and glucose tolerance (Borschmann et al., 2017; Larsson et al., 2017), may aggravate acute blood glucose fluctuations and thus lead to a worse outcome in critically ill patients with stroke. This contradicts the obesity paradox. These findings led us to question whether the protective effect of high BMI on prognosis will be masked or weakened by hyperglycemia. Therefore, we designed this study to talk about the obesity paradox in critically ill patients and the potential role of blood glucose in this process.

Materials and methods

Study population

The present study was conducted in the ICU. The first day following the ICU admission was defined as the first day in the analysis. Baseline characteristics were collected using structured query language, including age, gender, weight, height, date of birth and death, and comorbidities (hypertension and diabetes). The vital signs and physiology variables within the first day were also recorded, including systolic pressure, diastolic pressure, heart rate, respiratory rate, temperature, blood urea nitrogen, and creatinine. We use the average of each variable if they were measured more than once. The blood glucose measurement in the acute period was defined as the average of all random blood glucose measurements within the first 24 h.

In stroke patients, it is widely accepted that the NIH stroke score (NHISS) is a specific scale to evaluate the severity of illness and predict prognosis. Unfortunately, in the ICU, patients with stroke always often lack accurate NHISS on admission due to several reasons, such as coma, unstable vital signs, and poor mental status. In addition, stroke patients are often complicated with multiple system injuries and face a complex risk of death. Therefore, in the present study, critical illness scores involving multiple systems at admission were adopted.
to assess the disease severity, for example, Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score II (SAPS II), and Elixhauser Comorbidity Index (ECI) score (Le Gall et al., 1984; Vincent et al., 1996; van Walraven et al., 2009). The SOFA score is a prediction system for assessing the incidence of organ dysfunction or failure in ICUs. SAPS II score includes 12 physiological variables, age, type of hospitalization, and 3 chronic diseases. It is reported that a higher SAPS II score means worse disease severity and worse outcome. ECI score is a comprehensive scoring system for evaluating the prognosis of patients in the ICU by baseline diseases and has an advantage in predicting long-term outcomes.

Statistical analysis

The skewness distribution was presented as median (quartile) while the categorical variables were presented as total number (percentage). The baseline characteristics of different groups were analyzed by the Mann–Whitney U test (continuous variables) and the χ² test or Fisher’s exact test (categorical variables). The effect of BMI on survival was investigated by the Cox regression models. To assess confounding, those related to the outcome in the univariate analysis (p < 0.10) were entered into a Cox regression model in the basic model or eliminated the covariates in the complete model one by one, then compared the regression coefficients. Those covariates altering initial regression coefficients by more than 10% were adjusted in the multivariate Cox regression model. The interactions between BMI and sex were analyzed in the subgroup analysis.

We used propensity score matching (PSM) to reduce the potential confounding between the normal group and the excessive group. A multivariable logistic regression model was performed to compute the propensity score, including crucial variables which are known to impact clinical stroke outcomes. We excluded patients or between included and all patients. Compared with the normal weight group, the group with excessive BMI was more likely to be male (52.8% vs. 42.4%, p = 0.031) or younger (median: 67 vs. 76, p < 0.001). The excessive weight group had a lower proportion of diabetes, but higher admission blood glucose levels. In the present study, excessive weight patients had lower SAPS II scores (Median: 31.0 vs. 37.0, P = 0.002), but there was no significant difference in SOFA (Median: 3.0 vs. 3.0, P = 0.731) and ECI scores (Median: 5.0 vs. 5.0, P = 0.081). After PSM and IPTW, all variables showed no statistical difference (SMD < 0.1) (Table 1). We found that, in critically ill patients with ischemia stroke, the excessive weight group had lower mortality at 30 and 90 days, and at 1 year (Table 2).

Body mass index and mortality

Univariate analysis showed that the dominant factors for 30-day mortality were age, heart rate, SOFA, SAPS II, and ECI scores and glucose, while the dominant factors for 90-day and 1-year mortality were age, heart rate, respiration rate, SOFA, SAPS II, and ECI scores (Table 3). To assess confounding, covariates including age, heart rate, respiration rate, SOFA, SAPS II, ECI, and glucose were entered into a Cox regression model in the basic model, or were eliminated one by one in the complete model, then the regression coefficients were compared. Initial regression coefficients altering by more than 10% were considered to be significant. Therefore, we adjusted the gender, age, SAPS II score, and glucose when analyzing the association between BMI and 30-day mortality by the multivariable Cox regression analysis (Table 4). In addition, we adjusted the covariates, including

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1 http://www.R-project.org
TABLE 1 Characteristics of the study population stratified into two classifications of body mass index (BMI).

| Variables                  | Normal weight | Excessive weight | p     | SMD  | Normal weight | Excessive weight | SMD  |
|----------------------------|---------------|------------------|-------|------|---------------|------------------|------|
| N                          | 177           | 345              |       |      | 166           | 166              |      |
| Age, years                 | 76.0 (64.0, 83.0) | 67.0 (57.0, 77.0) | <0.001 | 0.338 | 75 (63.0, 82.0) | 72 (64.0, 80.0) | 0.038 |
| Male, n (%)                | 75 (42.4%)    | 182 (52.8%)      | 0.031 | 0.209 | 72 (43.9%)    | 68 (41.0%)       | 0.049 |
| Comorbidity                |               |                  |       |      |               |                  |      |
| Hypertension               | 29 (16.4%)    | 51 (14.8%)       | 0.724 | 0.044 | 27 (16.3%)    | 26 (15.7%)       | 0.016 |
| Diabetes                   | 41 (23.2%)    | 129 (37.4%)      | 0.001 | 0.313 | 41 (24.7%)    | 43 (25.9%)       | 0.028 |
| Heart failure              | 35 (19.8%)    | 64 (18.6%)       | 0.826 | 0.031 | 33 (18.1%)    | 27 (16.3%)       | 0.048 |
| Cardiac arrhythmias        | 69 (39.0%)    | 116 (33.6%)      | 0.265 | 0.112 | 65 (39.2%)    | 65 (38.0%)       | 0.025 |
| Chronic pulmonary          | 41 (23.2%)    | 63 (18.3%)       | 0.226 | 0.121 | 36 (21.7%)    | 36 (21.7%)       | <0.001 |
| Renal failure              | 32 (18.1%)    | 56 (16.2%)       | 0.082 | 0.049 | 30 (18.1%)    | 31 (18.7%)       | 0.016 |
| Liver disease              | 7 (4.0%)      | 14 (4.1%)        | 1     | 0.005 | 6 (3.6%)      | 8 (4.8%)         | 0.06  |
| Vital signs                |               |                  |       |      |               |                  |      |
| SBP, (mmHg)                | 125.1 (113.4, 142.8) | 130.0 (115.6, 143.9) | 0.148 | 0.129 | 126.0 (115.4, 143.7) | 126.0 (115.4, 143.7) | 0.032 |
| DBP, (mmHg)                | 62.4 (56.0, 67.7) | 63.8 (55.6, 73.2) | 0.083 | 0.198 | 62.6 (56.2, 68.5) | 61.7 (54.5, 71.5) | 0.059 |
| Heart rate, (bpm)          | 81.0 (68.5, 95.3) | 80.7 (71.3, 91.6) | 0.83  | 0.038 | 79.8 (68.4, 94.5) | 80.7 (71.5, 94.5) | 0.004 |
| Respiratory rate, (bpm)    | 18.3 (16.4, 21.0) | 18.4 (16.3, 20.5) | 0.937 | 0.006 | 18.1 (16.3, 21.0) | 18.6 (16.2, 21.2) | 0.051 |
| Temperature, (°C)          | 36.8 (36.5, 37.2) | 36.8 (36.5, 37.2) | 0.918 | 0.037 | 36.8 (36.5, 37.2) | 36.8 (36.5, 37.2) | 0.033 |
| Score                      |               |                  |       |      |               |                  |      |
| SAPS II                    | 37.0 (29.0, 45.0) | 31.0 (26.0, 42.0) | 0.002 | 0.238 | 37.0 (28.0, 45.0) | 34.0 (27.0, 45.0) | 0.04  |
| SOFA                       | 3.0 (2.0, 6.0)  | 3.0 (2.0, 3.0)   | 0.731 | 0.011 | 3.0 (2.0, 5.0)  | 3.0 (2.0, 5.0)   | 0.098 |
| ECI                        | 5.0 (0.0, 12.0) | 5.0 (0.0, 11.0)  | 0.088 | 0.136 | 5.0 (0.0, 12.0) | 5.0 (0.0, 11.0)  | 0.061 |
| Glucose, (mg/dL)           | 123.7 (107.5, 143.3) | 133.0 (116.8, 158.7) | <0.001 | 0.339 | 123.9 (108.2, 144.9) | 128.0 (113.5, 147.9) | 0.041 |

SBP, systolic blood pressure; DBP, diastolic blood pressure; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; ECI, Elixhauser-vanwalraven comorbidity index.

Bold values indicate that they are statistically significant.

TABLE 2 Outcomes of normal weight group and excessive weight group.

| Mortality                  | Normal group | Excessive group | p     | Normal group | Excessive group | p     |
|----------------------------|--------------|-----------------|-------|--------------|-----------------|-------|
| 30-day, n (%)              | 39 (22.0%)   | 46 (11.6%)      | 0.002 | 35 (21.1%)   | 17 (10.2%)      | 0.01  |
| 90-day, n (%)              | 56 (31.6%)   | 54 (15.7%)      | <0.001| 52 (31.3%)   | 22 (13.3%)      | <0.001|
| 1-year, n (%)              | 66 (37.3%)   | 79 (22.9%)      | <0.001| 62 (37.3%)   | 32 (19.3%)      | <0.001|

gender, age, and SAPS II in the Cox regression analysis for 90-day and 1-year mortality. Results indicated that excessive BMI was related to lower 30-day (HR 0.57, 95% CI 0.35–0.90, p = 0.017), 90-day (HR 0.53, 95% CI 0.36–0.78, p = 0.001), and 1-year (HR 0.65, 95% CI 0.46–0.91, p = 0.013) mortality. After PSM and IPTW, we obtained a similar conclusion for 30-day mortality (PSM: HR 0.46, 95% CI 0.35–0.69, p < 0.001; IPTW: HR 0.45, 95% CI 0.30–0.69, p < 0.001; IPTW: HR 0.46, 95% CI 0.36–0.76, p < 0.001), and 1-year mortality (PSM: HR 0.45, 95% CI 0.30–0.69, p < 0.001; IPTW: HR 0.66, 95% CI 0.48–0.91, p = 0.013) (Table 4). The Subgroup analyses for the relationship between BMI and mortality were performed by sex. As shown in Table 5, the conclusion was stable in all subgroups (p for interaction > 0.05).

Causal mediation analysis

The excessive weight group has higher level of blood glucose concentration (Median: 123.7.0 vs. 133.0, P < 0.001) (Table 1). Excessive BMI is associated with a lower 30-day mortality (Table 4), while the blood glucose concentration is associated with higher 30-day mortality (Table 3). To validate how BMI affects mortality, we next performed causal mediation analysis on the causal structure (Table 6). The ACME (indirect effect)
was 0.019 (95% CI, 0.004, 0.040; \( p = 0.008 \)), the ADE (direct effect) was \(-0.181 \) (95% CI, \(-0.309, -0.060 \); \( p = 0.001 \)), and the total effect was \(-0.162 \) (95% CI, \(-0.289, -0.040 \); \( p = 0.001 \)). Although the excessive BMI group performed better on the 30-day mortality after stroke, it had a negative effect by enhancing the level of blood glucose, which reduced the protective effect of BMI on 30-day mortality by 11.94%.

### Discussion

In our study, we confirmed in critically ill stroke patients that excessive BMI can decrease mortality, including short-term and long-term mortality. This finding was consistent with many previous articles (Bagheri et al., 2015), but there are still some opposite voices (Bagheri et al., 2015). Ryu et al. (2011) pointed out that when talking about the obesity paradox, the initial neurological severity may be a “mediator.” This is because there are clear differences in stroke patterns between patients with normal and excessive BMI, which lead to different degrees of initial neurological injury. It has been demonstrated that the main etiology of stroke in patients with low BMI is cardiac embolism, while the main etiology of stroke in patients with high BMI is small vessel occlusion. Patients with high BMI are considered to have a higher proportion of lacunar infarction compared to atherosclerotic thrombosis and myocardial infarction (Tanizaki et al., 2000). This suggests that the protective effect of high BMI may be an illusion caused by lighter initial severity. In the present study, we use the SOFA, SAPS II, and ECI scores to assess the severity of the disease and the excessive weight group had a lower SAPS II score.

In subgroup analysis, there was no interaction between BMI and sex. Contrarily, a reported article claimed that, in ischemic stroke patients, the mortality benefits associated with obesity are restricted in men, while the same conclusion could not be reached in women (Saini et al., 2014). But differ from our study, the previous study did not discuss the interaction between BMI and sex.
and sex in their work. There are a few theories supporting sex difference between males and females. First, BMI is calculated by height and weight and cannot directly show the percentage of lipid variation across sexes. In general, thought with the same body mass index, women generally have a higher percentage of body fat than men. Second, women store more lipid in the gluteal-femoral region, whereas men store more in the visceral depot (Blaak, 2001; Bagheri et al., 2015), which often leads to a better outcome in females (Strulov Shachar and Williams, 2017; Cao et al., 2018). Third, sex hormone differences may underlie the observed gender disparity (WHO Expert Consultation, 2004). However, in our study, the protective effect of excessive BMI was not modified by sex.

The reason for the “obesity paradox” is not evident at present and several hypotheses regarding the role of obesity in stroke pathogenesis have been proposed. First, the increased nutritional reserves provided by excess fat stores may provide an added advantage in the first moments of acute illness (Gioulbasanis et al., 2011; Karagozian et al., 2016). Second, as documented by several studies (Wannamethee and Atkins, 2004). However, in our study, the protective effect of excessive BMI was not modified by sex.

As reported before, hyperglycemia is related to the growth of acute cerebral infarct volume, the disruption of the blood-brain barrier and the aggravation of brain edema after stroke, and often leads to a poorer outcome. In a study published in 2014, the glucose level on admission was shown to be associated with the growth of infarct volume (Shimoyama et al., 2016). Shimoyama et al. (2016) prospectively measured the serum glucose concentration every 5 min for up to 72 h and showed a significant correlation between hyperglycemia and infarct volume growth in patients with ischemic stroke. Moreover, research in mice has demonstrated that rats with hyperglycemia suffer from increased blood-brain barrier disruption and cerebral edema (Kamada et al., 2007; Huang et al., 2013; Desilles et al., 2017). The activation of inflammations and oxidative stress is thought to be the key mechanisms for the pathological changes mentioned above (Shukla et al., 2017). Contrarily, patients with excessive BMI have been proposed to more strongly resist inflammation (Rodríguez-Castro et al., 2019) and oxidative stress (Salie et al., 2014) after stroke. Perhaps, the different effects on inflammation and oxidative stress may be the cause for the opposite mediating role of glucose in the obesity paradox. To our knowledge, there is no preclinical study that can directly support this hypothesis and further study are needed. A preclinical study observed a better performance of the diaphragm diaphragmatic function in obese rats, but not in diabetic obese rats (De Jong et al., 2017). The article also

### Table 5

| Variables | 30-day mortality | 90-day mortality | 1-year mortality |
|-----------|------------------|------------------|------------------|
|           | HR (95% CI)      | P for interaction | HR (95% CI)      | P for interaction | HR (95% CI)      | P for interaction |
| Gender    |                  |                  |                  |                  |                  |                  |
| Male (257)| 0.38 (0.19 0.74) | 0.118            | 0.35 (0.20 0.61) | 0.059            | 0.46 (0.28 0.75) | 0.087            |
| Female (265)| 0.81 (0.43 1.55) |                  | 0.77 (0.45 1.31) |                  | 0.87 (0.55 1.38) |                  |

### Table 6

Causal mediation analysis for the effect of elevation of blood glucose on 30-day mortality.

| Estimate (95% CI) | p     |
|-------------------|-------|
| ACME              | 0.019 (0.004, 0.040) | 0.008  |
| ADE               | −0.181 (−0.309, −0.060) | 0.001  |
| Total effect      | −0.162 (−0.289, −0.040) | 0.001  |
| Prop. Mediated    | −11.94% (−3.00%, −42.35%) | 0.009  |

ACME, average causal mediation effects (indirect effect); ADE, average direct effects (direct effect); Prop. Mediated, Conceptually ACME/Total effect (The proportion of mediating variables that mediate the outcome).
suggested that this difference was partly caused by the different activation of AKT pathway signaling. This inspired us that glucose may influence the benefit of obesity in ischemic stroke by specific pathway and further study are needed.

In our study, the obesity paradox is evident in critically ill patients with acute ischemic stroke. Also, we are the first ones to point out that excessive BMI may have negative implications on the prognosis of severe stroke patients by enhancing blood glucose levels. However, our study also has some limitations that need to be tackled in future studies. Firstly, since the data in MIMIC-III is generated within a single electronic medical record system, it might contain systematic biases. This may not allow to generalize the findings to other care settings, thus, more repetitive studies are needed to test the universality of our conclusion. Secondly, this is a retrospective study without follow-up data about weight change, home care and treatment schemes after discharge. Thirdly, though BMI is a convenient clinical index, it cannot provide accurate measurement of body fat content and distribution. So, some variables will become more significant, for example, waist circumference, waist-hip ratio, skinfold estimates, and bioelectrical impedance analysis. Fourthly, the underlying mechanism of our study remained unclear. Further preclinical work is need to better understand how excessive BMI and glucose affect the prognosis of stroke and how glucose decrease the mortality benefit associated with excessive BMI. The disclosure of mechanism may provide a new treatment strategy in the future.

Conclusion

Excessive BMI is associated with lower mortality after severe stroke. However, excessive BMI plays a dual role in the short term, 30-day prognosis of stroke patients in the ICU. Not only can it reduce the risk of death, but also can worsen the outcome by increasing the levels of blood glucose.

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Data availability statement

The datasets presented in this article are not readily available because as the data cannot be made publicly available due to the regulation of the database MIMIC-III database. Researchers should apply their own study plans to the website of MIMIC database. After finishing the ethical review, a username and password will be provided for them to access the complete data at: https://archive.physionet.org/works/MIMICIIIIClinicalDatabase/files/.

Author contributions

ZM: conceptualization, data curation, formal analysis, methodology, software, visualization, and writing—original draft preparation. SL: formal analysis, methodology, validation, and writing—original draft preparation. XL: conceptualization, methodology, project administration, supervision, and writing—review and editing. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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