The potential effect of blood glucose on the obesity paradox in patients with severe stroke: a retrospective observational study

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Research Article

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Abstract

Background: On the one hand, according to the obesity paradox, patients with excessive BMI will have lower mortality after onset. On the other hand, due to higher levels of glucose induced by excessive BMI, they will suffer a worse prognosis. This is contradictory. In the present study, we aim to prove the obesity paradox in critically ill stroke patients and find out the potential role of increased glucose.

Methods: This was a retrospective observational study about patients with acute stroke in the intensive care unit (ICU) and all data were extracted from the Medical Information Mart for Intensive Care III (MIMIC-III) database. The main exposure was BMI classified into normal group ($18.5 \leq \text{BMI} < 25$), excessive group ($\text{BMI} \geq 25$). The outcome concluded 30-day, 90-day and 1-year mortality. The association between two BMI 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: A total of 522 patients were included in our study, of which 177 were the normal group and 345 were the excessive group. 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, $p = 0.013$). The conclusions were stable after propensity score matching and inverse probability of treatment weighting. There were no interactions between BMI, gender, age, and diabetes. The causal mediation analysis showed that the increased glucose level would reduce the protective effect of excessive BMI on 30-day mortality.

Conclusions: In severe stroke patients, those with excessive BMI are linked to lower mortality, while the protective effect on 30-day mortality weakened accompanied by the acute increase of glucose level.

Background

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.¹ 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 for stroke from 1990 to 2019.² Although excessive BMI (including overweight and obese) were associated with the higher morbidity, it can also link to the lower mortality after onset, which is called obesity paradox. It has been observed in atrial fibrillation³, heart failure⁴, coronary artery disease⁵, acute myocardial infarction⁶, end-stage kidney⁷ as well as stroke⁸⁻¹⁰. However, the exact mechanism of the obesity paradox is still unclear.

In stroke patients, the obesity paradox had been demonstrated in a recent review that included 25 studies with about 300,000 cases⁹. Moreover, a recent study pointed out that the protection would gradually enhance with time¹¹. But there are still some articles holding different opinions^{12,13}. 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, a normal weight is often considered not 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 in critically ill stroke patients.

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^{14,15}. 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 hyperglycemia¹⁶. Due to this, obesity, associated with insulin resistance and glucose tolerance^{17,18}, may aggravate acute blood glucose fluctuations and thus lead to a worse outcome in severe stroke patients. This contradicts the obesity paradox. These findings led us to speculate 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 sugar in this process.

Method

Study population

The present subject is a retrospective cohort based on the data stored in the MIMIC III version v1.4 (Medical Information Mart for Intensive Care). Briefly, the MIMIC-III database is a large freely accessible critical single-center database and contains more than 50,000 ICU admissions between June 2001 and October 2012¹⁹. In the present analysis, 943 patients with severe ischemic stroke were extracted, of which 421 were excluded according to the following criteria (Fig 1): (1) Non-first ICU stays, (2) Died within the first 24h, (3) Lack of height and weight data, (4) Without complete data of covariates, (5) BMI less than 18.5. There were only 14 patients with BMI less than 18.5, it was too minimal to draw a significant conclusion. The patients with BMI less than 25 were defined as normal weight group, while else were excessive weight group.

Data extraction

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, creatinine, urea nitrogen, and glucose. We use the average of each variable if they were measured more than once. There were some scores used to assess the severity of the disease,

including sequential organ failure assessment (SOFA), simplified acute physiology score II (SAPS II), Elixhauser-vanwalraven comorbidity index (ECI).

Statistical analysis

The skewness distribution was presented as median (INQ) while the categorical variables were presented as total number (percentage). The baseline characteristics of different groups were analyzed by Student's t test or the Mann-Whitney U test (continuous variables) and the χ^2 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. To ensure the robustness of the results, we used propensity score matching (PSM) and propensity score-based inverse probability of treatment weighting (IPTW) to adjust the covariates. We adopted the one-to-one nearest neighbor matching and set caliper width to 0.2. We created an IPTW model according to the estimated propensity scores estimated by a multivariate logistic regression model. The stratification analyses were performed by age, gender, and diabetes using the multivariate Cox regression model. Then the interactions between BMI, gender, age, and diabetes were analyzed. To explore the potential effect of blood glucose on the obesity paradox, we conducted the causal mediation analysis by the "mediation" R package²⁰. The analysis was conducted by the Bootstrap test and the seeds were set to 2000. The results would be presented as average causal mediation effect (ACME), average direct effect (ADE), and total effect. All the analyses were performed with the statistical software packages R 3.3.2 (<http://www.R-project.org>, The R Foundation). A two-tailed test was performed and $p < 0.05$ was considered statistically significant. P values less than 0.05 (two-sided) were considered statistically significant.

Results

Characteristics and survival outcomes

In the original cohort, 522 patients who fulfilled the inclusion criteria were admitted to the analysis and were divided into two groups by BMI: normal weight group (BMI < 18.5 , $n = 177$) and excessive weight group (BMI ≥ 18.5 , $n = 345$) (table.1). The group with excessive BMI is more likely to be the male (52.8% vs 42.4%, $p = 0.031$) or the younger (median: 67 vs 76, $p < 0.001$). Compared with the normal weight group, the excessive weight group had a lower proportion of diabetes, but higher admission blood glucose levels. SOFA, SAPS II, and ECI are indicators of the severity of the patient's condition and can predict the risk of death. In the present study, excessive weight patients had lower SAPS II scores ($p = 0.002$), but there was no significant difference in SOFA ($p = 0.731$) and ECI scores ($p = 0.081$). We found that, in patients with severe stroke, the excessive weight group had lower mortality, including 30-day, 90-day, and 1-year mortality. After propensity score matching, all variables in the matched cohort show no statistical difference (SMD < 0.1).

Univariable and multivariate Cox regression analysis

Univariate analysis showed that the dominant factors for 30-day mortality were age, heart rate, SOFA, SAPS II, ECI, BUN, and glucose, while the dominant factors for 90-day and 1-year mortality were age, heart rate, SOFA, SAPS II, ECI, and BUN (table.2). According to the method mention before, we adjusted the gender, age, SAPS II, and glucose when analyzing the association between BMI and 30-day mortality by the multivariate Cox regression analysis (table.3). Besides, we adjusted the covariates including gender, age, and SAPS II in the Cox regression analysis for 90-day and 1-year mortality. In our research, the excessive BMI are related to the 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 mortality (HR 0.65, 95%CI 0.46-0.91, $p = 0.013$). After propensity score matching and inverse probability of treatment weighting, we can get the similar conclusion: 30-day mortality (PSM: HR 0.51, 95%CI 0.29-0.87, $p = 0.014$, IPTW: HR 0.55, 95%CI 0.36-0.87, $p = 0.014$), 90-day mortality (PSM: HR 0.42, 95%CI 0.26-0.68, $p < 0.001$, IPTW: HR 0.49, 95%CI 0.34-0.70, $p < 0.001$) and 1-year mortality (PSM: HR 0.44, 95%CI 0.29-0.68, $p < 0.001$, IPTW: HR 0.61, 95%CI 0.44-0.84, $p = 0.003$) (table.3).

Subgroup analyses

The subgroup analyses for the relationship between BMI and mortality were presented in Table 4, which were performed by gender, age, and diabetes. As shown in Table 4, the conclusion was stable in all subgroups (P for interaction < 0.05).

Causal mediation analysis

To validate how BMI affects mortality, we next performed a causal mediation analysis on the causal structure (table.5). the average causal mediation effects (indirect effect) were 0.022 (95%, 0.006, 0.040, $p = 0.003$), the average direct effects (direct effect) were -0.187 (95%, -0.060, -0.320, $p = 0.001$) and the Total effect were -0.164 (95%, -0.050, -0.293, $p = 0.001$). Although the excessive BMI group performs 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 13.76%.

Discussion

In our study, we confirmed that excessive BMI can decrease mortality in severe stroke patients, including short-term and long-term mortality. Wi-Sun Ryu et al pointed out that when talking about the obesity paradox, the initial neurological severity may be a 'mediator'. This is because that there are clear differences in stroke patterns between patients with normal or excessive BMI, which lead to different degrees of initial neurological injuries¹². It is 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 stroke is small vessel occlusion. In another study, high BMI is considered to have a higher proportion of lacunar infarction compared to atherosclerotic thrombosis and myocardial infarction²¹. This suggests that the protective effect of high BMI may be an illusion caused by lighter initial severity. Interestingly, even if all the patients with mild stroke were excluded from our study, the excessive weight group still had a lower

SAPS II score. In addition, the univariable analysis showed that the SAPS II score was associated with higher mortality. Therefore, we further adjusted the impact of admission SAPS II scores in multivariate Cox regression analysis and found that the correlation between BMI and mortality rate was attenuated, but still significant. There are several pathogeneses proposed to explain this phenomenon. It is reported that more energy reserve^{22,23} and muscle mass^{24,25}, as well as the stronger ability to resist inflammation²⁶ and oxidative stress²⁷, maybe the reason for this obesity paradox.

In the subgroup analysis, there was no interaction between BMI and gender, age as well as diabetes. The protective effect of excessive BMI was not modified by age, sex, or the presence of diabetes. However, a reported article claimed that mortality benefits associated with obesity were restricted in men, while the same conclusion couldn't be reached in women.⁸ Although no evidence can confirm this conclusion in our research, there were still some supporting hypotheses. Firstly, BMI is calculated by height and weight and cannot directly show the percentage of lipid varied across sex. In general, women generally have a higher percentage of body fat than men. Secondly, women store more lipid in the gluteal-femoral region, while men store more in the visceral depot,^{9,28} which often leads to a better outcome in females.^{29,30} Thirdly, the sex hormone differences may underlie the observed gender disparity.³¹

In previous literature, the effect of prior history of diabetes mellitus on the mortality of stroke was undetermined. Shihab Masrur et al believe that prior history of diabetes is an important risk factor for increased mortality after stroke¹⁵. But more people hold the opposite opinions that mortality has nothing to do with diabetes³²⁻³⁴. The univariable analysis in our study also showed no significant association between diabetes and increased mortality after stroke. Besides, in the subgroup analysis, the obesity paradox was stable in those stroke sufferers with or without diabetes, which was consistent with a former research³⁵. Notably, two studies about the prognosis of acute coronary syndrome have pointed out that the benefit of obesity only showed in non-diabetes^{6,36}.

Stress hyperglycemia is common in acute stroke patients^{37,38}. A prospective observational study showed that about 60% of people with hyperglycemia returned to a normal glucose tolerance by 3–12 months after discharge the majority³⁹. Patients with excessive BMI, are more likely to suffer hyperglycemia in the acute period, which is a strong negative prognostic indicator of death after stroke. Published researches demonstrated that increased fat mass can provoke glucose metabolism disorder by an array of pathways⁴⁰⁻⁴². In another experimental study, it is also reported that a high-fat diet could induce hyperglycemia and aggravate the growth of cerebral infarct volume⁴³. In our research, we found that the excessive BMI group exactly had higher blood glucose concentration in the first 24 hours. Besides, the level of blood glucose was also independently linked to lower 30-day mortality, whereas irrelevant with 90-day and 1-year mortality. The causal mediation analysis showed that excessive BMI was significantly associated with lower mortality in total effect while worsening the prognosis in 30 days by raising the level of blood glucose. This implies that BMI has a two-sided effect on the mortality of stroke patients in ICU. Moreover, maybe stricter standards are needed to control early blood glucose levels of patients with excess weight.

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, which often led to a poorer outcome. In a study published in 2014, the glucose level on admission was proved to be associated with the growth of infarct volume⁴⁴. Besides, in another study, Takashi Shimoyama et al prospectively measured the serum glucose concentration every 5 min for up to 72 h and proved the significant correlation between hyperglycemia and infarct volume growth in patients with ischemic stroke⁴⁵. Moreover, researches in mice have demonstrated that rats with hyperglycemia suffered increased blood-brain barrier disruption and cerebral edema⁴⁶⁻⁴⁸. The activation of inflammations and oxidative stress was thought to be the key mechanisms for the pathological changes mentioned above⁴⁹. Contrarily, patients with excessive BMI were proposed to have the stronger ability to resist inflammation²⁶ and oxidative stress²⁷ 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.

In our study, the obesity paradox was evidenced in critically ill patients with acute stroke. Also, we were 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. But 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 EHR system, it might contain systematic biases. Secondly, this is a retrospective study without the follow-up data about the weight change, home care and treatment schemes after discharging. However, it is reported that intentional weight loss was associated with improvement in obese patients with heart failure⁵⁰. Besides, weight loss was curtailed as an important secondary prevention therapy for stroke as well. Thirdly, though BMI is a convenient clinical index, it can't provide accurate measurement of body fat content and distributions. In the future study, some variables would be more significant, for example, waist circumference, waist-hip ratio, skinfold estimates, and bioelectrical impedance analysis. Fourthly, the exact mechanism to explain the obesity paradox and mediating the role of glucose are still uncertain and need more researches.

Conclusion

Collectively, in the present study, we confirmed the "obesity paradox" in critically ill patients with acute stroke. Besides, excessive BMI played a dual role in the short-term prognosis of stroke patients in ICU. Not only can it reduce the risk of death, but also can worsen the outcome by increasing the levels of blood glucose.

Abbreviations

Body mass index = BMI, intensive care unit = ICU, sequential organ failure assessment = SOFA, simplified acute physiology score II = SAPS II, Elixhauser comorbidity index = ECI

Declarations

Ethics approval and consent to participate

The establishment of this database was approved by the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA). We also got the access to the original data collection. Therefore, the ethical approval statement and the need for informed consent were waived for this manuscript.

Consent for publication

Not applicable.

Availability of data and materials

The datasets presented in the current study are available in the MIMIC-III database (<https://archive.physionet.org/works/MIMICIIIClinicalDatabase/files/>).

Competing interests

None

Funding

None

Authors' contributions

Zisheng Ma and Shunxian Li contributed equally to this work.

Zisheng Ma: conception and design of the study, acquisition and analysis of data, drafting the text and preparing the figures.

Shunxian Li: conception and design of the study, drafting the text and preparing the figures.

Xinjing Lin: conception and design of the study, guiding the literature review, modifying the text and the figures.

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Tables

Table 1 Characteristics of the study population stratified into 3 classifications of BMI

Variables	Original cohort				Matched cohort		
	Normal weight	Excessive weight	p	SMD	Normal weight	Excessive weight	SMD
N	177	345			167	167	
Male, n (%)	75 (42.4%)	182 (52.8%)	0.031	0.209	72 (43.1%)	70 (41.9%)	0.024
Age, years	76.0 (64.0, 83.0)	67.0 (57.0, 77.0)	< 0.001	0.338	84.7 ± 59.4	82.7 ± 59.2	0.034
Hypertension, n (%)	29 (15.8%)	29 (15.3%)	0.724	0.044	26 (15.6%)	26 (15.6%)	< 0.001
Diabetes, n (%)	29 (16.4%)	51 (14.8%)	0.001	0.313	40 (24%)	42 (25.1%)	0.028
Vital signs							
Heart rate, (bpm)	81.0 (68.5, 95.3)	80.7 (71.3, 91.6)	0.83	0.038	80.4 (69.5, 95.1)	80.9 (71.4, 92.9)	0.023
SBP, (mmHg)	125.1 (113.4, 142.8)	130.0 (115.6, 143.9)	0.148	0.129	125.1 (114.5, 142.2)	127.6 (112.2, 141.0)	0.024
DBP(mmHg)	62.4 (56.0, 67.7)	63.8 (55.6, 73.2)	0.083	0.198	62.6 (56.1, 68.4)	61.5 (53.7, 70.4)	0.017
Respiratory rate, (bpm)	18.3 (16.4, 21.0)	18.4 (16.3, 20.5)	0.937	0.006	18.1 (16.3, 20.9)	18.6 (16.2, 20.9)	0.013
Temperature, (°C)	36.8 (36.5, 37.2)	36.8 (36.5, 37.2)	0.918	0.037	36.8 (36.5, 37.2)	36.9 (36.5, 37.2)	0.065
Score							
SOFA	3.0 (2.0, 6.0)	3.0 (2.0, 5.0)	0.731	0.011	3.0 (2.0, 6.0)	3.0 (1.0, 5.0)	0.07
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 (28.0, 45.0)	0.051
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, 12.0)	0.032
Blood specimen							
Cr, (mg/dL)	0.9 (0.7, 1.4)	1.0 (0.8, 1.3)	0.06	0.023	0.9 (0.7, 1.3)	1.1 (0.8, 1.3)	0.028
BUN, (mg/dL)	20.2 (13.5, 30.4)	19.0 (14.2, 29.6)	0.966	0.06	19.2 (13.3, 29.3)	18.3 (14.8, 30.2)	0.007
Glucose, (mg/dL)	123.7 (107.5,	133.0 (116.8,	< 0.001	0.339	123.7 (107.8,	126.9 (112.9,	0.018

	143.3)	158.7)			143.9)	142.4)	
Mortality							
30-day, n (%)	41 (22.4%)	23 (12.1%)	0.004	-	37 (22.2%)	20 (12%)	-
90-day, n (%)	58 (31.7%)	31 (16.3%)	< 0.001	-	54 (32.3%)	25 (15%)	-
1-year, n (%)	68 (37.2%)	50 (26.3%)	< 0.001	-	64 (38.3%)	32 (19.2%)	-

Abbreviations: 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, Cr, Creatinine, BUN, blood urea nitrogen.

Table 2. Dominant mortality factors by univariable analysis

Variables	30-day mortality		90-day mortality		1-year mortality	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Excessive BMI	0.49 (0.32,0.77)	0.002	0.45 (0.31,0.66)	<0.001	0.55 (0.39,0.72)	<0.001
Male	0.94 (0.61,1.47)	0.793	0.95 (0.65,1.38)	0.777	0.9 (0.65,1.24)	0.506
Age	1.01(1.00,1.01)	<0.001	1.00 (1.00,1.01)	<0.001	1.00 (1.00,1.01)	<0.001
Hypertension	0.69 (0.35,1.39)	0.303	1.05 (0.63,1.74)	0.854	1.25 (0.82,1.9)	0.297
Diabetes	0.89 (0.55,1.44)	0.637	1.00 (0.67,1.49)	0.987	1.05 (0.75,1.48)	0.775
Heart rate	1.02 (1.00,1.03)	0.019	1.02 (1.01,1.03)	0.004	1.01 (1.01,1.02)	0.009
Systolic pressure	1.00 (0.99,1.01)	0.771	1.00 (0.99,1.01)	0.364	0.99 (0.99,1.00)	0.166
Diastolic pressure	0.99 (0.97,1.01)	0.155	0.99 (0.97,1.00)	0.170	0.99 (0.98,1.00)	0.134
Respiratory rate	1.08 (1.03,1.13)	0.002	1.06 (1.01,1.10)	0.016	1.05 (1.01,1.09)	0.024
Temperature	1.29 (0.89,1.88)	0.177	1.22 (0.89,1.67)	0.223	1.10 (0.83,1.45)	0.513
SOFA	1.10 (1.03,1.17)	0.006	1.1 (1.04,1.17)	<0.001	1.08 (1.03,1.14)	0.002
SAPS II	1.04 (1.03,1.06)	<0.001	1.04 (1.03,1.05)	<0.001	1.04 (1.03,1.05)	<0.001
ECI	0.69 (0.35,1.39)	0.004	1.04 (1.02,1.06)	<0.001	1.05 (1.03,1.07)	<0.001
Creatinine	0.88 (0.70,1.11)	0.291	0.93 (0.79,1.11)	0.421	0.97 (0.84,1.11)	0.613
BUN	1.01 (1.00,1.02)	0.045	1.01 (1.00,1.02)	0.034	1.02 (1.01,1.02)	<0.001
Glucose	1.01 (1.00,1.01)	0.033	1.00 (1.00,1.01)	0.253	1.00 (1.00,1.00)	0.749

Abbreviations: SOFA, sequential organ failure assessment, SAPS II, simplified acute physiology score II, ECI, Elixhauser-vanwalraven comorbidity index, BUN, blood urea nitrogen.

Table 3. Association between the excessive BMI and mortality in critically ill patients with acute ischemic stroke

Variables		30-day mortality		90-day mortality		1-year mortality	
		HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Multivariate regression	Cox	0.57 (0.35,0.90)	a 0.017	0.53 (0.36,0.78)	b 0.001	0.65 (0.46,0.91) ^b 0.013	
PSM		0.51 (0.29,0.87)	0.014	0.42 (0.26,0.68)	<0.001	0.44 (0.29,0.68) <0.001	<0.001
IPTW		0.55(0.36,0.84)	0.006	0.49 (0.34,0.70)	<0.001	0.61 (0.44,0.84)	0.003

Abbreviations: a, adjusted for gender, age, SAPS II, glucose, b, adjusted for gender, age, SAPS II, PSM, propensity score matching, IPTW, inverse probability of treatment weighting.

Table 4. The association between BMI and ischemic stroke outcomes stratified by age, sex, and diabetes.

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		0.118		0.059		0.087
Male (257)	0.38 (0.19~0.74)		0.35 (0.20~0.61)		0.46 (0.28~0.75)	
Female (265)	0.81 (0.43~1.55)		0.77 (0.45~1.31)		0.87 (0.55~1.38)	
Age		0.560		0.433		0.717
<65 years (189)	0.50 (0.15~1.62)		0.34 (0.13~0.90)		0.45 (0.19~1.06)	
≥65 years (233)	0.61 (0.36~1.02)		0.57 (0.37~0.88)		0.67 (0.46~0.98)	
Diabetes		0.632		0.949		0.703
No (252)	0.65 (0.37~1.15)		0.57 (0.35~0.92)		0.69 (0.46~1.05)	
Yes (170)	0.44 (0.19~1.05)		0.46 (0.23~0.90)		0.58 (0.32~1.05)	

Table 5. Causal mediation analysis for the effect of elevation of blood glucose on 30-day mortality

	Estimate (95%CI)	p
ACME	0.022 (0.006, 0.040)	0.003
ADE	-0.187 (-0.060, -0.320)	0.001
Total effect	-0.164 (-0.050, -0.293)	0.001
Prop. Mediated	-13.76% (-4.00%, -43.72%)	0.005

Abbreviations: 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).

Figures

Figure 1

The flow diagram of study patients