

Association Between Glucose Variability And Postoperative Delirium In Acute Aortic Dissection Patients: An Observational Study

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Abstract

Background: Blood glucose variability is associated with poor prognosis after cardiac surgery, but the relationship between glucose variability and postoperative delirium in patients with acute aortic dissection is unclear. The study aims to investigate the association of blood glucose variability with postoperative delirium in acute aortic dissection patients.

Methods: We prospectively analyzed 257 patients including 103 patients with delirium. The patients were divided into two groups according to whether delirium was present. The outcome measures were postoperative delirium, the length of the Intensive Care Unit stay, and the [duration of hospital stay](#). Multivariable Cox competing risk survival models was used to assess.

Results: A total of 257 subjects were enrolled, including 103 patients with delirium. There were statistically significant differences between the two groups in age, body mass index, first admission blood glucose, white blood cell counts, Acute Physiology and Chronic Health Evaluation II score, hypoxemia, mechanical ventilation duration, and the length of Intensive Care Unit stay ($P<0.05$). The median of the mean of blood glucose and the standard deviation of blood glucose were higher in the delirium group than in the non-delirium group, and the difference was statistically significant ($P<0.05$). In model 1, the adjusted hazard ratio of the standard deviation of blood glucose was 1.436 ($P<0.05$). In Model 2, the standard deviation of blood glucose (AHR=1.418, 95% CI=1.195-1.681, $P<0.05$) remained significant after adjusting for confounders ($P<0.05$). The area under the curve of the standard deviation of blood glucose was 0.763 (95% CI=0.704-0.821, $P<0.01$). The sensitivity was 81.6%, and the specificity was 57.8%.

Conclusions: Glucose variability is associated with the risk of delirium in patients after aortic dissection surgery, and high glycemic variability increases the risk of postoperative delirium.

Background

Postoperative delirium (POD) is a severe cerebral dysfunction, and is characterized by episodes of confusion, inattention, thinking disorder and mental state change of mental state change¹. It is one of the neurological complications after cardiac surgery with the incidence of as high as 11.0%-54.9%^{2,3}. And the incidence of delirium after aortic dissection surgery is 32.5%-52.0%⁴. Studies have shown that POD leads to prolonged mechanical ventilation, prolonged Intensive Care Unit (ICU) stay, a 20% increased risk of long-term hospitalization for each day, the lasting delirium, and increased hospital costs⁵⁻⁷. The patients' activity ability and quality of life are decreased were also reported⁸.

In recent years, more attention has been paid to the study of blood glucose variability (GV) on disease progression and prognosis of patients, and it has important clinical significance for monitoring and controlling of blood GV in severe patients^{9,10}. Compared with hyperglycemia, blood GV better reflects changes in the condition and has greater adverse effects on the body, which may have higher clinical

value^{10,11}. It is well known that blood GV increases the risk of adverse events after cardiac surgery, such as acute kidney injury, and the risk of short-term and long-term death^{12,13}. At present, only one article has pointed out that hypoglycemia is positively correlated with delirium in mixed ICU diabetic patients, but high blood GV is not correlated with delirium¹⁴. And there is no study on the correlation between POD and blood GV in patients after cardiac surgery, nor the effect of blood GV on POD after acute aortic dissection (AAD).

According to reports, the annual incidence of AD was 3.0–6.0 per 100,000¹⁵. The mortality rate was 36–72% in AAD in the hospital during 48 h, and an increase of 1–2% in the hourly mortality rate¹⁶. Surgery is an important way to AAD. Therefore, this study conducted an observational study to investigate the relationship between blood GV after postoperative aortic dissection and POD, and to further clarify whether blood GV affects POD.

Methods

The aim and design

The study is to investigate the relationship between blood GV after postoperative aortic dissection and POD, and to further clarify whether blood GV affects POD, which is an observational study

Participants

All patients who underwent AAD surgery at Fujian Heart Medical Center from June 2017 to June 2019. All patients were ≥ 18 years old, no metabolic disease, no history of malignant tumor, autoimmune disease, or no severe liver and kidney dysfunction. Excluding those who stayed in ICU less than 48 hours after the operation, a history of transcranial trauma, congenital deafness or schizophrenia, epilepsy before surgery, and patients who had been using glucocorticoids for a long time. Besides, patients who remained in a coma in the ICU after the operation were also excluded. The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)¹⁷ was used to assess whether the patient had positive delirium.

The acute physiology and chronic health evaluation (APACHE-II) is the most authoritative critical illness evaluation system that has been widely used in ICU. The more serious the illness is, the higher the score is. Studies have shown that the severity of the disease is closely related to the risk of delirium^{18,19}.

Delirium Assessment

Delirium was assessed by two ICU nurses who have been worked in the ICU for more than 3 years. Evaluation time was from 8:00 to 11:00, 15:00 to 17:00, and 20:00 to 23:00 on the first day after surgery, until delirium occurred or the patient transferred out of ICU.

The CAM-ICU scale can identify the following four characteristics: (1) acute onset of change or fluctuation in mental status; (2) attention disorder; (3) altered level of consciousness; (4) disorganized

thinking. At the same time satisfy the features 1, 2, and 3 or 1, 2, and 4 can be diagnosis of positive delirium.

Data collection

After the patient was transferred to the ICU, the general demographic data, intraoperative data, and postoperative data were collected by a single investigator. And the blood glucose level was collected at 8 am on the first day and continuously collected for 48 hours. The blood glucose value is obtained from the arterial blood gas analysis, If the interval was longer than 6 hours, the patient was excluded. The mean of the blood glucose (MBG) is the average blood glucose value of 48 hours, and the variability of blood glucose was assessed by the standard deviation of blood glucose (SDBG).

Statistical Analysis

We used Excel (Microsoft Corporation, Redmond, WA, USA) to calculate the SDBG and the MBG, and SPSS statistical package of 21.0 version to statistical analysis, using the appropriate statistical methods to describe data. The continuity variable conforms with the normal distribution uses the t-test and the non-compliance with the normal distribution uses the Wilcoxon signed rank-sum test. The length of ICU stay was the time index, calculating in days. It started from the first day when patients stay in the ICU until the patient was treated as a truncated value. Multivariate Cox regression analysis was performed to determine whether delirium occurred as a dependent variable (event), and hazard ratio (HR) values and 95% confidence intervals (CI) were obtained. $P < 0.05$ was considered statistically significant.

Results

From June 2017 to June 2019, 296 patients with AAD were included, and 257 patients were finally included, as shown in Fig. 1. There were 103 patients with delirium and 154 patients with non-delirium, and the incidence of delirium was 40.01%.

Table 1 shows the demographic and clinical characteristics of the delirium group and the non-delirium group. There was no statistically significant difference in age between the two groups ($P > 0.05$). There were statistically significant differences between the two groups in body mass index (BMI), first admission blood glucose, white blood cell (WBC) count, APACHE-II score, hypoxemia, mechanical ventilation duration, and the length of ICU stay ($P < 0.05$). The median of MBG and SDBG were higher in the delirium group than in the non-delirium group, and the differences were statistically significant ($P < 0.05$).

Table 1
 Characteristics of delirium patients and non-delirium patients

Variables	Delirium (n = 103)	Without Delirium (n = 154)	P
General information			
Age, mean (SD), years	53.27 (10.46)	51.06 (12.76)	0.145
BMI, median IQR, kg/m ²	25.35 (23.51, 27.68)	24.00 (22.20, 26.68)	0.014
Male	81 (78.6)	113 (73.4)	0.336
Smoker	41 (39.8)	60 (39.0)	0.892
Drinker	41 (39.8)	56 (36.4)	0.577
High school and above	20 (19.4)	36 (23.4)	0.374
Married	100 (97.1)	152 (98.7)	0.648
Hypertension	83 (80.6)	112 (72.7)	0.149
History of cardiac surgery,	7 (5.5)	2 (1.6)	0.084
Preoperative data			
First time blood glucose, IQR, mmol/L	7.58 (6.60, 9.20)	6.86 (5.90, 7.75)	< 0.001
WBC, mean (SD), [$\times 10^9/L$]	12.91 (4.11)	11.82 (3.91)	0.033
Neutrophil, median (IQR), [$\times 10^9/L$]	10.0 (6.96, 12.63)	8.54 (4.57, 11.54)	0.061
Lymphocyte, median (IQR), [$\times 10^9/L$]	6.50 (4.10, 10.0)	7.10 (4.10, 11.28)	0.330
Monocyte, median (IQR), [$\times 10^9/L$]	5.00 (3.50, 8.00)	5.4 (2.6, 7.60)	0.344
RBC, median (IQR), [$\times 10^9/L$]	4.31 (3.93, 4.77)	4.32(4.00, 4.68)	0.922
Platelet, median (IQR), [$\times 10^9/L$]	196.0 (149.8, 235.0)	193.0 (149.75, 217.0)	0.138
Hb, median (IQR), g/L	134.0 (122.0, 146.0)	131.0 (118.0, 142.0)	0.175

Values are n (%) unless otherwise indicated.

BMI = Body Mass Index; IQR = Interquartile; WBC = White Blood Cell; RBC = Red Blood Cell; Hb = hemoglobin; ASA = American Society of Anesthesiologists; CPB = Cardiopulmonary Bypass; APACHE = Acute Physiology and Chronic Health Evaluation Score; MBG = Mean of Blood Glucose; SDBG = Standard Deviation of Blood Glucose.

Variables	Delirium (n = 103)	Without Delirium (n = 154)	P
Anemia	18 (17.5)	21 (13.6)	0.896
ASA grade			0.608
III level	20 (19.4)	24 (22.1)	
≥IV level	83 (80.6)	120 (77.9)	
Entry status			0.173
Quiet	50 (48.5)	64 (41.6)	
nervous	33(32.0)	67 (43.5)	
confused	20 (19.4)	23 (14.9)	
Intraoperative data			
Operating time, median (IQR), minutes	299.0 (255.0, 365.0)	290.5 (253.5, 362.5)	0.642
Aortic cross-clamp time, median (IQR), minutes	65.0 (46.0, 95.0)	57.0 (43.0, 95.0)	0.326
CPB, median (IQR), minutes	155.0 (130.0, 188.0)	149.0 (125.0, 186.5)	0.600
Blood loss, median (IQR), ml	800.0 (600.0, 1000)	800.0 (600.0, 1000)	0.367
Postoperative data			
APACHE-II scores			< 0.001
< 15	38 (36.9)	111 (72.1)	
15–20	46 (44.7)	32 (20.8)	
> 20	19 (18.4)	11 (7.1)	
Hypoxemia	52 (50.5)	25(16.2)	< 0.001
MBG, mmol	13.07 (11.6, 15.02)	10.68 (9.56, 11.91)	0.001

Values are n (%) unless otherwise indicated.

BMI = Body Mass Index; IQR = Interquartile; WBC = White Blood Cell; RBC = Red Blood Cell; Hb = hemoglobin; ASA = American Society of Anesthesiologists; CPB = Cardiopulmonary Bypass; APACHE = Acute Physiology and Chronic Health Evaluation Score; MBG = Mean of Blood Glucose; SDBG = Standard Deviation of Blood Glucose.

Variables	Delirium (n = 103)	Without Delirium (n = 154)	<i>P</i>
SDBG, mmol	2.90 (2.18, 3.87)	1.73 (1.26, 2.54)	< 0.001
ICU stay, median (IQR), day	7.0 (5.0, 10.0)	5.0 (4.0, 7.0)	< 0.001
Mechanical ventilation duration, median (IQR), hours	61.0 (37.0, 139.0)	42.5 (27.8, 82.3)	< 0.001
Hospitalization days, median (IQR), day	21.0 (15.0, 26.0)	18.0 (14.0, 25.0)	0.357
Values are n (%) unless otherwise indicated.			
BMI = Body Mass Index; IQR = Interquartile; WBC = White Blood Cell; RBC = Red Blood Cell; Hb = hemoglobin; ASA = American Society of Anesthesiologists; CPB = Cardiopulmonary Bypass; APACHE = Acute Physiology and Chronic Health Evaluation Score; MBG = Mean of Blood Glucose; SDBG = Standard Deviation of Blood Glucose.			

In Table 2, patients were divided into lower GV group and higher GV group according to the median of the SDBG. There were no statistically significant differences in age, BMI, gender, smoker, drinker, education level, marital status, hypertension, and history of cardiac surgery, etc. Compared with the lower GV group, the length of ICU stay in the higher GV was longer, and the difference between the two groups was statistically significant ($P < 0.05$).

Table 2
Baseline characteristics of patients with low and high GV

Variables	Lower GV N = 129	Higher GV N = 128	P
Age, mean (SD), years	50.78 ± 12.67	53.12 ± 11.04	0.117
BMI, median IQR, kg/m ²	24.75 (22.78, 27.18)	24.22 (22.50, 26.72)	0.575
Male	97 (75.2)	97 (75.8)	0.913
Smoker	52 (40.3)	45 (35.2)	0.394
Drinker	53 (41.1)	48 (37.5)	0.556
High school and above	31 (24.0)	25 (19.5)	0.190
Hypertension	92 (71.3)	103 (80.5)	0.086
Married	127 (98.4)	125 (97.7)	0.645
History of cardiac surgery	2 (1.6)	7 (5.5)	0.088
First time blood glucose, median (IQR), mmol	6.98 (5.93, 8.45)	7.19 (6.19, 8.27)	0.274
WBC, median (IQR), [$\times 10^9/L$]	12.38 ± 3.82	12.15 ± 4.21	0.643
Neutrophil, median (IQR), [$\times 10^9/L$] (IQR)	9.24 (5.70, 11.74)	8.96 (5.48, 12.28)	0.880
Lymphocyte, median (IQR), [$\times 10^9/L$]	6.70 (3.70, 10.40)	7.15 (4.53, 11.50)	0.202
Monocyte, median (IQR), [$\times 10^9/L$]	4.80 (2.20, 7.65)	5.80 (3.80, 7.90)	0.085
RBC, median (IQR), [$\times 10^9/L$]	4.29 (4.0, 4.72)	4.38 (3.92, 4.74)	0.909
Platelet, median (IQR), [$\times 10^9/L$]	192.0 (150.0, 234.50)	187.50 (149.30, 225.75)	0.846
Hb, median (IQR), g/L	131.0 (119.5, 141.50)	134.0 (121.0, 145.0)	0.251
Anemia	21 (16.3)	18 (14.1)	0.620
Mechanical ventilation duration, median (IQR), hours	45.0 (33.5, 96.0)	48.3 (28.26, 102.15)	0.609
ICU stay, median (IQR), day	6.0 (4.0, 8.0)	6.0 (4.0, 10.0)	0.040

Values are n (%) unless otherwise indicated.

GV = Glucose Variability ;BMI = Body Mass Index; IQR = Interquartile Range; WBC = White Blood Cell; RBC = Red Blood Cell; Hb = Hemoglobin.

Variables	Lower GV	Higher GV	<i>P</i>
	N = 129	N = 128	
Hospitalization days, median (IQR), day	19.5 (14.25, 25.0)	20.0 (15.0, 27.0)	0.455
Values are n (%) unless otherwise indicated.			
GV = Glucose Variability ;BMI = Body Mass Index; IQR = Interquartile Range; WBC = White Blood Cell; RBC = Red Blood Cell; Hb = Hemoglobin.			

As shown in Table 3, after adjusting for age, gender, and BMI in model 1, the adjusted hazard ratio (AHR) of WBC was 0.932 ($P > 0.05$), which was not correlated with the risk of POD; the AHR of APACHE-II > 20 scores was 2.178 (95% CI = 1.108–4.281), the AHR of hypoxemia was 1.563 (95% CI = 1.070–2.518), and the AHR of SDBG was 1.436 (95% CI = 1.205–1.711), all three increased the risk of delirium ($P < 0.05$). In Model 2, the AHR of APACHE-II > 20 scores was 2.376 (95% CI = 1.342–3.876), the AHR of hypoxemia was 1.778 (95% CI = 1.122–2.818), and the AHR of SDBG was 1.418 (95% CI = 1.195–1.681), all three remained significant after adjusting for confounding factors ($P < 0.05$).

Table 3
Multivariable Cox regression analysis of Possible Predictors of delirium

Variables	Model 1		Model 2	
	AHR(95% CIs)	<i>P</i>	AHR(95% CIs)	<i>P</i>
Age, years	1.007 (0.985–1.028)	0.547	1.002 (0.983–1.002)	0.813
BMI, kg/m ²	1.029 (0.971–1.091)	0.336	1.021 (0.963–1.083)	0.482
Male	1.381 (0.801–2.381)	0.246	–	–
WBC	0.932 (0.852–1.020)	0.124	0.993 (0.994–1.046)	0.802
First time blood glucose	1.012 (0.968–1.058)	0.607	1.015 (0.973–1.058)	0.931
Neutrophil	1.062 (0.988–1.143)	0.105	–	–
APACHE-II (> 20 scores)	2.178 (1.108–4.281)	0.024	2.376 (1.342–3.876)	0.002
Hypoxemia	1.563 (1.070–2.518)	0.046	1.778 (1.122–2.818)	0.014
SDBG, mmol	1.436 (1.205–1.711)	< 0.001	1.418 (1.195–1.681)	0.001
Mechanical ventilation duration	1.000 (0.999–1.002)	0.791	1.000 (0.998–1.001)	0.931
BMI = Body Mass Index; WBC = White Blood Cell; APACHE = Acute Physiology and Chronic Health Evaluation Score; SDBG = Standard Deviation of Blood Glucose.				

According to the receiver operating characteristic (ROC) curve, the area under the curve of the SDBG was 0.763 ($P < 0.01$). The sensitivity was 81.6%, and the specificity was 57.8%. The area under the curve of the MBG was 0.628 ($P = 0.001$). The sensitivity was 75.7%, and the specificity was 53.2%. The difference of area under the curve between the two groups was statistically significant ($P = 0.002$), which was shown in Fig. 2.

Discussion

Delirium is a common complication after aortic dissection surgery with an incidence of 32.5–52.0%⁴, and the results of this study showed that the incidence of delirium was 40.01%, which was consistent with other studies. The area under the curve of the SDBG was greater than the MBG. After adjusting for confounding factors, the SDBG was independently correlated with the risk of delirium.

No matter how the quality of perioperative blood glucose controls in patients who underwent cardiac surgery, blood glucose changes are reported they are related to postoperative complications^{20,21}. After linear regression analysis, the difference between the two groups was statistically significant, which showed that blood GV was a significant predictor of prolonged ICU stay. Multi-factor results showed that blood GV could predict prolonged ICU stay (OR = 1.016, $P = 0.006$). Hypoglycemia and hyperglycemia have been identified as risk factors for delirium^{22,23}, but there are few reports on the relationship between glucose fluctuation and delirium. Keulen et al.¹⁴ shows that delirium is positively associated with hypoglycemia in severe patients with diabetes, but not associated with pronounced glycemically variability. And Heymann et al.²⁴ found that patients with hyperactive delirium have higher MBG than the non-hyperactive delirium patients. There is no consensus on the relationship between glucose fluctuation and delirium, and this study showed that high glycemically variability increases the risk of postoperative delirium.

Glucose, a simple carbohydrate, is the main source of energy for many cells. Studies have shown that the brain consumes 50% of the total body's consumption of glucose²⁵. Glucose sensory neurons are present in several areas of the brain. The activity of neurons changes with the level of glucose, and the brain function depends on the stable glucose levels, which is why the brain is particularly sensitive to glucose level. Therefore, the blood glucose level needs to be maintained in a narrow physiological range²⁶. A study shows that people with diabetes are at least 1.5 times more likely to develop dementia than people without diabetes, further highlighting the effect of glucose changes on the brain function and long-term consequences²⁵. Both acute and chronic hyperglycemia has been shown to cause oxidative stress, subsequent neuronal damage, and cognitive decline²⁷, and the reason is closely related to delirium.

At present, the mechanism of blood glucose volatility promoting the development of critical illness and poor prognosis is not clear. However, blood glucose volatility is the biological basis of the human body²⁸. According to the theory of oxidative stress, fluctuating hyperglycemia can easily cause oxidative stress than persistent hyperglycemia²⁹. The specific mechanism may be that intermittent hyperglycemia can increase the overexpression of reactive oxygen species in the mitochondrial transport chain, thereby

promoting oxidative stress response, increasing the apoptosis rate of endothelial cells, and ultimately causing damage to central nervous function²⁷. Meanwhile, it has been reported that the oxidative stress of intermittent hyperglycemia is greater than that of sustained hyperglycemia under experimental conditions, which has been confirmed by clinical studies. Besides, high blood glucose will also cause the release of a large number of pro-inflammatory cytokines, resulting in coagulation dysfunction, vascular reactivity abnormalities, and other injuries. However, patients with acute aortic dissection often present intermittent hyperglycemia due to acute illness, surgical stress, drugs, and other reasons, which is closely involved in central nervous injury.

Cardiopulmonary bypass is the main technology for acute aortic dissection. Inflammatory mediators are released in large quantities during cardiopulmonary bypass cardiac surgery, and the inflammatory state is another common phenomenon of stress response. The inflammatory response itself has a protective effect on the body. But when the balance between inflammatory and anti-inflammatory is broken, the body shows an inflammatory state and a large number of inflammatory factors in the peripheral circulation enter the central nervous system through various channels, which can cause inflammation in the central nervous system³⁰. A large number of studies have suggested that neuron inflammation may be one of the mechanisms of cognitive impairment. Cibelli et al.³¹ founds that surgical trauma activates the innate immune system, which in turn triggers an IL-1-mediated inflammatory response in the hippocampus, resulting in memory impairment in mice. Besides, the operation itself is a kind of serious trauma, causing the organism to appear stress state. The imbalance of the central nervous system about noradrenaline and acetylcholine decreases the acetylcholine content, resulting in a series of neurological complications.

There are several limitations to this study. First, the sample size was small, and the relevant conclusions need to be further demonstrated with a larger sample. Second, we only evaluated delirium in ICU patients without long-term follow-up. Finally, the number of glucose we measure per day may be less.

Conclusions

Glucose variability is associated with the risk of delirium in patients after aortic dissection surgery, and high glyceic variability increases the risk of POD. Therefore, we should pay more attention to it.

Abbreviations

POD: Postoperative delirium

GV: Glucose variability

ICU: the Intensive Care Unit

AAD: Acute aortic dissection

MBG: Mean of blood glucose

SDBG: Standard deviation of blood glucose

CAM-ICU: The Confusion Assessment Method for the Intensive Care Unit

HR: Hazard ratio

CI: Confidence intervals

BMI: Body mass index

WBC: White blood cell

APACHE-II: Acute physiology and chronic health evaluation

ROC: Receiver operating characteristic

Declarations

Ethical approval and consent to participate

The work was conducted at the Department of Cardiac Surgery, Fujian Medical University Union Hospital. The study was approved by the Ethics Committee of Fujian Medical University Union Hospital (Ethical Review No. 2017KY009). All subjects or their families informed consent form to participate in the study.

Consent for publication Parental/guardian consent obtained.

Availability of data and material The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests No competing interests.

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Authors' contributions

L-YL and X-ZH assessed the delirium of the subjects. H-RZ and QC collected socio-demographic and clinical data. Y-CP, L-YL, and L-WC analyzed and interpreted the data; Y-JL, L-YL, and H-RZ drafted the manuscript; all authors critically revised the manuscript. All authors read and approved the final manuscript.

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Figures

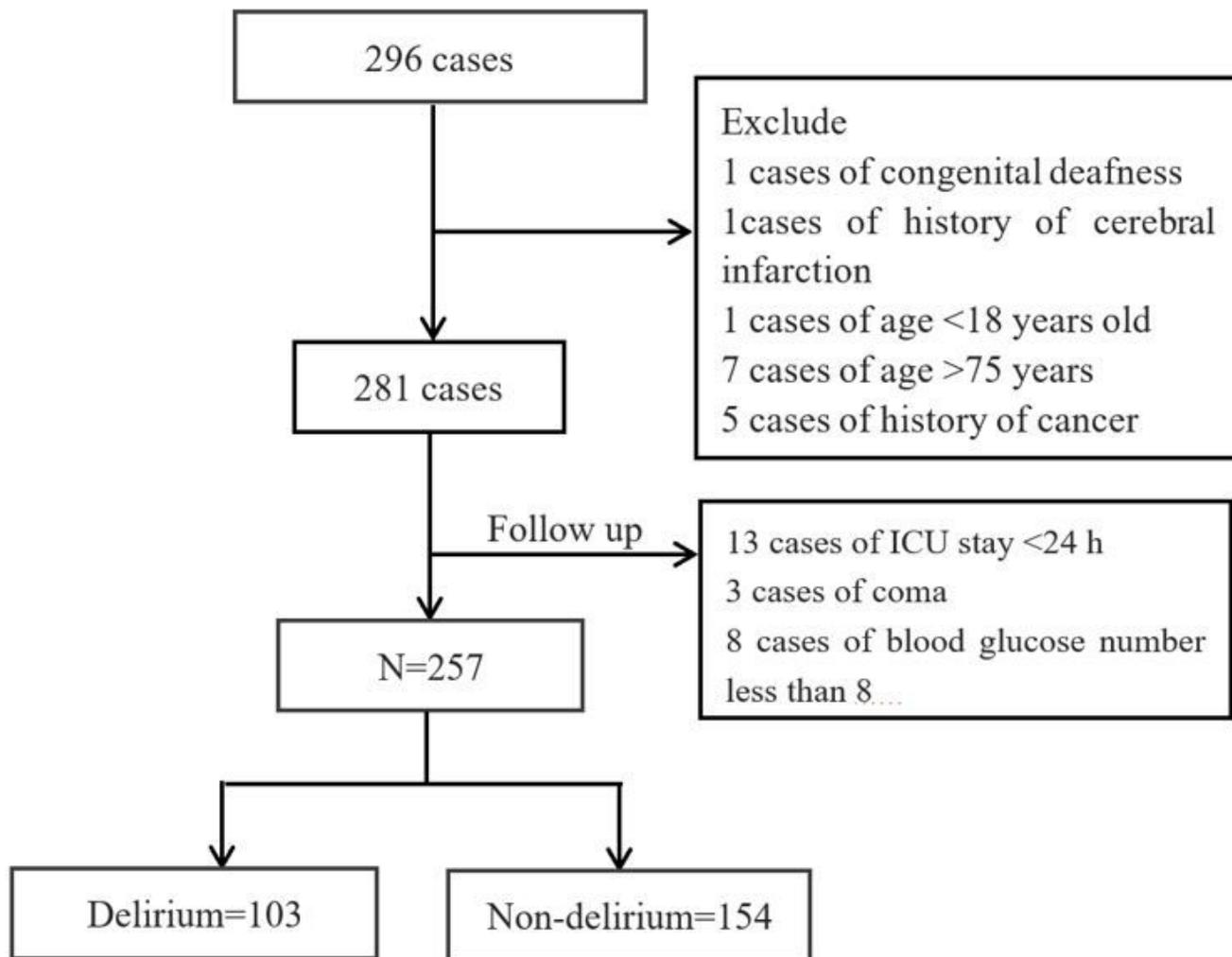


Figure 1

Flowchart of the study From June 2017 to June 2019, 296 patients with AAD were included, and 257 patients were finally included. There were 103 patients with delirium and 154 patients with non-delirium.

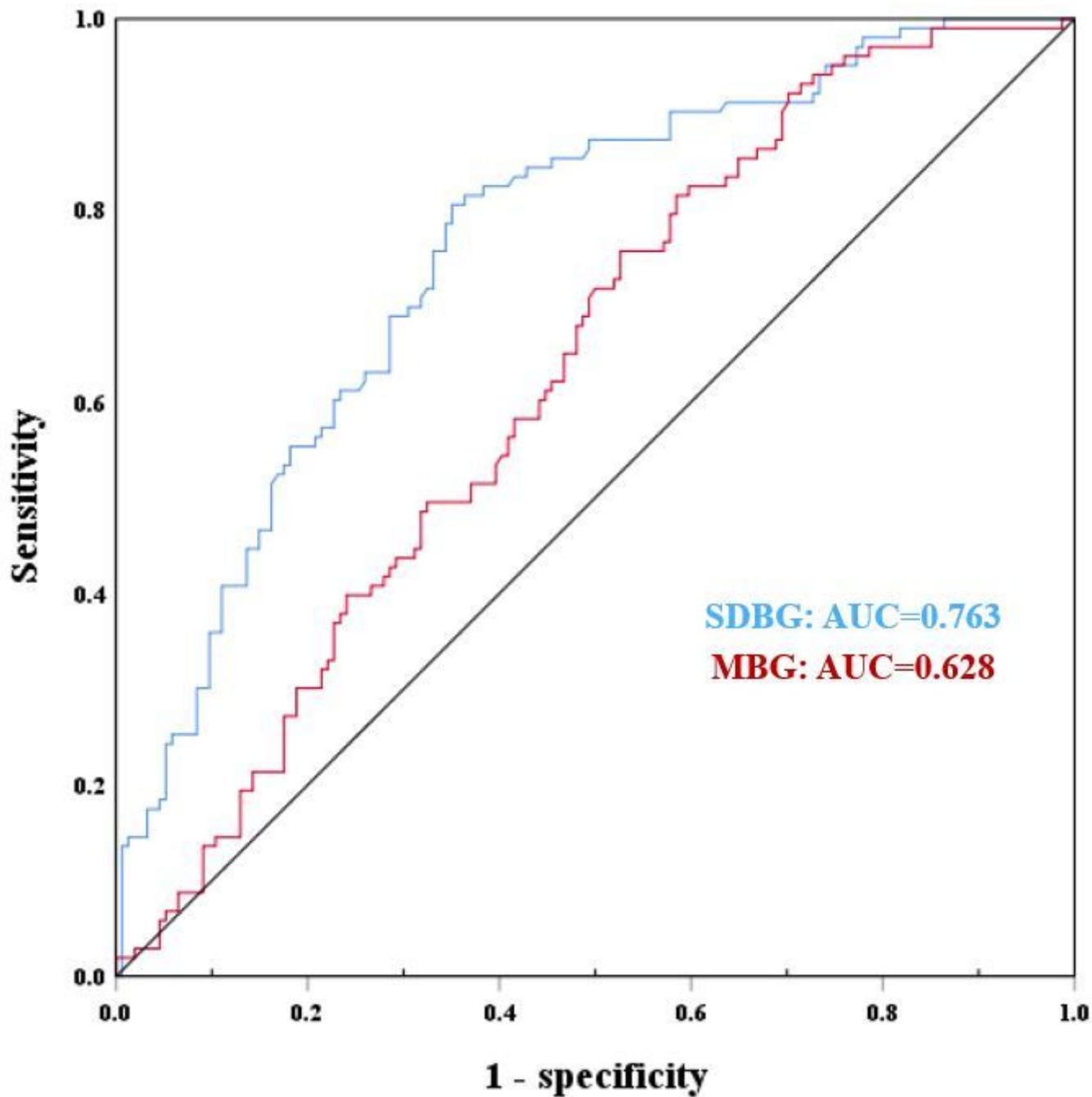


Figure 2

The ROC curves of predict POD of patients with A AD The area under the curve of the SDBG was 0.763 ($P < 0.001$). The sensitivity was 81.6%, and the specificity was 57.8%. The area under the curve of the MBG was 0.628 ($P=0.001$). The sensitivity was 75.7%, and the specificity was 53.2%.