

Serum glucose as an important predictor of delayed cerebral ischemia in angiogram-negative subarachnoid hemorrhage

Zeyu Zhang

Zhejiang University School of Medicine Second Affiliated Hospital

Anke Zhang

Zhejiang University School of Medicine Second Affiliated Hospital

Xiaoyu Wang

Zhejiang University School of Medicine Second Affiliated Hospital

Yuanjian Fang

Zhejiang University School of Medicine Second Affiliated Hospital

Yibo Liu

Zhejiang University School of Medicine Second Affiliated Hospital

Yujie Luo

Zhejiang University School of Medicine Second Affiliated Hospital

Cameron Lenahan

Loma Linda University School of Medicine

Sheng Chen (✉ saintchan@zju.edu.cn)

Zhejiang University School of Medicine Second Affiliated Hospital <https://orcid.org/0000-0002-8374-136X>

Jianmin Zhang

Zhejiang University School of Medicine Second Affiliated Hospital

Research

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Abstract

Background

Despite benign overall course, angiogram-negative subarachnoid hemorrhage (AN-SAH) still companies with risk of delayed cerebral ischemia (DCI). Serum glucose was previously found to be related to DCI occurrence in aneurysmal subarachnoid hemorrhage (aSAH), but this has not been confirmed in AN-SAH. The aim of this study was to clarify the significance of serum glucose in DCI prediction in AN-SAH patients.

Methods

We included patients with AN-SAH admitted to our hospital between January 2013 and December 2018. According to different bleeding patterns, patients were divided into perimesencephalic AN-SAH (PAN-SAH) and non-perimesencephalic AN-SAH (NPAN-SAH) patients. DCI was defined as symptomatic vasospasm or/and delayed cerebral infarction. A statistical analysis of the clinical, radiological, and laboratory risk factors of DCI was conducted. Logistic regression analysis was performed to identify the independent predictors of DCI.

Results

A total of 244 AN-SAH patients (mean age 55.7 years, 55.7% men) were included with 164 (67.2%) PAN-SAH patients and 80 (32.8%) NPAN-SAH patients. There were significant correlations between high DCI incidence and high serum glucose levels in the first five days after admission in both PAN-SAH patients and NPAN-SAH patients ($p < 0.05$). High admission serum glucose was significantly related to higher World Federation of Neurosurgeons Scale (WFNS) ($p < 0.05$). Multivariate logistic regression analysis showed that admission serum glucose ($p = 0.001$, OR 1.705, 95% CI 1.232–2.360) and WFNS ($p = 0.008$, OR 2.889, 95% CI 1.322–6.311) were both significant and independent predictors for DCI occurrence in PAN-SAH patients. Admission serum glucose ($p = 0.016$, OR 2.307, 95% CI 1.167–4.562), standard deviation (SD) of the serum glucose in the first three days after admission ($p = 0.049$, OR 5.684, 95% CI 1.006–32.114) and modified Fisher scale (mFS) ($p = 0.033$, OR 1.859, 95% CI 1.051–3.288) were significant and independent predictors for DCI occurrence in NPAN-SAH patients.

Conclusions

Serum glucose is an early biomarker to predict DCI risk in both PAN-SAH and NPAN-SAH patients, which has an important value in guiding intensive care in AN-SAH patients.

Background

Despite repeated cerebral angiography, the source of bleeding cannot be identified in approximately 15% of patients with spontaneous subarachnoid hemorrhage (SAH). This subgroup has been classified as angiogram-negative SAH (AN-SAH) [1–3]. According to different bleeding patterns shown on computed tomography (CT), AN-SAH is divided into perimesencephalic AN-SAH (PAN-SAH) and non-perimesencephalic AN-SAH (NPAH-SAH) [4]. It was previously believed that AN-SAH has a different natural history and better outcome compared to aneurysmal SAH (aSAH). However, recent studies have shown that the clinical course and outcome of NPAN-SAH are similar to that of aSAH [5]. Although the overall course is relatively benign, AN-SAH still has a certain incidence of delayed cerebral ischemia (DCI) and poor outcome, particularly in NPAN-SAH patients [5]. Therefore, it is important to find early risk factors that predict DCI and unfavorable outcome for patients with AN-SAH.

Previous studies have confirmed the clinical value of several biomarkers for DCI after aSAH, such as serum glucose, lactate, D-dimer, C-reactive Protein (CRP), and white blood cell (WBC) count [6–8]. However, few studies have focused on the risk factors of DCI in patients with AN-SAH. Previous studies found that hyperglycemia at admission was associated with increased short-term mortality in aSAH patients without diabetes [9]. Moreover, another study found a correlation between early serum glucose levels and the occurrence of DCI and poor outcome in patients with aSAH [6]. In addition, serum glucose variability during hospitalization was also confirmed to be related to mortality, delayed cerebral infarction and neurological outcome after aSAH [10–12]. However, there was no study exploring the clinical value and predictive role of serum glucose levels in AN-SAH.

In this study, we analyzed our institutional data to illustrate the relationship between serum glucose and risk of DCI occurrence, and we investigated whether early serum glucose could be a predictor of DCI in AN-SAH.

Methods

Study population

In this study, consecutive patients with AN-SAH admitted to the Second Affiliated Hospital, School of Medicine, Zhejiang University, between January 1, 2013 and December 31, 2018 were retrospectively reviewed. All patients were admitted to the hospital within 24 hours after onset. AN-SAH was defined as non-traumatic SAH with negative findings in the first cerebral digital subtraction angiography (DSA) examination, which was performed according to strict standards within 72 hours of admission [4]. Some patients underwent a repeated DSA examination 10–14 days later. In addition, the following patients were excluded: (1) history of head injury or suspicious head injury; (2) history of previous diabetes; (3) missing/lost radiological data; (4) missing/lost serum glucose data on admission or during hospitalization.

All aspects of this study were approved by the local Institutional Review Board. Due to the approval of the Institutional Review Board, patient consent was not required in this study.

Patient management

All patients were diagnosed as AN-SAH by CT and DSA performed at admission. According to different bleeding patterns, AN-SAH was divided into PAN-SAH and NPAN-SAH [4, 13, 14]. The characteristics of PAN-SAH are as follows: (1) hemorrhage anterior to the midbrain and/or pons; (2) no extension into parenchyma or ventricle; (3) no complete extension into the anterior interhemispheric fissure; (4) possible extension into the basal parts of the sylvian fissures, but not into the lateral sylvian fissures; (5) no significant intraventricular hemorrhage. Those that did not meet the bleeding pattern described above were classified as NPAN-SAH.

We reviewed the baseline characteristics of the patients, including age, gender, past medical history, social history, hospital stay, and body mass index (BMI). The clinical and radiological data obtained during hospitalization were used to assess the severity of SAH. The clinical data included the World Federation of Neurosurgeons Scale (WFNS) and Hunt and Hess (HH) grade [15, 16]. The radiological data included the modified Fisher scale (mFS), Subarachnoid Hemorrhage Early Brain Edema Score (SEBES), and intraventricular hemorrhage (IVH) [17, 18]. Additionally, we investigated the laboratory data on admission, including sodium, potassium, glucose, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A1 (ApoA1), and apolipoprotein B (ApoB). We reviewed the serum glucose levels in the first 5 days after admission. All the patients had at least one arterial glucose measurement per day for the first 3 days after admission, and at least one measurement on days 4 and 5. If the serum glucose was measured multiple times in one day, the median measurement would be used for that daily value. Moreover, SAH-related complications, such as rebleeding, acute hydrocephalus, seizure, and DCI were also reviewed [19-21].

All patients were treated in accordance with SAH guidelines provided by the Neurocritical Care Society and the American Heart Association [22, 23]. Hemodynamic values were monitored via electrocardiogram on admission. All patients received nimodipine and intravenous hydration to prevent cerebral vasospasm and maintain euvoolemia, respectively.

Outcome assessment

This study defined outcomes in terms of the occurrence of DCI. DCI was defined as symptomatic vasospasm and/or delayed cerebral infarction. Symptomatic vasospasm was diagnosed as a focal neurological impairment or decrease of at least 2 points on the Glasgow Coma Scale (GCS) lasting for at least 1 hour, is not immediately apparent after SAH onset, and is not attributable to other causes [24]. Delayed cerebral infarction referred to a new infarction emerging on CT or magnetic resonance imaging (MRI), which was not present within the first 24 to 48 hours after SAH onset, and was not attributable to other causes [24]. Two senior neurologists independently evaluated all the radiological data. If there was a divergence between the two neurologists, a third examiner would be used.

Statistical analysis

Statistical analysis was performed using IBM-SPSS V24.0 (SPSS Inc, Armonk, NY) and Prism 8 (GraphPad Software, Inc, LA Jolla, CA). All p-values were two-tailed with statistical significance set at p-value < 0.05. Demographic data, clinical data, radiological data, laboratory data, and SAH-related complications were compared between the DCI and the non-DCI groups. The Shapiro-Wilk test was used to evaluate normality of the data. Normally and abnormally distributed variables were respectively expressed as means ± standard deviations (SD), as well as median and interquartile range (IQR). Categorical variables were expressed as the number of patients (percentage). Student's t-test was used to compare the normally distributed variables. Mann-Whitney U-test was used to compare the non-normally distributed variables. Chi-square or Fisher's exact test was used to compare the categorical variables. Subsequently, the variables of PAN-SAH and NPAN-SAH patients were compared. After dividing AN-SAH patients into PAN-SAH patients and NPAN-SAH patients, the variables between the DCI group and non-DCI group were compared again. In addition, the characteristics of the high glucose and the low glucose groups were compared. Finally, univariate and multivariate binary logistic regression analysis were performed. The odds ratio (OR) and 95% confidence interval (CI) were calculated. Multivariate logistic regression analysis, using a backward selection method, was performed for the variables with a p-value < 0.15 in univariate analysis to identify the independent predictors of DCI.

Results

Patient characteristics

A total of 296 patients were diagnosed with AN-SAH. Thirteen patients had a history of head injury or suspicion of head injury. Twenty-two patients suffered from diabetes. Ten patients were missing radiological data and seven patients were missing serum glucose data on admission or during hospitalization. Therefore, 244 patients were included in the final cohort, with 164 (67.2%) PAN-SAH patients and 80 (32.8%) NPAN-SAH patients. Males comprised 136 (55.7%) of the patients. The average age of the patients was 55.7 years.

According to the occurrence of DCI, 244 AN-SAH patients were divided into DCI group ($n = 62$) and non-DCI group ($n = 182$). There were significant correlations between the DCI group and age ($p = 0.045$), hypertension ($p = 0.021$), hospital stay ($p < 0.001$), ICU stay ($p < 0.001$), PAN ($p < 0.001$), WFNS ($p < 0.001$), HH grade ($p < 0.001$), mFS ($p < 0.001$), SEBES ($p < 0.001$), IVH ($p < 0.001$), rebleeding ($p < 0.001$), acute hydrocephalus ($p < 0.001$), and admission serum glucose ($p < 0.001$; Table 1).

Comparison of variables between PAN-SAH and NPAN-SAH patients

The evaluation of associations regarding bleeding patterns with patient characteristics is shown in Table 2. Hospital stay, WFNS, HH grade, mFS, SEBES, IVH, and admission serum glucose presented significant differences between PAN-SAH patients and NPAN-SAH patients (all $p < 0.001$). Additionally, there were significant differences in some complications, including DCI ($p < 0.001$), rebleeding ($p = 0.001$), and acute hydrocephalus ($p < 0.001$) between the two populations.

Comparison of variables between DCI and non-DCI groups in two bleeding patterns

Due to the significant differences in the characteristics between two bleeding patterns, we analyzed the data of PAN-SAH and NPAN-SAH patients (Table 3). The DCI group was still significantly associated with high admission serum glucose in both populations (both $p < 0.001$; Fig. 1A, B). There was a significant association between high SD of serum glucose in the first three days and DCI group in both PAN-SAH ($p = 0.038$; Fig. 1C) and NPAN-SAH ($p = 0.001$; Fig. 1D) patients. In addition, there were significant correlations between the DCI group and an extended stay in the hospital and ICU stay, as well as high WFNS, high HH grade, high mFS, IVH, and high serum glucose in the first five days after admission in both PAN-SAH patients and NPAN-SAH patients (all $p < 0.05$).

Dynamic changes of serum glucose after admission

Serum glucose levels of DCI and non-DCI groups showed similar trends after admission in both PAN-SAH (Fig. 2A) and NPAN-SAH (Fig. 2B) patients. Shortly after admission, the serum glucose levels gradually decreased and reached the lowest value on the third day. However, in the four or five days after admission, glucose levels increased slightly. In both bleeding patterns, the serum glucose of the DCI group was consistently higher than that of the non-DCI group in the first five days after admission.

Comparison of variables between high and low glucose groups in two bleeding patterns

We then divided the PAN-SAH patients and the NPAN-SAH patients into either high or low glucose groups according to the median serum glucose on admission of each group (6.575 mmol/L in PAN-SAH patients and 7.235 mmol/L in NPAN-SAH patients). The results are shown in Additional file 1: Table S1. In the PAN-SAH population, patients in the high glucose group had higher age ($p = 0.036$), WFNS ($p < 0.001$), HH grade ($p = 0.004$), and DCI incidence ($p = 0.003$). In the NPAN-SAH population, patients in the high glucose group had an extended hospital stay ($p = 0.009$), as well as high WFNS ($p = 0.004$) and increased incidence of DCI ($p < 0.001$) and acute hydrocephalus ($p = 0.039$). The distributions of WFNS, HH grade, mFS, SEBES, and DCI in the two groups are shown in Additional file 2: Figure S1. The percentages of patients with high WFNS, HH grade, mFS, SEBES, and DCI incidence were often higher in the high glucose group than in the low glucose group.

Multivariate analysis of predictors for DCI in PAN-SAH and NPAN-SAH patients

The results of univariate and multivariate analyses concerning variables that influence the occurrence of DCI in PAN-SAH and NPAN-SAH patients are provided in Table 4. Multivariate logistic regression analysis revealed admission serum glucose ($p = 0.001$, OR 1.705, 95% CI 1.232-2.360) and WFNS ($p = 0.008$, OR 2.889, 95% CI 1.322-6.311) as significant and independent predictors for the occurrence of DCI in PAN-SAH patients. Admission serum glucose ($p = 0.016$, OR 2.307, 95% CI 1.167-4.562) and SD of the serum glucose in the first three days after admission ($p = 0.049$, OR 5.684, 95% CI 1.006-32.114) and mFS ($p = 0.033$, OR 1.859, 95% CI 1.051-3.288) were significant and independent predictors for the occurrence of DCI in NPAN-SAH patients.

Discussion

The main findings of our study were that high early serum glucose levels significantly correlated with high incidence of DCI in both PAN-SAH and NPAN-SAH patients, despite similar time-dependent changes in DCI and non-DCI groups. In addition, high serum glucose levels on admission were associated with high WFNS. Multivariate logistic regression analysis showed that admission serum glucose was a significant and independent predictor for DCI occurrence in both PAN-SAH and NPAN-SAH patients. To our knowledge, this is the first article to illustrate the association of serum glucose and occurrence of DCI after AN-SAH.

AN-SAH occurs in approximately 15% of SAH patients, and is characterized as either PAN-SAH or NPAN-SAH according to their bleeding patterns [3]. Although the overall prognosis is good, a certain percentage of AN-SAH patients still have DCI and poor outcome, especially NPAN-SAH [4, 5]. It is generally believed that patients with NPAN-SAH have a worse neurological outcome and a higher incidence of complications than PAN-SAH patients, which is consistent with our findings [3, 25]. The prognosis of NPAN-SAH is considered similar to that of aSAH [5]. Therefore, it is necessary to identify early risk factors of DCI and unfavorable outcome in AN-SAH. However, few studies have focused on factors related to the occurrence of DCI in AN-SAH patients thus far.

Previous studies have verified the relationship between serum glucose and DCI or vasospasm after aSAH. One study found that post-aSAH symptomatic vasospasm significantly correlated with admission serum glucose levels ($p = 0.003$), which was congruent with our findings. However, in multivariate analysis, admission glucose levels were not a significant predictor of symptomatic vasospasm (OR, 0.99 [95% CI, 0.99–1.01]) [26]. In another study, maximum serum glucose levels shortly after aSAH were associated with an increased risk of DCI ($p = 0.002$). Multivariate analysis showed that glucose was an independent predictor of DCI (OR, 1.17 [95% CI, 1.05–1.30]) [6]. This is consistent with the results we found in patients with AN-SAH. However, this study differs in that it defined DCI as a new hypodensity on CT not otherwise explained by cerebral infarction due to DCI after admission. To more accurately understand the relationship between serum glucose and DCI after AN-SAH, we also analyzed the mean, maximum, minimum, range, SD, and CV of serum glucose shortly after admission. In addition, another study found that the serum glucose/potassium ratio was an independent predictor of cerebral vasospasm after aSAH [27].

Although the mechanisms underlying the relation between serum glucose and risk of DCI are still unclear, the SAH-induced stress response may explain this association. Catecholamines, glucagon, and corticosteroids are the main hormones involved in causing hyperglycemia [27]. Neurogenic stress can cause the release of these hormones, which may induce inflammation and cause systemic damage [28]. Elevation of serum catecholamine concentrations, which induce sympathetic activation, has been confirmed after aSAH, and was found to be associated with a poor outcome [29]. One study found that early sympathetic activation after bleeding reflected the severity of aSAH, and was related to the development of DCI and poor outcomes [30]. A cohort study showed that using a beta-blocker to inhibit

sympathetic activity was associated with a lower incidence of cerebral vasospasm in patients with aSAH [31]. An experimental study also confirmed the correlation between sympathetic suppression and decreased cerebral vasospasm after SAH [32]. Therefore, elevated serum glucose after SAH may reflect the stress response and severity of the neurological insult. In the present study, patients with higher serum glucose on admission showed had increased severity when assessed using WFNS, as well as increased risk of DCI. NPAN-SAH patients have higher serum glucose levels, as well as higher clinical and radiological severity than PAN-SAH patients. This may reflect that NPAN-SAH patients have a stronger stress response and more severe neurological damage when compared with PAN-SAH patients, and may explain the higher risk of DCI in patients with NPAN-SAH. However, after controlling for some risk factors, including WFNS and mFS, the admission serum glucose was still associated with the occurrence of DCI, suggesting that there might be other mechanisms mediating the link between serum glucose and risk of DCI.

It remains unclear whether hyperglycemia plays a role in the occurrence of DCI or if it is just a stress response to SAH. Previous studies have shown that hyperglycemia may exacerbate secondary brain injury after stroke [33]. Moreover, hyperglycemia provides an abundant substrate for anaerobic glycolysis in ischemic brain tissue, which leads to excessive lactate accumulation, acidosis, and cell death [34]. In a rat SAH model, hyperglycemia exacerbated cerebral vasospasm by dysregulating endothelial nitric oxide synthase (eNOS) and inducing nitric oxide synthase (iNOS) [35]. Another experimental study indicated that hyperglycemia may activate the extrinsic caspase cascade through the extracellular regulated kinase (ERK) signal pathway to contribute to neuronal apoptosis after SAH [36]. Aggressive glucose management may help improve outcome in aSAH [33]. However, some studies held an opposite view. A previous prospective study found that hyperglycemia preceded aSAH onset, as evidenced by the elevated glycated hemoglobin (HbA1c) levels, but did not lead to poor outcome [37]. Low cerebral glucose, which is related to severe metabolic distress, may exert deleterious effects in patients with aSAH [38]. Intensive glycemic control with insulin after aSAH may reduce cerebral glucose, leading to worse outcome [39, 40]. However, some studies have shown that increasing serum glucose through enteral nutrition could increase cerebral glucose levels without causing abnormal cerebral glucose metabolism, which may improve the prognosis of patients with aSAH [41, 42]. Therefore, post-SAH hyperglycemia may be a protective factor in the brain that compensates for insufficient cerebral glucose after brain injury.

Our study is the first to examine the relationship between early serum glucose levels and risk of DCI in patients with AN-SAH. In this study, high serum glucose at admission correlated with high WFNS, indicating that admission serum glucose may reflect the severity of AN-SAH. Serum glucose levels at admission and early after admission, which may reflect the degree of SAH-induced stress, were significantly associated with the occurrence of DCI in both PAN-SAH patients and NPAN-SAH patients. Multivariate analysis showed that admission serum glucose was an independent predictor of DCI risk after PAN-SAH or NPAN-SAH. Since serum glucose is routinely collected in SAH patients, it seems to be a convenient method to identify patients at high risk of DCI after AN-SAH to guide intensive care. It remains unclear whether the elevated serum glucose after AN-SAH has a harmful effect. Therefore, tight glycemic control is not recommended.

Several limitations of this study should be considered. First, we did not study stress-related indicators after AN-SAH. Other parameters must be collected to further establish the relationship between serum glucose and DCI risk. Second, due to the mild condition and short hospital stay of AN-SAH patients, we only collected the serum glucose data in the first five days after admission. In addition, glucose infusion, diet, drug use, and number of glucose measurements during hospitalization were not taken into account as a potential confounder, which may have introduced bias. Third, potential bias may exist in how DCI is defined. To address this problem, we defined the DCI according to the criteria of the previous study [24]. Two senior neurologists who were blind to the clinical information independently evaluated the DCI. Additionally, we did not record the specific time when the patients developed DCI. Fourth, because patients with missing radiological and serum glucose data often have better neurological status at admission, our results likely apply to patients in a moderately worse condition at admission. Finally, our study was retrospective and conducted at a single center. A multicenter collaborative prospective validation with an increased cohort size is recommended in future studies.

Conclusions

Among patients with PAN-SAH or NPAN-SAH, those with higher early serum glucose tend to have more severe conditions and a higher incidence of DCI. Admission serum glucose is an independent predictor of the occurrence of DCI after PAN-SAH or NPAN-SAH, which can serve as an early biomarker to predict DCI risk, and may guide intensive care in AN-SAH patients. Further studies with larger cohorts are needed to verify our findings.

Abbreviations

SAH: subarachnoid hemorrhage; AN-SAH: angiogram-negative subarachnoid hemorrhage; CT: computed tomography; PAN-SAH: perimesencephalic angiogram-negative subarachnoid hemorrhage; NPAH-SAH: non-perimesencephalic angiogram-negative subarachnoid hemorrhage; aSAH: aneurysmal subarachnoid hemorrhage; DCI: delayed cerebral ischemia; CRP: C-reactive Protein; WBC: white blood cell; DSA: digital subtraction angiography; BMI: body mass index; WFNS: World Federation of Neurosurgeons Scale; HH: Hunt and Hess; mFS: modified Fisher scale; SEBES: Subarachnoid Hemorrhage Early Brain Edema Score; IVH: intraventricular hemorrhage; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ApoA1: apolipoprotein A1; ApoB: apolipoprotein B; GCS: Glasgow Coma Scale; MRI: magnetic resonance imaging; SD: standard deviation; IQR: interquartile range; OR: odds ratio; CI: confidence interval; eNOS: endothelial nitric oxide synthase; iNOS: inducing nitric oxide synthase; ERK: extracellular regulated kinase; HbA1c: glycated hemoglobin

Declarations

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Not applicable.

Authors' contributions

ZYZ designed the study and wrote the manuscript; AKZ and XYW collected the study data; YJF, AKZ, JMZ, and CL revised the manuscript; YBL, YJL, and SC participated in the design and coordination of the study. All authors read and approved the final version of the manuscript.

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Availability of data and materials

The data is not available because of patients' privacy.

Ethics approval and consent to participate

This retrospective study was approved by the institutional review board of the Second Affiliated Hospital of Zhejiang University School of Medicine. The requirement for written informed consent was waived due to its retrospective nature.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Characteristics of DCI and non-DCI groups

Total (n=244)			
Variable	DCI (n=62)	non-DCI (n=182)	P value
Age, yr	58.2±10.7	54.9±11.2	0.045
Gender, male	35 (56.5)	101 (55.5)	0.896
Hypertension	28 (45.2)	53 (29.1)	0.021
Alcohol	21 (33.9)	73 (40.1)	0.383
Smoke	20 (32.3)	68 (37.4)	0.470
Hospital stay, d	13 (9.5-18)	6 (4-9)	≤0.001
ICU stay	48 (77.4)	95 (52.2)	≤0.001
PAN-SAH	19 (30.6)	145 (79.7)	≤0.001
BMI, kg/m ²	23.9±2.9	23.7±2.8	0.548
WFNS	2 (1-4)	1 (1-1)	≤0.001
HH grade	2 (2-3)	2 (1-2)	≤0.001
mFS	3 (2-4)	1 (1-2)	≤0.001
SEBES	0 (0-2)	0 (0-0)	≤0.001
IVH	27 (43.5)	27 (14.8)	≤0.001
Sodium, mmol/L	139.3±4.2	139.0±3.3	0.522
Potassium, mmol/L	3.72±0.45	3.81±0.38	0.137
Glucose, mmol/L	8.78±2.39	6.68±1.26	≤0.001
TC, mmol/L	4.75±1.00	4.84±1.07	0.602
TG, mmol/L	1.46±0.72	1.42±0.79	0.699
HDL-C, mmol/L	1.32±0.35	1.29±0.29	0.516
LDL-C, mmol/L	2.59±0.81	2.68±0.81	0.473
ApoA1, g/L	1.20±0.24	1.23±0.21	0.529
ApoB, g/L	0.91±0.28	0.92±0.24	0.739
Rebleeding	6 (9.7)	0 (0)	≤0.001
Hydrocephalus	13 (21.0)	4 (2.2)	≤0.001
Seizure	2 (3.2)	1 (0.5)	0.325

DCI, delayed cerebral ischemia; PAN-SAH, perimesencephalic angiogram-negative subarachnoid hemorrhage; BMI, body mass index; WFNS, World Federation of Neurosurgeons Scale; HH, Hunt and Hess; mFS, modified Fisher scale; SEBES, Subarachnoid Hemorrhage Early Brain Edema Score; IVH, intraventricular hemorrhage; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B

Table 2 Comparison of variables between PAN-SAH and NPAN-SAH patients

Total (n=244)			
Variable	PAN-SAH (n=164)	NPAN-SAH (n=80)	P value
Age, yr	55.3±10.8	56.7±11.9	0.342
Gender, male	86 (52.4)	50 (62.5)	0.137
Hypertension	52 (31.7)	29 (36.3)	0.479
Hospital stay, d	7 (4-10.75)	10 (6-15)	≤0.001
ICU stay	90 (54.9)	53 (66.3)	0.090
WFNS	1 (1-1)	1 (1-2)	≤0.001
HH grade	2 (1-2)	2 (2-3)	≤0.001
mFS	1 (1-1)	4 (2-4)	≤0.001
SEBES	0 (0-0)	0.5 (0-2)	≤0.001
IVH	24 (14.6)	30 (37.5)	≤0.001
Glucose, mmol/L	6.92±1.68	7.80±2.08	≤0.001
DCI	19 (11.6)	43 (53.8)	≤0.001
Rebleeding	0 (0)	6 (7.5)	0.001
Hydrocephalus	3 (1.8)	14 (17.5)	≤0.001
Seizure	1 (0.6)	2 (2.5)	0.523

PAN-SAH, perimesencephalic angiogram-negative subarachnoid hemorrhage; NPAN-SAH, non-perimesencephalic angiogram-negative subarachnoid hemorrhage; WFNS, World Federation of Neurosurgeons Scale; HH, Hunt and Hess; mFS, modified Fisher scale; SEBES, Subarachnoid Hemorrhage Early Brain Edema Score; IVH, intraventricular hemorrhage; DCI, delayed cerebral ischemia

Table 3 Comparison of variables between DCI and non-DCI groups

	PAN-SAH (n=164)			NPAN-SAH (n=80)		
Variable	DCI (n=19)	non-DCI (n=145)	P value	DCI (n=43)	non-DCI (n=37)	P value
Age, yr	58.4±10.2	54.9±10.8	0.182	58.1±11.0	55.1±12.9	0.259
Gender, male	8 (42.1)	78 (53.8)	0.337	27 (62.8)	23 (62.2)	0.954
Hypertension	9 (47.4)	43 (29.7)	0.119	19 (44.2)	10 (27.0)	0.111
Hospital stay, d	12 (10-16)	6 (4-9)	□ 0.001	14 (8-19)	6 (4-10)	□ 0.001
ICU stay	15 (78.9)	75 (51.7)	0.046	33 (76.7)	20 (54.1)	0.032
WFNS	2 (1-3)	1 (1-1)	□ 0.001	2 (1-4)	1 (1-1)	0.001
HH grade	2 (2-2)	2 (1-2)	0.043	2 (2-4)	2 (1-2)	0.005
mFS	1 (1-2)	1 (1-1)	0.046	4 (3-4)	2 (2-4)	0.006
SEBES	0 (0-0)	0 (0-0)	0.313	2 (0-4)	0 (0-1)	0.003
IVH	6 (31.6)	18 (12.4)	0.026	21 (48.8)	9 (24.3)	0.024
Glucose, mmol/L						
Day 1	8.93±2.56	6.67±1.33	□ 0.001	8.72±2.34	6.73±0.95	□ 0.001
Day 2	7.40±2.63	5.81±1.48	□ 0.001	7.34±2.23	6.12±1.28	0.004
Day 3	6.92±1.73	5.39±1.05	□ 0.001	6.92±1.92	5.63±1.09	0.001
Mean of day 4 to day 5	7.25±2.53	5.58±1.30	□ 0.001	7.00±2.06	5.70±1.13	0.001
Mean of the first three days	7.75±2.01	5.95±1.11	□ 0.001	7.66±1.90	6.16±0.96	□ 0.001
Max	9.30±2.60	6.89±1.45	□ 0.001	9.13±2.40	6.89±1.00	□ 0.001
Min	6.40±1.95	5.08±0.97	□ 0.001	6.49±1.73	5.41±1.02	0.001
Max-min	2.36 (1.36-3.92)	1.60 (1.09-2.36)	0.037	2.27 (1.57-3.55)	1.43 (0.98-1.93)	□ 0.001
SD of the first three days	0.92 (0.61-1.49)	0.68 (0.46-0.91)	0.038	0.92 (0.62-1.46)	0.61 (0.40-0.83)	0.001
CV of the first three days	0.11 (0.09-0.16)	0.11 (0.09-0.15)	0.687	0.13 (0.09-0.19)	0.11 (0.06-0.15)	0.050

Day 1-day 2	1.31 (0.39-1.71)	0.76 (0.21-1.58)	0.227	1.15 (0.43-2.29)	0.38 (-0.09-1.30)	0.012
Day 1-day 3	1.46 (1.00-2.91)	1.20 (0.77-1.61)	0.118	1.48 (0.83-2.95)	1.10 (0.53-1.79)	0.048
(Day 1-day 2)/day 1*100%	15.5 (5.6-21.3)	11.6 (3.3-23.1)	0.760	13.5 (3.9-25.9)	6.3 (-1.3-19.4)	0.057
(Day 1-day 3)/day 1*100%	19.2 (10.1-27.0)	18.8 (12.9-23.8)	0.785	19.4 (10.5-31.1)	17.3 (8.1-25.0)	0.245

PAN-SAH, perimesencephalic angiogram-negative subarachnoid hemorrhage; NPAN-SAH, non-perimesencephalic angiogram-negative subarachnoid hemorrhage; DCI, delayed cerebral ischemia; WFNS, World Federation of Neurosurgeons Scale; HH, Hunt and Hess; mFS, modified Fisher scale; SEBES, Subarachnoid Hemorrhage Early Brain Edema Score; IVH, intraventricular hemorrhage; Max, maximum; Min, minimum; SD, standard deviation; CV, coefficient of variation

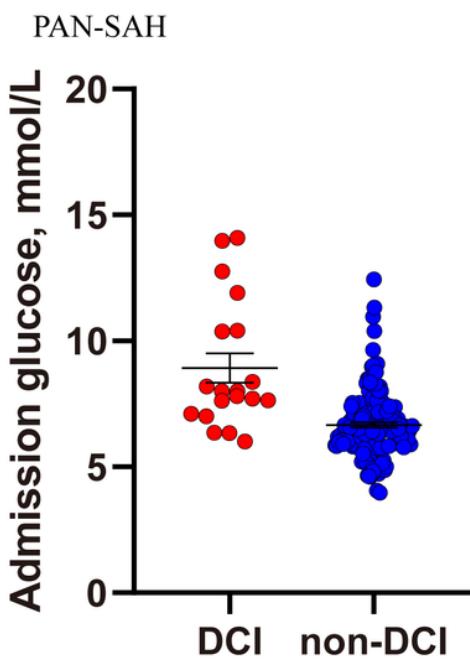
Table 4 Univariate and multivariate logistic regression analysis of predictors for DCI

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
PAN-SAH				
Age, yr	1.033 (0.985-1.083)	0.182		
Gender, male	0.625 (0.237-1.644)	0.341		
Admission glucose, mmol/L	1.862 (1.402-2.473)	0.001	1.705 (1.232-2.360)	0.001
SD of the first three days	3.163 (1.428-7.006)	0.005		
WFNS grade	3.738 (1.873-7.461)	0.001	2.889 (1.322-6.311)	0.008
HH grade	3.101 (1.268-7.585)	0.013		
mFS grade	1.830 (1.099-3.048)	0.02	1.658 (0.875-3.141)	0.121
SEBES score	1.456 (0.854-2.480)	0.167		
IVH	3.256 (1.099-9.647)	0.033		
NPAN-SAH				
Age, yr	1.022 (0.984-1.062)	0.258		
Gender, male	1.027 (0.414-2.546)	0.954		
Admission glucose, mmol/L	3.257 (1.748-6.067)	0.001	2.307 (1.167-4.562)	0.016
SD of the first three days	8.202 (2.241-30.026)	0.001	5.684 (1.006-32.114)	0.049
WFNS grade	2.103 (1.316-3.359)	0.002	1.550 (0.863-2.786)	0.143
HH grade	2.402 (1.334-4.324)	0.003		
mFS grade	1.810 (1.170-2.800)	0.008	1.859 (1.051-3.288)	0.033
SEBES score	1.772 (1.225-2.564)	0.002	1.443 (0.894-2.328)	0.133
IVH	2.970 (1.137-7.756)	0.026		

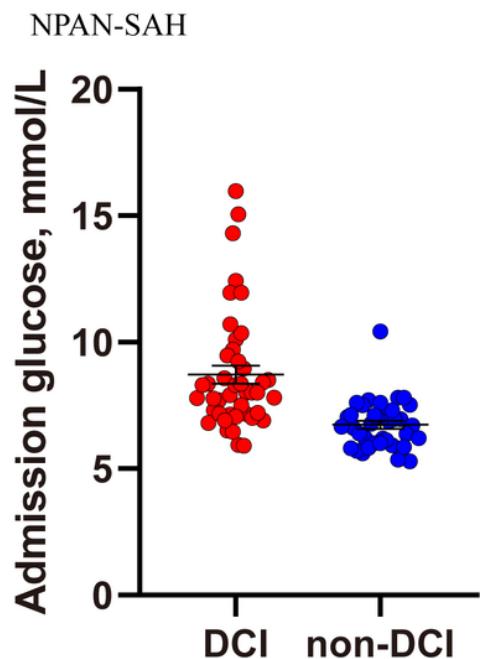
DCI, delayed cerebral ischemia; PAN-SAH, perimesencephalic angiogram-negative subarachnoid hemorrhage; NPAN-SAH, non-perimesencephalic angiogram-negative subarachnoid hemorrhage; SD, standard deviation; WFNS, World Federation of Neurosurgeons Scale; HH, Hunt and Hess; mFS, modified Fisher scale; SEBES, Subarachnoid Hemorrhage Early Brain Edema Score; IVH, intraventricular hemorrhage; OR, odds ratio; CI, confidence interval

Figures

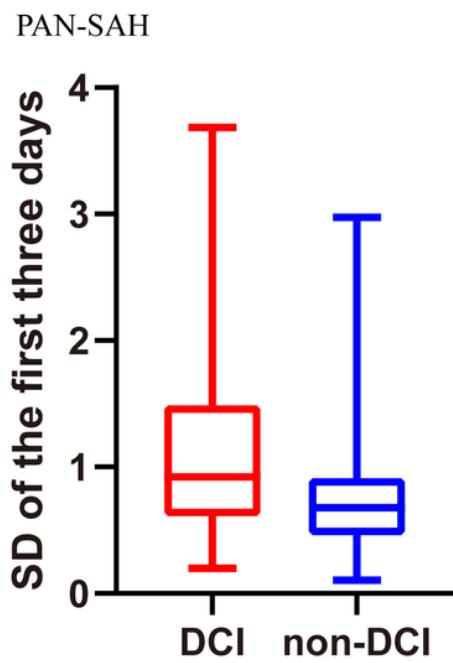
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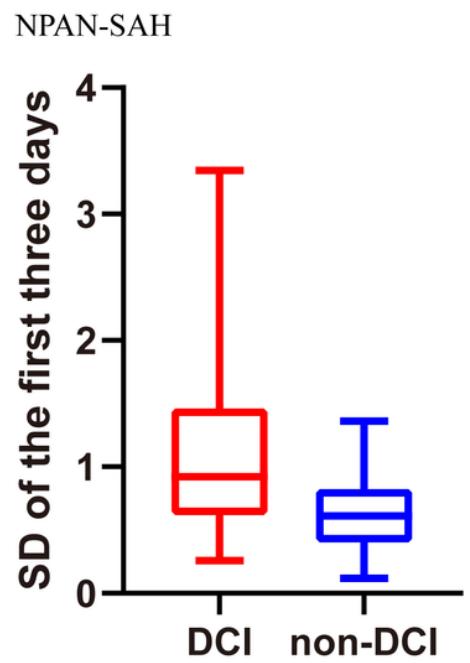
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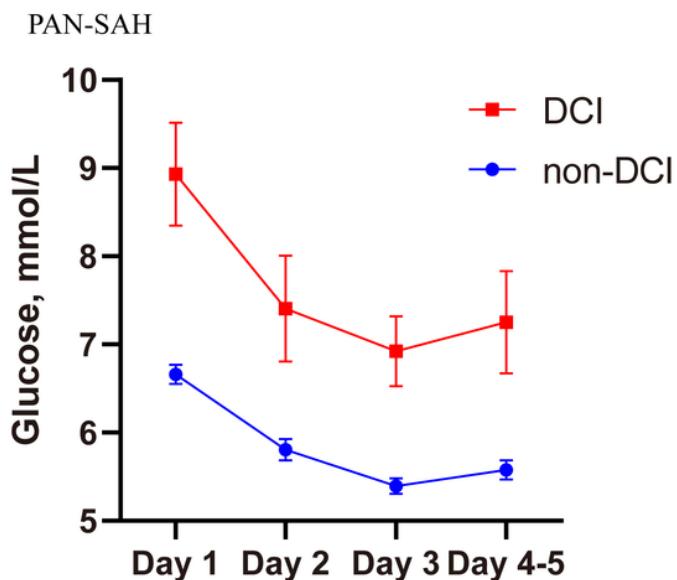
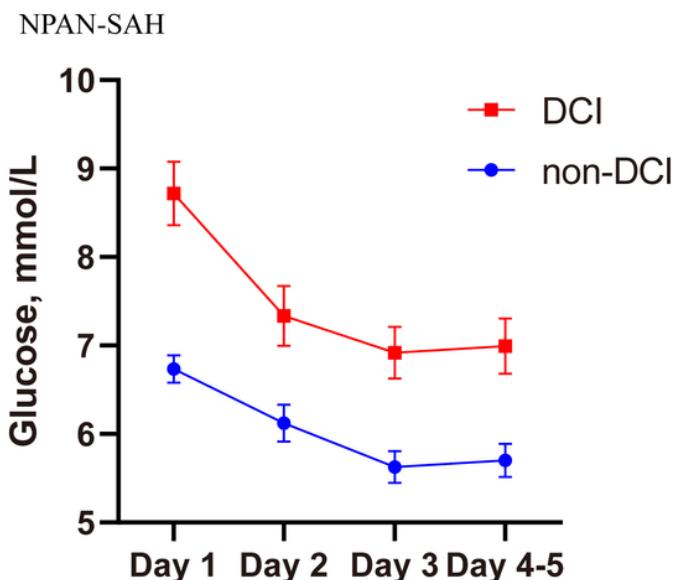
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D

**Figure 1**

Comparisons of admission glucose and SD of serum glucose in the first three days between DCI and non-DCI groups. DCI group was significantly related to higher admission serum glucose than non-DCI group in both PAN-SAH (A, $p < 0.001$) and NPAN-SAH (B, $p < 0.001$) patients. There was a significant association between high SD of serum glucose in the first three days and DCI group in both PAN-SAH (C, $p = 0.038$) and NPAN-SAH (D, $p = 0.001$) patients. SD, standard deviation; DCI, delayed cerebral ischemia; PAN-SAH, perimesencephalic angiogram-negative subarachnoid hemorrhage; NPAN-SAH, non-perimesencephalic angiogram-negative subarachnoid hemorrhage

A**B****Figure 2**

Dynamic changes of serum glucose after admission. Serum glucose of DCI and non-DCI groups showed a similar trend in both PAN-SAH (A) and NPAN-SAH (B) patients, reaching the lowest value on the third day after admission. In both two populations, the serum glucose of DCI group was consistently higher than that of non-DCI group in the first five days after admission. DCI, delayed cerebral ischemia; PAN-SAH, perimesencephalic angiogram-negative subarachnoid hemorrhage; NPAN-SAH, non-perimesencephalic angiogram-negative subarachnoid hemorrhage

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