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ORIGINAL RESEARCH

The Association of Glycemic Gap with Cognitive Function After Ischemic Stroke or Transient Ischemic Attack

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Background: Glycemic gap (GG), as a measure of an acute derangement in glucose level in response to an active disease state, has been found to be associated with adverse outcomes in many diseases. This study aimed to determine the relationship of GG with cognitive function after ischemic stroke or transient ischemic attack (TIA).

Methods: Patients included were enrolled from a subgroup of China National Stroke Registry-III (CNSR-III). Cognitive function was assessed by the Beijing edition of the Montreal cognitive assessment (MoCA) scale. Post-stroke cognitive impairment (PSCI) was diagnosed as a MoCA score≤22. Post-stroke cognitive decline (PSCD) was defined as a decrease of >2 points on the MoCA score between the 3-month and 1-year assessments. GG was calculated using admission blood glucose minus hemoglobin A1c-derived average blood glucose. Multivariable logistic regression analysis was used to evaluate the correlation between GG and cognitive function.

Results: We enrolled 767 patients with a median age of 60 years old, including 247 (32.2%) patients with PSCI in 3 months, 228 (29.73%) with PSCI in 1 year, and 166 (21.64%) patients with PSCD. The highest GG levels were related to PSCI in 3 months after adjusted for multiple potential confounders (adjusted odd ratio (OR): 2.021, 95% CI: 1.055–3.869, P=0.0338), but not in patients with PSCI in 1 year or PSCD. No significant interactions for the impact on PSCI were observed in subgroups (P interaction > 0.05 for all).

Conclusion: Our findings show that GG is associated with acute post-stroke cognitive impairment, but not with the long-term cognitive impairment or cognitive decline.

Keywords: cognitive function, glycemic gap, stroke, transient ischemic attack

Introduction

Ischemic cerebrovascular disease, encompassing ischemic stroke and transient ischemic attack (TIA), ranks as one of the leading global causes of disability and mortality.[1] One of the most significant complications of stroke or transient ischemic attack is post-stroke cognitive impairment (PSCI), a condition that can lead to a poor functional prognosis, a reduction in the quality-of-life and an increase in economic burden for the patient's family and healthcare system.[2] Post-stroke hyperglycemia is a form of stress-induced hyperglycemia (SIH) and can induce breakdown of the brain-blood barrier during the initial inflammatory response, thus leading to a poor outcome.[3] Stress-induced hyperglycemia (SIH) elevates post-stroke cognitive impairment (PSCI) risk, which may be mediated by glucose metabolism disorders that drive neuronal damage via oxidative stress and neuroinflammation.[4]

Historically, a large number of synthetic indicators have been used to detect SIH; however, many of these indicators do not consider the status of glycemic control at the time of the stroke event. The glycemic gap (GG) is a measure of an acute abnormality in glucose level in response to an active disease state and is calculated as the difference between the capillary glucose level and the estimated average glucose (eAG) level derived from the serum level of hemoglobin A1c

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(HbA1c).[5] The GG is a more simple and direct method with which to quantify the level of acute SIH relative to the baseline glycemic status and is considered to be superior to glucose and HbA1c upon admission with regards to predicting the functional outcome at discharge in post-stroke patients[6] and in diabetic patients suffering from acute myocardial infarction.[7] In terms of post-stroke cognitive impairment, little is known about the specific relationship between GG, long-term cognitive assessment and changes in cognitive function.

Therefore, in the present study, we investigated the association between the GG and cognitive function following ischemic stroke or transient ischemic attack (TIA) by analyzing data held by the China National Stroke Registry-III (CNSR-III).

Methods

Study Design and Subjects

We obtained 2700 patients' data from the Impairment of Cognition and Sleep (ICONS) subgroup of the third China National Stroke Registry (CNSR-III) database, a prospective multicenter registry that enrolled patients within seven days after symptom onset with a diagnosis of acute ischemic stroke or TIA between August 2015 and March 2018 from 201 hospitals that cover 22 provinces and 4 municipalities in China.[8]

The inclusion criteria of ICONS for patients are age older than 18 years; in-hospital acute ischemic stroke or TIA patients within seven days after onset. The exclusion criteria included: prior diagnosis of cognitive impairment, schizophrenia or psychosis disease, illiterate patients, and concomitant neurological disorders that interfere with cognitive or sleep evaluation; Without HbA1c and fasting blood glucose measurement in 2 weeks; Without Montreal Cognitive Assessment (MoCA) assessment in 3 months and 1 year.

The collection of data for ICONS was approved by the ethics committee of all participating hospitals. All patients provided written informed consent.

Clinical Data Collection

The baseline data were collected prospectively using an electronic data capture system by face-to-face interviews, which included age, gender, education level, medical histories, the causative subtypes of IS classified according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria, Symptomatic intracranial atherosclerotic stenosis (ICAS), severity of stroke on admission National Institutes of Health Stroke Scale score (NIHSS). Laboratory data were measured on admission from blood samples, including the levels of homocysteine (Hcy), systolic blood pressure (SBP), glycated Hemoglobin A1c (HbA1c), and fasting blood glucose (FPG). We dichotomized the levels of Hcy as follows, normal Hcy (<15 mmol/L), HHcy (≥15 mmol/L).[9]

Cognitive Assessment

Patients were followed up for MoCA assessment at 3 months and 1 year after onset. In this study, we defined PSCI as MoCA≤22. This node has been shown to be more applicable in our patients with minor stroke and TIA.[10] Post-stroke cognitive decline (PSCD) is defined as a decline of 2 or more points at 1 year compared to three months.[11]

Classification of Glycemic Gap

Estimated average blood glucose (eAG) levels could be derived from HbA1c according to the equation eAG = 28.7 * HbA1c - 46.7.[5] GG was defined as admission blood glucose minus eAG,[12] and then categorized into four groups according to their quartiles.

Statistical Analyses

Mean ± Standard Deviation (SD) or median with interquartile was used to describe continuous variables, and percentages were used to describe categorical variables. We used analysis of variance (ANOVA) to compare groups for normally distributed variables, Kruskal–Wallis tests for non-normal distribution variables. χ^2 test for categorical parameters.

The associations between GG and PSCI or PSCD were analyzed using crude and multivariable binary logistic regression. In the multivariable regression analyses, We adjusted for all the potential covariates. Results were reported as odds ratios (ORs) with 95% confidence interval (95% CI). Additionally, gender, age, and other potential indicators were also evaluated in subgroups, to assess if there was any significant interaction between these variables and the relationship between GG and cognitive impairment.

Statistical analyses were performed with the SAS software version 9.4 (SAS Institute, Cary, NC, USA). All the statistical tests were two-sided, and a $P < 0.05$ was set as the threshold for statistical significance.

Results

Baseline Characteristics

By excluding 1249 individuals with missing baseline HbA1c and fasting blood glucose and 684 individuals without follow-up data of 3-months and 1-year MoCA assessments, we finally included 767 subjects for subsequent analysis (Figure 1).

The ranges of GG for quartiles 1–4 (Q1-4) were <-147, −147 ~ −118, −118 ~ −106,>-106. Significant differences in age, gender, body mass index (BMI), education level, hypertension, dyslipidemia, homocysteine (Hcy) and National Institutes of Health Stroke Scale (NIHSS) were observed among the groups with different GG levels (Table 1). Participants in the high GG groups were more likely to have higher Hcy baseline levels. Thus, the four groups had no significant differences in cognitive function at 3 months and 1 year follow-up (P>0.05).

Association Between GG and Outcomes

In multiple regression analyses, after adjusting for age, gender, BMI, education level, current smoking, heavy drinking, medical history, SBP, Hcy levels, TOAST classification, and NIHSS scores at admission, patients in Q4 were more likely to have a higher 3-month PSCI (adjusted OR: 2.021, 95% CI: 1.055–3.869, P=0.0338). Compared with the Q1 group, patients in Q4 had an approximately 2.02-fold higher risk of PSCI at 3 months. However, the GG levels are not associated with 1-year PSCI or PSCD (P>0.05) (Table 2).

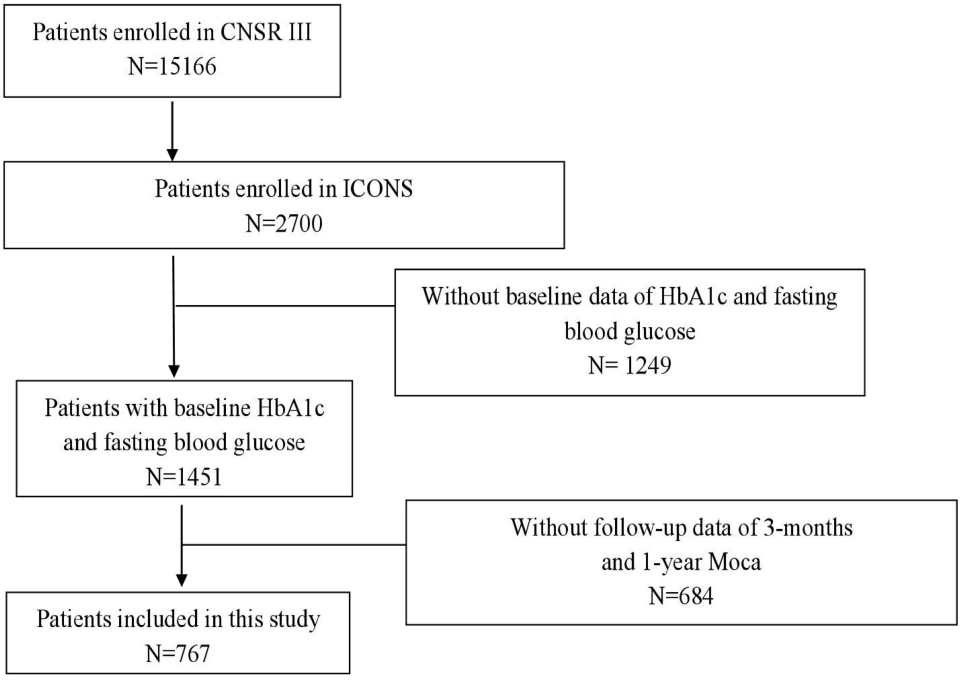

Figure 1 Study flow chart.

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Table 1 Baseline Characteristics of Participants According to Diabetes Status

Characteristic	GG levels				*P* value
	Q1 N=192(25.03%)	Q2 N=192(25.03%)	Q3 N=191(24.90%)	Q4 N=192(25.03%)	
Age, (years, mean±SD)	60.64±9.86	62.38±9.57	59.99±11.19	56.98±10.36	<0.001*
Male, n (%)	117 (61.26)	136 (71.20)	146 (75.65)	146 (76.04)	0.004*
BMI, (mean±SD)	25.83±3.34	25.36±3.00	24.93±3.78	24.98±2.98	0.005*
Education level, n (%)					
Elementary or below	46 (24.08)	47 (24.61)	56 (29.02)	36 (18.75)	0.034*
Middle school	64 (33.51)	71 (37.17)	62 (32.12)	84 (43.75)	
High school or above	70 (36.65)	60 (31.41)	68 (35.23)	70 (36.46)	
Unknown	11 (5.76)	13 (6.81)	7 (3.63)	2 (1.04)	
Current smoking, n (%)	63 (32.98)	66 (34.55)	68 (35.23)	78 (40.63)	0.431
Heavy drinking (>60g/d) n (%)	11 (5.76)	5 (2.62)	11 (5.70)	17 (8.85)	0.076
Medical history, n (%)					
Ischemic Stroke	45 (23.56)	46 (24.08)	32 (16.58)	40 (20.83)	0.255
TIA	5 (2.62)	10 (5.24)	5 (2.59)	4 (2.08)	0.280
Hypertension	133 (69.63)	126 (65.97)	112 (58.03)	111 (57.81)	0.036*
Dyslipidemia	32 (16.75)	27 (14.14)	13 (6.74)	24 (12.50)	0.024*
Atrial fibrillation	4 (2.09)	6 (3.14)	12 (6.22)	6 (3.13)	0.156
Laboratory test					
SBP, median,mmHg	149.21±20.14	148.19±19.46	146.07±20.97	146.95±22.71	0.186
Hcy, median,μmol/L	15.84±7.81	19.42±9.16	20.56±11.37	25.81±17.26	<0.001*
Symptomatic ICAS, n(%)	49 (36.57)	46 (34.33)	39 (28.47)	35 (26.52)	0.241
TOAST, n(%)					
Large artery atherosclerosis	48 (25.13)	51 (26.70)	39 (20.21)	39 (20.31)	0.360
Cardiogenic embolism	4 (2.09)	8 (4.19)	9 (4.66)	7 (3.65)	
Small artery occlusion	56 (29.32)	39 (20.42)	55 (28.50)	47 (24.48)	
Other cause	83 (43.46)	93 (48.69)	90 (46.63)	99 (51.56)	
NIHSS at admission (mean±SD)	3.89±3.41	3.41±3.14	3.34±3.22	3.23±2.62	0.036*
Cognitive evaluation (mean±SD)					
3-month MoCA score	23.69±4.84	24.13±4.76	24.37±4.82	24.38±4.45	0.130
1-year MoCA score	23.78±4.75	24.47±4.62	24.52±4.82	24.55±4.61	0.122

Notes: **P*<0.05. The range of GG levels for each group: Q1:<-147; Q2:-147 ~ −118; Q3:-118 ~ −106; Q4:>-106.
Abbreviations: GG, Glycemic gap; BMI, Body mass index; TIA, transient ischemic attack; Hcy, Homocysteine; SBP, systolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; ICAS, intracranial atherosclerotic stenosis; TOAST, Trial of Org 10172 in Acute Stroke Treatment; MoCA, Montreal Cognitive Assessment; SD, standard deviation.

Table 2 Multivariate Binary Logistic Regression Analysis for Investigating the Association Between GG Levels and Post-Stroke Cognitive Function

Outcomes	GG Levels (mmol/L)	No	Event (%)	Crude	*P* value	Multivariable Adjusted	*P* value
				Odds Ratios (95% CI)		Odds Ratios (95% CI)	
PSCI[#] in 3-months	Q1	69	36.13	Ref		Ref	
	Q2	61	31.94	0.830 (0.543–1.268)	0.3879	0.930 (0.496–1.742)	0.8201
	Q3	52	26.94	0.652 (0.423–1.006)	0.0534	0.905 (0.469–1.748)	0.7664
	Q4	65	33.85	0.905 (0.595–1.377)	0.6412	2.021 (1.055–3.869)	0.0338*
PSCI[#] in 1-year	Q1	66	34.55	Ref		Ref	
	Q2	54	28.27	0.747 (0.484–1.152)	0.1865	0.579 (0.308–1.086)	0.0886
	Q3	54	27.98	0.736 (0.477–1.135)	0.1651	0.797 (0.415–1.530)	0.4949
	Q4	54	28.13	0.741 (0.480–1.143)	0.1755	1.201 (0.626–2.306)	0.5815

(*Continued*)

Table 2 (Continued).

Outcomes	GG Levels (mmol/L)	No	Event (%)	Crude	*P* value	Multivariable Adjusted	*P* value
				Odds Ratios (95% CI)		Odds Ratios (95% CI)	
PSCD[$]	Q1	50	26.18	Ref		Ref	
	Q2	41	21.47	0.771 (0.480–1.236)	0.2802	0.526 (0.274–1.009)	0.0547
	Q3	37	19.17	0.669 (0.413–1.083)	0.1020	0.595 (0.303–1.168)	0.1090
	Q4	38	19.79	0.696 (0.431–1.124)	0.1384	0.795 (0.407–1.551)	0.4796

Notes: The ranges of GG levels: Q1:<-147; Q2:-147 ~ −118; Q3:-118 ~ −106; Q4:>-106. *:P<0.05. #: MoCA≤22. $: a decline of 2 or more points at 1 year compared to three months. Adjusted for age, gender, BMI, education level, current smoking, heavy drinking, medical history, SBP, Hcy levels, TOAST classification, and NIHSS scores at admission.

Abbreviations: GG, Glycemic gap; PSCI, Post-stroke cognitive impairment; PSCD, Post-stroke cognitive decline; 95% CI, 95% Confidence Interval.

Furthermore, after classifying patients according to age, gender, symptomatic ICAS, SBP, TOAST classification HbA1c and Hcy levels, those who were ≥60 years old (adjusted OR: 2.74, 95% CI: 1.07–7.04, $P = 0.036$), female (adjusted OR: 5.27, 95% CI: 1.30–21.31, $P = 0.019$), having no symptomatic ICAS (adjusted OR: 3.01, 95% CI: 1.12–8.06, $P = 0.029$) were more likely to have cognitive impairment if presenting high GG levels at the same time (Table 3).

Stratified analyses showed that age, gender, symptomatic ICAS, SBP, TOAST classification, HbA1c and Hcy levels had no interaction effect with GG levels on 3-month post-stroke cognitive impairment (*P* interaction=0.457, 0.820, 0.295, 0.279, 0.246, and 0.764).

Table 3 Multivariable Adjusted Odds Ratios(OR) of Subgroup Analysis for PSCI* in 3 Months According to GG Levels

	N (%)	Q1	Q2	Q3	Q4	*P* Interaction
Age OR (95% CI)						
≥60y	392 (51.11)	Ref	1.061 (0.461–2.442)	0.737 (0.299–1.815)	2.741 (1.068–7.038)	0.457
<60y	375 (48.89)	Ref	0.631 (0.186–2.137)	0.922 (0.321–2.646)	1.172 (0.440–3.121)	
GENDER OR (95% CI)						
Female	222 (28.94)	Ref	1.468 (0.379–5.682)	2.057 (0.543–7.792)	5.269 (1.302–21.313)	0.820
Male	545 (71.06)	Ref	0.862 (0.391–1.903)	0.770 (0.333–1.780)	1.807 (0.792–4.127)	
Symptomatic ICAS,OR (95% CI)						
No	368 (68.53)	Ref	0.845 (0.292–2.445)	1.116 (0.401–3.104)	3.005 (1.120–8.061)	0.295
Yes	169 (31.47)	Ref	2.387 (0.534–10.671)	3.445 (0.636–18.668)	1.381 (0.275–6.939)	
TOAST OR (95% CI)						
Large artery atherosclerosis	177 (23.08)	Ref	2.550 (0.644–10.100)	3.521 (0.748–16.571)	2.960 (0.643–13.632)	0.279
Cardiogenic embolism	28 (3.65)	Ref	–	–	–	
Small artery occlusion	197 (25.68)	Ref	0.425 (0.077–2.353)	1.575 (0.345–7.184)	0.733 (0.117–4.606)	
Other cause	365 (47.59)	Ref	0.545 (0.189–1.575)	0.278 (0.087–0.883)	2.485 (0.936–6.595)	
HbA1c OR (95% CI)						
HbA1c< 6.5%	517 (67.41)	Ref	–	–	–	–
HbA1c≥6.5%	250 (32.59)	Ref	–	–	–	
SBP OR (95% CI)						
SBP ≥140mmHg	505 (65.84)	Ref	0.635 (0.280–1.442)	1.014 (0.443–2.322)	2.046 (0.893–4.688)	0.246
SBP<140mmHg	262 (34.16)	Ref	1.726 (0.537–5.549)	0.915 (0.273–3.067)	1.949 (0.567–6.705)	
Hcy OR (95% CI)						
≥15 mmol/L	167 (30.93)	Ref	0.686 (0.341–1.377)	0.470 (0.235–0.939)	0.448 (0.219–0.916)	0.764
<15 mmol/L	373 (69.07)	Ref	1.297 (0.505–3.335)	1.673 (0.636–4.402)	4.064 (1.541–10.721)	

Notes: The ranges of GG levels: Q1:<-147; Q2:-147 ~ −118; Q3:-118 ~ −106; Q4:>-106. *: MoCA≤22. Adjusted for age, gender, BMI, education level, current smoking, heavy drinking, medical history, SBP, Hcy levels, TOAST classification, and NIHSS scores at admission.

Abbreviations: GG, Glycemic gap; PSCI, Post-stroke cognitive impairment; PSCD, Post-stroke cognitive decline; 95% CI, 95% Confidence Interval.

Discussion

In the present study, we identified that patients with a higher GG were more likely to experience cognitive impairment in three months after stroke. However, GG was not significantly associated with long-term cognitive impairment or a significant decline in cognitive function following stroke. Furthermore, stratified analysis failed to identify any significant interaction between the levels of inflammatory markers and the GG. We put forward a new explanation and extend previous findings for the potential mechanism of the effect of post-stroke hyperglycemia on cognitive functions in PSCI and provide an index for predicting and evaluating PSCI in the acute stage.

PSCI pertains to the cognitive deficits that arise from various causes following stroke and represents one of the most predominant factors leading to post-stroke disability.[13] Post-stroke hyperglycemia is a form of SIH and can lead to an increase in infarct volume, the failure of reperfusion therapy after thrombolysis, and the risk of hemorrhagic transformation. The occurrence of these events is related to a number of processes, including acidosis, the generation of free radicals, inflammation and mitochondrial dysfunction.[14] Consequently, post-stroke hyperglycemia is associated with a significantly poorer prognosis following stroke.[15–17] Previous researchers reported that post-stroke hyperglycemia was associated with a higher level of in-hospital mortality in patients who had suffered from a minor ischemic stroke or a transient ischemic attack.[3,18]

In the present study, we used the GG as an indicator of SIH; the application of this tool can eliminate the interference caused by chronic and baseline levels of blood glucose.[12] Compared with other indicators, the GG can reflect SIH and fluctuations in glucose levels.[19] A previous retrospective study demonstrated that GG is superior to the stress-relevant hyperglycemia ratio, glucose levels upon admission, and HbA1c with regards to predicting unfavorable functional outcomes upon discharge.[6] Other research revealed that the GG is a reliable predictor of disease severity and adverse clinical effects in patients with a range of specific conditions, including community-acquired pneumonia, acute myocardial infarction, liver abscesses, and aneurysmal subarachnoid hemorrhage.[4,20,21]

A previous study investigated short-term cognitive impairment three months post-stroke and found that a significant elevation of GG represents an important predictor of PSCI; these findings concur with those of our present study.[10] However, in the present study, we used the Montreal Cognitive Assessment (MoCA) as this tool is widely recognized for its ability to comprehensively evaluate cognitive impairment (CI) in a user-friendly manner.[22] Using the MoCA, we investigated the effects of SIH on the long-term cognitive function of patients following stroke.

Our analysis failed to identify an association between SIH and long-term cognitive impairment following stroke. We believe that this might be related to the normal evolution of regularity with regards to the incidence of PSCI, which is known to vary in a manner that is dependent on a number of factors, including pathogenesis, clinical features, and prognosis. A previous study reported that 17–92% of stroke patients were diagnosed with mild cognitive impairment three months after stroke.[23] This decline in cognitive function may be attributed to alterations in white matter connectivity,[24] thus resulting in the functional impairment of adjacent cortical tissues. Another potential mechanism involves the activation of glial cells during cognitive decline and the interference of functional pathways in complex learning and memory processes.[25] Previous research observed improvements in cognitive impairment during the first year post-stroke and reported that this improvement may have been the result of a combination of real recovery and practical effects.[26,27] Secondly, the mechanisms responsible for the effects of acute and chronic hyperglycemia on the brain are different. Acute hyperglycemia induces neuronal damage through osmotic stress triggered by altered cerebral blood flow and subsequent oxidative injury,[28] whereas chronic hyperglycemia predominantly mediates neuronal injury via the gradual accumulation of advanced glycation end-products (AGEs).[29] This discrepancy suggests that acute-phase and chronic-phase hyperglycemia induce tissue damage through distinct molecular mechanisms: acute glucose fluctuations exert a more direct impact on the oxidative stress system, whereas chronic hyperglycemia-induced damage is associated with the progressive accumulation of glycation products.[30] Thirdly, the pathogenesis of PSCI is still unclear at present. Some inflammatory factors only play a role in the occurrence of cognitive impairment during the subacute and chronic phases, and the influencing factors are quite complex.[31] Additionally, changes in the cognitive function of post-stroke patients can vary depending on infarction severity, lesion location, etiological classification, and cognition assessment. These possibilities need to be investigated further in future studies involving larger cohorts.

The extent of PSCI is known to depend on the duration of the initial inflammatory response.[32] However, in the present study, we did not identify any specific interaction between the levels of homocysteine (Hcy) and the GG in patients with cognitive impairment three months post-stroke. This may be because Hcy is not a specific indicator of inflammation.

A previous study found that microglial activation appears to play an important role in the inflammatory response.[33] Hyperglycemia is also known to lead to pro-inflammatory microglial proliferation via the endothelin-1 system.[34] In addition, the levels of C-reactive protein (CRP) and HbA1c are independently associated with mild cognitive impairment.[35] Future studies need to incorporate additional inflammatory indicators in order to investigate the relationship between inflammation and post-stroke hyperglycemia.

There are several limitations in this study. First, this cohort study was conducted exclusively in the Chinese population and ischemic cerebrovascular disease, which restricts the generalizability of our findings to other populations. Second, we did not take into account the specific infarct location, the severity of cerebral infarction, and the rehabilitation status of patients, which might have an impact on the patient's cognitive functions. Third, emerging evidence implicates that neuroinflammation is a key pathophysiological mechanism in PSCI. The limitation of our study lies in using homocysteine (Hcy) as the sole inflammatory biomarker. Future investigations should incorporate multidimensional inflammatory markers (e.g.CRP) to elucidate interactions between glycemic variability and inflammatory cascades in PSCI pathogenesis. Therefore, a more comprehensive analysis of this measure is needed in a longer follow-up cohort to better demonstrate our findings.

Conclusion

Our current analysis suggests that the GG may be an efficient predictor of acute post-stroke cognitive impairment, but is not associated with long-term cognitive impairment or cognitive decline. Our findings provide a new concept and deepen our understanding of the potential neuroinflammatory mechanisms underlying the effect of post-stroke hyperglycemia on cognitive function in patients suffering from PSCI.

Data Sharing Statement

The datasets used and analysed during the current study available from the corresponding author on reasonable request.

Ethics Approval

This study was approved by the medical Ethics Committee of Beijing Tiantan Hospital (No:KY2015-001-01). All the study participants provided informed consent to take part in this study. The study protocol was in accordance with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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