ORIGINAL RESEARCH

Factors Influencing Post-Stroke Cognitive Impairment in Patients with Type 2 Diabetes Mellitus

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Objective: Type 2 diabetes mellitus (T2DM) and ischemic stroke, which are common diseases among older people, are closely related to cognitive impairment. This study aims to investigate the influencing factors of post-stroke cognitive impairment (PSCI) in patients with T2DM.

Methods: We enrolled 161 patients with T2DM who experienced acute ischemic stroke and were hospitalized in the Department of Neurology, Jinan Central Hospital, Shandong, China. Cognitive function was evaluated with the Montreal Cognitive Assessment scale. According to the results, patients were divided into three groups—the cognitively normal group, mild cognitive impairment group, and severe cognitive impairment group. We analyzed general demographic data, laboratory information, imaging data, the results of neuropsychological evaluation, and clinical features as well as influencing factors of PSCI in these patients and established a prediction model.

Results: The three groups of patients were significantly different in terms of age, education level, course of diabetes mellitus (DM), recurrent cerebral infarction (RCI), and other factors. RCI, course of DM, and glycated hemoglobin (HbA1c) were independent risk factors of PSCI in patients with T2DM, with odds ratio (95% confidence interval): 7.17 (2.09, 30.37), 5.39 (2.40, 14.59), and 3.89 (1.66, 10.04), respectively, whereas female, senior high school, serum albumin were protective factors: 0.28 (0.07, 0.95), 0.05 (0.01, 0.21), 0.20 (0.08, 0.42), respectively. Furthermore, we constructed a prediction model using sex, age, education level, RCI, DM course, HbA1c and serum albumin and obtained a receiver operating characteristic (ROC) curve. The area under the ROC curve is 0.966, suggesting the significant association of these influencing factors with PSCI in patients with T2DM.

Conclusion: In this study, the occurrence of PSCI in patients with T2DM was related to RCI, course of DM, and HbA1c, among other factors. Attention to influencing factors is needed in these patients for early diagnosis and timely intervention of cognitive impairment.

Keywords: blood glucose, cognitive impairment, ischemic stroke, risk factor

Introduction

Recent years have seen an increasing incidence of type 2 diabetes mellitus (T2DM), acute ischemic stroke (AIS), and cognitive impairment (CI). Characterized by high rates of disability and mortality, these diseases tend to place huge life pressure and a heavy economic burden on families as well as society. There is increased prevalence of brain damage and mental illness in patients with T2DM. Cognitive impairment, depression, and stroke, which are considered to be complications of diabetic microangiopathy,[1] are likely caused by hyperglycemia, obesity, and insulin resistance. Motor dysfunction, speech impairment, sleep disorders, epilepsy, emotional disorders, and CI can remain to varying degrees after the onset of ischemic stroke. Recent studies have shown that vascular risk factors are related to CI, and

cerebrovascular disease is the second most common cause of dementia.[2] Post-stroke cognitive impairment (PSCI) is not only an important factor leading to slow physical recovery and a decline in the work capacity and social ability of patients with stroke but also a risk factor for recurrence of stroke and severe stroke.[3,4] Studies have shown that patients with stroke develop dementia 10 years earlier than those without stroke.[5] According to statistics, the incidence of PSCI is as high as 20%–80%.[6] PSCI mainly includes two phases, post-stroke cognitive impairment with no dementia and post-stroke dementia.

To investigate the influencing factors of PSCI, researchers have used different methods based on their respective interests,[7–12] including demographic information (advanced age and low education level), chronic brain injury (white matter hyperintense signal and temporal lobe atrophy), clinical data (hypertension, diabetes, and large artery occlusion), and biological information (apolipoprotein E, neuroinflammation, and intestinal flora). However, there are a great variety of factors affecting cognitive function, and it is difficult to completely cover the baseline data in specific practice, so opinions vary regarding the research results. Cognitive impairment does not have typical early symptoms, which often encompass a wide range. Older people with mild cognitive impairment (MCI) may experience cognitive dysfunction whereas those with severe CI may progress to dementia or Alzheimer's disease without effective treatment and intervention measures.[13] Thus, early diagnosis and prevention play critical roles in delaying the occurrence of CI. Identifying effective indicators to predict the occurrence of PSCI can provide clinicians with important information to conduct early diagnosis and cognitive rehabilitation, improve cognition through proper management, delay disease progression, and reduce early mortality.[14] Overall, this study has explored the relationship of influencing factors with PSCI in patients with T2DM, which can provide insights into the early diagnosis and intervention treatment.

Methods

Study Population

The research participants in this study comprised 161 patients with T2DM who had experienced AIS and were hospitalized in the Department of Neurology, Jinan Central Hospital Affiliated to Shandong University between September 2017 and February 2020.

The inclusion criteria were as follows: 1) patients with the onset form and symptoms suspicious for acute stroke and onset time within 72 hours were examined using brain magnetic resonance imaging (MRI); patients determined to have AIS were hospitalized (met the criteria for AIS stated in the 2014 Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke in China[15]); 2) patients who had been previously diagnosed with T2DM or who had venous plasma fasting glucose ≥7.0 mmol/L on the second day after hospital admission (met the diagnostic criteria for T2DM stipulated in the China Guidelines for the Prevention and Treatment of Type 2 Diabetes (2017)[16]); 3) patients aged ≤85 years; and 4) right-handed.

The exclusion criteria were as follows: 1) patients with massive cerebral infarction or severe cerebral infarction with obvious disorder of consciousness; 2) patients with obvious apraxia, aphasia, and acute complications of diabetes mellitus (such as diabetic ketoacidosis) who were unable to complete the questionnaire; 3) patients complicated with diseases affecting cognitive function, eg, cerebral trauma, brain tumor, intracranial infection; 4) patients with degenerative diseases of the nervous system such as Parkinson's syndrome and frontotemporal dementia; 5) patients with mental diseases such as schizophrenia and severe depression, as well as drug and alcohol abuse; 6) patients with severe cardiopulmonary diseases, liver and kidney diseases, and malignant tumors; 7) patients complicated with severe stress response-related diseases such as acute infection and trauma; and 8) patients with previous hypoglycemia.

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Research and Ethics Committee of Jinan Central Hospital (AF/SC-08/04.0). All participants were informed about the purpose of the study. Written informed consent was obtained from all participants, or from informants in the case of participants with severe cognitive impairment.

Demographic and Clinical Characteristics

We collected patients' demographic data (sex, age, and education level), lifestyle information (smoking history and drinking history), influencing factors of cardiovascular and cerebrovascular diseases (hypertension, coronary artery disease, atrial fibrillation, history of cerebral infarction, total cholesterol, triglyceride, low-density lipoprotein, glycated hemoglobin [HbA1c], uric acid, fibrinogen, and serum albumin; the peripheral blood samples were taken by automatic biochemical analyzer [cs-600b, Changchun Dirui, China]), blood pressure on admission to the hospital, and the course of DM. Patients with hypertension were defined as those with systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg measured three times using an electronic sphygmomanometer (hem-7127j, OMRON, Kyoto, Japan) on different days in the clinic without antihypertensive drugs, as well as those who had been diagnosed with hypertension in the past and were currently taking antihypertensive drugs. Coronary artery disease was determined according to a history of myocardial infarction, angina pectoris, or dynamic changes on an electrocardiogram (CM300, Shenzhen Branch, China) related to symptoms, as reported by patients. Cerebral infarction and atrial fibrillation were determined according to the medical history provided by patients. The course of DM spanned from the first time when the patient was diagnosed with diabetes to the time of this study, according to the patient's self-reported medical history or existing medical records. Patients with a smoking history were defined as those who had smoked at least 100 cigarettes or 100 g of tobacco leaves in the past, and who were smoking within 1 month before this study was carried out. Patients with a drinking history were defined as those who had consumed alcohol for more than 1 year and who drank more than 30 mL of liquor or more than 150 mL of beer every day.

Imaging Examination

All participants underwent brain MRI after admission. All MR scans were performed using a standard 3.0 T scanner (GE Discovery750, Milwaukee, WI, USA) in a standard manner. The sequence included T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), T2-weighted axial fluid-attenuated inversion recovery (FLAIR) images, diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC) sequences. The infarcted tissue showed isointense or hypointense signals on T1WI and hyperintense signals on T2WI, with hyperintense signals found in the DWI phase of the corresponding parts. According to the results of brain MRI, we recorded the location of cerebral infarction (anterior circulation, posterior circulation, and anterior circulation + posterior circulation), the number of infarct lesions (single cerebral infarction and multiple cerebral infarction), TOAST classification–a system for categorization of subtypes of ischemic stroke mainly based on etiology–(atherosclerosis type, arteriole occlusion type, cardiogenic embolism, other cause type, and unexplained type), and OCSP classification-a simple clinical stroke classification system that has been associated with size and location of the infarct- (partial anterior circulation infarction, lacunar infarction, and posterior circulation infarction).

Chronic Brain Injury

Cerebral small vessel disease refers to a pathological process involving intracerebral arterioles and venules caused by chronic diseases. Cerebral small vessel disease has diverse pathological mechanisms. Its neuroimaging features include white matter hyperintensity (WMH), new subcortical infarction, lacuna, cerebral microbleeds, brain atrophy, and perivascular space. Patients with WMH, lacuna, perivascular space, and temporal lobe atrophy were included in this study. WMH was evaluated using the Fazekas scale, which gives a score ranging from 0 to 3 each for periventricular white matter hyperintense (PVH) and deep white matter hyperintense (DWMH); these two scores can be summed to give a total score from 0 to 6, with lower scores indicating less WMH burden. Lacuna refers to a round or oval subcortical hole with diameter 3–15 mm (the signal is close to that of cerebrospinal fluid), which originates from an acute subcortical small infarction or hemorrhage in the perforating artery. Perivascular space refers to a circular or linear lacuna with a diameter less than 3 mm and the same signal as cerebrospinal fluid. 4) Temporal lobe atrophy refers to a decrease in temporal lobe brain volume unrelated to visible focal injury, which is determined according to medical imaging.

Neuropsychological Evaluation

A professionally trained neurologist measured the cognitive function of patients using the Montreal Cognitive Assessment (MoCA) scale, administered within 10 minutes. The total score is 30 points. Patients with a score ≥26 points are considered to have normal cognitive function, those with a score <26 points are considered to have MCI, and those with a score <20 points are classified as having severe CI. To correct for errors, 1 point was added to the total score in patients with less than 12 years of education.

Statistical Analysis

The data were preprocessed and analyzed using R, version 4.0.1 (The R Project for Statistical Computing, Vienna, Austria). Number (n) and percentage (%) are used to report the data. χ^2 test and Fisher's exact test were used for comparisons among groups. Measurement data conforming to a normal distribution and satisfying the homogeneity test of variance are expressed using mean ± standard deviation. One-way analysis of variance was applied for intergroup comparison. Measurement data with a non-normal distribution are denoted using median and interquartile range. The Kruskal–Wallis *H*-test was used for intergroup comparison. Logistic regression analysis was carried out as multivariate regression analysis. We considered $P < 0.05$ to indicate statistical significance. The backward stepwise regression method was used to analyze influencing factors. The optimal model was selected based on the Akaike information criterion (AIC). Once the model was determined, a prediction model was built based on the logistic regression model and a receiver operating characteristic (ROC) curve was drawn. The area under the ROC curve (AUC) was calculated to evaluate the predictability of each index. The Youden index of the most predictive index was calculated, and the critical point, sensitivity, and specificity were determined.

Results

Demographic and Imaging Characteristics

As shown in Table 1, 94 (58.39%) were identified with CI. Thereinto 61 (37.89%) of CI was characterized as MCI and 33 (20.50%) as severe CI. Compared with CN group, the patients in both of MCI and severe CI groups had the significant increase at age, the lower education level, the longer course of DM, the higher mRS and NIHSS scores. Moreover, the significant differences between CN and MCI or severe CI were observed in RCI, multiple cerebral infarction and TOAST classification ($P < 0.05$).

Laboratory Data

The collected laboratory data were compared among the three groups of patients. As shown in Table 2, the levels of HbA1c and serum albumin in MCI and severe CI groups were higher than CN group ($P < 0.05$). There were no significant differences in triglyceride, total cholesterol, low density lipoprotein, fibrinogen and uric acid among the three groups ($P > 0.05$).

Chronic Brain Injury and Neurocognitive Characteristics

Table 3 shows the characteristics of chronic brain dysfunction. There were significant differences among the three groups in terms of each index. As shown in Table S1, compared with cognitively normal (CN) patients, those with CI had poorer performance in all cognitive domains ranging from visual space to naming, attention, language, abstraction, memory, and orientation ($P < 0.05$).

Age, Education Level, and HbA1c

As shown in Figures 1–3, cognitive levels gradually declined with increasing age and steadily improved with years of education. The cognitive level, which was negatively correlated with the level of HbA1c, showed an obvious downward curve.

Logistic Regression Analysis and Model Building

As shown in Figure S1, the Spearman correlation test was used to conduct correlation analysis on all variables. Fazekas score, PVH score, and other variables with high correlation were excluded to ensure the rationality of the model. Table 4

Table 1 Demographic and Clinical Characteristics by Cognition Groups

	CN	MCI	Severe CI	P value
N	67	61	33	
Age, years	65 (63, 67)	68 (63, 72)	74 (67, 78)	<0.001
Male, n (%)	35 (52.2)	36 (59.0)	16 (48.5)	0.575
Educated Level, n (%)				<0.001
Primary	20 (29.9)	42 (68.9)	28 (84.8)	
Senior high school	36 (53.7)	11 (18.0)	4 (12.1)	
University or above	11 (16.4)	8 (13.1)	1 (3.0)	
Diabetes duration, years	4 (3, 5)	6 (5, 8)	8 (6, 8)	<0.001
Smoker, n (%)	24 (35.8)	23 (37.7)	11 (33.3)	0.914
Drinker, n (%)	16 (23.9)	22 (36.1)	8 (24.2)	0.259
Hypertension, n (%)	44 (65.7)	47 (77.0)	22 (66.7)	0.329
Recurrent cerebral infarction, n (%)	19 (28.4)	40 (65.6)	25 (75.8)	<0.001
Coronary Artery Disease, n (%)	21 (31.3)	17 (27.9)	14 (42.4)	0.346
Atrial fibrillation, n (%)	10 (14.9)	4 (6.6)	1 (3.0)	0.101
SBP, n (%)	29 (43.3)	35 (57.4)	16 (48.5)	0.278
DBP, n (%)	17 (25.4)	17 (27.9)	4 (12.1)	0.208
Brain Vascular Circulation Distribution, n (%)				0.273
Anterior infarction	42 (62.7)	30 (49.2)	17 (51.5)	
Posterior infarction	24 (35.8)	28 (45.9)	13 (39.4)	
Anterior & Posterior	1 (1.5)	3 (4.9)	3 (9.1)	
TOAST Classification, n (%)				<0.001
Large artery atherosclerosis	37 (55.2)	47 (77.0)	31 (93.9)	
Cardioembolism	10 (14.9)	4 (6.6)	2 (6.1)	
Small vessel occlusion	17 (25.4)	4 (6.6)	0 (0.0)	
Other determined etiology	2 (3.0)	3 (4.9)	0 (0.0)	
Undetermined etiology	1 (1.5)	3 (4.9)	0 (0.0)	
OCSP Classification, n (%)				0.462
PACI	33 (49.3)	27 (44.3)	18 (54.5)	
LACI	12 (17.9)	8 (13.1)	2 (6.1)	
POCI	22 (32.8)	26 (42.6)	13 (39.4)	
Single infarction, n (%)	55 (82.1)	36 (59.0)	16 (48.5)	0.001
mRS, score	1 (0, 2)	2 (1, 3)	3 (2, 3)	<0.001
NIHSS, score	1 (0, 2)	2 (2, 3)	3 (3, 4)	<0.001

Note: *P*<0.05, statistical significance.
Abbreviations: CN, cognitively normal; MCI, mild cognitive impairment; SBP, systolic blood pressure; DBP, diastolic blood pressure; PACI, partial anterior circulation infarction; LACI, lacunar infarction; POCI, posterior circulation infarction.

shows the results obtained using the optimal model of multivariate logistic regression. RCI, course of DM, and HbA1c were risk factors of CI, with OR (95% confidence interval) 7.17 (2.09, 30.37), 5.39 (2.40, 14.59), and 3.89 (1.66, 10.04), respectively. Female, senior high school education level, and serum albumin were protective factors of cognitive function, with OR (95% confidence interval) 0.28 (0.07, 0.95), 0.05 (0.01, 0.21), 0.20 (0.08, 0.42), respectively. We constructed a prediction model and drew a receiver operating characteristic (ROC) curve. As shown in Figure 4, the AUC of the model was 0.966, which indicates that the diagnosis was highly accurate. The optimal threshold was 0.511, with specificity 0.910, sensitivity 0.957, and Youden index 0.867.

Discussion

In this study, we included patients with T2DM who experienced AIS and were hospitalized in the Department of Neurology, Jinan Central Hospital affiliated to Shandong University. Using cognitive assessment, the patients were divided into a CN group, MCI group, and severe CI group. According to the analyses of medical history, clinical

Table 2 Biochemical Criterion by Cognition Groups

	CN	**MCI**	**Severe CI**	**P value**
N	67	61	33	
HbA1c	6.00 (5.50, 6.75)	7.30 (6.60, 8.20)	8.40 (7.30, 10.50)	<0.001
Triglyceride	1.47 (1.09, 1.88)	1.35 (1.01, 1.92)	1.45 (1.05, 1.78)	0.797
TC	4.06 (1.11)	4.24 (1.16)	4.19 (1.29)	0.678
LDL	2.66 (2.06, 3.09)	2.45 (1.97, 3.06)	2.52 (1.62, 2.88)	0.811
Albumin	39.20 (38.15, 39.85)	36.4 (35.45, 37.50)	35.30 (33.11, 36.50)	<0.001
Fibrinogen	3.29 (2.86, 3.78)	3.23 (2.76, 3.86)	3.47 (3.05, 3.95)	0.685
Uric Acid	299 (235, 343)	301 (263, 403)	278 (235, 365)	0.196

Note: $P<0.05$, statistical significance.
Abbreviations: HbA1c, glycated hemoglobin; TC, total cholesterol; LDL, low density lipoprotein.

Table 3 Features of Small Vascular Lesions by Cognition Groups

	CN	**MCI**	**Severe CI**	**P value**
N	67	61	33	
Lacune, n (%)	28 (41.8)	41 (67.2)	26 (78.8)	<0.001
Perivascular space, n (%)	37 (55.2)	51 (83.6)	28 (84.8)	<0.001
Fazekas Score	1 (0, 2)	3 (2, 3)	3 (2, 4)	<0.001
PVH	1 (0, 1)	1 (1, 2)	2 (1, 2)	<0.001
DWMH	0 (0, 1)	1 (1, 2)	2 (1, 2)	<0.001
Temporal atrophy, n (%)	13 (9.4)	35 (57.4)	22 (66.7)	<0.001

Note: $P<0.05$, statistical significance.
Abbreviations: PVH, periventricular white matter hyperintense; DWMH, deep white matter hyperintensities.

examination, neuropsychological questionnaire, laboratory tests, and imaging examinations, we found that RCI, course of DM, and HbA1c were independent risk factors of PSCI in patients with T2DM, whereas female, senior high school, serum albumin were protective factors. We constructed a prediction model using sex, age, education level, RCI, DM course, HbA1c and serum albumin and obtained a receiver operating characteristic (ROC) curve, suggesting the significant association of these influencing factors with PSCI in patients with T2DM.

In this study, PSCI was significantly correlated with age and education level, and the risk of PSCI was higher in patients with older age and low education level, which is consistent with previous research results.[5,17,18] With increased age, brain atrophy is aggravated, and synaptic connections between neurons are reduced in older individuals. Older patients often have accompanying cerebral arteriosclerosis and decreased cerebral blood flow, which increase the risk of CI. Older people with a low education level are more likely to develop age-related cognitive decline. Studies have shown that older individuals with an education background of junior high school or below are 3.03 times more likely to have PSCI than those with senior high school education level. Stroke survivors with higher education levels tend to have a larger cognitive reserve capacity, which can make up for brain damage.[19–21]

We also found that patients with a long course of DM are at higher risk for PSCI. Previous studies have shown that the course of DM is a risk factor for CI.[18] Patients with a long course of DM have severe microangiopathy, longer exposure to glycolipid metabolic disorders, and severer oxidative stress responses.[22] All of the above factors play a critical role in the development of atherosclerosis and CI in patients with T2DM.[23,24] We found an increased risk of PSCI in patients with recurrent cerebral infarction, which is verified in previous research results.[5,25] Studies have shown that the probability of dementia in patients with a previous stroke history is similar to that in patients who are 10 years older but without a stroke history.

By analyzing the differences between patients in the three subgroups classified using TOAST, we found that patients with large artery atherosclerosis and small artery occlusion had an increased risk of CI. According to a previous study, patients with stroke caused by cardiac cerebral embolism are prone to aphasia whereas patients with stroke owing to
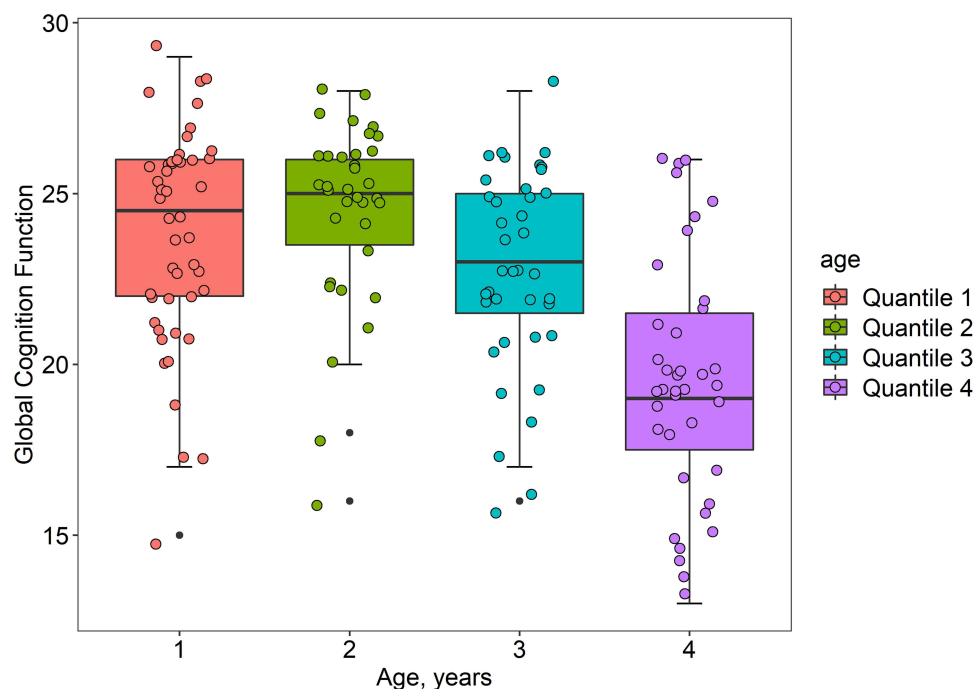
Figure 1 Distribution of cognitive function by age. The age of the enrolled patients was divided into four groups through the quartile interval, which increasing sequentially from left to right. The boxplot of the distribution of the four groups in the overall cognitive function was drawn by R analysis. The older patients had lower scores in cognitive function.
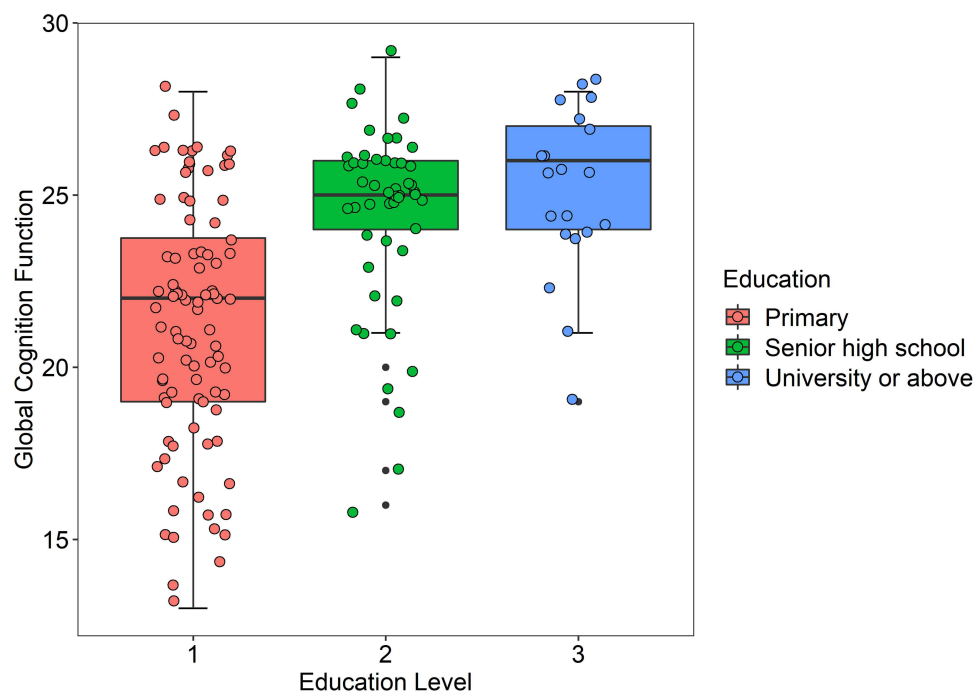

Figure 2 Distribution of cognitive function at educational level. Patients with less than 9 years of education were defined as primary, 9–11 years as Senior high school, and the patients with more than 11 years of education were defined as University or above. The boxplot of the distribution of the three groups in the overall cognitive function was drawn through R analysis. It can be seen that the cognitive function scores of patients with high education level are on the high side.
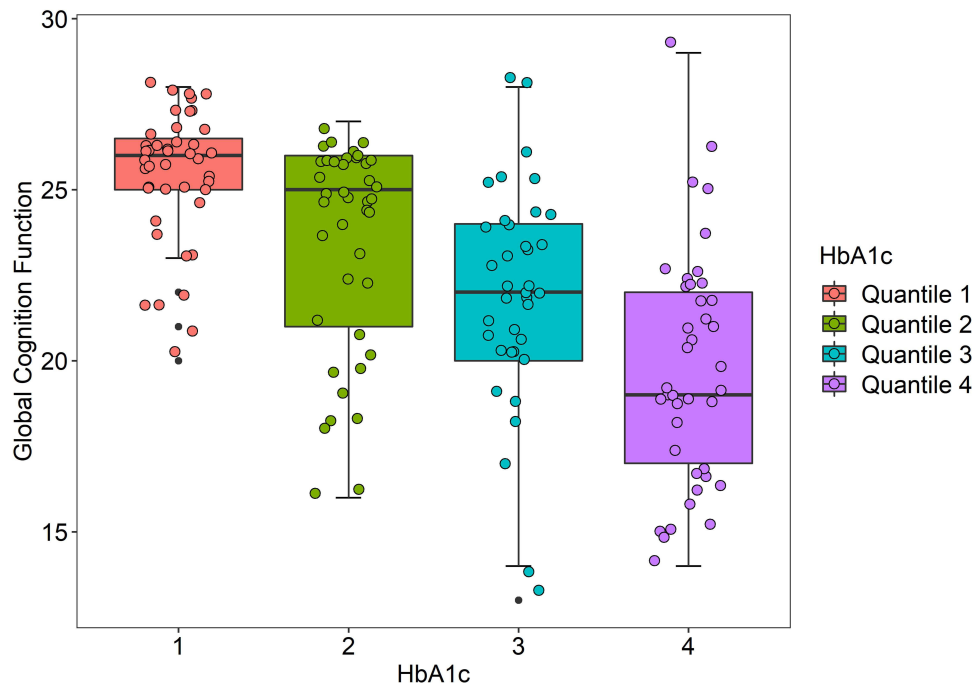
Figure 3 Distribution of cognitive function on HbA1c. The HbA1c were divided into four groups through the quartile interval, which increased from left to right. The boxplot of the distribution of HbA1c in the overall cognitive function was drawn by R analysis. Patients with high HbA1c scored lower in cognitive function.
Abbreviation: HbA1c, glycated hemoglobin.

other causes are associated with executive function, memory, and emotional disorders. However, large artery athero-sclerosis and small vessel occlusion can lead to nearly all types of CI.[26] This also indicates the importance of monitoring cognition in specific stroke subtypes, so as to provide a warning of early stages of neurological impairment. Many studies have shown that the severity of infarction and low score for activities of daily living are effective in predicting PSCI.[17,27] Patients with PSCI have a higher NIHSS score and a lower Barthel index. This study included the NIHSS score and mRS score, which were significantly different in single-factor analysis. It should be pointed out that our study findings were not in agreement with the results of previous studies when it comes to the relationship between the number of infarcts and CI.[17,28] We found a significant correlation between multiple infarcts and the risk of CI, and the volume of cerebral infarction was non-significantly correlated with cognitive function.

The results of analysis of laboratory indexes, HbA1c was found to be a risk factor for the development of PSCI. HbA1c represents the average blood glucose level of patients in the past 8–12 weeks. Most researchers believe that

Table 4 Demographic, Clinical Characteristics and Laboratory Data Adjusted for PSCI in Patients with T2DM Predictive Model Using Binary Logistic Regression

Variables	Std OR (95% CI)	Estimate	Std. Estimate	P value
Sex	0.28 (0.07, 0.95)	−1.27	−1.27	0.050
Age	1.75 (0.92, 3.68)	0.08	0.56	0.110
Education				
Primary	Reference	reference	Reference	
Senior high school	0.05 (0.01, 0.21)	−3.00	−3.00	<0.001
University or above	0.33 (0.05, 1.83)	−1.12	−1.12	0.211
Recurrent cerebral infarction	7.17 (2.09, 30.37)	1.97	1.97	0.003
Diabetes duration	5.39 (2.40, 14.59)	0.84	1.68	<0.001
HbA1c	3.89 (1.66, 10.04)	0.84	1.36	0.003
Albumin	0.20 (0.08, 0.42)	−0.60	−1.63	<0.001

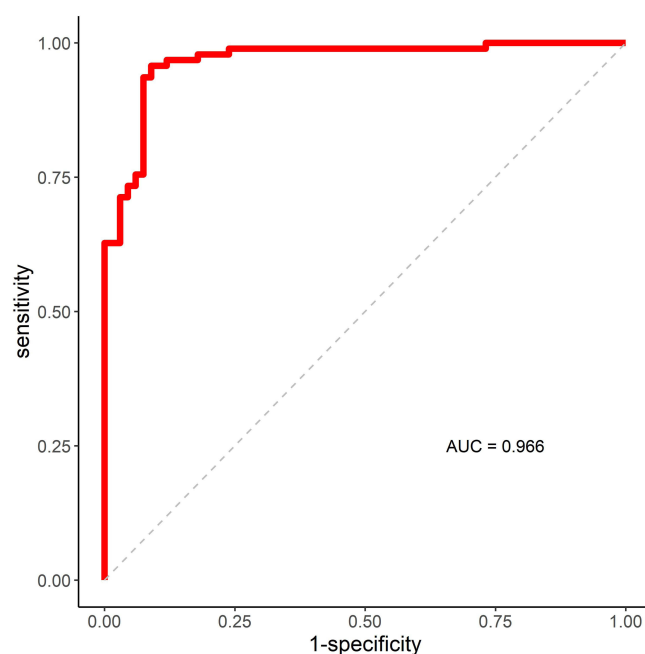**Note**: $P<0.05$, statistical significance.

Figure 4 The receiver operating characteristic curve and area under the curve of the cognition function prediction model. Area under the curve of PSCI in patients with T2DM was predicted by the optimal model, including sex, age, education level, recurrent cerebral infarction, course of diabetes and serum albumin. The AUC of the model was 0.966, the optimal threshold was 0.511, with specificity 0.910, sensitivity 0.957, and Youden index 0.867.

hyperglycemia represented by increased HbA1c is negatively correlated with cognitive function because it can accelerate brain damage and aging.[25,29] Nevertheless, a few researchers hold the opposite view, believing that cognitive function improves with increased HbA1c.[30] Moreover, we found that high serum albumin was a protective factor for cognitive function, which has been verified in previous studies.[31–33] This may be related to nutritional status, blood volume, and oxidative stress reflected in serum albumin. We did not find any significant correlation between lipids and CI, which is inconsistent with previous data.[34,35] This is probably because some patients were taking oral lipid-lowering drugs before the onset of stroke.

It has been found that microvascular lesions, vascular endothelial damage, and insulin resistance caused by diabetes are related to WMH, and an increased load of WMH will lead to CI.[12,36] Cerebral small vessel disease is an important influencing factor of CI. In this study, WMH, lacuna, perivascular space, and temporal lobe atrophy were included as representative types of chronic brain injury in cerebral small vessel diseases; cerebral microbleeds were not included because most research participants were not scanned with susceptibility-weighted imaging during hospitalization. Univariate analysis revealed significant differences among the three groups in terms of chronic brain injury. However, this variable with relatively high correlation was excluded in the final regression analysis; chronic brain injury caused by cerebral small vessel diseases is very common in patients with CI. In future research, we can further increase the sample size and quantitatively analyze chronic brain injuries such as lacuna and perivascular space. Our study shows a comparison of neuropsychological evaluations conducted among the different groups. Significant differences were found among the three groups in terms of each cognitive domain.

We entered the abovementioned influencing factors into the regression model and selected the optimal model according to the AIC. Once the model was determined, we predicted the occurrence of PSCI in patients with T2DM based on the logistic regression model. RCI, the course of DM, and HbA1c were risk factors of PSCI. For every unit of increased course of DM, the risk of PSCI increased by 5.39 times, and the risk of PSCI in patients with recurrent cerebral infarction was 7.17 times that of patients with a first cerebral infarction. However, sex (female), senior high school and serum albumin were protective factors of cognitive function. There are differences between men and women when it comes to cognitive status and the prevalence of many mental diseases, which involves many aspects such as sex hormones, brain neuroanatomy, neurotransmitters, and sleep disorders. According to most studies, men have more

serious cognitive deficits than women.[37–39] Women perform well in speech and episodic memory whereas men have better visual spatial abilities. Given the same estrogen level, women outperform men in terms of memory and speech,[40–44] and women with acute cerebrovascular diseases have stronger cognitive reserve abilities than men.[41] In addition, the volume of brain regions related to cognitive functions such as learning and memory has been proven to be significantly different between men and women. The volume of the hippocampus, caudate nucleus, dorsolateral prefrontal cortex, and anterior cingulate gyrus is larger in women than in men.[45–47] Our study showed that female was a protective factor of cognitive function. Nonetheless, some researchers hold differing opinions,[48–51] believing that women are more likely to have CI than men or that the incidences of CI are quite similar between men and women. Through stepwise regression, we finally determined that recurrent cerebral infarction, the course of DM, and HbA1c were the most effective in predicting PSCI in patients with T2DM. The AUC of the model was 0.966, which indicates that the diagnostic accuracy is high. These clinical variables provide the basis for early screening of CI. In future clinical work, clinicians should suggest that patients at high risk for CI manage their lifestyle and control vascular risk factors, such as through smoking cessation, alcohol restriction, diet management, exercise, and control of blood pressure and blood glucose. If necessary, patients should receive cognitive rehabilitation training and drug intervention, such as with cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists,[52,53] which will help to improve patients' cognitive function and delay the progression of disease.

Currently, only a small number of researchers have studied the cognitive function of patients with T2DM after stroke. Compared with the other research, this study included more detailed information about demographic data, imaging, laboratory data, stroke types, nerve injury, and recovery evaluation. We used the MoCA Scale,[54] which has relatively high sensitivity and specificity for CI caused by vascular factors, to screen the cognitive function of patients. We excluded patients with major diseases like depression and hypoglycemia that may affect cognitive function, as well as patients with severe brain injury, many complications, and aphasia who could not complete the scale. However, because of this, the research participants in this study had mild symptoms of nerve damage (median NIHSS 2), with the corresponding cognitive performance being better than expected. Hence, these research participants cannot represent all patients with T2DM who have PSCI.

Owing to some limitations, these results must be carefully interpreted. First, the sample size was not sufficiently large and this was a single-center study. The results of this study were in-sample results, lacking external verification. Second, the severity and extent of CI among the included patients might be underestimated as a single administration of the MoCA scale was used to evaluate the cognition of patients at specific time points.[55,56] Third, no data were collected regarding the cognitive status of research participants before stroke (1 year earlier or longer), which may affect our research results to some extent. Therefore, as a preliminary study, this study was initially aimed at screening the influencing factors of CI after T2DM ischemic stroke with the aim to establish a prediction model. More prospective, longitudinal, and multicenter studies will be needed in the future to confirm the results of this study, so as to better diagnose and intervene CI in such patients.

Conclusion

This study screened for factors affecting cognitive function after ischemic stroke in patients with T2DM. RCI, course of DM, and HbA1c were independent risk factors of PSCI in patients with T2DM, whereas female, senior high school, serum albumin were protective factors. We constructed a prediction model using sex, age, education level, RCI, DM course, HbA1c and serum albumin. It showed the significant association of these influencing factors with PSCI in patients with T2DM. Our study emphasized the importance of a patient's history, laboratory testing, and imaging examination for patients with type 2 diabetes after stroke. After further external validation, the predictive model results of this study may serve as a potential tool to identify high-risk patients with CI, provide a basis for early management strategies for patients with PSCI, help delay disease progression, and improve the quality of life of post-stroke patients.

Ethical Approval and Informed Consent

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Research and Ethics Committee of Jinan Central Hospital (AF/SC-08/04.0). All participants were informed about the

purpose of the study. Written informed consent was obtained from all participants, or from informants in the case of participants with severe cognitive impairment.

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Disclosure

The authors report no conflicts of interest in this work.

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