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ORIGINAL ARTICLE

Serum Direct Bilirubin and Hemoglobin A1c Predict Cognitive Impairment After Diabetes Mellitus Combined with Cerebral Infarction

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SUMMARY

Background: **The aim of this study was to investigate the influencing factors and possible predictors of cognitive impairment in patients with type 2 diabetes mellitus complicating cerebral infarction (T2DM/CI).**
Methods: **The clinical data of 130 patients with T2DM/CI were retrospectively analyzed. According to MMSE score and MoCA score, they were divided into cognitive impairment group (78 cases) and no cognitive impairment group (52 cases). Multifactorial logistic regression analysis was used to explore the independent influencing factors of cognitive impairment in patients with T2DM/CI. Pearson analysis was used to analyze the correlation between DBIL and HbA1c and MoCA score. In turn, ROC curves were plotted to analyze the predictive efficacy of DBIL and HbA1c in cognitive impairment in T2DM/CI patients.**
Results: **DBIL in serum was significantly lower in the cognitive impairment group compared with the no cognitive impairment group and was an independent protective factor for cognitive impairment in T2DM/CI patients. In contrast, HbA1c levels were completely opposite and acted as an independent risk factor for cognitive impairment in patients with T2DM/CI. There was a negative correlation between MoCA scores and HbA1c as well as between HbA1c and DBIL. There was a positive correlation between MoCA scores and DBIL. Combined DBIL and HbA1c was more effective in predicting the cognitive impairment in patients with T2DM/CI.**
Conclusions: **Low DBIL and high HbA1c levels are independent risk factors for cognitive impairment in T2DM/CI patients with some predictive efficacy and are positively correlated with the severity of cognitive impairment.**
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KEYWORDS

Type 2 diabetes mellitus, cerebral infarction, cognitive impairment, direct bilirubin, hemoglobin A1c, predictive efficacy

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is the third most common non-communicable disease in terms of mortality after tumors and cardiovascular diseases. Atherosclerosis of the great vessels is one of the major complications of T2DM and increases the risk of cerebral infarction (CI) in patients with T2DM. T2DM patients have a 1.5- to 3-fold higher risk of CI, particularly ischemic CI, than nondiabetic patients [1]. CI can lead to narrowing

or even blockage of cerebral arteries, which reduces the metabolic rate of brain tissue and slows down neurotransmitter response, resulting in cognitive decline [2]. More importantly, most of the ischemic lesions after CI are concentrated in the prefrontal cortex, which is closely related to cognitive function and behavior [3]. Abnormal central nervous system function can affect cognitive function through cascade reactions.

HbA1c is the product of the reaction between hemoglobin and glucose in the blood, and it can be a reliable indicator to reflect the level of glucose control in diabetic patients over a long period of time. HbA1c can persist in the life cycle of erythrocytes, and the rate of synthesis is positively correlated with blood glucose levels, so it can accurately reflect the blood glucose levels. HbA1c is involved in the process of vascular injury [4]. HbA1c reduces the oxygen affinity of erythrocytes, leading to hypoxia in tissues. Under hypoxia, the production of oxygen free radicals increases, and subsequent inflammatory cascade is the main pathological basis of atherosclerosis. At the same time, in a hyperglycemic environment, platelets are activated to aggregate and adhere to the vascular endothelium, accelerating atherosclerosis and plaque formation, and gradually aggravating vascular lesions over time [5]. In this process, HbA1c is significantly upregulated [6]. Furthermore, although HbA1c has been identified as a predictor of chronic complications of diabetes in studies [7], it remains unclear whether HbA1c is involved in the pathologic processes that complicate CI in patients with T2DM.

Bilirubin (BIL), a metabolite produced by the breakdown and metabolism of hemoglobin, is often considered a waste product only and is potentially neurotoxic, causing neurological dysfunction and psychiatric disorders at high levels [8,9]. Serum BIL is negatively correlated with peroneal nerve conduction velocities as well as with the severity of autonomic dysfunction. BIL is a potent endogenous plasma antioxidant with anti-oxidative stress capacity [10]. And oxidative stress is considered part of the pathophysiology of neuropathy. In patients with mild cognitive impairment, serum total BIL concentration is correlated with the cognitive function [11]. Moreover, physiologic serum total BIL concentrations are negatively correlated with diabetic peripheral neuropathy in patients with T2DM [12]. It is speculated that BIL may be involved in neurological function in patients with T2DM [13,14].

It is important to address the potential impact of HbA1c and BIL on cognitive impairment after T2DM/CI. The aim of this study was to analyze the correlation between HbA1c and BIL levels and cognitive function in patients with T2DM/CI through a retrospective investigation.

MATERIALS AND METHODS

Participants

The clinical data of 130 patients with T2DM/CI admitted to Putian 95th Hospital from February 2022 to March 2023 were retrospectively analyzed. According to the results of mini-mental state examination (MMSE) and Montreal cognitive assessment (MoCA), the enrolled patients were divided into a cognitive impairment group (78 cases) and a no cognitive impairment group (52 cases). All patients gave informed consent, and the study was approved by the Ethics Committee of Putian 95th Hospital.

Inclusion and exclusion criteria in the cognitive impairment and no cognitive impairment groups

Inclusion criteria: 1) T2DM was diagnosed before the onset of CI, in accordance with the Guideline for the Prevention and Treatment of Type 2 Diabetes Mellitus in China (2020) [15]. The criteria were in line with the World Health Organization diagnostic criteria for T2DM; 2) CI diagnosis was in line with the 2019-updated 2018 guidelines for the early management of patients with acute ischemic stroke [16] and cranial imaging; 3) age ≤ 85 years; 4) relevant clinical data were complete; and (5) patients were within 14 days after CI and cooperate in completing the scale screening.

Exclusion criteria: 1) other neurological diseases such as congenital mental retardation, brain tumor, epilepsy, intracranial infection, Parkinson's disease, or history of taking psychotropic medication in the last 6 months; 2) severe visual, auditory, or speech disorders or negative emotions such as obvious anxiety or depression; 3) impaired consciousness; and 4) diseases with a diagnosis of possible cognitive impairment, such as carbon monoxide poisoning, epilepsy, Parkinson's disease, intracranial infections, etc.

Inclusion and exclusion criteria for patients with T2DM

Inclusion criteria: 1) T2DM had been diagnosed before the onset of CI and met the diagnostic criteria in the Guideline for the Prevention and Treatment of Type 2 Diabetes Mellitus in China (2020); 2) patients could cooperate in completing the scale assessment; (3) age ≥ 65 years; (4) relevant clinical data were complete.

Exclusion criteria: (1) combined congenital mental retardation, brain tumor, epilepsy, intracranial infection, Parkinson's disease, and other neurological disorders or history of taking psychotropic medication in the last 6 months; (2) severe visual, auditory, or speech disorders or significant negative emotions such as anxiety or depression; (3) impaired consciousness; and (4) diseases with a previous diagnosis of cognitive disorders that may cause cognitive impairment, such as carbon monoxide poisoning, epilepsy, Parkinson's disease, intracranial infections, etc.

General information
General data of all study subjects were collected, including gender, age, education level, BMI, past disease history (coronary heart disease and hypertension), history of smoking and drinking, onset-to-treatment time, systolic blood pressure, diastolic blood pressure, etc.

Clinical information
Patients' blood was drawn early in the morning after 12 hours of fasting to test the indexes, including fasting plasma glucose, 2-hour postprandial plasma glucose, fibrinogen, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total BIL, direct BIL (DBIL), indirect BIL (IBIL), and HbA1c. Hcy levels were measured by Beckman Coulter AU5800 automatic biochemistry and HbA1c was measured by immunoturbidimetry assay in HLC-XG automatic instrument. CRP was measured by the Elx800 microplate reader (BioTek, USA) using enzyme-linked immunosorbent assay kit (Mindray, China).

Cognitive function assessment
All study subjects underwent a cognitive functioning examination within 48 hours of admission, and neuropsychological scales including NIHSS, MMSE, and MoCA were completed in a quiet environment by a specialized physician.
Neurological impairment was assessed in patients with CI by the NIHSS score, with ≤ 4 categorized as mild impairment, 5 - 14 categorized as moderate impairment, and ≥ 15 categorized as severe impairment.
MMSE measures orientation, attention, concentration, naming verbal memory, and visuospatial skills. The score results were categorized according to education level. No education ≤ 17 points, primary school education (≤ 6 years) ≤ 20 points, secondary school and above (> 6 years) ≤ 24 points were considered to have cognitive impairment [17].
MoCA included 7 items, including visuospatial and executive function, orientation, attention, etc., with a full score of 30 points. Higher scores indicate better cognitive function. If the subjects had < 12 years of education, 1 point was added to the test result to correct for the bias of education level. A score of ≥ 26 indicated no cognitive impairment; a score of < 26 indicated that the patient had existing cognitive impairment; and patients with a score of < 20 were categorized as having severe cognitive impairment.

Statistical methods
SPSS 26.0 was used for statistical analysis. The data underwent normality testing, with those exhibiting a normal distribution represented as mean ± standard deviation, and the *t*-test was employed for comparing two groups. Non-normally distributed data were expressed as median and interquartile range M (Q_{25} - Q_{75}), and comparisons between groups were made using the Mann-Whitney U test. Qualitative information was expressed as cases (n) and the constitutive ratio (%) using the chi-squared test. Multifactorial logistic regression was performed for variables with $p < 0.05$ in the univariate analysis. Correlations between variables were analyzed using Pearson correlation analysis. Receiver operating curve (ROC) analysis was used to obtain the area under the curve (AUC), which was compared using MedCalc software. $p < 0.05$ means there is a significant difference.

RESULTS

Clinical general data of patients
As shown in Table 1, the cognitive impairment group was older than the no cognitive impairment group ($p < 0.05$), ranging from 63 - 79 years, with a mean age of (71.88 ± 7.92) years. The patients in the cognitive impairment group showed higher levels of CRP (38.99 ± 7.19 mg/L) and Hcy (17.14 ± 2.08 μmol/L), which were higher than those of the patients in the no cognitive impairment group ($p < 0.05$). In addition, patients in the cognitive impairment group had a lower level of education than those in the no cognitive impairment group ($p < 0.05$). There was no significant difference in gender, BMI, course of T2DM, past disease history (hypertension and coronary heart disease), smoking and drinking history, and blood routine test indexes between the no cognitive impairment group and cognitive impairment group ($p > 0.05$).

Serum BIL, HbA1c levels, and MoCA scores in 2 groups of patients
DBIL and HbA1c indicators were higher in the cognitive impairment group than in the no cognitive impairment group, and the MMSE score and MoCA score were lower ($p < 0.05$, Table 2).

Logistic regression analysis
Variables with $p < 0.05$ in univariate analysis showed that age, education, Hcy, CRP, DBIL, HbA1c, and MMSE score and MoCA score were the relevant risk factors for cognitive impairment in patients with T2DM/CI. After adjusting for all the factors that were significantly associated in the univariate analysis (age, education level, CRP, and Hcy), multifactorial logistic regression found, in Table 3, that HbA1c [95% CI: 2.884 (1.745 - 6.019), $p = 0.029$] was a risk factor for cognitive impairment in T2DM/CI patients. In addition, DBIL [95% CI: 0.870 (0.210 - 0.909), $p = 0.011$] and MoCA score [95% CI: 0.753 (0.479 - 0.902), $p = 0.031$] were independent protective factors for cognitive impairment in T2DM/CI patients.

Correlation analysis between MoCA score, DBIL, and HbA1c
There was a negative correlation between HbA1c and DBIL ($r = -0.224$, $p < 0.05$). There was no correlation between MoCA score and HbA1c in T2DM/CI patients.

Table 1. Comparison of clinical general data between T2DM/CI patients in the group without cognitive impairment and in the group with cognitive impairment.

Characteristics	T2DM/CI (n = 130)	
	No cognitive impairment (n = 52)	Cognitive impairment (n = 78)
Gender (male)	22 (42%)	36 (46%)
Age (year)	66.52 ± 8.06	71.88 ± 7.92 *
Education (year)	9 (6, 12)	6 (5, 11) *
BMI	22.29 ± 2.18	22.34 ± 2.16
Duration of T2DM (year)	10 (5, 17)	10 (6, 17)
Coronary heart disease	12 (23%)	20 (26%)
Hypertensive renal disease	32 (62%)	53 (68%)
Smoking	27 (52%)	39 (50%)
Alcohol use	10 (19%)	17 (22%)
OTT (minute)	159.65 ± 60.28	159.62 ± 63.57
NIHSS score	4 (2, 6)	4 (3, 6)
FPG (µmol/L)	8.55 ± 1.84	8.61 ± 1.54
2h PG (µmol/L)	13.73 ± 4.58	13.75 ± 4.82
Total cholesterol (mmol/L)	4.25 ± 0.84	4.37 ± 0.64
Total triglycerides (mmol/L)	2.30 ± 0.29	2.31 ± 0.32
High-density lipoprotein cholesterol (mmol/L)	1.06 ± 0.26	1.07 ± 0.24
Low-density lipoprotein cholesterol (mmol/L)	2.83 ± 0.55	2.83 ± 0.64
CRP (mg/L)	30.26 ± 9.18	38.99 ± 7.19 *
Hcy (µmol/L)	14.64 ± 2.51	17.14 ± 2.08 *
FIB (g/L)	3.45 ± 0.84	3.51 ± 0.79
SBP (mmHg)	141.74 ± 22.94	142.17 ± 23.46
DBP (mmHg)	80.19 ± 10.82	80.99 ± 11.68

Data are expressed as mean ± standard deviation or n (%). Continuous variables were tested using Student´s *t*-test, and qualitative data were tested using the chi-squared test. * compared with the no cognitive impairment group, p < 0.05.
T2DM type 2 diabetes mellitus, CI cerebral infarction, BMI body mass index, OTT onset-to-treatment time, NIHSS national institutes of health stroke scale, MMSE mini-mental state examination, FPG fasting plasma glucose, 2h PG 2-hour postprandial plasma glucose, CRP C-reactive protein, Hcy homocysteine, FIB fibrinogen, SBP systolic blood pressure, DBP diastolic blood pressure.

Table 2. Comparison of serum bilirubin, HbA1c levels, and MoCA score in 2 groups of patients.

Characteristics	T2DM/CI (n = 130)	
	No cognitive impairment (n = 52)	Cognitive impairment (n = 78)
TBIL (µmol/L)	14.00 (11.50, 18.00)	14.20 (11.00, 18.50)
DBIL (µmol/L)	5.74 ± 0.98	6.46 ± 1.15 *
IBIL (µmol/L)	11.70 (8.50, 15.50)	11.70 (8.50, 15.80)
HbA1c (%)	6.50 ± 0.91	7.12 ± 1.04 *
MMSE score	26.77 ± 1.22	23.51 ± 2.08 *
MoCA score	23.77 ± 2.24	18.17 ± 4.60 *

Data are expressed as mean ± standard deviation. Statistical analyses were performed using Student´s *t*-test. * compared with the no cognitive impairment group, p < 0.05.
T2DM type 2 diabetes mellitus, CI cerebral infarction, TBIL total bilirubin, DBIL direct bilirubin, IBIL indirect bilirubin, HbA1c glycated hemoglobin A1c, MMSE mini-mental state examination, MoCA Montreal cognitive assessment.

Table 3. Multifactorial logistic regression modeling to analyze risk factors for the development of cognitive impairment in T2DM/CI patients.

Indices	OR	95% CI	p-value
Age	1.84	0.927 - 2.962	0.068
Education	1.347	0.715 - 1.992	0.154
Hcy	1.27	0.844 - 2.510	0.288
CRP	1.076	0.738 - 1.175	0.325
DBIL	0.87	0.210 - 0.909	0.011
HbA1c	2.884	1.745 - 6.019	0.029
MMSE score	0.827	0.599 - 1.462	0.159
MoCA score	0.753	0.479 - 0.902	0.031

T2DM type 2 diabetes mellitus, CI cerebral infarction, Hcy homocysteine, CRP C-reactive protein, DBIL direct bilirubin, HbA1c glycated hemoglobin A1c, MMSE mini-mental state examination, MoCA Montreal cognitive assessment, OR odds radio, CI confidence interval, $p < 0.05$.

Table 4. Predictive effects of serum DBIL and HbA1c levels on the development of cognitive impairment in T2DM/CI patients.

Indices	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	p-value
HbA1c	6.93	56.41%	73.08%	57.26%	72.39%	< 0.001
DBIL	5.75	83.33%	48.08%	60.12%	81.86%	< 0.001
Combination	7.69	56.41%	84.62%	77.50%	75.23%	< 0.001

T2DM type 2 diabetes mellitus, CI cerebral infarction, DBIL direct bilirubin, HbA1c hemoglobin A1c, PPV positive predictive value, NPV negative predictive value, $p < 0.05$.

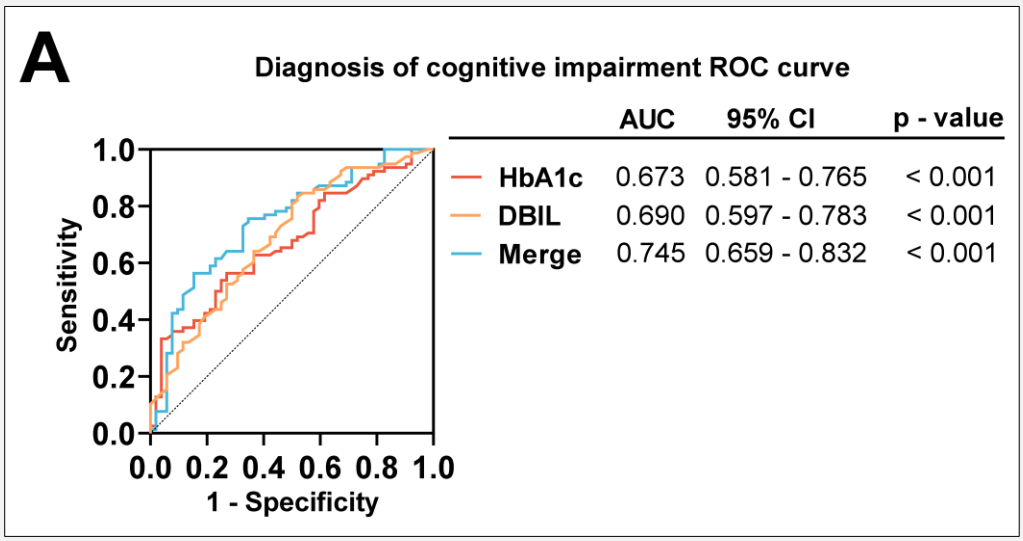

Figure 1. ROC curve analysis of the predictive value of DBIL and HbA1c for cognitive impairment in patients with T2DM/CI ($p < 0.05$).

There was also no correlation between MoCA score and DBIL.

Predictive effect of DBIL and HbA1c levels on cognitive impairment in T2DM/CI patients

The efficacy of the factors with significant differences, in Table 3 (DBIL and HbA1c), in predicting cognitive impairment in patients with T2DM/CI was further explored. ROC curves were plotted with the cognitive impairment group as a positive sample and the no cognitive impairment group as a negative sample. The AUC for DBIL was 0.690 (95% CI: 0.597 - 0.783, $p < 0.05$). When the cutoff value was taken as DBIL < 5.75 μmol/L, the sensitivity for predicting cognitive impairment was 83.33% and the specificity was 48.08%. The AUC for HbA1c was 0.673 (95% CI: 0.581 - 0.765, $p < 0.05$). When the cutoff value was taken as HbA1c > 6.93%, the sensitivity was 56.41% and the specificity was 73.08%. The AUC of combined DBIL and HbA1c for predicting cognitive impairment in T2DM/CI patients was higher than that of the single index, which was 0.745 (95% CI: 0.659 - 0.832, $p < 0.05$), with a sensitivity and specificity of 56.41% and 84.62%, respectively (Table 4 and Figure 1).

DISCUSSION

T2DM and CI are both strongly associated with intellectual disability, and people with T2DM combined with CI may be more likely to have cognitive impairment [18,19]. Therefore, early identification of risk factors for cerebrovascular disease can help reduce the risk of cognitive impairment in patients with T2DM/CI. In this retrospective study, decreased DBIL and increased HbA1c were associated with an increased risk of developing cognitive impairment in patients with T2DM/CI and were independent influences on cognitive impairment in patients with T2DM/CI. Combined DBIL and HbA1c showed a higher predictive efficacy for cognitive impairment in T2DM/CI patients.

MMSE is currently the easiest and most widely used cognitive function assessment scale, with good discriminatory properties between normal and dementia, but is not as sensitive as the MoCA for detecting mild cognitive impairment [20,21]. Therefore, in this study, MMSE and MoCA were jointly evaluated, and all T2DM/CI patients were categorized into a cognitive impairment group (78 patients) and a no cognitive impairment group (52 patients), according to the scoring results, in order to improve the sensitivity of the diagnosis of mild cognitive impairment. MoCA score had better sensitivity than the MMSE score in diagnosing cognitive impairment in T2DM/CI patients and could be used as an independent predictor. This is also confirmed by previous studies, in which the MMSE was not sensitive in identifying early changes associated with mild cognitive impairment [21]. The same idea holds true in diabetic patients, as Anu et al. specifically validated the validity of the MoCA score for detecting cognitive impairment in T2DM patients [22]. In this regard, we further analyzed the independent influences on cognitive impairment in T2DM/CI patients with the MoCA score. This study showed that HbA1c and DBIL levels were not correlated with MoCA score of T2DM/CI patients. Some studies reported that BIL was positively correlated with good prognosis. Perlstein et al. [23] have found that elevated BIL is associated with improved stroke outcomes. Decreased DBIL can predict early neurological deterioration in AIS patients [24]. In patients with mild stroke (NIHSS ≤ 5), elevated BIL after AIS indicates a good prognosis [25]. However, there are also studies supporting the relationship between BIL and poor prognosis. Increased DBIL before thrombolysis is associated with poor functional outcomes [26], and DBIL levels are significantly associated with mortality in acute ischemic stroke [27]. After adjusting for confounding factors, there is no independent relationship between TBIL and functional outcomes at discharge [28]. There was no significant correlation between DBIL and short-term clinical outcomes (NIHSS ≥ 10 at discharge) or in-hospital death [29]. This is basically consistent with the findings of this study. Combined with previous studies, we believe that there is a great independent relationship between the severity of stroke and DBIL level. The probability of severe stroke in patients with higher DBIL level is almost three times that of patients with lower DBIL level. However, no significant association was found between DBIL and initial stroke severity or outcome. In addition, patients in this study did not obtain continuous BIL measurements at admission. Whether the dynamics of DBIL is associated with cognitive impairment is unclear and needs further investigation.

Abnormal DBIL concentration in the brain can lead to activation of microglia and astrocytes, impaired myelination, and neuronal cell death [30]. Interestingly, cognitive impairment is found to be closely related to the abnormality of leukocytosis, and the abnormality of leukocytes is affected by the decrease of BIL concentration [31]. These findings suggest that DBIL may play a key role in cognitive impairment. We found that the serum DBIL level in the cognitive impairment group was significantly lower than that in the T2DM group and the no cognitive impairment group. Multivariate logistic regression analysis showed that serum DBIL was significantly associated with the occurrence of cognitive impairment after controlling all potential confounding factors. This suggests that DBIL may be a predictive biomarker for cognitive impairment in patients with T2DM/CI. In different subtypes of BIL, elevated DBIL may be more predictive of neurological dysfunction. It does not need to analyze all BIL subtypes, but can reduce the cost of analyzing DBIL in clinical testing, especially when repeated analysis is required during the disease process [32]. In addition, DBIL allows greater interaction between the drug and albumin, which may serve as a protective mechanism.

Low DBIL level and high HbA1c level were risk factors for cognitive impairment in T2DM/CI patients. Further analysis of the plotted ROC curves showed that the AUCs of DBIL and HbA1c for diagnosing cognitive impairment in T2DM/CI patients were 0.690 and 0.673, respectively, and the optimal diagnostic cutoffs of 5.75 μmol/L and 6.93% corresponded to diagnostic sensitivities of 83.33% and 56.41%, respectively, and specificities of 48.08% and 73.08%, respectively. The negative predictive values of DBIL and HbA1c were higher, indicating that the ability of DBIL and HbA1c to exclude negative results was higher than the diagnostic value, and the possibility of "false negative" was smaller. The combination of DBIL and HbA1c was even more predictive and had strong diagnostic and exclusion values. These results indicate that DBIL and HbA1c are used as auxiliary diagnostic indicators for cognitive impairment in patients with T2DM/CI. Continuous monitoring of DBIL and HbA1c as negative screening may have higher clinical application value. The efficacy of screening for the occurrence of cognitive impairment in patients with T2DM/CI was improved by combining high-risk factors for the occurrence of cognitive impairment in patients with T2DM/CI, which resulted in a higher rate of positive detections and a reduction in misdiagnoses. This provides a new possibility for screening for the occurrence of cognitive impairment in T2DM/CI patients. However, for practical application in clinical settings, it is still necessary to further expand the sample size to increase the percentage of positive results, to further analyze the risk factors for the development of cognitive impairment, and to provide a more comprehensive and accurate screening method.

This study's constraint lies in its retrospective nature and limited sample size, necessitating larger samples for future research to verify DBIL and HbA1c's clinical values in diagnosing cognitive impairment in T2DM/CI patients. Prospective studies with longitudinal follow-up should be conducted to confirm the association between serum DBIL and HbA1c concentrations and immediate memory scores in T2DM/CI patients. Our study only analyzed the relationship between serum BIL levels at admission and the development of cognitive impairment. Since there are individual differences in baseline serum BIL, trends in serum BIL levels may better reflect the intensity of oxidative stress and disease progression. Future studies could further explore the correlation between cognitive impairment prognosis and serum BIL levels at different time points to find out whether changes in BIL are a better prognostic indicator for CI.

In summary, reduced DBIL and elevated HbA1c levels pose risks for cognitive impairment in T2DM/CI sufferers, showing a direct correlation with the intensity of cognitive impairment. Therefore, clinical attention should be paid to DBIL and HbA1c levels in T2DM/CI patients, and intensive hypoglycemic and hypolipidemic therapy should be actively adopted to minimize the risk of neurological disorders.

Availability of Data and Materials:

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethical Approval:

The present study was approved by the Ethics Committee of Putian 95th Hospital, and written informed consent was provided by all patients prior to the study start. All procedures were performed in accordance with the ethical standards of the Institutional Review Board and The Declaration of Helsinki and its later amendments or comparable ethical standards.

Declaration of Interest:

The authors have no conflicts of interest to declare.

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