

# Triglyceride Glucose Index is Related with the Risk of Mild Cognitive Impairment in Type 2 Diabetes

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**Background:** The triglyceride glucose (TyG) index reflects insulin resistance; the latter being associated with mild cognitive impairment (MCI).

**Objective:** To investigate the clinical value of the TyG index to identify MCI in patients living with type 2 diabetes (T2D) using a cross-sectional study.

**Methods:** This cross-sectional study was performed on 517 patients with T2D. The diagnosis of MCI was based on criteria established by the National Institute on Aging-Alzheimer's Association workgroup, and patients were divided into the MCI group and the normal cognitive function (NCF) group. The logistic regression analysis determines whether the TyG index is related to MCI. Subsequently, we constructed the receiver operating characteristic curve (ROC) and calculated the area under the curve (AUC). The nomogram model of the influence factor was established and verified.

**Results:** Compared to the type 2 diabetes-normal cognitive function (T2D-NCF) group, the MCI subjects were older and had higher TyG indexes, lower cognitive scores, and lower education levels ( $p < 0.01$ ). After adjusting for the confounders, the TyG index was associated with MCI (OR = 7.37, 95% CI = 4.72–11.50,  $p < 0.01$ ), and TyG-BMI was also associated with MCI (OR = 1.02, 95% CI = 1.01–1.02,  $p < 0.01$ ). The TyG index AUC was 0.79 (95% CI = 0.76–0.83). The consistency index of the nomogram was 0.83 [95% CI (0.79, 0.86)].

**Conclusion:** Our results indicate that the TyG index and TyG-BMI are associated with MCI in T2D patients, and the TyG index is an excellent indicator of the risk of MCI in T2D patients. The nomogram incorporating the TyG index is useful to predict MCI risk in patients with T2D.

**Keywords:** triglyceride glucose index, TyG, mild cognitive impairment, MCI, insulin resistance, IR, type 2 diabetes, T2D

## Introduction

The incidence rate of diabetes has increased significantly in almost every country over the past few decades and is likely to increase further, making its complications a major public health problem.<sup>1,2</sup> With the attention paid to the quality of life of diabetes patients, cognitive dysfunction in diabetes has attracted more attention. A recent retrospective meta-analysis from China showed that the estimated prevalence of mild cognitive impairment in T2D patients reached 45%.<sup>3</sup> Compared to non-diabetic patients, the T2D patients had an average 0.3–0.4SDs reduction in the cognitive ability of memory, processing speed, and executive function.<sup>4,5</sup> A prospective meta-study showed that the risk of dementia in patients with diabetes increased by 73%, the risk of Alzheimer's disease (AD) increased by 56%, and the risk of vascular dementia (VAD) increased by 12%.<sup>6</sup> Throughout the screening, the newly discovered T2D patients, impaired fasting glucose patients, and metabolic syndrome patients have decreased in the same cognitive domains as patients with T2D. Therefore, it is speculated that the process of cognitive dysfunction starts at the early stage of diabetes and progresses over time.<sup>7–9</sup> In addition, we also know that patients with diabetes have an increased risk of dementia and a transition from mild cognitive impairment (MCI) to dementia. Therefore, it is very important to identify high-risk people with cognitive decline at an early stage.<sup>2</sup>

Although the mechanism of cognitive dysfunction in diabetic people is not well understood, the mechanism of insulin resistance has been recognized by most scholars.<sup>10,11</sup> For nearly 40 years, the euglycemic-hyperinsulinemic clamp has always been the gold standard for measuring human insulin sensitivity.<sup>12</sup> However, the application of the euglycemic-hyperinsulinemic clamp is complicated, time-consuming, and laborious, with poor experience and high cost, so it is not suitable for the detection of insulin sensitivity in a large population. Therefore, low-cost and readily available alternative indicators of insulin sensitivity need to be developed. For the past few decades, insulin resistance has been measured mainly by the homeostasis model insulin resistance index (HOMA-IR).<sup>13</sup> Recently, some researchers have proposed to calculate the TyG index using the products of fasting triglycerides and blood glucose values. Compared with the euglycemic-hyperinsulinemic clamp, the TyG index has high sensitivity and specificity and can be used to identify subjects with reduced insulin sensitivity.<sup>14</sup> A study showed that the TyG index was better at predicting insulin resistance than the HOMA-IR index.<sup>15</sup> In addition, the TyG index was reported to be sensitive for identifying metabolic syndrome,<sup>16</sup> cardiovascular diseases,<sup>17</sup> and dementia.<sup>18</sup> Metabolic syndrome and cardiovascular disease are risk factors for MCI,<sup>19,20</sup> and dementia is the progressive outcome of MCI.<sup>21</sup>

In addition, in a cohort study based on healthy people, when the dementia risk was evaluated by the quartile of the TyG index, the dementia risk of the fourth quartile participants increased by 14% compared with the first quartile participants, and the dementia risk increased with the increase of the quartile of TyG.<sup>18</sup> A recent study on cognitive function in people aged 60 to 90 suggested that the TyG index is independently associated with MCI in older people.<sup>22</sup> Another recent cross-sectional study of the elderly aged 60 years and older indicated that the TyG index is an independent risk factor for cognitive impairment and severe cerebral small vessel disease burden in elderly patients with T2D.<sup>23</sup> As we mentioned earlier, cognitive impairment appears to develop earlier in T2D patients. Therefore, this study provides a possibility for the identification of MCI in patients aged 40 years and older with T2D.

To standardize adipose tissue composition, TyG-BMI was first proposed based on the TyG index by Leay-Kiaw in 2016. It showed that the TyG-BMI was a clinically useful surrogate marker for the identification of IR.<sup>24</sup> In a Chinese cohort study, when ROC curve analysis was performed to compare the predictive value of TyG-BMI for new-onset diabetes, the AUC of TyG-BMI was significantly higher than that of BMI or TyG alone (both  $P < 0.001$ ).<sup>25</sup> Therefore, we investigated the association between the TyG index and TyG-BMI with MCI in T2D patients.

## Materials and Methods

### Subjects

T2D patients hospitalized in the Department of Endocrinology, the First Affiliated Hospital of Harbin Medical University from May 2020 to September 2021 were randomly selected and included according to the following criteria. Inclusion criteria: 1) T2D was diagnosed using the American Diabetes Association's criteria.<sup>26</sup> 2) They were hospitalized for poor blood glucose control. 3) They were 40 years of age and older.<sup>18</sup> 4) They had the ability of informed consent. Exclusion criteria: 1) Acute diabetes complications in the past 3 months. 2) Acute inflammation, autoimmune disease, heart, respiratory, liver, or kidney failure. 3) History of central nervous system problems that may lead to dementia or dementia. 4) History of hearing / visual impairment or psychological impairment. 5) Any incomplete data sets.

### Data Collection

After enrollment, each participant received a standardized assessment of demographic characteristics, physical examination, laboratory tests, lifestyle risk factors, education level, duration of diabetes, diabetes complications, MCI screening, and self-reported information about diabetes treatment, other medical histories, and medication use. When the patient was wearing light clothing and no shoes, height and weight were measured by nurses. Body mass index (BMI) was calculated by dividing body weight (kg) by height (m)squared ( $\text{kg} / \text{m}^2$ ). Five minutes after the break, the systolic and diastolic blood pressure (mmHg) of the non-dominant arm of the seated subject was measured three times using the standard mercury blood pressure gauge, and the average value was recorded. Fasting ( $\geq 8$  h) venous blood parameters included glycosylated hemoglobin A1c (HbA1c), fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-c), low-density lipoprotein-cholesterol (LDL-c), blood urea nitrogen (BUN), creatinine (Cr), and uric acid (UA). All tests were measured at

the endocrinology laboratory of the First Affiliated Hospital of Harbin Medical University. The TyG index was an indicator calculated using triglyceride and blood glucose,  $\text{Ln}(\text{fasting blood glucose [mg/dL]} \times \text{fasting triglyceride [mg/dL]}/2)$ .<sup>14</sup> The TyG-BMI was calculated by the TyG index  $\times$  BMI.<sup>24</sup>

## Assessment of Diabetic Complications

Diabetic nephropathy (DN) was defined as  $\text{eGFR} < 60 \text{ mL/min/1.73m}^2$  or continuously increased urine albumin to creatine ratio (UACR) ( $>30 \text{ mg/g Cr}$ ) for more than three months in T2D patients without other kidney diseases. The ophthalmologist of Harbin Medical University confirmed the diagnosis of diabetes retinopathy (DR) according to the subjects' fundus fluorescein angiography (FFA). The diabetic peripheral neuropathy (DPN) diagnosis should be confirmed in patients with medical records clearly describing the occurrence and diagnosis of DPN (typical symptoms, signs, or both), or the nerve conduction velocity measured by the First Affiliated Hospital of Harbin Medical University electromyography room indicated that the conduction velocity was slowed. Fatty liver was diagnosed based on abdominal ultrasonography.<sup>27</sup>

## Assessment of Cognitive Function

The diagnosis of MCI is based on criteria established by the National Institute on Aging-Alzheimer's Association workgroups.<sup>28</sup> Criteria include 1) attention to cognitive change from self/informant/clinician report, 2) objective evidence of disorders in one or more cognitive regions. It was evaluated in this study using the Montreal Cognitive Assessment (MoCA), 3) maintenance of independence in daily functional ability, and 4) the absence of dementia (according to the DSM-V standard). MoCA is a highly sensitive cognitive screening tool that detects MCI quickly and discriminates MCI patients from normal individuals. In this study, MCI was defined as scores greater than or equal to 19 and less than 26, scores greater than or equal to 26 for cognitive normal, and one point was added to one participant if the participant had formal education of fewer than 12 years.<sup>29</sup>

## Analytical Procedures

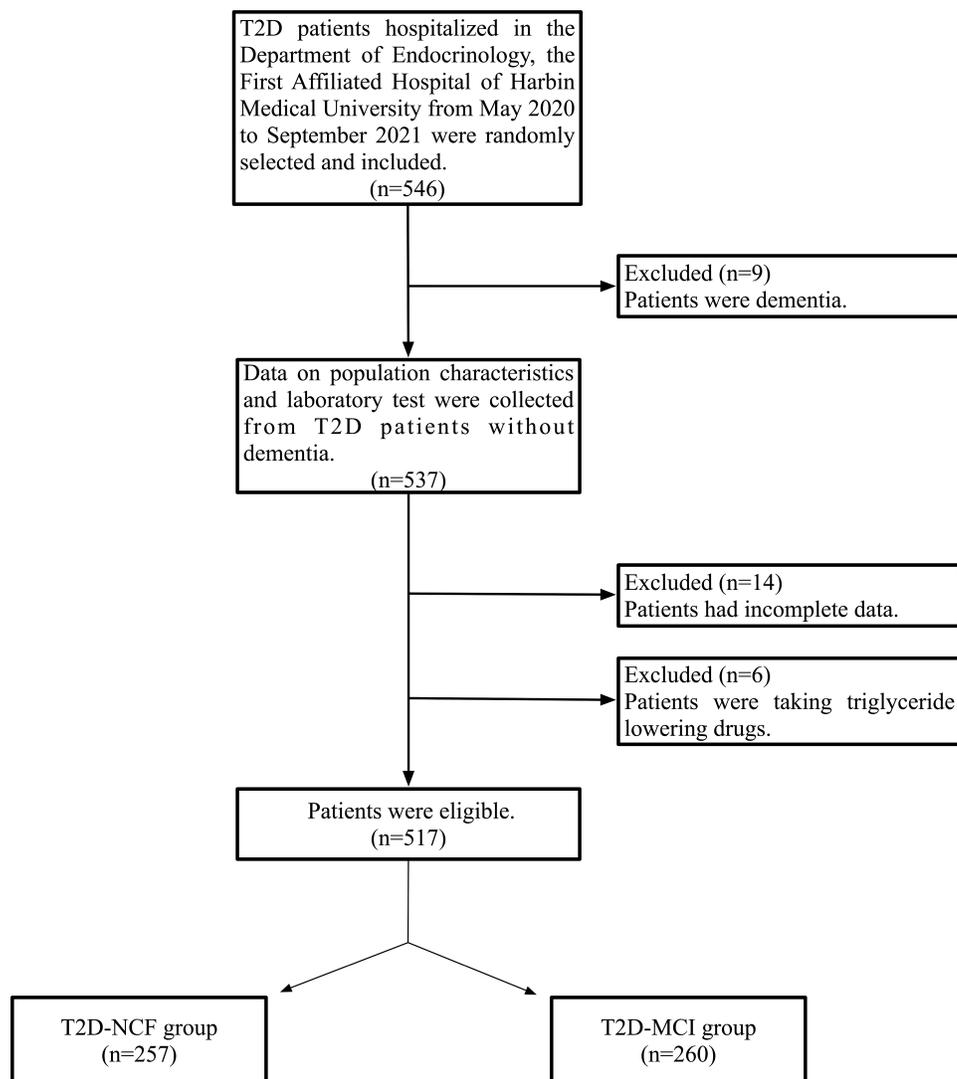
First, the clinical and biochemical characteristics of the subjects were analyzed by descriptive statistics. Continuous variables were described by means  $\pm$  standard deviations or medians (interquartile range, IQR), and categorical variables were expressed as percentages. The comparison of different types of variables between the T2D-NCF group and the T2D-MCI group was as follows: The two-independent samples *t*-test was used for normally distributed variables. The Mann-Whitney U-test was used for non-normally distributed variables, and the Chi-square test was used for categorical variables.

Second, univariate and multivariate binary logistic analyses were performed on the TyG index and cognitive state to estimate an independent association between the TyG index and MCI. The independent association between TyG-BMI and MCI was explored in the same way. The final model was determined according to the Hosmer-Lemeshow goodness of fit. The confounders that were included for adjustment in the multivariate binary logistic regression model included age, gender, smoking history, drinking history, duration of diabetes, education level, TC, HbA1c, DN, fatty liver, insulin use, and statins use. Third, a receiver operating characteristic (ROC) curve was prepared and the area under the curve (AUC) was calculated. In the end, statistically significant variables in the multivariate binary regression analysis were selected to develop a nomogram prediction model for MCI. The consistency index (C index) and the calibration curve were used to evaluate the performance of the prediction model. Statistical analysis was performed using the statistical software SPSS (version 26.0) and R (version 4.1.3).  $P < 0.05$  was statistically significant.

## Results

### Clinical and Laboratory Characteristics of Groups

After a series of exclusions and screenings, 517 T2D patients were eligible and their medical documents were recorded (Figure 1). Demographic characteristics and laboratory data were described for the T2D-NCF group, T2D-MCI group, and overall subjects (Table 1). The median age of T2D subjects was 58 years (54.40% males and 45.60% females). The



**Figure 1** Flow chart showing the patients included in the study.

**Abbreviations:** T2D, type 2 diabetes; NCF, normal cognitive function; MCI, mild cognitive impairment.

T2D-NCF group was 257 cases, and the T2D-MCI group was 260 cases. The T2D-MCI group was significantly higher in age, TG, FBG, HbA1c, TC, LDL-c, TyG index, and TyG-BMI than the T2D-NCF group ( $p < 0.01$ ). The prevalence of diabetic nephropathy, fatty liver, and statins use in the T2D-MCI group were significantly higher than that of the T2D-NCF group ( $p < 0.05$ ), while education level, MMSE scores, and MoCA scores in the T2D-NCF group were significantly higher compared with the T2D-MCI group ( $p < 0.01$ ). There was no significant difference between the two groups in terms of gender, duration of diabetes, SBP, DBP, smoking history, drinking history, BMI, HDL-c, BUN, UA, Cr, diabetic retinopathy, diabetic peripheral neuropathy, carotid atherosclerosis, lower limb arteriosclerosis, insulin use, and DPP-4 inhibitor use ( $p > 0.05$ ).

## Association Between the TyG Index and MCI

Univariate and multivariate binary logistic analysis of the TyG index and cognitive status (Table 2). The result of the univariate logistic analysis showed that the higher the TyG index, the higher the risk of MCI (OR = 6.11, 95% CI = 4.23–8.83  $p < 0.01$ ). After adjustment for age and gender (model 2), (OR = 7.70, 95% CI = 5.18–11.45,  $p < 0.01$ ), the TyG index continued to be associated with increased MCI risk (OR = 7.37, 95% CI = 4.72–11.50,  $p < 0.01$ ), after further adjustment for

**Table 1** Clinical and Biochemical Characteristics of T2D-NCF Group and T2D-MCI Group

Variables	Total (n=517)	T2D-NCF group (n=257)	T2D-MCI group (n=260)	P-Value
Age (y)	58(52,64)	56(50,62.5)	59(53,65)	<0.01
Male (%)	281(54.4%)	131(51.0%)	150(57.7%)	0.125
SBP (mmHg)	139(126.5,153)	139(125,153)	140.5(127,154)	0.392
DBP (mmHg)	81(74,90)	81(73,89.5)	82 (75,90)	0.385
Duration of diabetes (y)	8(3,15)	8(3,14)	8(3,15.75)	0.558
Smoking (%)	130(25.1%)	62(24.1%)	68(26.2%)	0.595
Drinking (%)	136(26.3%)	69(26.8%)	67(25.8%)	0.781
BMI (kg/m <sup>2</sup> )	25.30(23.34,27.16)	25.16(23.05,27.07)	25.37(23.51,27.23)	0.242
Education level (y)	12(9,14.5)	12(9,15)	9(9,12)	<0.01
TG (mmol/L)	1.72(1.24,2.46)	1.37(1.02,1.87)	2.17(1.52,3.06)	<0.01
FBG (mmol/L)	8.19(6.52,10.20)	7.15(5.83,8.96)	9.25(7.46,11.41)	<0.01
HbA1c (%)	8.4(7.0,9.9)	7.8(6.7,9.4)	8.8(7.3,10.4)	<0.01
TyG Index	9.38(8.90,9.84)	9.05(8.62,9.39)	9.69(9.35,10.10)	<0.01
TyG-BMI	237.77(212.40,259.98)	227.58 (204.24,248.84)	246.29 (221.96,269.82)	<0.01
TC (mmol/L)	4.69(4.05,5.62)	4.51(3.84,5.31)	4.85(4.22,5.88)	<0.01
HDL-c (mmol/L)	1.12(0.96,1.30)	1.14(0.97,1.34)	1.11(0.95,1.26)	0.124
LDL-c (mmol/L)	2.80(2.39,3.37)	2.71(2.27,3.26)	2.92(2.47,3.51)	0.004
BUN (mmol/L)	5.77(4.84,7.05)	5.65(4.81,6.93)	5.88(4.97,7.08)	0.238
Cr (umol/L)	60.70(50.65,69.5)	60.80(49.2,69.05)	60.55(51.2,70.05)	0.403
UA (umol/L)	325.50(270.10,390.15)	321.10 (266.35,379.15)	329.65 (274.55,400.18)	0.175
MMSE score	27(26,28)	28(27,29)	26(25,26)	<0.01
MoCA score	25(24,27)	27(26,28)	24(22,25)	<0.01
DN (%)	49(9.5%)	16(6.2%)	33(12.7%)	0.012
DR (%)	135(26.1%)	61(23.7%)	74(28.5%)	0.221
DPN (%)	203(39.3%)	104(40.5%)	99(38.1%)	0.578
Lower limb atherosclerosis (%)	397(76.8%)	190(73.9%)	207(79.6%)	0.126
Carotid atherosclerosis (%)	374(72.3%)	181(70.4%)	193(74.2%)	0.334
Fatty liver (%)	336(65.0%)	150(58.4%)	186(71.5%)	<0.01
Insulin use (%)	315(60.9%)	155(60.3%)	160(61.5%)	0.775
Statins use (%)	152(29.4%)	58(22.6%)	94(36.2%)	<0.01
DPP-4 inhibitor use (%)	115(22.2%)	63(24.5%)	52(20.0%)	0.217

**Notes:** Continuous variables conforming to the normal distribution were presented as mean  $\pm$  standard deviation and compared by the two-independent samples t-test. Continuous variables according to the non-normal distribution were expressed as medians (25th–75th percentiles) and compared by Mann–Whitney U-test. Categorical variables were expressed as percentages and compared by Chi-square test. The significance level was set at  $p < 0.05$ .

**Abbreviations:** NCF, normal cognitive function; MCI, mild cognitive impairment; T2D, type 2 diabetes; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; TG, triglyceride; FBG, fasting plasma glucose; TyG, triglyceride glycemc; TyG-BMI, triglyceride glycemc-body mass index; HbA1c, hemoglobinA1c; TC, total cholesterol; HDL-c, high-density lipoprotein-cholesterol; LDL-c, low-density lipoprotein-cholesterol; VLDL-c, very low-density lipoprotein-cholesterol; UA, uric acid; Cr, creatinine; BUN, blood urea nitrogen; MoCA, Montreal Cognitive Assessment; MMSE, Mini-mental State Examination; DN, diabetic nephropathy; DR, diabetic retinopathy; DPN, diabetic peripheral neuropathy; DPP-4, dipeptidyl peptidase-4.

smoking, drinking history, duration of diabetes, education level, total cholesterol, HbA1c, diabetic nephropathy, fatty liver, insulin use, and statins use (model 3). No interaction between the TyG index and education level on MCI ( $p = 0.62$ ).

## Association Between the TyG-BMI and MCI

In the same way, univariate and multivariate logistic analysis of the TyG-BMI and cognitive status (Table 3). Higher levels of TyG-BMI were significantly associated with an increased risk of MCI (OR = 1.02, 95% CI = 1.01–1.02

**Table 2** Associations Between TyG Index and MCI

	OR	95%CI	P
<b>Model 1</b>			
TyG index	6.11	4.23-8.83	<0.01
<b>Model 2</b>			
TyG index	7.70	5.18-11.45	<0.01
<b>Model 3</b>			
TyG index	7.37	4.72-11.50	<0.01
Age	1.07	1.04-1.10	<0.01
Education level	0.87	0.81-0.93	<0.01

**Notes:** Model 1: Crude model; Model 2: Adjust for age, and gender; Model 3: Model 2+ Smoking, drinking history, duration of diabetes, education level, total cholesterol, HbA1c, diabetic nephropathy, fatty liver, insulin use, statins use.

**Table 3** Associations Between TyG-BMI and MCI

	OR	95%CI	P
<b>Model 1</b>			
TyG-BMI	1.02	1.01-1.02	<0.01
<b>Model 2</b>			
TyG-BMI	1.02	1.01-1.03	<0.01
<b>Model 3</b>			
TyG-BMI	1.02	1.01-1.02	<0.01
Age	1.05	1.02-1.08	<0.01
Education level	0.89	0.84-0.95	<0.01

**Notes:** Model 1: Crude model; Model 2: Adjust for age, and gender; Model 3: Model 2+ Smoking, drinking history, duration of diabetes, education level, total cholesterol, HbA1c, diabetic nephropathy, fatty liver, insulin use, statins use.

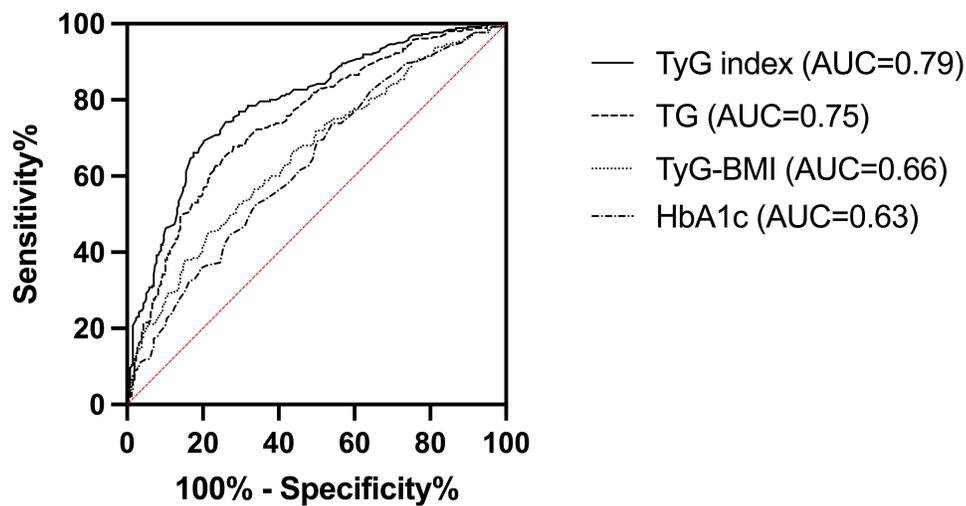
$p < 0.001$ ) of model 1, (OR = 1.02, 95% CI = 1.01–1.03,  $p < 0.001$ ) of model 2, and (OR = 1.02, 95% CI = 1.01–1.02,  $p < 0.001$ ) of model 3.

## Parameters for Diagnosing MCI

The AUC of the TyG index was 0.79 (95% CI = 0.76–0.83), 0.75 (95% CI = 0.70–0.79) of TG, 0.66 (95% CI = 0.61–0.71) of TyG-BMI, and 0.63 (95% CI = 0.59–0.68) of HbA1c (Figure 2). The optimal cut-off point for the MCI diagnosis of the TyG index was 9.45 [sensitivity: 0.69 (95% CI = 0.64–0.75), specificity: 0.80 (95% CI = 0.75–0.85)]. The positive predictive value for TyG was 0.78 and the negative predictive value for TyG was 0.72.

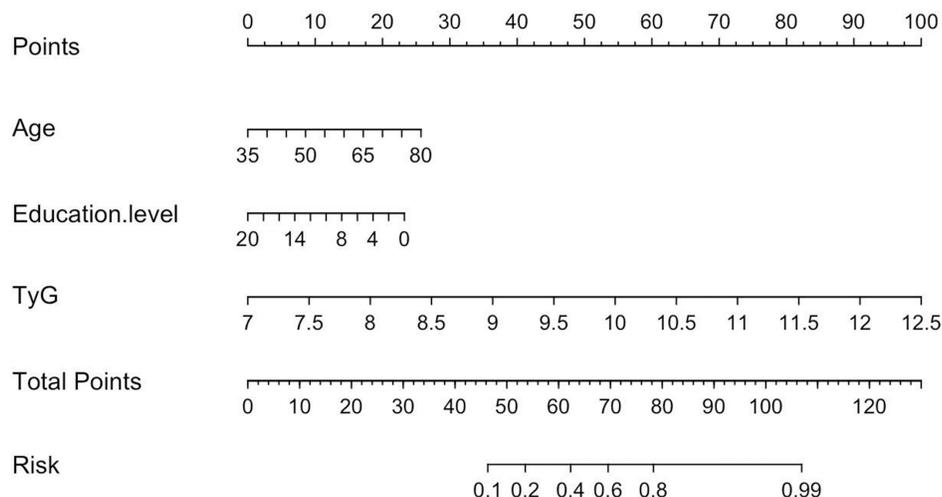
## Establishment of a Nomogram and Validation

As seen in the nomogram (Figure 3), selected predictors were assigned a score according to the value in the nomogram based on the established prediction model. Then a vertical line perpendicular to the point axis was drawn from this point. The intersection points on the point axis represented the score under the determined value of the predictor, the sum of these points, plotted on the “total points” line, corresponded to the prediction of MCI occurrence rates in patients with T2D. The calibration curve showed good homogeneity between the prediction by nomogram and the actual observation, as shown in Figure 4. The C-index of the nomogram was 0.83 [95% CI (0.79, 0.86)].



**Figure 2** The ROC curve of the TyG index, TyG-BMI, TG, and HbA1c for diagnosing.

**Abbreviations:** TyG, triglyceride glyemic; TyG-BMI, triglyceride glyemic-body mass index; TG, triglyceride; HbA1c, hemoglobinA1c.



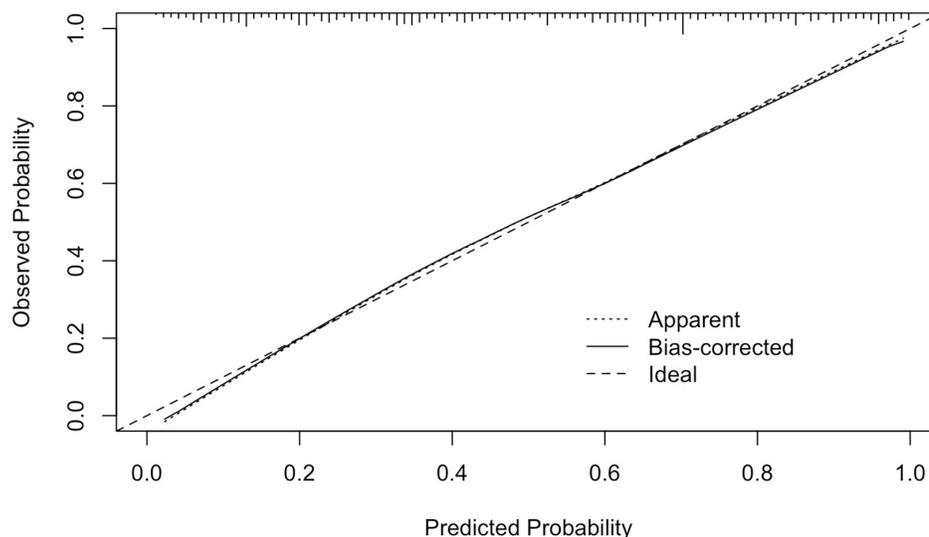
**Figure 3** Nomogram showed the risk of MCI.

**Abbreviation:** TyG, triglyceride glyemic.

## Discussion

In this study, the TyG index was used as a surrogate indicator of insulin resistance. It was proved that the increased TyG index was associated with an elevated risk of MCI ( $p < 0.01$ ). Similarly, high TyG-BMI was also related independently to an increased risk of MCI ( $p < 0.01$ ), but the diagnostic efficacy was lower than the TyG index, which may be why the impact of BMI on cognitive function remains controversial.<sup>30–32</sup> On one hand, increased BMI may contribute to cognitive impairment risk through changes in brain structure, changes in white matter, disturbances in the blood-brain barrier, and age-related regulatory changes in protein, carbohydrate, and lipid metabolism.<sup>33</sup> On the other hand, higher BMI may protect by increasing insulin-like growth factor I (IGF-I) levels<sup>34</sup> as well as leptin levels<sup>35</sup> and estrogen secretion,<sup>36</sup> all of which are associated with better cognitive performance.

The relationship between insulin resistance and cognitive function may be as follows. Insulin and insulin receptors stimulate the release of various enzymes involved in glucose metabolism in neural tissues. The essential brain function of insulin is the regulation of learning and memory.<sup>37</sup> Insulin can not only regulate energy metabolism but also provide nutritional support for nerve cells.<sup>38</sup> IR is a characteristic metabolic disorder coexisting with hyperinsulinemia that



**Figure 4** The calibration curve of the nomogram model.

reduces the sensitivity of insulin to the target organ. Long-term hyperinsulinemia impairs blood-brain barrier function and insulin activity.<sup>39</sup> Long-term exposure of neurons to high levels of insulin leads to neuronal degeneration and irreversible memory damage.<sup>40,41</sup> In addition, diabetes patients can promote cognitive impairment by transmitting insulin resistance of peripheral tissues to the central nervous system through the “hepatic brain axis”.<sup>42</sup>

IR may affect cognition by significantly altering synaptic plasticity in the hippocampus, changes in amyloid precursor protein (APP) metabolism, increased levels of tau protein concentration, and changes in brain inflammation.<sup>43</sup> The details are as follows: 1) Increase in insulin levels regulates glutamatergic neurotransmission at synapses and in the postsynaptic membrane the long-term depression (LTD) process was decreased by reducing the amount of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors.<sup>44,45</sup> 2) Insulin directly enhances the cleavage of App and converts it into soluble Appa (SAPPa). In addition, insulin regulates A $\beta$  levels by promoting A $\beta$  transport to the neuronal gap, preventing A $\beta$  degradation and accelerating APP/A $\beta$  aggregation.<sup>46</sup> 3) IR in the central nervous system increases activity in glycogen synthase kinase-3 beta (GSK-3 $\beta$ ) and promotes tau protein phosphorylation.<sup>47</sup> 4) IR affects the microglia-mediated brain inflammatory response by decreasing insulin sensitivity and activating brain proinflammatory cytokines.<sup>48</sup>

However, no association between insulin resistance and cognitive function has been observed in some studies. A study using HOMA2-IR to calculate the insulin resistance index showed that HOMA2-IR was not associated with cognitive performance in patients with T2D.<sup>49,50</sup> Some scholars believe brain IR may not be consistent with HOMA2-IR, which can only reflect the peripheral effects of insulin resistance such as liver and skeletal muscle.<sup>51</sup> Therefore, the relationship between the TyG index and brain IR remains to be further explored.

Studies show that MCI is an age-related disease that is considered an intermediate state between age-related cognitive changes and dementia.<sup>52</sup> Many protective factors have been identified regarding age-related or pathological cognitive decline, and education level is one of the most important factors. Studies have found that higher education levels are positively associated with cognitive performance in older adults.<sup>53,54</sup> Individuals with higher levels of education are thought to have a stronger cognitive reserve (CR) and to be better able to cope with brain pathology without exhibiting significant cognitive impairment.<sup>55–57</sup> Education level may compensate for the effects of reduced cerebral glucose metabolism on cognitive impairment.<sup>58</sup> However, increased insulin resistance may be associated with reduced cerebral glucose metabolic rate (CMRglu), with subtle cognitive deficits in the earliest stages of the disease, even before MCI.<sup>59</sup> Logistic regression analysis of this study confirmed that higher education level was better for cognitive function ( $p < 0.01$ ), but there was no interaction between the TyG index and education level on cognitive function.

In our study, we found that a raised TyG index, an alternative marker of insulin resistance, was associated with an increased risk of MCI in patients with T2D, which provides evidence for the role of insulin resistance in cognitive impairment. The TyG index is a simple and easy index for the identification of IR. Moreover, unlike the previously described complex measures, insulin is not included in the TyG index, and this simplicity has practical consequences such as better accessibility and lower cost, which may be important in large population studies. Therefore, the TyG index may be useful for the detection of MCI risk and as a criterion for establishing IR treatment focused on delaying MCI onset or its progression in T2D patients.

However, this study also has limitations that need attention. 1) This was only a cross-sectional study, and there was a correlation between the TyG index and the MCI. Causal inference is impossible. 2) In this study, T2D patients hospitalized due to poor blood glucose control were randomly selected, resulting in a selection bias. 3) In future studies, we hope to explore the association between the TyG index and the severity and progression of cognitive impairment in patients with T2D through longitudinal studies and whether there is an important difference between the TyG index in various cognitive fields.

## Conclusion

In this cross-sectional study, the following findings were found: 1) In the T2D patients, the TyG index and TyG-BMI were related independently to the risk of MCI. 2) Among the relevant indicators in this study, the TyG index has the highest efficiency in diagnosing MCI, which is useful for MCI screening of T2D patients. 3) The nomogram provides an effective tool for clinical quantitative assessment of MCI risks and benefits and helps clinicians make scientific clinical decisions regarding the prevention of MCI in patients with T2D.

## Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available due to [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

## Ethics Approval and Consent to Participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the First Affiliated Hospital of Harbin Medical University.

## Consent for Publication

Informed consent was obtained from all individual participants included in the study.

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## Disclosure

The authors report no conflicts of interest in this work.

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