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ORIGINAL RESEARCH

A Nomogram Including Total Cerebral Small Vessel Disease Burden Score for Predicting Mild Vascular Cognitive Impairment in Patients with Type 2 Diabetes Mellitus

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Background: Total cerebral small vessel disease (CSVD) burden score is an important predictor of vascular cognitive impairment (VCI). However, few predictive models of VCI in type 2 diabetes mellitus (T2DM) patients have included the total CSVD burden score, especially in the early stage of VCI.

Objective: To develop and validate a nomogram that includes the total CSVD burden score to predict mild VCI in patients with T2DM.

Methods: A total of 322 eligible participants with T2DM who were divided into mild and normal cognitive groups were enrolled in this retrospective study. Demographic data, laboratory data and imaging markers of CSVD were collected. The total CSVD burden score was calculated by combining the different CSVD markers. Step-backward multivariable logistic regression analysis with the Akaike information criterion was applied to select significant predictors and develop a best-fit predictive nomogram. The performance of the nomogram was assessed in terms of discriminative ability, calibrated ability, and clinical usefulness.

Results: The nomogram model consisted of five variables: age, education, hemoglobin A1c level, serum homocysteine level, and total CSVD burden score. A nomogram with these variables showed good discriminative ability (area under the receiver operating characteristic curve was 0.801 in internal verification). In addition, the Hosmer-Lemeshow test (χ^2 =9.226, P=0.417) and bootstrap-corrected calibration plot indicated that the nomogram had good calibration. The Brier score of the predictive model was 0.178. Decision curve analysis demonstrated that when the threshold probability ranged between 16% and 98%, the use of the nomogram to predict mild VCI in patients with T2DM provide a greater net benefit.

Conclusions: The nomogram, composed of age, education, stroke, HbA1c level, Hcy level, and total CSVD burden score, had good predictive accuracy and may provide clinicians with a practical tool for predicting the risk of mild VCI in T2DM patients.

Keywords: vascular cognitive impairment, mild cognitive impairment, cerebral small vessel disease, type 2 diabetes mellitus, nomogram

Introduction

Vascular cognitive impairment (VCI) has emerged as a leading public health challenge due to an increase in population aging and vascular risk factors.[1] VCI is the second most common cause of dementia after Alzheimer's disease (AD) and accounts for at least 20–40% of dementia.[1,2] VCI refers to cognitive impairment due to vascular risk factors or diseases, including mild VCI and vascular dementia (VaD).[1,3,4] Mild VCI is generally recognized as an early and reversible stage of VaD.[1,3,5]

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Accumulating evidence indicates that T2DM is associated with an increased risk of VCI.[6–9] Individuals with T2DM exhibit a heightened risk of developing dementia, ranging from 1.5 to 2.8 times more likely than those without T2DM.[10,11] In the T2DM population, approximately 20% of individuals older than 60 years may have dementia.[8] What's more, T2DM increases the risk of incident mild cognitive impairment (MCI) and accelerates the conversion from MCI to dementia.[8,12,13] In addition, VCI, especially VaD, may lead to poor self-management of T2DM, which in turn leads to more cerebrovascular events and poorer cognitive function.[8] Therefore, the early diagnosis of mild VCI in patients with T2DM plays a crucial role in halting or delaying the progression of VCI.

Although the underlying neuropathological mechanisms of T2DM-related cognitive impairment is complicated, multifactorial and incompletely understood, evidence from preclinical and clinical studies support that cerebral microvascular dysfunction may play an important role.[14–16] Cerebral microvascular dysfunction can be reflected noninvasively by assessing the magnetic resonance imaging (MRI) features of cerebral small vessel disease (CSVD).[15–17] Visible imaging markers of CSVD mainly include white matter hyperintensity, lacune, enlarged perivascular space and cerebral microbleed.[18,19] Previous studies mostly focus on the association between a specific imaging marker of CSVD and cognitive impairment in the T2DM population.[20–23] However, CSVD is a dynamic whole-brain disorder and different imaging markers of CSVD can co-exist or be transformed into each other.[24,25] The total CSVD burden score, including above four main imaging markers, has good construct validity and may better represent the severity of CSVD or cerebral microvascular dysfunction.[19,26]

Therefore, the total CSVD burden score should be an important predictor of VCI in T2DM patients. However, few predictive nomogram models of VCI in patients with T2DM have included the total CSVD burden score, which reflects underlying cerebral microvascular dysfunction, especially in the early stage of VCI. Therefore, this study aimed to develop an accurate and individualized predictive nomogram, including the total CSVD burden score for mild VCI in patients with T2DM, by comprehensively evaluating the contributions of demographic data, laboratory data, and imaging markers of CSVD.

Materials and Methods

Study Design and Participants

This retrospective observational prediction model development and validation study included participants from the Department of Neurology of Hebei General Hospital between October 2016 and January 2022. Participants were included in this study if they met the following inclusion criteria: (a) aged ≥ 50 years; (b) diagnosed with T2DM based on the criteria of the World Health Organization;[27] (c) completed whole MRI sequences to assess the total CSVD burden score; and (d) completed assessment of cognitive function. Participants were excluded if they had dementia or conditions that may affect the results of the cognitive function assessment, such as acute cerebrovascular events, epilepsy, anxiety, depression, brain injuries, schizophrenia, hypothyroidism, malignancy, or metabolic encephalopathy. This study followed the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Hebei General Hospital (No.2023176).

Assessment of Mild Vascular Cognitive Impairment

All participants underwent neuropsychological testing, including the standardized translated version of the Montreal Cognitive Assessment (MoCA) Beijing version (www.mocatest.org), basic and instrumental activities of daily living (ADL), Hamilton Anxiety Scale (HAMA) with 14 items, and Hamilton Depression Scale (HAMD) with 24 items. Objective evidence of cognitive impairment was based on the results of neuropsychological testing as follows: MoCA (≤13 for illiterate, ≤19 for 1–6 years of education, ≤24 for 7 or more years of education), HAMA <6, and HAMD <8.[28] The diagnosis of mild VCI was based on the previously established criteria,[3,29] including (a) objective evidence of cognitive impairment, (b) clinical features consistent with a vascular etiology, (c) evidence of cerebrovascular disease that was considered sufficient to account for cognitive impairment, and (d) no dementia (basic ADL was normal and instrumental ADL<10).

Predictors Collection

The following candidate predictors for further analysis were collected: demographic data, including age, gender, years of education, height, and weight; clinical data, including systolic blood pressure, diastolic blood pressure, current smoking or drinking, duration of T2DM, anti-diabetic drugs, history of stroke, hypertension, and coronary heart disease; and laboratory data, including fasting plasma glucose, hemoglobin A1c (HbA1c), lipid profile, uric acid, fibrinogen, serum homocysteine (Hcy), and imaging markers of CSVD. Body mass index (BMI) was calculated as the weight (kg) divided by the square of height (m^2). The total CSVD burden score (range, 0–4) was calculated using four different imaging markers of CSVD, which were described in detail in our previous researches.[30,31]

Statistical Analysis

Statistical analyses were performed using the R statistical software (version 4.2.3; R Foundation for Statistical Computing, Vienna, Austria). The variables were described as mean (standard deviation), median (interquartile range), and case (percentage), as appropriate. The Mann–Whitney *U*-test, *t*-test, or chi-square test was used to analyze the differences in characteristics between the normal cognitive group and the mild VCI group. $P < 0.05$ was considered to be statistically significant. To develop the nomogram of mild VCI in patients with T2DM, multivariable logistic regression analysis with Akaike information criterion was applied to select the significant predictors using a backward selection method that included variables with a $P < 0.1$ in the univariable analysis. Additionally, a dynamic nomogram was built using the "DynNom" package, which is conveniently available to clinicians. Validation of the predictive model was carried out based on the following aspects: 1) discriminative ability was assessed by calculating the area under the receiver operating characteristic curve (AUC); 2) calibrated ability was performed using the calibration plot and Hosmer-Lemeshow test; 3) overall performance was evaluated using the Brier score, which captures aspects of both calibration and discrimination; and 4) clinical usefulness was evaluated by decision curve analysis (DCA). To reduce overfitting bias, the bootstrapping method (resampling=2000) was used for internal validation.

Results

Participants Characteristics

A total of 322 eligible participants with T2DM were included in this study: 189 with mild VCI and 133 with normal cognitive function. The prevalence of mild VCI in T2DM patients was 58.7%. The characteristics of the study population between the two groups are presented in Table 1. Compared to the normal cognitive group, patients in the mild VCI

Table 1 Characteristics of the Study Participants with T2DM Between Normal Cognitive Group and Mild VCI Group

Variable	Total (n=322)	Normal Cognitive Group (n=133)	Mild VCI Group (n=189)	*P* value
Age, year	68 (62–74)	66 (60–72)	71 (64–75)	<0.001*
Gender, n(%)				0.965
Male	169 (52.5)	70 (52.6)	99 (52.4)	
Female	153 (47.5)	63 (47.4)	90 (47.6)	
Education, year	9 (9–12)	12 (9–15)	9 (6–12)	0.001*
BMI, kg/m^2	25.1 (23.2–27.4)	25.0 (23.4–27.2)	25.2 (23.0–27.9)	0.655
Smoking, n(%)	52 (16.1)	20 (15.0)	32 (16.9)	0.649
Alcohol use, n(%)	37 (11.5)	12 (9.0)	25 (13.2)	0.244
Hypertension, n(%)	232 (72.0)	93 (69.9)	139 (73.5)	0.476
SBP, mmHg	139 (130–153)	138 (129–153)	139 (130–157)	0.347
DBP, mmHg	81 (75–88)	80 (74–87)	83 (75–90)	0.175
Duration of T2DM, year	10 (5–16)	10 (4–16)	10 (5–16)	0.720
CHD, n(%)	82 (25.5)	30 (22.6)	52 (27.5)	0.315
Stroke, n(%)	121 (37.6)	42 (31.6)	79 (41.8)	0.062

(*Continued*)

Table 1 (Continued).

Variable	Total (n=322)	Normal Cognitive Group (n=133)	Mild VCI Group (n=189)	*P* value
Anti-diabetic drugs, n(%)				
Metformin	156 (48.4)	61 (45.9)	95 (50.3)	0.437
Insulin	78 (24.2)	34 (25.6)	44 (23.3)	0.638
Sulfonylureas	75 (23.3)	28 (21.1)	47 (24.9)	0.425
FPG, mmol/L	6.87 (5.73–8.73)	6.82 (5.86–8.25)	6.94 (5.65–9.07)	0.872
HbA1c, %	7.20 (6.50–8.10)	7.00 (6.45–7.90)	7.30 (6.60–8.40)	0.005*
TG, mmol/L	1.66 (0.98–2.03)	1.34 (1.03–2.13)	1.38 (0.96–2.00)	0.737
TC, mmol/L	4.35 (3.63–5.23)	4.33 (3.60–5.39)	4.37 (3.64–5.12)	0.560
HDL-C, mmol/L	1.06 (0.92–1.27)	1.05 (0.93–1.26)	1.06 (0.92–1.28)	0.913
LDL-C, mmol/L	2.78 (2.21–3.46)	2.79 (2.21–3.65)	2.76 (2.22–3.40)	0.625
VLDL-C, mmol/L	0.44 (0.29–0.63)	0.48 (0.31–0.64)	0.42 (0.27–0.63)	0.150
ApoA1, g/L	1.22 (1.08–1.36)	1.23 (1.09–1.35)	1.21 (1.08–1.36)	0.760
ApoB, g/L	0.76 (0.61–0.93)	0.81 (0.62–0.98)	0.74 (0.61–0.89)	0.071
UA, μmol/L	291 (239–345)	296 (256–360)	287 (234–336)	0.186
FIB, g/L	2.78 (2.38–3.17)	2.74 (2.40–3.15)	2.82 (2.38–3.22)	0.408
Hcy, umol/L	13.3 (10.7–16.7)	12.5 (9.85–15.3)	14.2 (11.4–17.4)	0.001*
CSVD burden score, n(%)				<0.001*
0	49 (15.2)	38 (28.6)	11 (5.8)	
1	66 (20.5)	39 (29.3)	27 (14.3)	
2	74 (23.0)	33 (24.8)	41 (21.7)	
3	77 (23.9)	15 (11.3)	62 (32.8)	
4	56 (17.4)	8 (6.0)	48 (25.4)	

Note: *Denotes significance at a P value of <0.05.

Abbreviations: T2DM, type 2 diabetes mellitus; VCI, vascular cognitive impairment; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; VLDL-C, very low density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; UA, uric acid; FIB, fibrinogen; Hcy, homocysteine; CSVD, cerebral small vessel disease.

group were older and less educated (P <0.05). The mild VCI group had higher HbA1c, serum Hcy levels, and total CSVD burden scores than the normal cognitive group (P <0.05).

Development of the Predictive Model

The results of the univariate and multivariate logistic regression analyses for risk factors associated with mild VCI in patients with T2DM are shown in Table 2. According to the results of univariate analysis, age, education, stroke, HbA1c,

Table 2 Binary Logistic Regression Analysis of the Associated Factors for the Risk of Mild VCI in Participants with T2DM

Variable	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age	1.064 (1.016~1.052)	<0.001	1.039 (1.004~1.075)	0.028
Education	0.925 (0.874~0.979)	0.007	0.930 (0.872~0.991)	0.026
Stroke	1.556 (0.976~2.480)	0.063	–	–
HbA1c	1.283 (1.073~1.535)	0.006	1.310 (1.065~1.612)	0.011
Hcy	1.077 (1.026~1.130)	0.003	1.053 (1.000~1.110)	0.052
CSVD burden score				
0 (reference)				
1	2.392 (1.041~5.492)	0.040	2.628 (1.083~6.373)	0.033
2	4.292 (1.904~9.674)	<0.001	3.903 (1.642~9.279)	0.002
3	14.279 (5.943~34.307)	<0.001	11.371 (4.514~28.641)	<0.001
4	20.727 (7.585~56.639)	<0.001	17.653 (6.067~51.360)	<0.001

Abbreviations: T2DM, type 2 diabetes mellitus; VCI, vascular cognitive impairment; HbA1c, hemoglobin A1c; Hcy, homocysteine; CSVD, cerebral small vessel disease.

Hcy, and total CSVD burden score were potential predictors of mild VCI in patients with T2DM (P <0.1). In multivariable logistic regression analysis, age (odds ratio [OR]: 1.039, 95% confidence interval [CI]: 1.004–1.075, P<0.001), education (OR: 0.930, 95% CI: 0.872–0.991, P=0.026), HbA1c (OR: 1.310, 95% CI: 1.065–1.612, P=0.011), Hcy (OR: 1.053, 95% CI: 1.000–1.110, P=0.052), and total CSVD burden score (0 score: reference; 1 score: OR: 2.628, 95% CI: 1.083–6.373, P=0.033; 2 score: OR: 3.903, 95% CI: 1.642–9.279, P=0.002; 3 score: OR: 11.371, 95% CI: 4.514–28.641, P<0.001; 4 score: OR: 17.653, 95% CI: 6.067–51.360, P<0.001) were detected by Akaike information criterion as predictors of mild VCI in patients with T2DM.

Based on these five significant predictors, a nomogram for mild VCI in T2DM patients was developed (Figure 1). Additionally, to facilitate clinical applications, a dynamic nomogram was developed and is available online (https://tengzhenjie.shinyapps.io/DynNomapp3/). For example, in a T2DM patient with an age of 68 years, education of 9 years, HbA1c level of 7%, Hcy level of 15 μmol/L, and CSVD burden score of 2, the probability of mild VCI was estimated to be 56.0% (Figure 2).

Validation of the Predictive Model

The results of the 2000 bootstrap samples estimated the AUC to be 0.801 (95% CI: 0.752–0.849), which indicated good discrimination of the nomogram (Figure 3).

The bootstrap-corrected (bootstrapping with 2000 repetitions) calibration plot for the probability of mild VCI in patients with T2DM demonstrated an optimal agreement between the prediction by the nomogram and the actual observation (Figure 4). In addition, the Hosmer-Lemeshow test suggested that the predictive model was goodness-of-fit (χ^2 =9.226, P=0.417), and the Brier score of the predictive model was 0.178. In summary, these results indicate that the model has a good predictive accuracy.

As shown in Figure 5, DCA indicated that when the threshold probability ranged between 16% and 98%, the use of the nomogram to predict mild VCI in patients with T2DM provided a greater net benefit, which suggested the clinical usefulness of the nomogram.

Discussion

In the present study, we developed and internally validated a nomogram based on age, education, HbA1c level, Hcy level, and total CSVD burden score to predict the probability of mild VCI in T2DM patients. A dynamic nomogram was developed to facilitate clinical application. The predictive nomogram showed good discriminatory ability, calibration, and clinical usefulness, which could facilitate the detection of mild VCI by clinicians in T2DM patients.

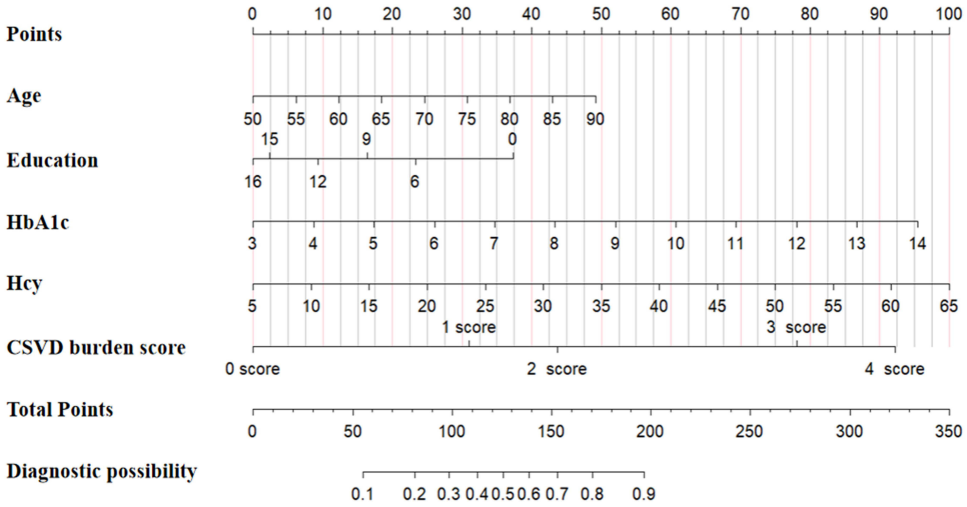

Figure 1 Nomogram for the prediction of the probability of mild VCI risk in participants with T2DM. The nomogram was developed by incorporating the following five parameters: age, education, HbA1c, Hcy, and total CSVD burden scores.

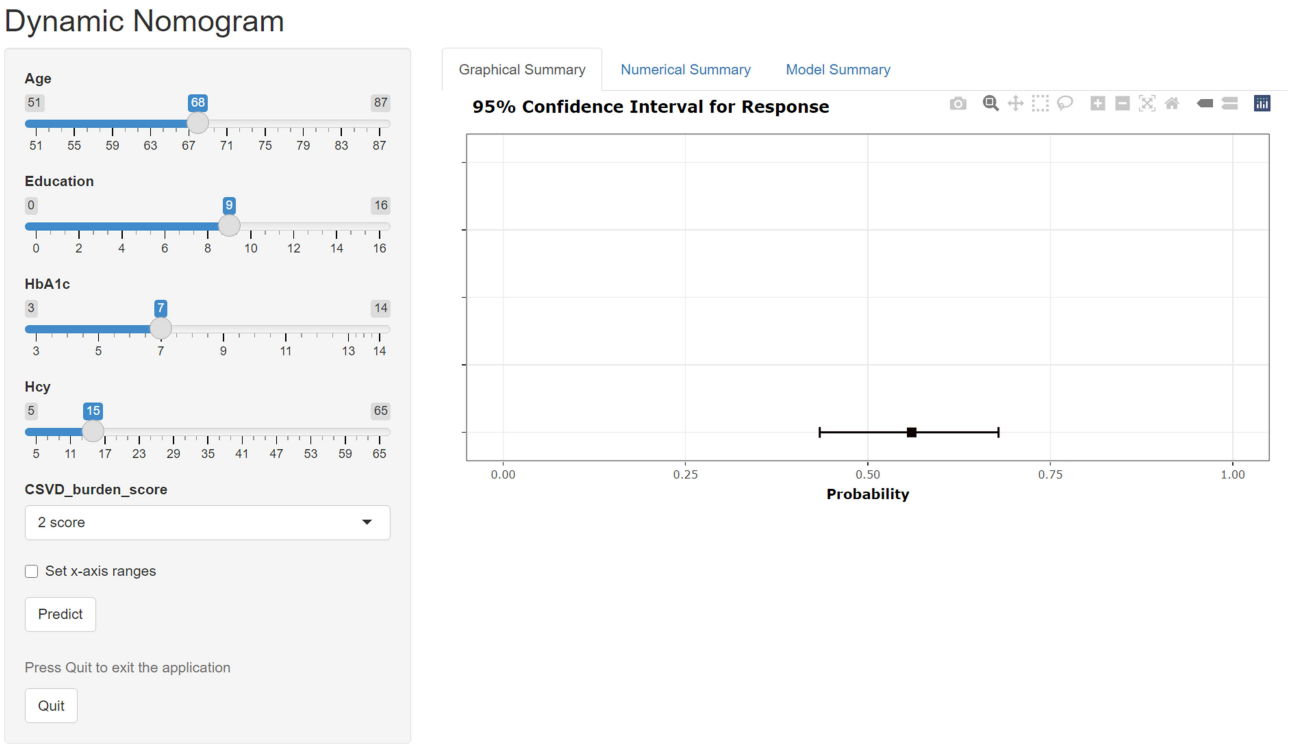

Figure 2 Dynamic nomogram for predicting the probability of mild VCI risk in participants with T2DM. An online dynamic nomogram accessible at https://tengzhenjie.shinyapps.io/DynNomapp3/, depicting an example for predicting the probability of having a mild VCI risk in participants with T2DM for a 68 years old patient with 9 years, HbA1c of 7%, Hcy of 15 μmol/L, and the CSVD burden score of 2.

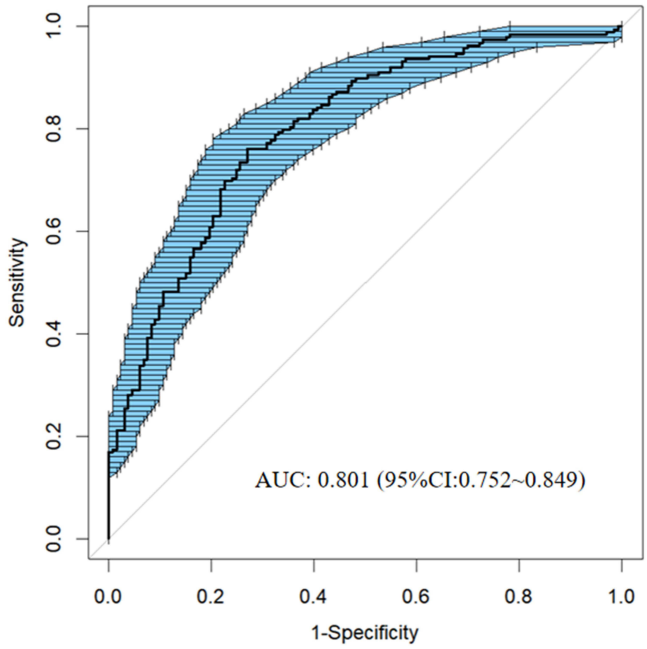

Figure 3 Receiver operating characteristic curve of the nomogram for predicting mild VCI in participants with T2DM using bootstrap resampling (2000 times).

MCI is common in T2DM patients. A meta-analysis showed that the pooled estimated prevalence of MCI in T2DM patients was 45.0%.[32] However, the prevalence of mild VCI in patients with T2DM is unknown. Our study utilized the MoCA to assess cognitive function and found that the prevalence of mild VCI was higher (58.7%) than that of MCI in

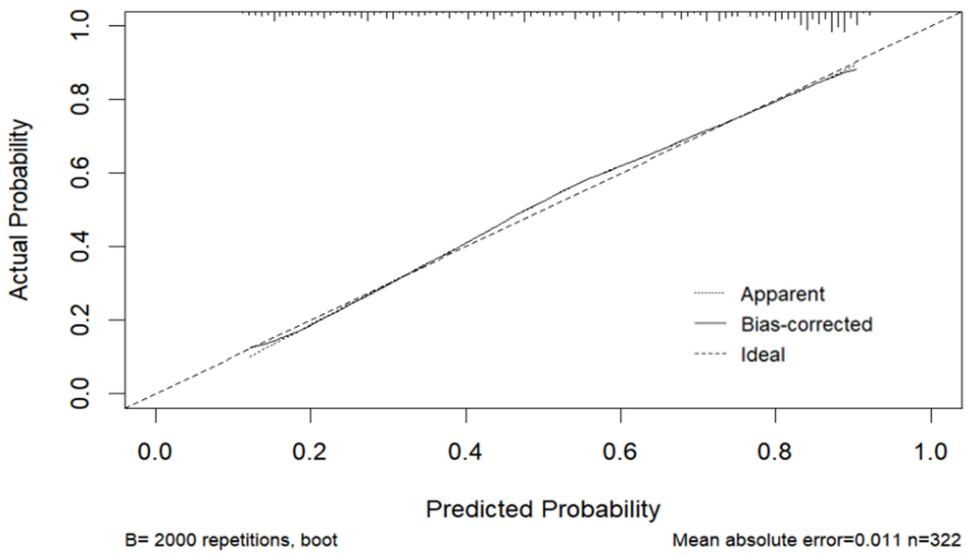

Figure 4 Calibration plot of the nomogram for predicting mild VCI in participants with T2DM. The dotted line represents the performance of the nomogram, whereas the solid line indicates nomogram bias. The dashed line represents the reference line in which the ideal nomogram lies. The prediction accuracy of the nomogram was better when the solid line was closer to the dotted one.

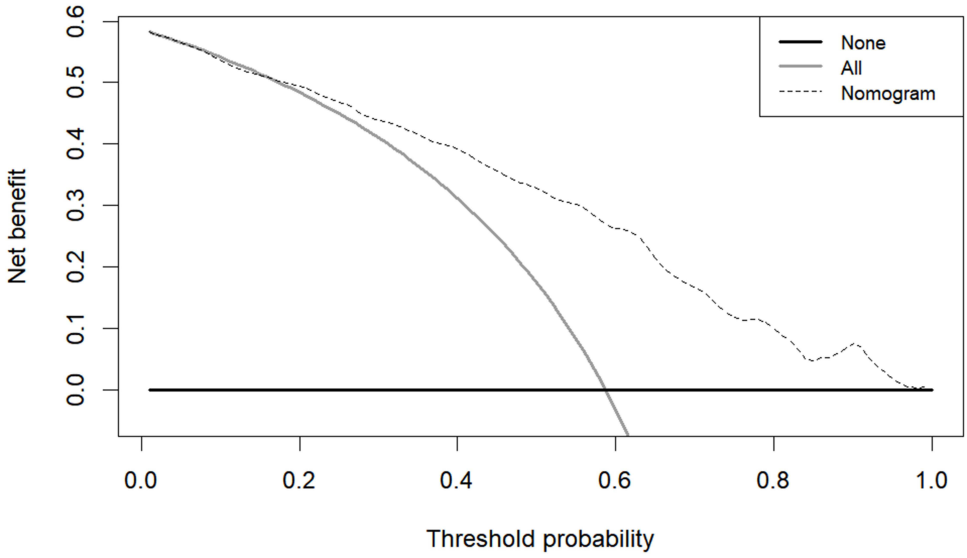

Figure 5 DCA curves of the nomogram for predicting mild VCI in participants with T2DM. The y-axis represents the net benefit. The gray line represents the assumption that all the patients had mild VCI. The black line represents the assumption that none of the patients had cognitive impairments. The dotted line represents the risk nomogram.

T2DM patients.[32,33] One reason for this change might be that the MoCA was more sensitive to the diagnosis of MCI than the mini-mental state examination (MMSE).[34]

Age is one of the important risk predictors for VCI,[1] and prevalence of T2DM or T2DM-related cognitive impairment increases with age.[35] The increased risk of mild VCI with older age has also been found in our study. In addition, this study observed that patients with low education levels were at a higher risk of mild VCI, which is consistent with previous studies.[3,35] This can be explained by the fact that a high education level was associated with a higher cognitive reserve.[36]

The association between HbA1c level and T2DM-related cognitive impairment remains controversial. A prospective population-based study found the linear correlation between HbA1c levels and global cognitive decline over a longterm 10 year follow-up period.[37] In contrast, another prospective study found a J-shaped rather than linear association between

HbA1c levels and incident dementia.[12] However, a randomised open-label study indicated that using intensive therapy to reduce the HbA1c levels did not improve cognitive function.[38] We found that the level of HbA1c was an important predictor and was related to the increased risk of mild VCI in patients with T2DM. A possible explanation is that a higher HbA1c level is associated with more aggravated T2DM-related microvascular complications.[37] Tian et al[39] reported that increased serum Hcy levels were associated with T2DM-related MCI, especially executive dysfunction. However, another study found no association between serum Hcy levels and T2DM-related MCI after further adjustment for potential confounders,[40] which is consistent with the findings of our previous study.[41] To the best of our knowledge, few studies have explored the relationship between serum Hcy levels and mild VCI in T2DM patients. In this study, we found that the level of serum Hcy was an important predictor of mild VCI in patients with T2DM, which suggests that increased serum Hcy levels were more strongly correlated with MCI due to vascular risk factors.

One of the key underlying mechanisms of T2DM-related VCI may be cerebral microvascular dysfunction,[14,15] which is common in T2DM patients.[42] Detrimental changes in cerebral microcirculation in T2DM include thickening of the basement membrane, increased angiogenesis, increased permeability of the blood-brain barrier, and altered regulation of microvascular blood flow.[15] These changes can further lead to a range of reactions, such as hypoperfusion, hypoxia, oxidative stress, and inflammation,[15] resulting in brain dysfunction and T2DM-related VCI. It is commonly recognized that features of CSVD, as measured by MRI, might reflect cerebral microvascular dysfunction in the T2DM population.[15,24] Previous studies have suggested that the severity of white matter hyperintensity or lacunes is independently associated with cognitive impairment in T2DM patients.[21,23] In addition, the enlarged perivascular space or cerebral microbleed may be a potential biomarker of cognitive impairment in patients with T2DM.[20,22]

However, these studies did not further distinguish between the degree (MCI or dementia) and subtype (VCI or AD) of cognitive impairment. Moreover, as a whole-brain disorder,[24] different imaging markers of CSVD are interrelated, and it may be one-sided to consider only one specific imaging marker of CSVD. Therefore, the total CSVD burden score, which may better represent the severity of CSVD or cerebral microvascular dysfunction,[19,26] should be considered when developing a predictive model for mild VCI in patients with T2DM, which is rarely performed. In our study, we found that the total CSVD burden score was an important predictor of mild VCI in patients with T2DM and that severe CSVD burden (total CSVD burden score $\geq$3 points) had a more significant predictive ability. These findings indicate that the total CSVD burden score may be a potential biomarker for mild VCI in T2DM patients. Furthermore, our results may provide evidence for the important role of cerebral microvascular dysfunction in T2DM-related VCI and provide clues for future studies to investigate early diagnostic imaging markers of VCI in T2DM patients.

Taken together, we constructed and internally validated a nomogram to predict the probability of mild VCI in T2DM patients. The predictive nomogram exhibited a good discriminatory ability, calibration, and clinical usefulness. Compared with previous studies, this study has several advantages. First, to the best of our knowledge, this is the first predictive nomogram model for mild VCI in T2DM patients. Second, total CSVD burden score, an important predictor of T2DM-related cognitive impairment, was taken into account in our study, whereas others do not.[33,43,44] Third, the online dynamic nomogram that we constructed is more convenient and intuitive for clinical applications.

Limitations

Our study had some limitations. First, this was a single-center retrospective study with a relatively small sample size. Second, the nomogram developed in this study was internally validated using bootstrapping without external datasets. Third, the patients were recruited from a single center in our study, which may have some restrictions when generalizing to other populations. Future multicenter prospective studies with larger sample sizes and external datasets are warranted to address these issues.

Conclusion

In conclusion, the nomogram based on age, education, stroke, HbA1c, Hcy, and total CSVD burden scores may predict the risk of mild VCI in patients with T2DM. The predictive nomogram showed good discriminatory ability, calibration, and clinical usefulness, which could facilitate the detection of mild VCI by clinicians in T2DM patients. Future prospective studies with larger populations and external validation are warranted to enhance the stability of this model.

Ethical Approval

This study followed the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Hebei General Hospital (No.2023176). Informed consent was waived because the study was a retrospective analysis and the data of all participants were anonymized.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Rundek T, Tolea M, Ariko T, et al. Vascular Cognitive Impairment (VCI). *Neurotherapeutics*. 2022;19:68–88. doi:10.1007/s13311-021-01170-y
2. Jia L, Du Y, Chu L, et al. Prevalence, risk factors, and management of dementia and mild cognitive impairment in adults aged 60 years or older in China: a cross-sectional study. *Lancet Public Health*. 2020;5:e661–e671. doi:10.1016/S2468-2667(20)30185-7
3. van der Flier WM, Skoog I, Schneider JA, et al. Vascular cognitive impairment. *Nat Rev Dis Primers*. 2018;4:18003. doi:10.1038/nrdp.2018.3
4. Iadecola C, Duering M, Hachinski V, et al. Vascular cognitive impairment and dementia: JACC scientific expert panel. *J Am Coll Cardiol*. 2019;73:3326–3344. doi:10.1016/j.jacc.2019.04.034
5. Lissek V, Suchan B. Preventing dementia? Interventional approaches in mild cognitive impairment. *Neurosci Biobehav Rev*. 2021;122:143–164. doi:10.1016/j.neubiorev.2020.12.022
6. Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. *Nat Rev Endocrinol*. 2018;14:591–604. doi:10.1038/s41574-018-0048-7
7. Biessels GJ, Whitmer RA. Cognitive dysfunction in diabetes: how to implement emerging guidelines. *Diabetologia*. 2020;63:3–9. doi:10.1007/s00125-019-04977-9
8. Srikanth V, Sinclair AJ, Hill-Briggs F, et al. Type 2 diabetes and cognitive dysfunction-towards effective management of both comorbidities. *Lancet Diabetes Endocrinol*. 2020;8:535–545. doi:10.1016/S2213-8587(20)30118-2
9. Lyu F, Wu D, Wei C, et al. Vascular cognitive impairment and dementia in type 2 diabetes mellitus: an overview. *Life Sci*. 2020;254:117771. doi:10.1016/j.lfs.2020.117771
10. Biessels GJ, Strachan MW, Visseren FL, et al. Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions. *Lancet Diabetes Endocrinol*. 2014;2:246–255. doi:10.1016/S2213-8587(13)70088-3
11. Schnaider BM, Goldbourt U, Silverman JM, et al. Diabetes mellitus in midlife and the risk of dementia three decades later. *Neurology*. 2004;63:1902–1907. doi:10.1212/01.wnl.0000144278.79488.dd
12. Rawlings AM, Sharrett AR, Albert MS, et al. The association of late-life diabetes status and hyperglycemia with incident mild cognitive impairment and dementia: the ARIC study. *Diabetes Care*. 2019;42:1248–1254. doi:10.2337/dc19-0120
13. Xu W, Caracciolo B, Wang HX, et al. Accelerated progression from mild cognitive impairment to dementia in people with diabetes. *Diabetes*. 2010;59:2928–2935.
14. Luo A, Xie Z, Wang Y, et al. Type 2 diabetes mellitus-associated cognitive dysfunction: advances in potential mechanisms and therapies. *Neurosci Biobehav Rev*. 2022;137:104642. doi:10.1016/j.neubiorev.2022.104642
15. van Sloten TT, Sedaghat S, Carnethon MR, et al. Cerebral microvascular complications of type 2 diabetes: stroke, cognitive dysfunction, and depression. *Lancet Diabetes Endocrinol*. 2020;8:325–336. doi:10.1016/S2213-8587(19)30405-X
16. Rensma SP, van Sloten TT, Houben A, et al. Microvascular dysfunction is associated with worse cognitive performance: the maastricht study. *Hypertension*. 2020;75:237–245. doi:10.1161/HYPERTENSIONAHA.119.13023
17. Jiang C, Wang Y, Dong Y, et al. Associations of microvascular dysfunction with mild cognitive impairment and cognitive function among rural-dwelling older adults in China. *J Alzheimers Dis*. 2023;93:1111–1124. doi:10.3233/JAD-221242
18. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12:822–838. doi:10.1016/S1474-4422(13)70124-8
19. Duering M, Biessels GJ, Brodtmann A, et al. Neuroimaging standards for research into small vessel disease-advances since 2013. *Lancet Neurol*. 2023;22:602–618. doi:10.1016/S1474-4422(23)00131-X
20. Zhou H, Yang J, Xie P, et al. Cerebral microbleeds, cognitive impairment, and MRI in patients with diabetes mellitus. *Clin Chim Acta*. 2017;470:14–19. doi:10.1016/j.cca.2017.04.019
21. van Gennip A, Stehouwer C, van Boxtel M, et al. Association of type 2 diabetes, according to the number of risk factors within target range, with structural brain abnormalities, cognitive performance, and risk of dementia. *Diabetes Care*. 2021;44:2493–2502. doi:10.2337/dc21-0149
22. Choi EY, Park YW, Lee M, et al. Magnetic resonance imaging-visible perivascular spaces in the basal ganglia are associated with the diabetic retinopathy stage and cognitive decline in patients with type 2 diabetes. *Front Aging Neurosci*. 2021;13:666495. doi:10.3389/fnagi.2021.666495
23. Imamine R, Kawamura T, Umemura T, et al. Does cerebral small vessel disease predict future decline of cognitive function in elderly people with type 2 diabetes? *Diabet Res Clin Pract*. 2011;94:91–99. doi:10.1016/j.diabres.2011.06.014
24. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol*. 2019;18:684–696. doi:10.1016/S1474-442(19)30079-1
25. Ter Telgte A, van Leijsen E, Wiegertjes K, et al. Cerebral small vessel disease: from a focal to a global perspective. *Nat Rev Neurol*. 2018;14:387–398. doi:10.1038/s41582-018-0014-y
26. Staals J, Makin SD, Doubal FN, et al. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. *Neurology*. 2014;83:1228–1234. doi:10.1212/WNL.0000000000000837
27. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15:539–553. doi:10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S

28. Lu J, Li D, Li F, et al. Montreal cognitive assessment in detecting cognitive impairment in Chinese elderly individuals: a population-based study. *J Geriatr Psychiatry Neurol*. 2011;24:184–190. doi:10.1177/0891988711422528
29. Skrobot OA, Black SE, Chen C, et al. Progress toward standardized diagnosis of vascular cognitive impairment: guidelines from the vascular impairment of cognition classification consensus study. *Alzheimers Dement*. 2018;14:280–292. doi:10.1016/j.jalz.2017.09.007
30. Teng Z, Feng J, Dong Y, et al. Triglyceride glucose index is associated with cerebral small vessel disease burden and cognitive impairment in elderly patients with type 2 diabetes mellitus. *Front Endocrinol*. 2022;13:970122. doi:10.3389/fendo.2022.970122
31. Teng Z, Feng J, Qi Q, et al. Long-term use of metformin is associated with reduced risk of cognitive impairment with alleviation of cerebral small vessel disease burden in patients with type 2 diabetes. *Front Aging Neurosci*. 2021;13:773797. doi:10.3389/fnagi.2021.773797
32. You Y, Liu Z, Chen Y, et al. The prevalence of mild cognitive impairment in type 2 diabetes mellitus patients: a systematic review and meta-analysis. *Acta Diabetol*. 2021;58:671–685. doi:10.1007/s00592-020-01648-9
33. Maimaitituerxun R, Chen W, Xiang J, et al. The use of nomogram for detecting mild cognitive impairment in patients with type 2 diabetes mellitus. *J Diabetes*. 2023;15:448–458. doi:10.1111/1753-0407.13384
34. Zhuang L, Yang Y, Gao J. Cognitive assessment tools for mild cognitive impairment screening. *J Neurol*. 2021;268:1615–1622. doi:10.1007/s00415-019-09506-7
35. Suain BR, Ariaratnam S, Mat SZ, et al. Cognitive impairment and its associated risk factors in the elderly with type 2 diabetes mellitus. *Front Psychiatry*. 2021;12:669725. doi:10.3389/fpsyt.2021.669725
36. Zijlmans JL, Lamballais S, Vernooij MW, et al. Sociodemographic, lifestyle, physical, and psychosocial determinants of cognitive reserve. *J Alzheimers Dis*. 2022;85:701–713. doi:10.3233/JAD-215122
37. Zheng F, Yan L, Yang Z, et al. HbA(1c), diabetes and cognitive decline: the English longitudinal study of ageing. *Diabetologia*. 2018;61:839–848. doi:10.1007/s00125-017-4541-7
38. Launer LJ, Miller ME, Williamson JD, et al. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. *Lancet Neurol*. 2011;10:969–977. doi:10.1016/S1474-4422(11)70188-0
39. Tian S, Han J, Huang R, et al. Increased plasma homocysteine level is associated with executive dysfunction in type 2 diabetic patients with mild cognitive impairment. *J Alzheimers Dis*. 2017;58:1163–1173. doi:10.3233/JAD-170162
40. Damanik J, Mayza A, Rachman A, et al. Association between serum homocysteine level and cognitive function in middle-aged type 2 diabetes mellitus patients. *PLoS One*. 2019;14:e224611. doi:10.1371/journal.pone.0224611
41. Teng Z, Feng J, Liu R, et al. Cerebral small vessel disease is associated with mild cognitive impairment in type 2 diabetes mellitus. *Diabetes Metab Syndr Obes*. 2022;15:1985–1994. doi:10.2147/DMSO.S368725
42. Stehouwer C. Microvascular dysfunction and hyperglycemia: a vicious cycle with widespread consequences. *Diabetes*. 2018;67:1729–1741. doi:10.2337/dbi17-0044
43. Exalto LG, Biessels GJ, Karter AJ, et al. Risk score for prediction of 10 year dementia risk in individuals with type 2 diabetes: a cohort study. *Lancet Diabetes Endocrinol*. 2013;1:183–190. doi:10.1016/S2213-8587(13)70048-2
44. Li CI, Li TC, Liu CS, et al. Risk score prediction model for dementia in patients with type 2 diabetes. *Eur J Neurol*. 2018;25:976–983. doi:10.1111/ene.13642