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CLINICAL TRIAL

Predictive value of biliverdin reductase-A and homeostasis model assessment of insulin resistance on mild cognitive impairment in patients with type 2 diabetes

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Keywords
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ABSTRACT

Aims/Introduction: To investigate the predictive value of the biliverdin reductase-A (BVR-A) and the homeostasis model assessment for insulin resistance (HOMA-IR) on mild cognitive impairment (MCI) in patients with type 2 diabetes mellitus, and to establish a nomogram model.

Materials and Methods: This study included 140 patients with type 2 diabetes mellitus. Based on Montreal Cognitive Assessment (MoCA) scores, participants were categorized into the normal cognitive function (T2DM-NCF) group (65 cases) and the mild cognitive impairment (T2DM-MCI) group (75 cases). Multivariate logistic regression analysis was performed to identify the factors associated with MCI in patients with type 2 diabetes mellitus. A nomogram prediction model was developed using R software for the selected factors, and its predictability and accuracy were verified.

Results: Compared with the T2DM-NCF group, subjects with MCI were older, had a longer duration of diabetes, higher HOMA-IR, lower BVR-A, lower cognitive scores, and lower education levels (all $P < 0.05$). Multivariate logistic regression analysis showed that duration of diabetes (OR = 1.407, 95% CI: 1.163–1.701), HOMA-IR (OR = 1.741, 95% CI: 1.197–2.53), and BVR-A (OR = 0.528, 95% CI: 0.392–0.712) were significantly associated with the development of MCI in patients with type 2 diabetes mellitus. The C-index of the nomogram was 0.863 (95% CI: 0.752–0.937).

Conclusions: Our findings suggest that BVR-A and HOMA-IR are significantly associated with the development of MCI in patients with type 2 diabetes mellitus. The nomogram incorporating BVR-A and HOMA-IR aids in predicting the risk of developing MCI in these patients.

INTRODUCTION

Diabetes mellitus is a prevalent metabolic disease, with cognitive impairment being its most significant central nervous system complication[1]. The increasing prevalence of type 2 diabetes mellitus has led to dementia becoming a major public health issue worldwide, significantly reducing patients' quality of life of and placing a heavy burden on healthcare resources[2,3]. A meta-analysis revealed that the prevalence of mild cognitive impairment (MCI) in patients with type 2 diabetes mellitus is as high as 45%, particularly in China and other Asian

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countries[4]. Therefore, it is essential to identify individuals at an elevated risk of cognitive decline at an early stage.

Research suggests that cognitive impairment in diabetes may be related to various factors, such as oxidative stress, aggregation of amyloid beta (Aβ) peptides, abnormal phosphorylation of Tau protein, inflammation, damage to the blood–brain barrier, and other potential contributors[5]. Accumulating evidence supports the essential role of insulin resistance (IR) in the pathogenesis of cognitive impairment and neurodegeneration[6,7].

Changes in biliverdin reductase-A (BVR-A) protein levels affect various metabolic processes, including glucose uptake, lipid and protein metabolism regulation, cell proliferation, differentiation, and death[8,9]. Additionally, BVR-A also has serine, threonine, and tyrosine (Ser/Thr/Tyr) kinase activity and may be involved in regulating the insulin signaling pathway[10,11]. In Alzheimer's disease (AD), damage to BVR-A occurs prior to the inhibition of insulin receptor substrate-1 (IRS-1), leading to an increase in Aβ production in the parietal cortex. This contributes to the development of IR and metabolic changes in the brain. Targeted activation of BVR-A can delay the development of brain insulin resistance (BIR)[12,13]. Another animal experiment demonstrated that BVR-A deficiency led to the development of IR, and intranasal insulin (INI) administration prevented the early BVR-A damage in mice, thereby preventing BIR by restoring BVR-A activity[14]. Thus, reduced or impaired BVR-A protein levels may be an early marker of IR.

Reduced or absent levels of BVR-A protein may adversely affect cognitive function. A lack of BVR-A has been shown to impair synaptic plasticity in hippocampal neurons, leading to defects in learning and memory in mice[15]. BVR-A deficiency in AD leads to increased phosphorylation of tau proteins in the brain, which affects cognitive function[16]. Conversely, increased BVR-A reduce oxidative stress in the parietal cortex and improve cognitive function[17,18]. This indicates that BVR-A contributes to neuroprotection and plays a vital role in the development of cognitive impairment. While previous studies have demonstrated a strong link between BVR-A, IR, and cognitive decline, no research has clarified whether changes in BVR-A levels are associated with MCI in type 2 diabetes mellitus patients.

The HOMA-IR is a widely used method to assess IR. Research indicates that elevated HOMA-IR levels are linked to cognitive decline in both healthy and diabetic populations[19,20]. Therefore, we hypothesize that the reduction of BVR-A and the increase of HOMA-IR are closely associated with the occurrence of MCI in type 2 diabetes mellitus patients. This study aims to explore the predictive value of BVR-A and HOMA-IR for MCI in patients with type 2 diabetes mellitus and to establish a nomogram predictive model. This model could serve as a reference for early screening and prevention of MCI in individuals with type 2 diabetes mellitus.

METHODS

Study population

We enrolled 200 patients with type 2 diabetes mellitus from the Endocrinology Department of the Affiliated Hospital of Xuzhou Medical University between December 2023 and March 2024. The inclusion criteria were: (1) Patients diagnosed with type 2 diabetes mellitus according to the 2022 American Diabetes Association guidelines[21]; (2) Hospitalization due to poor blood glucose control (poor blood glucose control is defined by the following criteria: fasting blood glucose levels below 3.9 mmol/L or above 7.0 mmol/L; non-fasting blood glucose levels at or exceeding 10.0 mmol/L; and glycated hemoglobin (HbA1c) levels at or above 7%[22]); (3) Age 40 years or older; (4) Ability to provide informed consent. The exclusion criteria were: (1) Type 1 diabetes (T1DM) or other specific types of diabetes; (2) Acute diabetic complications within the past 3 months, including diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic syndrome (HHS); (3) Serious infections, gastrointestinal bleeding, acute cardiovascular events, or surgeries within the past month; (4) Conditions potentially related to cognitive impairment, such as brain injury, epilepsy, malignant tumor, carbon monoxide poisoning, schizophrenia, anxiety, depression, or a history of drug or alcohol dependence; (5) Thyroid dysfunction; (6) Severe aphasia, blindness, or critical conditions preventing questionnaire completion; (7) Congenital mental retardation; (8) Patients with missing data. Based on these criteria, 140 eligible patients were included in the study (Figure S1). The study was approved by the Medical Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (Ethics batch number: XYFY2023-KL459-01). The project was registered with the Chinese Clinical Trial Registry (Registration Number: ChiCTR2300078678). All participants provided informed consent.

Data collection

The study recorded the gender, age, education level, and duration of diabetes mellitus of the patients. Additionally, data on their smoking history, alcohol consumption, and hypertension (including systolic and diastolic blood pressure at the time of hospital admission) were collected. Height and weight were measured to calculate body mass index (BMI). Fasting venous blood samples were taken from all participants after an 8-h overnight fast. Postprandial blood samples were collected 120 min after a steamed bread meal to assess post-load glucose. The following parameters were measured: fasting plasma glucose (FPG), HbA1c, fasting insulin (FINS), C-peptide (C-P), aspartate aminotransferase (AST), alanine aminotransferase (ALT), triglyceride (TG), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipid-cholesterol (HDL-C), blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA), and estimated glomerular filtration rate(eGFR). Insulin resistance was assessed using the HOMA-IR, calculated as (FPG [mmol/L] × FINS [μIU/mL])/22.5.

Data of BVR-A measurements

About 2mL of fasting venous blood was collected and immediately centrifuged to separate the plasma, which was then stored at −80°C. The plasma level of BVR-A protein was determined using enzyme-linked immunosorbent assay (ELISA) kits (Shanghai Jianglai, Shanghai, China) following the manufacturer's instructions.

Assessment of cognitive function

Each group completed the Montreal Cognitive Assessment (MoCA) after admission. The MoCA scale, with a total score of 30 points, was administered by a uniformly trained physician, and the results were recorded. MoCA is a highly sensitive cognitive screening tool that quickly detects MCI and distinguishes MCI patients from those with normal cognition. In this study, MCI was defined as scores between 19 and 25, inclusive, while scores of 26 or higher indicated normal cognition. One point was added for participant with fewer than 12 years of formal education[23]. Based on the MoCA scores, the study subjects were divided into the T2DM-NCF group and T2DM-MCI group.

Statistical analysis

Firstly, the clinical and biochemical characteristics of the subjects were used by descriptive statistics. Normally, distributed measurements were described by means ± standard deviations (x ± s), and comparisons between the two groups were made using the independent samples *t*-test. Non-normally distributed variables were expressed as median [M (Q1, Q3)], with group comparisons made using the Mann–Whitney *U*-test. Categorical variables were expressed as a percentage and analyzed using the Chi-square test.

Secondly, the total sample was divided into the training set and the test set in a 7:3 ratio. The training set was used to screen variables and construct the predictive model, while the test set was used to validate the results. In the training set, stepwise logistic regression based on the Akaike information criterion (AIC) was employed to identify factors associated with MCI in patients with type 2 diabetes mellitus. A receiver operating characteristic (ROC) curve was then generated, and the area under the curve (AUC) was calculated.

Finally, a nomogram prediction model for MCI was developed based on the results of the multivariate logistic regression analysis. The performance of the prediction model was evaluated using the ROC curve, calibration curve, and decision curve analysis (DCA) to assess its discrimination, calibration, and clinical utility. Additionally, the stability and predictive power of the model are assessed using fivefold cross-validation. Statistical analysis was performed using SPSS statistical software (version 27.0) and R software (version 4.4.0). A *P*-value of <0.05 was considered statistically significant.

RESULT

Clinical and laboratory characteristics of groups

Following a series of exclusions and screenings, 140 subjects were ultimately enrolled in the study. Demographic characteristics and laboratory data for the T2DM-NCF and T2DM-MCI groups are presented in Table 1. The T2DM-NCF group included 65 cases, while the T2DM-MCI group included 75 cases. The T2DM-MCI group exhibited significantly higher age, longer duration of diabetes, higher FINS, and higher HOMA-IR compared with the T2DM-NCF group ($P < 0.01$). Conversely, the T2DM-NCF group had significantly higher education level, AST, ALT, BVR-A, and MoCA scores compared with the T2DM-MCI group ($P < 0.05$). There was no significant difference between the two groups in terms of gender, smoking history, drinking history, SBP, DBP, BMI, FPG, HbA1c, C-P, TG, TC, LDL-c, HDL-c, BUN, UA, Cr, and eGFR ($P > 0.05$).

Factors associated with developing MCI in patients with type 2 diabetes mellitus

In the training set, three optimal variables were selected based on the AIC minimum criterion: duration of diabetes, HOMA-IR, and BVR-A. Among them, a longer duration of diabetes (OR = 1.407, 95% CI: 1.163–1.701), high levels of HOMA-IR (OR = 1.741, 95% CI: 1.197–2.53), and low levels of BVR-A (OR = 0.528, 95% CI: 0.392–0.712) are significantly associated with the development of MCI in patients with type 2 diabetes mellitus ($P < 0.05$, Table 2).

Parameters for diagnosing MCI

The AUC of the BVR-A was 0.791 (95% CI: 0.655–0.926), for HOMA-IR, it was 0.737 (95% CI: 0.581–0.893), and for the duration of diabetes, it was 0.684 (95% CI: 0.522–0.864) (Figure 1). The optimal cut-off point for diagnosing MCI using BVR-A was 3.84, with a sensitivity of 60.9% and a specificity of 89.5%.

Establishment of a nomogram and validation

Based on three associated factors for the development of MCI in patients with type 2 diabetes mellitus, including duration of diabetes, HOMA-IR, and BVR-A, this study established a nomogram model to predict MCI in type 2 diabetes mellitus patients (Figure 2). In terms of discrimination, the AUC of the training set was 0.897 (95% CI: 0.837–0.958) and the AUC of the test set was 0.863 (95% CI: 0.752–0.973), indicating good model discrimination (Figure S2). Calibration results showed that the predicted values were consistent with the observed results, demonstrating good predictive performance (Figure 3a). From a clinical utility perspective, the DCA curve of the model was above the no-intervention and intervention conditions (black and gray line), indicating better clinical utility (Figure 3b). Internal validation results showed a C-index of 0.863 (95% CI: 0. 752–0. 937), indicating good accuracy and

Table 1 | Clinical and biochemical characteristics of T2DM-NCF group and T2DM-MCI group

	T2DM-NCF (n = 65)	T2DM-MCI (n = 75)	$t/z/\chi^2$	P-value
Age (year)	54.29 ± 7.36	58.19 ± 7.73	−3.040	0.003**
Male (%)	35 (53.80%)	45 (60.00%)	0.538	0.463
Duration of diabetes (year)	4.00 (3.00, 7.00)	7.00 (5.00, 13.00)	−4.551	<0.001**
Education level (year)	12.00 (8.00, 15.00)	8.00 (5.00, 12.00)	−2.952	0.003*
Smoking (%)	10 (15.40%)	17 (22.70%)	1.186	0.276
Drinking (%)	9 (13.80%)	13 (17.30%)	0.320	0.572
SBP (mmHg)	130.00 (122.00, 140.00)	130.00 (124.00, 147.00)	−0.711	0.477
DBP (mmHg)	88.00 (80.00, 94.50)	84.00 (80.00, 90.00)	−1.631	0.103
BMI (kg/m^2)	25.24 ± 3.17	25.27 ± 3.00	−0.069	0.945
FPG (mmol/L)	8.31 (6.59, 9.79)	8.62 (6.52, 10.51)	−0.445	0.656
FINS (μIU/mL)	6.85 (5.13, 8.79)	8.89 (5.98, 15.61)	−3.180	0.001**
C-P (ng/mL)	1.85 (1.34, 2.21)	1.72 (0.99, 2.42)	−0.912	0.362
HbA1c (%)	8.00 (6.90, 9.50)	8.10 (7.10, 10.00)	−0.669	0.504
HOMA-IR	2.42 (1.74, 3.08)	3.31 (2.31, 4.98)	−3.854	<0.001**
AST (U/L)	19.00 (14.50, 26.00)	16.00 (13.00, 21.00)	−2.267	0.023*
ALT (U/L)	23.00 (15.50, 32.50)	16.00 (12.00, 22.00)	−3.055	0.002**
TC (mmol/L)	4.74 (4.11, 5.45)	4.63 (3.58, 5.72)	−0.512	0.609
TG (mmol/L)	1.64 (1.28, 2.56)	1.40 (0.96, 2.23)	−1.653	0.098
HDL-C (mmol/L)	1.07 ± 0.28	1.10 ± 0.32	−0.604	0.547
LDL-C (mmol/L)	2.58 ± 1.10	2.49 ± 0.88	0.532	0.596
BUN (mmol/L)	5.95 (4.68, 7.16)	5.84 (5.03, 7.01)	−0.459	0.647
Cr (μmol/L)	52.00 (45.25, 63.00)	56.00 (49.00, 65.00)	−1.072	0.284
UA (μmol/L)	285.58 ± 88.78	284.79 ± 79.23	0.056	0.956
eGFR (mL/min)	120.00 (111.61, 120.00)	120 (109.62, 120.00)	−0.443	0.625
BVR-A (ng/mL)	5.78 ± 2.47	3.25 ± 2.02	6.659	<0.001**
MoCA score	27.00 (26.00, 27.00)	23.00 (22.00, 24.00)	−10.309	<0.001**

Continuous variables conforming to the normal distribution were presented as mean ± 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 $P < 0.05$. *$P < 0.05$. **$P < 0.01$. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; BVR-A, biliverdin reductase-A; C-P, C-peptide; Cr, creatinine; DBP, diastolic blood pressure; eGFR estimated glomerular filtration rate; FINS, fasting insulin; FPG, fasting plasma glucose; HbA1c, hemoglobinA1c; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; LDL-C, low-density lipoprotein-cholesterol; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; NCF, normal cognitive function; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; UA, uric acid.

Table 2 | Logistic regression analysis of the factors associated with the development of cognitive dysfunction in patients with type 2 diabetes mellitus

	β	Wald	OR (95% CI)	P value
Duration of diabetes	0.341	12.278	1.407 (1.163–1.701)	<0.001**
HOMA-IR	0.554	8.451	1.741 (1.197–2.53)	0.004**
BVR-A	−0.638	17.682	0.528 (0.392–0.712)	<0.001**

The significance level was set at $P < 0.05$. *$P < 0.05$. **$P < 0.01$. BVR-A, biliverdin reductase-A; HOMA-IR, homeostasis model assessment for insulin resistance.

discrimination (Figure 1). Subsequently, we utilized a fivefold cross-validation to assess the stability and predictive accuracy of our model. The ROC curve for each fold shows the performance of the model under different data partitions, with AUC values ranging from 0.738 to 0.964. The average AUC value, at 0.884, underscores the model's stability and strong discriminatory capabilities (Figure S3). Collectively, the outcomes from the 5-fold cross-validation confirm that our model exhibits impressive generalization capabilities when applied to new data. This makes it a potent instrument for the early diagnosis of MCI in individuals with type 2 diabetes mellitus.

DISCUSSION

Diabetic cognitive impairment refers to the impairment of cognitive function in diabetic patients, an increasingly common complication of diabetes[5]. Once clinical symptoms appear, existing treatment cannot reverse or delay the progression of dementia[24]. Previous studies have shown that 5.4–11.5% of MCI cases progress to dementia. In contrast, 40–70% of MCI cases do not progress within 10 years, and a small proportion

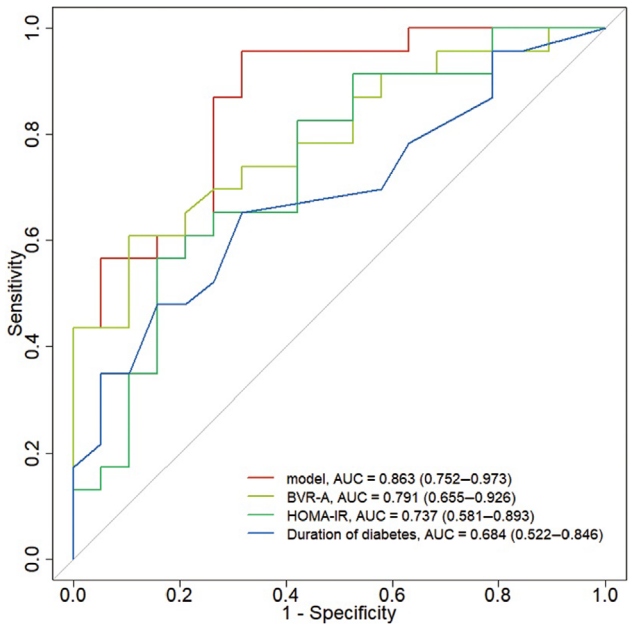

Figure 1 | The ROC curve of duration of diabetes, HOMA-IR, BVR-A, and prediction model for diagnosing. BVR-A, biliverdin reductase-A; HOMA-IR, homeostasis model assessment for insulin resistance.

of MCI may even show cognitive improvement[25]. Therefore, MCI is considered a critical period for dementia intervention. This study aimed to investigate the predictive value of BVR-A and HOMA-IR for MCI in patients with type 2 diabetes mellitus, providing new insights for clinical identification and prediction of cognitive dysfunction. The goal is to achieve early intervention and treatment, thereby improving patients' quality of life.

IR is a common feature of type 2 diabetes mellitus, cognitive decline, and dementia. Studies have shown a strong association between IR and cognitive dysfunction in both pre-diabetic and diabetic populations[26,27]. IR may affect cognition by altering glucose metabolism in the brain, increasing the deposition of Aβ peptides and hyperphosphorylation of tau, altering hippocampal synaptic plasticity, modifying amyloid precursor protein (APP) metabolism, and promoting inflammation and oxidative stress[7,28,29]. An 11-year follow-up study also revealed that IR is likely to predict cognitive decline[30]. Our study supports these findings, indicating that IR is more pronounced in the T2DM-MCI group compared to controls. Furthermore, our findings suggest that elevated HOMA-IR levels are associated with an increased risk of MCI in patients with type 2 diabetes mellitus.

In type 2 diabetes mellitus and AD, BVR-A plays a crucial role in insulin signaling. Abnormal levels of BVR-A are linked to IR and impaired mitochondrial energy metabolism, which correlate with a decline in cognitive function[31]. Barone *et al.*[12,14] found that impaired BVR-A activity leads to BIR in AD. They confirmed this in animal experiments, proposing that damage to BVR-A promotes overactivation of the mammalian target of rapamycin (mTOR), reducing autophagy and leading to increased accumulation of oxidative damage proteins, which is associated with neurodegenerative disease progression[32]. In a rat model of postoperative delayed neurocognitive recovery (dNCR), BVR-A expression levels were decreased in the hippocampus, prefrontal cortex, and temporal lobes[17]. Currently, BVR-A is strongly associated with IR and cognitive decline in AD and various animal models. Only one clinical study has

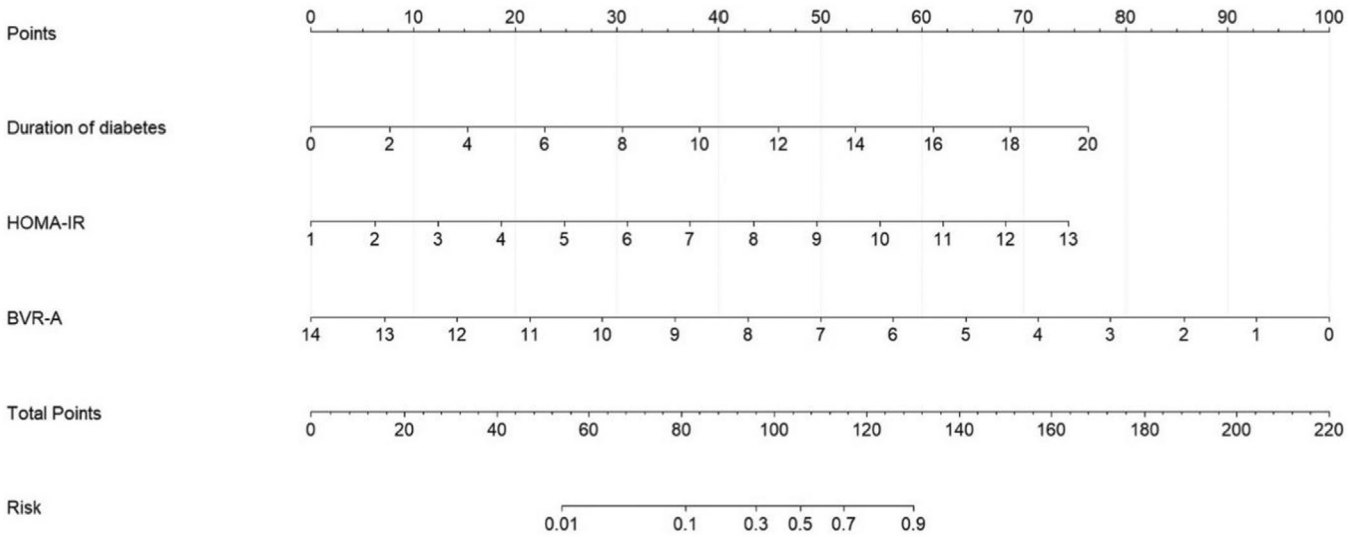

Figure 2 | Nomogram showed the risk of MCI. BVR-A, biliverdin reductase-A; HOMA-IR, homeostasis model assessment for insulin resistance.

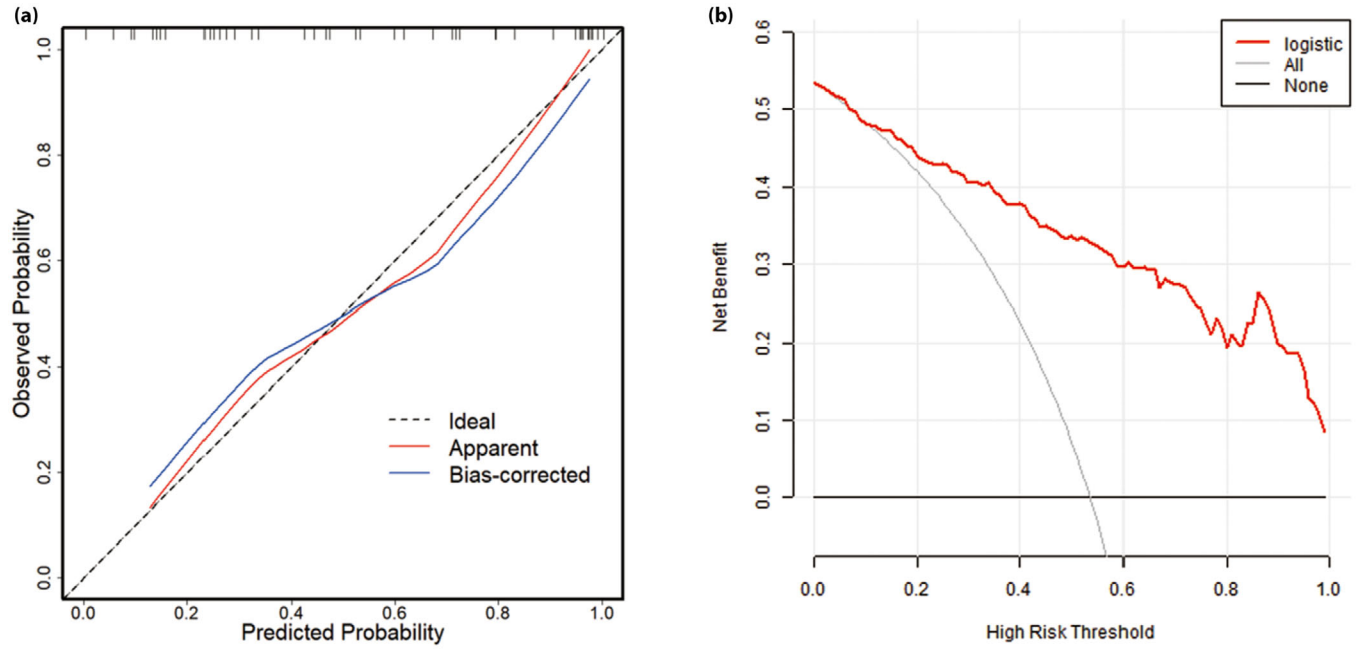

Figure 3 | (a) The calibration curve of the model. (b) The DCA curve of the model.

found significantly lower levels of BVR-A protein in patients with type 2 diabetes mellitus, which was associated with more severe dysglycemia and inflammation[33]. There is a lack of validated clinical studies to demonstrate whether reduced BVR-A levels are potentially correlated to the development of MCI in patients with type 2 diabetes mellitus. Our study found that plasma BVR-A levels were significantly lower in the T2DM-MCI group compared to controls ($P < 0.001$). Logistic regression analysis confirms that a decrease in BVR-A is significantly associated with the occurrence of MCI in patients with type 2 diabetes mellitus. We also found that BVR-A is more advantageous than HOMA-IR in predicting MCI in these patients. However, the specific mechanisms by which reduced BVR-A leads to type 2 diabetes mellitus and MCI require further investigation.

A large cohort study showed that patients with diabetes for more than 5 years have a 1.59 times greater risk of cognitive impairment than those with a shorter duration of diabetes[34]. Age plays a significant role in cognitive decline; as people age, the likelihood of experiencing cognitive impairment increases[35]. Additionally, studies have found that higher education levels are negatively associated with the prevalence of dementia[36]. This may be because more educated individuals have a stronger cognitive reserve (CR), which reduces the risk of cognitive decline and dementia, and delays clinical expression[37,38]. IR may mediate the development of cognitive impairment by affecting glucose metabolism in the brain[7]. However, higher education levels can help compensate for this deficiency, thereby delaying the onset of cognitive impairment[39]. Consistent with previous studies, our study found that the T2DM-MCI group was older, had a longer disease duration, and had fewer years of education than the control group ($P < 0.01$). Logistic regression analysis confirmed that the duration of diabetes mellitus is significantly associated with the development of MCI in patients with type 2 diabetes mellitus ($P < 0.001$). However, the effects of age and education level on cognitive function were not significant. This may be due to our small sample size and the influence of other factors selected first in the stepwise logistic regression, which may have obscured the effects of age and education. Therefore, further study the influence of age and education level in MCI by expanding the sample size.

The findings of this study also indicated that the development of MCI in patients with type 2 diabetes mellitus may be associated with reduced levels of AST and ALT. An 8-year follow-up study of 1,581 older adults found that reduced levels of ALT levels were linked to increased deposition of amyloid-beta peptides, decreased brain glucose metabolism, and more severe brain atrophy[40]. Another follow-up study also found that reduced AST and ALT were strongly associated with an increased risk of dementia, with ALT being more significant[41]. One possible explanation for this phenomenon is that ALT and AST promote the synthesis of glutamate, a key excitatory neurotransmitter, and low levels of ALT or AST may lead to impaired memory[40,42]. However, the specific mechanisms by which AST and ALT influence the onset of cognitive function in patients with type 2 diabetes mellitus need to be further exploration.

Most currently available prediction models are based on the general population or older patients with type 2 diabetes mellitus[43,44], using predictors such as gender, age, education level, and marital status. This study developed a predictive model based on IR, a potential pathogenesis of diabetes and cognitive impairment. The ROC curve generated from this model, along with a C-index of 0.863 from internal validation, indicates good prediction accuracy and discrimination. The calibration curve and DCA curve also demonstrated that the nomogram prediction model fits well and has good clinical utility, confirming the reliability of model established based on BVR-A and HOMA-IR. Moreover, the results of the 5-fold cross-validation also confirmed the good generalization ability of our model on the new data.

This study is the first to reveal that the development of MCI in patients with type 2 diabetes mellitus is closely related to the reduction of BVR-A. These findings provide new insights and ideas for predicting and treating this disease. Current findings show that atorvastatin can exert neuroprotective effects by modulating BVR-A in the brains of aged canines and human neuroblastoma cells[45]. In preclinical models of heart disease, BVR-A-based peptides have been demonstrated to prevent cardiomyocyte cell death and preserve myocardial contractility[46]. Therefore, further study and development of peptides that activate BVR-A kinase and reductase for treating neurodegenerative diseases is of significant research importance.

This study also has some limitations: (1) The limited sample size of this study may not fully reflect the predictive value of BVR-A, HOMA-IR, and the duration of diabetes on the occurrence of cognitive dysfunction; (2) As a cross-sectional study, it lacks a healthy control group, which cannot directly prove a causal relationship between low BVR-A and type 2 diabetes mellitus MCI. Further long-term follow-up of cases is needed in the future; (3) Only internal validation was employed to evaluate the discrimination, consistency, and clinical effects of the prediction model. External validation is needed to assess the reliability of the model. Furthermore, the molecular mechanisms by which BVR-A damage results in insulin resistance, metabolic disorders, and cognitive dysfunction require further investigation.

CONCLUSION

In this study, the following findings were found: (1) In patients with type 2 diabetes mellitus, BVR-A and HOMA-IR are significantly associated with the development of MCI; (2) Among the indicators studied, BVR-A had the highest efficiency in diagnosing MCI, making it useful for screening MCI in type 2 diabetes mellitus patients; (3) The nomogram is an effective tool for the clinical assessment of MCI risks, aiding clinicians in making evidence-based decisions regarding the prevention of MCI in type 2 diabetes mellitus patients.

Although this study provides exciting findings, a larger sample size is needed to further confirm its effectiveness in early identification and prediction of MCI in type 2 diabetes mellitus patients to be truly applied in clinical practice.

DISCLOSURE

The authors have no conflicts of interest to disclose.

Approval of the research protocol: The study was approved by the Medical Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (Ethics batch number: XYFY2023-KL459-01). Approval date: November 27th, 2023.

Informed consent: All participants provided written informed consent.

Registry and the registration no. of the study/trial: This project was registered online with Chinese Clinical Trial Registry. Registration Number: ChiCTR2300078678. Approval date of registry: December 14th, 2023.

Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Flowchart of our study.

Figure S2 | The ROC curve of the training set and test sets.

Figure S3 | ROC curves analysis with 5-fold cross-validation shows the diagnostic performance of constructed nomogram model.