

Risk Prediction Models for Mild Cognitive Impairment in Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Objective: This study aimed to systematically review the existing research on risk prediction models for mild cognitive impairment in patients with type 2 diabetes mellitus and to analyze the predictive performance of these models.

Methods: A systematic computerized search was conducted for studies published in CNKI, Wanfang, VIP, CBM, PubMed, Embase, Cochrane Library, CINAHL, and Web of Science regarding risk prediction models for mild cognitive impairment in patients with type 2 diabetes mellitus, covering the period the inception of the databases through November 10, 2024. Two independent reviewers performed literature screening and data extraction based on predefined inclusion and exclusion criteria. The risk of bias and the applicability of the included studies were subsequently evaluated using the Risk of Bias Assessment Tool for Prediction Models. A meta-analysis of the predictive performance of the models was performed using Stata 17.0 software.

Results: A total of 12 studies and 17 prediction models were included in the analysis, with the area under the receiver operating characteristic curve (AUC) for the models ranging from 0.743 to 0.987. All studies were assessed to be at high risk of bias, particularly concerning the issue of underreporting in the area of data analysis. The combined AUC value of the six validated models was 0.854, indicating that these models exhibited favorable predictive performance. The multivariate models consistently identified age, education, disease duration, depression, and glycosylated hemoglobin level as independent predictors.

Conclusion: The development of risk prediction models for mild cognitive impairment in patients with type 2 diabetes mellitus is still in its infancy. In order to develop more accurate and practical risk prediction models for mild cognitive impairment in patients with type 2 diabetes mellitus, future studies must rely on large-sample, multicenter prospective cohorts and adhere to rigorous study designs.

Keywords: type 2 diabetes mellitus, cognitive impairment, prediction model, systematic review, meta-analysis

Introduction

Diabetes mellitus, particularly type 2 diabetes mellitus (T2DM), has emerged as a significant public health concern on a global scale. The latest data from the International Diabetes Federation (IDF) indicate that the number of individuals with diabetes worldwide has reached an alarming 537 million,¹ with China accounting for the largest number of patients at 140 million. T2DM is a chronic metabolic disease that accounts for over 90% of all diabetes cases. It is characterized by insulin resistance and impaired insulin secretion, which result in persistently elevated blood glucose levels.² Prolonged hyperglycemia can cause damage to blood vessels and nerves, leading to a variety of complications, including cardiovascular disease, nephropathy, retinopathy, and foot problems. Of particular concern is the association with cognitive impairment, which not only affects the quality of daily life but also shortens life expectancy.^{3–5} Mild Cognitive Impairment (MCI) represents a significant health concern for individuals with diabetes. MCI is defined as a gradual decline in cognitive function that does not yet meet the criteria for dementia. However, it is a condition that warrants attention and monitoring. The symptoms of MCI manifest as memory loss, diminished executive function, and

difficulties with concentration. However, these symptoms typically do not significantly impair the individual's ability to perform in daily activities.⁶ As a critical transitional phase between healthy aging and dementia, MCI presents a valuable opportunity for early detection and intervention. It is regarded as a crucial target for the slowing of cognitive decline and the prevention or postponement of dementia development.⁷ A growing body of evidence indicates that individuals with T2DM are at a significantly elevated risk of developing MCI, with a reported prevalence of up to 45%. This heightened risk is associated with an increased likelihood of progression to dementia, which represents a substantial burden on individuals, families, and the healthcare system.^{8–11}

In light of the strong correlation between T2DM and MCI, as well as the significant impact that MCI can have on both individuals and the healthcare system, it is crucial to identify and manage the risk of MCI in patients with T2DM. Although the association between T2DM and MCI has been extensively studied, a comprehensive evaluation of MCI risk prediction models specifically for patients with T2DM is lacking. This study presents the first systematic review and analysis of existing risk prediction models for MCI in patients with T2DM. The aim is to assess the predictive performance and applicability of these models, as well as to explore strategies for optimizing them to improve the early identification of MCI risk and contribute to the development of effective prevention and intervention strategies. The findings of this study are expected to provide a solid scientific basis for managing the risk of MCI in patients with T2DM. In the long term, these efforts are anticipated to improve patient prognosis, refine treatment options, reduce healthcare costs, and alleviate the economic and social burdens faced by patients and their families, yielding far-reaching implications for clinical practice and public health policy.

Methods

Establishment of the Question

This study employed the PICOTS framework, as recommended by the Cochrane Prognostic Methodology Group, to construct evidence-based questions.¹² The study population (P) comprised of patients with T2DM. The intervention (I) evaluated was the risk prediction models for MCI. There was no comparison (C). The outcome (O) measured was the occurrence of MCI during the progression of the disease. The timing of model use (T) involved real-time measurements throughout the course of the disease, while the setting (S) included both hospital or community environments. In this context, T refers to the real-time measurement of T2DM patients, and S denotes the scenarios in which the model is applied, encompassing both hospital and community settings.

Search Strategy

A comprehensive literature search on MCI risk prediction models for patients with T2DM was conducted using several databases, including CNKI, Wanfang, VIP, CBM, PubMed, Embase, Cochrane Library, CINAHL, and Web of Science. The search was restricted to literature published up to November 10, 2024. The search terms and expressions used for both Chinese and English databases are detailed in [Appendix S1](#).

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) The study subjects were patients with T2DM;² (2) The study focus on the construction and/or validation of risk prediction models for MCI in T2DM patients; (3) The study design was either cross-sectional, case-control, or cohort.

The exclusion criteria were as follows: (1) Studies that were genetic, cellular, or pharmacological in nature; (2) Studies that were research protocols; (3) Studies for which the full text could not be accessed.

Literature Screening and Data Extraction

The literature was organized using EndNote 20, and two researchers (LT and ZY) screened the literature based on the title, abstract, and full text according to the established inclusion and exclusion criteria. In the event of a discrepancy, a third researcher (XZR) was consulted for resolution. Standardized forms were created, and information was extracted in accordance with the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies

(CHARMS).¹³ The data extraction was conducted independently by two researchers (LT and QY), and any discrepancy were discussed with the third researcher (XZR). The extraction process was carried out in two stages. The first stage involved gathering basic information, which included the following: the first author, year of publication, country, type of study, study population, sample source, and definitions of endpoints. The second stage concentrated on model-related information, encompassing the following: the modeling method, number of candidate variables, treatment method for continuous variables, model performance, model validation, method for handling missing data, and predictors.

Literature Quality Assessment

In this study, both the Agency for Healthcare Research and Quality (AHRQ) and the Prediction Model Risk of Bias Assessment Tool (PROBAST) were employed to assess the quality of the literature and the potential for bias in the models.^{14,15} The AHRQ was utilized to evaluate the risk of bias in the criteria for cross-sectional studies, which consisted of 11 items answered with “yes”, “no”, or “unclear”. A score of 1 was assigned for “yes”, while a score of 0 was given for “unclear or no”. A total score of 8 to 11 was deemed indicative of high quality, a score of 4 to 7 was considered indicative of moderate quality, and a score of 0 to 3 was regarded as indicative of low quality (Appendix S2). The PROBAST tool was used to assess the risk of bias, which includes four parts: study participants, predictors, outcomes, and statistical analysis.¹⁵ It consists of 20 key questions that are answered with “yes or probably yes”, “no or probably no”, or “unclear”. If all questions receive a response of “yes or probably yes”, the risk is classified as low. Conversely, if any question is answered with “no or probably no”, the risk is classified as high. If some questions marked as “unclear” while all other questions are answered with “yes or probably yes”, the risk is deemed “unclear”. The final assessment of risk of bias and applicability is categorized as low, high, or unclear. (Appendix S3). Two researchers independently evaluated the quality of the literature, the risk of bias in the models, and the applicability risk. In the event of disagreement, a discussion with a third researcher was held.

Statistical Analysis

A meta-analysis of the area under the receiver operating characteristic curve (AUC) for the predictive models was conducted using Stata 17.0 software. The heterogeneity index I^2 and the Q-test were employed to assess the heterogeneity of the included models. An I^2 value $\leq 25\%$ indicated low heterogeneity, $25\% \leq I^2 < 50\%$ indicated moderate heterogeneity, and $I^2 \geq 50\%$ indicated high heterogeneity. Based on the extent of heterogeneity observed in the analysis results, either a random effects model or a fixed effects model was selected. Subgroup analysis was performed to identify the sources of substantial heterogeneity. Sensitivity analysis was conducted to evaluate the robustness of the results. The Egger’s test was utilized to assess the potential for publication bias, with a P -value of less than 0.05 generally accepted as indicative of possible publication bias.

Results

Literature Screening Process and Results

A search of the database yielded 439 pieces of literature, which were subsequently subjected to a screening process. Of these, 12 pieces were ultimately deemed suitable for inclusion (Figure 1).

Basic Characteristics of the Included Literature

All twelve papers were published between 2023 and 2024, comprising five in Chinese and seven in English. Each study utilized a cross-sectional design and was conducted during the hospitalization of patients with T2DM, with two of the studies being multicenter investigations. Among the publications, two were dissertations and ten were journal articles (Table 1).

Establishment of the Models

The present study encompasses twelve papers, comprising a total of 17 predictive models. Of these, eleven studies constructed models based on logistic regression analysis.^{16–23,25–27} The total number of T2DM patients included in the

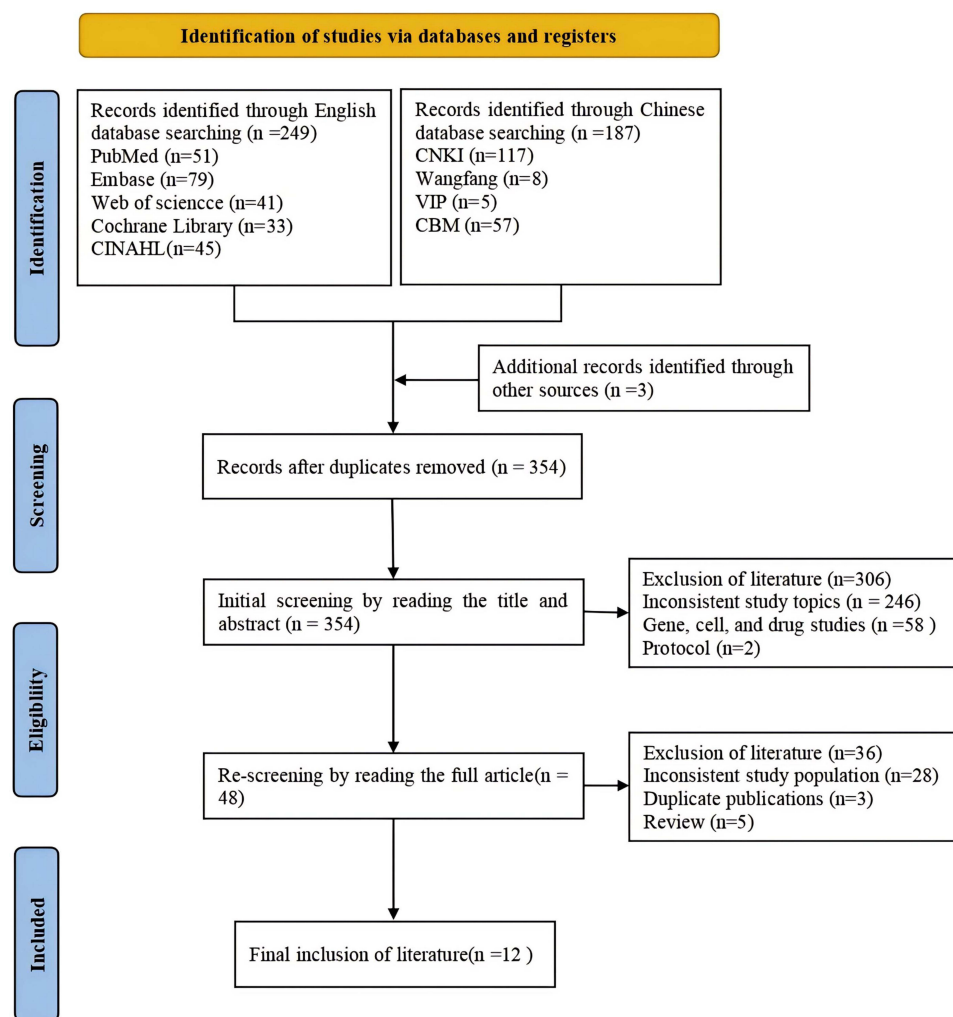


Figure 1 Flow chart of literature screening.

studies ranged from 124 to 1319, with the incidence of MCI varying from 6.10% to 60.78%. Five studies reported missing data and treatment methods.^{17,19,22–24} Of these, three studies excluded missing data directly,^{17,20,23} while two studies employed multiple interpolation or a combination of methods to process the missing data.^{19,24} (Table 2).

Performance of the Model and Predictors

The area under the curve (AUC) of the subjects' operating characteristics was reported to be range from 0.743 to 0.987 across twelve studies. Furthermore, all models exhibited favorable predictive performance, with an AUC exceeding 0.70. Five studies employed both calibration curve plots and Hosmer-Lemeshow (H-L) goodness-of-fit tests to assess the calibration of the models.^{18,20,23,26,27} Four studies utilized either calibration graphs or H-L goodness-of-fit tests to evaluate model calibration.^{17,21,22,25} Nine studies conducted internal validation of the models.^{17,18,20–23,25–27} Two studies conducted external validation of the models.^{26,27} (Table 2). Ultimately, 17 models reported between 3 and 8 predictors, with age, education, duration of T2DM, depression, and hemoglobin level (HbA1c) appearing with greater frequency (Table 3).

Literature Quality Assessment

A total of twelve studies were included in this study. The AHRQ evaluation revealed that four of these papers exhibited a high level of quality,^{17,19,22,23} while the remaining eight studies demonstrated a moderate level of quality.^{16,18,20,21,24–27}

Table I Basic Characteristics of the Included Literature

First Author (Year)	Country	Type of Study	Populations	Diagnostic Criteria for T2DM	Sample Sources	Assessment Tools
Zhang (2023) ¹⁶	China	Cross-sectional study	T2DM patients	①	Department of Endocrinology, Nanjing Drum Tower Hospital	MoCA
Maimaituerxun (2023) ¹⁷	China	Cross-sectional study	T2DM patients	③	Department of Endocrinology, Xiangya Hospital	MMSE
Zhang (2023) ¹⁸	China	Cross-sectional study	T2DM patients	④	A Grade 3A hospital in Gansu Province	MMSE
Wang (2023) ¹⁹	China	Cross-sectional study	T2DM patients	①	Department of Endocrinology, one of the three tertiary hospitals in Tianjin, China	MoCA
Jiang (2024) ²⁰	China	Cross-sectional study	Older T2DM patients	③	Department of Endocrinology, Qilu Hospital of Shandong University	MoCA
Zhao (2024) ²¹	China	Cross-sectional study	Older T2DM patients	—	Beijing Chaoyang Hospital, Capital Medical University	MoCA
Kang (2024) ²²	Korea	Cross-sectional study	T2DM patients	—	Gyeongsang National University Hospital Diabetes Clinic	MoCA
Ding (2024) ²³	China	Cross-sectional study	T2DM patients	⑤	Department of Endocrinology, Nanjing Drum Tower Hospital	MoCA
Zhang (2024) ²⁴	China	Cross-sectional study	Older T2DM patients	②	Department of Endocrinology, Yantai Penglai People's Hospital	MoCA
Liu (2024) ²⁵	China	Cross-sectional study	T2DM patients	①	Department of Endocrinology, Yanan University Affiliated Hospital and Department of General Internal Medicine, Dongguan Branch Hospital	MMSE
Yu (2024) ²⁶	China	Cross-sectional study	Older T2DM patients	③	Department of Geriatrics and Endocrinology of the First Affiliated Hospital, Jinzhou Medical University	MoCA
Yang (2024) ²⁷	China	Cross-sectional study	Middle aged and older T2DM patients	①	Department of Endocrinology, Nanjing Drum Tower Hospital	MoCA

Notes: MoCA (Montreal Cognitive Assessment) indicates Montreal Cognitive Assessment; MMSE (Mini-Mental Status Examination) indicates Brief Mental Status. ①Guideline for the prevention and treatment of type 2 diabetes mellitus in China (2020 edition); ②Guideline for the management of diabetes mellitus in the elderly in China (2021 edition); ③Clinical guidelines for prevention and treatment of type 2 diabetes mellitus in the elderly in China (2022 edition); ④American Diabetes Association: Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes (2022 edition); ⑤American Diabetes Association: Classification and Diagnosis of Diabetes (2015 edition).

However, the PROBAST evaluation indicated that all the literature was at a high risk of bias. In terms of outcome areas, only three study was classified as low risk,^{17,26,27} while the others were classified as unclear. This classification was primarily due to the lack of clarity regarding the risk of bias, as the researchers did not provide sufficient information on whether the outcome assessors were blinded. Regarding the domain of data analysis, all studies were identified as being at high risk of bias. The number of events per independent variable in all studies had an events per variable (EPV) ratio of less than 20, indicating an inadequate sample size. Additionally, six studies converted continuous variables into

Table 2 Establishment of a Risk Prediction Model for MCI in Patients with T2DM

Study	Methods	Candidate Variables (Number)	EPV	Screening VARIABLE Methods	Continuous Variable Handling Methods	T2DM Patients (Cases)	MCI Patients (Cases)	Model Performance		Model Validation Methods
						D/V	D/V	AUC (95% CI)	Calibration Method	
Zhang (2023) ¹⁶	LR, DT	35	11.97	Model 1: single-factor, multi-factor analysis Model 2: lasso analysis	Maintain continuity	1284/—	419/—	D: 0.763 (0.737, 0.790) D: 0.743 (0.715, 0.771)	—	—
Maimaitiuerxun (2023) ¹⁷	LR	26	6.50	Single-factor, multi-factor analysis	Transfer to categorical variables	496/—	169/—	V: 0.849 (0.815, 0.883)	Calibration curve	Internal validation (bootstrap)
Zhang (2023) ¹⁸	LR	23	5.52	Single-factor, multi-factor analysis	Maintain continuity	284/142	127/66	D: 0.859 (0.816, 0.902) V: 0.819 (0.749, 0.888)	Calibration curve H-L: P=0.791/ 0.678	Internal validation (randomized splitting)
Wang (2023) ¹⁹	LR, ANN, SVM	40	4.63	Single-factor, multi-factor analysis	Transfer to categorical variables	357/144	185/80	D: 0.919 (0.886, 0.945) V: 0.915 (0.857, 0.955) D: 0.908 (0.873, 0.936) V: 0.917 (0.859, 0.956) D: 0.920 (0.887, 0.946) V: 0.916 (0.858, 0.956)	—	Internal validation (randomized splitting)
Jiang (2024) ²⁰	LR	16	11.63	Single-factor, multi-factor analysis	Transfer to categorical variables	306/—	186/—	V: 0.893 (0.856, 0.930)	Calibration curve H-L: P=0.501	Internal validation (bootstrap)
Zhao (2024) ²¹	LR	14	4.43	Single-factor, multi-factor analysis	Transfer to categorical variables	480/—	62/—	D: 0.912 (0.874, 0.950)	H-L: P=0.855	—
Kang (2024) ²²	LR	18	2.17	Single-factor, multi-factor analysis	Maintain continuity	124/—	39/—	D: 0.832 (-)	Calibration curve	Internal validation (bootstrap)
Ding (2024) ²³	LR	23	12.39	Single-factor, multi-factor analysis	Maintain continuity	880/376	285/127	D: 0.751 (0.717, 0.784) V: 0.776 (0.727, 0.824)	Calibration curve H-L: P=0.936/ 0.153	Internal validation (randomized splitting)

Zhang (2024) ²⁴	BPNN, RF, XGBoost	25	18.40	Single-factor, multi-factor analysis	Maintain continuity	923/396	460/197	V: 0.746 (0.698, 0.794) V: 0.755 (0.708, 0.802) V: 0.756 (0.709, 0.803)	—	Internal validation (ten-fold cross)
Liu (2024) ²⁵	LR	26	2.69	Single-factor, multi-factor analysis	Maintain continuity	133/—	70/—	D: 0.853 (0.788, 0.919)	H-L: P=0.698	—
Yu (2024) ²⁶	LR	18	6.44	Lasso	Transfer to categorical variables	414/141	116/38	D: 0.914 (0.887, 0.941) V: 0.859 (0.788, 0.931)	Calibration curve H-L: P=0.698	Internal validation (bootstrap) external validation (temporal validation)
Yang (2024) ²⁷	LR	18	1.33	Lasso	Transfer to categorical variables	298/128	24/2	D: 0.969 (-) V: 0.987 (-)	Calibration curve H-L: P=0.938/ 0.657	Internal validation (bootstrap) External validation (temporal validation)

Notes: T2DM indicates type 2 diabetes mellitus; MCI indicates mild cognitive impairment; D indicates modeling set; V indicates validation set; EPV (events per variable) indicates the number of events per independent variable; AUC indicates area under the ROC curve; CI indicates 95% confidence interval; H-L indicates Hosmer-Lemeshow goodness-of-fit test; LR denotes logistic regression; DT denotes decision trees; ANN denotes artificial neural network; SVM denotes support vector machines; BPNN denotes back propagation neural network; XGBoost denotes extreme gradient enhancement; RF denotes random forest; — denotes missing information.

Table 3 Predictors of MCI Risk Prediction Model in T2DM Patients

Study	Predictors
Zhang (2023) ¹⁵	Model 1 (6 predictors): age, years of education, peripheral neuropathy, abnormal bone metabolism, lower extremity macrovascular disease, HOMA-IS
Maimaituerxun (2023) ¹⁶	Model 2 (3 predictors): age, years of education, HOMA-IS
Zhang (2023) ¹⁷	(7 predictors): age, marital status, household income, duration of T2DM, DR, anxiety, depression
Wang (2023) ¹⁸	(6 predictors): literacy, duration of T2DM, hypertension, DR, HbA1c, FPG
	Model 1 (8 predictors): age, education, reading, glucose control level, homocysteine, peripheral neuropathy, depression, social support
	Model 2 (7 predictors): reading, economic income, educational attainment, social support, anxiety, exercise, blood glucose control level
	Model 3 (7 predictors): age, education, economic income, exercise, homocysteine, depression, social support
Jiang (2024) ¹⁹	(6 predictors): educational attainment, duration of T2DM, HbA1c, walking speed, sedentary time, depression
Zhao (2024) ²⁰	(4 predictors): age, infrequent exercise, lack of sleep, depression
Kang (2024) ²¹	(3 predictors): age, education, cardiac vagal function
Ding (2024) ²²	(5 predictors): age, education, HbA1c, self-reported history of severe hypoglycemia, microvascular disease
Zhang (2024) ²³	(4 predictors): age, duration of T2DM, FPG, diastolic blood pressure
Liu (2024) ²⁴	(3 predictors): duration of education, duration of T2DM, FIB
Yu (2024) ²⁵	(7 predictors): age, physical activity, smoking, living alone, HbA1c, depression, social support
Yang (2024) ²⁶	(7 predictors): smoking, duration of T2DM, history of hypoglycemia, insulin 30 minutes after meals, TC, anxiety, social support

Notes: T2DM, type 2 diabetes mellitus; DR, diabetic retinopathy; HbA1c, glycosylated hemoglobin; FPG, fasting glucose; FIB, fibrinogen level; HOMA-IS, insulin sensitivity index; TC, total cholesterol.

categorical variables for analysis.^{17,19–21,26,27} Three studies excluded missing data outright.^{17,22,23} Only three of the 17 models employed Lasso analysis to screen predictors,^{16,26,27} while all utilized single-factor analysis. Notably, none of the studies reported any complexity in the data. Furthermore, only three studies did not provide information on the model calibration,^{16,19,24} and two studies assessed calibration using only H-L goodness-of-fit tests.^{21,25} Additionally, three studies did not indicate whether the model was internally validated,^{16,21,25} and three studies used randomized split validation for internal validation.^{18,19,23} The results of the overall suitability evaluation of the model indicated that all studies were at low risk regarding suitability (Table 4).

Table 4 Evaluation of Risk of Bias and Applicability of the Included Literature

Study	ROB				Applicability			Overall	
	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	ROB	Applicability
Zhang (2023) ¹⁶	+	+	?	–	+	+	+	–	+
Maimaituerxun (2023) ¹⁷	+	+	+	–	+	+	+	–	+
Zhang (2023) ¹⁸	+	+	?	–	+	+	+	–	+
Wang (2023) ¹⁹	+	+	?	–	+	+	+	–	+
Jiang (2024) ²⁰	+	+	?	–	+	+	+	–	+
Zhao (2024) ²¹	+	+	?	–	+	+	+	–	+
Kang (2024) ²²	+	+	?	–	+	+	+	–	+
Ding (2024) ²³	+	+	?	–	+	+	+	–	+
Zhang (2024) ²⁴	+	+	?	–	+	+	+	–	+
Liu (2024) ²⁵	+	+	?	–	+	+	+	–	+
Yu (2024) ²⁶	+	+	+	–	+	+	+	–	+
Yang (2024) ²⁷	+	+	+	–	+	+	+	–	+

Notes: ROB indicates risk of bias; – indicates high risk of bias/low applicability; + indicates low risk of bias/high applicability; ? Indicates unclear.

Meta-Analysis Results

Some of the predictive models included in the literature lacked validation or provided insufficient data regarding the area under the curve (AUC). Ultimately, only six studies were included in the meta-analysis.^{17–20,23,26} One of these studies developed and validated multiple models using various modeling approaches,¹⁹ but all were based on the same sample. Consequently, only one model developed using logistic regression was included in the meta-analysis. The analysis was

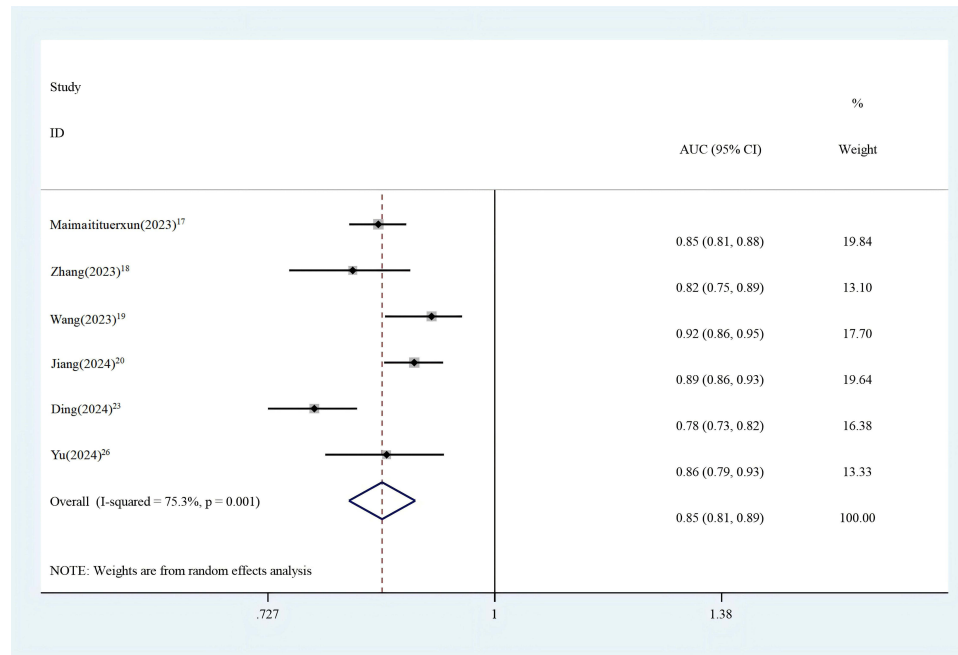


Figure 2 Forest plot of AUC Meta-analysis of MCI prediction model in T2DM patients.

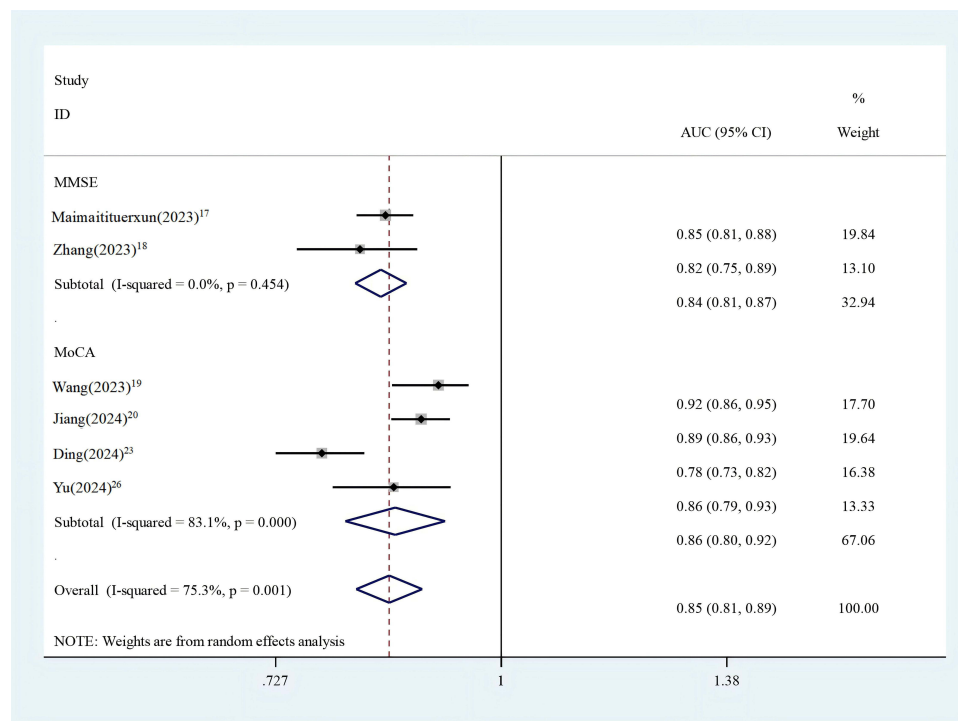


Figure 3 AUC subgroup analysis plot of the MCI prediction model in T2DM patients.

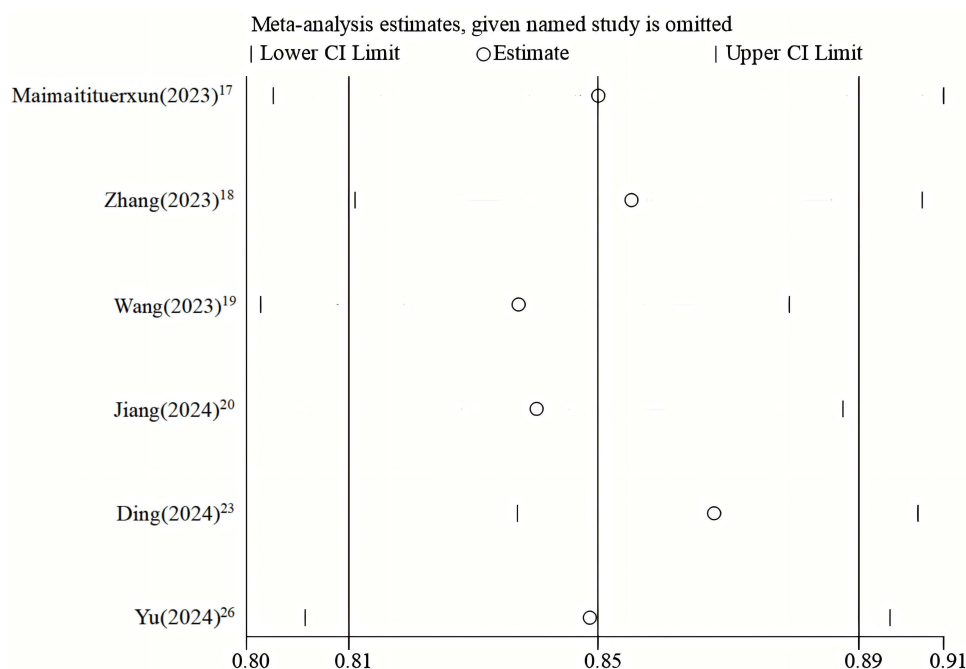


Figure 4 AUC sensitivity analysis of MCI prediction model for T2DM patients.

conducted using a random-effects model, yielding a combined AUC value of 0.854 (95% *CI*: 0.815–0.894) and a heterogeneity test I^2 of 75.3% ($P = 0.001$). These results indicate a significant degree of heterogeneity among the studies (Figure 2). To identify the source of the observed heterogeneity, further subgroup analyses were conducted based on the type of assessment tool. The results of the analysis demonstrated that the I^2 of the heterogeneity test for the MMSE group was 0.0% ($P = 0.454$), indicating the absence of significant heterogeneity among the studies. In contrast, the I^2 of the heterogeneity test for the MoCA group was 83.1% ($P < 0.001$), indicating the presence of significant heterogeneity. The observed heterogeneity suggests that the type of assessment tool was not a source of variability in the analyzed results (Figure 3). Furthermore, the combined results of both subgroups exhibited a statistically significant outcome, indicating that the MCI prediction models for T2DM patients in the study were effectively differentiated, regardless of whether the MMSE or MoCA assessment tools were utilized. Upon exclusion of individual studies from the sensitivity analysis, the results remained consistent with the original combined results, indicating a certain degree of robustness (Figure 4). The results of Egger's test demonstrated the absence of publication bias ($P=0.462 > 0.05$).

Discussion

MCI Risk Prediction Models for T2DM Patients are Still in the Developmental Phase

In recent years, prediction models for the risk of MCI in patients with T2DM have increasingly become a focus point of research within the academic community, both domestically and internationally. This study presents a comprehensive analysis of 17 prediction models derived from 12 papers, all of which demonstrated high predictive efficacy ($AUC > 0.7$). Among these, six validated models exhibited a combined AUC value of 0.854. However, significant heterogeneity was observed in the analysis results. It was noted that the Mini-Mental State Examination (MMSE) exhibits high sensitivity for diagnosing dementia; however, its specificity and sensitivity as a screening tool for MCI are limited and influenced by the educational level of the subjects.²⁸ In contrast, the Montreal Cognitive Assessment (MoCA) demonstrates enhanced sensitivity and specificity, even identifying patients with MCI who score within the normal range on the MMSE.⁹ This suggests that the choice of different MCI assessment instruments may impact the outcomes. Nevertheless, the subgroup analysis in this study did not identify the assessment tool as a source of heterogeneity, which may be attributed to the

limited number of models included in the meta-analysis and the small number of studies in each subgroup. Consequently, further investigation into whether different assessment tools affect the predictive performance of models is warranted.

Despite the improved predictive efficacy of the models, shortcomings in study design and statistical methodology resulted in a heightened risk of bias across all studies. Regarding the outcome domain, nine studies did not report blinding in outcome determination,^{16,18–25} leaving the risk of bias remains uncertain. The lack of blinding not only compromises the internal validity of the studies but also undermines the objectivity and generalizability of the results. Future studies should provide comprehensive details regarding the blinded evaluations of predictor indicators. This includes ensuring mutual blinding between predictor and outcome indicators, as well as minimizing the potential for subjective judgments among predictors. In terms of data analysis, all studies were found to be at high risk of bias. The EPV for each study was less than 20, indicating that the sample size was insufficient. This limitation could easily lead to overfitting of the model, thereby affecting prediction accuracy. Future studies should aim to increase the sample size, utilize external data for validation, or adopt statistical methods that are appropriate for small samples. Additionally, three studies did not validate their models,^{16,21,25} and three studies employed random splitting for model validation,^{18,19,23} which may increase the risk of overfitting and reduce the predictive accuracy of the models. Internal validation evaluates the consistency of a model's performance. Common methods for internal validation include random split validation, K-fold cross-validation, and bootstrap methods. Future researchers should consider factors such as sample size, model complexity, and intended application when selecting appropriate internal validation techniques. External validation reflects the generalizability of the model. While it does not directly validate internal validity, external validation is essential for confirming the model's generalizability and extrapolation. This process necessitates validation with datasets that differ from the original study, which may be either temporally and geographically independent or entirely distinct, in order to provide reliable estimates of the model's performance on other datasets. Three studies excluded missing data directly,^{17,22,23} and inappropriate treatment of missing data may lead to overestimation of model discrimination. Researchers are advised to select suitable processing strategies, such as multiple imputation, which has been shown to outperform other methods in terms of bias and precision, depending on the characteristics of the data and the objectives of the research. Six studies converted continuous variables into categorical variables,^{17,19–21,26,27} and nine studies used single-factor analysis to screen predictors,^{16,18–25} which may have led to the omission of significant predictors. In conclusion, the research and development of MCI risk prediction models for patients with T2DM is an ongoing process that necessitates continuous optimization and updates to align with advancements in medical technology and the evolving needs of clinical practice.

Analysis of Risk Predictors for MCI in Patients with T2DM

The predictive models in this study identified several common predictors, with high-frequency predictors proving critical for the rapid identification of individuals at higher risk of MCI in patients with T2DM. The high-frequency predictors most frequently identified by the models included age, education, duration of T2DM, depression, and glycosylated hemoglobin (HbA1c). Age is an irreversible risk factor that significantly impacts the development of MCI in patients with T2DM. Cognitive decline occurs at a rate approximately 50% faster in elderly patients with T2DM compared to the general elderly population.²⁹ This phenomenon may be attributed to the increased likelihood of older patients with T2DM accumulating diabetes-related risk factors, such as chronic poor glycemic control, insulin resistance, and vascular complications, which accelerate cognitive decline.^{30,31} Additionally, degenerative changes in the brain associated with aging, such as a reduction in neural cells and diminished nerve conduction velocity, interact with diabetic pathological processes, potentially exacerbating cognitive impairment.^{32,33} Furthermore, a high level of education served as a protective factor for cognitive function in patients with T2DM. Higher educational attainment is closely linked to an enhanced cognitive reserve, which improves an individual's health awareness and disease self-management abilities, effectively delaying the external manifestations of cognitive decline.^{30,32,33} Furthermore, disease duration is the most significant risk factor for the emergence of MCI in patients with T2DM. A substantial increase in the risk of MCI has been demonstrated with the prolongation of T2DM disease duration.³⁴ This may be associated with chronic ischemia and hypoxia of brain tissue due to long-term metabolic disorders, as well as a notable increase in the levels of inhibitory neurotransmitters.^{33,35} Moreover, prolonged depressive disorders not only intensify psychological stress and impair brain structures through the action of stress hormones, such as cortisol, particularly affecting critical areas for cognition, such as the hippocampus; they may also alter patients' daily routines by reducing social

and physical activities, which diminishes cognitive stimulation in the brain and consequently impacts cognitive functions.²⁹ A negative correlation has been observed between HbA1c levels and cognitive function test scores. For each 1% increase in HbA1c levels in patients with T2DM, test scores associated with cognitive decline are significantly lower.^{29,34} This phenomenon may be attributed to chronic hyperglycemia and the accumulation of advanced glycosylation end-products (AGEs) resulting from it. AGEs exert toxic effects on nerve cells through multiple mechanisms, thereby accelerating cognitive decline.^{29,30,32,35–37} Additionally, the history of hypoglycemia, low-density lipoprotein cholesterol levels, and monthly household income were identified as risk factors for the development of MCI in patients with T2DM in this study. Future research should consider multiple dimensions when exploring potential predictors of MCI risk in patients with T2DM. Key factors to examine include age, educational background, disease duration, psychological status, and biochemical indicators. It is essential to emphasize that studies should not focus solely on the isolated effects of individual factors. Instead, researchers should investigate how these risk factors interact with one another and the cumulative impact of these interactions on the risk of MCI. This approach will improve the accuracy of predictions and assessments related to the potential risk of developing MCI in patients with T2DM. Consequently, it will facilitate the development of more precise prevention and intervention strategies for clinical practice.

Implications for Future Research

Given the limitations of current MCI risk prediction models for patients with T2DM related to study design and statistical methods, there is generally a high risk of bias. Existing models are mostly constructed based on cross-sectional studies, which may encounter several limitations, including unclear causality, restricted generalizability, an inability to capture dynamic changes, and sample size constraints. These factors can adversely affect the accuracy and utility of the models. In the future, prospective study designs should be implemented to investigate causality through multi-center, real-time data collection. Additionally, it is essential to validate the effectiveness of these models in clinical settings to ensure it can effectively support practical medical decision-making. Simultaneously, a mechanism for the dynamic updating of the model should be established to incorporate the latest medical research findings promptly, thereby maintaining the model's relevance and accuracy. Furthermore, establishing a data-sharing platform will facilitate data comparison and validation across studies, promoting standardization in data collection and reporting. This approach will enhance the generalizability and replicability of study results. The objective of predictive modeling is to provide a foundation for clinical interventions. Consequently, the development of these models should be closely integrated with early interventions to more effectively manage the risk of MCI in patients with T2DM. To achieve this goal, future research should promote interdisciplinary collaboration and integrate expert knowledge from various fields, including endocrinology, neurology, epidemiology, and statistics. Such collaboration will facilitate a more comprehensive study design and enable a deeper interpretation of results, ultimately enhancing the accuracy, generalizability, and applicability of predictive models in clinical settings. This approach will ensure that these models maximize their utility in real-world applications.

Limitations

In this systematic evaluation, we conducted a comprehensive review of MCI risk prediction models for patients with T2DM, but it is important to acknowledge several limitations that may impact our conclusions: (1) This study includes only literature published before November 2024, which means our findings may not reflect scientific developments that have occurred since then. As medical research continues to advance, we recognize that our existing conclusions may need to be updated in light of the latest findings. (2) Although we evaluated the overall predictive performance of the models, the variability in data processing methods across the original studies imposed limitations on our in-depth analyses at the predictor level. This variability may have hindered our comprehensive understanding of the models' predictive power. Future research should address these limitations by enhancing the consistency and comparability of studies through the standardization of data collection and analysis methods. (3) Most of the predictive models included in this study were based on research conducted within Chinese populations. This geographic bias may have constrained our insight into the variations in MCI risk prediction across different populations. Consequently, our conclusions may not fully represent the specifics of various populations worldwide. Despite these limitations, our systematic evaluation offers a valuable perspective on the current state of MCI risk prediction models in patients with T2DM. We recommend

that future studies expand the scope of literature screening, update the timeframe, harmonize statistical methods, and consider the representation of diverse ethnic groups to obtain more comprehensive and accurate findings.

Conclusion

The twelve papers and seventeen prediction models included in this study exhibited AUC values ranging from 0.743–0.987. The meta-analysis revealed a combined AUC value of 0.854, indicating that the models demonstrated a good overall performance; however, they generally presented a high risk of bias. It is recommended that future research involve prospective cohort studies with large sample sizes and multicenter designs to enhance the generalizability and applicability of the results. Additionally, researchers should adhere to the PROBAST assessment framework to optimize study design and follow the TRIPOD reporting statement. A comprehensive report on the model construction process should be provided to further refine the MCI risk prediction model for patients with T2DM, thereby offering a more robust scientific basis for clinical decision-making.^{15,38}

Data Sharing Statement

The data used and analyzed in this study can be obtained by contacting the corresponding author.

Ethics Approval and Informed Consent

This study is based on previously conducted research and does not include any new studies involving human participants or animals performed by any of the authors.

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Disclosure

All authors declare that they have no conflicts of interest.

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