

Effect of glycosylated hemoglobin on cognitive impairment related to White Matter Hyperintensity in non diabetes patients: A retrospective study

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Research Article

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Abstract

Background

White Matter Hyperintensity (WMH) are closely related to cognitive decline. Cognitive decline is a prolonged process preceding the onset of dementia, identifying relevant associated factors helps facilitate early intervention and long-term prognosis. This study aimed to explore the effect of glycated hemoglobin (HbA1c) and cognitive impairment in non diabetes people with WMH.

Methods

A total of 497 non diabetes patients with WMH were enrolled. Montreal Cognitive Assessment Basic (MoCA-BC) was used to assessed cognitive function. Fasting venous blood samples were collected to test HbA1c levels. WMH severity was graded using the Age-Related White Matter Changes Rating Scale (ARWMC). Univariate and multivariate logistic regression as well as restricted cubic spline (RCS) analyses were performed to explore the correlation between HbA1c and cognitive impairment. Receiver operating characteristic (ROC) curve analysis was used to assess the discriminative ability of HbA1c for cognitive impairment in non diabetes patients with WMH.

Results

HbA1c levels were significantly associated with cognitive impairment ($P < 0.001$), and this correlation remained significant after adjustment for multiple covariates ($P < 0.001$). A significant nonlinear correlation was also detected between HbA1c and cognitive impairment ($P < 0.001$). ROC analysis showed that HbA1c exhibited good discriminative ability for cognitive impairment, with an area under the curve (AUC) of 0.813 (95% CI: 0.773–0.853, $P < 0.001$).

Conclusions

HbA1c levels had warning value for cognitive impairment in non diabetes patients with WMH, and a nonlinear correlation exists between HbA1c and WMH-related cognitive impairment.

Introduction

Cognitive impairment and dementia affect tens of millions of people worldwide, bringing heavy distress to patients and caregivers and imposing a substantial economic burden on families and healthcare systems[1]. White matter hyperintensities (WMH) are hyperintense lesions detected on magnetic resonance imaging (MRI) and represent a common imaging marker of cerebral small vessel disease. WMH are closely associated with cognitive impairment[2]. As an important correlate of cognitive impairment related to cerebral small vessel disease, WMH are linked to reduced cognitive and executive

function in affected patients[3, 4]. Since cognitive decline is a progressive pathological process preceding clinical dementia, identifying modifiable associated factors is critical for implementing timely interventions and improving long-term outcomes[5]. Therefore, exploring factors correlated with WMH-related cognitive impairment is of great clinical significance.

Previous studies have demonstrated that elevated fasting blood glucose and systolic blood pressure are correlated with vascular cognitive impairment[6]. Among patients with type 2 diabetes, hypoglycemia history, longer diabetes duration, higher HbA1c levels and greater HbA1c variability are all associated with dementia[7]. HbA1c is formed when circulating glucose binds to hemoglobin in red blood cells. Given the 8–12 week lifespan of red blood cells, HbA1c reflects average blood glucose levels over the preceding two to three months[8]. It is widely used for diabetes diagnosis and evaluating diabetes-related complications[9]. Appropriate glycemic status is essential for maintaining brain health and preventing metabolic and cognitive dysfunction. Accumulating evidence indicates that HbA1c can also reflect glucose intolerance and is correlated with alterations in brain structure and function among normoglycemic individuals[10]. HbA1c is associated with cognitive decline in older adults[11] and presents a nonlinear correlation with cognitive impairment in patients with acute mild stroke[12]. HbA1c is also correlated with cognitive function in patients with type 2 diabetes[13]. Although HbA1c is well-established as a marker for long-term glycemic control in diabetes, its correlation with cognitive impairment in non diabetes patients with WMH remains poorly understood.

Clarifying factors associated with WMH-related cognitive impairment is conducive to slowing disease progression. Nevertheless, the correlation between HbA1c and WMH-related cognitive impairment has not been fully elucidated. Accordingly, this study explored the association between HbA1c and cognitive impairment in non diabetes patients with WMH, aiming to provide evidence for clinical practice.

Methods

Study Design and Participants

A total of 497 non diabetes patients with WMH confirmed by cranial MRI admitted to hospital from January 2024 to January 2026. All participants provided written informed consent. This study was conducted in accordance with the principles of the Declaration of Helsinki regarding informed consent and privacy protection. The study protocol was approved by the Ethics Committee .

Inclusion criteria: (1) WMH confirmed on cranial MRI; (2) No pre-existing mood disorders or psychiatric diseases, with complete clinical data; (3) Voluntary participation and signed informed consent; (4) Without diabetes. Exclusion criteria: (1) Complicated with cerebral hemorrhage or active bleeding; (2) History of other cerebrovascular diseases; (3) Acute myocardial infarction within 6 months prior to enrollment; (4) Malignant tumors, hyperthyroidism, tuberculosis, severe malnutrition, organ transplantation history, carbon monoxide poisoning, or severe organic diseases of the liver, kidney and

other vital organs; (5) Use of drugs that may affect cognitive function; (6) Epilepsy, brain tumor or encephalitis; (7) Poorly controlled hypertension.

Covariates and HbA1c Collection

We collected baseline information including gender, age, body mass index (BMI), educational level, and potential risk factors including smoking history, drinking history and coronary heart disease were recorded sequentially. Fasting venous blood samples were collected on the second day after admission to detect indicators including HbA1c, cholesterol, triglyceride (TG), low-density lipoprotein (LDL), uric acid, homocysteine (Hcy) and estimated glomerular filtration rate (eGFR).

Cognitive Function Assessment

Cognitive function was assessed using the Montreal Cognitive Assessment Basic (MoCA-BC). The MoCA-BC is a 30-point scale with education-adjusted cutoffs for cognitive impairment[14]: a score < 19 points indicates cognitive impairment for participants with ≤ 6 years of education; a score < 22 points for those with 7–12 years of education; a score < 24 points for those with > 12 years of education. All assessments were performed by professionally trained independent physicians.

WMH Assessment

Cranial MRI was performed using a 3.0T scanner, and WMH lesions were evaluated via T2 fluid-attenuated inversion recovery (FLAIR) sequences. Two independent radiologists completed the rating work, and both were blinded to all clinical data including cognitive status and HbA1c levels. Inter-rater reliability was calculated and reported. Any disagreements were resolved through group discussion and consensus.

WMH severity was graded using the Age-Related White Matter Changes Rating Scale (ARWMC)[15]. Assessments were performed separately for the left and right cerebral hemispheres across five regions: frontal lobe, parieto-occipital lobe, temporal lobe, infratentorial region (brainstem and cerebellum), and basal ganglia. Scoring criteria for white matter hyperintensities: 0 = no lesion; 1 = punctate lesions; 2 = partial confluent lesions; 3 = diffuse lesions involving the entire region (with or without U-fiber involvement). Scoring criteria for basal ganglia hyperintensities: 0 = no lesion; 1 = single punctate lesion (≥ 5 mm); 2 = multiple punctate lesions; 3 = diffuse lesions. WMH severity was classified as mild (0–3 points), moderate (4–7 points) and severe (≥ 8 points)[16, 17].

Statistical Analysis

Data analysis and visualization were performed using SPSS 25.0 and RStudio (R 4.4.0). Categorical variables were presented as numbers and percentages, and compared using the chi-square test.

Normally distributed continuous variables were expressed as mean $\pm$ standard deviation and compared using the independent-samples t-test. Non-normally distributed continuous variables were presented as median [interquartile range] and compared using the Mann-Whitney U test. Univariate and multivariate logistic regression models were used to explore the correlation between HbA1c and cognitive impairment. Restricted cubic spline (RCS) analysis was applied to evaluate the nonlinear correlation between HbA1c and cognitive impairment status. ROC curves were constructed, and the corresponding AUC was calculated to assess the discriminative ability of HbA1c. All statistical tests were two-sided, and a P value < 0.05 was considered statistically significant.

Results

Demographic and Baseline Characteristics

A total of 497 patients with WMH were enrolled in this study. Participants were divided into the cognitive impairment (CI) group (n = 315) and non-cognitive impairment (non-CI) group (n = 182). Table 1 summarizes the baseline clinical characteristics of the two groups. Compared with the non-CI group, the CI group had more severe WMH, lower educational attainment, a higher prevalence of hypertension, older age and higher HbA1c levels (all P < 0.05).

Table1. Subject characteristics

	N=497	non-CI N=182	CI N=315	$\chi^2/t/z$	P
ARWMC degree				27.034	<0.001
mild	167 (33.60%)	87 (47.80%)	80 (25.40%)		
moderate	151 (30.38%)	48 (26.37%)	103 (32.70%)		
severe	179 (36.02%)	47 (25.82%)	132 (41.90%)		
Sex				0.612	0.434
male	279 (56.14%)	98 (53.85%)	181 (57.46%)		
female	218 (43.86%)	84 (46.15%)	134 (42.54%)		
Education level				16.563	0.001
illiterate	155 (31.19%)	51 (28.02%)	104 (33.02%)		
elementary school	126 (25.35%)	34 (18.68%)	92 (29.21%)		
middle school	103 (20.72%)	39 (21.43%)	64 (20.32%)		
>middle school	113 (22.74%)	58 (31.87%)	55 (17.46%)		
Smoking	172 (34.61%)	62 (34.07%)	110 (34.92%)	0.037	0.847
Drinking	144 (28.97%)	53 (29.12%)	91 (28.89%)	0.003	0.956
Hypertension	328 (66.00%)	109 (59.89%)	219 (69.52%)	4.771	0.029
Age (years)				9.519	0.009
<60	175 (35.21%)	74 (40.66%)	101 (32.06%)		
60-70	148 (29.78%)	60 (32.97%)	88 (27.94%)		
>70	174 (35.01%)	48 (26.37%)	126 (40.00%)		
Height (cm)	164.52±7.74	164.36±8.09	164.61±7.54	-0.338	0.735
Weight (kilograms)	67.45±11.10	68.07±11.78	67.09±10.69	0.945	0.345
BMI (kg/m ²)	24.91±3.77	25.23±4.34	24.73±3.40	1.442	0.150
HbA1c (%)	4.80 [4.40;5.70]	4.40 [4.20;4.70]	5.20 [4.60;5.80]	-11.653	<0.001
LDL (mmol/L)	2.62 [1.99;3.11]	2.64 [1.99;3.10]	2.61 [1.98;3.15]	-0.657	0.511
TG (mmol/L)	1.20 [0.89;1.69]	1.19 [0.85;1.69]	1.21 [0.90;1.67]	-0.703	0.482
Cholesterol (mmol/L)	4.03 [3.27;4.86]	4.02 [3.26;4.82]	4.04 [3.36;4.88]	-0.742	0.458

Hcy (μmol/L)	11.30 [9.70;14.40]	11.20 [9.40;14.28]	11.40 [9.80;14.50]	-0.644	0.519
uric acid (μmol/L)	288.10 [241.50;348.10]	287.80 [246.70;350.38]	288.80 [238.80;346.85]	-0.711	0.477
eGFR (ml/min)	91.60 [80.40;98.90]	91.60 [82.50;98.92]	91.70 [78.90;98.85]	-0.596	0.551

Abbreviations: CI, cognitive impairment; ARWMC, Age-Related White Matter Changes Rating Scale; LDL, low-density lipoprotein; Hcy, homocysteine; eGFR, estimated glomerular filtration rate

Correlation between HbA1c and cognitive impairment

HbA1c levels were significantly correlated with cognitive impairment among patients with WMH. In the univariate logistic regression model (Model 1), continuous HbA1c showed a strong correlation with cognitive impairment (OR = 2.518, 95% CI: 1.964–3.228, $P < 0.001$). When HbA1c was divided into quartiles (Q1 as the reference group), the correlation became stronger across higher quartiles. Relative to Q1, Q2, Q3 and Q4 showed strong correlational relationship between higher HbA1c levels and the presence of cognitive impairment (all $P < 0.001$).

The above correlation remained stable after further adjustment for WMH severity, educational level, hypertension and age group (Model 2). Continuous HbA1c still had a significant correlation with cognitive impairment (OR = 2.482, 95% CI: 1.939–3.177, $P < 0.001$), and a graded correlation was observed across HbA1c quartiles.

In Model 3, we additionally adjusted for gender, smoking, alcohol consumption, BMI, LDL, TG, total cholesterol, Hcy, uric acid and eGFR. The correlation between HbA1c and cognitive impairment remained statistically significant. Each one-unit increment in continuous HbA1c corresponded to an OR of 2.537 (95% CI: 1.973–3.264, $P < 0.001$). In quartile analyses, Q2, Q3 and Q4 all showed stronger correlations with cognitive impairment compared with Q1 (all $P < 0.001$) (Table 2).

Notably, the large OR values observed in quartile comparisons may be attributable to the high prevalence of cognitive impairment in upper HbA1c quartiles, the common nature of the study outcome, and the inherent tendency of OR statistics to inflate effect sizes for prevalent binary endpoints. This large OR does not represent a true elevation in clinical risk, but only reflects a strong statistical correlation between higher HbA1c and cognitive impairment status.

Table 2. Correlation between HbA1c and cognitive impairment

	Model1		Model2		Model3	
	OR(95%CI)	P	OR(95%CI)	P	OR(95%CI)	P
HbA1c						
Overall	2.518 [1.964–3.228]	<0.001	2.482 [1.939–3.177]	<0.001	2.537 [1.973–3.264]	<0.001
Q1	Reference		Reference		Reference	
Q2	5.588 [3.319–9.408]	<0.001	5.885 [3.371–10.274]	<0.001	6.590 [3.678–11.809]	<0.001
Q3	8.433 [5.286–10.590]	<0.001	7.873 [5.739–10.556]	<0.001	11.642 [9.219–13.834]	<0.001
Q4	9.373 [7.449–11.71]	<0.001	9.572 [6.151–12.800]	<0.001	11.946 [9.999–13.039]	<0.001

Notes: Model 1: Univariate logistic regression

Model 2: Adjusted for leukoencephalopathy severity, educational level, hypertension, and age grouping

Model 3: Further adjusted for gender, smoking, alcohol consumption, BMI, LDL, TG, cholesterol, Hcy, uric acid, and eGFR on the basis of Model 2

Nonlinear Correlation between HbA1c and Cognitive Impairment

Further analyses revealed a significant nonlinear correlation between HbA1c and cognitive impairment (Nonlinear $P < 0.001$) (Table 3). This nonlinear correlation remained significant across subgroups stratified by WMH severity, hypertension status and age (Nonlinear $P < 0.001$) (Figure 1A). Interaction analyses showed no significant interaction between HbA1c and WMH severity (P for interaction = 0.257), HbA1c and hypertension (P for interaction = 0.548), or HbA1c and age group (P for interaction = 0.885) (Figure 1B–1D). These results indicated that the correlation pattern between HbA1c and cognitive impairment was consistent across different WMH severity, hypertension status and age groups. WMH severity, hypertension and age did not significantly modify the correlation between HbA1c and cognitive impairment.

Exploratory Discriminative Ability of HbA1c for Cognitive Impairment

ROC curve analysis was performed to explore the discriminative ability of HbA1c for cognitive impairment in patients with WMH (Figure 2A). In the overall cohort, HbA1c presented good discriminative performance, with an AUC of 0.813 (95% CI: 0.773–0.853, $P < 0.001$). The optimal cutoff value derived from this single cohort was 4.75%, with a sensitivity of 0.689, a specificity of 0.802, and an

overall accuracy of 0.730 (Table 3). This cutoff value is an exploratory result and not recommended as a universal clinical diagnostic threshold.

Stratified analyses by WMH severity showed stable discriminative performance of HbA1c across all subgroups. For patients with mild WMH, the AUC was 0.783 (95% CI: 0.714–0.853) with an optimal cutoff of 5.05%. For patients with moderate WMH, the AUC was 0.865 (95% CI: 0.798–0.933), with a sensitivity of 0.806 and a specificity of 0.833. For patients with severe WMH, the AUC was 0.802 (95% CI: 0.724–0.880), accompanied by high sensitivity (0.909) but relatively low specificity (0.596). All stratified analyses reached statistical significance (all $P < 0.001$) (Table 3, Figure 2B).

In hypertension-stratified analyses, the non-hypertensive subgroup had an AUC of 0.841 (95% CI: 0.783–0.900), while the hypertensive subgroup had an AUC of 0.794 (95% CI: 0.740–0.848) with high sensitivity (0.890) and low specificity (0.596). Both results were statistically significant (all $P < 0.001$) (Table 3, Figure 2C).

In age-stratified analyses, HbA1c maintained stable discriminative ability. The AUC values were 0.805 (95% CI: 0.738–0.872) for participants aged <60 years, 0.793 (95% CI: 0.718–0.868) for 60–70 years, and 0.843 (95% CI: 0.777–0.909) for >70 years. The subgroup aged over 70 years showed the best discriminative performance, with a sensitivity of 0.905 and an accuracy of 0.839 (Table 3, Figure 2D). All age-stratified ROC analyses were statistically significant (all $P < 0.001$).

Table 3. Exploratory discriminative performance of HbA1c for cognitive impairment

	Cutoff	AUC	ACC	SEN	SPE	AUC.low	AUC.up	P
Overall	4.75	0.813	0.730	0.689	0.802	0.773	0.853	<0.001
ARWMC degree								
mild	5.05	0.783	0.737	0.575	0.885	0.714	0.853	<0.001
moderate	4.55	0.865	0.815	0.806	0.833	0.798	0.933	<0.001
severe	4.45	0.802	0.827	0.909	0.596	0.724	0.880	<0.001
Hypertension								
no	4.75	0.841	0.751	0.656	0.877	0.783	0.900	<0.001
yes	4.45	0.794	0.793	0.890	0.596	0.740	0.848	<0.001
Age (years)								
<60	4.55	0.805	0.749	0.782	0.703	0.738	0.872	<0.001
60-70	4.75	0.793	0.730	0.693	0.783	0.718	0.868	<0.001
>70	4.45	0.843	0.839	0.905	0.667	0.777	0.909	<0.001

Discussion

The primary finding of this study is that HbA1c levels are significantly affect cognitive impairment in non diabetes patients with WMH, and an independent nonlinear correlation exists between HbA1c and WMH-related cognitive impairment. ROC analyses revealed that HbA1c has good discriminative ability for cognitive impairment in this patient population.

This study explored the correlation between HbA1c and cognitive decline among patients with WMH. Previous studies have reported that elevated HbA1c and type 2 diabetes are correlated with cognitive decline in older adults, and higher HbA1c levels are associated with cognitive impairment in elderly patients with coronary heart disease[18,19]. Different from those studies focusing on the general elderly population or patients with coronary heart disease, the present study targeted non diabetes patients with WMH. Accumulated evidence has shown that HbA1c and diabetes duration are correlated with cognitive impairment[20], and elevated HbA1c is linked to poorer cognitive function in nonagenarians; HbA1c has also been identified as an independent correlate of cognitive impairment[21-24]. These findings are consistent with our results regarding the the effect of HbA1c on cognitive impairment in non diabetes patients with WMH.

We confirmed an independent nonlinear correlation between HbA1c and WMH-related cognitive impairment. A previous study focusing on diabetic patients with lacunar infarction found that each 1% increase in baseline HbA1c was correlated with a slight decrease in cognitive assessment scores[25]. Our study further expanded the research population to non diabetes patients with WMH. Studies have also demonstrated that among patients with long-standing type 2 diabetes and poor glycemic control, larger WMH volume correlates with reduced processing speed, indicating that cerebral small vessel disease may mediate the association between diabetes and cognitive impairment[26]. In addition, blood glucose fluctuation is more harmful to diabetic chronic complications than sustained hyperglycemia[27,28], which further highlights the value of exploring the correlation between HbA1c and WMH-related cognitive impairment.

Limitations

Several limitations of this study must be acknowledged. First, these results are only applicable to patients without diabetes and not applicable to other populations. Additionally, this is a single-center retrospective. Consequently, the external validity and generalizability of our findings are restricted, and the conclusions may not be applicable to diverse populations across different regions and medical systems. Longitudinal, multicenter studies with comprehensive adjustment for confounders are required to confirm our conclusions and explore the progression of cognitive impairment.

Conclusions

HbA1c levels are significantly correlated with cognitive impairment among non diabetes patients with WMH. An independent nonlinear correlation exists between HbA1c and WMH-related cognitive impairment.

Declarations

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Authors' roles

L.X. conceived and designed the study, analysis and editing of the manuscript; H.Y. design, methods, subject recruitment and revised the manuscript draft; Q.T. help for data collections. All authors reviewed the manuscript.

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None.

Data statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

All participants provided written informed consent. The study was conducted in strict accordance with the provisions of the Declaration of Helsinki regarding informed consent and privacy protection. The study protocol was approved by the [Wenzhou Third Clinical Institute Affiliated To Wenzhou Medical University Ethics Committee]

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

Clinical trial number: not applicable.

References

1. Pérez Palmer N, Trejo Ortega B, Joshi P. Cognitive Impairment in Older Adults: Epidemiology, Diagnosis, and Treatment. *Psychiatr Clin North Am.* 2022;45(4):639–61.
2. Luo W, Dai Z, Wu W, et al. White matter hyperintensities and the risk of vascular dementia: a systematic review and meta-analysis. *PeerJ.* 2025;13:e19460.
3. Pavlovic AM, Pekmezovic T, Tomic G, et al. Baseline predictors of cognitive decline in patients with cerebral small vessel disease. *J Alzheimers Dis.* 2014;42(Suppl 3):S37–43.
4. Jacobs HI, Visser PJ, Van Boxtel MP, et al. Association between white matter hyperintensities and executive decline in mild cognitive impairment is network dependent. *Neurobiol Aging.* 2012;33(1):e2011–8.
5. Zheng F, Yan L, Yang Z, et al. HbA1c, diabetes and cognitive decline: the English Longitudinal Study of Ageing. *Diabetologia.* 2018;61(4):839–48.
6. Rönnekaa E, Zethelius B, Lannfelt L, et al. Vascular risk factors and dementia: 40-year follow-up of a population-based cohort. *Dement Geriatr Cogn Disord.* 2011;31(6):460–6.
7. Tabesh M, Sacre JW, Mehta K, et al. Associations of glycaemia-related risk factors with dementia and cognitive decline in individuals with type 2 diabetes: A systematic review and meta-analysis. *Diabet Med.* 2025;42(10):e70123.
8. Colagiuri S. Glycated haemoglobin (HbA1c) for the diagnosis of diabetes mellitus—practical implications. *Diabetes Res Clin Pract.* 2011;93(3):312–3.
9. Sherwani SI, Khan HA, Ekhzaimy A, et al. Significance of HbA1c Test in Diagnosis and Prognosis of Diabetic Patients. *Biomark Insights.* 2016;11:95–104.
10. Soleymani Y, Batouli SAH, Ahangar AA, et al. Association of glycosylated hemoglobin concentrations with structural and functional brain changes in the normoglycemic population: A systematic review. *J Neuroendocrinol.* 2024;36(11):e13437.
11. Kim JS, Chun BC, Lee K. Association between elevated glycosylated hemoglobin and cognitive impairment in older Korean adults: 2009–2010 Ansan cohort of the Korean genome and epidemiology study. *Front Public Health.* 2024;12:1417236.
12. Xu L, Xiong Q, Du Y, et al. Nonlinear relationship between glycated hemoglobin and cognitive impairment after acute mild ischemic stroke. *BMC Neurol.* 2023;23(1):116.
13. Maan HB, Meo SA, Rouq FA, et al. Impact of Glycated Hemoglobin (HbA1c) on cognitive functions in Type 2 diabetic patients. *Eur Rev Med Pharmacol Sci.* 2021;25(19):5978–85.
14. Chen KL, Xu Y, Chu AQ, et al. Validation of the Chinese Version of Montreal Cognitive Assessment Basic for Screening Mild Cognitive Impairment. *J Am Geriatr Soc.* 2016;64(12):e285–90.
15. Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke.* 2001;32(6):1318–22.
16. Kreisel SH, Blahak C, Bänzner H, et al. Deterioration of gait and balance over time: the effects of age-related white matter change—the LADIS study. *Cerebrovasc Dis.* 2013;35(6):544–53.

17. Jickling G, Salam A, Mohammad A, et al. Circulating endothelial progenitor cells and age-related white matter changes. *Stroke*. 2009;40(10):3191–6.
18. Reitz C, Guzman VA, Narkhede A, et al. Relation of Dysglycemia to Structural Brain Changes in a Multiethnic Elderly Cohort. *J Am Geriatr Soc*. 2017;65(2):277–85.
19. Zheng W, Xin QJ, Wang XX, et al. Association between glycated hemoglobin and cognitive impairment in older adults with coronary heart disease: a multicenter prospective cohort Study. *J Geriatr Cardiol*. 2025;22(3):381–8.
20. van Harten B, Oosterman J, Muslimovic D, et al. Cognitive impairment and MRI correlates in the elderly patients with type 2 diabetes mellitus. *Age Ageing*. 2007;36(2):164–70.
21. Legdeur N, Badissi M, Yaqub M, et al. What Determines Cognitive Functioning in the Oldest-Old? The EMIF-AD 90 + Study. *J Gerontol B Psychol Sci Soc Sci*. 2021;76(8):1499–511.
22. Liu C, Liu W, Yang Y, et al. Enlarged perivascular spaces in the basal ganglia mediate the negative impact of HbA1c levels on mild cognitive impairment. *Front Hum Neurosci*. 2025;19:1673301.
23. Li X, Chen B, Liu X, Ma J. Effects of exercise on cognitive function and glycated hemoglobin A1c among patients with type 2 diabetes mellitus and cognitive impairment: A systematic review and meta-analysis. *Geriatr Gerontol Int*. 2025;25(2):148–59.
24. Xiao Y, Hong X, Neelagar R, et al. Association between glycated hemoglobin A1c levels, control status, and cognitive function in type 2 diabetes: a prospective cohort study. *Sci Rep*. 2025;15(1):5011.
25. Cukierman-Yaffe T, McClure LA, Risoli T, et al. The Relationship Between Glucose Control and Cognitive Function in People With Diabetes After a Lacunar Stroke. *J Clin Endocrinol Metab*. 2021;106(4):e1521–8.
26. Mankovsky B, Zherdova N, van den Berg E, et al. Cognitive functioning and structural brain abnormalities in people with Type 2 diabetes mellitus. *Diabet Med*. 2018;35(12):1663–70.
27. Zhou R, Wei C, Zhao M, et al. Association between short-term glucose fluctuations and cognition in patients with acute ischemic stroke complicated by type 2 diabetes mellitus. *J Nutr Health Aging*. 2024;28(7):100252.
28. Dove A, Shang Y, Xu W, et al. The impact of diabetes on cognitive impairment and its progression to dementia. *Alzheimers Dement*. 2021;17(11):1769–78.

Figures

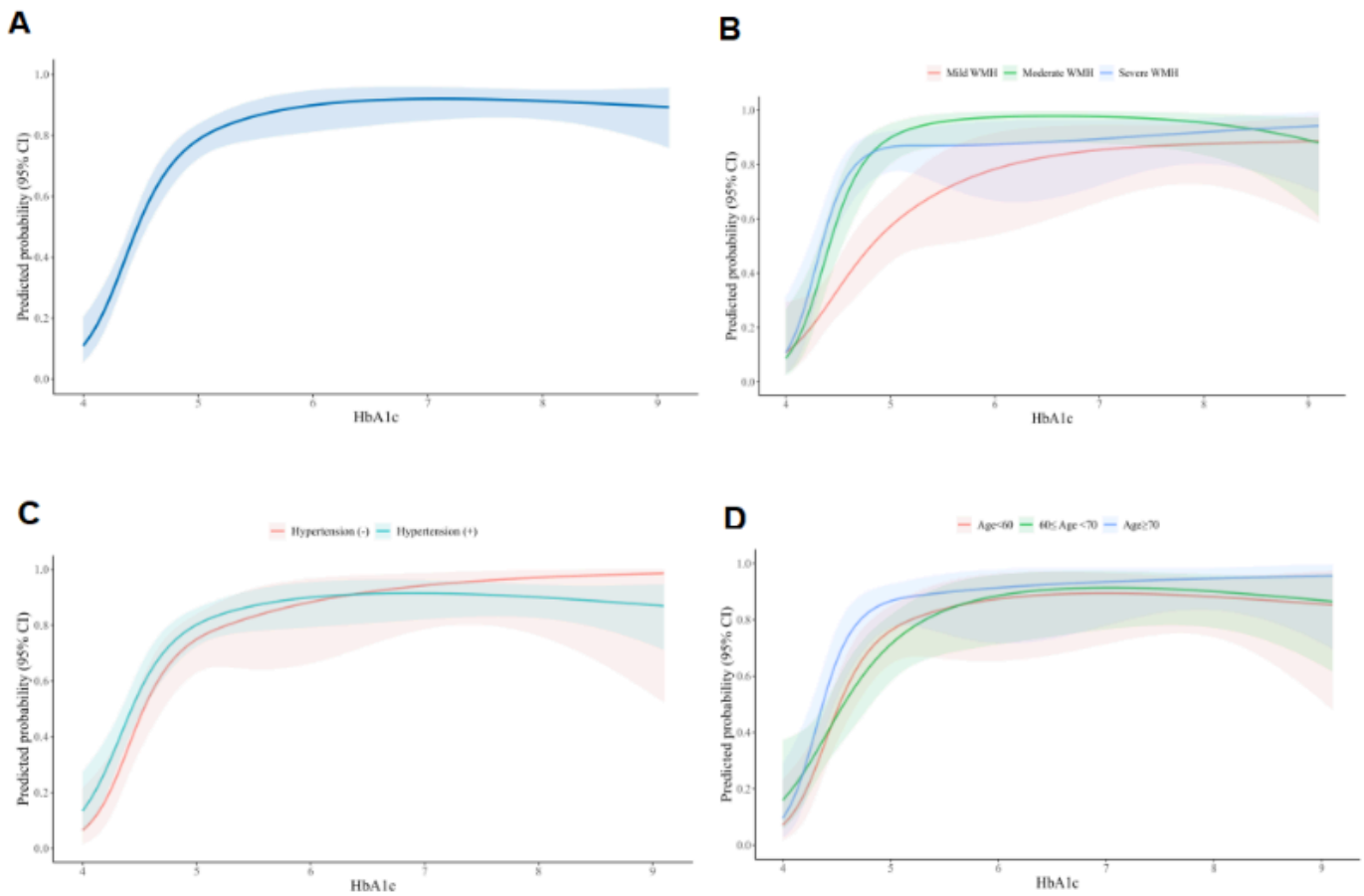


Figure 1

nonlinear association between HbA1c and cognitive impairment (A); correlation stratified by WMH severity (B), hypertension status (C), and age group (D).

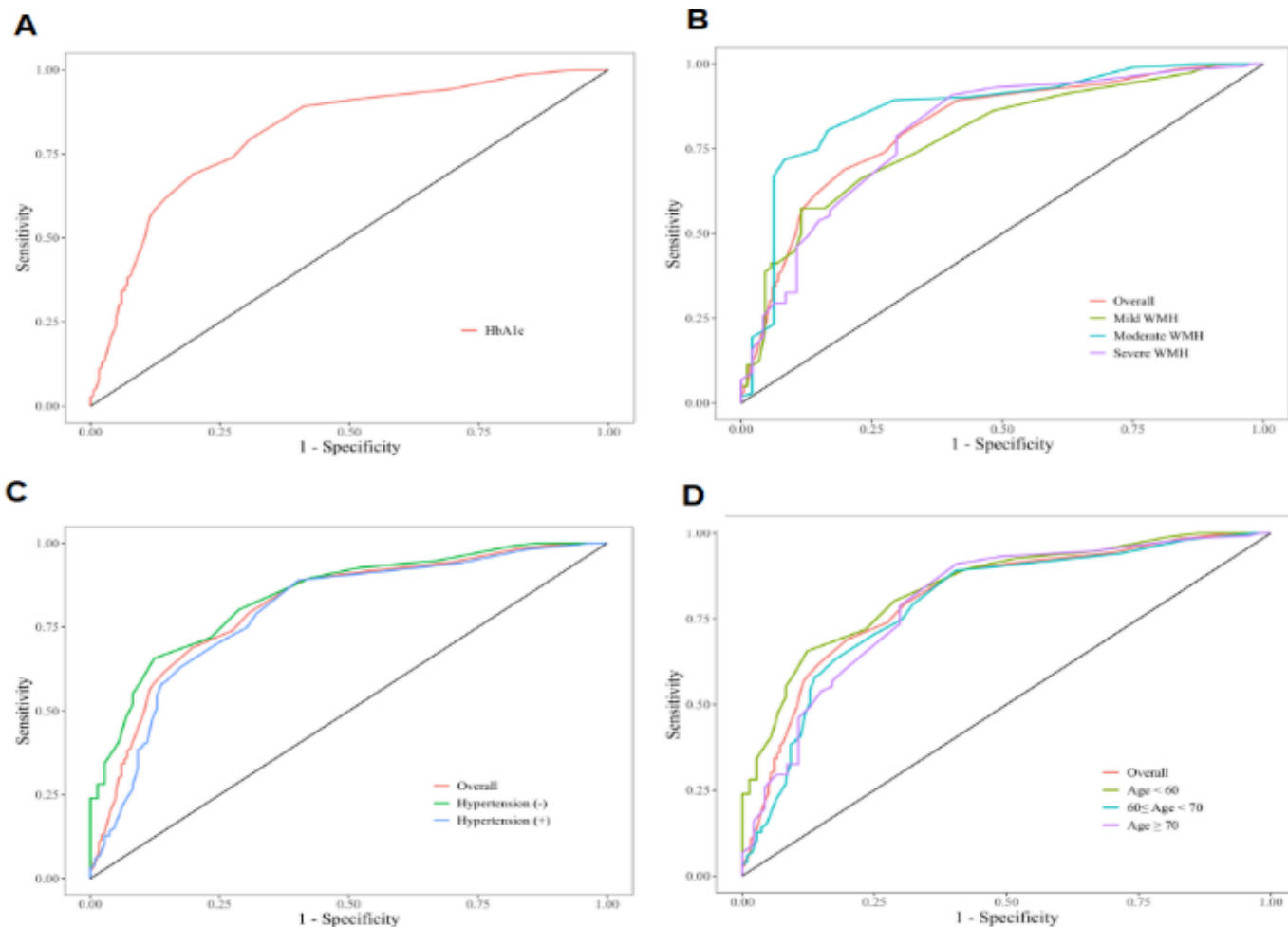


Figure 2

ROC curves of HbA1c for cognitive impairment: overall population (A); subgroups by WMH severity (B); subgroups by hypertension status (C); subgroups by age (D).