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Research paper

Predicting the reversion from mild cognitive impairment to normal cognition based on magnetic resonance imaging, clinical, and neuropsychological examinations

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ABSTRACT

Background: Reversion from mild cognitive impairment (MCI) to normal cognition (NC) is not uncommon and indicates a better cognitive trajectory. This study aims to identify predictors of MCI reversion and develop a predicting model.

Method: A total of 391 MCI subjects (mean age = 74.3 years, female = 61 %) who had baseline data of magnetic resonance imaging, clinical, and neuropsychological measurements were followed for two years. Multivariate logistic analyses were used to identify the predictors of MCI reversion after adjusting for age and sex. A stepwise backward logistic regression model was used to construct a predictive nomogram for MCI reversion. The nomogram was validated by internal bootstrapping and in an independent cohort.

Result: In the training cohort, the 2-year reversion rate was 19.95 %. Predictors associated with reversion to NC were higher education level ($p = 0.004$), absence of *APOE*4 allele ($p = 0.001$), larger brain volume ($p < 0.005$), better neuropsychological measurements performance ($p < 0.001$), higher glomerular filtration rate ($p = 0.035$), and lower mean arterial pressure ($p = 0.060$). The nomogram incorporating five predictors (education, hippocampus volume, the Alzheimer's Disease Assessment Scale-Cognitive score, the Rey Auditory Verbal Learning Test-immediate score, and mean arterial pressure) achieved good C-indexes of 0.892 (95 % confidence interval [CI], 0.859–0.926) and 0.806 (95 % CI, 0.709–0.902) for the training and validation cohort.

Limitation: Observational duration is relatively short; The predicting model warrant further validation in larger samples.

Conclusion: This prediction model could facilitate risk stratification and early management for the MCI population.

1. Introduction

Mild cognitive impairment (MCI) is characterized by the objective decline in cognition and function relative to normal aging (Langa and Levine, 2014; *Alzheimers Dement.*, 2022). Approximately 12 % to 18 % of people older than 60 worldwide are living with MCI (*Alzheimers Dement.*, 2022). MCI is always regarded as a transitional state between normal cognition and dementia (Petersen et al., 2018). Nonetheless, the diagnosis of MCI does not forebode inevitable progression to dementia (Thomas et al., 2019). Meta-analyses in recent years have indicated that 18 % to 30 % of subjects who were diagnosed with MCI would revert to normal cognition (NC) after one year or more (Wood, 2016; Malek-Ahmadi, 2016). Importantly, it has been reported that MCI reverters had a lower risk of progression to dementia than MCI non-reverters (Koepsell and Monsell, 2012; Roberts et al., 2014; Aerts et al., 2017). Therefore, identifying the predictors of MCI reversion would facilitate risk

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[1] The data used in preparation for this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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stratification and early management for the MCI population.

Existing research has indicated some predictors associated with MCI reversion, including younger age (Sanz-Blasco et al., 2022), absence of an apolipoprotein E (*APOE*) 4 allele (Pandya et al., 2017), better neuropsychological test performance and functional abilities (Thomas et al., 2019; Sachdev et al., 2013), larger amygdala and hippocampus volumes (Sachdev et al., 2013), and normal Alzheimer's disease (AD) biomarker profiles (Park and Han, 2015). However, it is still controversial whether some factors were significantly associated with MCI reversion, such as gender (Thomas et al., 2019; Roberts et al., 2014), marital status (Roberts et al., 2014; Pandya et al., 2017), education (Roberts et al., 2014; Pandya et al., 2017; Osone et al., 2016), smoking and drinking (Xue et al., 2019), hypertension (Sanz-Blasco et al., 2022; Xue et al., 2019), depression (Sanz-Blasco et al., 2022; Welstead et al., 2021), and so on. Besides, currently, there is a lack of a specific and practical predictive method for MCI reversion.

Therefore, we plan to identify predictive factors for MCI reversion and further develop and validate a predictive nomogram by the Alzheimer's Disease Neuroimaging Initiative (ADNI) database.

2. Method

2.1. Study design and participants

Data used in the study were obtained from the ADNI database (http://adni.loni.usc.edu/). The ADNI currently includes over 2200 participants with longitudinal follow-up, including individuals with NC, MCI, and early AD dementia. The ADNI collected the participants' information about magnetic resonance imaging (MRI), biological markers, and clinical and neuropsychological assessment. The institutional review boards at each of the participating institutions approved it and all participants or authorized representatives wrote informed consents.

The MCI diagnosis referenced Petersen criteria (Petersen, 2004; Angevaare et al., 2022): (1) subjective memory complaint; (2) objective cognitive impairment in at least one cognitive domains, which is defined as scoring 1 standard deviation (SD) below age, education, and gender-adjusted norms for a composite score of neuropsychological measures within that domain (Albert et al., 2011; Folstein et al., 1975); (3) relative independent daily function, which is quantified as the Functional Assessment Questionnaire (FAQ) score < 9 (Bondi et al., 2014); (4) non-dementia. The MCI participants at baseline were dichotomized into two groups at the 2nd year visit: MCI reverters who reverted to NC, and non-reverters including those who were still MCI or progressed to dementia.

Based on the above-mentioned criteria, a total of 571 MCI subjects with a longitudinal follow-up period of a maximum 6 years met the inclusion criteria for the study. The detialed selection process was described in s-Fig. 1. Among the 571 subjects, a subset of 391 MCI participants with complete baseline exposure information was included in the training cohort. Among the remaining subjects ($n = 180$), a total of 98 MCI participants with complete information of 5 variables incorporated in the nomogram were included in the validation cohort. Fig. 1 demonstrated the whole process of this study.

2.2. Candidate predictors

Thirty-seven candidate variables based on magnetic resonance imaging (MRI) radiomics, clinical, and neuropsychological examinations were identified based on previous literature and availability in the ADNI database. We did not incorporate biomarkers of cerebrospinal fluid or positron emission computed tomography because these are based on invasive or expensive approaches.

2.2.1. Demographic and lifestyle information

All participants self-reported data on age, sex, and schooling years. *APOE*4 status was determined according to rs7412 and rs429358, which were genotyped separately by an *APOE* genotyping kit to define the *APOE* ε2/ε3/ε4 isoforms. Cohabitation status was dichotomized as living alone versus married or living with a partner. Obesity (yes or no) was defined as body mass index $\geq$ 28 kg/m^2. Smoking habits were categorized as current use or former/never use. Limited by sample size, alcohol use history was not incorporated because all MCI reverters in the training cohort do not have alcohol use history.

2.2.2. Clinical features

Brachial artery systolic blood pressure and diastolic blood pressure were collected by certificated medical professionals using a standardized ADNI protocol. In brief, blood pressure was measured when the individual was seated and resting. A calibrated mercury sphygmomanometer recorded blood pressure from the forearm, which was arranged at the horizontal level of the fourth intercostal space at the sternum. Pulse pressure was calculated as the difference between systolic blood pressure and diastolic blood pressure. Mean arterial pressure (MAP) was equal to diastolic blood pressure adding 1/3 pulse pressure. Estimated glomerular filtration rate (eGFR) (ml/min) was calculated using the equation [(140-age)*weight(kg)*1.23]/serum creatinine (μmol/L) in men and equation [(140-age)*weight(kg)*1.04]/serum creatinine (μmol/L) in women. Medical history of hypertension, coronary heart disease, stroke, hyperlipidemia, diabetes, cancer, obstructive sleep apnea syndrome, insomnia, depression, anxiety, and hearing loss was collected from self-reporting to whether the subjects had been diagnosed or treated for these diseases.

2.2.3. Imaging characteristics

All subjects were scanned by 1.5 T or 3 T MRI scanners as specified by the ADNI protocol (Jack Jr. et al., 2008). For volumetric analyses, 1 mm isotropic 3D T1 sequences without contrast injection were performed. Here, whole brain, bilateral hippocampus, entorhinal and middle temporal, ventricular, and intracranial volume were analysed. White Matter Hyperintensities was acquired from the T1WI and T2-FLAIR images. The detailed White Matter Hyperintensities measurement method had been displayed on the ADNI site (http://adni.loni.usc.edu). Infarcts were dichotomized as yes or no from MRI images.

2.2.4. Neuropsychological assessment

Neuropsychological assessments included the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), which evaluated the written and verbal abilities of participants that were associated with overall cognition. The composite score of 13 items was the total score ranging from 0 to 85 and participants with higher scores had worse cognitive levels. Additional measurements of verbal memory were the Rey Auditory Verbal Learning Test (RAVLT immediate and RAVLT forgetting). Executive function was assessed by the Trails A and Trails B time to complete, with a longer time reflecting worse executive function. The FAQ was used to assess subjects' daily functional and behavioral abilities. It had 10 items with scores ranging from 0 to 30, with higher scores indicating less functional independence. The geriatric depression scale was included to objectively evaluate the depressive symptoms in the elderly.

2.3. Statistical analysis

Samples were categorized into MCI reverters and non-reverters groups. The χ2 test or Fisher exact test was used for the comparison of categorical variables and the student's *t*-test or Mann-Whitney *U* test was used for the comparison of continuous variables between the groups at baseline. Multivariate logistic analysis adjusting age and sex was used to calculate the odds ratio (OR) and their 95 % confidence interval (CI) of the predictors for MCI reversion. Intracranial volume was additionally adjusted for the analyses of the regions of interest.

The significance of all variables in the training cohort was assessed by univariate logistic regression analysis. Each variable associated with MCI reversion at a significant level ($p < 0.2$) was chosen as the candidate

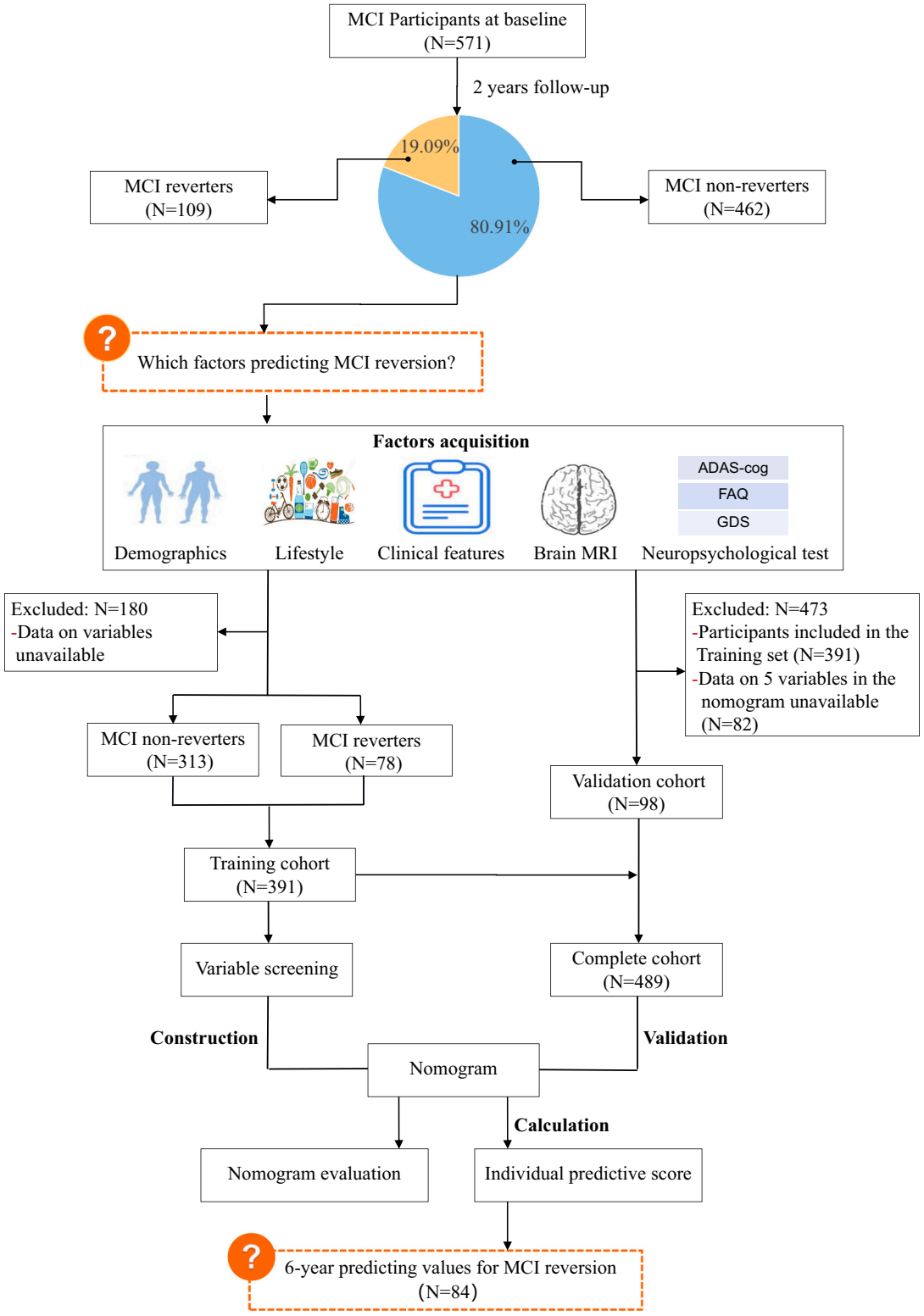

Fig. 1. Flow diagram of the study design.
Based on the MCI diagnostic criteria, a total of 571 MCI subjects with a longitudinal follow-up period of at least 2 years were eligible for the study. Two years later, 19.09 % of MCI subjects reverted to NC. To identify the predictors associated with MCI reversion, and construct and validate a predictive nomogram, we incorporated 38 variables from demographics, lifestyles, clinical features, imaging characteristics, and neuropsychological assessments. Among the 571 subjects, a subset of 391 MCI participants with complete information was included in the training cohort. Among the remaining subjects (n = 180), a total of 98 MCI participants with complete information of 5 variables incorporated in the nomogram were included in the validation cohort. A total of 489 participants in the training and validation cohort constituted the complete cohort. To explore the 6-year predicting value of the nomogram, we further calculated the individuals' predictive scores.
Abbreviations: MCI, Mild Cognitive Impairment.

for stepwise backward multivariate logistic analysis. The nomogram was constructed based on the results of stepwise backward multivariate logistic regression analysis.

The performance of the nomogram was assessed by three approaches (Steyerberg et al., 2010). Firstly, Harrell's concordance index (C-index) and its 95 % confidence interval (CI) and receiver operating characteristic (ROC) curve were used to measure the discrimination of the nomogram. Secondly, calibration curves (1,000 resampling bootstraps) were used to assess the consistency between the nomogram-predicted MCI reversion probability and observed probability. Thirdly, the clinical usefulness of the nomogram was evaluated by the decision curve analysis which quantified the net benefits at different threshold probabilities. The nomogram was internally validated by a bootstrap resampling process to provide an unbiased estimation of the nomogram performance, as the C-index. It was also evaluated in the validation and complete cohort by calculating the C-index and plotting the calibration plots and decision curves.

To explore the long-term predicting ability of the MCI reversion nomogram, we calculated the predictive scores for each participant. ROC curve was used to calculate the optimal cutoff point which was obtained by maximizing Youden's index (ie, sensitivity+specificity-1). The optimal cutoff point was used to divide participants in the complete cohort into high predictive score group and low predictive score group. The Kaplan-Meier method was used to calculate 6-year cumulative MCI reversion rates in the two subgroups. The log-rank test was applied to determine if the cumulative MCI reversion rates differed between the two subgroups. The statistical significance levels were two-sided, with $p < 0.05$ except for special descriptions. All analyses were performed using R version 4.2.1 for Windows with the "ggplot", "leaps", "car", "glmnet", "QuantPsyc", "relaimpo", "foreign", "regplot", "rms", "readr", "caret", "pROC", "ResourceSelection", "rmda", "nomogramFormula", "survival", "survminer", "ggpubr", and "magrittr" packages.

3. Result

3.1. Demographic and clinical characteristics

During the 2-year follow-up, 109 (19.09 %) MCI subjects reverted to NC, and 462 (80.91 %) remained MCI or progressed to dementia (Figure1). A total of 391 individuals (19.95 % MCI reverters) with predictor variables were included in the training cohort. The average age was 74.28 years and 240 (61.38 %) were women. The average education level was 15.72 years and 173 (44.25 %) carried the *APOE*4 allele. Significant differences were observed in education level, the percentage of *APOE*4 carrier, eGFR, hypertension, hyperlipidemia, brain volume (whole brain, hippocampus, entorhinal, and mid-temporal), and all neuropsychological assessments except geriatric depression scale between MCI reverters and non-reverters ($p < 0.050$) (Table 1). Population characteristics in the validation cohort were shown in s-Table 1.

3.2. Predictors of MCI reversion

After adjusting age and gender, a total of fourteen predictors were identied, seven of which were protective. The probability of MCI reversion was significantly higher for individuals who had larger entorhinal volume (OR: 2.765, 95 % CI: 1.869–4.196, $p < 0.001$), larger hippocampus volume (OR: 2.326, 95 % CI: 1.735–3.187, $p < 0.001$), larger mid-temporal volume (OR: 1.311, 95 % CI: 1.167–1.484, $p < 0.001$), more schooling years (OR: 1.157, 95 % CI: 1.049–1.281, $p = 0.004$), higher RAVLT-immediate scores (OR: 1.138, 95 % CI: 1.100–1.182, $p < 0.001$), higher GFR (OR: 1.013, 95 % CI: 1.001–1.025, $p = 0.035$), and larger whole brain volume (OR: 1.009, 95 % CI: 1.005–1.014, $p < 0.001$). The probability of MCI reversion was significantly lower for individuals who had *APOE*4 allele (OR: 0.376, 95 % CI: 0.212–0.647, $p = 0.001$), higher ADAS-cog scores (OR: 0.755, 95 % CI: 0.700–0.808, p < 0.001), higher FAQ scores (OR: 0.742, 95 % CI:

Table 1
Population characteristics in the training cohort at baseline.

Characteristics	Total (N = 391)	Reverters (N = 78)	Non-reverters (N = 313)	p
1. Demographic information				
Age, years, mean (SD)	74.28 (6.74)	73.31 (6.20)	74.52 (6.86)	0.134
Female, %	240 (61.38 %)	46 (58.97 %)	194 (61.98 %)	0.626
Education, years, mean (SD)	15.72 (2.86)	16.49 (2.73)	15.52 (2.86)	0.007
*APOE*4 allele carrier, %	173 (44.25 %)	22 (28.21 %)	151 (48.24 %)	0.001
2. Lifestyle				
Obesity, %	129 (32.99 %)	27 (34.62 %)	102 (32.59 %)	0.733
Current smoker, %	60 (15.35 %)	14 (17.95 %)	46 (14.70 %)	0.476
Married or living with a partner, %	302 (77.24 %)	63 (80.77 %)	239 (76.36 %)	0.406
3. Clinical features				
Blood pressure				
SBP, mmHg, mean (SD)	134.50 (17.09)	131.70 (17.41)	135.20 (16.96)	0.113
DBP, mmHg, mean (SD)	74.11 (9.58)	72.58 (9.27)	74.49 (9.63)	0.109
PP, mmHg, mean (SD)	60.42 (15.38)	59.15 (16.41)	60.74 (15.13)	0.440
MAP, mmHg, mean (SD)	94.25 (10.29)	92.29 (9.93)	94.73 (10.34)	0.056
eGFR, ml/min, mean (SD)	83.10 (24.77)	89.66 (24.91)	81.46 (24.50)	0.010
Medical history				
Hypertension, %	190 (48.59 %)	30 (38.46 %)	160 (51.12 %)	0.005
CHD, %	35 (8.95 %)	6 (7.69 %)	29 (9.27 %)	0.663
Stroke, %	17 (4.35 %)	3 (3.85 %)	14 (4.47 %)	0.808
Hyperlipidemia, %	185 (47.31 %)	30 (38.46 %)	155 (49.52 %)	0.010
Diabetes, %	36 (9.21 %)	7 (8.97 %)	29 (9.27 %)	0.938
Cancer, %	64 (16.37 %)	8 (10.26 %)	56 (17.89 %)	0.103
OSAS, %	35 (8.95 %)	8 (10.26 %)	27 (8.63 %)	0.652
Insomnia, %	21 (5.37 %)	4 (5.13 %)	17 (5.43 %)	0.915
Depression, %	82 (20.97 %)	12 (15.38 %)	70 (22.36 %)	0.176
Anxiety, %	16 (4.09 %)	5 (6.41 %)	11 (3.51 %)	0.248
Hearing loss, %	84 (21.48 %)	17 (21.79 %)	67 (21.41 %)	0.940
4. Imaging characteristics				
Whole brain volume, cm^3, mean (SD)	1033.00 (105.37)	1061.50 (96.93)	1025.90 (106.33)	0.005
Hippocampus volume, cm^3, mean (SD)	6.81 (1.07)	7.42 (0.89)	6.66 (1.05)	0.000
Entorhinal volume, cm^3, mean (SD)	3.56 (0.73)	3.92 (0.70)	3.46 (0.71)	0.000
Mid-temporal volume, cm^3, mean (SD)	19.72 (2.75)	20.85 (2.47)	19.44 (2.75)	0.000
Ventricular volume, cm^3, mean (SD)	39.54 (22.06)	36.25 (20.93)	40.36 (22.29)	0.128
Infarcts, %	32 (8.18)%	6 (7.69 %)	26 (8.31 %)	0.859
WMH, mean (SD)	3.75 (7.39)	3.18 (5.82)	3.90 (7.73)	0.369
5. Neuropsychological assessment				
ADAS-cog, points, mean (SD)	15.83 (6.06)	10.44 (3.52)	17.17 (5.82)	0.000

(continued on next page)

Table 1 (*continued*)

Characteristics	Total (N = 391)	Reverters (N = 78)	Non-reverters (N = 313)	p
RAVLT-immediate, points, mean (SD)	33.52 (8.93)	40.69 (8.12)	31.74 (8.21)	0.000
RAVLT-forgetting, points, mean (SD)	4.73 (2.37)	3.94 (2.81)	4.93 (2.20)	0.004
Trails A Time to Complete, s, mean (SD)	41.88 (18.74)	36.47 (10.21)	43.23 (20.10)	0.000
Trails B Time to Complete, s, mean (SD)	111.30 (56.58)	91.97 (37.94)	116.10 (59.42)	0.000
FAQ, points, mean (SD)	1.52 (2.10)	0.79 (1.45)	1.70 (2.19)	0.000
GDS, points, mean (SD)	1.36 (1.37)	1.17 (1.37)	1.41 (1.37)	0.165

Abbreviations: SD, Standard Deviation, APOE, Apolipoprotein E; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; PP, Pulse Pressure; MAP, Mean Arterial Pressure; eGFR, estimated Glomerular Filtration Rate; CHD, Coronary Heart Disease; OSAS, Obstructive Sleep Apnea Syndrome; WMH, White Matter Hyperintensities; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; RAVLT, Rey Auditory Verbal Learning Test; FAQ, Functional Activities Questionnaire; GDS, Geriatric Depression Scale.

0.617–0.868, $p = 0.001$), higher RAVLT-forgetting scores (OR: 0.827, 95 % CI: 0.739–0.921, $p = 0.001$), spent longer time to complete Trails B (OR: 0.990, 95 % CI: 0.983–0.996, $p = 0.002$) and Trails A (OR: 0.973, 95 % CI: 0.952–0.991, $p = 0.006$), and had higher MAP (OR: 0.976, 95 % CI: 0.952–1.001, $p = 0.060$) (s-Table 2).

3.3. Nomogram development and validation

Twenty-three variables were included in backward stepwise logistic regression analysis (s-Table 3). Finally, five variables were used to construct the MCI reversion prediction nomogram (Fig. 2): hippocampus volume (OR: 1.955, 95 % CI: 1.375–2.846, p < 0.001), education (OR: 1.213, 95 % CI: 1.075–1.379, $p = 0.002$), RAVLT-immediate (OR: 1.089, 95 % CI: 1.044–1.140, $p < 0.001$), MAP (OR: 0.953, 95 % CI: 0.920–0.985, $p = 0.006$), and ADAS-cog (OR: 0.814, 95 % CI: 0.745–0.884, $p < 0.001$) in the training cohort. (Table 2).

The nomogram displayed good accuracy in estimating the MCI reversion, with an unadjusted C-index of 0.892 (95 % CI: 0.859–0.926) and a bootstrap-corrected C-index of 0.882 in the training cohort. The C-index was 0.806 (95 % CI: 0.709–0.902) and 0.870 (95 % CI: 0.837–0.904) in the validation and complete cohort, respectively (s-Table 4). Moreover, ROC analysis displayed that the nomogram had higher discrimination than single variable used to construct the nomogram in all cohorts (Fig. 3A, D, G). The calibration plot demonstrated an optimal agreement on the probability of MCI reversion between the prediction by nomogram and actual observation in the training cohort ($p = 0.692$) (Fig. 3B), validation cohort ($p = 0.167$) (Fig. 3E), and complete cohort ($p = 0.691$) (Fig. 3H). The decision curve analysis indicated that nomogram-assisted clinical decisions yielded higher net benefit than 'treat-all' or 'treat-none' strategies at risk thresholds up to 76 % in the training cohort (Fig. 3C), 65 % in the validation cohort (Fig. 3F), and 73 % in the complete cohort (Fig. 3I).

3.4. Long-term prediction of MCI reversion based on the nomogram score

A total of 491 participants in the complete cohort were stratified into two groups (high predictive score group and low predictive score group) based on the optimal cutoff value (218.667 points) (Fig. 4A). Among the 491 participants, 84 subjects had 6 years of follow-up. Kaplan-Meier curve showed that the 6-year cumulative MCI reversion rate was significantly higher in the high predictive score group than in the low predictive score group ($p < 0.001$) (Fig. 4B).

4. Discussion

In the present study, approximately 20 % of MCI individuals reverted to NC two years later. Fourteen predictors were associated with MCI reversion. To our best knowledge, our study was the first to construct and validate the prediction model for MCI reversion. The nomogram included five predictors: education, MAP, hippocampus volume, and the score of ADAS-cog and RAVLT-immediate. The nomogram had good accuracy and discrimination, which could be used to calculate the probability of MCI reversion.

The one of important findings of our research was the identified MCI reversion predictors. We found that higher education level was significantly associated with a higher probability of MCI reversion, which was lined with some previous studies (Thomas et al., 2019; Iraniparast et al., 2022). Individuals with higher education always had more literacy and knowledge about health (Bakker et al., 2017), healthier lifestyles, and better socioeconomic status (Adler et al., 2013), which might promote MCI reversion. Besides, education was associated with cognitive reserves. Cognitive reserve might influence the MCI reversion through mechanisms like neural compensation, which means the brain forms compensatory paths to offset the initial neural changes that result in MCI (Iraniparast et al., 2022; Stern et al., 1995; Stern, 2012). However, a few studies demonstrated that the years of receiving education have no significant cognitive protection role (Koepsell and Monsell, 2012; Qin et al., 2023). Since educational attainment was a dynamic event, it could not reflect subsequent cognitive endeavors (Sharp and Gatz, 2011). Thus, the impact of education on MCI reversion required further study.

Regarding genetic factors, the absence of *APOE4* allele has been identified as a predictor for reversion (Thomas et al., 2019; Xue et al., 2019). Our study also supported this result. The *APOE4* allele was closely associated with the status and stability of MCI as *APOE4* allele was related to increased Aβ accumulation and amyloid plaque formation in the brain (Huang and Mucke, 2012; Dixon et al., 2014; Harris and Deary, 2011). Therefore, the absence of *APOE4* allele might associate with a lower risk of AD pathogenesis, thereby relating to a higher probability of MCI reversion.

To our best knowledge, it was the first study that identified higher eGFR, and lower MAP as MCI reversion predictors. Although there was no report on the relationship between eGFR and MCI reversion, many studies have reported the associations between kidney function decline (decreased eGFR) and cognitive impairment (Drew et al., 2019; Shi et al., 2018; Wang et al., 2021). Decreased kidney function was always

Table 2
Multivariate logistic regression analysis of selected variables on MCI reversion.

Variable	Training cohort (N = 391)			Validation cohort (N = 98)			Complete cohort (N = 489)		
	β	OR (95%CI)	p	β	OR (95%CI)	p	β	OR (95%CI)	p
Education, years	0.193	1.213 (1.075–1.379)	0.002	−0.011	0.988 (0.802–1.219)	0.911	0.135	1.144 (1.034–1.271)	0.010
MAP, mmHg	−0.048	0.953 (0.920–0.985)	0.006	−0.020	0.980 (0.923–1.037)	0.496	−0.042	0.959 (0.932–0.986)	0.004
Hippocampus volume, cm^3	0.670	1.955 (1.375–2.846)	0.000	0.871	2.388 (1.338–4.739)	0.006	0.693	2.000 (1.492–2.731)	0.000
ADAS-cog, points	−0.205	0.814 (0.745–0.884)	0.000	−0.120	0.887 (0.778–0.994)	0.053	−0.179	0.836 (0.779–0.893)	0.000
RAVLT-immediate, points	0.086	1.089 (1.044–1.140)	0.000	0.029	1.029 (0.963–1.098)	0.385	0.071	1.073 (1.037–1.112)	0.000

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; MAP, Mean Arterial Pressure; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; RAVLT, Rey Auditory Verbal Learning Test.
β, unstandardized β coefficients were calculated from the multivariate logistic regression model.

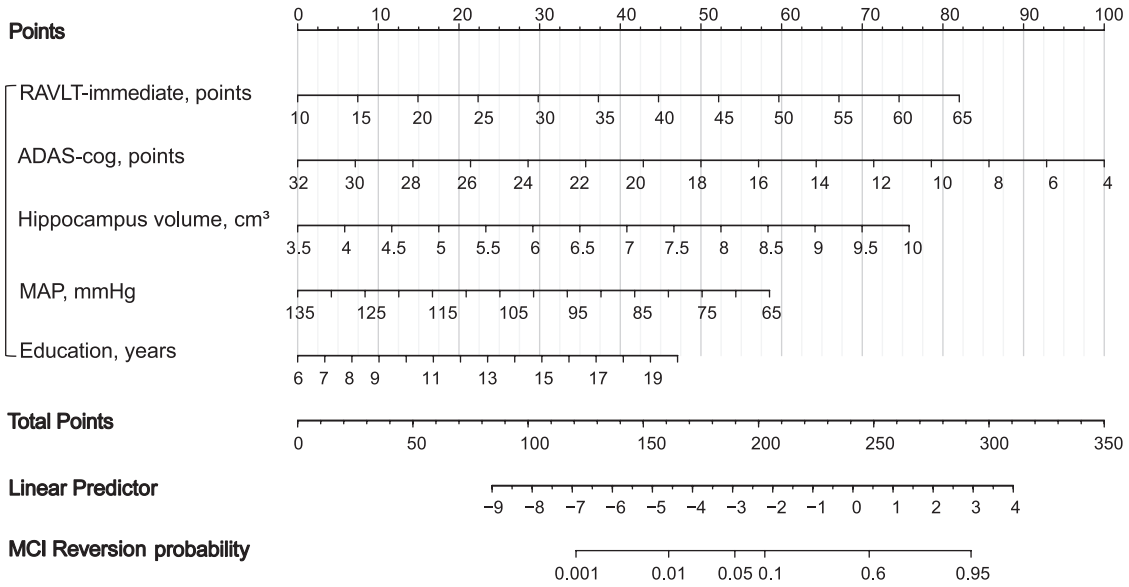

Fig. 2. Nomogram for predicting the 2-year MCI reversion probability.
Abbreviations: RAVLT, Rey Auditory Verbal Learning Test; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; MAP, Mean Arterial Pressure.

accompanied by poorer vascular endothelial function and cerebral vasculature, lower vitamin D and serum α-Klotho, and higher homocysteine and cystatin-C levels (Drew et al., 2019; Shi et al., 2018; Wang et al., 2021; Khatri et al., 2009). Factors mentioned above were directly or indirectly correlated with the higher risk of dementia (Drew et al., 2019; Wang et al., 2021; Khatri et al., 2009). Hence, the improvement of kidney function might benefit cognitive improvement. These studies supported our result that eGFR was an important factor correlated with MCI reversion. Lower MAP was found to be a predictor for MCI reversion in this study. It was consistent with the findings in a meta-analysis that people without hypertension had a higher probability of MCI reversion (Xue et al., 2019). Higher blood pressure could induce cerebrovascular endothelial dysfunction and impair the structure and function of cerebral microcirculation, which would damage the cerebral blood supply (Ungvari et al., 2021; Valcarcel-Ares et al., 2012; Tsao et al., 2013). Besides, hypertension might injure the blood-brain barrier, thereby exacerbating neuroinflammation and promoting amyloid pathologies (Wang et al., 2021; Carnevale et al., 2012). It has been reported that lowering blood pressure with antihypertensive agents was significantly related to a lower risk of cognitive impairment (Hughes et al., 2020). Therefore, reducing blood pressure through medical and lifestyle interventions could help to prevent or delay the pathogenesis of cognitive impairment and even revert MCI in subjects with hypertension.

Our analysis of neuroimaging data showed that larger brain reserve represented by larger volume of whole brain, hippocampus, entorhinal, and mid-temporal area was significantly associated with MCI reversion. Sachdev et al. reported that MCI reverters had significantly larger volumes of the hippocampus than non-reverters (Sachdev et al., 2013). Additionally, the entorhinal and mid-temporal cortex atrophy has been considered significant characteristics of the structural changes associated with MCI progression (Li et al., 2016; Huang et al., 2020). Thus, it was expected that larger hippocampus, entorhinal, and mid-temporal volumes were correlated with an increased probability of MCI reversion.

In addition, we found that better neuropsychological assessments (ADAS-cog, RAVLT-immediate and forgetting, Trails A and Trails B time to complete, and FAQ) performance was associated with higher a probability of MCI reversion. This was consistent with previous studies (Thomas et al., 2019; Pandya et al., 2017). The better performance mentioned above always reflected higher cognitive, executive, and functional levels at baseline. These assessments would facilitate early detection and risk stratification of the MCI population.

Our study had some strengths. Firstly, we identified predictors of MCI reversion from comprehensive factors covering demographic and lifestyle characteristics, clinical features and history of diseases, brain imaging characteristics, and neuropsychological assessments. Secondly, to our best knowledge, this was the first prediction model for MCI reversion and the predictors included in this predictive nomogram were non-invasive and readily available. Thirdly, the nomogram was validated by internal bootstrapping and in an independent cohort, which had high accuracy and good discrimination.

Our study had some limitations. Firstly, MCI is a clinical diagnosis, which is inherently influenced by participants' subjective performance (Roberts et al., 2014). MCI can be the secondary manifestation of other neurologic, vascular, metabolic, or psychiatric disorders (Petersen et al., 2018). The management of psychiatric symptoms could contribute to cognitive reversion (Petersen et al., 2018; Sanz-Blasco et al., 2022). Though no differences of Geriatric Depression Scale scores or history of depression and anxiety were found between groups, we cannot fully exclude the potential bias of MCI misclassification due to limited data in broad psychometric assessments of psychiatric symptoms. Secondly, the biomarkers of cerebrospinal fluid and positron emission computed tomography were not considered because these are based on invasive or expensive approaches. Thus, future studies are required to consider the effect of AD pathological biomarkers on MCI diagnosis and reversion. Thirdly, the observation of MCI reversion in previous studies was 1 to 5 years (Thomas et al., 2019; Sanz-Blasco et al., 2022). Although participants in our study were followed 2 years, the reversion rate was consistent with the findings of meta-analyses (Wood, 2016). Besides, the supplementary analysis based on 84 individuals showed that this predictive nomogram could predict 6-year MCI reversion. Fourthly, the independent validation cohort only incorporated 98 subjects due to the limited sample size and we did not perform external validation in other populations. Therefore, external validation in other populations and centers with larger scale sample sizes is needed to verify the accuracy and improve the generalizability of this predictive model.

5. Conclusion

In our study, approximately 20 % of MCI individuals reverted to NC two years later. Fourteen predictors for MCI reversion were identified. These factors consisted of vascular factors, reserve capability, genetic etiology, and baseline cognitive levels, strengthening the complex

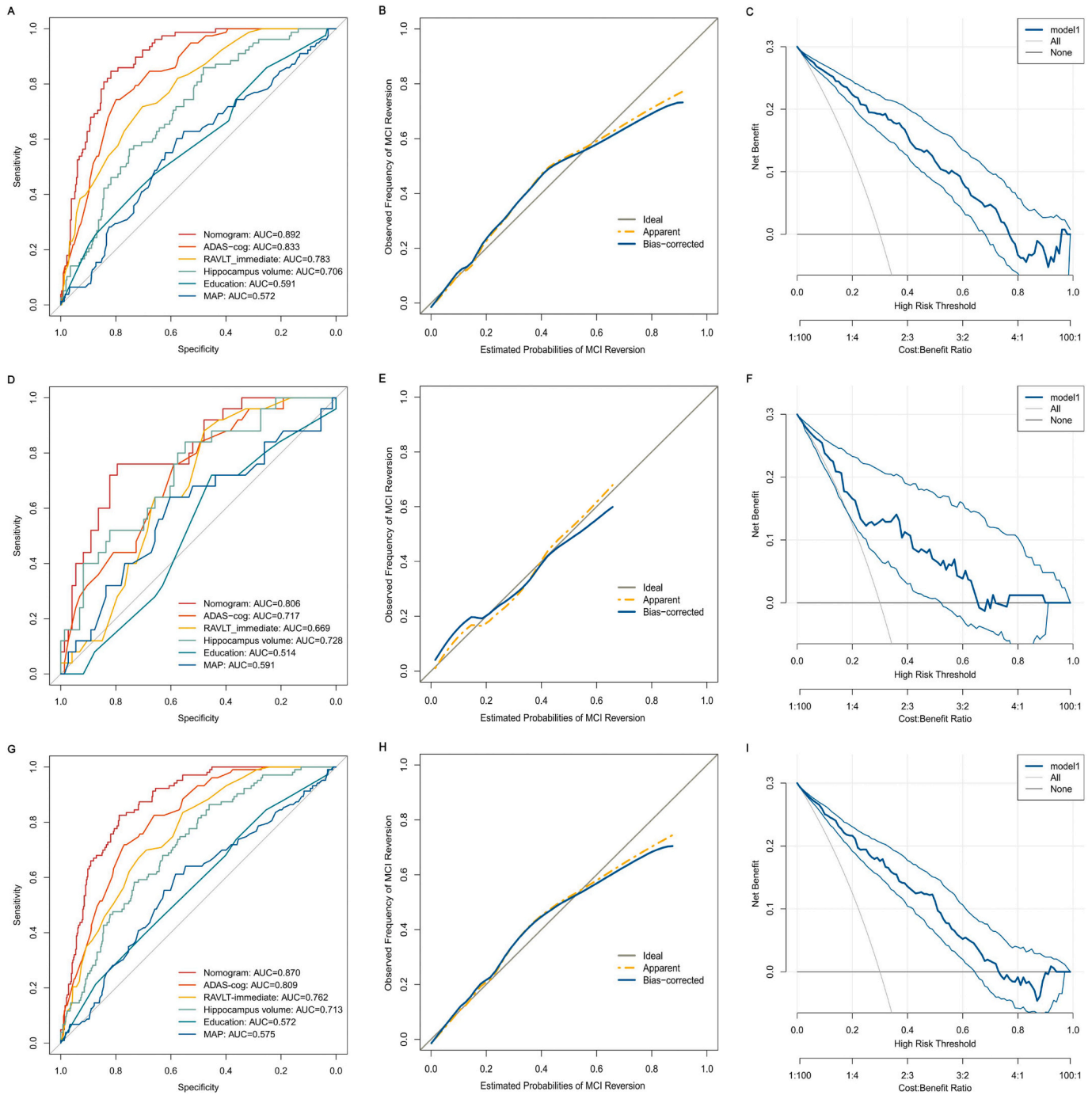

Fig. 3. Nomogram performance and clinical usefulness.
Receiver operating curves of the model for predicting MCI reversion probabilities in the training cohort (A), validation cohort (D), and complete cohort (G).
Calibration curves for estimating 2-year MCI reversion probabilities in the training cohort (B), validation cohort (E), and complete cohort (H).
Decision curves of the nomogram model in the training cohort (C), validation cohort (F), and complete cohort (I).
Abbreviations: MCI, Mild Cognitive Impairment; AUC: Area Under the Curve; RAVLT, Rey Auditory Verbal Learning Test; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; MAP, Mean Arterial Pressure.

etiological components for predicting MCI prognosis. We first constructed and validated the prediction model for MCI reversion. Further studies are warranted to incorporate more factors to develop and validate it in larger external populations.

Ethics approval and consent to participate

The ADNI was approved by the institutional review boards of all participating centers, and written informed consent was obtained from all participants or authorized representatives according to the 1975 Declaration of Helsinki.

Consent for publication

Not applicable.

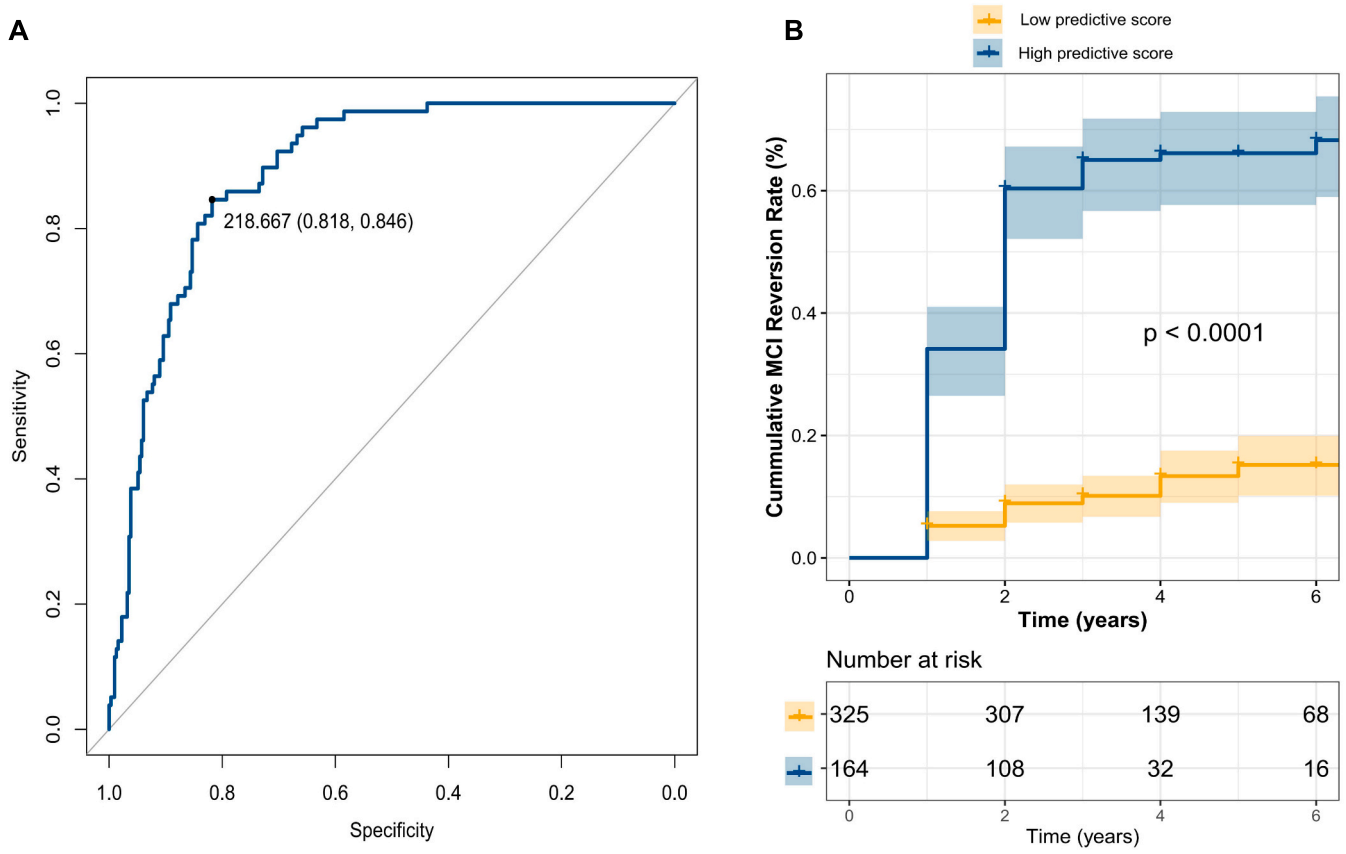

Fig. 4. Long-term prediction of MCI reversion based on the nomogram score.
The optimal cut-off value (218.667 points) was calculated by the receiver operating characteristic curve (A).
Kaplan-Meier curves for subjects with MCI based on predictive score stratification (B).

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CRediT authorship contribution statement

Hai-Hong Yu: Formal analysis, Visualization, Writing – original draft. **Chen-Chen Tan:** Writing – review & editing, Data curation. **Shu-Juan Huang:** Writing – review & editing. **Xin-Hao Zhang:** Writing – review & editing. **Lan Tan:** Supervision, Writing – review & editing. **Wei Xu:** Conceptualization, Data curation, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no competing interests.

Data availability

All data are available upon reasonable request or can be obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.03.009.

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