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Clinical study

A simple nomogram prediction model to identify relatively young patients with mild cognitive impairment who may progress to Alzheimer's disease

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ABSTRACT

Aim: Construct a clinical predictive model based on easily accessible clinical features and imaging data to identify patients 65 years of age and younger with mild cognitive impairment(MCI) who may progress to Alzheimer's disease(AD).

Methods: From the ADNI database, patients with MCI who were less than or equal to 65 years of age and who had been followed for 6–60 months were selected.We collected demographic data, neuropsychological test scale scores, and structural magnetic images of these patients. Clinical characteristics were then screened, and VBM and SBM analyses were performed using structural nuclear magnetic images to obtain imaging histology characteristics. Finally, predictive models were constructed combining the clinical and imaging histology characteristics.

Results: The constructed nomogram has a cross-validated AUC of 0.872 in the training set and 0.867 in the verification set, and the calibration curve fits well.We also provide an online model-based forecasting tool.

Conclusion: The model has good performance and uses convenience,it should be able to provide assistance in clinical work to screen relatively young MCI patients who may progress to AD.

1. Introduction

Alzheimer's disease(AD) is a neurodegenerative disorder characterized by cognitive impairment and limited behavioral ability, it's the 5th leading cause of death for people aged 65 and older [1]. In addition, the incidence of AD increases exponentially with age greater than 65 years [2]. This places a heavy financial burden on families and society [2,3]. Mild cognitive impairment(MCI) is the prodromal stage of AD. Studies have shown that the earlier the disease is identified and intervened in, the higher the probability of successful treatment [4]. A number of existing prediction studies on AD have combined demographic characteristics, neuropsychological test scales, cerebrospinal fluid markers, genes, and PETCT, and have obtained good predictive performance [5–8]. However, in view of the high cost and inconvenience of PETCT and the unavailability of primary hospitals, as well as the invasiveness of cerebrospinal fluid, the clinical application of these research results is limited. In addition, the identification of relatively young patients with MCI who may progress to AD is of greater socioeconomic importance. Due to the relative youth of the patients, we therefore chose a relatively midium-term (5 tears) follow-up period, and medium-term(5-years) based follow-up also helps to improve the predictive performance of predictive models [9]. Therefore, there is a strong need to have a simple predictive tool suitable for most clinical conditions to primary screen relatively young MCI patients who are likely to progress to AD for further testing and clinical medication decisions.

Nomogram is a graph-based and easy-to-understand prediction tool, which can be easily used in complex clinical settings, and it is easy to communicate the results with patients [10]. Moreover, nomograms can predict individualized specific risk for each patient [11].

In this study, based on easily accessible clinical features and structural MRI, we hypothesized that a predictive model

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combining simple clinical and imaging features would correctly identify patients aged 65 years and younger with MCI who are likely to progress to AD with a follow-up of 6 to 60 months and guide further clinical decision making.We also provide a web-based calculation software based on this model to make this predictive screening tool easier to use in clinical practice (https://chenwh2020.shinyapps.io/DynNomapp/).

2. Materials and methods

2.1. Participants

Our data were all from Alzheimer's Disease Neuroimaging Initiative (ADNI) databases. Full inclusion and exclusion criteria are described in detail at (http://adni.loni.usc.edu/methods/documents/). Demographics and clinical data of participants were collected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu/). All patients diagnosed with mild cognitive impairm- ent(MCI)(included EMCI and LMCI) at baseline, and were followed up for 6–60 months were selected. The stage of MCI (early and late) patients are determined using the Wechsler Memory Scale (WMS) Logical Memory II [6]. Exclusion criteria were those older than 65 years of age and lack of follow-up information. Finally, a total of 151 patients were selected. Subsequently, we removed cases with incomplete information and abnormal image processing results. To that point, we retained 138 patients, 103 of whom did not convert to AD(MCI-MCI) and 35 of whom eventually converted to AD(MCI-AD),We randomly divided all patients into a training set and a varidation set at a ratio of 6:4. The detailed process is shown in Fig. 1.

2.2. Clinical preditor collection and selection

In order to make clinical application more convenient and feasible [12], we only collected clinical features that are more accessible.Demographic characteristics we collected age, gender, years of education, marital status, family history and MCI stage. Neuropsychological test scale including Clinical Dementia Rating Scale Sum of Boxes(CDRSB), Functional Activities Questionnaire (FAQ), Mini-Mental State Examination(MMSE) scores. We classify patients whose parents or brothers/sisters have a clear history of AD diseaseas as Yes, others as No. Furthermore, we classify married status as Yes, divorce and others as No.All grouped data were tested for normality and homogeneity of variance. Continuous data using two independent sample T test or Mann-Whitney U test. Counting data using chi-square test or Fisher's exact test, $P < 0.05$ as statistically significant. And then, the logistic regression (Forward:LR) was further used to select the clinical features, in this step,only those variables that retained $p < 0.01$ were determined to be significant and incorporated into the final prediction model. The above statistical analyses were performed using SPSS 26.0.

2.3. Image acquisition

Only 3.0T T1-weighted anatomical MRI images were used in this study. The ADNI website (http://adni.loni.usc.edu/methods/documents/) provided the detailed imaging protocols.

2.4. Image processing and feature selection

The T1-weighted anatomical MRI images were preprocessed using automated procedures in Computational Anatomy Toolbox (CAT12) (http://www.neuro.uni-jena.de/cat/) within SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) while running in MATLAB (R2018a; MathWorks, Natick, MA, USA). All settings were default. Briefly, T1 images were biasfield corrected, skull-stripped, aligned to a Montreal Neurological Institute standard space (MNI-152 template), and split into gray matter(GM), white matter (WM) and cerebros pinal fluid [13]. According to the cat12 manual (http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf), we get the Voxel-Based Morphometry (VBM) features. VBM is a more common voxel-based approach to analyzing gray matter volume in the whole brain,Jhon Ashburner et al. [14,15] detailed the VBM. Additionally, this study also obtains the surface-based morphometry (SBM) features based on the region of interest (ROI). These articles have a detailed introduction to SBM [16–18]. As suggested by the CAT12 manual and previous reports [17], 18 mm and 25 mm FWHM kernels for CT(local cortical thickness) and folding data,

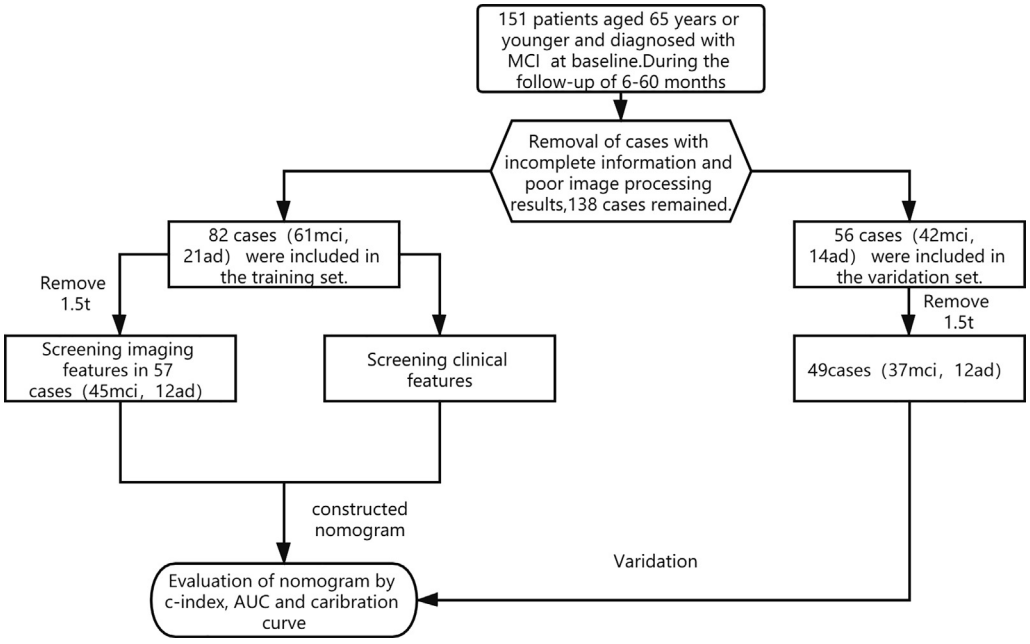

Fig. 1. Detailed process.

respectively, were used. Extraction of SBM measures was applied according to the gyral based Desikan-Killiany cortical atlas (DK40) [19].

We analyzed the volume of whole brain gray matter obtained based on VBM. In the training set, we used two groups of data, MCI-AD and MCI-MCI, to establish full Factorial modle, was corrected using sex, age and total intracranial volume (TIV) as covariates.We used MarsBaR ROI toolbox (http://marsbar.sourceforge.net) to obtain the gray volume of the corresponding regions of interest in the validation set. Clusters with Uncorrected $p < 0.001$ would be used as VBM features.

SBM is able to provide measurements with features such as: Cortical Thickness [16], Fractal Dimensionality Index (Cortical Surface Complexity) [20], Gyrification Index [17], Sulcal Depth [20–22]. The SBM feature selection based on the region of interest uses lasso regression.We added gender and age to the equation to correct the effects of both. Because of insufficient samples, 3-fold cross-validation was used to obtain more robust results. Finally, we combined the VBM features and SBM features to construct a regression formula, which resulted in the final imaging histology score(Imgscore) for each individual. The general process of VBM and SBM is shown in Fig. 2.

2.5. Image feature's validation

In order to verify the effectiveness of image features, We used a logistic regression classifier for validation. Given the unbalanced data distribution due to more MCI individuals than AD individuals, we double-sampled the data.Sensitivity, specificity, accuracy, and area under the receiver operating characteristic curve(AUC) were obtained for the training and validation sets, respectively.

2.6. Nomogram construction, varidation and calibration

Detailed methods about nomogram construction have been described previously [12]. Using the selected clinical features and imaging features, a multi-factor logical regression equation was constructed to reconfirm the effectiveness of the selected features. The features of $p < 0.05$ were preserved and used to construct a nomogram in the training set. To evaluate the discriminative ability of the nomogram, we used the concordance index (C-index) and the receiver operating characteristic curve (ROC) and assessed the area under the curve (AUC).Internal validation of performance was estimated with a bootstrapping method (500 replications) and a 3-fold cross validation of the training dataset, and the testing dataset. Calibration was graphically assessed with the relationship between the actual observed probabilities and predicted probabilities (calibration curve). The selection of image features and the establishment and verification of nomogram were carried out on R3.4.3 (Vienna, Austria; http://www.R-project.org/).

3. Results

3.1. Characteristics of study participants

Demographic and clinical characteristics of the training set and validataion set are shown in Table 1. The total number of cases was 138, aged 55–65 years, with an average age of 61.4 (SD = 2.55) years. There was no significant difference in age,years of educaion,-family history, gender and marital status between MCI converters and MCI nonconverters in both cohorts ($p > 0.05$). Both the training set and validation set, the CDRSB scores and FAQ scores of the MCI-AD group were larger than those of the MCI-MCI group, according to the Mann–Whitney U test,the difference between the two groups ($p < 0.001$) was statistically significant.MCI staging in the MCI-AD group was later than that in the MCI-MCI group,according to two-sample independent T tests,the difference was significant, both the training set ($p = 0.003$) and the testing set ($p = 0.001$). However,the MMSE scores has no statistical difference in training set ($p = 0.062$), but statistical difference in varidation set ($p < 0.001$).

3.2. Clinical predictors selection

We retained the clinical indicators with statistical differences in the significance test of the training set, and make further choices. There were only three indicators left, including the CDRSB scores ($p < 0.001$), FAQ scores ($p < 0.001$) and MCI stage ($p = 0.003$). Used these three indicators to construct a multivariable logical regression(Forward:LR). The results showed CDRSB (OR 3.36,95%

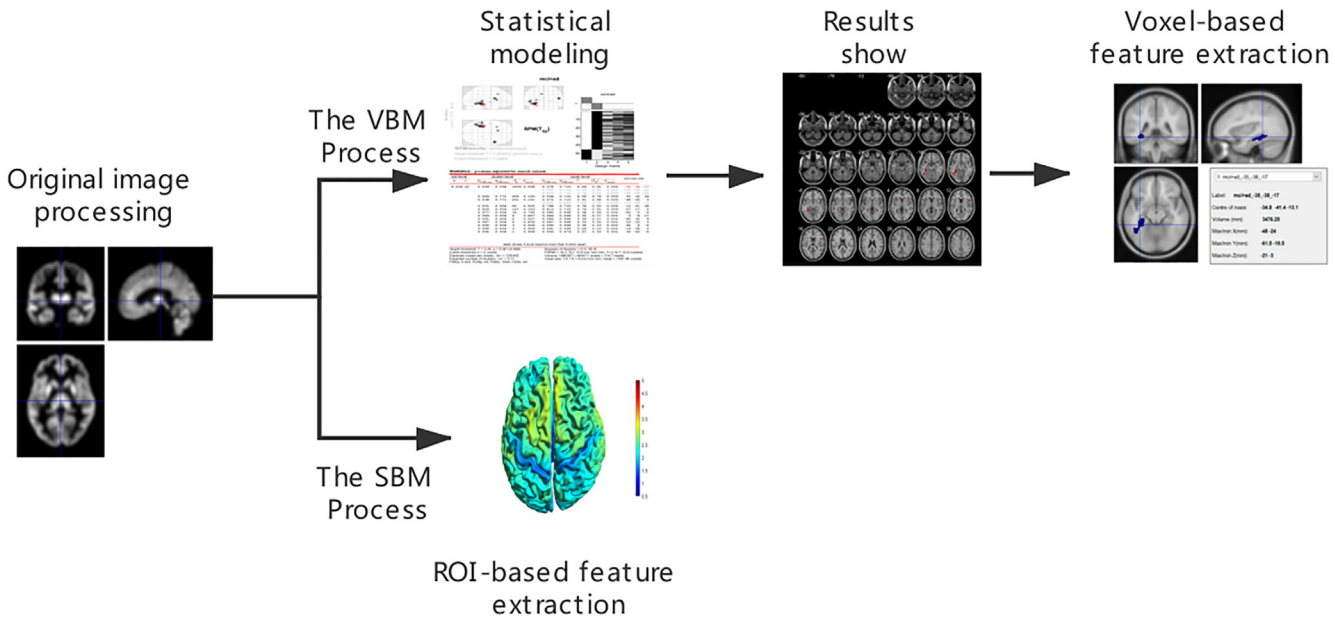

Fig. 2. VBM and SBM processes.

Table 1
Demographic and neuropsychological characteristics of the training and validation data set.

	The training set			The validation set		
	MCI–AD (N = 21)	MCI-MCI (N = 61)	p	MCI-AD (N = 14)	MCI-MCI (N = 42)	p
Age,y(SD)	61.4(2.4)	61.4(2.5)	0.996	60.2(3.3)	61.7(2.4)	0.076
CDRSB,y(SD)	2.1(1.1)	1.2(0.7)	<0.001	2.3(0.8)	1.3(0.7)	0.000
MCI stage						
EMCI,N(%)	2(6.7)	28(93.3)	0.003	2(6.9)	27(93.1)	0.001
LMCI,N(%)	19(36.5)	33(63.5)		12(44.4)	15(55.6)	
Education,y(SD)	16.2(2.5)	16.5(2.6)	0.696	15.9(2.9)	16.4(2.6)	0.526
FAQ(SD)	5.3(4.6)	2.0(3.7)	<0.001	6.1(3.6)	1.5(2.3)	<0.001
FHx						
Yes,N(%)	6(18.8)	26(81.3)	0.255	6(20.0)	24(80.0)	0.353
No,N(%)	15(30.0)	35(70.0)		8(30.8)	18(69.2)	
Gender						
Male,N(%)	11(26.2)	31(73.8)	0.902	5(19.2)	21(80.8)	0.353
Female,N(%)	10(25.0)	30(75.0)		9(30.0)	21(70.0)	
MaritalS						
Yes,N(%)	18(26.1)	51(73.9)	1.000	13(27.1)	35(72.9)	0.664
No,N(%)	3(23.1)	10(76.9)		1(12.5)	7(87.5)	
MMSE(SD)	27.4(1.5)	28.2(1.8)	0.062	26.34(2.0)	28.7(1.6)	<0.001

SD standard deviation; y years; CDRSB Clinical Dementia Rating Scale Sum of Boxes score; EMCI early mild cognitive impairment; LMCI late mild cognitive impairment; N number;FAQ Functional Activities Questionnaire; FHx family history of AD, we classify patients whose parents or brothers/sisters have a clear history of AD diseaseas as Yes, others as No; MaritalS marital status,we classify married status as Yes, divorce and others as No; MMSE mini-mental state examination.

CI 1.57–7.20, p = 0.002), MCI stage (OR 6.89, 95%CI 1.37–34.57, p = 0.019). In order to make the model more simplified, we only keep the indicator of p < 0.01.Only the CDRSB scores was left as a clinical indicator to be included in the construction of the nomogram.

3.3. Image feature's selection

After VBM analysis of whole brain based on voxel level, no statistically significant cluster was obtained.

The screening of SBM features used Lasso regression in the training data set. Fig. 3a shows the coefficients for all features that have undergone lasso regression Then,minimized the mean square error (0.23) and having undergone 3-fold cross-validation, only one feature remained as the indicator:left:lbankssts.thick (Banks of Superior Temporal Sulcus), coefficienct equal to −0.05. Then verified in the veridation set and obtained the mean square error as 0.19. The fearture selection by LASSO sea in the Fig. 3b.

3.4. Image feature's validation

Validation of impact histological features using logistic regression classifiers. The data from the training set was double-sampled, and the predictive power had shown accuracy 0.702, sensitivity 0.714, specificity 0.690,AUC 0.702. The validation set exhibited accuracy 0.735, sensitivity 0.583, specificity 0.784, AUC 0.684.We constructed a linear equation based on the imaging characteristic coefficient and intercept obtained by LASSO regression equation,and the imaging scores were obtained for each individual,used those imaging scores as the final imaging feature.

3.5. Nomogram construction, varidation and calibration

The nomogram constructed using clinical features and imaging features in the training set is shown in Fig. 4. The modle achived C-Index = 0.872(95%CI 0.74–1), $R\hat{2}$ = 0.533, Imgscores (OR 12.39, 95%CI 1.77–86.99, p = 0.011), CDRSB (OR 10.05, 95%CI 2.00–50.40, p = 0.005). The calibation curve shown in Fig. 5a. The closer the cal-

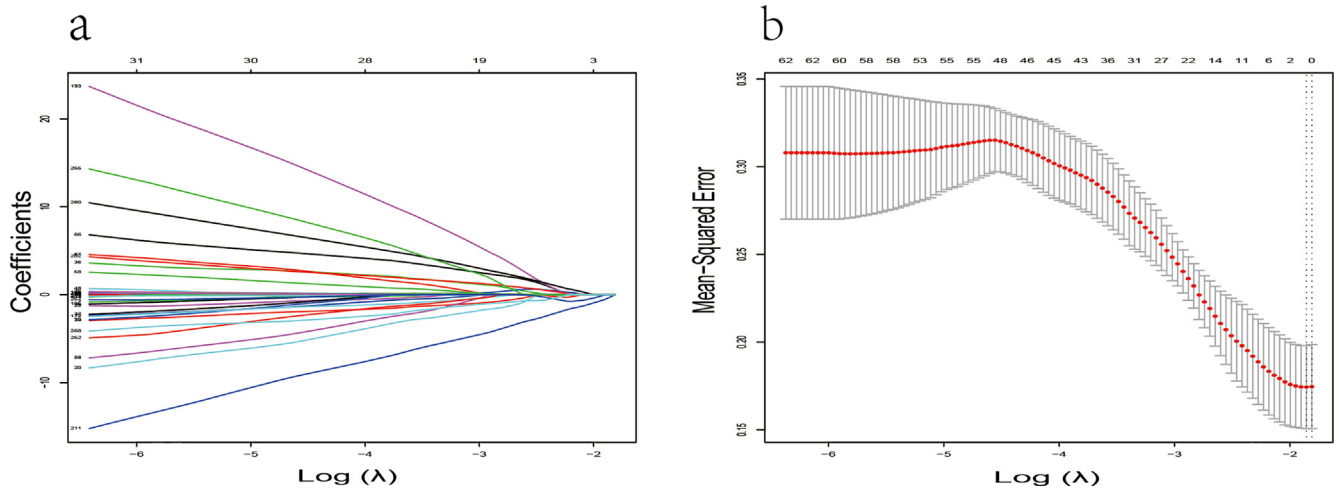

Fig. 3. Filtering features using lasso regression. Fig3: text a:Feature coefficients obtained using lasso regression.b:After 3-fold cross-validation and minimizing the mean square error, the features were selected,only one feature remains at this point.

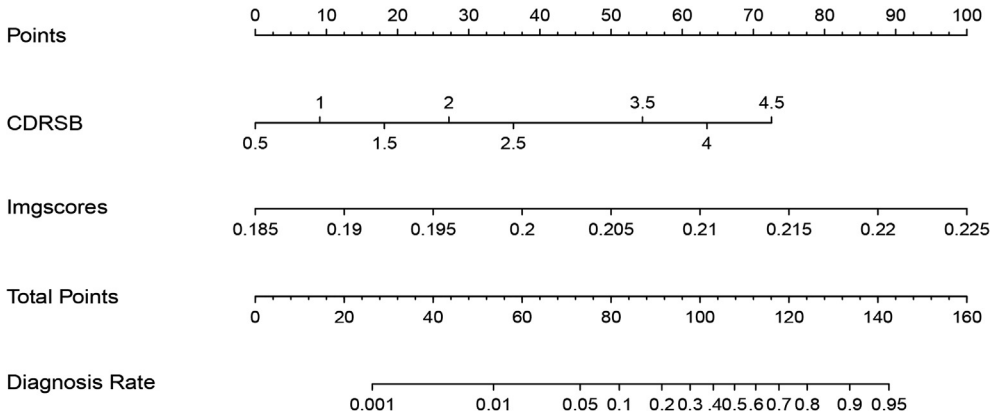

Fig. 4. Nomogram for predicting the conversion of MCI to AD.

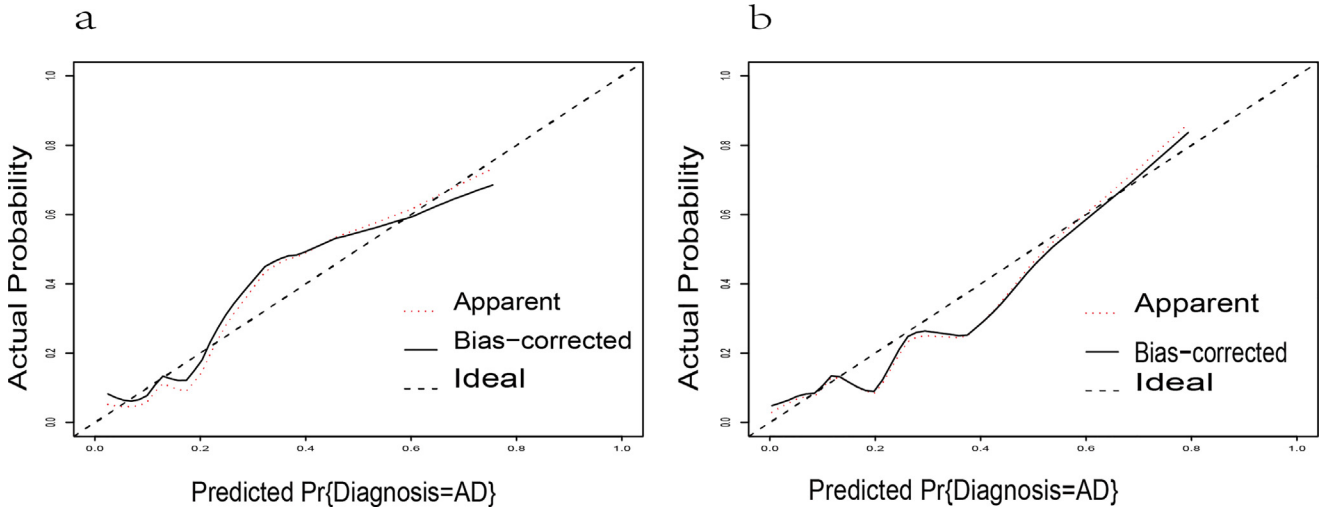

Fig. 5. The calibration curve. Fig 5: Calibration curves validated by 500 bootstrap methods and 3-fold cross-validation. Dotted line:apparent calibration accuracy; solid line: bias-corrected calibration curve; dashed line:ideal. The closer the bias-corrected calibration curve is to the 45 degree slope, the better the calibration. a: Calibration curves for training sets. b: Calibration curves for verification sets.

ibration curve is to the diagonal, the better the predictive power of the nomogram. Then verify in the verification set. The modle of the validation set got C-Index = 0.867(95%CI 0.72–1) $R\hat{2}$ = 0.48, Imgscores(OR 2.75, 95%CI 1.07–7.06, p = 0.036), CDRSB(OR 4.30, 95%CI 1.34–13.80, p = 0.014). The calibration curve shown in Fig. 5b. The results show that the nomogram performs well in the training set and the verification set.

4. Discussion

We divided patients followed for 6–60 months into MCI-MCI and MCI-AD groups by final outcome,and constructed the nomogram using the screened clinical and imaging features. The prediction model achieves good prediction performance in both the training set (c-index 0.872) and the validation set (c-index 0.867). The results showed that the prediction model of this study could better predict the probability of AD conversion in MCI patients aged 65 years and younger in 5 years. Most of the existing studies on Alzheimer's disease prediction models have achieved a high level of accuracy, but also mostly include cerebrospinal fluid marker tests, genetic screening and PETCT examination [5–8]. The invasive nature of cerebrospinal fluid examination, the high cost of genetic screening and PETCT testing, and the lack of necessary equipment result in the low applicability of these findings in clinical practice [23]. We therefore selected only low-cost and widely available clinical features and sMRI to construct this model [24], and provided an online computational tool to facilitate clinical use.

In the process of screening clinical features, we found that CDRSB (p = 0.002) and MCI stage (p = 0.019) were related to outcome events according to logistic regression. CDRSB is widely used in clinical practice and has shown good sensitivity in the staging of dementia [1,25]. The MCI stage also correlates with the final outcome of AD, which is consistent with previous studies [26–28]. Given the relative lack of sample to avoid overfitting of subsequent predictive models, and to simplify the model, we use a more rigorous of the statistical results, only clinical indicators with p < 0.01 were included.

VBM-based whole-brain gray matter analysis is considered one of the more reliable methods for the diagnosis of AD, and some VBM studies have shown that pathological brain regions associated with AD may be concentrated in the medial temporal lobe, frontal lobe, and hippocampus, which can be used as an important biomarker [29–31]. A multicenter, long-term study confirms the stable predictive value of medial temporal lobes in MCI transformation [32]. For VBM analyses, the statistical significance threshold was set to p < 0.001 uncorrected.In the present study, no statistically significant clusters were found in the training group

after correction for sex and age. This may be due to insufficient sample size.

SBM has received a lot of attention and is used in research for a variety of diseases including Alzheimer's disease. Previous studies have shown that cortical thickness, cortical surface complexity, etc. are strongly associated with Alzheimer's disease [33]. CAT12 provides ROI-based SBM measurements with robust and reliable results [34]. We use LASSO regression to screen SBM features. LASSO regression is especially suitable for small samples and high dimensional data. After cross-verification, we select the index filtered when the minimum value is selected as the final feature.In the end, lbankssts.thick was the only indicator left. This is consistent with previous studies that lesions in the brain regions of AD may be concentrated in the temporal lobe [5,35]. We used a logistic regression classifier to validate the imaging features, with an AUC of 0.702 for the training set and 0.684 for the validation set, which confirmed the effectiveness of the imaging features.

Finally, we combined clinical features and imaging features to construct and verify the nomogram.Our model performs well in both training and validation sets. Our conclusion is that this model can be used to screen MCI patients who may progress to Alzheimer's disease under most medical conditions. At the same time, our model inevitably has some shortcomings. We are committed to making the model more suitable for use in most clinical conditions, and the study population is relatively young patients, Clinical data is therefore very insufficient. Additionally, only one screening of imaging features remains in this study, the generalization ability, stability and relationship between imaging features and disease pathology of the model need to be proved by further studies. In addition, we only selected a single research center for modeling, which is not necessarily suitable for all other races or other groups, therefore, external optimization of future model optimization is necessary.

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Conflict of interest

No conflict of interest exits in the submission of this manuscript, and manuscript is approved by all authors for publication. I would like to declare on behalf of my co-authors that the work described was original research that has not been published previously, and not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript that is enclosed.

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