Risk Prediction of Alzheimer's Disease Conversion in Mild Cognitive Impaired Population Based on Brain Age Estimation

Weijia Liu, Qunxi Dong, Shuting Sun, Jian Shen, Kun Qian, *Senior Member, IEEE*, and Bin Hu, *Fellow, IEEE*

***Abstract*— Alzheimer's disease (AD) is one of the most common neurodegenerative diseases in the world. To reduce the incidence of AD, it's essential to quantify the AD conversion risk of mild cognitive impaired (MCI) individuals. Here, we propose an AD conversion risk estimation system (CRES), which contains an automated MRI feature extractor, brain age estimation (BAE) module, and AD conversion risk estimation module. The CRES is trained on 634 normal controls (NC) from the public IXI and OASIS cohorts, then it is evaluated on 462 subjects (106 NC, 102 stable MCI (sMCI), 124 progressive MCI (pMCI) and 130 AD) from the ADNI dataset. Experimental results show that the MRI derived age gap (AG, chronological age subtracted from the estimated brain age) significantly distinguish NC, sMCI, pMCI and AD groups with *p*-value = 0.000017. Considering AG as the primary factor, incorporating gender and Minimum Mental State Examination (MMSE) for more robust Cox multi-variate hazard analysis, we concluded that each additional year in AG is associated with 4.57% greater AD conversion risk for the MCI group. Furthermore, a nomogram was drawn to describe MCI conversion risk at the individual level in the next 1 year, 3 years, 5 years and even 8 years from baseline. This work demonstrates that CRES can estimate AG based on MRI data, evaluate AD conversion risk of the MCI subjects, and identify the individuals with high AD conversion risk, which is valuable for effective intervention and diagnosis within an early period.**

***Index Terms*— Alzheimer's disease, conversion risk prediction, brain age, cox hazard analysis, nomogram.**

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This work involved human subjects or animals in its research. The authors confirm that all human/animal subject research procedures and protocols are exempt from review board approval.

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I. Introduction

ALZHEIMER'S disease (AD) is one of the most common neurodegenerative diseases and the incidence increases exponentially [1]. There will be 1 in 85 persons living with it by 2050 [2], which will greatly increase the global social burden. Mild cognitive impairment (MCI) is a transitional state of normal aging to dementia [3] and individuals with MCI may at high conversion risk to AD [4]. Predicting AD conversion risk of MCI individuals is crucial for disease early intervention and delaying the pathology process [5], [6], [7].

Abnormal changes in brain are associated with cognitive decline [8], [9], [10]. Brain age has been developed as an effective AD biomarker to estimate the patients' faster neurodegenerations compared to normal controls [11], [12], [13], [14]. Compared with the neuroimaging biomarkers, such as the cerebrospinal fluid (CSF) and MRI biomarkers, brain age performs better in detecting cognitive decline [15] and has stronger clinical interpretability and applicability. In this study, we introduce the "Age Gap" (AG) [16], [17], formulated as the difference between the estimated brain age and the individual's chronological age. A positive AG value represents that the individual's estimated brain age is older than his/her chronological age, indicating the accelerate neurodegeneration.

Many studies have utilized CSF biomarkers, including amyloid-β (Aβ42), total tau (P-tau), and phosphorylated tau (T-tau) to evaluate the conversion risk of MCI [18], [19]. MCI individuals with high CSF tau and no proportional increase in p-tau-181 are at a higher conversion risk to AD [19]. However, the detection of the CSF biomarkers is invasive and may cause discomfort and side effects in subjects, thus limiting the application of this method in early AD diagnosis. In addition, classification of MCI into progressive MCI (pMCI) and stable MCI (sMCI) is also currently popular method for MCI conversion risk prediction [20], [21], [22], [23], [24]. These studies construct deep learning models based on the extracted neuroimaging features, such as tissue volumes and cortical thickness, etc. The accuracy of pMCI identification is up to 86% [23]. However, the construction and operation costs of the models are relatively high, requiring a large amount of raw data and strong computing power as support. The common deficiency of all the above studies is that little is known about the quantitative conversion risk. Therefore, this study sets out to predict the conversion risk to AD in MCI population based on Cox proportional hazards analysis.

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Cox proportional hazards model (Cox regression model) [25] has been widely used in the medical research for multi-variate survival analysis. Compared with machine learning models, Cox model performs better in dementia risk prediction [26]. Available studies [27], [28] applied it based on neuroimaging features to analyze the correlation between neuroimaging features and risk probability but lack studies of individualized prediction. Based on the Cox regression or other multi-variate regression analysis, the nomogram was used widely in disease diagnosis [29] due to its ability to reduce the complex statistical prediction into a single numerical estimation of the probability of outcome event. The nomogram transforms the complex regression equation into a visual graph, making the results of the prediction model more readable and interpretable. Therefore this study intends to utilize AG as the main risk variate of the Cox regression model to analyze the hazard of MCI converting to AD and then build a nomogram to quantify and visualize the individual conversion risk. To our best knowledge, this is the first study applying nomogram based on the Cox regression for AD conversion quantitative prediction at individual level.

The contributions of the current research are organized as following. Firstly, we proposed a novel and fully automated AD conversion estimation system (CRES). Secondly, we consider AG as the primary variate and incorporate other clinical factors, such as gender and MMSE score, to build more robust Cox hazard model. Lastly, we implemented risk estimation at the individual level which is of great clinical significance for early intervention of Alzheimer's disease.

II. Methods

A. Data Acquisition

1) Training Data: All neuroimaging data used in this study are structural T1-weighted MRI scans. To increase the robust and generalization of brain age prediction, MR images of 634 cognitively normal controls (NC) subjects from two independent cohorts were used in the training task. The first cohort was Information Extraction from Images (IXI) http://brain-development.org/ixi-dataset/ and 562 T1w MRI scans of NC were selected. The second cohort was Open Access Series of Imaging Studies (OASIS) https://www.oasis.brains.org and 72 T1w MRI scans were selected. The same pre-processing procedure was conducted to ensure consistency among images from different cohorts.

2) Evaluating Data: Data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset www.loni.ucla.edu/ADNI/ were used for evaluating, including 106 NC subjects, 207 mild cognitive impairment (MCI) and 130 Alzheimer disease subjects (AD). The AD subjects were diagnosed as AD at baseline and had no reversion at follow-up. These MCI subjects were diagnosed as MCI during the baseline visit. Adopting the diagnostic classification at baseline and follow-up, MCI subjects were grouped as: (i) sMCI (stable MCI), if diagnosis was MCI at all available time points (n=102); (ii) pMCI (progressive MCI), if diagnosis was MCI at baseline but converted to AD at follow-up without reversion to MCI (n=125). The demographic information are shown in Table I. All studies are approved by their respective Institutional Review Boards. And informed consent has been obtained from all study participants or their authorized representatives before data collection.

B. The Overview of CRES

This work proposes the AD conversion risk estimation system (CRES) to estimate the AD conversion risk of MCI individuals, as shown in Fig. 1. This system consists of the automated MRI feature extractor, brain age estimation (BAE) module and AD conversion risk estimation module. First, individual MRI scans in the training and evaluating dataset were pre-processed with the SPM12 package https://www.fil.ion.ucl.ac.uk/spm/software/spm12/ and the standard CAT12 toolbox http://dbm.neuro.uni-jena.de/cat/ under the Matlab. We obtained the segmented and smoothed grey matter (GM) and white matter (WM) images. Second, we applied the Principal Component Analysis (PCA) to refine the features of the processed images. On the basis of the refined features of the NC samples in the training dataset, different regression models were established and compared and the best one was chosen as the final brain age estimation (BAE) model. The BAE model was performed on the refined features in the evaluating data to estimate the individual brain age. We obtained and analyzed the AG values for groups at different cognitive stages. Finally, considering the AG, gender, MMSE score of sMCI and pMCI samples as risk variables, Cox proportional hazard analysis was conducted. We analyzed the cumulative conversion risk of MCI subjects to AD in the following ten years. Then a nomogram was drawn to visualize the complicated Cox analysis. It can be easily and intuitively observed of the conversion risk for any MCI patient at any year-point in the next decade.

C. Data Pre-Processing

The data format from the IXI cohort was NIFTI and the others were DICOM. MRIcron https://www.nitrc.org/projects/mricron was used to convert DICOM to NIFTI. Pre-processing of the T1w MRI scans were performed using the SPM12 package and the standard CAT12 toolbox. All of the T1w-MRI scans were linearly registered into a standard space (MNI152), segmented into the white matter (WM), grey matter (GM) and cerebrospinal fluid (CSF) tissues. Then segmentations were bias corrected of intensity non-uniformities and modulated by scaling with the amount of volume changes due to spatial registration. To improve the signal-to-noise ratio of the image, the WM and GM images were smoothed with an 8mm full-width-half-maximum (FWHM) smoothing kernel [16], [30]. The voxel intensities of the smoothed WM and GM were used as MRI features.

D. Data Reduction

There are lots of redundant voxels due to the spatial correlations in voxel-based sMRI [16]. So, dimension reduction or feature refining is necessary for the follow-up brain age estimation modeling. PCA is a widely used dimension reduction method [16], [30], [31]. We applied PCA on the pre-processed WM and GM images in the training dataset. And the same PCA transformation was used on the

TABLE I
CHARACTERISTICS OF SUBJECTS IN THE STUDY

	Training Data		Evaluating Data			
Data Source	**IXI**	**OASIS**	**ADNI**	**ADNI**	**ADNI**	**ADNI**
Category	NC	NC	NC	sMCI	pMCI	AD
No. of subjects	562	72	106	102	124	130
Females/Males	312/250	50/22	48/58	40/62	53/71	62/68
Age (years)	48.64±16.47	76.00±8.00	75.01±5.99	73.59±7.76	73.56±7.36	74.67±7.54
MMSE	n/a	29.19±0.84	29.18±1.14	27.41±2.05	26.74±2.18	22.97±2.68

Only data at the baseline were used.
All data are presented in mean ± standard deviation mode; n/a=not available.
NC=normal controls; sMCI=stable MCI; pMCI=progressive MCI; AD=Alzheimer disease.

evaluation images. We reduced the dimensions of the original 80*80*80 image to 421 principal components and retained 98% of the feature information

E. Brain Age Estimation and Model Validation

The support vector regression (SVR) algorithm was widely used to estimate the brain age in a series of neuroimaging studies and shown to be a robust estimation model [11], [32], [33], [34], [35]. We also made the performance comparison analysis of the SVR model with other similar regression models. For each regression method, the GM and WM features of the NC samples in the training dataset were as independent variables respectively and the individual chronological age as the dependent variable. We used 10-fold cross validation [36] to assess the reliability of the brain age estimation frameworks and the accuracy of each framework was validated by the mean absolute error (MAE), and r^2 score (between chronological and estimated brain age). The expression of MAE and r^2 are shown in Eq. 1-2.

$$MAE = \frac{1}{m}\sum_{i=1}^{m}\left|\hat{y}_i - y_i\right| \tag{1}$$

$$r^2 = 1 - \frac{(\sum_i(\hat{y}_i - y_i))^2}{\sum_i(\hat{y}_i - y_i)^2} \tag{2}$$

where m is the number of total subjects, $\hat{y}_i$ is the estimated brain age and y_i is the individual chronological age. MAE is used to evaluate the degree of closeness between the predicted result and the real value. The smaller MAE value represents the better prediction performance. r^2 score is to explain the variance score of the regression model. The closer r^2 to 1 represents the better regression.

The best framework was chosen as the final brain age estimation (BAE) model. Then the BAE model was applied to estimate the brain age in the evaluating dataset and analyze the AG at different cognitive stages.

F. Cox Proportional Hazards Analysis

Cox proportional hazards model (Cox regression model) [25] is a common procedure for multi-factor survival analysis and has been widely used in medical research [15], [28], [37]. We counted the AG, gender, and MMSE scores of all MCI patients in the evaluating dataset, including sMCI and pMCI. Then we utilized AG as the main risk variable, gender and MMSE score as additional variables, conversion to AD as the outcome event and whether the outcome event occurs as the survival state. In this study, the observation period was ten years. The survival time is the time interval from the baseline visit to first visit with AD diagnosis for pMCI and the time from baseline to the last follow-up for sMCI. Then the risk variables, survival state and survival time were adopted to establish the Cox regression model for evaluating the hazard of MCI patients converting to AD in the follow-up decade. The Cox regression can be denoted as:

$$h(t, X) = h_0(t)e^{\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3} \tag{3}$$

where $h(t, X)$ is the hazard rate function, that is, the probability of the outcome event occurring at time t. x_1, x_2 and x_3 represent gender (male or female), AG (years) and MMSE score respectively, β is the partial regression coefficient of the independent variable and $h_0(t)$ is the baseline hazard rate. Before applying the Cox regression model, we need to determine whether the proportional hazards (PH) assumption is satisfied, that is, the hazard rate (HR) of each risk variable does not change over time. And we checked the PH assumption [38] by Schoenfeld residuals. Cox analysis was performed using R language. In order to evaluate the performance of the Cox model, concordance index (C-index) was applied to estimate the probability of the predicted result consistent with the actual result.

G. Nomogram

To transform the complex Cox regression equation into a simple and visual graph, making the results of the prediction model more readable and more valuable, the nomogram was applied based on the Cox analysis for quantitative prediction of the AD conversion risk in the MCI population. The principle of the nomogram is to assign a score to each variable based on the contribution (regression coefficient) of the variable to the outcome, and then sum up these scores to the total score. Through the functional relationship between the total score and the probability of the outcome event, the predicted probability of the individual outcome event was calculated. In this study, the nomogram was developed using the rms package of R language. A total score can be calculated for each MCI patient, and then the probability of AD conversion risk at any time-point in the next decade can be obtained. The "rms" package was used to draw and calculate the calibration curve for evaluating the prediction credibility of the nomogram.

III. RESULT

A. Brain Age Estimation Model

To estimate the brain age, we built SVR, Linear and Bayesian regression frameworks using the refined features

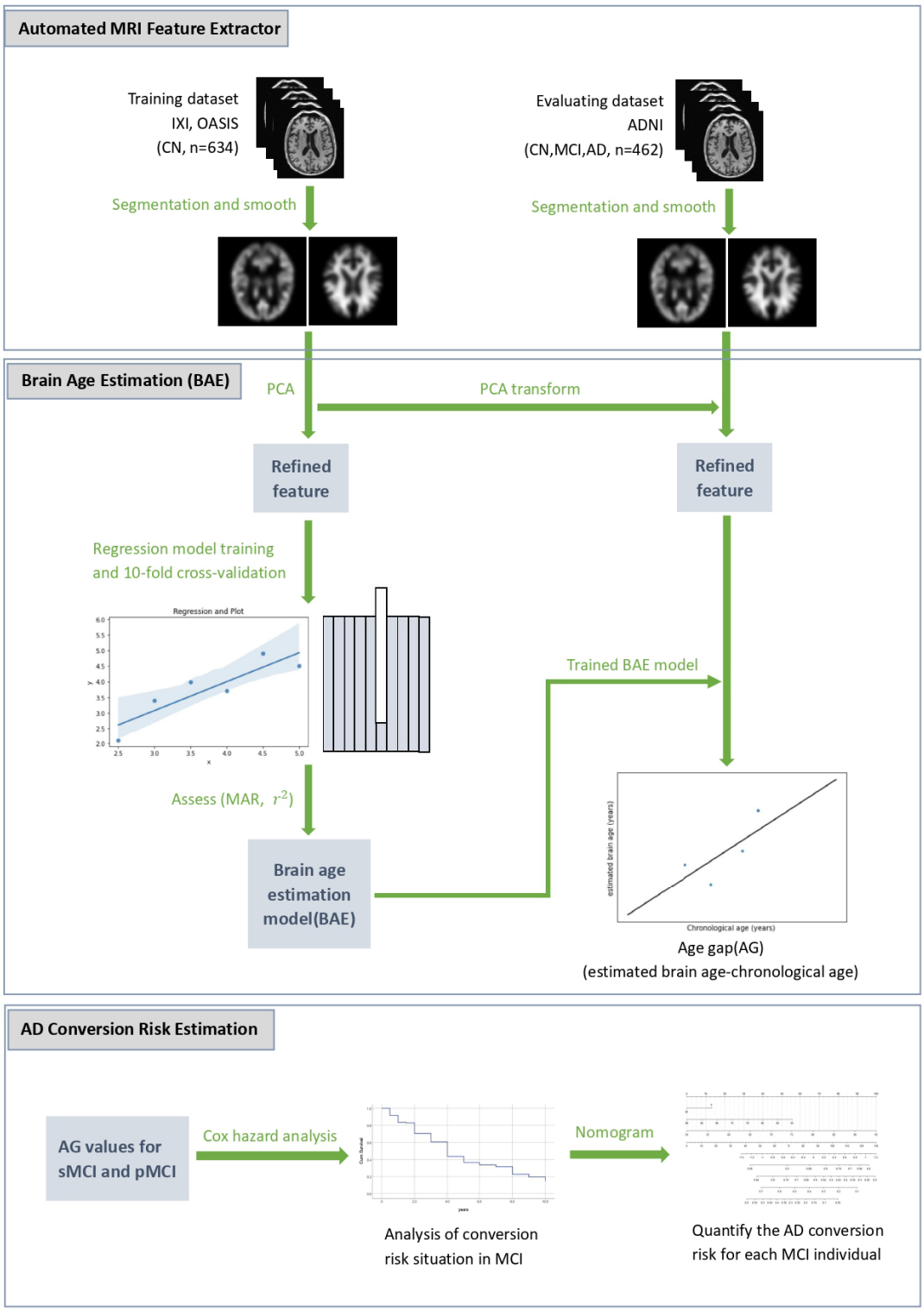


Fig. 1. An illustration of the novel AD conversion risk estimation system. First, all MRI scans were pre-processed by the automated MRI feature extractor, and the segmented and smoothed GM and WM images were obtained as the MRI features. Second, PCA was applied to refine the MRI features and reduct the dimension. Taking the refined features of the NC samples in the training dataset as independent variable and the individual chronological age as dependent variable, different regression models was established and the best one was chosen as the brain age estimation(BAE) model by comparison. The trained BAE model was performed on the evaluating features to obtain the brain age and calculate the AG values. Finally, Cox hazard analysis was conducted according to the AG, gender and MMSE score of the MCI samples and Nomogram was draw to visualize the complex hazard model. The conversion risk for any MCI patient at any year-point in the next decade can be easily and intuitively observed.

of GM and WM respectively in the training set. MAE and r^2 score were used to compare the performance of the brain age estimation frameworks based on 10-fold cross-validation. The MAE (r^2) values was 4.336 (0.897) for SVR training on

TABLE II
THE PERFORMANCE COMPARISON OF THE BRAIN AGE REGRESSION FRAMEWORKS

Regression Method	GM	WM
SVR	**4.336 (0.897)**	5.129 (0.864)
Linear	5.213 (0.883)	5.021 (0.874)
Bayesian	5.086 (0.893)	5.945 (0.817)

All the represented data are in MAE (r^2) mode.
SVR = support vector regression.
Linear = Linear regression.
Bayesian = BayesianRidge regression.

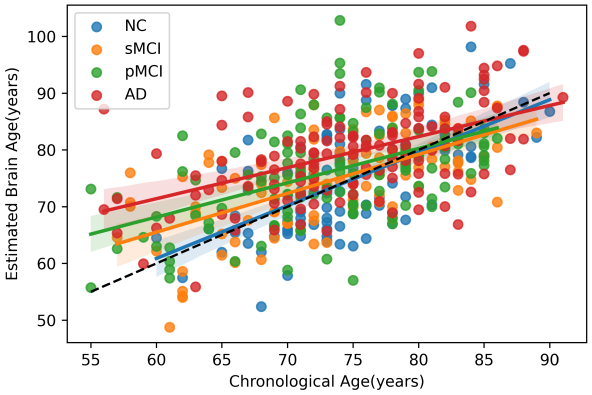


Fig. 2. **Chronological age versus estimated brain age for NC** (blue spot, blue regression line), **sMCI** (orange spot, orange regression line), **pMCI** (green spot, green regression line), **and AD patients** (red spot, red regression line) in the evaluating dataset.

the GM features, which was the best regression model and chosen as the final BAE model. Table II illustrates the details of the comparison among different frameworks.

B. Brain Age Estimation in the Evaluating Group

The trained BAE model was applied to the GM features of NC, sMCI, pMCI and AD samples in the evaluating dataset. Fig. 2 illustrates the estimated brain age versus chronological age at different cognitive status. The dashed line represents brain age equal to chronological age. We found that the predicted brain age of NC was close to the actual chronological age, which verified the predictive accuracy of our BAE model. From NC to AD, with the decline of cognition, the difference between brain age and chronological age becomes larger. The AG value can be calculated by subtracting the chronological age from the brain age. A positive AG indicates that the individual's estimated brain age is older than his/her chronological age. Conversely, a negative AG represents younger brain age. The box plot showing the mean of AG for NC and sMCI, pMCI, AD patients is presented in Fig. 3. The details are as follows: NC (-0.147±5.118 years), sMCI patients (1.287±5.099 years), pMCI patients (2.805±6.247 years) and AD patients (4.769±5.943 years). With the decline of cognitive ability, the mean of AG values increases. F−test is applied to verify the significance of these AGs after removing the outliers, the p-value is 0.000017 ($p < 0.05$), as shown in Table III, indicating that the AG of different groups were significantly different.

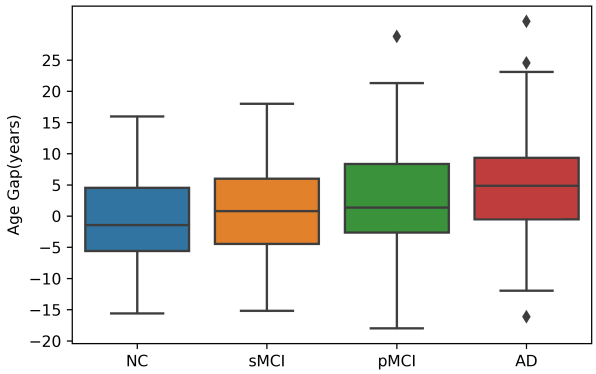


Fig. 3. Comparison of AG values of NC, sMCI, pMCI and AD patients.

TABLE III
ANALYSIS OF SIGNIFICANT DIFFERENCES OF AG AMONG GROUPS AT DIFFERENT COGNITIVE STAGES

	df	sum_sq	mean_sq	F	PR(>F)
Groups	3.0	1400.564	466.855	8.498	**0.000017**
Residual	453.0	24887.088	54.938	NaN	NaN

C. Analysis of the Conversion Risk to AD for MCI Patients

The Schoenfeld residuals was checked to determine whether the PH assumption was met for the cox regression model. Normally, the Schoenfeld residuals should be time independent. As shown in Fig. 4, the p-value of gender, AG and MMSE are 0.5368, 0.3219 and 0.1298 respectively, which are all greater than 0.05, indicating that the harzard rate of each variable has no significant relationship with time, so the PH assumption is satisfied. The same result can be drawn from the fitted curve. The solid line is the fitted spline smooth curve, and the dashed line represents the standard deviation of 2 units above and below the fitted curve. The proportional hazards assumption is not satisfied if the curve deviates by 2 standard deviations. We can concluded that there is no time-dependent change in each risk variables, indicating that the variables satisfy the PH assumption.

The statistics of cox hazard analysis are shown in Table IV. The overall Wald test is significant (p<0.001). The p-value for AG is 0.00195, with a hazard rate (HR=e^{β}) = 1.0457, indicating a strong relationship between the AG and the AD conversion risk in the MCI population. Each additional year in AG was associated with a 4.57% greater risk. Similarly, the p-value of MMSE was less than 0.001 indicates a significant correlation between MMSE score and conversion risk. The HR corresponding to MMSE is 0.8027, indicating that the higher the MMSE score, the lower the conversion risk. By contrast, the variable gender fails to be significant (p=0.0743). The C-index of the cox model was 0.7506 indicating the good discriminating ability. Fig. 5 reflects the MCI survival condition when each varibale is averaged. We can see that as time goes on, the survival probability (SP, interpreted as the probability of non-convert to AD) in MCI is getting lower, that is, the AD conversion risk is getting higher.

Nomogram was applied to visualize the Cox model and intuitively display the quantitative AD conversion risk for the MCI population at the individual level. We can calculate the total risk points corresponding to the three variables (gender, AG and MMSE) to obtain the 1-year, 3-year, 5-year and 8-year

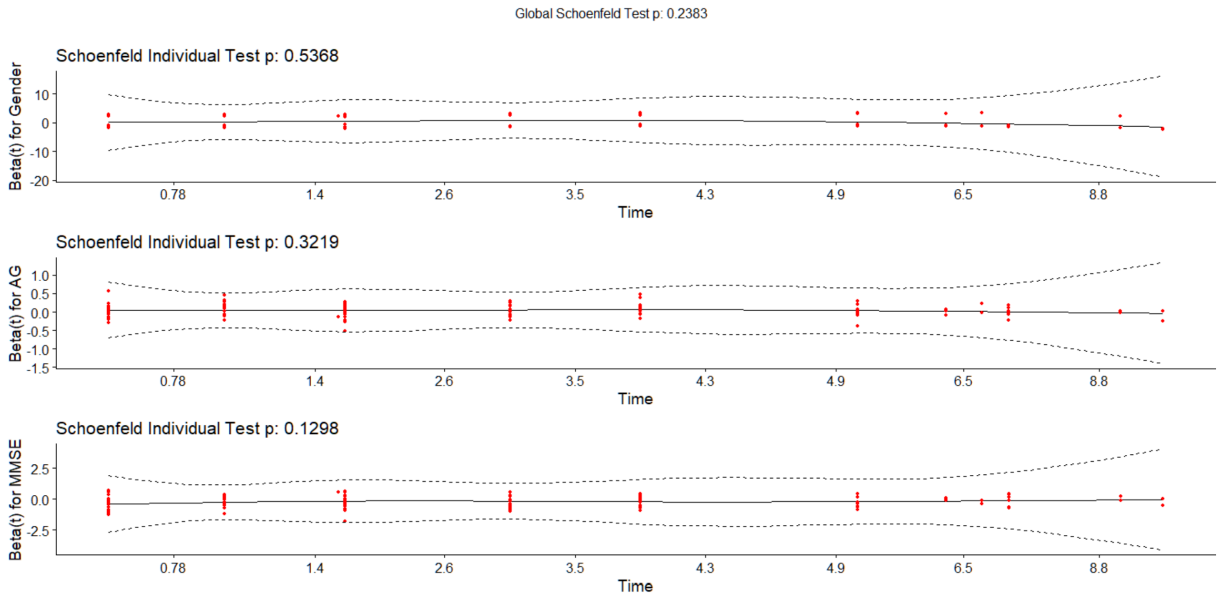


Fig. 4. Schoenfeld residuals test of gender, AG and MMSE for PH assumption. The solid line is the fitted spline smooth curve, and the dashed line represents the standard deviation of 2 units above and below the fitted curve. The PH assumption is not satisfied if the curve deviates by 2 standard deviations.

TABLE IV
STATISTICS OF COX REGRESSION MODEL FOR ALL BASELINE SCORES

Risk variable	β	p	HR	95% CI for HR Lower	95% CI for HR Upper
Gender	0.32838	.	1.3887	0.9683	1.9916
AG	0.04470	**	1.0457	1.0166	1.0757
MMSE	-0.21972	***	0.8027	0.7377	0.8735
Overall model	–	***	–	–	–

β: regression coefficient of the risk variable; HR:Hazard Rate.
The relationship between β and HR: $HR = e^{\beta}$.
*** p<0.001; ** p<0.01; * p<0.05; . p<0.1.

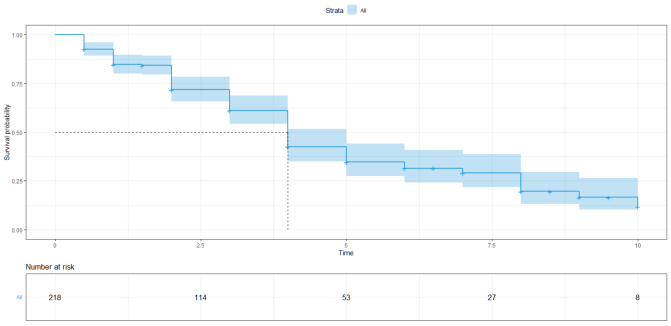


Fig. 5. The survival condition of MCI samples in the next decade according to the Cox analysis. The x-axis represents time and the y-axis represents the number of surviving MCI samples in our collection. Survival represents that the MCI individual didn't convert to AD.

predicted risk (Pr) of the individual, as shown in Fig. 6. Pr can be interpreted as the predicted AD conversion risk at the follow-up time. For example, there is a man diagnosed with MCI, whose AG value is 10 years and the MMSE score is 28. From the nomogram we can obtain the point corresponding to each variable (Gender, AG and MMSE) is 35, 49, 27 and the total points is 101. It could be concluded that in the next year, the person has an 12.5% risk probability of developing AD. Similarly, in the next 3 years, 5 years or even 8 years, the AD conversion risk probability of this person is 33%, 58%, 74%, respectively. As the follow-up time increases, MCI patients are more likely to developing AD.

Calibration chart was used to calibrate the prediction nomogram in Fig. 6. It verifies the predictive performance of the nomogram based on the Bootstrap resampling method in the internal dataset. The x axis represents the nomogram-predicted survival probability (SP), and the y axis represents the actual survival probability. The closer the blue line is to the dashed line, the more accurate the prediction is. Fig. 7 shows the calibration of the nomogram, where we can see that the prediction of 1-year SP, 3-year SP and 5-year SP is relatively accurate, but the prediction of 8-year SP is not.

IV. DISCUSSION

This study proposed a quantitative framework for AD conversion risk prediction of the MCI based on the baseline MRI. We merged the gender, AG index and MMSE of MCI samples as the reliable predictors to establish a Cox hazard regression model. The Cox model can analyze the specific relationship between each predictor and the conversion risk and then predict the overall AD conversion risk of the MCI subjects. A nomogram was performed to visualize the complicated Cox model and quantitatively display the risk probability for each MCI patient. Experimental results demonstrated that the quantitative prediction framework had a good performance for predicting the AD conversion risk of the MCI.

To date, several studies have utilized brain age as a reliable biomarker in predicting the abnormal brain changes in AD pathological progress [15], [35], [39], [40]. The increase of chronological age will cause changes in brain structure. AG is calculated by subtracting the physiological age value from the estimated brain age, and only the abnormal brain structure changes are retained for analysis. Using the structural MRI, the complex patterns of aging across the whole brain were aggregated into a single value, AG, based on our proposed CRES. In order to achieve robust and high-precision brain age

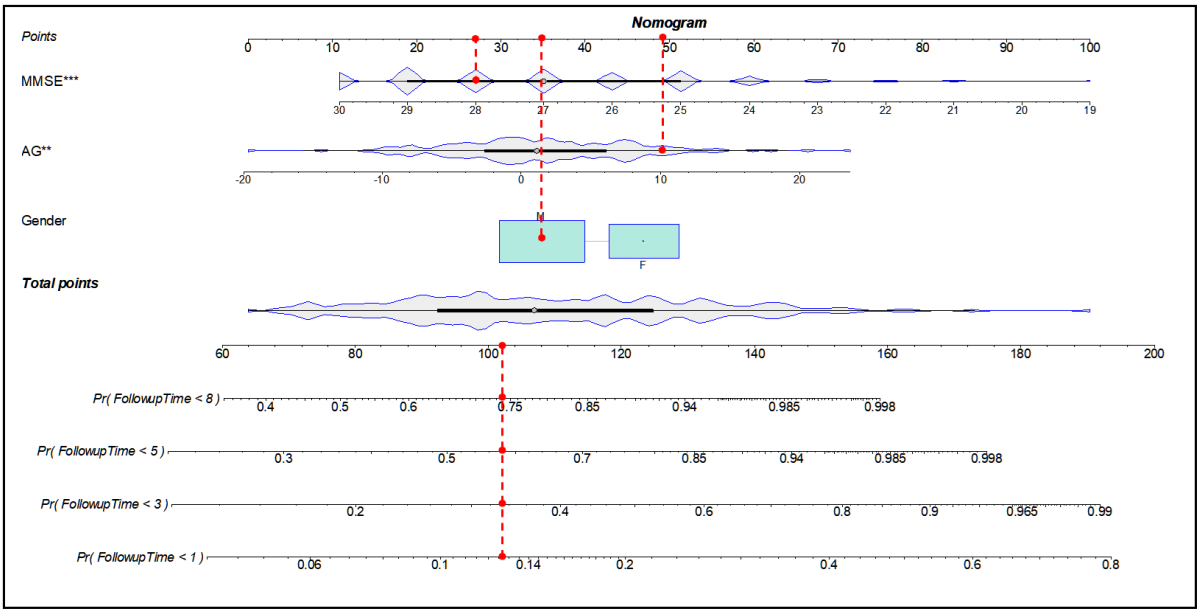
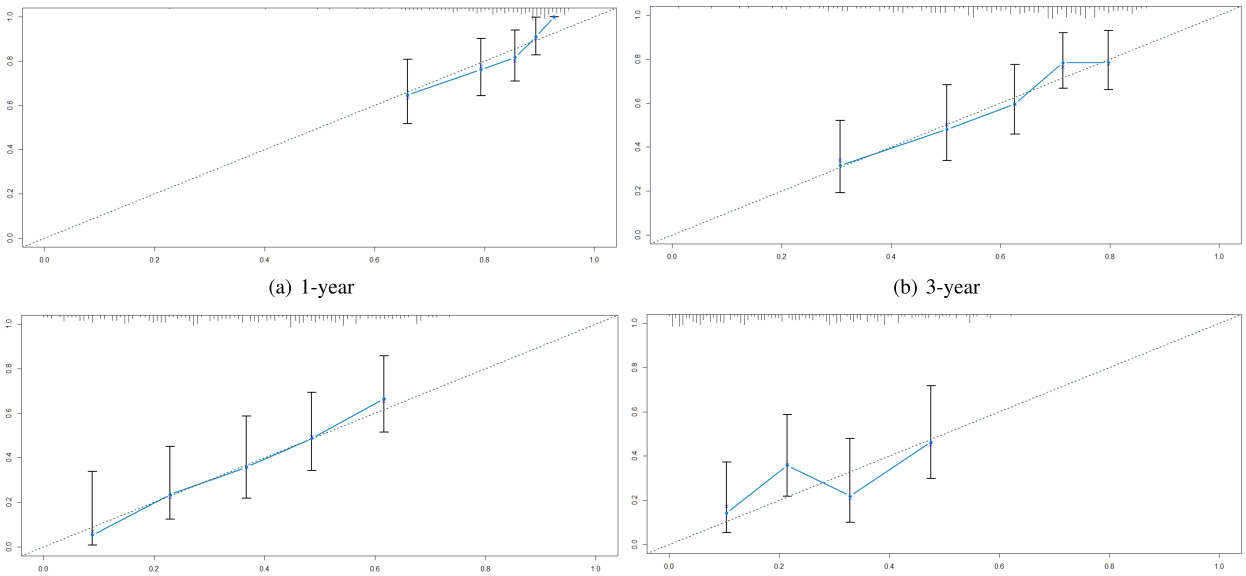


Fig. 6. The nomogram based on the Cox model for quantitative risk prediction of developing AD in the MCI population. We can calculate the total risk points corresponding to the three variables (gender, AG and MMSE) to obtain the 1-year, 3-year, 5-year and 8-year predicted risk (Pr) of the individual.



(a) 1-year (b) 3-year

(c) 5-year (d) 8-year

Fig. 7. Nomogram-predicted probability of n-year SP versus actual n-year SP. The dotted lines on the diagonal represent the perfect prediction of the ideal model, and the blue lines represent the performances of the nomogram prediction model. The closer the blue line is to the dotted line, the better the predictive effect. SP is the survival ability (not converting to AD). The *x* axis represents the nomogram-predicted survival probability, and the *y* axis represents the actual survival probability.

estimation, we selected NC samples from two independent cohorts, age spanning from 20 to 93 years old and verified kinds of regression models. Evaluated on NC smaples from ADNI, it was found that the average AG was -0.147, which confirmed the prediction accuracy and stability of the CRES trained on the IXI cohort and OASIS cohort. As the cognitive decline, the abnormal structural changes are being significant (see Fig. 3).

It can be seen from the previous study [15] that the greater difference between brain age and chronological age indicates the higher risk of developing AD, which is consistent with our experimental results. However, the specific relationship between AG and cognitive decline risk remains to be explored. Our AG predictions and cox analysis are all based on the baseline. From our cox analysis, we concluded that each additional year of AG indicates a 4.57% higher risk (see Table IV) of developing AD for MCI individuals, which is highly valuable for early intervention and treatment of cognitive decline. This study has demonstrated the feasibility and the good performance of CRES.

Many studies focused on the binary classification of MCI [20], [21], [41], and identifying MCI participants at AD conversion risk using CSF biomarkers [18], [19], blood-based biomarkers [42]. However, few studies concerned when conversion occurs and how likely the conversion risk possibility. It is crucial to identify the abnormal time onset

and quantify the risk possibility, which will provide great help for MCI intervention and treatment. This is the first study that performed nomogram based on the cox model to quantitatively predict the probability of the AD conversion risk for MCI patients at the individual level. The derived predictors are at the baseline. According to the experimental results, the quantitative AD conversion risk probability of the MCI patients in the next 1 year, 3 years, 5 years or even 8 years are effective. Based on CRES, it is possible to make reasonable interventions and treatments based on the individual AD risk evaluation.

We counted the follow-up time of MCI subjects in the ADNI dataset, details as following: 78 pMCI patients converted to AD within three years from baseline, 30 patients converted to AD within five years, and the remaining 16 pMCI patients converted within 10 years. 69 sMCI patients had follow-up records within five years, and the remaining sMCI patients had follow-up records for 10 years or more. To make a more accurate and longer-term prediction of the AD conversion risk in MCI patients, we selected 10 years as the study observation period. As shown in Fig. 7, we validated the prediction ability of the nomogram. The prediction accuracy is high in 5 years, but poor in the 8th year. This is because the MRI scans used in this study were all baseline data, and the impact radiation was 1-5 years. Eight years is too long to predict status at that time from baseline data, and a fifth year of follow-up data may be required to calculate conversion risk at the eighth years even later. But to a certain extent, it can provide a reference for the current intervention.

Prior to brain age prediction, we used PCA for feature dimensionality reduction of gray and white matter images. PCA reduced the dimension of redundant voxels and only focused on voxels that had a significant effect on the prediction of brain age. PCA has been applied as a standard data reduction technique in many studies to extract principal components associated with brain age prediction from neuroimaging [1], [6], [7]. It tends to be better when the dimensionality of the data was reduced via PCA[5]. However, the disadvantage of PCA is the lack of interpretability. It is difficult to visualize principal components extracted from 3D medical images. Therefore, in the future, the application of feature extraction with deep model to predict brain age and visualization of intermediate feature map is a direction of improvement.

Nevertheless, there are still some limitations in the study. Firstly, simple machine learning models have limited learning ability for image features. Deep learning has been one of the mainstream for MR images study with their super learning ability and high accuracy [43], [44], [45]. Secondly, it's unknown that which regions of interest (ROIs) play crucial roles for brain age estimation. Prior to brain age prediction, we used PCA for feature dimensionality reduction of gray and white matter images, which has been applied as a standard data reduction technique in many studies to extract principal components associated with brain age prediction from neuroimaging [15], [31], [46]. However, the disadvantage of PCA is the lack of interpretability. PCA results in difficult one-to-one correspondence between subsequent features and brain regions. Every feature obtained by PCA is the result of the combined action of all brain regions. In the future, the application of deep learning model to predict brain age and visualization of intermediate feature map is a direction of improvement. Utilizing "saliency maps" or "explanation maps" to represent the effect of each voxel in the BAE's prediction [47], [48], [49] is a helpful approach to this issue.

V. Conclusion

This work proposed a comprehensive brain age estimation and longitudinal AD conversion risk prediction framework, i. e., the CRES. Results showed that the CRES revealed significant AG patterns of different clinical groups, which lays a good foundation for the following AD conversion risk analysis. The established cox model and nomogram analysis quantitatively predict the AD conversion risk for MCI individuals, reveal the AD pathological progress patterns of MCI patients, and identify the MCI individuals with high conversion risk to AD. It is valuable for providing effective interventions in a relatively early period.

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