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Original Research

Predicting Cognitive Decline for Non-Demented Adults with High Burden of Tau Pathology, Independent of Amyloid Status

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Abstract

BACKGROUND: Abnormal tau proteins are independent contributors to cognitive impairment. Nevertheless, not all individuals exposed to high-level tau pathology will develop cognitive dysfunction. We aimed to construct a model to predict cognitive trajectory for this high-risk population.

METHOD: Longitudinal data of 181 non-demented adults (mean age= 73.1; female= 45%), who were determined to have high cerebral burden of abnormal tau by cerebrospinal fluid (CSF) measurements of phosphorylated tau (ptau181) or total tau, were derived from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Cognitive decline was defined as Mini-Mental State Examination scores decline ≥ 3 over three years. A predictive nomogram was constructed using stepwise backward regression method. The discrimination, calibration, and clinical usefulness of the nomogram were evaluated. The model was validated in another 189 non-demented adults via a cross-sectional set (n=149, mean age = 73.9, female = 51%) and a longitudinal set (n= 40, mean age = 75, female = 48%). Finally, the relationships of the calculated risk scores with cognitive decline and risk of Alzheimer's disease were examined during an extended 8-year follow-up.

RESULT: Lower volume of hippocampus (odds ratio [OR] = 0.37, p< 0.001), lower levels of CSF sTREM2 (OR = 0.76, p = 0.003), higher scores of Alzheimer's Disease Assessment Scale-Cognitive (OR = 1.15, p = 0.001) and Functional Activities Questionnaire (OR = 1.16, p = 0.016), and number of APOE ε4 (OR = 1.88, p = 0.039) were associated with higher risk of cognitive decline independent of the amyloid status and were included in the final model. The nomogram had an area of under curve (AUC) value of 0.91 for training set, 0.93 for cross-sectional validation set, and 0.91 for longitudinal validation set. Over the 8-year follow-up, the high-risk group exhibited faster cognitive decline (p< 0.001) and a higher risk of developing Alzheimer's dementia (HR= 6.21, 95% CI= 3.61-10.66, p< 0.001).

CONCLUSION: APOE ε4 status, brain reserve capability, neuroinflammatory marker, and neuropsychological scores can help predict cognitive decline in non-demented adults with high burden of tau pathology, independent of the presence of amyloid pathology.

Key words: Tau, predict, nomogram, cognitive decline, Alzheimer's disease.

Introduction

Tau is a critical protein functionally responsible for stabilizing microtubules and maintaining neuronal function and cognitive health (1). Under pathological conditions, the abnormal misfolding and aggregation of tau proteins will damage the normal functions of microtubules and lead to neuronal loss and neurodegeneration, such as Alzheimer's disease (2). Tau proteins in cerebrospinal fluid have been used to reflect the cerebral burden of abnormal tau proteins and assist in disease diagnosis. For example, CSF phosphorylated tau (p-tau181, T) and total tau (t-tau, N) proteins are important components of A/T/N research framework to define AD biological continuum along with amyloid pathology marker (A) (3, 4). Recently, lines of evidences are increasingly strengthening the roles of abnormal tau proteins in contributing to cognitive decline independent of amyloid pathology. A recent longitudinal study indicated that early neocortical tau accumulation partially mediated the interactive association of vascular risk factors and Aβ on cognitive decline (5). A cohort study verified that tau accumulated in medial temporal region was associated with declined memory without Aβ (6). Moreover, another cohort study demonstrated that tau deposition was associated with reduced cortical volumes and thickness of temporal and parietal regions independently of Aβ (7).

Interestingly, some autopsy studies found that high levels of neurofibrillary tangles were found in the brains of elder subjects who were cognitively normal during their lifetime (8-11). A possible explanation is that the detrimental impact of tau burden on cognitive impairments might be offset by certain factors (12, 13). Identifying these factors could help cognitive prognosis prediction and risk stratification, but also promote the precise development of disease-modifying treatment for this specific high-risk population (14). Therefore, the present study is aimed 1) to screen the factors associated with better cognitive trajectory for individuals who are free of dementia but living with high burden of cerebral

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tau proteins and 2) to construct a model for prognosis prediction and risk stratification.

Method

Participants and outcomes

The data of our study were acquired from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort (http://adni.loni.usc.edu), which recruited volunteers from multiple centers across North America. The participants were older adults aged 55-90 years, consisting of normal cognition (NC), mild cognitive impairment (MCI), or AD dementia. The ADNI collected a comprehensive range of information from the participants, including demographics, lifestyle factors, clinical data, neuroimaging scans, biological markers, and neuropsychological assessments. Our study focused on the non-demented participants at enrollment, was based on the diagnostic criteria established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA).

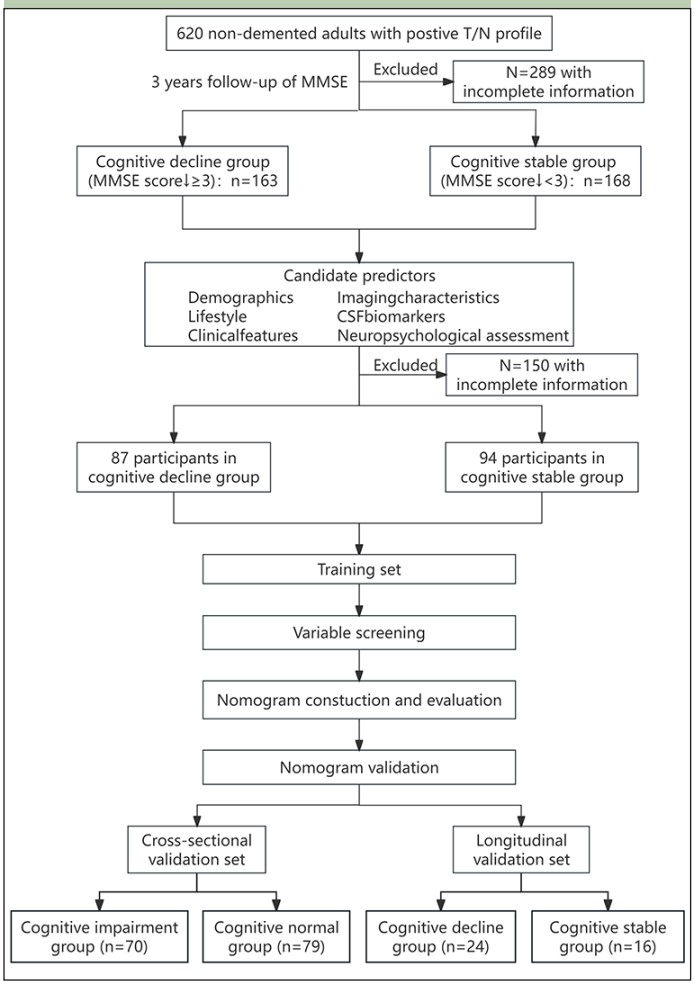
In our study, we used the 2018 NIA-AA "research framework" 3 to describe the biomarker profile of each participant: (i) aggregated Aβ (A) was defined by CSF Aβ1-42; (ii) neurofibrillary tangles (T) was defined by CSF p-tau181; and (iii) neurodegeneration (N) was defined by CSF t-tau. We divided each biomarker into positive (+, abnormal) and negative (-, normal) groups based on their established cut-offs 15. CSF Aβ1-42 < 976.6 pg/ml, CSF p-tau181 > 21.8 pg/ml and CSF t-tau > 245 pg/ml were defined as A+, T+ and N+, respectively. Notably, the scatter plot showed CSF p-tau had a strong correlation with CSF t-tau ($p < 0.001$, $r = 0.97$; Supplementary Figure 1) and we merged these groups to simplify groups as Suárez-Calvet et al described 16. If either aggregated tau (T) or neurodegeneration (N) was abnormal (T+ or N+), participants were classified as abnormal T/N (T/N+).

Among 620 T/N+ non-demented participants, a total of 181 participants (mean age= 73.1; female= 45%) were assigned to the training set to construct a nomogram for predicting cognitive decline. Forty (mean age= 75.0; female= 48%) and 149 (mean age= 73.9; female= 51%) participants were assigned to the longitudinal and cross-sectional validation sets, respectively. The individuals of the training set provided data of all candidate factors at baseline and an MMSE score during the three-year follow-up. The change in the MMSE score was used to define cognitive decline (≥3) and stable cognitive performance (<3). The process of constructing and validating the nomogram were described in Figure 1.

Candidate predictors at baseline

The following 41 candidate predictors were collected, including demographics (5 variables), lifestyle exposures (4 variables), clinical features (14 variables), neuroimaging characteristics (5 variables), CSF neurodegenerative biomarker (5 variables), and neuropsychological assessment (8 variables). These variables were selected because they were predictors associated with cognitive decline or dementia (4, 17).

Figure 1. Flow chart showing the process of nomogram construction and validation



Demographics

The demographics included age, gender, education, marital status, and APOE ε4 status. Education was defined as schooling years. The marital status was described as living alone versus married or living with a partner. Rs7412 and rs429358 were used to define the APOE ε2/ε3/ε4 isoforms 18. The number of ε4 alleles (ε2/ε2, ε2/ε3, or ε3ε3= 0, ε2/ε4 or ε3/ε4= 1, ε4/ε4= 2) was used to describe APOE ε4 status.

Lifestyle exposures

The lifestyle exposures included obesity, smoking habit and drinking habit. Obesity (yes or no) was defined as body mass index ≥ 28 kg/m^2. Smoking and drinking

habits were classified either as "yes" (current users) or "no" (never users).

Clinical features

The clinical features included self-reported medical history of hypertension, coronary heart disease (CHD), stroke, hyperlipidemia, diabetes, cancer, depression, anxiety, and hearing loss, as well as systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP) and mean arterial pressure (MAP). All the features were collected by certificated medical professionals using a standardized ADNI protocol.

Neuroimaging features

The volume of brain region was measured by the 3D T1-weighted volumetric imaging. The voxel dimensions were roughly 1 cubic millimeter, with no single direction exceeding 1.5 mm19. Herein, we chose the whole brain, bilateral hippocampus, entorhinal region, middle temporal region, and intracranial volume as regions of interest. White matter hyperintensities (WMH) volume were acquired by 3D T1-weighted and T2FLAIR images. The details for MRI acquisition and image processing can be found in prior publications (20, 21).

CSF neurodegenerative biomarkers

The CSF samples were collected in the morning after an overnight fast and delivered to ADNI Biomarker Core laboratory at the University of Pennsylvania Medical Center, which storing these samples at −80 °C. The detailed procedures for measuring the CSF Aβ1-42, t-tau, p-tau181 sTREM2 and PGRN have been described as previous (16, 22).

The levels of CSF Aβ1-42, t-tau, and p-tau181 were measured at the multiplex xMAP platform using immunoassay kit-based reagents. The kits were consisted of monoclonal antibodies 4D7A3, AT120 and AT270 to capture Aβ1-42, t-tau and p-tau181. CSF PGRN was quantified through an ELISA protocol, involving a Streptavidin-coated 96-well plate, a biotinylated polyclonal goat anti-human PGRN capture antibody, a monoclonal mouse anti-human PGRN detection antibody, and a SULFO-TAG-labelled goat polyclonal anti-mouse IgG secondary antibody. CSF sTREM2 was assessed using a similar ELISA protocol, comprising a Streptavidin-coated 96-well plate, a biotinylated polyclonal goat IgG anti-human TREM2 antibody as the capture antibody, a monoclonal mouse IgG anti-human TREM2 antibody as the detection antibody, and a SULFO-TAG-labelled goat polyclonal anti-mouse IgG secondary antibody.

Neuropsychological assessments

Cognitive performance and functional performance were measured using eight commonly used neuropsychological scales, including Mini-Mental State Examination (MMSE) (23), Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog) (24), Rey Auditory Verbal Learning Test (RAVLT) immediate and forgetting (25), Trail Making Test (A and B) (26), Functional Activities Questionnaire (FAQ) (27) and Geriatric Depression Scale (GDS) (28).

Cognitive measurements

The roles of risk scores in predicting changes of ADAS-Cog, memory (29) (MEM), executive functions (30) (EF), and AD occurrence during eight years were further tested. MEM and EF were composite scores calculated using psychometrically optimized approaches with items from ADNI neuropsychological assessments. In brief, the EF score were calculated by Trail Making Test (A and B), digit span backward, digit symbol, animal naming, vegetable naming, and the clock drawing test. The MEM score were calculated by the RAVLT, the ADAS-Cog, the MMSE, and the Logical Memory test. AD was diagnosed by certificated medical professionals according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for probable AD (31).

Statistical analyses

Descriptive statistics about population characteristics were presented as proportions (for categorical variables) or mean with standardized deviation (SD) (for continuous variables). Differences between groups were compared by Pearson chi-squared test or independent samples t-test. To primarily screen the predictors, univariate and multivariate logistic regression analyses were separately conducted to calculate the odds ratio (OR) and the corresponding 95% confidence interval (CI), after adjusting for amyloid status, gender, age, WMH, and clinical diagnosis at baseline.

Next, we performed univariate screening using the stepwise backward regression to determine the best combination of predictive factors ($p< 0.05$) for constructing the nomogram. The stepwise backward regression was used to select variables for inclusion in the nomogram based on the Akaike information criterion (AIC) minimum (32). The nomogram was constructed based on the scaling of regression coefficient in the multivariate logistic regression. The effect of the variable with the highest β coefficient (absolute value) was assigned a score of 100 points. The points were added across independent variables to derive total points, which were converted to predicted probabilities of cognitive decline (33).

Table 1. Candidate variables of the training cohort

Variables	Total (n = 181)	Cognitive stable (n = 94)	Cognitive decline (n = 87)	p-value
1. Demographics				
Age, years, mean ± SD	73.06 ± 7.09	72.68 ± 6.98	73.47 ± 7.22	0.441
Female, n (%)	82 (45)	42 (45)	40 (46)	0.861
Education, years	16.33 ± 2.73	16.48 ± 2.76	16.17 ± 2.78	0.863
Cohabitation status, n (%)				
Living alone	36 (20)	23 (24)	13 (15)	0.109
Married or living with partner	145 (80)	71 (76)	74 (85)	
APOEε4 alleles (n = 0, 1, 2)	0.72 ± 0.73	0.51 ± 0.65	0.94 ± 0.74	<0.001
2. Lifestyle				
Obesity	48 (27)	32 (34)	16 (18)	0.017
Current smoker, n (%)	76 (42)	41 (44)	35 (40)	0.645
Current drinker, n (%)	5 (3)	2 (2)	3 (3)	0.588
3. Clinical features				
Hypertension, n (%)	83 (46)	39 (41)	44 (51)	0.220
Blood pressure (mmHg)				
SBP	133 ± 15.25	132.9 ± 14.03	133.1 ± 16.54	0.997
DBP	73.78 ± 9.76	73.86 ± 9.36	73.69 ± 10.24	0.837
PP	59.19 ± 14.02	59.01 ± 13.88	59.39 ± 14.25	0.756
MAP	93.51 ± 9.87	93.53 ± 9.01	93.49 ± 10.77	0.945
CHD, n (%)	19 (10)	9 (10)	10 (11)	0.674
Stroke, n (%)	11 (6)	5 (5)	6 (7)	0.657
Hyperlipidemia, n (%)	86 (48)	43 (46)	43 (49)	0.620
Diabetes, n (%)	16 (9)	6 (6)	10 (11)	0.226
Cancer, n (%)	20 (11)	10 (11)	10 (11)	0.854
Depression, n (%)	34 (19)	14 (15)	20 (23)	0.164
Anxiety, n (%)	10 (6)	4 (4)	6 (7)	0.437
Hearing loss, n (%)	36 (20)	21 (22)	15 (17)	0.391
4. Imaging characteristics (cm^3)				
Total brain volume	1040.30 ± 114.17	1065.40 ± 105.08	1013.10 ± 117.91	0.001
Hippocampus volume	6.76 ± 1.12	7.30 ± 1.03	6.17 ± 0.90	<0.001
Entorhinal volume	3.51 ± 0.74	3.73 ± 0.67	3.27 ± 0.74	<0.001
Mid-temporal volume	19.74 ± 2.83	20.75 ± 2.60	18.65 ± 2.67	<0.001
WMH volume	4.62 ± 8.20	3.64 ± 8.59	5.68 ± 7.68	0.005
5. CSF biomarkers				
Aβ1-42 (ng/ml)	1.05 ± 0.64	1.28 ± 0.69	0.79 ± 0.47	<0.001
P-tau181 (pg/ml)	0.03 ± 0.01	0.03 ± 0.01	0.04 ± 0.01	0.002
T-tau (pg/ml)	0.35 ± 0.11	0.33 ± 0.10	0.37 ± 0.11	0.006
PGRN (ng/ml)	1.61 ± 0.44	1.62 ± 0.33	1.59 ± 0.53	0.106
STREM2 (ng/ml)	4.72 ± 2.30	5.21 ± 2.58	4.19 ± 1.83	0.002
6. Neuropsychological assessment				
MMSE (point)	27.81 ± 1.81	28.20 ± 1.63	27.38 ± 1.91	0.003
ADAS-cog (point)	15.82 ± 7.29	11.82 ± 5.24	20.13 ± 6.73	<0.001
RAVLT-immediate (point)	35.07 ±10.26	39.71 ± 9.39	30.06 ± 8.70	<0.001
RAVLT-forgetting (point)	5 ± 2.38	4.51 ± 2.64	5.53 ± 1.94	0.003
Trail Making Tests A (second)	39.57 ± 18.73	35.93 ± 16.30	43.51 ± 20.41	0.001
Trail Making Tests B (second)	106 ± 60.45	89.63 ± 47.65	123.8 ± 67.68	<0.001
FAQ (point)	3.11 ± 4.40	1.48 ± 2.83	4.87 ± 5.08	<0.001
GDS (point)	1.45 ± 1.35	1.40 ± 1.36	1.49 ± 1.34	0.542

Abbreviations: APOE = Apolipoprotein E; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; PP = Pulse Pressure; MAP = Mean Arterial Pressure; CHD = Coronary Heart Disease; GFR = Glomerular Filtration Rate; WMH = White Matter Hyperintensities; CSF = Cerebrospinal fluid; PGRN = Progranulin; sTREM2 = soluble triggering receptor expressed on myeloid cells 2; MMSE = Mini-Mental State Examination; ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognition; RAVLT = Rey Auditory Verbal Learning Test; FAQ = Functional Activities Questionnaire; GDS = Geriatric Depression Scale.

To evaluate the performance of the nomogram, we assessed discrimination, calibration, and clinical utility (34). The area under the curve (AUC) was calculated by the receiver operating characteristic curve (ROC) to assess the discriminatory ability of the nomogram model. The AUC ranged from 0.5 to 1.0, where a value of 0.5 indicated no discriminatory power, while a value of 1.0 indicated optimal separation (35). The Bootstrap method was used for internal validation of the calibration. The consistency of the model was evaluated using the Hosmer-Lemeshow test with a p-value > 0.05 considered good predictive conformity of the model. Decision curve analysis (DCA) was used to assess the predictive value and clinical utility of the model (36).

Finally, we examined the values of the constructed risk scores in predicting long-term risk of cognitive decline and developing AD among T/N+ population. The risk scores for each subject were calculated according to the nomogram. Participants were categorized into two groups (high-risk and low-risk) using the best cutoff value in ROC curve by maximizing Youden's index (ie, sensitivity+specificity-1). Linear mixed-effects (LME) regression models can handle unbalanced value, censored data and continuous variables for time (37). Regression diagnostics were conducted and outliers were excluded to indicate that all models met the necessary assumptions: model residuals were normally distributed and did not exhibit heteroscedasticity. The LME regression models were used to examine the longitudinal relationship of risk score group with changes in ADAS-Cog, MEM and EF scores during 8-year follow-up, after adjusting for age, gender, education level, and baseline cognitive diagnosis. The cumulative incidence curve for each group was measured using the Kaplan–Meier method. With the proportional hazards assumption tested, the time-dependent Cox proportional hazards regression models were used to assess whether the high-score group was associated with a higher risk of incident AD compared to the low-score group.

All statistical analyses were performed using the statistical software package R, version 4.2.1 (https://cran.r-project.org). The packages of R used included "rms", "foreign", "reader", "ResourceSelection", "readr", "lme4", "lmerTest", "arm", "nlme", "survival", "ggplot2", "ggpubr", "magrittr", and "survminer".

Data statement

The data that support this study are available from the corresponding author.

Results

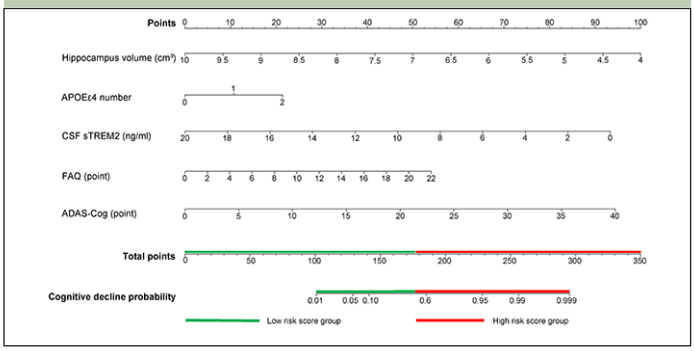
Characteristics of participants

The characteristics of demographics, lifestyle, clinical features, imaging, CSF biomarkers, and neuropsychological assessment for training set were summarized in Table 1. The corresponding characteristics of factors included in the nomogram for two validation sets were described in Supplementary table 1.

Predictors of cognitive decline in T/N+ population

The detailed results of univariable logistic regression were presented in the Supplementary table 2. After adjusting for A status, gender, age, WMH volume, and baseline diagnosis, ten factors were significantly associated with risk of cognitive decline in non-demented adults with T/N+ profile, including APOE ε4 status [odds ratio (OR): 1.81, 95% CI: 1.08-3.09], FAQ score (OR: 1.26, 95% CI: 1.13-1.43), ADAS-Cog score (OR: 1.23, 95% CI: 1.15-1.33), Trail Making Test B score (OR: 1.01, 95% CI: 1.00-1.01), total brain volume (OR: 0.99, 95% CI: 0.98-0.99), RAVLT-immediate score (OR: 0.89, 95% CI: 0.84-0.93), CSF levels of sTREM2 (OR: 0.81, 95% CI: 0.69-0.95) and volumes of middle temporal region (OR: 0.66, 95% CI: 0.55-0.79), entorhinal region (OR: 0.40, 95% CI: 0.22-0.68), and hippocampus (OR: 0.28, 95% CI: 0.17-0.45). (Supplementary table 3)

Figure 2. Nomogram which predicts the probabilities of cognitive decline for T/N+ non-demented population

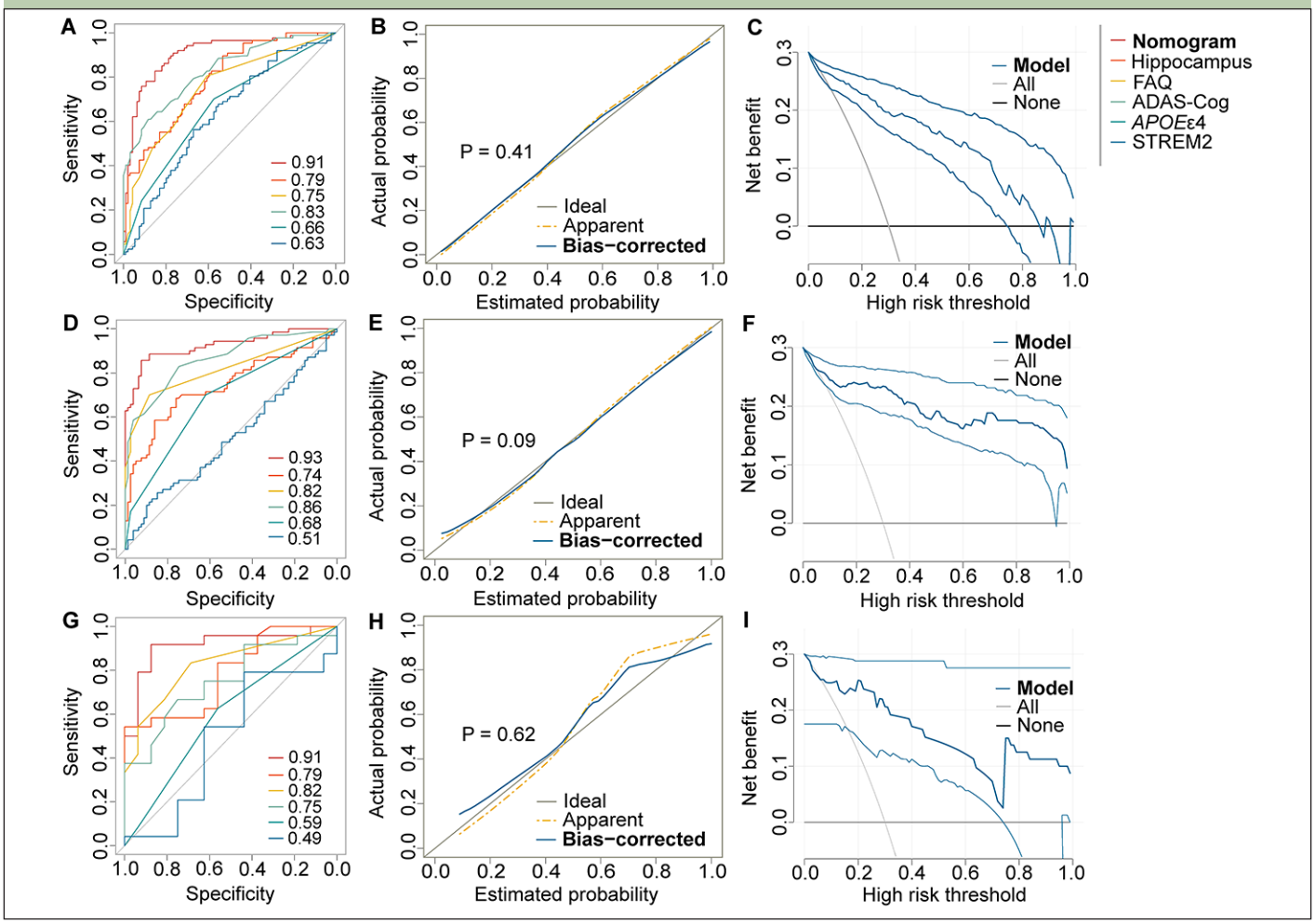


A total of five variables including APOE ε4 alleles, hippocampus volume, CSF sTREM2, ADAS-Cog score, and FAQ score were included to construct the nomogram with the minimum AIC.

Nomogram construction and validation

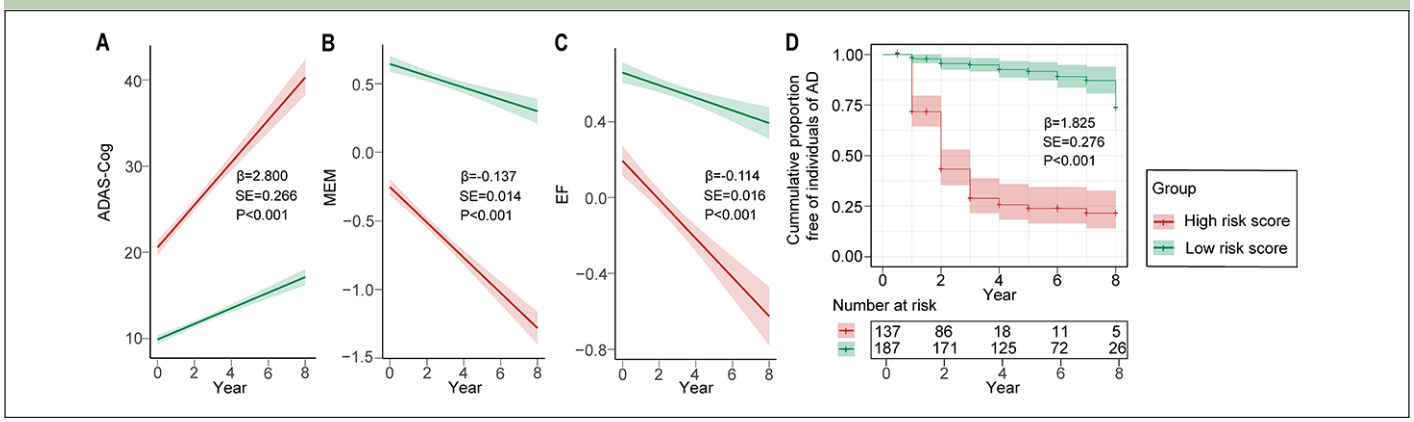
APOE ε4 alleles, hippocampus volume, CSF sTREM2, ADAS-Cog, and FAQ were finally included to construct the nomogram (Figure 2). The nomogram exhibited excellent AUC of 0.91 (95% CI: 0.86-0.95). The H-L test of calibration curve (p=0.41) indicated adequate agreement between the predictive nomogram and the actual observations (Figure 3). The good ability of discrimination and calibration of the nomogram was also demonstrated in the cross-sectional (AUC: 0.93, 95% CI: 0.88-0.97; H-L test, p = 0.09) and longitudinal (AUC: 0.91, 95% CI: 0.82-1.00; H-L test, p = 0.62) validation sets (Figure 3). To further evaluate the clinical utility of the nomogram, decision curve analysis (DCA) curves were

Figure 3. Performances the nomogram in training and validation sets



ROC curve (A), calibration curve (B), and decision curve (C) in training set; ROC curve (D), calibration curve (E), and decision curve (F) in cross-sectional validation set; ROC curve (G), calibration curve (H), and decision curve (I) in longitudinal validation set. Area under the receiver operating characteristic (ROC) curve indicated the discrimination ability of the nomogram and single factors included in the nomogram. In the calibration curves, X-axis is nomogram-predicted probability of cognitive decline. Y-axis is observed probability of cognitive decline, and the diagonal dashed line indicates the ideal prediction by a perfect model. In the decision curves, the grey reflects represents the net benefit assuming that all patients have cognitive decline; the black line reflects the net benefit assuming no patients have cognitive decline; and the blue line is expected net benefit of each patient based on the predictive nomogram. Abbreviations: FAQ: Functional Activities Questionnaire; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognition; CSF sTREM2: Cerebrospinal fluid soluble triggering receptor expressed on myeloid cells 2.

Figure 4. Roles of risk stratification by nomogram in predicting cognitive decline and incident risk of Alzheimer's disease during eight-year period among T/N+ non-demented population



ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognition; MEM: Memory; EF: Executive function.

Table 2. Factors associated with cognitive decline in univariable and stepwise multivariable logistic regression analyses for training set

Variables	Stepwise multivariable model			Selected factors in the final model		
	β	OR (95%CI)	p-value	β	OR (95%CI)	p-value
Marital status (living alone vs living with a partner)	0.90	2.46 (0.75-8.53)	0.144	-	-	-
APOE ε4 alleles (0, 1, 2)	0.80	2.23 (1.18-4.36)	0.015	0.63	1.88 (1.04-3.49)	0.039
Brain volume (cm^3)						
Hippocampus	-1.02	0.36 (0.18-0.65)	0.001	-0.99	0.37 (0.22-0.60)	<0.001
Mid-temporal	-0.15	0.86 (0.70-1.05)	0.151	-	-	-
CSF sTREM2 (ng/ml)	-0.34	0.71 (0.56-0.86)	0.001	-0.28	0.76 (0.62-0.90)	0.003
MMSE (point)	0.01	1.34 (1.00-1.84)	0.059	-	-	-
ADAS-Cog (point)	0.15	1.16 (1.06-1.27)	0.001	0.14	1.15 (1.07-1.25)	<0.001
Trail Making Test B (second)	0.01	1.01 (1.00-1.02)	0.041	-	-	-
FAQ (point)	0.14	1.15 (1.02-1.32)	0.034	0.15	1.16 (1.03-1.31)	0.016

Abbreviations: APOE = Apolipoprotein E; CSF sTREM2 = Cerebrospinal fluid Soluble Triggering Receptor Expressed On Myeloid Cells 2; MMSE = Mini-Mental State Examination; ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognition; RAVLT = Rey Auditory Verbal Learning Test; FAQ = Functional Activities Questionnaire.

plotted. Consistently, DCA curves also displayed a good applicability of nomogram (Figure 3).

Risk score predicts long-term risk of cognitive decline and incident AD

A total of 370 T/N+ subjects at baseline were divided into high-risk (57.6%) group and low-risk (42.4%) group using the cutoff value of 176.65 based on ROC curve. The high-risk group exhibited significantly faster decline in the general cognition ($p < 0.001$, Figure 4A), memory function ($p < 0.001$, Figure 4B), and executive functions ($p < 0.001$, Figure 4C). Compared to the low-risk group, higher scores were significantly associated with elevated risk of Alzheimer's dementia (HR= 6.21, 95% CI= 3.61-10.66, p< 0.001) (Figure 4D).

Discussion

To the best of our knowledge, our study is the first to construct a predictive model for cognitive decline among T/N+ non-demented adults. A total of ten risk factors were associated with the risk of cognitive decline independent of A status. The nomogram comprised five variables, including hippocampus volume, APOE ε4 status, ADAS-Cog score, FAQ score, and CSF sTREM2 levels. The nomogram demonstrated excellent discrimination, calibration, and clinical utility in both training and validation cohorts. Moreover, the nomogram generates risk scores which could help predict long-term cognitive trajectory and AD dementia incidence for T/N+ non-demented adults. As for clinical utility, these findings can not only help identify high-risk group and predict cognitive prognosis, but also provide new insights into the potential mechanisms for tau pathology-related cognitive impairments.

In the predicting model, FAQ and ADAS-Cog are simple questionnaires that do not require lumbar puncture, MRI, or genetic testing. They represent the global cognitive function and complex cognitive functions involved in social activities. Compared with other factors (such as CSF sTREM2 and hippocampus volume), they can be easily obtained. Future studies are expected to develop new models incorporating more variables which can be easily accessible and cost-effective.

Brain reserve capability played an important role in influencing cognitive trajectory for subjects with high burden of tau pathology. In our study, we found that the larger volume of hippocampal region was associated with cognitive stability in the presence of tau pathology. As acknowledged by previous researches, hippocampus is a crucial brain structure involved in cognitive processes, especially memory formation and retrieval. The pathological changes of tau proteins lead to a continuous loss of neurons in the hippocampus and other important brain regions (38, 39). According to the brain reserve theory, a larger volume indicates larger reserve of neurons, enhanced resilience to pathology (eg., abnormal tau proteins), and increased cognitive stability. It is noteworthy that cognitive reserve (CR) is another concept that help explicate the gap between pathology level and cognitive status (40). However, our study did not find significant difference for CR proxy such as educational years, possibly because most participants had a high level of education. Future studies should test the roles of CR-related exposures (e.g, education and cognitive stimulating activity) in resisting detrimental effects of abnormal tau proteins on cognitive impairments.

sTREM2, formed through the release of the extracellular domain of TREM2 under protease action, is mainly expressed in microglia in the brain 41. Our study demonstrated that CSF sTREM2 was

significantly associated with cognitive decline in T/N+ individuals. Consistently, Zhang et al. found that a receptor of sTREM2 expressed on neurons can decrease tau phosphorylation and aggregation. Moreover, they prove an active peptide of sTREM2 that rescues cognitive defects in the tau P301S transgenic mice (42). The association between cognitive stability and higher levels of CSF sTREM2 in the presence of tau pathology could be explained by the neuroinflammatory mechanism. Higher levels of CSF sTREM2 correspond with active microglial state, which can inhibit Aβ polymerization, prevent the progression of tau pathology, and surround plaques and fibrils to create a physical barrier obstructing their spreading and toxicity. These findings reinforced the critical roles of cerebral immune response in regulating tau-related homeostasis imbalance.

Our results also demonstrated that APOE ε4 is another independent predictor for cognitive prognosis in the presence of tau pathology. As the most significant genetic risk factor of sporadic Alzheimer's disease, apoE4 act via multiple pathways, such as provoking neuroinflammation, impairing cerebrovasculature and blood-brain barrier, and exacerbating amyloid and tau pathologies (43, 44). To promote the application in clinical utility, future studies should explore the potential influences of disclosing individual's apoe4 genotype information on their emotional burden or neuropsychological performances.

Based on this primary predictive model, early risk stratification and prognosis prediction for cognitive trajectory among T/N+ population could be feasible in clinical practice. Firstly, the AUC of the training set is 0.91. For individuals with different cognitive scores, our model can not only show the possibility of cognitive decline, but also indicate the trend of long-term cognitive function change and the risk of AD occurrence. Secondly, the DCA showed that using the prediction nomogram to predict cognitive decline of TN+ non-demented patients adds more benefit than either the treat-all-patients schedule or the treat-none schedule. Finally, a randomized clinical trial proved the feasibility of tau pathologically targets antisense oligonucleotides therapy (45). Our nomogram can be used to screen out people with high-risk scores, which can help us to adopt early intervention measures to slow cognitive decline in the future.

Nonetheless, it should be acknowledged it is too early to employ this model in clinical practice due to multiple limitations. First, the sample size and the generalizability of the cohort in our study is limited. Although ADNI is a multicenter study, most of the participants are relatively highly educated volunteers. The nomogram needs to be validated in larger community-based cohorts to lower the risk of chance findings. In addition, some categorical variables were not included, such as social activity and physical exercise, which could increase cognitive reserve and reduce cognitive decline. Moreover, the model requires the patient to undergo a lumbar puncture to obtain CSF, which is invasive and may narrow down the scope of use.

Conclusion

Our study revealed predictors for cognitive decline in non-demented adults with high burden of cerebral tau proteins. The nomogram is comprised of hippocampus volume, APOE ε4, ADAS-Cog, FAQ, and CSF sTREM2, which highlighted the importance of baseline performance, reserve capability, and immune activity in protecting cognition from tau pathology. Larger studies are required to validate and expand its clinical utility, possibly by incorporating more easily accessible and cost-effective variables.

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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Consent for publication: Not applicable.

Availability of data and materials: 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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