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Lipidomic markers for the prediction of progression from mild cognitive impairment to Alzheimer's disease

Wenjing Li[1] | **Yinhua Zhou**[2] | **Zhaofan Luo**[3] | **Rixin Tang**[1] | **Yuxuan Sun**[1,4] | **Qiangsheng He**[1,4] | **Bin Xia**[1,4] | **Kuiqing Lu**[4] | **Qinghua Hou**[5] | **Jinqiu Yuan**[1,4]

[1]Department of Epidemiology and Biostatistics, Clinical Big Data Research Center, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, Guangdong, China

[2]Center for Clinical Medical Humanities, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, Guangdong, China

[3]Department of Clinical Laboratory, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, Guangdong, China

[4]Chinese Health Risk Management Collaboration (CHRIMAC), Shenzhen, Guangdong, China

[5]Clinical Neuroscience Center, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, Guangdong, China

Correspondence
Qinghua Hou, Neurology Medicine Center, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, Guangdong, China.
Email: houqh5@mails.sysu.edu.cn

Jinqiu Yuan, Clinical Research Center, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, Guangdong 518107, China.
Email: yuanjq5@mail.sysu.edu.cn

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Abstract

Dementia is a well-known syndrome and Alzheimer's disease (AD) is the main cause of dementia. Lipids play a key role in the pathogenesis of AD, however, the prediction value of serum lipidomics on AD remains unclear. This study aims to construct a lipid score system to predict the risk of progression from mild cognitive impairment (MCI) to AD. First, we used the least absolute shrinkage and selection operator (LASSO) Cox regression model to select the lipids that can signify the progression from MCI to AD based on 310 older adults with MCI. Then we constructed a lipid score based on 14 single lipids using Cox regression and estimated the association between the lipid score and progression from MCI to AD. The prevalence of AD in the low-, intermediate- and high-score groups was 42.3%, 59.8%, and 79.8%, respectively. The participants in the intermediate- and high-score group had a 1.65-fold (95% CI 1.10 to 2.47) and 3.55-fold (95% CI 2.40 to 5.26) higher risk of AD, respectively, as compared to those with low lipid scores. The lipid score showed moderate prediction efficacy (c-statistics > 0.72). These results suggested that the score system based on serum lipidomics is useful for the prediction of progression from MCI to AD.

KEYWORDS

Alzheimer's disease, biomarker, lipidomics, prediction

Abbreviations: AD, Alzheimer's disease; ADCS, Alzheimer's Disease Cooperative Study; ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE4, apolipoprotein E ε4 allele; aSMase, acid sphingomyelinase; BMI, body mass index; CDR, Clinical Dementia Rating; CI, confidence interval; CN, cognitive normal; CSF, cerebrospinal fluid; DM, diabetes mellitus; HBP, high blood pressure; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LASSO, least absolute shrinkage and selection operator; LDL-C, low-density lipoprotein cholesterol; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; nSMase, neutral sphingomyelinase; PC, Phosphatidylcholine; PET, positron emission tomography; SCFAs, Short-chain fatty acids; TC, total cholesterol; TG, triglyceride; WMS-R, Wechsler Memory Scale-Revised.

Wenjing Li, Yinhua Zhou and Zhaofan Luo contributed equally to this study.

1 | INTRODUCTION

Dementia is prevalent in aging population. In 2015, the number of people affected by dementia worldwide was approximately 47 million and will reach 75 million by 2030 and 131 million by 2050.[1] The age-standardized prevalence of dementia is approximately 5%–7% in elders (age greater than 60 years old) worldwide.[1] Additionally, dementia leads to a considerable financial burden. The global economic costs of dementia were estimated to be more than 600 billion USD in 2010 and 818 billion USD in 2015.[2] Alzheimer's disease (AD) is the most common cause of dementia and the fifth leading cause of death.[3] As a neurodegenerative disease, the progression is pivotal to AD patients. For those who progressed from normal cognition to AD, mild cognitive impairment (MCI) is a transitional stage. Patients with MCI convert to dementia at a rate of 10% to 15% per year, which is approximately 10-fold higher than the conversion rate in healthy people.[4] Therefore, early identification of the MCI patients with a high risk of conversion to AD is of great importance for both the patients and healthcare providers.

Prediction of AD is commonly based on the image of a brain scan or the analysis of cerebrospinal fluid (CSF).[5,6] For example, Udit Singhania and colleagues reported a predictive model based on brain Aβ which can predict AD risk with high accuracy (c-index = 0.904).[6] However, these biomarkers are either invasive or too expensive for pre-clinical conditions. Compared with CSF biomarkers, blood biomarkers are more readily accessible for elders.[7] A number of blood biomarkers have been investigated for AD, including Aβ42,[8,9] T-tau,[10,11] P-tau18,[12,13] P-tau217,[14] Aβ42/Aβ40.[7,15,16] However, the findings were controversial. For example, Mielke et al. proposed that plasma total tau and pTau181 levels were higher in AD dementia patients than those cognitively unimpaired.[10] Nevertheless, a study from Mayo Clinic reported that plasma total tau did not predict cognitive decline among cognitively normal participants.[11] Hence, there is still an urgent need to find reliable alternative blood biomarkers for early AD prediction.

Lipids, as one of the major components of the brain, play a key role in the pathogenesis of AD. A study from China found that cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels have differential effects on neuropsychological performance.[17] In 2017, a meta-analysis of 17 cohort studies proposed that the association between dyslipidemia and the risk of cognitive decline is different in various stages of life.[18] Nevertheless, the current analyses of blood lipids and cognitive impairment are mainly based on the analysis of lipid profile that consists of total cholesterol, triglyceride, LDL-C and HDL-C. Lipidomics is a newly emerged discipline that studies lipids on a large scale based on analytical chemistry principles and technological tools, particularly mass spectrometry.[19] Lipidomics involves systems-level identification and quantitation of thousands of pathways and networks of lipids molecular species. Several studies have applied lipidomics to evaluate the link between specific lipid molecules and cognitive impairment, while most of them targeted the difference between cognitively normal elders and AD patients.[20–22] In this study, we explored the association between lipidomics and the progression from MCI to AD using the datasets from the Alzheimer's Disease Neuroimaging Initiative (ADNI).

2 | MATERIALS AND METHODS

2.1 | Study population

All data were obtained from the ADNI database (http://adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership led by principal investigator Michael W. Weiner. Its primary goal is to test whether serial magnetic resonance imaging (MRI), PET, biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. ADNI-1 is a non-randomized natural history non-treatment study in which a total of 800 subjects, including Alzheimer's disease (AD), mild cognitive impairment (MCI), and cognitively normal (CN) older adult controls. They were recruited at approximately 50 sites in the United States and Canada for longitudinal follow-up. All enrolled subjects were between 55 and 90 years of age, had a study partner able to provide an independent evaluation of functioning, and will speak either English or Spanish. For up-to-date information, see www.adni-info.org. ADNI was approved by the institutional review boards of all participating institutions. Written informed consent was obtained from all participants and collateral informants at each site.

Among the 800 participants in ANDI-1, we excluded those with cognitive normal (CN) or Alzheimer's disease (AD). Participants with incomplete lipid information or without follow-up time were also excluded (Figure 1). Finally, 310 mild cognitive impairment (MCI) participants were included in our study.

2.2 | Plasma lipid measurements

The plasma was analyzed by Baker Heart and Diabetes Institute, Metabolomics laboratory. The first step is lipid extraction. Pre-aliquoted 10 μL of blood plasma was mixed

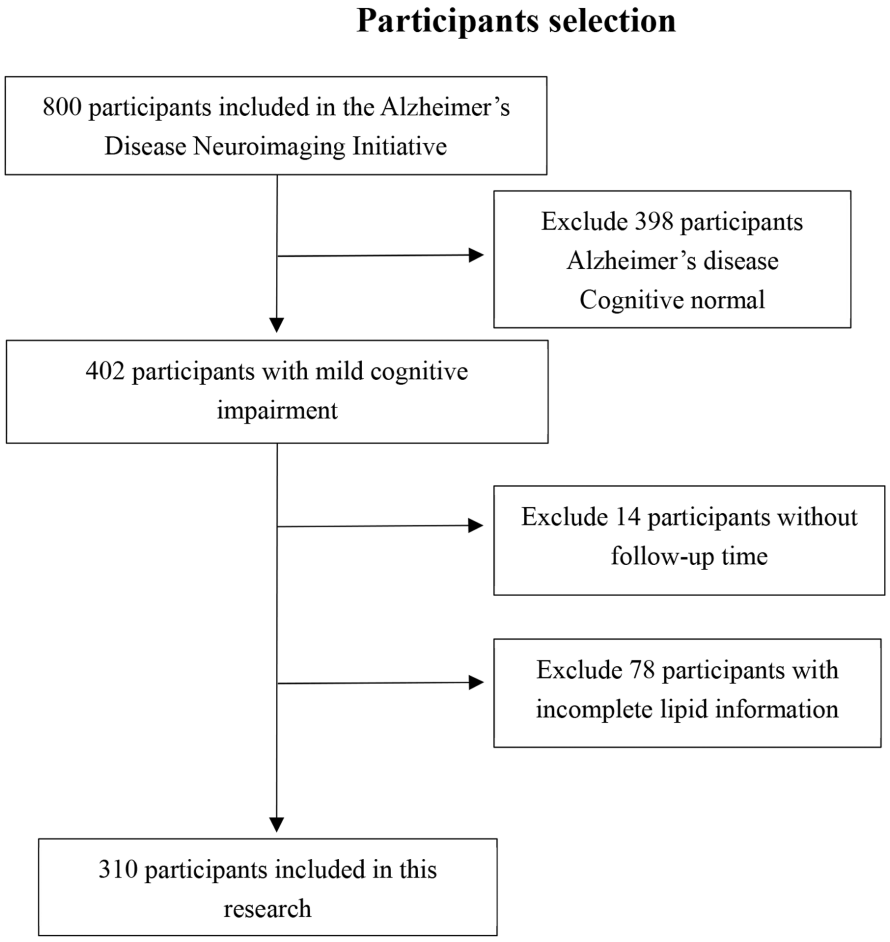

FIGURE 1 Flowchart of participants selected. AD, Alzheimer's disease; MCI, mild cognitive impairment.

with 100 μL of butanol-methanol (1:1 v/v) with 10 mM ammonium formate which contained a mixture of internal standards. Samples were vortexed thoroughly and set in a sonicator bath for 1 h maintained at room temperature. Samples were then centrifuged (14 000×*g*, 10 min, 20°C) before transferring the plasma supernatants into sample vials with glass inserts for analysis. The supernatant contained lipid components dissolved in organic solvents. Analysis of plasma extracts was performed on an Agilent 6490 QQQ mass spectrometer with an Agilent 1290 series HPLC system and a ZORBAX eclipse plus C18 column (2.1 × 100 mm 1.8 μm, Agilent) with the temperature set at 60°C. Through the interaction between the analyte and the surface of non-polar hydrophobic particles in the column, the hydrophobic phase was separated from the aqueous phase. Mass spectrometry analysis was performed in positive ion mode with dynamic multiple reaction monitoring (MRM). The solvent system consisted of solvent: (A) 50% H_2O/30% acetonitrile/20% isopropanol (v/v/v) containing 10 mM ammonium formate and 5 μM medronic acid; and (B) 1% H_2O/9% acetonitrile/90% isopropanol (v/v/v) containing 10 mM ammonium formate. The following mass spectrometer conditions were used: gas temperature, 150°C, gas flow rate 17 L/min, nebulizer 20 psi, Sheath gas temperature 200°C, capillary voltage 3500V, and sheath gas flow 10 L/min. Isolation widths for Q1 and Q3 were set to "unit" resolution (0.7 amu). A total of 781 lipids were examined by the ADMC Lipidomic Meikle Lab.

2.3 | Assessment of covariates

Covariates that may confound the relationship between lipidomics and conversion from MCI to AD were extracted from the merged file in the ANDI database (https://ida.loni.usc.edu/pages/access/studyData.jsp?project=ADNI). The covariates included demographic characteristics (age, sex, education years, race) number of apolipoprotein E (APOE4) ε4 allele, alcohol consumption, smoking, body mass index (BMI), family history of dementia, and medical history of hyperlipidemia, high blood pressure (HBP), and diabetes mellitus (DM). These covariates data were obtained from the ADCS (Alzheimer's Disease Cooperative Study) system.

2.4 | Assessment of outcome

We collected diagnosis information and follow-up time for each participant from the ADNI database. The

diagnosis of MCI was based on subjective or objective memory declines evaluated by education-adjusted scores on the Logical Memory II subscale (Delayed Paragraph Recall) from the Wechsler Memory Scale-Revised (WMS-R). The MMSE (Mini-Mental State Examination) score for MCI was between 24 and 30, the Clinical Dementia Rating (CDR) was 0.5, and Memory Box score should be at least 0.5. The MMSE score for AD was between 20 and 26, the CDR was 0.5 or 1.0. Follow-up visits were carried out at six-month intervals either in person or by telephone contact. Clinical and neuropsychological measures were collected at baseline, while neuroimaging assessments were collected in the follow-up visits.

All data were obtained from the ADNI database. All participants were amnestic MCI at baseline and were followed from the date of baseline until the first diagnosis of AD, last contact, or the end of the follow-up (April 15, 2021), whichever came first.

TABLE 1 Basic demographic characteristics of participants.

	Overall	Stable MCI	Convert to AD	*p* Value
Participant numbers	310	122	188	
Age (mean [SD])	74.59	74.30 (7.25)	74.78 (7.07)	.560
Sex (%)				.878
Female	114 (36.8)	46 (37.7)	68 (36.2)	
Male	196 (63.2)	76 (62.3)	120 (63.8)	
Education years (mean [SD])	15.72 (2.95)	15.71 (3.12)	15.72 (2.83)	.988
Race (%)				.555
Asian	6 (1.9)	2 (1.6)	4 (2.1)	
Black	11 (3.5)	6 (4.9)	5 (2.7)	
White	293 (94.5)	114 (93.4)	179 (95.2)	
Marry situation (%)				.409
Divorced	19 (6.1)	10 (8.2)	9 (4.8)	
Married	253 (81.6)	97 (79.5)	156 (83.0)	
Widowed	36 (11.6)	15 (12.3)	21 (11.2)	
Never married	2 (0.6)	0 (0.0)	2 (1.1)	
APOE-ε4 allele (%)				<.05
0	142 (45.8)	71 (58.2)	71 (37.8)	
1	132 (42.6)	41 (33.6)	91 (48.4)	
2	36 (11.6)	10 (8.2)	26 (13.8)	
Alcohol consumption (%)	13 (4.2)	7 (5.7)	6 (3.2)	.422
Smoking (%)	129 (41.6)	51 (41.8)	78 (41.5)	1.000
Family history of dementia (%)	129 (41.6)	45 (36.9)	84 (44.7)	.214
SBP (mean [SD])	135.72 (18.0)	133.87 (17.17)	136.93 (18.47)	.144
DBP (mean [SD])	74.83 (9.60)	74.98 (9.59)	74.73 (9.62)	.820
BMI (mean [SD])	26.14 (3.95)	26.61 (3.80)	25.83 (4.02)	.087
Hyperlipidemia (%)	100 (32.3)	36 (29.5)	64 (34.0)	.478
HBP (%)	122 (39.4)	49 (40.2)	73 (38.8)	.908
DM (%)	9 (2.9)	5 (4.1)	4 (2.1)	.507
CE (mean [SD])	5.01 (1.03)	4.96 (1.01)	5.05 (1.05)	.461
LDL_C (mean [SD])	2.01 (0.48)	1.99 (0.45)	2.02 (0.50)	.608
HDL_C (mean [SD])	1.45 (0.37)	1.43 (0.37)	1.47 (0.38)	.440
TG (mean [SD])	1.22 (0.55)	1.19 (0.57)	1.25 (0.54)	.363

Abbreviations: AD, Alzheimer's disease; BMI, body mass index; CE, cholesterol; DBP, diastolic blood pressure; DM, diabetes mellitus; HBP, high blood pressure; HDL_C, high-density lipoprotein cholesterol; LDL_C, low-density lipoprotein cholesterol; MCI, mild cognitive impairment, SBP, systolic blood pressure; TG, triglyceride.

2.5 | Statistical analysis

We presented continuous baseline variables as mean ± standard deviation and categorical variables as count (frequency). The least absolute shrinkage and selection operator (LASSO) Cox regression model was applied for the selection of the subset of baseline plasma lipids that were related to progression from MCI to AD. LASSO allows the selection of multiple variables in high-dimensional setting by shrinking the coefficients.[23] This approach relies on the controls of penalization parameters. We used a 10-fold cross-validation approach to optimize penalization. A total of 781 lipids were incorporated into the LASSO model.

We constructed a lipidomic risk score by multiplying the baseline lipids that were identified by LASSO regression, with the corresponding beta coefficients from Cox regression. Participants were then divided into low, intermediate, and high-risk groups based on quantiles of the lipid score.

The Cox proportional hazards model was used to assess the impacts of lipid score and common lipids on the risk of AD conversion. We calculated the hazard ratios (HRs) and 95% confidence intervals (CIs) by taking the low-score group as the reference. We adjusted for age at baseline (continuous) and sex (male or female) in the basic analysis model. In the multivariable-adjusted models, we controlled for years of education (continuous), race (Asia, Black, and White), number of apolipoprotein E (APOE4) ε4 allele (0,1,2), drinking (yes or no), smoking (yes or no), family history of dementia (yes or no), medical history of hyperlipidemia (yes or no), HBP (yes or no), DM (yes or no), BMI (continuous). We conducted subgroup analyses of the associations of each group with progression from MCI to AD by age (<75 years or ≥75 years), sex (male or female), years of education (<16 or ≥16), smoking histories (yes or no), family history of dementia (yes or no), history of hyperlipidemia (yes or no) and HBP (yes or no), BMI (<25 kg/m^2 or ≥25 kg/m^2). Time-dependent ROC curves were used to estimate the ability of prediction. A two-tailed p value <.05 was deemed statistically significant. All analyses were performed by R version 4.1.2 software.

3 | RESULTS

Table 1 presents the baseline characteristics of the participants. The average age of the 310 participants was 74.6 and 114 (36.8%) elders were female. Most of them were white (94.5%) and the converted group had a high rate of family history of dementia (44.7%) compared with the stable MCI group (36.9%). The progression from MCI to AD was positively associated with the number of APOE-ε4 ($p = .002$).

Over a median follow-up of 3.37 years, 188 (60.64%) subjects converted from MCI to AD. Figure 2 shows the result of LASSO regression. Through the shrinkage of lipids variable coefficients, 14 single lipids which were related to AD progression, were included for the lipidomics risk score, including Cer(d19:1/18:0), Cer(d19:1/20:0), PC(15-MHDA_20:4), PC(16:0_20:4), PC(P-15:0/20:4), PE(16:1_20:4), PE(P-15:0/22:6), PE(P-17:0/20:4), PE(P-18:0/22:6), PE(O-18:0/22:6), deDE(20:4), FA(14:0),

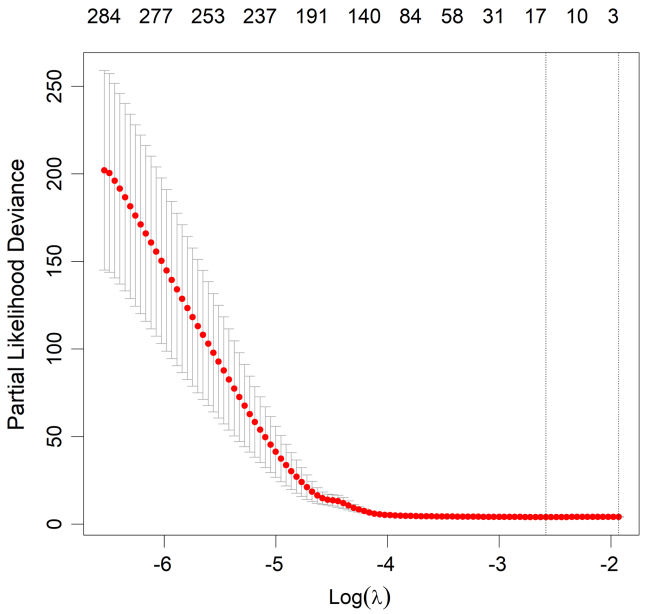

FIGURE 2 Potential lipid predictor selection using least absolute shrinkage and selection operator (LASSO) Cox regression.

TABLE 2 Results of Cox regression model.

	β	HR (95% CI)
Cer (d19:1/18:0)	0.03767	1.04 (0.84–1.29)
Cer (d19:1/20:0)	0.17916	1.20 (0.97–1.48)
PC (15-MHDA_20:4)	0.14377	1.16 (0.94–1.43)
PC (16:0_20:4)	0.04245	1.04 (0.84–1.29)
PC (P-15:0/20:4)	−0.09361	0.91 (0.67–1.23)
PE (16:1_20:4)	0.11927	1.13 (0.94–1.35)
PE (P-15:0/22:6)	−0.12225	0.89 (0.66–1.19)
PE (P-17:0/20:4)	−0.25215	0.78 (0.58–1.05)
PE (P-18:0/22:6)	0.01088	1.01 (0.77–1.33)
PE (O-18:0/22:6)	−0.19887	0.82 (0.64–1.04)
deDE (20:4)	0.29146	1.34 (1.18–1.52)
FA (14:0)	0.06887	1.07 (0.90–1.27)
FA (18:0)	0.11734	1.13 (0.96–1.32)
TG (O-54:4) [NL-17:1]	−0.12731	0.88 (0.74–1.05)

Abbreviations: Cer, ceramides; FA, fatty acid; PC, phosphatidylcholine; PE, phosphatidylethanolamine; TG, triglyceride.

		HR (95% CI)	
		Age and sex adjustment[a]	**Multivariable adjusted model[b]**
Score (−3.33~3.46)	188/310	2.75 (2.19–3.45)	2.74 (2.16–3.48)
Risk by score group			
Low	44/104	1.00 (Reference)	1.00 (Reference)
Intermediate	61/102	1.74 (1.18–2.57)	1.65 (1.10–2.47)
High	83/104	3.51 (2.42–5.10)	3.55 (2.40–5.26)
p-trend		<.001	<.001

TABLE 3 The association between constructed lipid score and risk of progression from MCI to AD.

[a]Age and sex adjustment: model adjusted for age and sex.

[b]Multivariable-adjusted model: adjusted for age, sex, education years, race (Asian, Black, and White), APOE-ε4 carriers, history of alcohol drinking (yes or no), history of smoking (yes or no), family history of dementia (yes or no), medical history of hyperlipidemia (yes or no), medical history of high blood pressure (yes or no), medical history of diabetes mellitus (yes or no), body mass index.

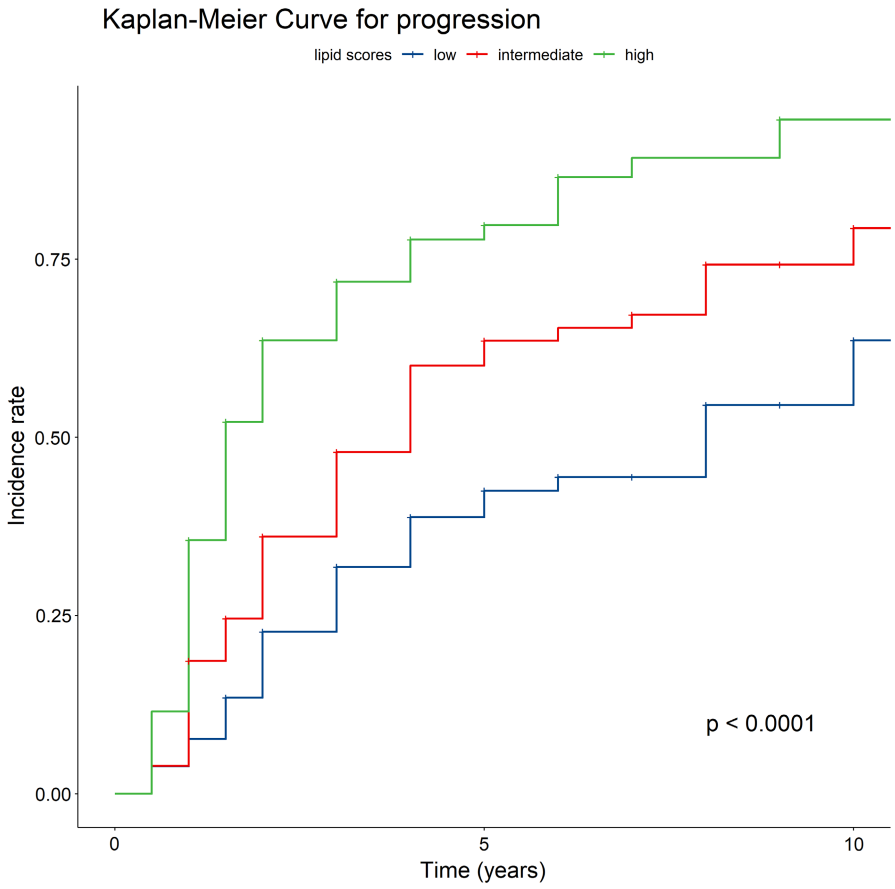

FIGURE 3 Comparison of survival probability by different groups of lipid score.

FA(18:0), TG(O-54:4) [NL-17:1] (Table 2). β values of each selected lipids were used to construct the lipid risk score.

Table S1 presents the importance of every selected lipid and its impacts on the progression from MCI to AD. Cer(d19:1/18:0), Cer(d19:1/20:0), PC(15-MHDA_20:4), PC(16:0_20:4), PE(16:1_20:4), deDE(20:4), FA(14:0), and FA(18:0) were positively associated with the risk of conversion, while PC(P-15:0/20:4), PE(P-15:0/22:6), PE(P-17:0/20:4), PE(P-18:0/22:6), PE(O-18:0/22:6), and TG(O-54:4) [NL-17:1] were negatively associated with the risk of conversion.

Table 3 shows the association between lipid score and conversion from MCI to AD. The lipid score was significantly associated with an increase in AD risk (p-trend < .001). Compared with participants with low lipid score, patients in the intermediate and high score

groups had a 1.65-fold (95% CI 1.10 to 2.47) and 3.55-fold (95% CI 2.40 to 5.26) higher risk of AD, respectively. The log-rank test suggested that participants with high lipid score have higher conversion risk compared with those with intermediate or low score (Figure 3). In the high lipid score group, the proportion of participants with two APOE-ε4 alleles was higher compared with the low and intermediate groups at baseline (Table S2). Figure 4 shows that the ROC analysis presented favorable prediction efficacy at a follow-up time of 3 years (c-index = 0.74), 5 years (c-index = 0.73), and 10 years (c-index = 0.77).

In the subgroup analyses, the estimates for risk of AD conversion associated with lipid score seem not to differ according to age, sex, education years, family history of dementia, history of smoking, hyperlipidemia, and HBP. The risk of conversion with higher lipid score seemed to be lower among participants with normal BMI or who had APOE-ε4 carriers (p for interaction <.05) (Table 4). There was no sufficient evidence of association between serum cholesterol with risk of AD conversion (Table 5). Common serum cholesterol includes total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG).

4 | DISCUSSION

In this study, we developed a lipid scoring system for predicting the risk of progression from MCI to AD. Our finding suggests that patients in the high lipid score group have a higher risk of progression from MCI to AD compare with the intermediate or low scores group. Over a median follow-up of 3.37 years, 188 (60.64%) subjects converted from MCI to AD. When the sample was restricted to 4 years of follow-up, the average conversion rate was 13.23% annually, which is consistent with results from other studies indicating that 12%–15% of amnestic MCI patients convert annually to AD.[24]

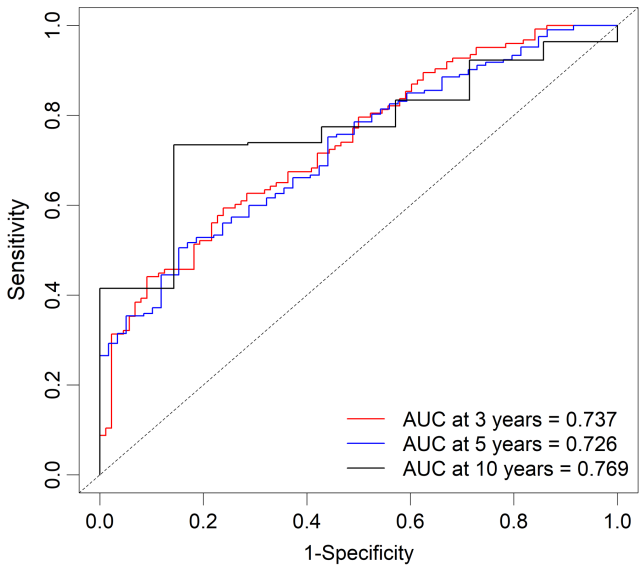

FIGURE 4 Time-dependent ROC curves present prediction efficacy in 3 years, 5 years, and 10 years.

A number of studies have reported the associations between AD and serum cholesterol.[25–27] However, the findings of these studies seem controversial. A study from Hyewon Lee pointed out that all lipid profiles (TC, LDL-C, HDL-C, and TG) have a positive association with the risk of AD.[28] Nevertheless, a case-control study suggested that higher TC and LDL-C, and lower HDL-C are associated with AD risk.[17] Due to the limitation of conventional plasm cholesterol, many studies evaluated lipidomics with the progression of AD. In 2006, a study from the UK performed a comprehensive lipidomics analysis of 300 participants (152 CN and 148 AD) and found an association between lipids and AD. This study also combined 24 molecules to predict disease progression ($R^2 = .10$),[21] revealing that lipidomics has a robust link with AD. However, the transitional stage MCI was not included in this study.

The mechanism underlying the association between lipidomics and AD is still unclear. According to our results, several lipids have been linked with the progression from MCI to AD. Ceramides could increase the risk of conversion. A cohort study found that oligomeric $A\beta_{1-40}$ and $A\beta_{1-42}$ can increase the activity of acid sphingomyelinase (aSMase) and neutral sphingomyelinase (nSMase) by a redox-sensitive, cytosolic calcium-dependent phospholipase A2-arachidonic acid pathway, that lead to neuronal death through ceramides accumulation.[29] Phosphatidylcholine (PC), as a major constituent of biological membranes, is vital to neurons and glial cells. Thus, the disorders of PC may lead to the death of neurons and glial cells.[30] Short-chain fatty acids (SCFAs) can penetrate the blood–brain barrier or affect the brain through the intestine-brain axis.[31] For example, Acetate was found to be downregulated in AD drosophila[32] affecting microglia and reducing blood–brain barrier permeability.[33] Other lipids have also been found to be associated with AD's progression.[34–37] The alteration of lipids in the brain is related to aging and contributes greatly to the progression of AD.[37] Combined effects caused by lipid dysregulation were observed in changes of intestinal microbiota,[31] blood–brain barrier disruption,[38] oxidative stress.[39] A single lipid may minimally contribute to the progression, but the accumulation of several lipids could improve prediction and reflect the lipid metabolism for individuals, highlighting the significance of this study. In addition, in all participants with complete lipid profiles, we observed no associations between serum triglycerides,

TABLE 4 Subgroup analyses of groups of lipid score and risk of progression.

Subgroup	Low	Intermediate	High	*p* for interaction
Age				.757
<75	1.00 (Reference)	1.50 (0.84–2.70)	3.87 (2.17–6.90)	
≥75	1.00 (Reference)	2.01 (1.08–3.72)	4.04 (2.17–7.51)	
Sex				.892
Male	1.00 (Reference)	1.82(1.11–2.98)	3.827(2.31–6.34)	
Female	1.00 (Reference)	1.64(0.76–3.55)	3.784(1.90–7.53)	
Education years				.917
<16	1.00 (Reference)	1.83 (0.90–3.73)	3.70 (1.82–7.50)	
≥16	1.00 (Reference)	1.75 (1.05–2.91)	3.31 (2.03–5.39)	
APOE-ε4 allele				.042
No	1.00 (Reference)	2.88 (1.51–5.50)	4.35 (2.19–8.64)	
Yes	1.00 (Reference)	1.17 (0.69–2.00)	3.38 (2.04–5.59)	
Smoking				.681
No	1.00 (Reference)	1.58 (0.94–2.65)	3.80 (2.31–6.26)	
Yes	1.00 (Reference)	1.92 (0.98–3.79)	3.74 (1.86–7.54)	
Family history of dementia				.431
No	1.00 (Reference)	1.74 (1.01–3.02)	3.80 (2.28–6.34)	
Yes	1.00 (Reference)	1.92 (1.03–3.59)	3.69 (1.94–7.01)	
BMI				.037
<25	1.00 (Reference)	1.78 (0.96–3.31)	3.59 (1.95–6.60)	
≥25	1.00 (Reference)	1.70 (0.99–2.92)	3.74 (2.19–6.39)	
Hyperlipidemia				.491
No	1.00 (Reference)	1.68 (1.05–2.71)	3.00 (1.87–4.81)	
Yes	1.00 (Reference)	1.99 (0.85–4.67)	5.27 (2.42–11.48)	
HBP				.877
No	1.00 (Reference)	1.59 (0.95–2.66)	3.57 (2.22–5.75)	
Yes	1.00 (Reference)	1.89 (0.93–3.83)	3.85 (1.84–8.04)	

Note: Estimated effects were based on the multivariable-adjusted model (see footnote in Table 3).

Abbreviations: BMI, body mass index; HBP, high blood pressure.

TABLE 5 The association between conventional serum cholesterol and risk of progression from MCI to AD.

	HR (95% CI)	
	Age and sex adjustment	Multivariable-adjusted model
CE	1.06 (0.92–1.23)	1.09 (0.93–1.28)
LDL_C	1.04 (0.90–1.20)	1.07 (0.91–1.25)
HDL_C	1.11 (0.95–1.29)	1.10 (0.93–1.29)
TG	1.03 (0.90–1.17)	1.02 (0.90–1.17)

Abbreviations: CE, cholesterol; HDL_C, high-density lipoprotein cholesterol; LDL_C, low-density lipoprotein cholesterol; TG, triglyceride.

total cholesterol, LDL cholesterol, and HDL cholesterol and AD progression. These findings highlight the relevance of studying smaller lipid components because they signify specific steps in their biosynthesis and metabolism that may be associated with AD. Further research is needed to investigate the specific lipid pathways that could be exploited to delay the progression of AD,[40] which means lipidomics can not only identify biomarkers to predict progression, but also pinpoint the target of novel therapeutics in the future.

A strength of this study is the comprehensive lipidomics data. Our study focused on the transitional stage of AD and mainly analyzed the conversion from MCI to AD. The constructed lipid score can be a reference for the prediction of AD's progression in future study. This study has limitations. First, the diagnosis was determined clinically and was not combined with imaging or other sensitive biomarkers (e.g., CSF amyloid, tau, and neurodegeneration [ATN] biomarkers or neurofilament light chains), which reduces the significance of our findings. In addition, the

sample size is small, and the results need to be validated in other population.

5 | CONCLUSION

This study established a serum lipidomics scoring system that is useful for predicting the risk of progression from MCI to AD. The findings might be used for developing novel therapeutics targeting specific lipids in the future. As our study design is observational, more studies are needed to validate these associations in the future.

AUTHOR CONTRIBUTIONS

Jinqiu Yuan, Wenjing Li, Yinhua Zhou, and Zhaofan Luo contributed to the study conception and design. Wenjing Li, Yinhua Zhou, Rixin Tang, and Yuxuan Sun contributed to data collection and analysis. Wenjing Li, Yinhua Zhou, Zhaofan Luo, Qinghua Hou, Qiangsheng He, Bin Xia, and Kuiqing Lu contributed to drafting the manuscript or drawing the figures.

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DISCLOSURES

The authors declare that there were no conflicts of interest.

DATA AVAILABILITY STATEMENT

All available data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (https://adni.loni.usc.edu/).

ORCID

Wenjing Li https://orcid.org/0000-0003-3569-7082

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