Plasma NfL, P-tau181, and P-tau181/Aβ42 Ratio in Predicting Mild Behavioral Impairment in Dementia-Free Multiethnic Asian Older Adults With Mixed Pathology in a 5-Year Clinical Cohort

Yingqi Liao, MSc; Joyce R. Chong, PhD; Cheuk Ni Kan, PGDip; Xuhao Zhao, MPH; Yuek Ling Chai, PhD; Saima Hilal, PhD; Mitchell K. P. Lai, PhD; Christopher P. Chen, FRCP; and Xin Xu, PhD

Abstract

Objective: The underlying mechanisms of mild behavioral impairment (MBI), a marker for cognitive impairment and dementia, have remained unclear especially in a multiethnic Asian population. The study aimed to examine whether baseline Alzheimer disease biomarkers, including plasma neurofilament light (NfL) chain, phosphorylated tau-181 (p-tau181), and the p-tau181-to-amyloid-β42 (p-tau181/Aβ42) ratio, could predict MBI incidence in dementia-free Asian older adults.

Methods: Participants were recruited from the community and memory clinics from August 2010 to April 2022. All participants underwent cognitive, neuropsychiatric, and clinical assessments annually and neuroimaging scans biennially at baseline and over a maximum of 5 years. Neuropsychiatric symptoms (NPS) and incident MBI were examined using Neuropsychiatric Inventory. Plasma NfL, p-tau181, and Aβ42 were measured using single molecule array assays. Neuroimaging measures of hippocampal volume (HV) and white matter hyperintensities (WMH) were obtained.

Results: A total of 305 dementia-free participants were included (age 72.1 ± 7.8 years, 52.5% female, 27.9% no cognitive impairment). Among 248 MBI-free participants at baseline, 55 (25.3%) participants developed incident MBI in 5 years. Higher baseline p-tau181, p-tau181/Aβ42 ratio, and NfL were predictive of increased NPS severity longitudinally and MBI incidence ($P < .05$). Higher p-tau181 levels (hazard ratio [HR] [95% CI], 2.40 [1.00–5.75], $P = .05$) were independently associated with an increased likelihood of incident MBI after accounting for incident dementia and plasma NfL. This relationship remained significant when controlling for HV and WMH (HR [95% CI], 2.69 [1.08–6.70], $P = .03$).

Conclusions: Our findings highlighted the relationship between amyloid burden and neuroaxonal degeneration with neurobehavioral changes in multiethnic Asian older adults with underlying mixed pathology.

J Clin Psychiatry 2025;86(1):24m15558

Author affiliations are listed at the end of this article.

Neuropsychiatric disturbances are frequently observed across all stages of dementia and suggested as an early manifestation of Alzheimer disease (AD).[1–4] This has led to the concept of mild behavioral impairment (MBI) which is characterized by late-life emergent and persistent behavioral changes in the dementia-free population.[5] Studies have shown that MBI is associated with a higher conversion to dementia in diverse cohorts.[6,7] As MBI occurs in 17.0%–45.5% of older adults in predementia stages or without cognitive impairment,[8] understanding the underlying mechanisms of MBI is essential for risk assessment and early intervention.

Neuropathological hallmarks of AD, including senile plaques containing aggregated, 40- or 42-amino acids β-amyloid (Aβ) peptides as well as intraneuronal neurofibrillary tangles of hyperphosphorylated tau protein, have been linked to MBI.[9,10] In the pursuit of less costly and invasive biomarkers, recent studies have reported promising results on the utility of AD- and neurodegeneration-related blood biomarkers, such as tau phosphorylated at serine181 (p-tau181) and

Scan Now

See supplementary material for this article at Psychiatrist.com

Editor's Note

We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Jordan F. Karp, MD, at psychiatrist.com/contact/karp, or Gary W. Small, MD, at psychiatrist.com/contact/small.

Clinical Points

- Mild behavioral impairment (MBI) as a marker for dementia has been increasingly recognized for early detection, but the understanding of its neurobiological mechanisms remained limited for intervention development.
- High baseline plasma p-tau181 levels were associated with a greater risk of incident MBI in Asian older adults with mixed pathology over the 5-year follow-up period.
- For older adults with increased amyloid burden and neurodegeneration, clinicians should consider early detection and intervention for behavioral symptoms.

neurofilament light (NfL) chain,[11] in identifying AD pathology and predicting cognitive decline.[12–15] Western-based studies have also explored the associations between these blood biomarkers and behavioral disturbances, showing that MBI was associated with reduced Aβ40/Aβ42 ratio cross-sectionally and increased p-tau181 and NfL longitudinally.[16–18] However, previous studies have yet to investigate the prognostic value of blood biomarkers for predicting incident MBI, especially in an Asian cohort. Given the potential effect of race and ethnicity on biomarker measures and MBI status,[19,20] it is important to examine the plasma biomarkers across diverse populations such as an Asian cohort with high prevalence of concomitant cerebrovascular disease (CeVD) burden (eg, increased white matter hyperintensities [WMH]).[21]

We therefore investigated the associations between plasma biomarkers, namely p-tau181 and NfL, with longitudinal NPS severity and incidence of MBI over a 5-year follow-up period in an Asian cohort of dementia-free individuals. Furthermore, as our previous study showed that plasma p-tau181/Aβ42 ratio could predict amyloid burden with higher sensitivity and specificity in an Asian cohort of dementia-free individuals with mixed-pathology, we assessed the relationship between p-tau181/Aβ42 ratio and behavioral changes.[22] Additionally, the independent pathological pathways of incident MBI will be further examined by accounting for neuroimaging measures of hippocampal volume (HV) and WMH, indicative of brain atrophy and CeVD burden, respectively.

METHODS

Sampling

This study was part of an ongoing prospective cohort study that recruited subjects from memory clinics and the community in Singapore from August 2010 to April 2022.[23] Participants aged ≥50 years were diagnosed with either (a) no cognitive impairment (NCI), defined as no cognitive impairment based on standardized neuropsychological battery or functional loss, or (b) cognitive impairment—no dementia (CIND), defined as having impairment on 1 or more than 1 cognitive domain on standardized neuropsychological battery without functional loss. Individuals with previously diagnosed major psychiatric disorders or substance abuse disorders based on the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (*DSM-IV*), cognitive impairment caused by a history of traumatic brain injury, multiple sclerosis, tumor, epilepsy or systematic diseases, a diagnosis of dementia based on *DSM-IV*, and significant visual or auditory impairment were excluded. Annual clinical assessments, blood tests and neuropsychological assessments and biennial magnetic resonance imaging (MRI) assessments were conducted at baseline and over the 5-year follow-up. Participants who had available data for baseline MBI diagnosis and baseline plasma biomarkers were included as the final study cohort (Figure 1). To ascertain the incidence of MBI, individuals had to have at least 2 years of follow-up assessments.

Ethics approval of this study was granted by the National Healthcare Group Domain Specific Review Board. This study was conducted in accordance with the Declaration of Helsinki. Participants' written informed consent was obtained in the preferred language of the participants prior to the study.

Neuropsychological Assessments and Research Diagnosis

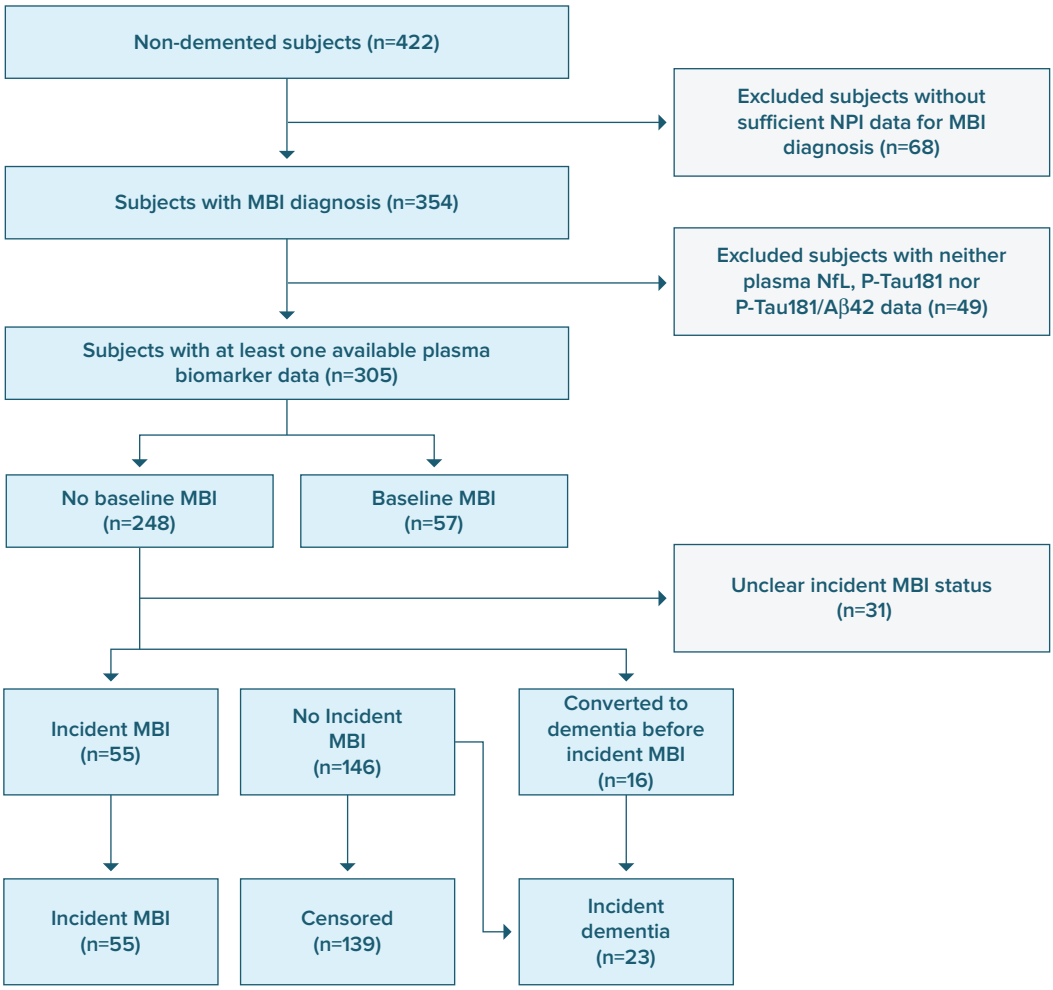
A locally validated standardized neuropsychological battery (the National Institute of Neurological Disorders and Stroke and Canadian Stroke Network Vascular Cognitive Impairment battery) was conducted to examine participants' cognitive functioning.[24] The neuropsychological battery examined 7 cognitive domains including attention, executive functioning, language, visuomotor speed, visuoconstruction, and memory. A composite *Z*-score of cognitive tests was calculated to indicate the global cognitive functioning.[23,25]

Research diagnosis was made during weekly research consensus meetings consisting of clinicians, neuropsychologists, radiologists and research personnel to review clinical records, neuropsychological performance, and brain scans. Detailed diagnosis criteria of NCI and CIND were described previously.[6,26] During follow-up assessments, the diagnosis of incident dementia was made based on the *DSM-IV*.

MBI Diagnosis

Using the Neuropsychiatric Inventory (NPI), MBI diagnosis was made following the International Society to Advance Alzheimer Research and Treatment of the Alzheimer Association (ISTAART-AA) criteria. The

Figure 1.
Flowchart of the Study Cohort[a]



[a]A total of 422 dementia-free participants were identified. Of these, 107 subjects were excluded as 68 participants lacked sufficient NPI data and 49 participants did not have available plasma biomarker data at baseline. As a result, participants (n = 305) with available baseline biomarker and MBI data were included for analyses. A total of n = 201 individuals (n = 55 incident MBI, n = 146 no incident MBI) were included in the longitudinal GEE analyses. n = 16 individuals had converted to dementia before having an incident MBI diagnosis and n = 7 from no incident MBI but developed incident dementia were considered as n = 23 in the competing risk survival analysis, and those without incident MBI or incident dementia (n = 139) were censored.

Abbreviations: Aβ42 = amyloid β 42, GEE = generalized estimating equations, MBI = mild behavioral impairment, NfL = neurofilament light, NPI = Neuropsychiatric Inventory, p-tau181 = phosphorylated tau-181.

total scores of NPI were calculated as the sum of the product of the frequency and severity of each NPS.[27] Domain scores were calculated as a sum of NPI frequency × severity of individual items belonging to each of the 5 domains of (i) decreased motivation, interest, and drive; (ii) emotional or affective dysregulation; (iii) impulse dyscontrol; (iv) social inappropriateness, and (v) abnormal thoughts and perception, following the previously established algorithm.[4] MBI criteria posit that symptoms persist ≥6 months, and hence 2 consecutive visits of NPI were used to operationalize the persistence criterion.

Baseline MBI was defined by the presence of NPS (ie, NPI ≥1) consecutively from baseline to Y1, or from Y1 to Y2 if baseline NPI data were unavailable (n = 11) (Figure 1).

Incident MBI was defined by the presence of NPS at any 2 consecutive visits from Y1 to Y5 follow-up among subjects without baseline MBI, otherwise recorded as *No Incident MBI* (Figure 1).

Plasma NfL, P-tau181, and Aβ42 Level Measurements

Nonfasting blood was collected in ethylenediaminetetraacetic acid (EDTA) tubes and centrifuged at 2,000 *g* for 10 minutes at 4°C.

Following centrifugation, plasma was extracted, mixed well, aliquoted into polypropylene tubes (0.2 mL per tube) and stored at −80°C until use. Plasma p-tau181, NfL, and Aβ42 levels were measured on the single molecule array (Simoa) HD-1 analyzer using commercially available Simoa pTau-181 Advantage V2 kit, Simoa NF-light Advantage kit, and Simoa Amyloid Beta 42 assay, respectively, per manufacturer's instructions (Quanterix, Billerica, MA).[28] Intra- and interassay variability assessed by the coefficient of variation were <15% and <25%, respectively, for all analytes based on 2 levels of quality controls run in duplicate with each sample batch. Fifteen subjects' blood samples were collected at a different visit due to subjects' availability.

Neuroimaging Measures

MRI scans were performed on a 3T Siemens Magnetom Trio Tim scanner, using a 32-channel head coil at the Clinical Imaging Research Centre, National University of Singapore. The MRI sequences included T1-weighted magnetization prepared rapid gradient recalled echo, fluid attenuated inversion recovery, and T2-weighted and susceptibility-weighted imaging sequences.[23] Quantitative and qualitative MRI analyses were performed, as described in detail previously.[23,29] Brain atrophy was indicated by the HVs which were calculated for right and left hemispheres, with the average volumes measured in cubic millimeters. WMH severity was graded based on the age-related white matter changes (ARWMC).[30]

Statistical Analyses

Group comparisons in demographics, clinical, neuropsychological and neuroimaging measures, and plasma biomarker levels were conducted using 1-way analysis of variance (ANOVA) or Mann-Whitney *U* tests for continuous variables and chi-square tests for categorical variables. Plasma biomarker levels were log-transformed due to the skewed data distribution and used as continuous variables for further analyses.

Literature review was conducted, and studies that compared the group differences in plasma biomarkers between MBI and no MBI groups and between NPS and no NPS groups in dementia-free participants were included. Authors, years of publication, regions, diagnostic groups, measures of plasma biomarkers, measures of behavioral symptoms, and the mean or median levels of plasma p-tau181 and NfL were extracted.

Linear mixed-effect (LME) models were employed to examine the effect of baseline biomarkers on the longitudinal NPS severity, with NPI total scores entered as the dependent variables, baseline biomarkers as the fixed effect and baseline biomarkers × time (y) as the interaction term in the models, and participants as the random effect. LME models were repeated for each MBI subdomain. Generalized estimation equations (GEE) models were constructed, respectively, to examine the effect of baseline plasma biomarkers on incident MBI over a maximum of 5-year follow-up. For longitudinal analyses of incident MBI, time (y) was included in the models.

To further evaluate the effect of individual plasma biomarkers on incident MBI without bias, survival analysis approaches considering competing risk were also performed. To examine the independent effect of amyloid burden and neuroaxonal degeneration on predicting incident MBI (event of interest), the effect of plasma biomarkers (ie, NfL and p-tau181, or NfL and p-tau181/Aβ42 ratio) on the incident MBI with the presence of incident dementia (competing risk event) was evaluated using the Fine and Gray model based on the subdistribution hazard function. Additional models were performed to examine plasma p-tau181 and p-tau181/Aβ42 ratio in relation to incident MBI, controlling for the HV and WMH.

For sensitivity analyses, we generated 2 datasets with missing values substituted by maximum and minimum NPI values over the follow-up period (Y1–Y5), respectively, to identify incident MBI cases among individuals with no baseline MBI (n = 248), and GEE models were subsequently performed. Identification of incident MBI followed the same procedure and inclusion criteria as the original dataset. All models were adjusted for age, sex, years of education, and baseline diagnostic groups (ie, NCI vs CIND). Statistical analyses were conducted using SPSS (IBM, 2020) and R (R studio, 2022.12.0). The significant level of statistical tests was set at $P < .05$. For analyses of subdomains, P values of individual biomarkers were adjusted using the Bonferroni correction ($P < .05/5 = .01$).

RESULTS

Study Cohort Characteristics

A total of 305 individuals were included in the final analyses (Figure 1). The baseline characteristics of participants are summarized in Table 1. There was a baseline MBI prevalence of 18.7%. Incident MBI was found in 25.3% of subjects without baseline MBI (n = 55, Figure 1). These subjects were older in age and were more likely to have a CIND diagnosis, lower global cognitive *z*-scores, smaller HV, and greater WMH (ie, higher ARWMC scores) at baseline (Table 1). Table 2 shows the comparison in mean or median levels of plasma p-tau181 and NfL in individuals with MBI or NPS across different cohorts of dementia-free participants.

Effects of Baseline Plasma Biomarkers on Longitudinal NPS Severity

Longitudinal increase in NPS severity was greater in individuals with higher plasma p-tau181 (β = 2.36, $P < .001$), p-tau181/Aβ42 ratio (β = 2.59, $P < .001$), and

Table 1.

Baseline Demographics of Baseline MBI Groups and Incident MBI Groups[a]

	Baseline MBI n = 57	No baseline MBI n = 248	*U*/*F*/ chi-square	*P* value	Incident MBI n = 55	No incident MBI n = 146	*U*/*F*/ chi-square	*P* value
Demographics								
Age, mean (SD), y	72.81 (7.62)	71.98 (7.82)	0.524	.470	75.11 (5.64)	70.36 (8.02)	16.258	**<.001**
Sex, F, n (%)	30 (52.6%)	130 (52.4%)	0.001	.977	27 (49.1%)	74 (50.7%)	0.041	.840
Years of education, mean (SD)	8.18 (5.61)	8.26 (4.91)	0.014	.907	8.18 (4.15)	9 (4.90)	1.207	.273
Race, n (%)			1.032	.794			1.948	.583
Chinese	50 (87.7%)	216 (87.1%)			48 (87.3%)	125 (85.6%)		
Malay	4 (7.0%)	15 (6.0%)			5 (9.1%)	9 (6.2%)		
Indian	2 (3.5%)	15 (6.0%)			2 (3.6%)	10 (6.8%)		
Others	1 (1.8%)	2 (0.8%)			0	2 (1.4%)		
Diagnosis, n (%)			6.674	**.010**			7.373	**.007**
NCI	8 (14.0%)	77 (31.0%)			10 (18.0%)	56 (38.4%)		
CIND	49 (86.0%)	171 (69.0%)			45 (81.6%)	90 (61.6%)		
Incident dementia, yes, n (%)	20 (35.1%)	39 (15.7%)	11.136	**<.001**	14 (25.5%)	7 (4.8%)	18.226	**<.001**
Baseline cognitive and functioning								
Global cognition *Z*-scores, mean (SD)	−1.99 (1.78)	−1.29 (1.64)	8.184	**.005**	−1.56 (1.48)	−0.91 (1.46)	7.795	**.005**
Baseline neuroimaging measures								
Hippocampal volume, mm^3, mean (SD)	3,256.99 (515.72)	3,517.31 (448.65)	14.503	**<.001**	3,416.32 (447.37)	3,596.07 (419.83)	7.064	**.009**
WMH, median (IQR)	6 (5)	5 (4)	7,594.0	.306	6 (6)	5 (5)	4,963.0	**.007**
Baseline plasma biomarkers								
p-tau181, pg/mL, median (IQR)[b]	2.58 (1.68)	2.15 (1.45)	3.746	.054	2.56 (2.28)	1.95 (1.17)	13.910	**<.001**
p-tau181/Aβ42 ratio, median (IQR)[b,c]	0.29 (0.28)	0.22 (0.17)	5.128	**.024**	0.28 (0.29)	0.20 (0.11)	13.772	**<.001**
NfL, pg/mL, median (IQR)[b]	23.90 (17.00)	19.40 (13.20)	6.380	**.012**	23.20 (17.55)	17.30 (11.65)	16.729	**<.001**

[a]Group comparisons were conducted between baseline MBI and no baseline MBI groups and between incident MBI and no incident MBI group using 1-way ANOVA, Mann-Whitney *U* tests, or chi-square tests. Significant test results with $P < .05$ are highlighted in bold.
[b]Median and IQR of NfL, p-tau181, and p-tau181/Aβ42 ratio raw values were reported, but one-way ANOVA was performed and reported using log-transformed values of NfL, p-tau181 levels, and p-tau181/Aβ42 ratio.
[c]Number of available data of p-tau181/Aβ42 ratio was 283 individuals with baseline MBI data (n = 54 baseline MBI, n = 229 no baseline MBI) and available in 187 individuals with follow-up MBI data (n = 49 incident MBI, n = 138 no incident MBI).
Abbreviations: Aβ42 = amyloid β 42, CIND = cognitive impairment no dementia, F = female, IQR = interquartile range, MBI = mild behavioral impairment, n = number, NCI = no cognitive impairment, NfL = neurofilament light, p-tau181 = phosphorylated tau-181, WMH = white matter hyperintensities.

NfL (β = 1.58, $P = .006$) (Table 3). Moreover, greater levels of baseline p-tau181, p-tau181/Aβ42, and NfL were linked to a greater change in the decreased motivation domain scores. Additionally, there was a trend between p-tau181 and p-tau181/Aβ42 with increased changes in the impulse dyscontrol domain, as well as between p-tau181/Aβ42 with longitudinal changes in abnormal perception or thought contents domain (Table 3).

Longitudinal Associations Between Individual Baseline Plasma Biomarkers and Incident MBI

Elevated baseline NfL levels (OR [95% CI] = 5.43 [1.97–14.97], $P = .001$) and p-tau181/Aβ42 ratio (OR [95% CI] = 3.50 [1.02–12.03], $P = .05$) were individually predictive of a greater risk of developing incident MBI over a 5-year follow-up after controlling age, sex, education, and baseline clinical diagnosis. As smaller HV and higher WMH severity were observed in individuals who developed incident MBI, we further adjusted the models and showed that all plasma biomarkers were significantly linked to an increased likelihood of incident MBI after additionally controlling for HV and WMH severity (Figure 2A).

Independent Effect of Baseline Plasma Biomarkers on Incident MBI With Incident Dementia as the Competing Risk

There were 16 individuals developed incident dementia before the occurrence of behavioral symptoms (ie, incident MBI), which were combined with individuals without incident MBI but developed incident dementia (n = 7) to form the group who developed incident dementia (n = 23) (Figure 1).

When accounting for incident dementia, plasma NfL levels, and covariates, higher baseline p-tau181 was significantly associated with a greater likelihood of incident MBI (hazard ratio [HR] [95% CI], 2.40 [1.00–5.75], $P = .05$) (Figure 2B; Model 1).

Table 2.

Comparison in Mean or Median Levels of Baseline Plasma p-tau181 and NfL in Individuals With MBI or NPS Among Dementia-Free Participants

Authors	Year	Regions	Diagnostic groups	Measures of blood biomarkers	Measures of MBI/NPS	Outcomes	% of change[a]
Current cohort	2024	Singapore	72.1% CIND	**SIMOA HD-1 platform** Plasma p-tau181: Simoa pTau-181 advantage V2 kit (Quanterix, Billerica, MA) Plasma NfL: Simoa NF-light advantage kit (Quanterix, Billerica, MA)	NPI	**Baseline MBI group (n = 57)** Plasma p-tau181: median (IQR) = 2.58 (1.68) pg/mL Plasma NfL: median (IQR) = 23.90 (17.00) pg/mL **Incident MBI group (n = 55)[b]** Plasma p-tau181: median (IQR) = 2.56 (2.28) pg/mL Plasma NfL: median (IQR) = 23.20 (17.55) pg/mL	**Baseline MBI** Plasma p-tau181: 20% Plasma NfL: 23% **Incident MBI** Plasma p-tau181: 31% Plasma NfL: 34%
Rabl et al[31]	2024	Switzerland	55.4% MCI	**SIMOA HD-X platform** Plasma p-tau181: In-house Simoa assay Plasma NfL: Simoa NF-light kit (Quanterix, Billerica, MA)	NPI-Q	**Baseline NPS group (n = 72)** Plasma p-tau181: mean (SD) = 13.7 (9.9) pg/mL Plasma NfL: mean (SD) = 22.9 (17.4) pg/mL	**Baseline NPS** Plasma p-tau181: 16% Plasma NfL: 19%
Ghahremani et al[16]	2023	North America	64.8% MCI	**SIMOA HD-X platform** Plasma p-tau181: In-house Simoa assay	NPI-Q	**Baseline MBI group (n = 103)** Plasma p-tau181: median (IQR) =16 (10.6) pg/mL	**Baseline MBI** Plasma p-tau181: 16%
Naude et al[17]	2020	North America	56.5% MCI	**SIMOA platform** Plasma NfL: In-house ultrasensitive enzyme linked immunosorbent assay	NPI-Q	**Baseline MBI group (n = 190)** Plasma NfL: mean (SD) = 36.43 (18.25) pg/mL **Emergent MBI (n = 64)** Plasma NfL: mean (SD) = 42.74 (26.30) pg/mL	**Baseline MBI** Plasma NfL: −7% **Emergent MBI** Plasma NfL: 13%

[a]The measured plasma biomarker concentration may differ due to the Simoa assays used. The percentage of change in plasma biomarkers in the symptomatic group from the no symptom group was calculated.
[b]Incident MBI was identified over the 5-year follow-up period. The mean time to incident MBI was 2.2 years.
Abbreviations: CIND = cognitive impairment no dementia, IQR = interquartile range, MBI = mild behavioral impairment, MCI = mild cognitive impairment, NfL = neurofilament light, NPI = Neuropsychiatric Inventory, NPI-Q = Neuropsychiatric Inventory Questionnaire, NPS = neuropsychiatric symptoms, p-tau181 = phosphorylated tau-181, SIMOA = single molecule array.

However, plasma NfL did not show significant associations with incident MBI (HR [95% CI], 2.05 [0.58–7.22], $P = .30$), when accounting for p-tau181 levels in the same model.

Moreover, we further tested if baseline amyloid burden was predictive of incident MBI by controlling for neuroimaging measures of HV and WMH. When replaced NfL with HV and WMH, higher baseline p-tau181 was also significantly predictive of an increased likelihood of MBI incidence (HR [95% CI], 2.69 [1.08–6.70], $P = .03$) (Figure 2B; Model 3). For the plasma p-tau181/Aβ42 ratio, no significant association was observed with incident MBI when adjusting for plasma NfL levels or HV and WMH in the respective competing risk regression models (Figure 2B; Models 2 and 4).

Sensitivity Analyses

In the current longitudinal analysis, the overall data loss rate is 12.5%. We identified 144 subjects (47%) with incident MBI in the imputed maximum NPI value dataset and 58 subjects (19%) with incident MBI in the minimum NPI value dataset. Using maximum and minimal NPI value datasets, results from GEE models were comparable for all baseline plasma biomarkers ($P < .05$) with incident MBI from the original dataset, except that the p-tau181/Aβ42 ratio was not significantly associated with incident MBI ($P = .13$) after controlling for covariates in the maximum NPI dataset. Overall, results from sensitivity analyses suggest the robustness of our original dataset, as the missing values due to loss to follow-up did not significantly affect our findings.

DISCUSSION

Baseline plasma p-tau181, p-tau181/Aβ42 ratio, and NfL were associated with increased 5-year neuropsychiatric disturbances, independent of baseline age, sex, education, and cognitive status. Furthermore, plasma biomarkers were significantly associated with incident MBI risk, even considering incident dementia as a competing risk event. In particular, increased plasma p-tau181 was independently predictive of incident MBI, when accounting for the presence of incident dementia, levels of neurodegeneration, and WMH severity.

Table 3.
Findings From LME on Associations Between Baseline Biomarkers and Longitudinal Changes in NPS and Subdomain Severity[a]

	NPS		Decreased motivation		Affective dysregulation		Impulse dyscontrol		Social inappropriateness		Abnormal perception or thought contents	
Variables	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Model 1[b]												
p-tau181 × time (y)	2.36 (1.08–3.65)	**<.001**	0.55 (0.19–0.92)	**.003***	0.15 (−0.06 to 0.36)	.166	0.61 (0.09–1.13)	**.022**	0.04 (−0.12 to 0.20)	.628	0.21 (−0.03 to 0.45)	.091
Model 2[c]												
p-tau181/Aβ42 × time (y)	2.59 (1.43–3.75)	**<.001**	0.42 (0.08–0.75)	**.016**	0.23 (0.03–0.42)	.021	0.70 (0.23–1.17)	**.004***	0.11 (−0.03 to 0.25)	.121	0.36 (0.14–0.58)	**.002***
Model 3[d]												
NfL × time (y)	1.58 (0.47–2.71)	**.006**	0.58 (0.27–0.89)	**<.001***	0.08 (−0.11 to 0.26)	.423	0.39 (−0.06 to 0.85)	.093	0.0001 (−0.13 to 0.14)	.999	0.05 (−0.16 to 0.26)	.622

[a]Linear mixed-effect models were constructed for respective baseline biomarkers to examine their associations with longitudinal NPS and subdomain severity, with baseline biomarker as the fixed effect and baseline biomarker × time (y) as the interaction term included in the models. All models were adjusted for age, sex, years of education, and baseline clinical diagnosis and included random slopes and intercepts. Significant test results with $P < 0.05$ are highlighted in bold.
[b]Model 1 (n = 305): p-tau181 (log-transformed), time (y), p-tau181 (log-transformed) × time (y), age, sex, years of education, and baseline clinical diagnosis.
[c]Model 2 (n = 283): p-tau181/Aβ42 ratio (log-transformed), time (y), p-tau181/Aβ42 ratio (log-transformed) × time (y), age, sex, years of education, and baseline clinical diagnosis.
[d]Model 3 (b = 304): NfL (log-transformed), time (y), NfL (log-transformed) × time (y), age, sex, years of education, and baseline clinical diagnosis.
*Significant after Bonferroni correction of multiple comparisons across 5 subdomains.
Abbreviations: Aβ42 = amyloid β 42, CI = confidence interval, NfL = neurofilament light, p-tau181= phosphorylated tau-181, y = year.

To the best of our knowledge, this is the first study to show the associations between plasma markers of p-tau181, p-tau181/Aβ42 ratio, and NfL levels with MBI in a multiethnic Asian dementia-free population. Over the 5-year follow up period, higher baseline biomarkers of amyloid burden and neuroaxonal degeneration predicted a greater increase in overall NPS severity longitudinally, regardless of brain structural disruptions. Our results have further demonstrated that greater level of baseline neurodegeneration and amyloid burden was associated with increased longitudinal changes in decreased motivation, impulse dyscontrol, and abnormal perception or thought contents domains. This was consistent with previous findings suggesting that more severe amyloid pathology at baseline, measured by CSF Aβ40/Aβ42 ratio, was predictive of increased apathy and anxiety over time in dementia-free individuals.[32] Moreover, consistent with our hypotheses, we observed the significant relationship between elevated p-tau181 levels and an increased likelihood of MBI incidence. Our findings are in concordance with a previous study showing that increased p-tau181 levels at baseline with MBI, but not with transient NPS (ie, NPS-not-MBI), when compared with no NPS individuals.[16] Plasma p-tau181 has demonstrated good diagnostic performance in detecting abnormal brain amyloid burden, as well as prognostic performance in predicting cognitive decline in predementia stages.[14,15] Using this assessable plasma biomarker measures of amyloid burden, we further confirmed these findings by implementing the more sophisticated survival modeling with competing risk event and baseline p-tau181 levels were significantly predictive of incident MBI, after accounting for another disease outcome (ie, incident dementia). When comparing our plasma biomarker levels with other populations, we observed that actual measured p-tau181 and NfL levels in our Asian cohort were lower than or comparable with those reported in studies involving predominantly non-Asian participants (Table 2). These discrepancies may reflect the differences across ethnicity[19,20,22] or methodological variations (eg, assays used for biomarker measures and inclusion criteria of participants) across cohorts, which highlighted the need for cautious usage and interpretation of plasma biomarker threshold across diverse populations.

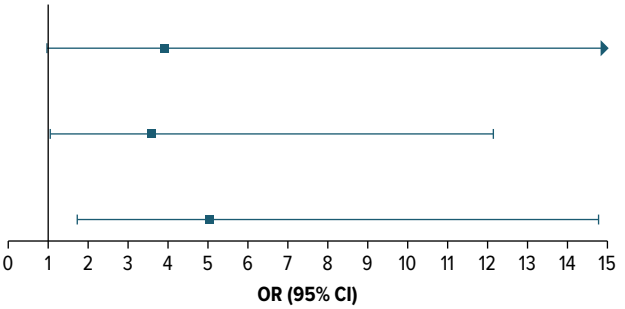
Furthermore, participants recruited from the current memory clinic cohort exhibited greater heterogeneity and a greater clinical burden, which may contribute to the underlying pathology of MBI. Mechanistically, NfL has been suggested as a nonspecific biomarker for ongoing neuroaxonal damage in various neurological disorders.[33–35] A recent study from our group further revealed the positive associations between elevated NfL levels with medial temporal atrophy and WMH, suggesting the link between NfL and neurodegenerative changes and vascular pathology.[28] Consistent with

Figure 2.

Longitudinal Associations Between Baseline Plasma Biomarker Levels and Incident MBI Over Follow-Up[a]

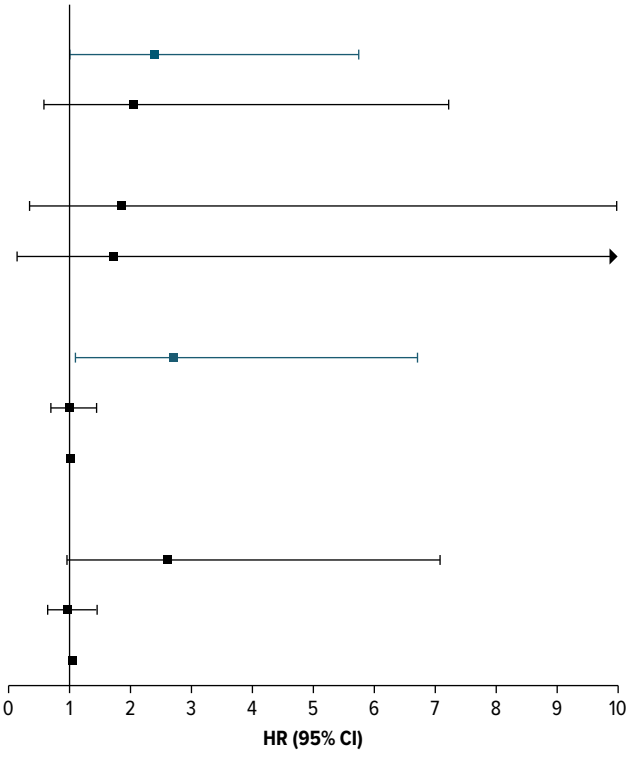
A. GEE model with logistic regressions

Variables	OR (95% CI)	*P*
Model 1[b]		
P-tau181	3.91 (0.97-15.69)	.05*
Model 2[c]		
P-tau181/Aβ42 ratio	3.58 (1.05-12.14)	.04*
Model 3[d]		
NfL	5.04 (1 .72-14.77)	.003*



B. Competing risk regressions

Variables	HR (95% CI)	*P*
Model 1[e]		
P-tau181	2.40 (1.00-5.75)	.05*
NfL	2.05 (0.58-7.22)	.27
Model 2[f]		
P-tau181/Aβ42 ratio	1.86 (0.34-9.98)	.47
NfL	1.72 (0.14-21.20)	.67
Model 3[g]		
P-tau181	2.69 (1.08-6.70)	.03*
Hippocampal volume	1.00 (0.70-1.44)	.98
WMH	1.02 (0.96-1 .08)	.53
Model 4[h]		
P-tau181/Aβ42 ratio	2.61 (0.96-7.08)	.06
Hippocampal volume	0.96 (0.64-1.44)	.85
WMH	1.04 (0.97-1 .11)	.27



[a](A): Generalized estimating equation (GEE) models with logistic regressions. GEE models were constructed to examine the relationship between respective baseline biomarkers and incident MBI. (B): Competing risk regressions (CRR) were conducted to examine the effect of baseline biomarkers on incident MBI, with incident dementia considered as the competing risk event. *Z*-scores of hippocampal volume were calculated and included in the model to improve the interpretability of estimates. Significant test results with $P < .05$ are denoted with an asterisk. [b]GEE Model 1 (n = 201): p-tau181 (log-transformed), time (y), age, sex, years of education, baseline clinical diagnosis, hippocampal volume (*z*-scores), and WMH. [c]GEE Model 2 (n = 187): p-tau181/Aβ42 ratio (log-transformed), time (y), age, sex, years of education, baseline clinical diagnosis, hippocampal volume (*z*-scores), and WMH. [d]GEE Model 3 (n = 200): NfL (log-transformed), time (y), age, sex, years of education, baseline clinical diagnosis, hippocampal volume (*z*-scores), and WMH. [e]CRR Model 1 (n = 217): p-tau181 (log-transformed), NfL (log-transformed), age, sex, years of education, and baseline clinical diagnosis. [f]CRR Model 2 (n = 202): p-tau181/Aβ42 (log-transformed), NfL (log-transformed), age, sex, years of education, and baseline clinical diagnosis. [g]CRR Model 3 (n = 215): p-tau181 (log-transformed), hippocampal volume (*z*-scores), WMH, age, sex, years of education, and baseline clinical diagnosis. [h]CRR Model 4 (n = 200): p-tau181/Aβ42 (log-transformed), hippocampal volume (*z*-scores), WMH, age, sex, years of education, and baseline clinical diagnosis.

Abbreviations: Aβ42 = amyloid β 42, CI = confidence interval, CR = competing risk regression, GEE = generalized estimating equations, HR = hazard ratio, NfL = neurofilament light, OR = odds ratio, p-tau181 = phosphorylated tau-181, WMH = white matter hyperintensities.

previous findings,[17,31] our study has shown the relationship between higher baseline NfL and more severe behavioral outcomes. Thus, by including NfL in the model of p-tau181 and incident MBI, we were able to show that amyloid burden predicted early behavioral changes, independent of neurodegenerative and vascular pathology. More importantly, this was further supported by robust results after adjusting for neuroimaging measures of HV and WMH. Our findings thus supported that MBI is an early manifestation of AD.

In addition to p-tau181, our study also explored the relationship between MBI and another AD-specific plasma biomarker p-tau181/Aβ42 ratio. We demonstrated that plasma p-tau181/Aβ42 ratio predicted NPS severity changes and incident MBI overtime, independent of neurodegeneration and vascular pathology at baseline. Our findings corroborated with a previous study which observed that MBI exhibited higher CSF p-tau181/Aβ42 ratio at baseline in both ADNI and MEMENTO cohorts.[36] Similar to p-tau181, higher CSF p-tau181/Aβ42 was only observed in the MBI group, but not in the NPS-not-MBI group. Of note, CSF p-tau181/Aβ42 showed a more accurate prediction of amyloid PET status than p-tau or Aβ alone.[22,37] Our group has previously showed that plasma p-tau181/Aβ42 ratio was a stronger indicator for amyloid burden in nondementia individuals, as well as distinguishing AD Aβ+ and VaD Aβ− subjects.[22] Given that p-tau181/Aβ42 ratio has taken into consideration of both amyloid and phosphorylated tau levels, this biomarker of amyloid burden could potentially be a more sensitive marker for screening MBI in cohorts of diverse clinical profiles prior to dementia. Nonetheless, further studies are needed to confirm the relationship between the longitudinal changes in p-tau181/Aβ42 ratio and MBI in the future.

Strengths of the current study include the identification of incident MBI using longitudinal NPI data in a well-characterized Asian cohort, as well as the use of assessable plasma biomarkers to represent separate pathophysiological processes in AD. Findings from the LME has taken in consideration of the fluctuations of NPS longitudinally, which was further supported by the associations between baseline biomarkers and incident MBI identified as a longitudinal outcome to highlight AD pathology in late-life behavioral outcomes. However, our study was not without limitations. First, the causality of neurodegeneration and AD pathology and MBI cannot be established without follow-up plasma biomarkers data. Additionally, participants who developed incident MBI were more prevalently found in the baseline CIND group. While the baseline diagnosis was accounted for in the analyses, the relationship in those without any cognitive impairment requires further investigation. Further longitudinal studies investigating MBI and these pathologies are needed to examine the disease progression of MBI among cognitively healthy older adults. Second, as our study commenced prior to the development of the Mild Behavioral Impairment-Checklist (MBI-C), MBI was not assessed directly using the MBI-C, which is the gold measure for MBI among dementia-free individuals. Instead, we operationalized MBI status based on 2 consecutive years of NPI assessments following previously published algorithms, which may not fully capture the MBI symptoms described in the MBI-C. Lastly, this study did not replicate previous findings[18] on the cross-sectional associations between Aβ40/Aβ42 ratio and MBI as we analyzed the plasma biomarker concentrations using the Simoa platform, which is a more accessible platform than the immunoprecipitation-mass spectrometry used for Aβ40 measures. Nevertheless, it was observed that CSF p-tau181/Aβ42 ratio demonstrated a stronger association with MBI compared to CSF Aβ40/Aβ42 ratio in the memory-clinic cohort.[36] Furthermore, future studies are recommended to explore other plasma P-tau isoforms, such as p-tau217 and p-tau231, with MBI to elucidate the mechanisms of early behavioral disturbances among dementia-free individuals.

To conclude, we demonstrated that not only were increased NfL and p-tau181 levels associated with MBI, but also p-tau181/Aβ42 ratio as a potential marker for incident MBI in predementia stages in an Asian memory clinic-based cohort. Our findings highlighted the potential utility of complementing clinical assessments with AD-related plasma biomarkers in clinical practice to identify individuals who are at heightened risk of developing behavioral disturbances in dementia.

Article Information

Published Online: March 5, 2025. https://doi.org/10.4088/JCP.24m15558

Submitted: August 12, 2024; accepted November 15, 2024.

To Cite: Liao Y, Chong JR, Kan CN, et al. Plasma NfL, p-tau181, and p-tau181/Aβ42 ratio in predicting mild behavioral impairment in dementia-free multi-ethnic Asian older adults with mixed pathology in a 5-year clinical cohort. *J Clin Psychiatry*. 2025;86(1):24m15558.

Author Affiliations: Memory, Aging and Cognition Centre, Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore (Liao, Chong, Kan, Chai, Hilal, Lai, Chen, Xu); School of Public Health and the Second Affiliated Hospital of School of Medicine, Zhejiang University, Hangzhou, China (Zhao, Xu); Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore (Hilal); Department of Psychological Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore (Chen).

Corresponding Author: Xin Xu, PhD, School of Public Health, The Second Affiliated Hospital of School of Medicine, 866 Yuhangtang Road, Hangzhou, Zhejiang University, China, 310058 (xuxinsummer@zju.edu.cn).

Relevant Financial Relationships: None.

Funding/Support: This research is funded by the Singapore National Medical Research Council (grants NMRC/CG/NUHS/2010 and NMRC/CG/013/2013).

Role of the Sponsors: The supporters had no role in the design, analysis, interpretation, or publication of this study.

Previous Presentation: Part of these data were presented in the form of oral presentation at the 17th International Congress of Asian Society Against Dementia; September 2023; Bandung, Indonesia.

Acknowledgments: The authors are grateful for all the kind support provided by the staff of the Memory, Ageing and Cognition Centre (MACC).

ORCID: Yingqi Liao: https://orcid.org/0000-0001-7499-8801.

Supplementary Material: Available at Psychiatrist.com.

References

1. Lyketsos CG, Lopez O, Jones B, et al. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive Impairment: results from the Cardiovascular Health Study. *JAMA*. 2002;288(12):1475–1483.
2. Xu X, Ang SL, Hilal S, et al. Association of neuropsychiatric symptoms and sub-syndromes with cognitive impairment in community-dwelling Asian elderly. *Int Psychogeriatr*. 2015;27(11):1839–1847.
3. Martin E, Velayudhan L. Neuropsychiatric symptoms in mild cognitive impairment: a literature review. *Dement Geriatr Cogn Disord*. 2020;49(2): 146–155.
4. Mortby ME, Ismail Z, Anstey KJ. Prevalence estimates of mild behavioral impairment in a population-based sample of pre-dementia states and cognitively healthy older adults. *Int Psychogeriatr*. 2018;30(2):221–232.
5. Ismail Z, Smith EE, Geda Y, et al. Neuropsychiatric symptoms as early manifestations of emergent dementia: provisional diagnostic criteria for mild behavioral impairment. *Alzheimers Dement*. 2016;12(2):195–202.
6. Kan CN, Cano J, Zhao X, et al. Prevalence, clinical correlates, cognitive trajectories, and dementia risk associated with mild behavioral impairment in Asians. *J Clin Psychiatry*. 2022;83(3):21m14105.
7. Creese B, Ismail Z. Mild behavioral impairment: measurement and clinical correlates of a novel marker of preclinical Alzheimer's disease. *Alzheimers Res Ther*. 2022;14(1):2.
8. Pan Y, Shea YF, Li S, et al. Prevalence of mild behavioural impairment: a systematic review and meta-analysis. *Psychogeriatrics*. 2021;21(1): 100–111.
9. Johansson M, Stomrud E, Insel PS, et al. Mild behavioral impairment and its relation to tau pathology in preclinical Alzheimer's disease. *Transl Psychiatry*. 2021;11(1):76.
10. Lussier FZ, Pascoal TA, Chamoun M, et al. Mild behavioral impairment is associated with β-amyloid but not tau or neurodegeneration in cognitively intact elderly individuals. *Alzheimers Dement*. 2020;16(1):192–199.
11. Chong JR, Ashton NJ, Karikari TK, et al. Blood-based high sensitivity measurements of beta-amyloid and phosphorylated tau as biomarkers of Alzheimer's disease: a focused review on recent advances. *J Neurol Neurosurg Psychiatry*. 2021;92(11):1231–1241.
12. Ashton NJ, Schöll M, Heurling K, et al. Update on biomarkers for amyloid pathology in Alzheimer's disease. *Biomark Med*. 2018;12(7):799–812.
13. Janelidze S, Mattsson N, Palmqvist S, et al. Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. *Nat Med*. 2020;26(3): 379–386.
14. Moscoso A, Grothe MJ, Ashton NJ, et al. Longitudinal associations of blood phosphorylated Tau181 and neurofilament light chain with neurodegeneration in Alzheimer disease. *JAMA Neurol*. 2021;78(4):396–406.
15. Smirnov DS, Ashton NJ, Blennow K, et al. Plasma biomarkers for Alzheimer's Disease in relation to neuropathology and cognitive change. *Acta Neuropathol*. 2022;143(4):487–503.
16. Ghahremani M, Wang M, Chen HY, et al. Plasma phosphorylated tau at threonine 181 and neuropsychiatric symptoms in preclinical and prodromal Alzheimer disease. *Neurology*. 2023;100(7):e683–e693.
17. Naude JP, Gill S, Hu S, et al. Plasma neurofilament light: a marker of neurodegeneration in mild behavioral impairment. *J Alzheimers Dis*. 2020;76(3): 1017–1027.
18. Miao R, Chen HY, Gill S, et al. Plasma β-amyloid in mild behavioural impairment - neuropsychiatric symptoms on the Alzheimer's continuum. *J Geriatr Psychiatry Neurol*. 2022;35(3):434–441.
19. Babulal GM, Quiroz YT, Albensi BC, et al. Perspectives on ethnic and racial disparities in alzheimer's disease and related dementias: update and areas of immediate need. *Alzheimers Dement*. 2019;15(2):292–312.
20. Schindler SE, Karikari TK, Ashton NJ, et al. Effect of race on prediction of brain amyloidosis by plasma Aβ42/Aβ40, phosphorylated tau, and neurofilament light. *Neurology*. 2022;99(3):e245–e257.
21. Chen C, Homma A, Mok VCT, et al. Alzheimer's disease with cerebrovascular disease: current status in the Asia-Pacific region. *J Intern Med*. 2016;280(4):359–374.
22. Chong JR, Ashton NJ, Karikari TK, et al. Plasma P-Tau181 to Aβ42 ratio is associated with brain amyloid burden and hippocampal atrophy in an Asian cohort of Alzheimer's disease patients with concomitant cerebrovascular disease. *Alzheimers Dement*. 2021;17(10):1649–1662.
23. Hilal S, Chai YL, Ikram MK, et al. Markers of cardiac dysfunction in cognitive impairment and dementia. *Medicine (Baltimore)*. 2015;94(1):e297.
24. Xu X, Chan YH, Chan QL, et al. Global cerebrovascular burden and long-term clinical outcomes in Asian elderly across the spectrum of cognitive impairment. *Int Psychogeriatr*. 2018;30(9):1355–1363.
25. Chai YL, Hilal S, Chong JPC, et al. Growth differentiation factor-15 and white matter hyperintensities in cognitive impairment and dementia. *Medicine (Baltimore)*. 2016;95(33):e4566.
26. Xu X, Chan QL, Hilal S, et al. The diagnostic utility of the NINDS-CSN neuropsychological battery in memory clinics. *Dement Geriatr Cogn Dis Extra*. 2016;6(2):276–282.
27. Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology*. 1997;48(5 suppl 6):S10–S16.
28. Chong JR, Hilal S, Ashton NJ, et al. Brain atrophy and white matter hyperintensities are independently associated with plasma neurofilament light chain in an Asian cohort of cognitively impaired patients with concomitant cerebral small vessel disease. *Alzheimers Dement*. 2023; 15(1):e12396.
29. Chia RSL, Minta K, Wu LY, et al. Serum brevican as a biomarker of cerebrovascular disease in an elderly cognitively impaired cohort. *Biomolecules*. 2024;14(1):75.
30. Kapeller P, Barber R, Vermeulen RJ, et al. Visual rating of age-related white matter changes on magnetic resonance imaging: scale comparison, interrater agreement, and correlations with quantitative measurements. *Stroke*. 2003; 34(2):441–445.
31. Rabl M, Clark C, Dayon L, et al. Blood plasma protein profiles of neuropsychiatric symptoms and related cognitive decline in older people. *J Neurochem*. 2023;164(2): 242–254.
32. Johansson M, Stomrud E, Johansson PM, et al. Development of apathy, anxiety, and depression in cognitively unimpaired older adults: effects of Alzheimer's disease pathology and cognitive decline. *Biol Psychiatry*. 2022;92(1):34–43.
33. Mattsson N, Andreasson U, Zetterberg H, et al. Association of plasma neurofilament light with neurodegeneration in patients with Alzheimer disease. *JAMA Neurol*. 2017;74(5):557–566.
34. Gaetani L, Blennow K, Calabresi P, et al. Neurofilament light chain as a biomarker in neurological disorders. *J Neurol Neurosurg Psychiatry*. 2019;90(8):870–881.
35. Ashton NJ, Janelidze S, Al Khleifat A, et al. A multicentre validation study of the diagnostic value of plasma neurofilament light. *Nat Commun*. 2021;12(1):3400.
36. Ismail Z, Leon R, Creese B, et al. Optimizing detection of Alzheimer's disease in mild cognitive impairment: a 4-year biomarker study of mild behavioral impairment in ADNI and MEMENTO. *Mol Neurodegener*. 2023;18(1):50.
37. Fowler CJ, Stoops E, Rainey-Smith SR, et al. Plasma p-tau181/$A\beta_{1-42}$ ratio predicts Aβ-PET status and correlates with CSF-p-tau181/$A\beta_{1-42}$ and future cognitive decline. *Alzheimers Dement*. 2022;14(1):e12375.

The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Plasma NfL, p-tau181, and p-tau181/Aβ42 Ratio in Predicting Mild Behavioral Impairment in Dementia-Free Multi-Ethnic Asian Older Adults With Mixed Pathology in a 5-Year Clinical Cohort

Authors: Yingqi Liao, MSc; Joyce R. Chong, PhD; Cheuk Ni Kan, PGDip; Xuhao Zhao, MPH; Yuek Ling Chai, PhD; Saima Hilal, PhD; Mitchell K. P. Lai, PhD; Christopher P. Chen, FRCP; and Xin Xu, PhD

DOI Number: 10.4088/JCP.24m15558

LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

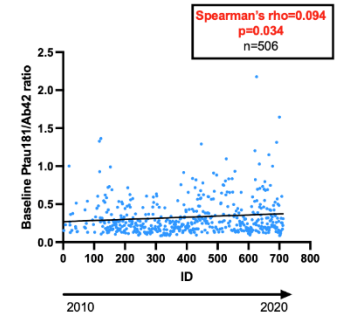
Supplementary Materials

Supplementary Methods

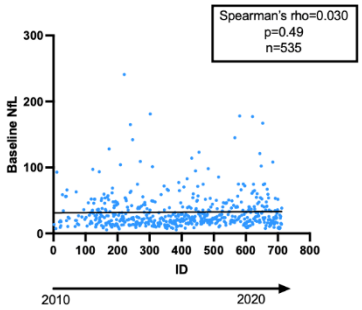
Fifteen (4.9%) subjects' blood sample were collected at a different visit from their NPI assessments used for baseline MBI status.

Plasma biomarkers measure time	NPI assessment time used for baseline MBI status		
	Baseline & Y1	Y1 &Y2	Total
Baseline	274	11	285
Y1	16	0	16
Y2	4	0	4
Total	294	11	305

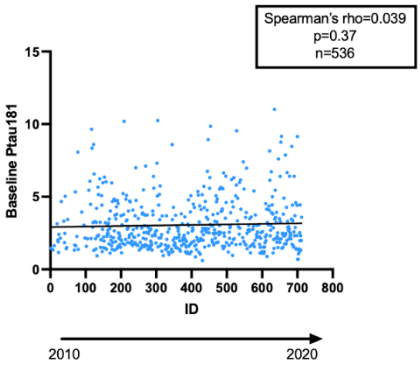
The blood biomarkers were measured in Dec 2021 for P-tau181 and NfL, and in Oct/Nov 2022 for Abeta42. The storage duration before biomarkers analyses varies among the participants. Correlation analyses showed that the storage duration has no/little impact on the biomarkers' concentrations (analyses performed in blood biomarkers measured using Baseline samples).



Note: The Figure (n=505) has HD264 removed (Plasma P-tau181/Ab42 ratio=4.951). The Spearman's rho is based on the entire cohort of n=506.



Note: The Figure (n=534) has HD304 removed (Plasma NfL=361 pg/mL). The Spearman's rho is based on the entire cohort of n=535.



Supplementary Table 1. Baseline plasma biomarker levels and incident MBI in the imputed dataset with maximum NPI values.

Variables	OR (95% CI)	P value
Model 1[a]		
Plasma P-Tau181 level (Log-transformed, pg/ml)		
P-Tau181 per unit increase	2.74 (1.08, 6.94)	**0.03**
Model 2[b]		
Plasma P-Tau181/Aβ42 ratio level (Log-transformed)[d]		
P-Tau181/Aβ42 ratio per unit increase	1.81 (0.83, 3.95)	0.13
Model 3[c]		
Plasma NfL level (Log-transformed, pg/ml)		
NfL per unit increase	3.35 (1.46, 7.68)	**0.004**

Aβ42, amyloid beta 42; CI, confidence interval; NfL, neurofilament light; OR, odd ratio; P-Tau181, phosphorylated tau-181; pg/mL, picograms per millilitre; SD, standard deviation; SE, standard errors. In the imputed NPI maximum value dataset, incident MBI (n=144) and no incident MBI (n=90) were identified. All generalised estimation equations (GEE) models were conducted in individuals with available incident MBI status (n=234) adjusting for age, gender, years of education and baseline diagnostic groups. *Significant test results with $p<0.05$ are highlighted in bold.

a. Model 1: P-Tau181 level (log transformed), age, gender, years of education and clinical diagnosis at baseline.
b. Model 2: P-Tau181/Aβ42 ratio level (log transformed), age, gender, years of education and clinical diagnosis at baseline.
c. Model 3: NfL level (log transformed), age, gender, years of education and clinical diagnosis at baseline.
d. Number of available data for P-Tau181/Aβ42 ratio was n=215.

Supplementary Table 2. Baseline plasma biomarker levels and incident MBI over follow-up in the imputed dataset with minimum NPI values.

Variables	OR (95% CI)	P value
Model 1[a]		
Plasma P-Tau181 level (Log-transformed, pg/ml)		
P-Tau181 per unit increase	3.93 (1.01, 15.28)	**0.05**
Model 2[b]		
Plasma P-Tau181/Aβ42 ratio level (Log-transformed)[d]		
P-Tau181/Aβ42 ratio per unit increase	3.12 (1.07, 9.09)	**0.04**
Model 3[c]		
Plasma NfL level (Log-transformed, pg/ml)		
NfL per unit increase	5.19 (1.69, 15.93)	**0.004**

Aβ42, amyloid beta 42; CI, confidence interval; NfL, neurofilament light; OR, odd ratio; P-Tau181, phosphorylated tau-181; pg/mL, picograms per millilitre; SD, standard deviation; SE, standard errors. In the imputed NPI minimum value dataset, incident MBI (n=58) and no incident MBI (n=177) were identified. All generalised estimation equations (GEE) models were conducted in individuals with available incident MBI status (n=235) adjusting for age, gender, years of education and baseline diagnostic groups.

a. Model 1: P-Tau181 level (log transformed), age, gender, years of education and clinical diagnosis at baseline.
b. Model 2: P-Tau181/Aβ42 ratio level (log transformed), age, gender, years of education and clinical diagnosis at baseline.
c. Model 3: NfL level (log transformed), age, gender, years of education and clinical diagnosis at baseline.
d. Number of available data for P-Tau181/Aβ42 ratio was n=217.