

RESEARCH ARTICLE

# Association of plasma GFAP with elevated brain amyloid is dependent on severity of white matter lesions in an Asian cognitively impaired cohort

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## Abstract

**INTRODUCTION:** While elevated blood glial fibrillary acidic protein (GFAP) has been associated with brain amyloid pathology, whether this association occurs in populations with high cerebral small vessel disease (CSVD) concomitance remains unclear.

**METHODS:** Using a Singapore-based cohort of cognitively impaired subjects, we assessed associations between plasma GFAP and neuroimaging measures of brain amyloid and CSVD, including white matter hyperintensities (WMH). We also examined the diagnostic performance of plasma GFAP in detecting brain amyloid beta positivity (A $\beta$ +).

**RESULTS:** When stratified by WMH status, elevated brain amyloid was associated with higher plasma GFAP only in the WMH- group ( $\beta = 0.383$ ;  $P < 0.001$ ). The diagnostic performance of plasma GFAP in identifying A $\beta$ + was significantly higher in the WMH- group (area under the curve [AUC] = 0.896) than in the WMH+ group (AUC = 0.712,  $P = 0.008$ ).

**DISCUSSION:** The biomarker utility of plasma GFAP in detecting brain amyloid pathology is dependent on the severity of concomitant WMH.

## KEYWORDS

Alzheimer's disease, amyloid pathology, blood biomarkers, cerebral small vessel disease, cognitive impairment, glial fibrillary acidic protein, white matter hyperintensity

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### Highlight

- Glial fibrillary acidic protein (GFAP)'s association with brain amyloid is unclear in populations with high cerebral small vessel disease (CSVD).
- Plasma GFAP was measured in a cohort with CSVD and brain amyloid.
- Plasma GFAP was better in detecting amyloid in patients with low CSVD versus high CSVD.
- Biomarker utility of GFAP in detecting brain amyloid depends on the severity of CSVD.

## 1 | BACKGROUND

Alzheimer's disease (AD) is characterized by abnormal accumulation of amyloid beta ( $A\beta$ ) plaques and neurofibrillary tangles (NFTs), as well as progressive neuronal loss, culminating in brain atrophy and clinical symptoms primarily of cognitive impairments. In addition, cerebral small vessel disease (CSVD) pathology not only contributes directly to vascular dementia (VaD), but also frequently coexists in AD brains,<sup>1-4</sup> where it interacts in an additive or synergistic manner with AD to exacerbate cognitive decline.<sup>2,5-7</sup> Importantly, the prevalence of concomitant AD and CSVD may be higher in specific populations, such as those in Asia, with consequent implications for preventative, diagnostic, and treatment strategies.<sup>8-11</sup>

AD and CSVD share major pathophysiological mechanisms, including dysregulated, chronic neuroinflammation.<sup>12-15</sup> Astrocytes, which contribute numerically to the highest proportion of glial cells in the central nervous system (CNS), are one of the key regulators of neuroinflammatory responses.<sup>16,17</sup> Physiologically, they are involved in brain signaling, modulating of synapses, transport of nutrients, homeostasis, and structural support. They also become reactive in response to a variety of disease processes in the brain including ischemic stroke and neurodegeneration,<sup>17-19</sup> during which they undergo characteristic morphological and functional changes, including the upregulation of a specific cytoskeletal protein, glial fibrillary acidic protein (GFAP), in a process termed reactive astrogliosis.<sup>17-20</sup> As such, elevated GFAP level is commonly used as a marker of reactive astrogliosis in human clinical studies. Higher GFAP levels have been reported in the cerebrospinal fluid of patients with AD and other non-AD neurodegenerative diseases.<sup>21-23</sup> Interestingly, recent advances in the use of ultra-sensitive immunoassay platforms such as single molecule arrays (Simoa) for blood biomarkers<sup>24</sup> have also facilitated reports of higher GFAP levels in AD blood.<sup>25-27</sup> Blood GFAP positively correlated with brain amyloid burden and demonstrated good diagnostic performance in detecting elevated brain amyloid.<sup>25,27-33</sup> However, because blood GFAP levels may be affected by a number of neurological conditions, further delineation of the effects of concomitant CSVD, which may confound associations based on blood GFAP measurements,<sup>34</sup> are needed for AD. However, current studies are based predominantly

on Caucasian cohorts from North America and Europe with relatively low CSVD burden; whether the proposed clinical utility of blood GFAP could be generalized to an Asian cohort which manifests a high prevalence of baseline CSVD remains unclear.

In this study, using a well-characterized Singapore-based cohort of cognitively impaired patients, we first examined the associations between plasma GFAP and neuroimaging measures of brain amyloid (amyloid positron emission tomography [PET]) and various CSVD pathologies (white matter hyperintensities [WMH], lacunes, and cerebral microbleeds [CMBs]). We also assessed the interaction effects between brain amyloid and each CSVD pathology. Finally, we determined the diagnostic performance of plasma GFAP in identifying elevated brain amyloid.

## 2 | METHODS

### 2.1 | Study population

From April 2016 to April 2019, 217 participants were recruited from the National University Hospital Memory Clinic and community in Singapore. Among the participants, 20 did not have sufficient plasma samples available. The remaining 197 participants had adequate plasma for GFAP measurements and were thus included in this study. Control subjects were defined as having no objective cognitive impairment (NCI;  $n = 41$ ) based on formal neuropsychological assessments. Clinical diagnoses of cognitive impairment no dementia (CIND;  $n = 93$ ) and dementia ( $n = 63$ ) were made as previously described.<sup>35</sup> The dementia cohort consisted of patients who were clinically diagnosed as AD ( $n = 45$ ) or VaD ( $n = 18$ ).<sup>35</sup> Participants provided detailed medical histories and underwent physical, clinical, and neuroimaging examinations and a neuropsychological battery consisting of seven cognitive domains<sup>35,36</sup> (see Data S1 in supporting information for component tests of each domain). Apolipoprotein E (APOE)  $\epsilon 4$  status was as previously described.<sup>37</sup> Approval for the study was obtained from the Singapore National Healthcare Group Domain-Specific Review Board (2018/00996, 2015/00406, and 2015/00441). Written informed consent was obtained for all participants prior to recruitment.

## 2.2 | Plasma GFAP, phosphorylated tau181, and A $\beta$ 42/A $\beta$ 40 ratio measurements

Non-fasting blood was collected into tubes containing ethylenediaminetetraacetic acid as anticoagulant. Mean blood sampling to neuroimaging intervals were 8 months (standard deviation [SD] = 6 months) and 0.5 months (SD = 1 month) for magnetic resonance imaging (MRI) and amyloid PET scans, respectively. Blood samples were centrifuged at 2000 rcf for 10 minutes at 4°C. Plasma was extracted and aliquoted in 0.2 mL aliquots that were stored in polypropylene tubes at -80°C until use. Plasma GFAP was measured on the Simoa HD-1 platform (Quanterix), using commercially available kits (Quanterix). Plasma phosphorylated tau (p-tau)181 and A $\beta$ 42/A $\beta$ 40 ratio were available in a subset of the participants ( $n = 185$ ). Measurements of plasma p-tau181 and A $\beta$ 42/A $\beta$ 40 ratio were as previously described.<sup>35</sup>

## 2.3 | MRI markers of CSVD

MRI scans were performed on a 3T Siemens Magnetom Trio Tim scanner, using a 32-channel head coil, at the Clinical Imaging Research Centre (CIRC) from the National University of Singapore (NUS). The sequences included T1-weighted, fluid attenuated inversion recovery (FLAIR), T2-weighted, and susceptibility-weighted imaging (SWI) sequences as previously described.<sup>38</sup>

A detailed description of the neuroimaging measures of WMH volume is provided in Data S2(a) in supporting information. Presence of elevated WMH (WMH+) was defined at the cut-off of 50th percentile (median) of log-transformed WMH volume.<sup>39</sup> WMH volume was available for 195 participants. The description for the visual gradings of lacunes and CMBs is found in Data S2(b). Lacune status was binarized (Lacune- vs. Lacune+) using lacune counts < 2 versus  $\geq 2$ . Similarly, CMB status was binarized (CMB- vs. CMB+) using CMB counts < 2 versus  $\geq 2$ . Lacune and CMB counts are available for all participants.

## 2.4 | Amyloid PET acquisition and quantification

PET imaging for brain amyloid burden was conducted at CIRC NUS using either the [<sup>11</sup>C]Pittsburgh compound B (PiB;  $n = 167$ ) or [<sup>18</sup>F]Flutafuranol ( $n = 30$ ) amyloid tracer radioligands, as previously described.<sup>35</sup> A comprehensive description of the amyloid PET measurement is provided in Data S2(c). PiB-PET standardized uptake value ratio (SUVR) is available for 166 participants. Brain amyloid status (A $\beta$ - vs. A $\beta$ +) was determined for all participants using visual assessment as previously described.<sup>35</sup>

## 2.5 | Statistical analyses

Statistical analyses were performed using SPSS version 26 (IBM SPSS) and R statistical software.<sup>40</sup> Group comparisons of continuous demo-

### RESEARCH IN CONTEXT

- 1. Systematic review:** Recent studies demonstrated the potential utility of blood glial fibrillary acidic protein (GFAP) as a biomarker for brain amyloid pathology in dementia. However, extant studies are based on Western cohorts with relatively low cerebral small vessel disease (CSVD) burden. Whether the postulated clinical utility of GFAP is generalizable to Asian cohorts known to manifest high concomitant CSVD remains unclear.
- 2. Interpretation:** Using a Singapore-based cohort of cognitively impaired patients with concomitant CSVD, we found elevated brain amyloid associated with higher plasma GFAP only in individuals with low white matter hyperintensities burden (WMH-). The diagnostic performance of plasma GFAP in identifying brain amyloid positivity was significantly higher in the WMH- group versus the WMH+ group.
- 3. Future directions:** The utility of plasma GFAP in detecting brain amyloid is dependent on the severity of concomitant WMH. Population differences need to be considered before the widespread application of plasma GFAP as a clinical biomarker for dementia.

graphic variables were performed using one-way analysis of variance (ANOVA) with Bonferroni post hoc tests for normally distributed data, and non-parametric Kruskal-Wallis test with post hoc Dunn-Bonferroni correction for skewed distributed data. Chi-square tests were used for categorical variables.

Correlation analyses were performed using Spearman rank correlations. WMH volumes and plasma GFAP levels were logarithmically transformed due to the skewed distribution for further analyses. In the entire cohort, we first assessed the association between each neuroimaging measure (PiB-PET SUVR, WMH volume, lacune counts, or CMB counts) with blood GFAP using separate linear regression models. All neuroimaging measures were treated as continuous variables in the regression analyses. A forward selection approach was also used to identify predictors of blood GFAP out of all the neuroimaging measures. At each step, variables were chosen and included in the final model based on  $P$  values (entry criterion  $P$  value < 0.05). All regression models were adjusted for covariates, including age, sex, APOE  $\epsilon$ 4, and education.

To determine potential interactions between brain amyloid and CSVD on plasma GFAP, the cross-product term for brain amyloid and each CSVD marker measurement were included in respective regression models. Outcome measures for the regression analyses were reported as mean differences ( $\beta$ ) with 95% confidence intervals (CIs). Differences in plasma GFAP among groups stratified by A and WMH status were assessed using a univariate

general linear model, adjusted for covariates, and post hoc Bonferroni tests for pairwise group comparisons of estimated marginal means.

Diagnostic performance was assessed using the area under the receiver operating characteristic curve (AUROC). Area under the curve (AUC) and 95% CIs were computed using DeLong method with the pROC package. AUROC analyses were performed in the entire cohort, as well as in groups stratified by WMH status (WMH- vs. WMH+). Comparisons of the ROC curves between WMH- and WMH+ groups were performed using DeLong method (unpaired ROC curves). Subgroup analyses were also performed for the cognitively impaired participants (CIND and dementia). Additionally, for AUROC analyses, subgroup analyses were also performed in the non-dementia (NCI+CIND) and CIND participants, respectively. Results were considered significant at  $P < 0.05$ .

## 3 | RESULTS

### 3.1 | Participant characteristics

Demographic data, neuroimaging, and plasma GFAP values are shown in Table 1. CIND and dementia participants had significantly higher WMH volume compared to NCI. For brain amyloid burden, dementia participants showed the highest PiB-PET SUVR values. Plasma GFAP correlated with age ( $\rho = 0.356$ ;  $P < 0.001$ ), sex (male median [interquartile range (IQR)] = 207 [122] pg/mL; female = 251 [224];  $P = 0.009$ ), APOE  $\epsilon 4$  genotype (carriers median [IQR] = 253 [241] pg/mL; non-carriers = 203 [149] pg/mL;  $P = 0.002$ ) and education ( $\rho = -0.231$ ,  $P < 0.001$ ). There was no significant association between plasma GFAP and vascular risk factors (Figure S1 in supporting information). After adjustment for covariates, plasma GFAP levels were significantly increased in dementia compared to CIND and controls ( $P = 0.003$  and  $P < 0.001$ , respectively, see Figure S2 in supporting information).

### 3.2 | Associations of neuroimaging measures with plasma GFAP

In all participants, plasma GFAP correlated only with brain amyloid burden (measured by PiB-PET SUVR,  $\rho = 0.489$ ;  $P < 0.001$ ) among the neuroimaging variables investigated (Table S1a in supporting information). The association remained after adjustments for age, sex, APOE  $\epsilon 4$  status, and education in linear regression analyses (PiB-PET SUVR,  $\beta$  [95% CI] = 0.232 [0.149, 0.316], see Table S1b). Notably, PiB-PET SUVR was also selected for the final regression model using a forward selection approach (Data S3a in supporting information). Similarly, within the cognitively impaired elderly, PiB-PET SUVR was positively associated with GFAP ( $\beta$  [95% CI] = 0.242 [0.151, 0.333]), see Table 2, Model 1).

### 3.3 | Interaction effects between brain amyloid and CSVD on plasma GFAP

Next, we determined if there was an interaction between brain amyloid and CSVD on plasma GFAP. A significant interaction was observed between brain amyloid and WMH measurements ( $P < 0.05$ , see Tables S2 and S3 in supporting information), suggesting that the effects of brain amyloid on plasma GFAP are dependent on WMH severity. Thus, we next performed the regression analyses in groups stratified by WMH status. In both the overall cohort and cognitively impaired subgroup, positive associations between PiB-PET SUVR and GFAP were observed in the WMH- participants (Table 2, Model 2 and Table S4a in supporting information), but not in the WMH+ participants (Table 2, Model 3 and Table S4b). No significant interaction was observed between brain amyloid and other CSVD markers on plasma GFAP ( $P > 0.05$ , see Tables S2 and S3).

### 3.4 | Plasma GFAP in participants stratified by brain amyloid and WMH status

To further investigate potential links among brain amyloid, white matter disease, and GFAP, we performed group comparisons stratified by A $\beta$  and WMH status (see Table S5 in supporting information for demographics table). Figure 1A shows, for the entire cohort, that plasma GFAP levels were 60% higher in the A $\beta$ + than A $\beta$ - individuals after adjustment for age, sex, APOE  $\epsilon 4$  status, and education (adjusted mean of plasma GFAP [pg/mL] = 200 vs. 318;  $P < 0.001$ ). With stratification by A $\beta$  and WMH status, plasma GFAP levels were increased in the A $\beta$ +WMH-, A $\beta$ -WMH+, and A $\beta$ +WMH+ subgroups compared to A $\beta$ -WMH- (all  $P \leq 0.05$ ). Notably, plasma GFAP levels were 99% higher in the A $\beta$ + compared to A $\beta$ - individuals among WMH- individuals (adjusted mean of plasma GFAP [pg/mL] = 179 vs. 356;  $P < 0.001$ ). In contrast, among WMH+ individuals, plasma GFAP levels were not significantly different between A $\beta$ + versus A $\beta$ - participants (adjusted mean of plasma GFAP [pg/mL] = 227 vs. 291;  $P = 0.091$ ).

Similarly, for cognitively impaired subjects, plasma GFAP levels were 54% higher in A $\beta$ + compared to A $\beta$ - individuals (adjusted mean of plasma GFAP [pg/mL] = 210 vs. 324;  $P < 0.001$ , see Figure 1B). Among WMH- individuals, plasma GFAP levels were 95% higher in those with A $\beta$ + compared to A $\beta$ - (adjusted mean of plasma GFAP [pg/mL] = 185 vs. 361;  $P < 0.001$ ). However, among WMH+ individuals, plasma GFAP levels were not significantly different between A $\beta$ + versus A $\beta$ - participants (adjusted mean of plasma GFAP [pg/mL] = 234 vs. 297;  $P = 0.198$ ).

### 3.5 | Diagnostic performance of plasma GFAP in identifying elevated brain amyloid

To test the diagnostic performance of plasma GFAP in detecting brain amyloid positivity (A $\beta$ +), we applied a AUROC curve analysis (Table 3).

**TABLE 1** Demographic and clinical characteristics.

	NCI	CIND	Dementia	P value
Maximum <i>n</i>	41	93	63	
Demographic factors				
Age, years, mean (SD)	74 (6)	76 (6)	76 (8)	0.429
Female, <i>n</i> (%)	27 (66)	46 (50)	43 (68)	<b>0.038</b>
Education, years, mean (SD)	10 (5)	8 (5)	5 (5) <sup>ab</sup>	< <b>0.001</b>
APOE ε4 carrier, <i>n</i> (%)	9 (22)	24 (26)	25 (40)	0.087
Vascular risk factors				
Hypertension, <i>n</i> (%)	28 (68)	67 (72)	50 (79)	0.409
Hyperlipidemia, <i>n</i> (%)	31 (76)	68 (73)	42 (67)	0.554
Diabetes, <i>n</i> (%)	7 (17)	31 (33)	17 (27)	0.154
Cardiovascular disease, <i>n</i> (%)	1 (3)	11 (12)	3 (5)	0.145
Brain amyloid burden				
PiB-PET SUVR, median (IQR)	1.1 (0.2)	1.2 (0.4)	1.6 (0.9) <sup>ab</sup>	<b>0.002</b>
Aβ+, <i>n</i> (%)	4 (10)	32 (34) <sup>a</sup>	32 (51) <sup>a</sup>	< <b>0.001</b>
Cerebral small vessel disease				
White matter hyperintensities (WMH) volume, mL, median (IQR)	1.3 (4)	3.6 (12) <sup>a</sup>	5.5 (13) <sup>a</sup>	< <b>0.001</b>
WMH+, <i>n</i> (%)	13 (32)	49 (53)	37 (61) <sup>a</sup>	<b>0.014</b>
Cerebral microbleeds count, median (IQR)	0 (1)	0 (1)	0 (2)	0.231
Lacunae count, median (IQR)	0 (0)	0 (1)	0 (1)	0.169
Plasma GFAP, pg/mL, median (IQR)	177 (93)	209 (160)	296 (265) <sup>ab</sup>	< <b>0.001</b>

Notes: *P* values are derived from chi-square tests for categorical variables, and from one-way ANOVA with post hoc Bonferroni test or Kruskal–Wallis test with post hoc Dunn–Bonferroni for multiple comparisons, for normally distributed or skewed continuous variables, respectively. **Bold** fonts indicate significant *P* values. Diabetes status was available for 196 participants. Cardiovascular status was available for 183 participants. PiB-PET SUVR data was available for 166 participants. Aβ+ was determined by visual assessment of amyloid PET using either the PiB or flutafuranol amyloid tracer radioligands. WMH volume data was available for 195 participants. For WMH+, the cut-off for log transformed WMH volume was at the 50th percentile. The dementia cohort consisted of patients who were clinically diagnosed as AD (*n* = 45) or VaD (*n* = 18), respectively.

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; ANOVA, analysis of variance; APOE, apolipoprotein E; CIND, cognitive impairment no dementia; IQR, interquartile range; NCI, no cognitive impairment; PET, positron emission tomography; PiB, Pittsburgh compound B; SD, standard deviation; SUVR, standardized uptake value ratio; VaD, vascular dementia; WMH, white matter hyperintensities.

<sup>a</sup>Significantly different from NCI.

<sup>b</sup>Significantly different from CIND.

In the entire cohort, the AUC obtained was 0.81 (95% CI [0.74, 0.87]). When stratified by WMH status, plasma GFAP performed significantly better in WMH− individuals (WMH−: AUC = 0.90, 95% CI [0.83, 0.96] vs. WMH+: AUC = 0.71, 95% CI [0.61, 0.82], *P* = 0.005). Among the cognitively impaired participants, the AUC obtained was 0.80 (95% CI = 0.73, 0.87). Stratification by WMH status again showed superior diagnostic performance of GFAP in WMH− individuals (AUC = 0.90, 95% CI [0.82, 0.97]) over WMH+ (AUC = 0.71, 95% CI [0.60, 0.82], *P* = 0.008).

Given the emerging use of blood biomarkers in disease-modifying trials to identify brain amyloid positivity among preclinical and prodromal elderly, we repeated AUROC analyses in the non-dementia (NCI+CIND) and CIND subgroups. Similar findings were derived in both subgroups, in which plasma GFAP performed significantly better in WMH− individuals (non-dementia: AUC = 0.87, 95% CI [0.77, 0.97]; CIND: AUC = 0.87, 95% CI [0.75, 0.99]) than WMH+ (non-dementia: AUC = 0.67, 95% CI [0.53, 0.81], *P* = 0.025; CIND: AUC = 0.66, 95%

CI [0.50, 0.82], *P* = 0.040). Together, these results suggest that the diagnostic performance of plasma GFAP in identifying elevated brain amyloid (Aβ+) could be dependent on severity of WMH burden.

Finally, we investigated if the diagnostic performance of other established plasma AD biomarkers, namely p-tau181 and Aβ42/Aβ40 ratio, are dependent on severity of WMH burden (Table 3). In contrast to plasma GFAP, for plasma p-tau181 and Aβ42/Aβ40 ratio, there was no significant difference in the AUCs between WMH+ and WMH− groups (all *P* ≥ 0.190). This implies that the effects of concomitant WM lesions on diagnostic performance were relevant to plasma GFAP, but not p-tau181 and Aβ42/Aβ40 ratio.

## 4 | DISCUSSION

To our knowledge, this is the first study to evaluate associations between plasma GFAP and neuroimaging measures of brain amyloid

**TABLE 2** Associations of brain amyloid burden with plasma GFAP.

Outcome: GFAP <sup>a</sup>		
Model 1	All participants	
	All participants (n = 166)	Cognitively impaired (n = 141)
PiB-PET SUVR	$\beta = 0.232$ (0.149, 0.316)	$\beta = 0.242$ (0.151, 0.333)
Model 2	WMH- participants only	
	All WMH- participants (n = 84)	Cognitively impaired (n = 66)
PiB-PET SUVR	$\beta = 0.351$ (0.244, 0.457)	$\beta = 0.383$ (0.260, 0.505)
Model 3	WMH+ participants only	
	All WMH+ participants (n = 82)	Cognitively impaired (n = 75)
PiB-PET SUVR	$\beta = 0.094$ (-0.033, 0.221)	$\beta = 0.112$ (-0.020, 0.244)

Notes: Brain amyloid burden as measured by PET. Results from linear regression in all participants (Model 1), as well as in groups stratified by WMH status (Models 2 and 3). The cognitively impaired group consisted of CIND and dementia participants. **Bold** fonts indicate significant ( $P < 0.05$ )  $\beta$  values and their respective 95% confidence intervals.

Independent variables in each model:

**Model 1:** PiB-PET SUVR, age, sex, APOE  $\epsilon 4$  status, education.

**Model 2:** PiB-PET SUVR, age, sex, APOE  $\epsilon 4$  status, education.

**Model 3:** PiB-PET SUVR, age, sex, APOE  $\epsilon 4$  status, education.

Abbreviations: APOE, apolipoprotein E; CIND, cognitive impairment no dementia; PET, positron emission tomography; PiB, Pittsburgh compound B; SUVR, standardized uptake value ratio; WMH, white matter hyperintensities.

<sup>a</sup>Log-transformed.

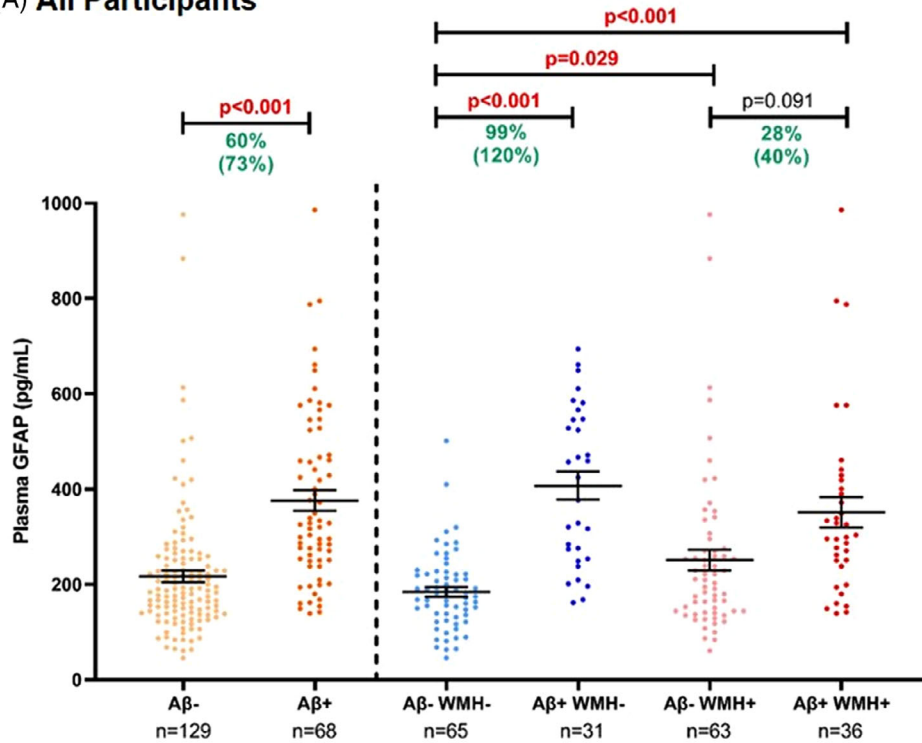
and CSVD in an Asian cohort with high baseline CSVD burden.<sup>10,39,41</sup> We showed that the utility of GFAP in detecting brain amyloid is dependent on concomitant WMH severity. Specifically, increased brain amyloid was significantly associated with higher GFAP levels only among subjects with low WMH burden (WMH-). Furthermore, GFAP demonstrated superior utility in detecting amyloid positivity among WMH- compared to WMH+ participants. Given that the recent studies reporting associations between GFAP and brain amyloid were generally performed in Western cohorts of European descent with relatively low CSVD burden,<sup>25,27,28,30-33</sup> our findings imply that the purported utility of plasma GFAP as a screening tool for amyloid positivity may be dependent on the baseline WMH burden of the population in question.

Elevated GFAP is thought to represent reactive astrogliosis, an inflammatory response of activated astrocytes to brain insults such as aberrant accumulation of protein aggregates, neuronal damage, and brain vascular injury. Therefore, both accumulating AD pathology such as brain amyloidosis,<sup>42</sup> as well as presence of vascular insults such as active, expanding WMH lesions,<sup>43,44</sup> may trigger astrogliosis and release of GFAP. In this context, while our finding of elevated plasma GFAP in A $\beta$ + participants corroborates previous studies,<sup>25,28,30,31,33</sup> this link was observed only within the WMH- group. On the other hand, GFAP was increased even in A $\beta$ -WMH+ participants (i.e., presence of elevated WMH only), which reduced the difference between A $\beta$ -WMH+ and A $\beta$ +WMH+ groups, resulting in non-significance. Interestingly, two other studies have shown positive association between blood GFAP and WMH burden,<sup>32,45</sup> with one study suggesting that the association is dependent on brain amyloid status.<sup>32</sup> Overall, these findings further support elevated blood GFAP as a biomarker for neuroinflammatory reaction to both brain amyloidosis and white mat-

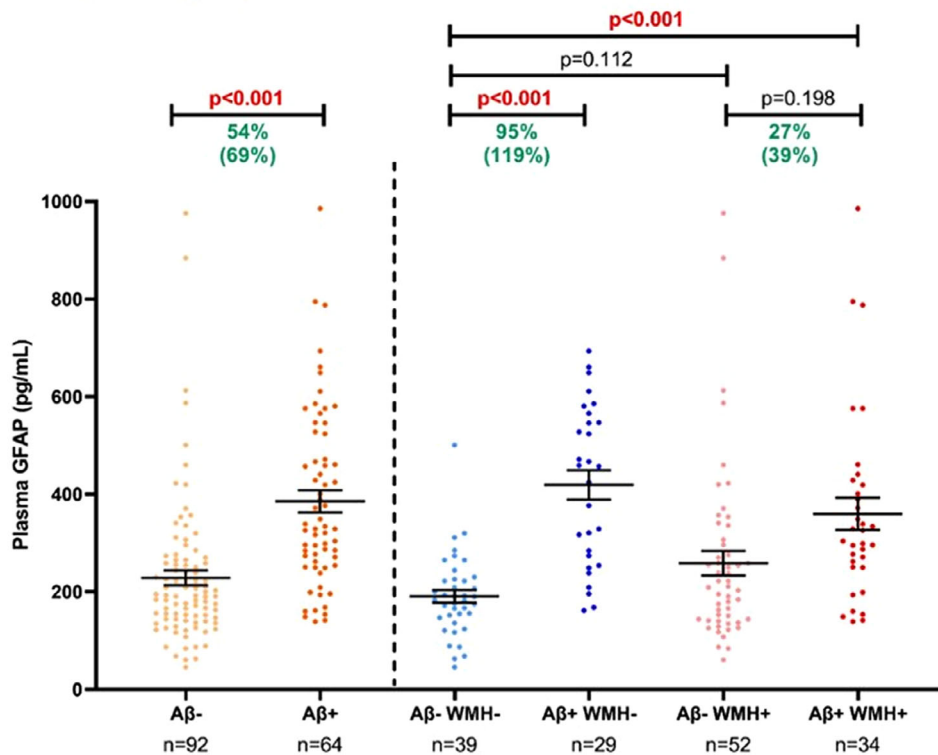
ter lesion. Previous studies have reported cross-sectional associations between higher degree of WMH and worse cognitive performance.<sup>46</sup> Longitudinally, WMH was associated with cognitive decline and incident dementia.<sup>46,47</sup> Importantly, studies have also demonstrated the combined, additive effect of AD and vascular pathologies in brain atrophy and cognition,<sup>46,48,49</sup> indicating the relevance of a biomarker that is associated with both pathologies.

In line with previous studies, we have also reported the good diagnostic performance of plasma GFAP in detecting brain amyloid positivity among elderly with different cognitive profiles (e.g., cognitively impaired or non-dementia subgroups). Notably, we further showed that the biomarker utility of plasma GFAP is dependent on the severity of concomitant WMH. Plasma GFAP demonstrated superior performance in the WMH- participants compared to the WMH+ participants. On further investigation of other established plasma AD biomarkers, p-tau181 and A $\beta$ 42/A $\beta$ 40 ratio, we did not observe such differential diagnostic performance. This could be due to the interaction between brain amyloid and WMH burden on GFAP levels, where the presence of WMH burden alleviated the associations between brain amyloid and GFAP. In contrast, there was no significant association between WMH burden and plasma p-tau181 or A $\beta$ 42/A $\beta$ 40 ratio, as previously reported.<sup>35</sup> This finding provides more insights into the potential roles that astrogliosis play in both AD and CSVD. It also has clinical implications as current findings suggest that population differences need to be considered before widespread adoption of plasma GFAP as a clinical biomarker of brain amyloid pathology. Plasma GFAP could potentially be used in clinical practice, in combination with other promising plasma AD-related biomarkers such as p-tau and neurofilament light chain (NfL), which have similarly demonstrated promising utility in AD diagnosis and predicting subsequent

(A) All Participants



(B) Cognitively Impaired Participants



**FIGURE 1** Plasma GFAP in groups stratified by amyloid and status of WMH. Plasma GFAP across groups stratified by amyloid ( $A\beta$ ) status, and further stratified by WMH status, in (A) all participants or (B) cognitively impaired group. The cognitively impaired group consisted of CIND and dementia participants. The graphs show the unadjusted mean and standard error of the mean. The groups' differences were assessed with univariate general linear model using log-transformed plasma GFAP levels, adjusted for age, sex, APOE  $\epsilon 4$  status, and education, with  $P$  values representing post hoc Bonferroni for pairwise group comparisons of estimated marginal means. The percentage increase of adjusted or unadjusted (in brackets) plasma GFAP levels in the A+ group from the A- group is shown in green font. Red fonts indicate significant  $P$  values.  $A\beta$ , amyloid beta APOE, apolipoprotein E; CIND, cognitive impairment no dementia; GFAP, glial fibrillary acidic protein; WMH, white matter hyperintensities.

**TABLE 3** AUROC analyses of plasma GFAP and other AD biomarkers for identifying elevated brain amyloid burden.

	ROC1 (Entire cohort)	ROC2 (WMH- participants only)	ROC3 (WMH+ participants only)	Difference in AUC (ROC 2 vs. ROC3)	p-value (ROC 2 vs. ROC3)
All participants					
GFAP (68 A $\beta$ + vs. 129 A $\beta$ -)	0.807 (0.744–0.870)	0.895 (0.827–0.962)	0.713 (0.610–0.817)	<b>0.182</b>	<b>0.005</b>
P-tau181 (64 A $\beta$ + vs. 121 A $\beta$ -)	0.839 (0.780–0.898)	0.808 (0.713–0.903)	0.870 (0.798–0.941)	–0.062	0.314
A $\beta$ 42/A $\beta$ 40 (63 A $\beta$ + vs. 122 A $\beta$ -)	0.814 (0.750–0.877)	0.849 (0.766–0.931)	0.786 (0.689–0.883)	0.063	0.336
Cognitively impaired participants					
GFAP (64 A $\beta$ + vs. 92 A $\beta$ -)	0.797 (0.726–0.868)	0.896 (0.819–0.973)	0.712 (0.602–0.822)	<b>0.184</b>	<b>0.008</b>
P-tau181 (60 A $\beta$ + vs. 85 A $\beta$ -)	0.839 (0.773–0.906)	0.793 (0.673–0.913)	0.870 (0.794–0.946)	–0.077	0.292
A $\beta$ 42/A $\beta$ 40 (59 A $\beta$ + vs. 85 A $\beta$ -)	0.787 (0.711–0.863)	0.800 (0.685–0.915)	0.778 (0.672–0.883)	0.022	0.778
Non-dementia participants					
GFAP (36 A $\beta$ + vs. 98 A $\beta$ -)	0.774 (0.688, 0.859)	0.866 (0.765, 0.966)	0.668 (0.530, 0.806)	<b>0.198</b>	<b>0.025</b>
P-tau181 (34 A $\beta$ + vs. 92 A $\beta$ -)	0.803 (0.723–0.884)	0.771 (0.650–0.893)	0.842 (0.736–0.948)	–0.071	0.393
A $\beta$ 42/A $\beta$ 40 (34 A $\beta$ + vs. 92 A $\beta$ -)	0.855 (0.784–0.926)	0.901 (0.827–0.975)	0.803 (0.679–0.928)	0.098	0.190
CIND participants					
GFAP (32 A $\beta$ + vs. 61 A $\beta$ -)	0.764 (0.663, 0.865)	0.869 (0.749, 0.989)	0.660 (0.504, 0.815)	<b>0.209</b>	<b>0.040</b>
P-tau181 (30 A $\beta$ + vs. 56 A $\beta$ -)	0.807 (0.713–0.901)	0.760 (0.604–0.917)	0.842 (0.722–0.961)	–0.082	0.420
A $\beta$ 42/A $\beta$ 40 (30 A $\beta$ + vs. 55 A $\beta$ -)	0.836 (0.747–0.925)	0.878 (0.770–0.986)	0.800 (0.661–0.937)	0.078	0.378

Notes: AUC and 95% confidence interval (CI) were derived from DeLong test. For WMH+, the cut-off for log transformed WMH volume was at the 50th percentile. The cognitively impaired group consisted of CIND and dementia participants. The non-dementia group consisted of NCI and CIND participants. Comparisons of the ROC curves between WMH- and WMH+ groups were performed using DeLong's method (unpaired ROC curves), with **bold** fonts denoting significant differences in AUC.

Abbreviations: A $\beta$ , amyloid beta; AD, Alzheimer's disease; AUC, area under the curve; AUROC, area under the receiver operating characteristic curve; CIND, cognitive impairment no dementia; GFAP, glial fibrillary acidic protein; NCI, no cognitive impairment; p-tau, phosphorylated tau; ROC, receiver operating characteristic; WMH, white matter hyperintensities.

cognitive decline.<sup>50,51</sup> However, more studies are needed to determine the optimal combinations of plasma biomarkers that improve the current diagnostic and prognostic work-up.<sup>50</sup> The examination of confounding factors, such as kidney disease and body mass index (BMI), which may affect blood GFAP concentrations independent of disease pathologies in the brain, is also warranted.<sup>50</sup> Given the cross-sectional association between plasma GFAP and WMH, future studies may assess the prognostic performance of plasma GFAP in predicting WMH progression.

The strength of this study is the thoroughly characterized Asian cohort with comprehensive neuroimaging measures of brain amyloid, CSVD, and brain atrophy.

However, a few limitations should also be recognized such as the relatively modest sample size and cross-sectional design. Further stud-

ies are required to validate the current findings in larger, independent cohorts using both cross-sectional and longitudinal study designs. Longitudinal studies may assess how trajectory of plasma GFAP changes associated with development and progression of AD and vascular pathology. Next, a head-to-head comparison of the prognostic performances of plasma GFAP and other promising plasma AD-related biomarkers, including p-tau, A $\beta$  and NfL, alone or in combination, is warranted. The inclusion of a PET imaging tracer such as [<sup>11</sup>C]-deuterium-1-deprenyl would be useful to examine the relationship between plasma GFAP and regional brain astrocytosis. Furthermore, though an increase in GFAP is a strong indication of reactive astrocyte remodeling, it is not an absolute or sole marker of reactivity.<sup>19</sup> Therefore, other astrogliosis markers such as YKL40 and S100B<sup>52</sup> should be investigated to compare to the GFAP results.



In conclusion, our results suggest that high blood GFAP levels is a non-specific biomarker for AD- and vascular-related injury. Additionally, depending on the prevalence of CSVD burden in the populations, blood GFAP holds promise as a non-invasive pre-screening tool for brain amyloid pathology, in clinical settings and disease-modifying trials.

#### AUTHOR CONTRIBUTIONS

Mitchell K. P. Lai had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Joyce R. Chong, Christopher P. Chen, and Mitchell K. P. Lai. Acquisition, analysis, or interpretation of data: Joyce R. Chong, Yuek Ling Chai, Amelia T. Y. Yam, Saima Hilal, Henri Vrooman, Narayanaswamy Venketasubramanian, Kaj Blennow, Henrik Zetterberg, Nicholas J. Ashton, Christopher P. Chen, and Mitchell K. P. Lai. Drafting of the manuscript: Joyce R. Chong and Mitchell K. P. Lai. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Joyce R. Chong, Yuek Ling Chai, and Saima Hilal. Obtained funding: Christopher P. Chen and Mitchell K. P. Lai. Administrative, technical, or material support: Joyce R. Chong, Yuek Ling Chai, Amelia T. Y. Yam, and Mitchell K. P. Lai. Supervision: Christopher P. Chen and Mitchell K. P. Lai.

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#### CONFLICT OF INTEREST STATEMENT

All authors declare no competing interests in regard to this manuscript. Author disclosures are available in the [supporting information](#).

#### DATA AVAILABILITY STATEMENT

Anonymized datasets generated during and/or analyzed in the current study are available from the corresponding author upon reasonable request.

#### CONSENT STATEMENT

Written informed consent was obtained from study participants or their next of kin.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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