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# Performance of plasma biomarkers for diagnosis and prediction of dementia in a Brazilian cohort

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Despite remarkable progress in the biomarker field in recent years, local validation of plasma biomarkers of Alzheimer's disease (AD) and dementia is still lacking in Latin America. In this longitudinal cohort study of 145 elderly Brazilians, we assess the diagnostic performance of plasma biomarkers, based on clinical diagnosis and CSF biomarker positivity. Follow-up data of up to 4.7 years were used to determine performance in predicting diagnostic conversions. Participants were clinically categorized as cognitively unimpaired ($n = 49$), amnestic mild cognitive impairment ($n = 29$), AD ($n = 38$), Lewy body dementia ($n = 22$), or vascular dementia ($n = 7$). Plasma Tau, $A\beta_{40}$, $A\beta_{42}$, NfL, GFAP, pTau231, pTau181 and pTau217 were measured on the SIMOA HD-X platform. Plasma pTau217 showed excellent performance determining CSF biomarker status in the cohort, either alone (ROC AUC = 0.94, 95% CI: [0.88–1.00]) or as a ratio to $A\beta_{42}$ (ROC AUC = 0.98, 95% CI: [0.94–1.00]). This study comprises an initial step towards local validation and adoption of dementia biomarkers in Brazil.

Dementia is a major public health concern in the developing world. Following trends of increasing life expectancy and declining mortality, it is predicted that 70 % of all people with dementia will be living in low- and middle-income countries (LMICs) by 2050[1,2]. Brazil, a middle-income country of 203 million people, recently experienced a sharper-than-expected increase in its elderly population, with the number of Brazilians 65 and older increasing by 57 % between 2010 to 2022[3].

Recent years have also witnessed a strong push for a biological definition of Alzheimer's disease (AD), the leading cause of dementia worldwide[4]. This push was fueled partly by the development of increasingly effective biomarkers capable of detecting AD pathology[5–9]. Blood-based biomarkers (BBMs) in particular show great promise in detecting AD quickly, safely and affordably[10,11], as well as aiding in distinguishing it from prevalent non-AD types of dementia[12,13]. Already relevant from a clinical perspective, this distinction will become increasingly so in the near future, as amyloid-targeting antibodies, the first disease-modifying therapies against AD, reach the public[4,14].

Given the limited availability of positron-emission tomography (PET)-based diagnostics and of clinics capable of cerebrospinal fluid

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(CSF) collection, Brazil may stand to benefit from the introduction of BBMs. Effective BBMs for the diagnosis of dementia and prognostication of cognitive decline may aid in reducing Brazil's high rates of misdiagnosis and underdiagnosis. Indeed, recent data from the large ELSI-Brazil study showed that ~77% of adults with dementia in Brazil have not been diagnosed[15]. However, local assessment and validation of the performance of BBMs in the Brazilian population is still lacking, despite the swift progress seen in the developed world.

Here, we describe the BBM profile of a Brazilian dementia cohort, including participants clinically diagnosed with AD, amnestic mild cognitive impairment (aMCI), Lewy body dementia (LBD), vascular dementia (VaD), and cognitively unimpaired (CU) elderly controls. Using the Single Molecule Array (SIMOA) platform, we measured NfL, GFAP, pTau217, pTau181, pTau231, $A\beta_{40}$, $A\beta_{42}$, and Tau in plasma samples from 145 included participants. BBM data is supported by a thorough clinical and neuropsychological characterization of the cohort, as well as by CSF biomarker data, available for 36% of the sample. Using up to 4.7-year follow-up clinical data, we further evaluate the performance of BBMs as predictors of cognitive decline.

## Results

The 145 participants included in this study were distributed across five clinical diagnostic groups, as described in Methods. At baseline, 49 were CU controls, 29 were diagnosed with aMCI, 38 with AD, 22 with LBD, and seven with VaD. Sample characteristics are summarized in Table 1. Minor differences were seen between groups in terms of education and age. On average, participants diagnosed with dementia were older and had fewer years of formal education than CU controls (Table 1). Data from routine laboratory assessments were available for most participants. Metabolic parameters were not considered as initial recruitment or sample selection criteria for this study. Most of the sample (81%) had a diagnosis of hypertension. Diabetes and dyslipidemia were also prevalent, at 37 and 52 % of the sample, respectively. These numbers reflect the high prevalence of metabolic conditions reported in Brazilian elderly populations[16–18]. CSF biomarker data, available for 52 participants, is detailed in Table 1 and Supplementary Fig. 3.

Using the SIMOA platform, we assessed the cohort for plasma NfL, tTau and GFAP. Compared to CU controls, significant increases in plasma NfL were seen in the AD (+44%; $p < 0.0001$) and LBD groups (+207%; $p = 0.0004$). NfL was also increased in both AD (+18%; $p < 0.0289$) and LBD (+152%; $p = 0.0329$) participants compared to the aMCI group. No statistically significant differences could be noted between CU and aMCI (Fig. 1a). Plasma tTau levels were not significantly altered in any of the diagnostic groups (Fig. 1b). GFAP was increased in AD, compared to CU (+61%; $p < 0.0001$) or aMCI (+43%; $p = 0.0133$; Fig. 1c). For both NfL and GFAP, no statistically significant differences could be detected between the VaD and CU groups despite the expected increase in mean values.

Using this same dataset, we conducted a secondary analysis limited to participants that had CSF biomarker data available. For this analysis, participants were initially stratified by cognitive status, into CU and cognitively impaired (CI) groups, then further stratified as CSF-biomarker-positive and CSF-biomarker-negative, using locally defined cutoffs (see Methods and Supplementary Methods). Statistically significant increases were seen when comparing CSF-biomarker-negative

**Table 1 | Demographic table**

| Clinical diagnosis | Cognitively unimpaired | Amnestic MCI | Alzheimer's Disease | Lewy body dementia | Vascular dementia | Data availability |
|---|---|---|---|---|---|---|
| Selected participants (n) | 49 | 29 | 38 | 22 | 7 | 145 |
| Sex (M/F) | 15 / 34 | 10 / 19 | 15 / 23 | 9 / 13 | 5 / 2 | 145 / 145 |
| Age (years, mean ± SD) | 72.31 ± 4.65 | 73.10 ± 5.66 | 78.07 ± 6.49 | 75.58 ± 7.02 | 75.52 ± 6.82 | 145 / 145 |
| Education (years, mean ± SD) | 14.67 ± 2.13 | 12.69 ± 4.02 | 11.47 ± 4.77 | 9.73 ± 4.64 | 9.43 ± 5.53 | 145 / 145 |
| MMSE (mean ± SD) | 27.89 ± 1.69 | 26.09 ± 2.10 | 21.21 ± 3.92 | 20.70 ± 4.81 | 23.29 ± 4.79 | 127 / 145 |
| RAVLT A7 (mean ± SD) | 9.25 ± 2.87 | 4.61 ± 2.74 | 1.23 ± 1.93 | 0.79 ± 1.62 | 1.71 ± 1.89 | 124 / 145 |
| BMI (mean ± SD) | 27.85 ± 3.80 | 25.92 ± 5.33 | 25.11 ± 3.72 | 27.16 ± 5.43 | 28.88 ± 6.73 | 129 / 145 |
| Abdominal circ. (cm, mean ± SD) | 98.12 ± 10.21 | 90.48 ± 15.24 | 87.72 ± 12.33 | 89.60 ± 12.42 | 99.00 ± 9.27 | 114 / 145 |
| Hypertension (present/absent) | 40 / 9 | 24 / 4 | 32 / 6 | 13 / 7 | 6 / 1 | 142 / 145 |
| Diabetes Mellitus (present/absent) | 21 / 28 | 12 / 16 | 10 / 28 | 7 / 13 | 2 / 5 | 142 / 145 |
| Dyslipidemia (present/absent) | 28 / 21 | 17 / 11 | 20 / 18 | 5 / 15 | 4 / 3 | 142 / 145 |
| Serum creatinine (mg/dl, mean ± SD) | 0.85 ± 0.17 | 0.87 ± 0.24 | 0.92 ± 0.28 | 0.94 ± 0.17 | 1.14 ± 0.23 | 139 / 145 |
| eGFR (mean ± SD) | 80.35 ± 13.36 | 78.45 ± 14.94 | 74.57 ± 16.08 | 73.22 ± 15.67 | 64.66 ± 13.32 | 139 / 145 |
| HbA1C (%, mean ± SD) | 5.86 ± 1.00 | 5.87 ± 0.85 | 5.81 ± 1.27 | 5.49 ± 0.55 | 5.74 ± 0.71 | 112 / 145 |
| ApoE4 (postitive/negative) | 3 / 9 | 2 / 5 | 7 / 6 | 4 / 4 | - | 40 / 145 |
| CSF pTau181 (pg/ml, mean ± SD, [n]) | 473.4 ± 443.8 [11] | 371.7 ± 158.9 [9] | 880.4 ± 503.4 [18] | 557.4 ± 316.0 [9] | 415.1 ± 99.21 [5] | 52 / 145 |
| CSF pTau217 (pg/ml, mean ± SD, [n]) | 28.40 ± 35.20 [11] | 16.97 ± 14.19 [9] | 54.16 ± 35.29 [18] | 32.51 ± 26.86 [9] | 18.94 ± 9.32 [5] | 52 / 145 |
| CSF Aβ42 (pg/ml, mean ± SD, [n]) | 598.4 ± 145.3 [9] | 539.7 ± 364.5 [8] | 403.0 ± 281.3 [18] | 347.7 ± 144.9 [9] | 520.6 ± 185.2 [4] | 48 / 145 |
| CSF Tau (pg/ml, mean ± SD, [n]) | 429.2 ± 307.3 [9] | 388.3 ± 93.71 [8] | 528.9 ± 232.2 [18] | 435.0 ± 243.2 [9] | 255.3 ± 159.6 [4] | 48 / 145 |
| CSF Aβ42/Tau (pg/ml, mean ± SD, [n]) | 2.07 ± 1.19 [9] | 1.37 ± 0.77 [8] | 0.98 ± 1.09 [18] | 1.00 ± 0.60 [9] | 2.47 ± 1.48 [4] | 48 / 145 |

Demographical, clinical, and CSF biomarker data of the sample are summarized. Data availability shows the number of datapoints available for each measurement.

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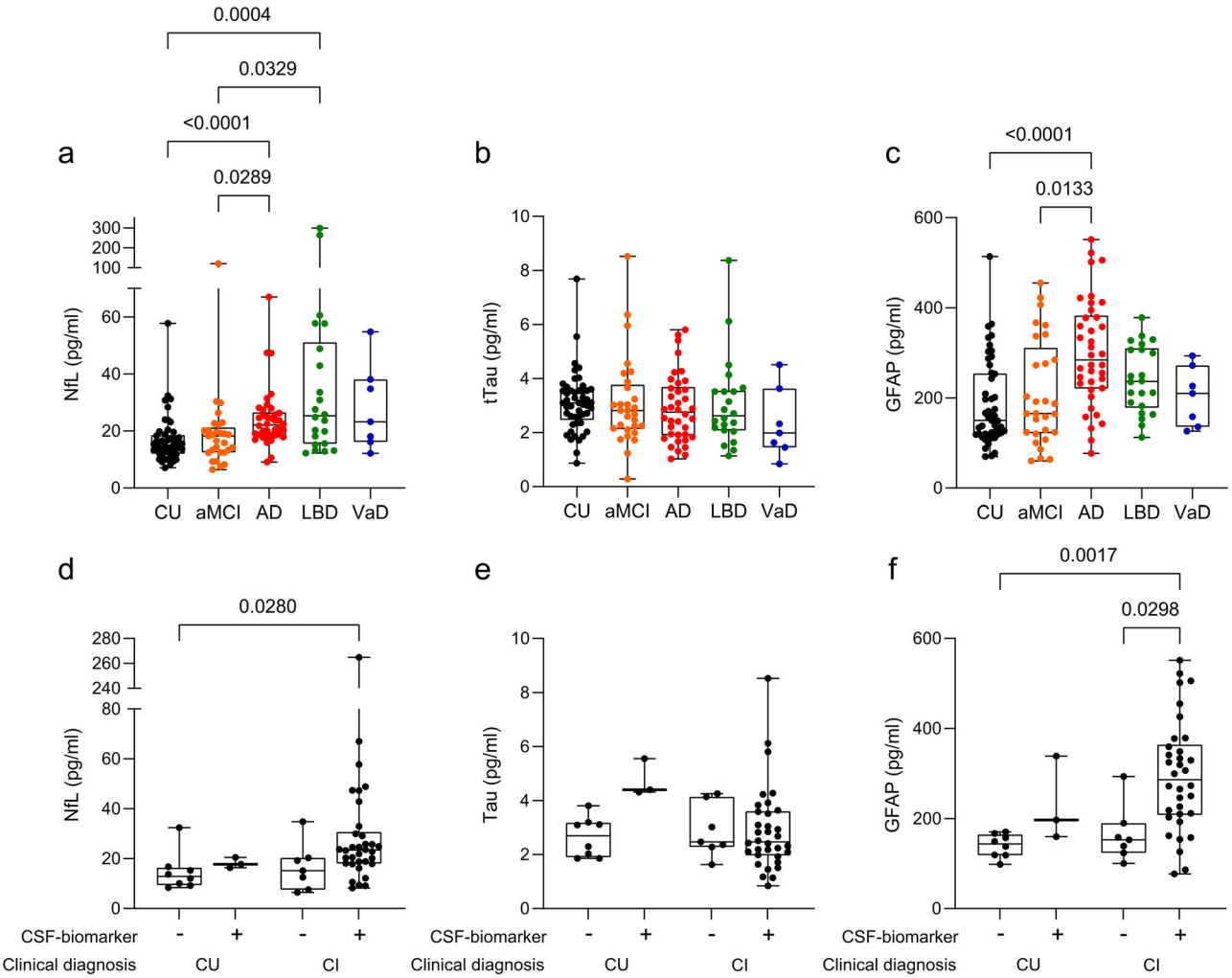


**Fig. 1 | Plasma NfL, tTau, and GFAP levels across clinical diagnoses.** In each graph, boxplots show median, 25th percentile, 75th percentile, and range. Plasma biomarker data across clinical diagnoses (N = 145) is shown for NfL (**a**), tTau (**b**), and GFAP (**c**). Analysis of a subset of participants with CSF biomarker data available (N = 52) shows levels of plasma NfL (**d**), t-Tau (**e**), and GFAP (**f**) stratified by cognitive and CSF biomarker status. (Kruskal-Wallis test followed by Dunn's multiple comparisons test; significant *p*-values are shown).

CU subjects to CSF-biomarker-positive CI subjects, for both plasma NfL (+125%; $p = 0.028$) and GFAP (+111%; $p = 0.0017$). GFAP levels were also significantly higher in CSF-biomarker-positive CI participants than in their CSF-biomarker-negative counterparts (+78%; $p = 0.0298$). Again, no significant differences among groups were seen for plasma tTau (Fig. 1d-f).

Next, we evaluated levels of plasma pTau181 and pTau217, biomarkers associated with AD pathology[19–23]. Clinically diagnosed AD participants had significantly higher levels of pTau181 when compared to participants in the CU (+71%; $p < 0.0001$), aMCI (+30%; $p = 0.0097$), or VaD (+67%; $p = 0.0249$) groups (Fig. 2a). A significant increase (+43%; $p = 0.015$) in pTau181 was also observed in the LBD group when compared to CU controls (Fig. 2a). When stratified by cognitive and CSF biomarker status, plasma pTau181 levels in CSF-biomarker-positive CI participants were significantly higher than in CSF-biomarker-negative controls (+69%; $p = 0.0029$; Fig. 2b).

Plasma pTau217 was increased in the clinical AD group compared to either CU (+186%; $p < 0.0001$) or aMCI (+60%; $p = 0.0148$). LBD participants also had higher levels of pTau217 compared to controls (+140%; $p < 0.0001$). Unlike pTau181, pTau217 was significantly increased in aMCI compared to CU controls (+79%; $p = 0.037$; Fig. 2c). When CSF-biomarker status was considered, plasma pTau217 showed notably higher levels in CSF-biomarker-positive CI participants than in CSF-biomarker-negative CU controls (+354%; $p < 0.0001$). Moreover, pTau217 was increased in CSF-biomarker-positive participants within the CI group (+235%; $p = 0.0095$; Fig. 2d).

We further measured plasma levels of pTau231, described as one of the earliest fluid biomarkers to show an increase in AD patients[24,25]. However, we were not able to determine pTau231 values for most samples, as only 31 (~22%) were above the mean blank value, and 10 (~7%) were above the lower limit of detection (LLoD) observed for these runs (defined as mean blank + 2.5 SDs). The commercial kit used is marketed by the manufacturer as suitable for CSF samples only, but it has been used successfully with plasma samples by other authors[26]. Although no significant differences or notable trends were found among groups (Supplementary Fig. 4a), weak but expected correlations were detected between raw signals produced by the plasma pTau231 assay and the two other pTau assays used in the study (Supplementary Fig. 4b-c).

Using available follow-up clinical data, we assessed the performance of plasma NfL, GFAP, pTau181, and pTau217 in predicting diagnostic conversions. Characteristics of the follow-up sample are detailed in Table 2. In the complete sample, mean follow-up time was 2.8 years (range: 0.7–4.7) for converters and 2.4 years (range: 1.7–4.4) for non-converters. Plasma NfL or GFAP were not significantly different

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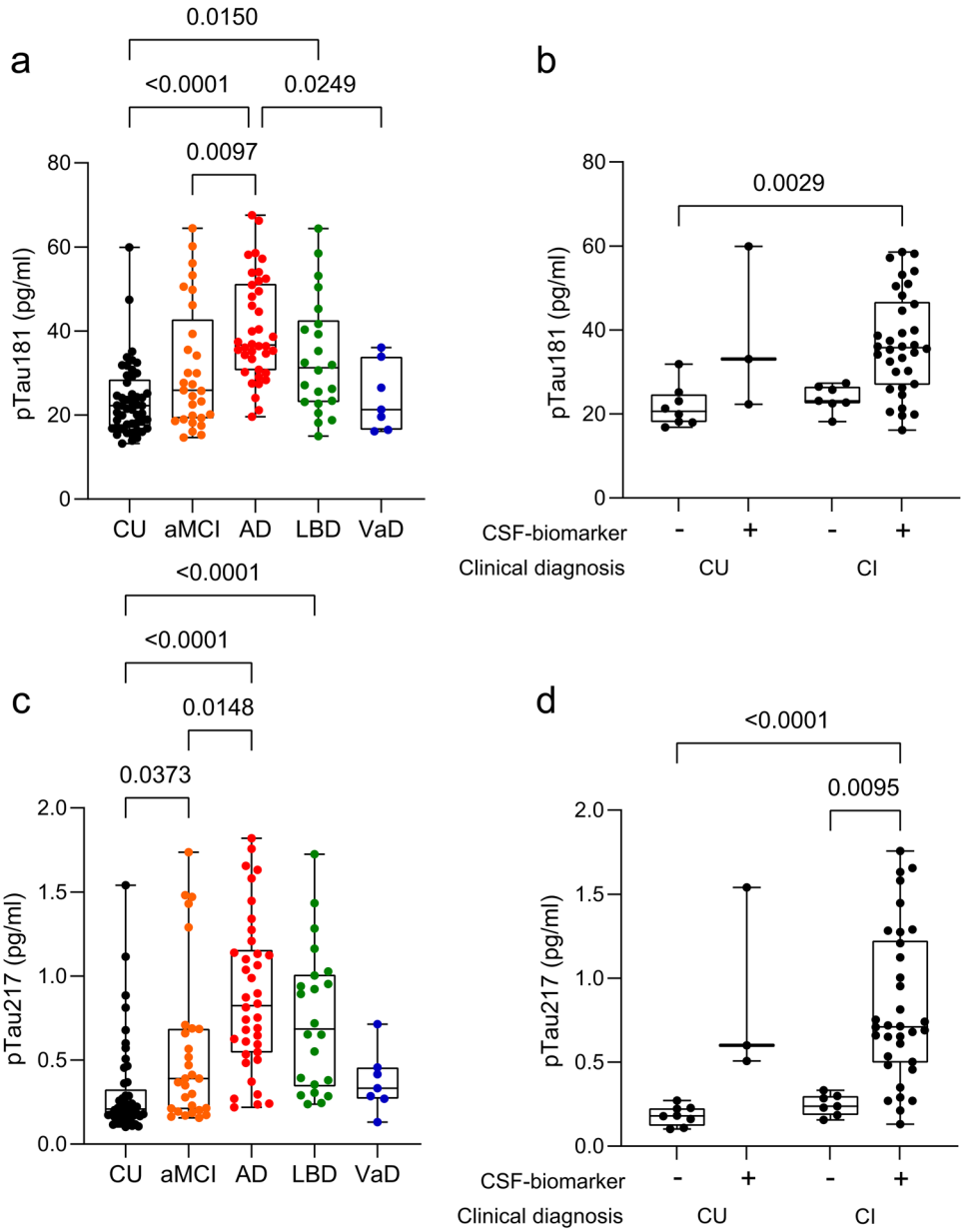


**Fig. 2 | Plasma pTau181 and pTau217 levels across clinical diagnoses.** In each graph, boxplots show median, 25th percentile, 75th percentile, and range. Plasma pTau181 and pTau217 levels are shown across clinical diagnoses (N = 145; **a**, **c**) and stratified by cognitive and CSF biomarker status (N = 52; **b**, **d**). (Kruskal-Wallis test followed by Dunn's multiple comparisons test; significant *p*-values are shown).

**Table 2 | General characteristics of the longitudinal subset of the sample**

| Initial diagnosis | Cognitively unimpaired | | Amnestic MCI | | Data availability |
|---|---|---|---|---|---|
| Follow-up diagnosis | Non-converters | Converters | Non-converters | Converters | |
| Participants (n) | 18 | 6 | 5 | 7 | 36 |
| Sex (M/F) | 6 / 12 | 0 / 6 | 3 / 2 | 4 / 3 | 36 / 36 |
| Age (at first visit) | 74.09 ± 3.88 | 68.79 ± 4.65 | 74.61 ± 3.03 | 76.91 ± 4.51 | 36 / 36 |
| Education (years, mean ± SD) | 14.61 ± 1.82 | 13.17 ± 5.49 | 12.80 ± 4.32 | 12.43 ± 2.82 | 36 / 36 |
| Follow-up time (years, mean ± SD) | 2.43 ± 0.82 | 3.39 ± 1.08 | 2.13 ± 0.32 | 2.34 ± 1.11 | 36 / 36 |
| ΔMMSE at follow-up (mean ± SD) | −0.36 ± 2.38 | −0.50 ± 0.70 | 0.20 ± 2.39 | −2.75 ± 3.20 | 22 / 36 |

between groups (Fig. 3a, b). However, baseline plasma pTau181 (+63%; $p = 0.0064$) and pTau217 (+96%; $p = 0.0337$) were both elevated in participants who had a diagnostic conversion during follow-up (Fig. 3c, d). When stratified by initial diagnosis (CU or aMCI), a significant increase was detected only for plasma pTau181, in aMCI participants converting to dementia (Supplementary Fig. 5a-e). Although the current study aimed for 2-year intervals between follow-ups, data from visits at other intervals were not excluded. Because participant adherence can be biased in such cases, with interest in follow-up increasing when a caregiver or primary care physician perceives cognitive decline, we also analyzed the sample including only participants that adhered strictly to the planned follow-up schedule ($n = 16$; Supplementary Table 2). Results were similar in this subset of the sample, with pTau181 significantly elevated in aMCI participants that converted to dementia at follow-up (Supplementary Fig. 5f-j).

The ratio of plasma $A\beta_{42}$ to $A\beta_{40}$ has been suggested as a marker of amyloidosis[27], but faces robustness issues[28,29]. This biomarker is often favored in mass spectrometry approaches and is present in the diagnostics market in several CSF-based kits[6,30,31]. Using the SIMOA platform, we found no relevant changes in plasma $A\beta_{42}$ / $A\beta_{40}$ ratio across clinically defined diagnostic groups in our cohort (Fig. 4a).

While more common in the CSF, the ratio of plasma pTau to $A\beta_{42}$ has also been used as an AD biomarker. In some cases, the pTau181 / $A\beta_{42}$ ratio has been found to outperform pTau181 alone as an indicator of CSF-confirmed AD or as a predictor of amyloid-PET positivity[32–34]. In our sample, clinically diagnosed AD participants had a significantly higher pTau181 / $A\beta_{42}$ ratio compared to both CU (+153%; $p < 0.0001$) and aMCI (+41%; $p = 0.0022$) groups. LBD participants also had an increased pTau181 / $A\beta_{42}$ ratio compared to controls (+46%; $p = 0.0361$; Fig. 4b). The pTau217 / $A\beta_{42}$ ratio was likewise significantly elevated across these three comparisons (CU x AD, +315%; $p < 0.0001$; aMCI x AD, +45%; $p = 0.0028$; CU x LBD, +139%; $p < 0.0001$), showing consistently higher fold changes than the pTau181 / $A\beta_{42}$ ratio (Fig. 4c).

In the sample subset classified by CSF biomarker status, no differences in plasma $A\beta_{42}$ / $A\beta_{40}$ ratio were seen among groups (Fig. 4d). Plasma pTau181 / $A\beta_{42}$ ratio was increased in CSF-biomarker-positive CI subjects compared to either CSF-biomarker-negative CU controls (+158%; p = 0.0004) or to CSF-biomarker-negative CI subjects (+151%;

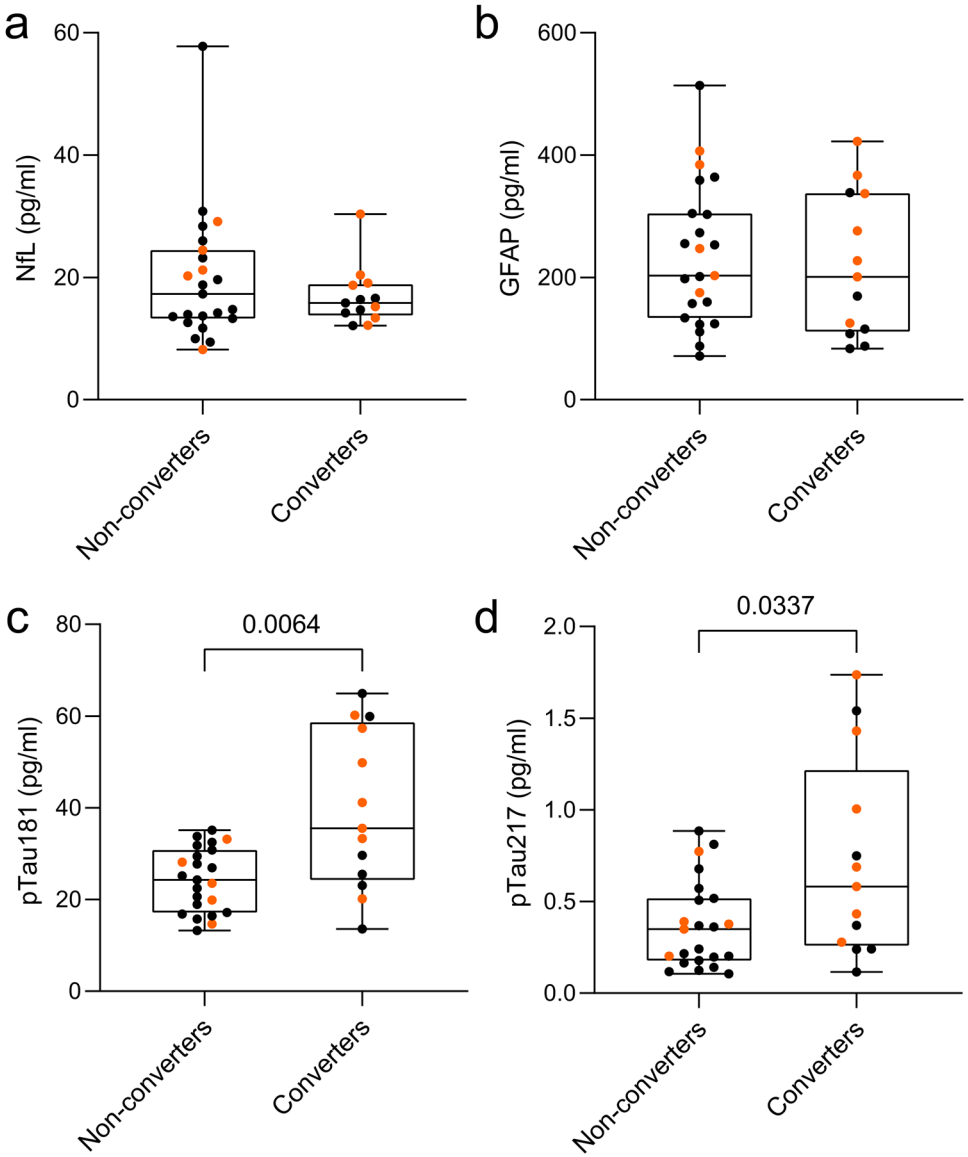


**Fig. 3 | Performance of plasma biomarkers in predicting diagnostic conversions.** In each graph, boxplots show median, 25th percentile, 75th percentile, and range. Levels of NfL (**a**), GFAP (**b**), pTau181 (**c**), and pTau217 (**d**) are shown for converters and non-converters (N = 36). Initial diagnoses are represented by colors, with black dots for CU and orange dots for aMCI participants (Two-tailed Mann-Whitney test; significant *p*-values are shown).

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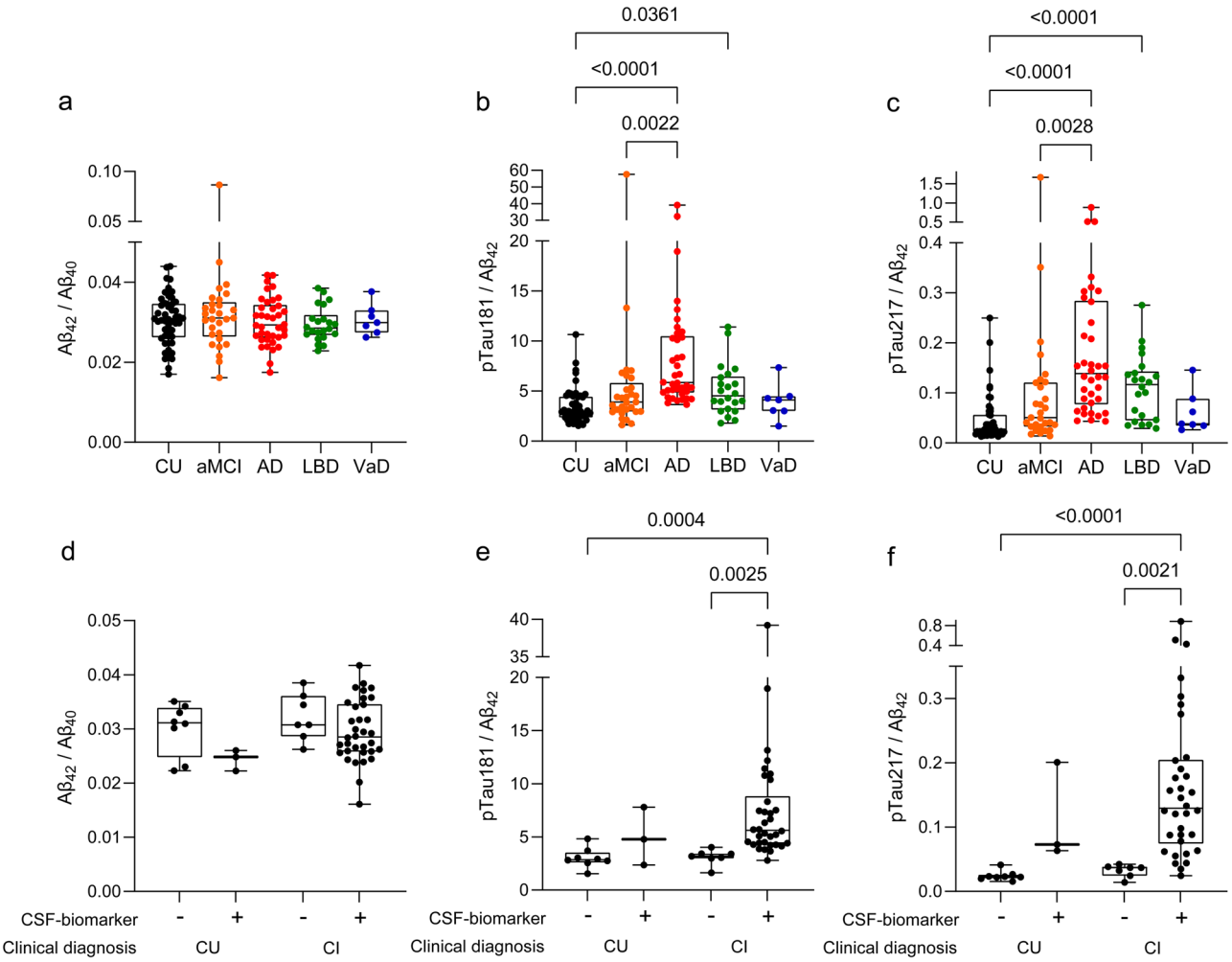


**Fig. 4 | Plasma Aβ$_{42}$ / Aβ$_{40}$, pTau181 / Aβ$_{42}$, and pTau217 / Aβ$_{42}$ ratios across clinical diagnoses.** In each graph, boxplots show median, 25$^{th}$ percentile, 75$^{th}$ percentile, and range. Plasma Aβ$_{42}$ / Aβ$_{40}$ ratios are shown for all included participants across clinical diagnoses (N = 145; **a**) and stratified by cognitive and CSF biomarker status (N = 52; **d**). The same is shown for pTau181 / Aβ$_{42}$ (**b**, **e**), and pTau217 / Aβ$_{42}$ ratios (**c**, **f**). (Kruskal-Wallis test followed by Dunn's multiple comparisons test; significant *p*-values are shown).

$p = 0.0025$; Fig. 4e). Again, the pTau217 / Aβ$_{42}$ ratio behaved similarly to pTau181/Aβ$_{42}$, with significant increases in the same two comparisons (CSF-biomarker-negative CU x CSF-biomarker-positive CI, +635%; $p < 0.0001$; CSF-biomarker-negative CI x CSF-biomarker-positive CI, +452%; $p = 0.0021$; Fig. 4d), albeit with notably higher fold changes.

To assess each biomarker's discriminative or diagnostic capacity, receiver operating characteristic (ROC) curve analysis was performed. In our sample, the pTau217 / Aβ$_{42}$ ratio was the top-performing biomarker for discrimination between CSF-biomarker-negative and CSF-biomarker-positive subjects (AUC = 0.98, 95% CI: [0.94–1.00]), followed by pTau217 alone (AUC = 0.94, 95% CI: [0.88–1.00]; Fig. 5a). When attempting to discriminate participants based on their cognitive status (CU x CI), pTau217 and pTau217 / Aβ$_{42}$ ratio were also the top performers, reaching identical AUCs of 0.82 (95% CI: [0.75–0.89]; Fig. 5b). Similar results were seen when discriminating CU from all-cause dementia, with pTau217 and pTau217 / Aβ$_{42}$ ratio tied at the highest AUCs (AUC = 0.87, 95% CI: [0.80–0.94]), followed by pTau181 / Aβ$_{42}$ and pTau181. pTau217 or its ratio to Aβ$_{42}$ were outperformed only when discriminating AD from other dementias in the cohort, with the pTau181 / Aβ$_{42}$ ratio reaching the highest AUC of 0.75 (95% CI: [0.63 – 0.87]; Fig. 5d). ROC curves also highlighted the poor performance of plasma tTau and the Aβ$_{42}$ / Aβ$_{40}$ ratio in our sample. Both biomarkers consistently failed to discriminate groups, overlapping chance values in all tested scenarios (Fig. 5a-d).

When examining the complete sample at baseline, MMSE scores showed significant correlations to plasma levels of NfL, GFAP, pTau181, and pTau217 (Supplementary Fig. 6a-d). In participants with longitudinal MMSE data (Table 2), no relevant correlations could be detected between plasma biomarkers and ΔMMSE scores at follow-up (Supplementary Fig. 6e-h).

Kidney function has been shown to influence plasma levels of dementia biomarkers[35,36]. In our sample, no significant correlations could be detected between serum creatinine or eGFR and NfL, GFAP, pTau181, or pTau217. HbA1c values were also not significantly correlated to these four plasma biomarkers (Supplementary Fig. 7a-l). Stratifying the cohort by sex and cognitive status did not reveal any significant influence of sex on any of the plasma biomarkers measured (Supplementary Fig. 8a-h).

Plasma tTau and NfL, the biomarkers most associated with neurodegeneration among those tested in the sample, showed only minor correlations to CSF tTau, reaching significance only for NfL ($r^2 = 0.086$; p = 0.0434; Supplementary Fig. 9a, b). GFAP, pTau181 and pTau217 were all highly correlated to available CSF biomarkers related to amyloidosis (Supplementary Fig. 10a-o).

In addition to its track record as a biomarker of traumatic brain injury (TBI) and CNS lesions in general[37], plasma GFAP may serve as a peripheral indicator of astrogliosis and brain inflammatory status[38]. To better examine the relationship between plasma GFAP, plasma pTau,

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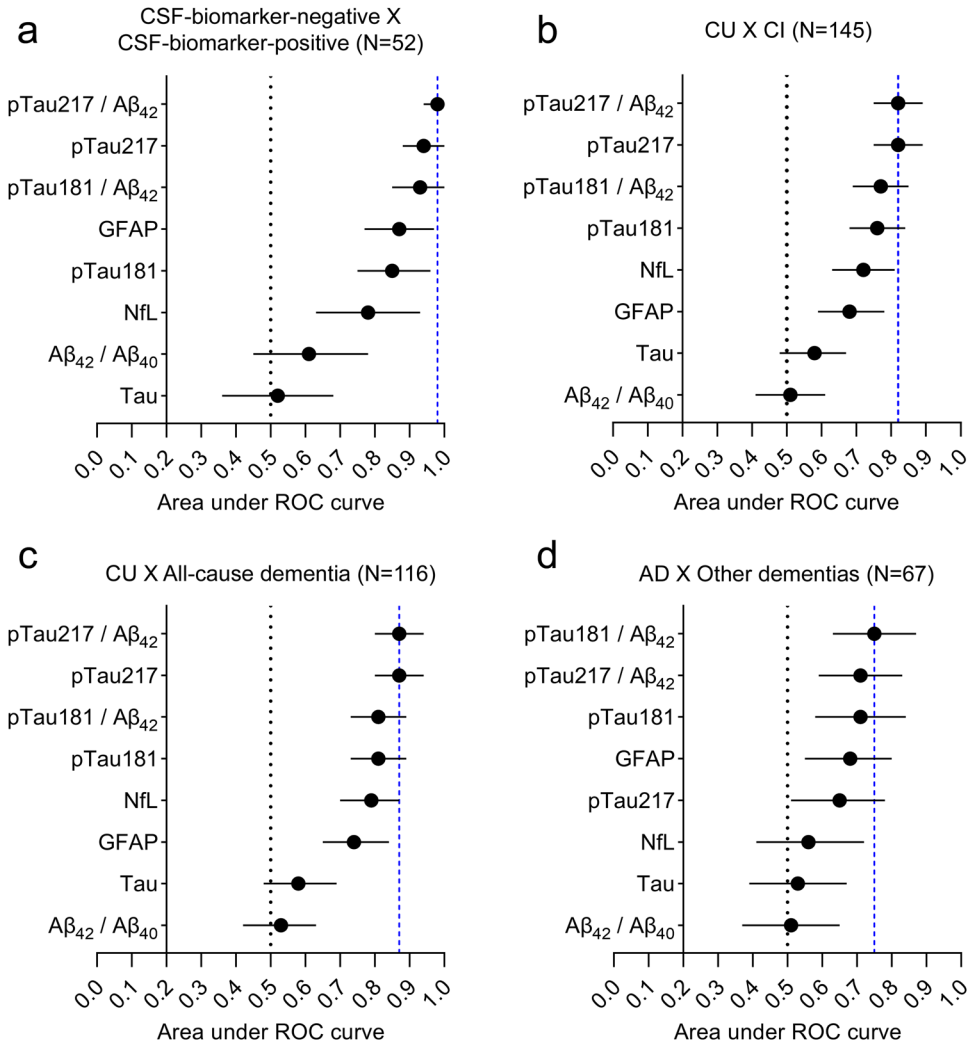


**Fig. 5 | Diagnostic performance of plasma biomarkers.** Forest plots comparing ROC AUCs are shown for all plasma biomarkers when discriminating participants in the following groups: CSF-biomarker-negative x CSF-biomarker-positive (N = 52; **a**), CU x CI (N = 145; **b**), CU x all-cause dementia (N = 116; **c**), and AD x other dementias (N = 67; **d**). For each panel, chance levels are indicated by a dotted line (ROC AUC = 0.5) and the AUC of the best-performing biomarker is indicated by a dashed blue line. Error bars represent 95% confidence intervals.

and cognitive performance, participants were grouped across quadrants, defined by cutoff values derived from the ROC analyzes described in Fig. 5c. These cutoffs were 25.38 pg/ml for pTau181, 0.29 pg/ml for pTau217, and 201.9 pg/ml for GFAP (Fig. 6a, c). Participants with elevated levels of plasma GFAP and, concomitantly, either elevated plasma pTau181 or pTau217 (labeled as quadrant "4" in Fig. 6a, c) scored significantly lower in the MMSE (Fig. 6b, d).

## Discussion

Results described here extend previous observations to an understudied LMIC cohort and restate the potential of BBMs as a complement to the clinical diagnosis of dementia, particularly in communities in which PET-based diagnostics are not likely to become available in the foreseeable future. Plasma pTau217, well-established as an AD biomarker in research settings in other parts of the world[23,39], is now shown to have excellent performance identifying CSF biomarker status in a Brazilian cohort (AUC = 0.94, 95% CI: [0.88–1.00], cutoff: > 0.34 pg/ml; Fig. 5a).

When discriminating AD from the two other types of dementia represented in our cohort (LBD and VaD), pTau181 showed the best performance among isolated plasma biomarkers (Fig. 5d), suggesting it could aid in differential diagnosis, a common challenge in clinical practice. Discriminating power was lowest when comparing LBD and AD participants. As previously observed, LBD can often present with brain amyloidosis and elevated plasma biomarkers, including pTau181 and pTau231, albeit to a lesser extent than in AD[40].

Longitudinal data further confirmed an association between higher baseline plasma levels of either pTau181 or pTau217 and risk of future diagnostic conversions (Fig. 3c, d), consistent with previous results in cohorts from other geographical regions[39,41].

Overall, when only clinical presentation was considered, our data showed comparable discriminative performances for plasma pTau181 and pTau217 (Fig. 5b-d). However, pTau217 showed consistently higher fold differences among groups (Fig. 2), and was notably more effective than pTau181 when discriminating participants based on their CSF biomarker status (Fig. 5a).

Interestingly, for some of the diagnostic scenarios tested (Fig. 5a, d), the pTau / $A\beta_{42}$ ratios surpassed pTau217 or pTau181 as the best-performing biomarkers observed in this study. Although relatively few authors have explored pTau / $A\beta_{42}$ ratios in plasma[32–34,42,43], previous results have been overall consistent with what we observed, with both ratios showing minor improvements over pTau alone.

Compared to either plasma pTau181 or pTau217, the pTau181 / $A\beta_{42}$ and pTau217 / $A\beta_{42}$ ratios also showed larger mean fold-changes

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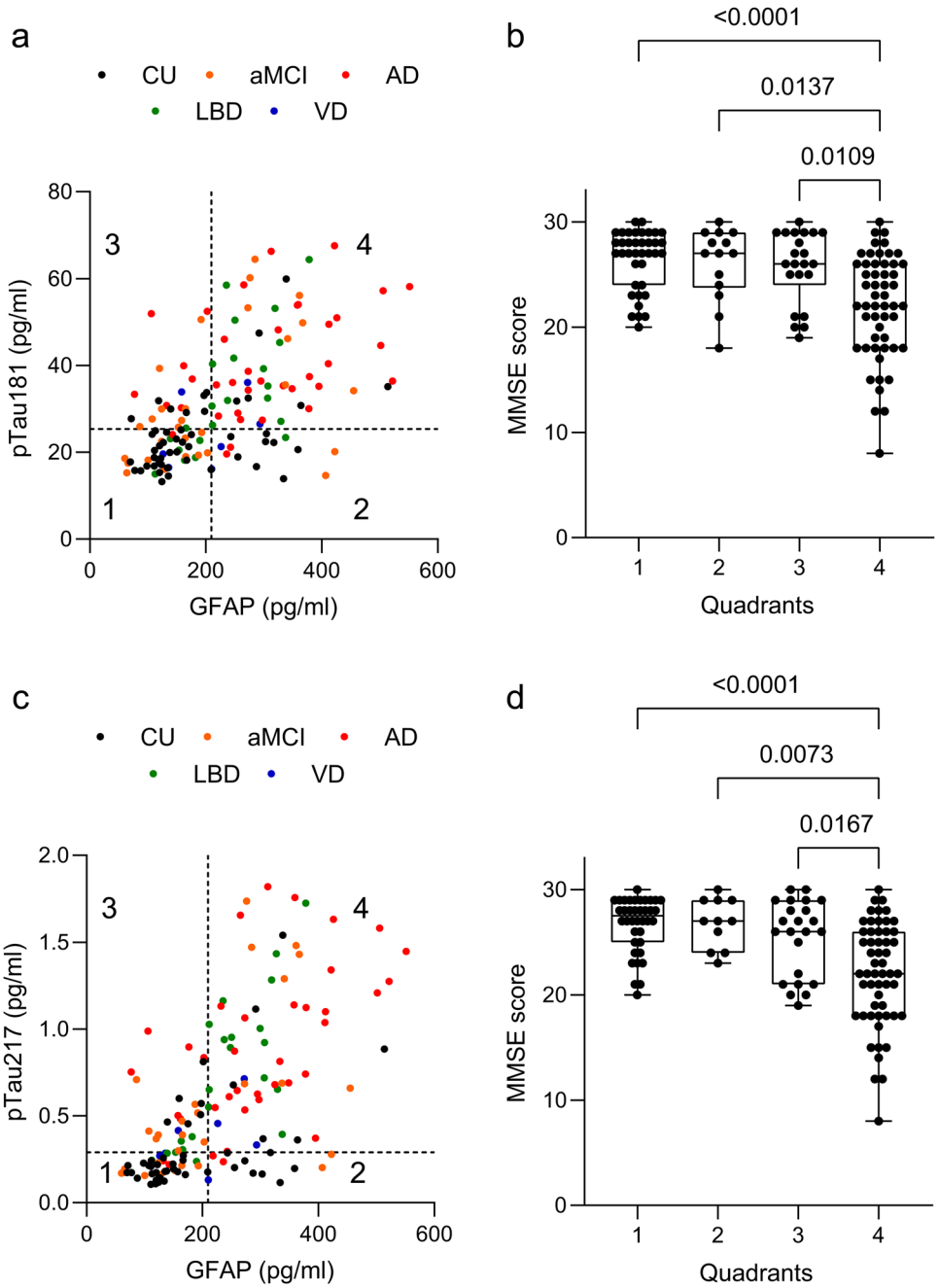


**Fig. 6 | Relationship between plasma pTau and GFAP levels with cognitive performance.** Scatter plots of plasma pTau181 (**a**) and pTau217 (**c**) against plasma GFAP levels are shown for all included participants (N = 145). Diagnoses are represented by colors, as indicated in the images, and the cutoff values of 25.38 pg/ml for pTau181; 0.29 pg/ml for pTau217; and 201.9 pg/ml for GFAP (defined by the ROC analyzes shown in Fig. 5C) are represented by dashed lines, dividing the sample into four quadrants. Available MMSE scores (N = 127) for participants in each of the four quadrants of the pTau181 x GFAP and pTau217 x GFAP graphs are shown in (**b**) and (**d**), respectively. Boxplots in (**b**) and (**d**) show median, 25$^{th}$ percentile, 75$^{th}$ percentile, and range. (Kruskal-Wallis test followed by Dunn's multiple comparisons test; significant *p*-values are shown).

across most comparisons between participant groups. Although the change in diagnostic performance using pTau / $A\beta_{42}$ ratios was small compared to the pTaus alone, such larger fold-changes may result in more robust assays, less vulnerable to analytical bias, as recently argued by Karikari and colleagues[5]. Of note, the SIMOA plasma $A\beta_{42}$ assay used in the current study could not distinguish clinical diagnostic groups or CSF status on its own, and is among the lowest-performing available[44]. It may be possible that better performing $A\beta_{42}$ assays could produce pTau / $A\beta_{42}$ ratios that show a relevant improvement over the diagnostic capacity of pTau217.

GFAP has also been shown to be an effective biomarker for tracking AD pathology, even in preclinical stages, and to perform better in plasma than in CSF[45,46]. Notably, in our cohort, plasma GFAP marginally outperformed pTau181 when identifying CSF biomarker positivity (Fig. 5a). Our data also indicated that individuals with high plasma levels of GFAP and high levels of either pTau181 or pTau217 are likely to have worse cognitive performance than those with an elevation in either biomarker alone (Fig. 6). This observation is in line with a recent report highlighting a link between plasma GFAP and AD progression, which provided evidence that abnormal levels of plasma

GFAP predict the emergence of soluble pTau abnormalities in Aβ-positive individuals[47].

Among the limitations of the current study is the lack of PET confirmation of amyloid status, which was instead derived from CSF biomarker data, available for a subset of the cohort. Additionally, small but significant differences in age, education levels, BMI, and abdominal circumference were verified across participant groups. These differences may reflect patient group characteristics in routine clinical settings, but they could skew the assessment of biomarker performance. The studied cohort also has a significant comorbidity burden, with most participants having a diagnosis of hypertension and 37% being diabetic. While such factors have been shown to affect AD plasma biomarker levels, in the context of diagnostic performance, their effect was not considered to be clinically relevant[36]. It should be noted, however, that at the stage of chronic kidney disease (CKD), kidney function has been shown to have an important impact on the interpretation of AD biomarker data[35]. In our cohort, using available metrics of kidney function, we could not detect any significant impact on plasma biomarker levels (Supplementary Fig. 7a, b, d, e, g, h, j, k).

In this description of the BBM profile of a Brazilian dementia cohort, plasma pTau217, either alone or as a ratio to $A\beta_{42}$, confirmed its potential as a locally viable alternative to CSF analysis for diagnosing AD and determining amyloid status. We hope the current study will contribute to the process of local validation and adoption of AD and dementia BBMs in Brazil and Latin America.

## Methods

### Sample

This study complied with all relevant ethical regulations and was approved by the IDOR Research Ethics Committee (protocol approval numbers: 47163715.0.0000.5249 and 43007915.5.0000.5249). All participants provided written informed consent. From an initial sample of 261 participants enrolled at the Memory Clinic at the D'Or Institute for Research and Education (IDOR) in Rio de Janeiro, 145 were included (Supplementary Fig. 1). Participants were volunteers referred to the service by physicians or other healthcare professionals. Included participants were native Brazilians, had Portuguese as their first language, were at least 60 years of age, had a clinical diagnosis within the scope of the study, and had plasma sample availability. Excluded diagnoses were primary progressive aphasia, Parkinson's disease, schizophrenia or other psychotic illness, non-amnestic MCI, bipolar disorder, epilepsy, alcohol or drug abuse, current severe depressive disorder, or severe head injury. Twenty participants opted to drop out during the study. All individuals underwent psychiatric, neurological and magnetic resonance imaging evaluation, followed, whenever possible, by structured neuropsychological and language assessments, which are described in detail elsewhere[48]. Participants presenting with uncorrected hearing or vision impairment severe enough to hinder cognitive assessment were excluded. Subjects were categorized as CU controls, aMCI, AD, LBD, or VaD at weekly multidisciplinary meetings coordinated by a senior certified psychiatrist (P.M.). Winblad et al. criteria[49] were adopted for the diagnosis of aMCI. Memory impairment was objectively defined as performance below 1.5 SD for age and schooling on the Logical Memory and Visual Reproduction subtests of the Wechsler Memory Scale (WMS-IV), or the Rey-Auditory Verbal Learning Test (RAVLT). AD was diagnosed according to criteria included in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) for probable major neurocognitive disorder due to AD[50]. Although the cohort is clinically defined, 52 participants (36 %) had CSF samples collected at the same visit as the available plasma and were also classified based on CSF biomarkers. Thirty-six (25 %) had follow-up samples and follow-up clinical evaluation data available, up to 4.7 years after the first assessment. Only clinical assessments were used when evaluating longitudinal diagnostic conversions and non-conversions. Reversal of an aMCI diagnosis to normal cognition was interpreted as a non-conversion, for the purposes of this study.

### Plasma biomarkers

Blood samples were collected by venipuncture into EDTA tubes (3 ml BD Vacutainer EDTA K2 or equivalent) and processed locally within 2 h, according to standard protocol. Plasma was aliquoted and stored at -80 °C until use. Plasma biomarkers were measured on a SIMOA HD-X instrument (Quanterix, Billerica, MA) installed at IDOR's clinical laboratory facility in Rio de Janeiro, Brazil. Commercially available Quanterix Neurology 3-Plex A ($A\beta_{1\text{-}40}$, $A\beta_{1\text{-}42}$, and t-Tau), Neurology 2-Plex B (NfL and GFAP), pTau181 V2.1, pTau231, and ALZpath pTau217 V2 Advantage kits were used. For the typical run, calibrators were included in triplicate, and manufacturer-provided controls in duplicate, as per kit instructions. ALZpath pTau217 kits were provided with quality control (QC) samples prepared in human plasma. For all other kits, manufacturer-provided controls consisted of sample diluent spiked with calibrators. As an additional QC, locally prepared, CSF-spiked, pooled plasma samples were also run in duplicates in every plate. The average intra-assay calibrator CV was 6.4 % (range: 3.8–10.0 %). Manufacturer-provided controls showed an average intra-assay CV of 3.7 % (range: 0.6–6.8 %). Spiked-plasma average CVs were 3.6 % intra-assay (range: 1.8–7.1 %) and 9.5 % inter-assay (range: 3.8–18.0 %). Cohort samples were centrifuged for 5 min at 10,000 g before loading on the plates and were run in singlicate. In line with available stability recommendations[51], samples were subjected to no more than two freeze-thaw cycles. Routine testing for creatinine, HbA1c, and other analytes was performed commercially, as part of the workflow of the clinical laboratory. Estimated glomerular filtration rate (eGFR) was calculated as described[52]. ApoE4 status was determined for a subset of 40 participants, using an ELISA kit (cat. 7635; MBL, Woburn, MA).

### CSF biomarkers

CSF samples (15 ml) were collected by a trained neurologist through lumbar puncture at the L3–4 or L4–5 interspace and were immediately stored at 4 °C. Within 2 h, collected CSF was centrifuged at 2000 *g* for 10 min at room temperature. Samples were aliquoted (0.5 ml) using polypropylene microtubes and stored immediately at −80 °C until testing. All lumbar punctures were performed around 11 a.m. to minimize possible circadian fluctuations in biomarker levels. $A\beta_{1\text{-}42}$, $A\beta_{1\text{-}40}$, and t-Tau were measured in duplicates using Euroimmun (Lübeck, Germany) ELISA kits. pTau181 and pTau217 were measured on the SIMOA HD-X platform. The procedure was as described above for plasma, but included an off-board dilution step. To accommodate the dynamic range of the SIMOA pTau181 V2.1 and pTau217 ALZpath V2 kits, CSF samples were diluted a total of 10 X and 9 X, respectively. To determine CSF biomarker positivity, locally defined cutoff values of <1.2 for $A\beta_{1\text{-}42}$ / t-Tau ratio, >346.9 pg/ml for pTau181, and >22.72 for pTau217 were used, as described in Supplementary Methods, Supplementary Table 1, and Supplementary Fig. 2.

### Statistics & Reproducibility

Statistical analysis was performed using GraphPad Prism 9 (GraphPad Software Inc., La Jolla, CA). REDCap (Research Electronic Data Capture; https://projectredcap.org/) software was used for data collection. Sample sizes were determined by sample availability within the study cohort. No data from the 145 included participants were excluded from the analyzes. Investigators were blind to sample identity during all analytical procedures. Values are presented as standard boxplots, showing median, 25$^{th}$ percentile, 75$^{th}$ percentile, and whiskers representing range. Where needed, hypothesis testing was performed using standard non-parametric approaches, as detailed in figure legends. Percent changes in biomarkers levels stated in the text refer to comparisons between group means. The Wilson/Brown method was used to calculate 95% confidence intervals for the area under the curve (AUC) values of the Receiver operating characteristic (ROC) curves. Exact p-values are shown for all statistically significant ($p < 0.05$) comparisons.

### Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

## Data availability

Anonymized participant data will be shared upon request, as long as the data transfer: (1) is compliant with all Brazilian data protection laws and regulations; (2) is approved by the IDOR Research Ethics Committee; and (3) is governed by a material transfer agreement. Source data are provided with this paper.

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## Author contributions

Conceptualization: F.G.D.F. and F.T-M. Design: L.E.S. and F.G.D.F. Acquisition, analysis, or interpretation of data: IDOR Memory Clinic Initiative, L.E.S., P.M.; T.L.P., A.S., C.D., F.K.S., F.B., B.V., C.O.B., S.T.F., and F.G.D.F. Writing—original draft: L.E.S. Writing—review: L.E.S. and F.G.D.F. Editing: all co-authors. Funding acquisition: F.G.D.F. and F.T-M.

## Competing interests

The authors declare no conflicts of interest.

## Additional information

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## IDOR Memory Clinic Initiative

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