

Plasma Endogenously Cleaved MTBR-tau243 Measured By An Automated Immunoassay Is Associated With Tau PET-based Braak Staging



Masanori Kurihara^{1, 2}, Kengo Ishiki³, Shun Murakami³, Yuki Hoshina³, Tomoko Ohashi³, Mayu Fujita⁴, Yoshifumi Shima⁴, Chihiro Suminaka³, Masahiro Miura³, Toshiyuki Sato³, Kenji Ishii^{2, 5}, Ryoko Ihara¹, Shigeki Iwanaga³, and Atsushi Iwata^{1, 2}

¹ Department of Neurology, Tokyo Metropolitan Institute for Geriatrics and Gerontology, Tokyo, Japan ² Department of Biomarkers, Integrated Research Initiative for Living Well with Dementia, Tokyo Metropolitan Institute for Geriatrics and Gerontology, Tokyo, Japan ³ Central Research Laboratories, Sysmex Corporation, Kobe, Japan ⁴ Reagent Engineering, Sysmex Corporation, Kobe, Japan ⁵ Research Team for Neuroimaging, Tokyo Metropolitan Institute for Geriatrics and Gerontology, Tokyo, Japan

Background

- Endogenously cleaved microtubule-binding region tau containing residue 243 (eMTBR-tau243), identified by immunoprecipitation–mass spectrometry (IP-MS), has been shown to reflect advanced neurofibrillary pathology in Alzheimer’s disease.
- For broader clinical translation, scalable assay platforms are needed. The Automated Immunoassay System HISCL™-5000, which enables rapid measurement within 17 min using only 30 µL of sample and offers a flexible assay menu for serial measurement of multiple biomarkers, may facilitate routine clinical implementation.
- In this study, we investigated whether a novel automated immunoassay for plasma eMTBR-tau243 can be used to estimate tau PET-based Braak staging and compared its performance with plasma p-tau217.

Results

1. Participant Characteristics Across Tau PET–Defined Braak Stages

- The cohort covered the full spectrum of tau PET–defined Braak stages.
- Amyloid positivity and cognitive decline increased with advancing Braak stage.
- Regional tau PET signals demonstrated a progressive increase from early to advanced stages.

Table 1. Participant demographics

PET-based Braak stage		0	I	II	III	IV	≥V
n (%)		37 (28.7%)	25 (19.4%)	20 (15.5%)	20 (15.5%)	9 (7.0%)	18 (14.0%)*
Age	Median (Q1~Q3)	79.0 (74.0~82.0)	79.0 (76.0~82.3)	81.5 (80.0~84.5)	80.0 (76.5~82.0)	81.0 (77.8~84.8)	73.5 (63.0~78.0)
Sex	Male / Female	24 / 13	12 / 13	13 / 7	9 / 11	3 / 6	5 / 13
Amyloid status	Positive / Negative	5 / 32	8 / 17	9 / 11	15 / 5	9 / 0	17 / 1
MMSE	Median (Q1~Q3)	28.0 (26.0~29.0)	27.0 (25.0~28.3)	26.5 (24.5~28.0)	27.0 (25.5~27.5)	22.0 (20.0~26.3)	21.0 (19.0~23.0)
Global_SUVR	Median (Q1~Q3)	0.962 (0.906~1.026)	1.010 (0.951~1.088)	1.099 (1.065~1.119)	1.112 (1.012~1.207)	1.504 (1.263~1.563)	2.316 (1.858~3.519)
Mesial_SUVR	Median (Q1~Q3)	0.961 (0.844~1.032)	1.075 (1.003~1.117)	1.476 (1.242~1.543)	1.755 (1.522~2.106)	2.254 (2.003~2.743)	2.807 (2.107~3.821)
Meta_SUVR	Median (Q1~Q3)	1.031 (0.968~1.109)	1.102 (1.028~1.172)	1.218 (1.153~1.290)	1.266 (1.149~1.392)	1.880 (1.654~2.202)	2.734 (2.070~3.688)
TP_SUVR	Median (Q1~Q3)	0.970 (0.919~1.033)	1.027 (0.954~1.099)	1.084 (1.059~1.120)	1.078 (1.007~1.183)	1.495 (1.234~1.542)	2.370 (1.795~3.654)
Frontal_SUVR	Median (Q1~Q3)	0.839 (0.762~0.953)	0.865 (0.785~0.919)	0.914 (0.829~0.972)	0.914 (0.804~1.038)	1.043 (0.916~1.125)	1.619 (1.011~2.751)

SUVR, standardized uptake value ratio; Mesial, mesial temporal; Meta, meta temporal; TP, Temporo-Parietal

*One case lacked SUVR data.

2. Plasma Biomarkers Across Braak Stages

- Plasma eMTBR-tau243 levels were low in Braak stages 0–III and increased in stages IV and ≥V.
- Plasma p-tau217 levels increased across Braak stages.

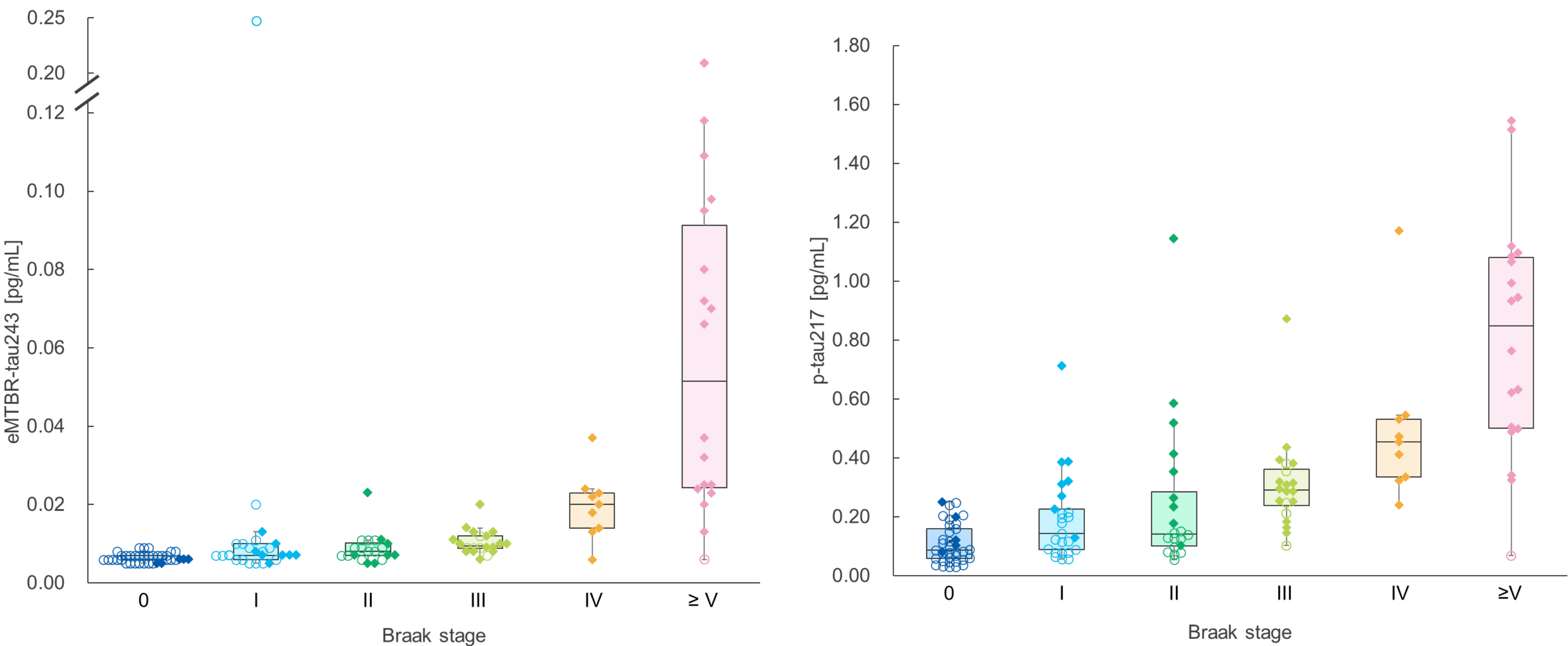


Figure 1. Distributions of Plasma eMTBR-tau243 and p-tau217 Across Tau PET–Defined Braak Stages

Left: eMTBR-tau243, Right: p-tau217, ◆: A(+), ○: A(-)

Discussions

- Plasma eMTBR-tau243 and p-tau217 showed distinct patterns across Braak stages, with eMTBR-tau243 demonstrating a more prominent increase at advanced stages.
- In amyloid-positive individuals, eMTBR-tau243 demonstrated higher discriminative performance than p-tau217. This finding suggests that while p-tau217 may reflect both amyloid- and tau-related processes, eMTBR-tau243 more specifically reflects tau pathology, particularly at advanced stages.
- In multi-class classification, eMTBR-tau243 achieved higher overall accuracy than p-tau217, supporting its utility in differentiating tau pathology across multiple Braak stages.

Methods

- Plasma samples were obtained from 129 participants of the Tokyo Metropolitan Institute for Geriatrics and Gerontology (TMIG) biobank, who had tau PET data using [¹⁸F]MK 6240.
- Plasma eMTBR-tau243 and p-tau217 concentrations were quantified using the Automated Immunoassay System HISCL™-5000. PET-based Braak stages were assigned according to established criteria (Pascoal et al., Brain 2020).
- Associations with Braak stage, global and regional tau PET SUVR in CenTauR VOIs (Villemagne et al., Alzheimer's Dement. 2023) were assessed using group comparisons, ROC, and age- and sex-adjusted regression using log- / z-transformed variables (βstd), with stratification by amyloid status. Multi-class classification into Braak 0–II, III–IV, and V–VI was performed using a two-cutoff approach, with cutoff values determined using the Youden index.

3. Diagnostic Performance for Advanced Braak Stages

- ROC curves showed high performance for both plasma biomarkers in identifying Braak stage ≥V.
- In the total cohort, the AUC was 0.934 for eMTBR-tau243 and 0.908 for p-tau217. In amyloid-positive individuals, the AUC was 0.967 for eMTBR-tau243 and 0.890 for p-tau217.

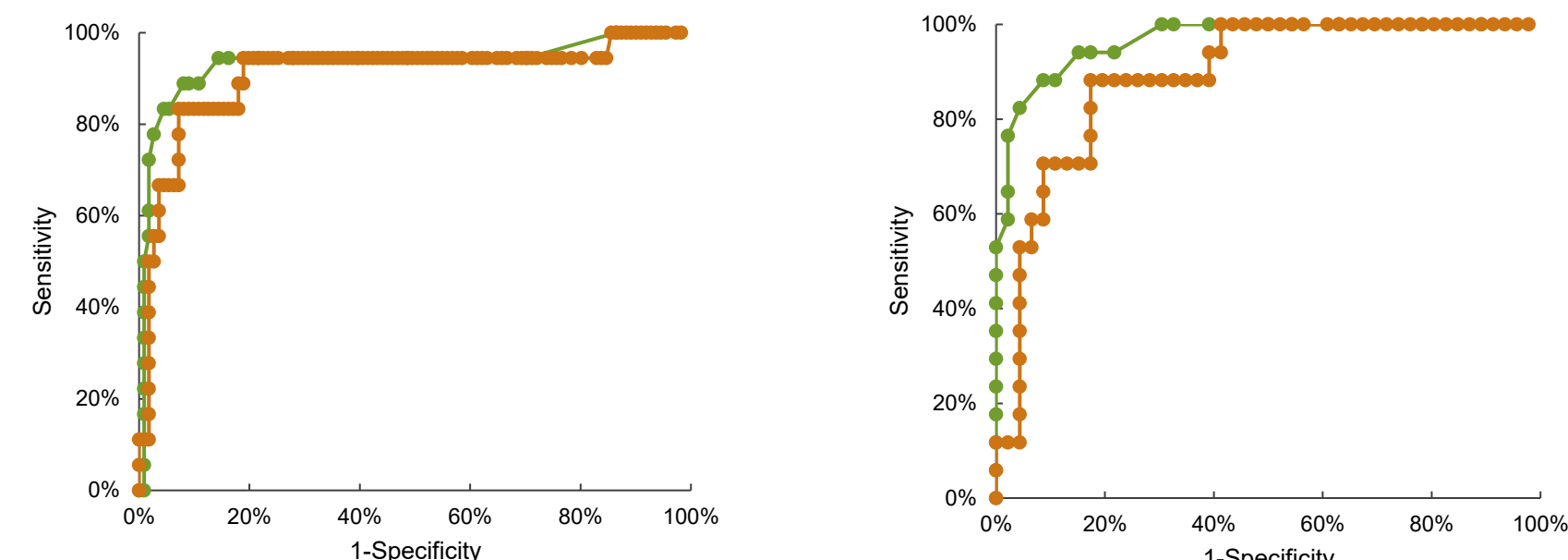


Figure 2. ROC Curves for Braak Stage ≥V

Left: Total cohort (N = 129), Right: Amyloid-positive individuals (N = 63)

4. Associations with Regional Tau PET Signals

- Plasma eMTBR-tau243 and p-tau217 levels were associated with global and regional tau PET burden, with eMTBR-tau243 showing a more linear relationship.
- This pattern was observed in both the total cohort (N = 128) and the amyloid-positive subgroup (N = 62).

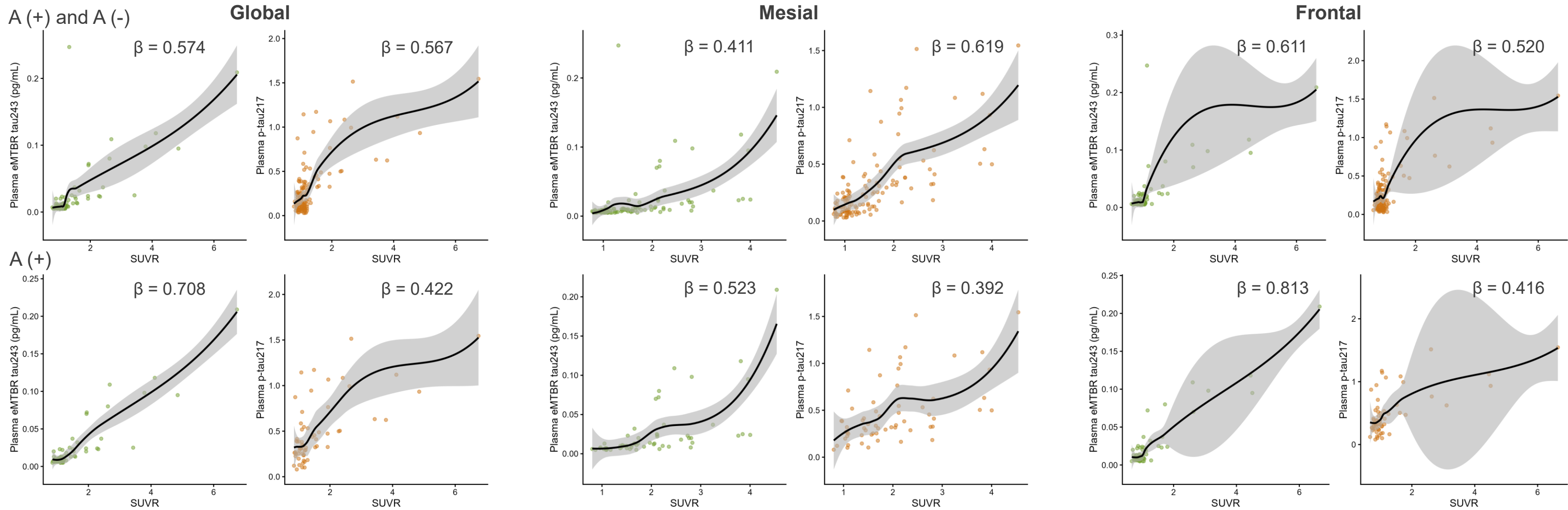


Figure 3. Associations with Regional Tau PET Signals

Top: Total cohort (N = 128); Bottom: Amyloid-positive individuals (N = 62); Left: Global; Middle: Mesial; Right: Frontal

5. Multi-Class Classification of Braak Stages

- Classification patterns differed between biomarkers.
- Using plasma eMTBR-tau243, the overall classification accuracy was 77.8% (49/63), whereas the accuracy for p-tau217 was 65.1% (41/63).

Table 3. Three-Level Braak Classification Using Plasma Biomarkers

		Left: eMTBR-tau243, Right: p-tau217		
eMTBR-tau243 levels (pg/mL)	Braak stage	0-II	III-IV	V-VI
Low < 0.008		15	2	0
Intermediate 0.008–0.023		6	19	2
High ≥ 0.023		1	3	15

p-tau217 levels (pg/mL)	Braak stage	0-II	III-IV	V-VI
Low < 0.287		12	6	0
Intermediate 0.287–0.488		6	14	2
High ≥ 0.488		4	4	15

Conclusions

- Plasma eMTBR-tau243 measured using an automated immunoassay reflects tau PET–defined Braak staging and regional tau pathology.
- Compared with p-tau217, eMTBR-tau243 showed higher accuracy for multi-level Braak classification, supporting its potential utility for assessing advanced tau pathology.
- These findings support the potential of automated immunoassays for scalable and non-invasive assessment of tau pathology in clinical and research settings.