

Comparison of Plasma Biomarkers for Early Detection of Amyloid Pathology in a Cognitively Unimpaired Population

Luna Buitrago, PhD¹, Francesca I. De Simone, PhD¹, M. Craig Miller, BS¹, Natalya Benina, MS¹, Rachel R. Radwan, MS¹, Nathalie Le Bastard, PhD², Amanda Calabro, PMS¹, Jessica Junfola, MS¹, Diana Dickson, MS¹, Douglas Hawkins, PhD³
¹Fujirebio Diagnostics Inc., Malvern, PA, USA. ²Fujirebio Europe N.V., Ghent, Belgium. ³School of Statistics, University of Minnesota, Minneapolis, MN, USA



Background

- Alzheimer’s disease (AD) pathology begins many years before the onset of cognitive symptoms, creating a need for biomarker strategies capable of identifying early biological changes in the preclinical stage of disease¹.
- Amyloid positron emission tomography (PET) provides an established in vivo measure of amyloid pathology, but its use is limited by cost and accessibility².
- Blood-based biomarkers have emerged as accessible tools to support the identification of amyloid pathology and are increasingly being incorporated into research and clinical settings^{3,4}.
- Aim:** To evaluate and compare the ability of plasma biomarkers to discriminate amyloid PET positivity, with a focus on cognitively unimpaired (CU) individuals.

Methods

- Participants were selected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort, with clinical, imaging, and biomarker data obtained through the Laboratory of Neuro Imaging (LONI) database.
- Inclusion required plasma biomarker measurements, amyloid PET imaging, and clinical assessments available within the predefined study windows.
- Clinical assessments were performed within 1 year of plasma collection, and plasma samples were collected within 6 months of amyloid PET imaging.
- For participants with multiple qualifying visits, the most recent visit meeting the predefined temporal requirements between plasma, PET, and clinical assessments was selected for analysis.
- Cognitive status was classified using the Clinical Dementia Rating (CDR) scale.
- Participants with a CDR score of 0 were classified as cognitively unimpaired (CU), while those with a CDR score >0 were classified as cognitively impaired (CI).
- Amyloid positivity was defined using florbetapir F18 PET imaging with a threshold of ≥20 Centiloids⁵.
- The performance of plasma Lumipulse **G** pTau 217, Lumipulse **G** Aβ 1-42/Aβ 1-40, the Lumipulse **G** pTau 217/Aβ 1-42 ratio, and Elecsys pTau 181 for the identification of amyloid PET positivity was evaluated.
- Discriminative performance was assessed using receiver operating characteristic (ROC) curve analysis.
- Differences in area under the ROC curve (AUC) were evaluated using DeLong tests.
- Associations between plasma biomarkers and amyloid PET burden were assessed using Spearman correlation analyses.

References

1. Sperling RA, et al. *Alzheimers Dement.* 2011;7(3):280-92
2. Hampel H, et al. *Neuron.* 2023;111(18):2781-2799.
3. Mielke MM, et al. *Alzheimers Dement.* 2024;20(11):8216-8224.
4. Hansson O, et al. *Alzheimers Dement.* 2022;18(12):2669-2686
5. Schaap T, et al. *Alzheimers Dement.* 2024;20(12):9060-9067.

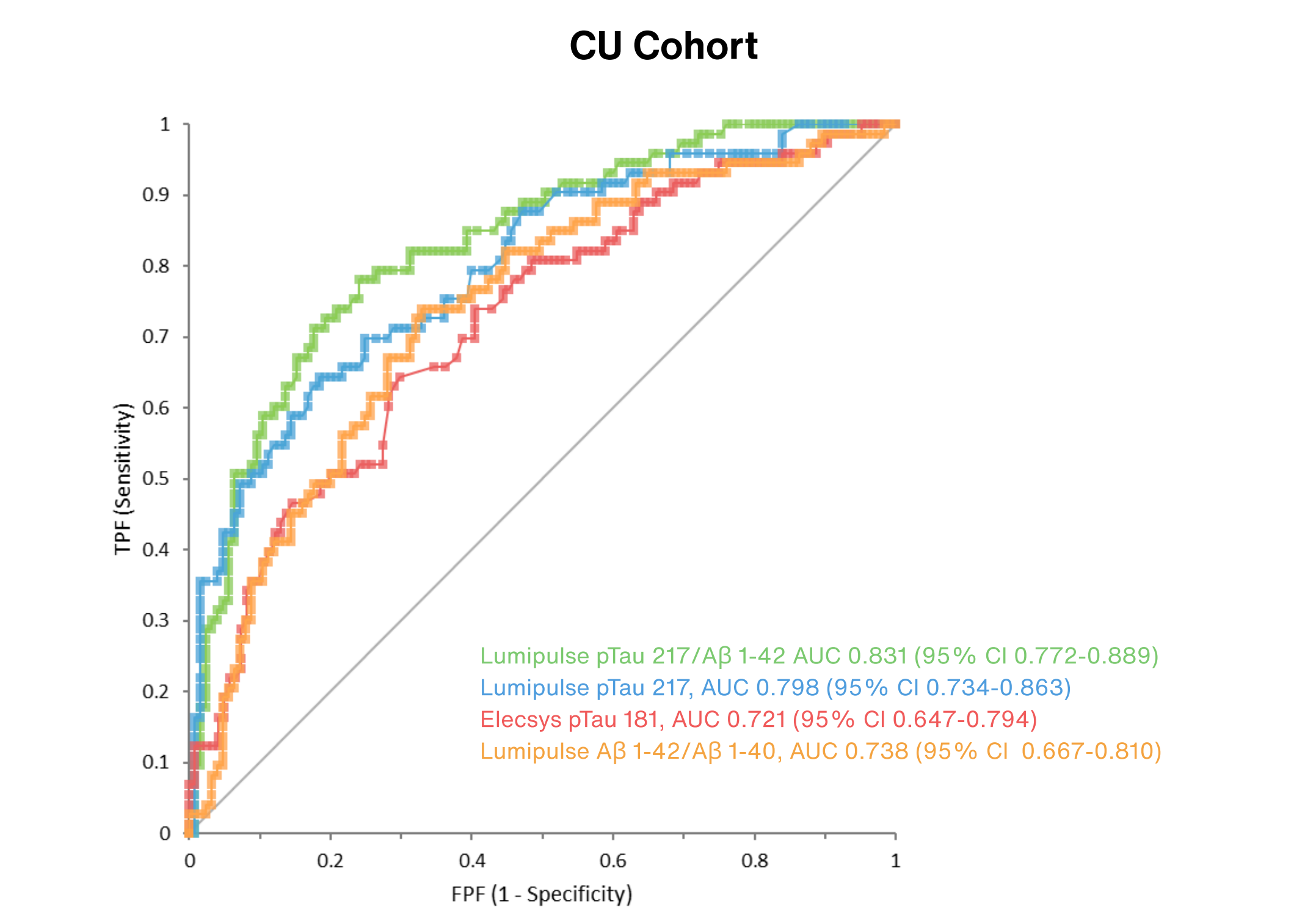
Results

Table 1. Demographic and Clinical Characteristics Stratified by Amyloid PET Status. Data are presented as mean ± SD or n (%). Participants were classified as amyloid positive (Aβ+) or amyloid negative (Aβ-) based on florbetapir PET Centiloid values.

Characteristic	Aβ-	Aβ+	Overall
N	201 (51.5%)	189 (48.5%)	390
Age, mean ± SD, years	77.1 ± 7.5	78.5 ± 7.1	77.7 ± 7.4
Female, n (%)	104 (54.2%)	88 (45.8%)	192 (49.2%)
CU, n (%)	125 (63.1%)	73 (36.9%)	198 (50.8%)
CDR, mean ± SD	0.0 ± 0.2	0.3 ± 0.6	0.2 ± 0.4
Centiloids, mean ± SD	-6 ± 15	72 ± 37	32 ± 48

Amyloid PET-negative and PET-positive participants were similar in age and sex, with expected differences in CDR and Centiloid values.

Figure 1. ROC curves for plasma pTau 217/Aβ 1-42, pTau 217, pTau 181, and Aβ 1-42/Aβ 1-40 for identification of amyloid PET positivity in CU individuals. The pTau 217/Aβ 1-42 ratio achieved the highest AUC (0.831, 95% CI 0.772–0.889) and demonstrated significantly greater discrimination than pTau 217, pTau 181, and Aβ 1-42/Aβ 1-40 (all p < 0.05, DeLong test).



Conclusions

- The Lumipulse pTau 217/Aβ 1-42 plasma ratio demonstrates consistently superior discrimination of amyloid PET positivity compared with individual biomarkers in both CU and CU+CI cohorts, supporting its robustness across disease stages.
- The stronger association with amyloid PET burden suggests closer alignment with underlying pathology.
- These findings support the potential utility of plasma biomarker ratios as scalable tools for identifying individuals for further diagnostic evaluation or clinical trial enrollment.
- While these findings were observed in the ADNI cohort, further validation in broader and more diverse populations is warranted.

Figure 2. ROC curves for plasma pTau217/Aβ1-42, pTau217, pTau181, and Aβ1-42/Aβ1-40 for identification of amyloid PET positivity in the CU+CI cohort. The pTau217/Aβ1-42 ratio achieved the highest AUC (0.883, 95% CI 0.849–0.916) and demonstrated significantly greater discrimination than pTau217, pTau181, and Aβ1-42/Aβ1-40 (all p < 0.05, DeLong test).

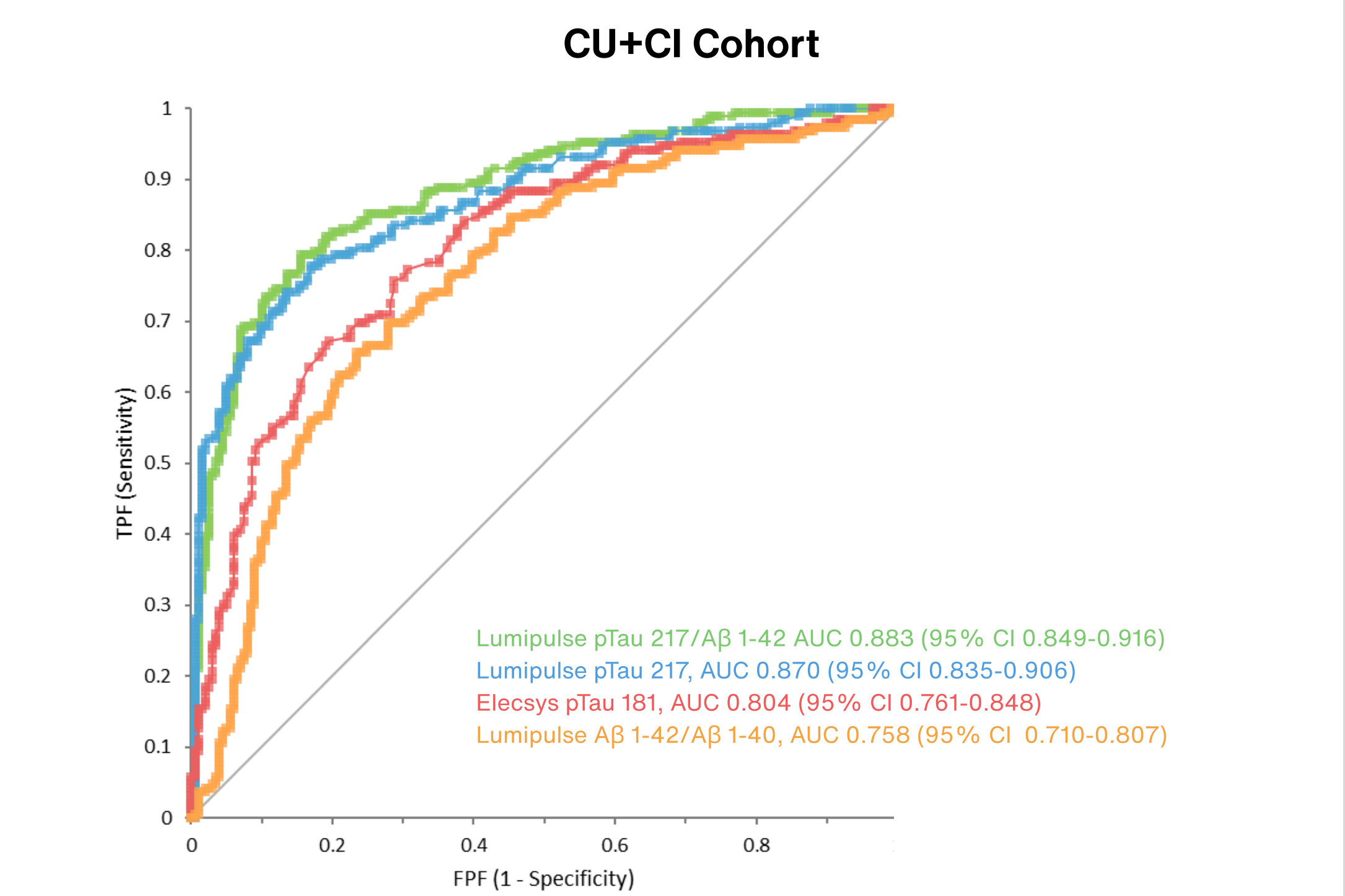


Figure 3. Correlation of plasma biomarkers with amyloid PET Centiloid values in CU and CU+CI cohorts. Spearman correlation analyses were performed using raw biomarker values and Centiloid measurements. Scatterplots are displayed using log₁₀-transformed biomarker axes for visualization purposes only. The pTau 217/Aβ 1-42 ratio showed the highest correlation in both cohorts (CU: ρ = 0.6074; CU+CI: ρ = 0.7210), followed by pTau 217 (0.5271, 0.6856), pTau 181 (0.3401, 0.5136), and Aβ 1-42/Aβ 1-40 (−0.4653, −0.4805).

