Diagnostic performance of plasma $pTau_{217}/A\beta_{42}$ ratio and a three-zone threshold model for Alzheimer's disease

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Background and aims

Early and accurate diagnosis of Alzheimer's disease (AD) typically relies on invasive or expensive methods like cerebrospinal fluid (CSF) biomarkers and amyloid PET imaging. Recent advances in blood-based biomarkers, particularly plasma phosphorylated tau ($pTau_{181}$, $pTau_{217}$) and amyloid-beta ratios ($A\beta_{42}/_{40}$), promise improved diagnostic accessibility and practicality. This study aimed to assess diagnostic accuracy of these plasma biomarkers and develop a three-zone classification model (low-, intermediate-, high-risk) to reduce reliance on invasive confirmatory tests.

Materials and methods

In this retrospective study, we evaluated 109 patients referred to the Memory Clinic of the University Hospital of Trieste, Italy. Participants underwent cognitive assessments, brain MRI, CSF biomarker analyses ($pTau_{181}$, $A\beta_{42}/_{40}$), and plasma biomarker measurements ($pTau_{181}$, $pTau_{217}$, $A\beta_{42}/_{40}$, $pTau_{217}/A\beta_{42}$ ratio). We used ROC curve analysis to determine biomarker accuracy and logistic regression modeling to define thresholds achieving ≥95% sensitivity and specificity, thus enabling a three-zone classification.

Study design

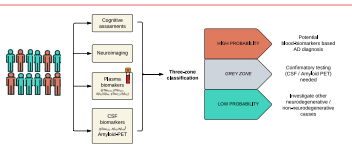

Figure 1. Plasma biomarker–based risk stratification (low, intermediate, high) as a tool to reduce invasive confirmatory diagnostics.

Results I

Plasma biomarkers significantly correlated with CSF biomarkers. For identifying AD pathology (A+/T+ vs. others), plasma $pTau_{217}$ and the $pTau_{217}/A\beta_{42}$ ratio demonstrated the highest accuracy (both AUC=0.95), significantly outperforming plasma $pTau_{181}$ (AUC=0.88) and $A\beta_{42}/_{40}$ ratio (AUC=0.73; $p<0.01$). At optimal thresholds, plasma $pTau_{217}$ alone had 87.5% sensitivity and 93.4% specificity, whereas the $pTau_{217}/A\beta_{42}$ ratio had slightly higher sensitivity (95.8%) but lower specificity (85.2%).

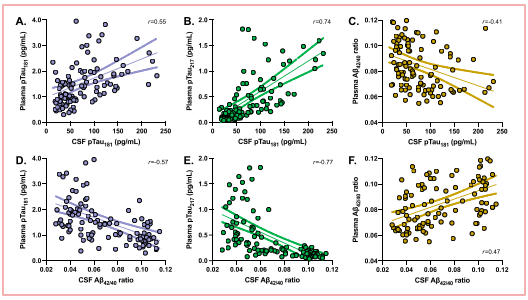

Figure 2. Correlations between CSF and plasma biomarkers. Correlations between CSF pTau181 and A) plasma pTau181, B) plasma pTau217, and C) plasma Aβ42/40 ratio. Correlations between CSF Aβ42/40 ratio and D) plasma pTau181, E) plasma pTau217 and F) plasma Aβ42/40 ratio.

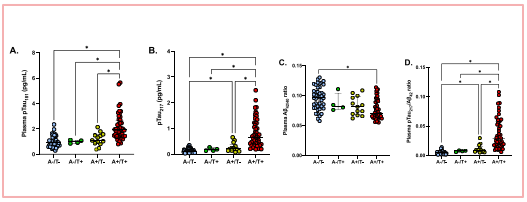

Figure 3. Plasma biomarkers according to A/T status. A) plasma pTau181, B) plasma pTau217, C) plasma Aβ42/40 ratio and D) plasma pTau217/Aβ42 ratio. Thick horizontal lines represent median values while thin horizontal lines represent the interquartile range; *p<0.05.

Results II

Using the three-zone classification model, plasma $pTau_{217}$ allowed definitive risk stratification in 80.7% of patients without invasive testing (36.7% high-risk, 44.0% low-risk, 19.3% intermediate-risk), while the $pTau_{217}/A\beta_{42}$ ratio increased definitive classification modestly to 84.4% (50.5% high-risk, 33.9% low-risk, 15.6% intermediate-risk). Among MCI patients specifically, plasma $pTau_{217}$ achieved excellent diagnostic performance (AUC=0.98), confirming suitability for early-stage AD detection.

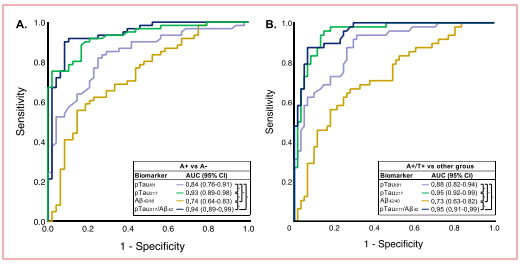

Figure 4. ROC curve analysis. ROC curves for differentiating A) A+ vs A- and B) A+/T+ vs other A/T groups, with AUCs and 95% CI. Comparisons between AUCs were performed using DeLong statistics: *p<0.05. ROC = receiver operating characteristic; AUC = area under the curve; 95% CI = 95% confidence interval.

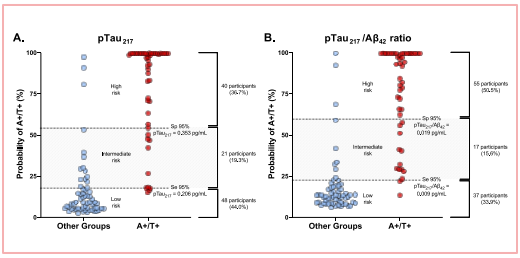

Figure 5. Risk stratification with plasma pTau217 and pTau217/Aβ42 ratio-based models. Distribution of predicted probabilities of A+/T+ from logistic regression models using (A) pTau217 and (B) pTau217/Aβ42 ratio as predictors. The values corresponding to risk thresholds (95% sensitivity and 95% specificity) are indicated, with dashed lines marking the low- and high-risk thresholds on the probability distribution.

Conclusions

In conclusion, this study strongly supports plasma $pTau_{217}$ and the $pTau_{217}/A\beta_{42}$ ratio as clinically valuable blood-based biomarkers for accurately diagnosing Alzheimer's disease. The implementation of a three-zone diagnostic model significantly improves clinical feasibility by reducing reliance on invasive confirmatory procedures. Plasma $pTau_{217}$ alone demonstrates robust diagnostic accuracy and clinical practicality, while the $pTau_{217}/A\beta_{42}$ ratio offers incremental benefits primarily by reducing diagnostic uncertainty in borderline cases. Ultimately, our findings reinforce the promising potential of blood-based biomarkers to transform AD diagnostics, providing scalable, cost-effective, and patient-friendly solutions for early diagnosis and optimal patient management.

References

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Disclosures

The authors report no disclosures.