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SYSTEMATIC REVIEW / META-ANALYSIS

Diagnostic Accuracy of Plasma Biomarkers for the Early Diagnosis of Alzheimer's Disease: A Systematic Review and Meta-analysis

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ABSTRACT

Objective: To compare the diagnostic accuracy of plasma phosphorylated tau 217 (p-tau217), phosphorylated tau 181 (p-tau181), the amyloid beta 42/40 ratio (Aβ42/40) and neurofilament light chain (NfL) for detecting amyloid pathology.

Methods: PubMed, Embase and Web of Science were searched for the period January 2015–December 2025 according to the PRISMA 2020 recommendations. Diagnostic accuracy studies using amyloid PET or cerebrospinal fluid biomarkers as the reference standard were included. Study quality was assessed with QUADAS-2, and pooled sensitivity, specificity and area under the curve (AUC) were calculated with a random-effects model.

Results: Of the 1,284 records screened, 38 studies (11,462 participants) were included. The pooled AUC was 0.92 (95% CI 0.90–0.94) for p-tau217, 0.85 (0.82–0.88) for p-tau181, 0.79 (0.75–0.83) for Aβ42/40 and 0.68 (0.63–0.73) for NfL. The pooled sensitivity of p-tau217 was 87% and its specificity 86%. Heterogeneity between studies was moderate.

Conclusion: Plasma p-tau217 has the highest accuracy for detecting amyloid pathology among the biomarkers studied. Assay methods and cut-off values need to be standardised before routine clinical use.

Keywords: Alzheimer disease; biomarkers; phosphorylated tau; diagnostic accuracy; meta-analysis

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INTRODUCTION

Alzheimer's disease is now defined as a biological process that begins years before clinical symptoms [1]. Amyloid PET and cerebrospinal fluid (CSF) analysis, used to show amyloid and tau pathology, are accurate but expensive, of limited availability and invasive. Blood-based biomarkers offer a promising option for screening in primary care and referral to specialist centres [2].

In recent years, ultrasensitive assays have shown that plasma p-tau217, p-tau181, the Aβ42/40 ratio and NfL can distinguish amyloid pathology with high accuracy [3]. However, an up-to-date synthesis comparing these biomarkers with the same criteria is limited. In this study, we aimed to compare the diagnostic accuracy of four plasma biomarkers with a systematic review and meta-analysis.

METHODS

Search and study selection

The systematic review was conducted according to the PRISMA 2020 recommendations [4]. PubMed, Embase and Web of Science were searched for the period January 2015–December 2025 with combinations of the terms "Alzheimer", "plasma", "phosphorylated tau", "amyloid beta", "neurofilament light" and "diagnostic accuracy". Studies using amyloid PET or CSF biomarkers as the reference standard, with at least 50 participants and enough data to build a two-by-two table, were included. Records were screened independently by two authors; disagreements were resolved with the third author.

Data extraction and quality assessment

Participant characteristics, assay method, cut-off value, reference standard and the numbers of true and false positives and negatives were extracted from each study. Risk of bias and applicability were assessed with the QUADAS-2 tool [5].

Statistical analysis

Sensitivity and specificity were pooled with a bivariate random-effects model, and the AUC was calculated from summary ROC curves. Heterogeneity was assessed with the I^2

statistic, and subgroup analyses were performed by assay platform and clinical stage.

RESULTS

Of the 1,284 records screened, 117 full texts were reviewed and 38 studies (11,462 participants) were included. The median age of the participants was 71 years and 53% were women; 22 studies were from memory clinics and 16 from community-based samples. In the QUADAS-2 assessment, most studies had a low risk of bias; the most common problem was the use of cut-off values that were not pre-specified. The pooled results are summarised in Table 1.

Table 1. Pooled diagnostic accuracy of plasma biomarkers

Biomarker	Studies	Participants	AUC (95% CI)	Sensitivity	Specificity
p-tau217	14	4,386	0.92 (0.90–0.94)	87%	86%
p-tau181	12	3,912	0.85 (0.82–0.88)	79%	80%
Aβ42/40	9	2,207	0.79 (0.75–0.83)	74%	72%
NfL	6	1,894	0.68 (0.63–0.73)	63%	66%

Because some studies reported more than one biomarker, the totals in the table exceed the numbers of studies and participants. Heterogeneity for p-tau217 was moderate (I^2 = 41%). The AUC was slightly higher for mass spectrometry-based assays than for immunoassays (0.94 vs 0.91), and accuracy was maintained in the subgroup with mild cognitive impairment.

DISCUSSION

In this meta-analysis, plasma p-tau217 showed clearly higher accuracy for detecting amyloid pathology than p-tau181, Aβ42/40 and NfL. The low specificity of NfL may be explained by the fact that it reflects general neuroaxonal injury that is not specific to Alzheimer's disease [2].

The findings suggest that plasma p-tau217 could be used in memory clinics to select the patients who need CSF or PET examination. However, differences between assay platforms and varying cut-off values across studies limit the direct translation of the results into clinical thresholds. Limitations of the review include the inclusion of English-language publications only and the different application of the reference standard in community-based studies.

CONCLUSION

Plasma p-tau217 is the strongest candidate among the biomarkers studied for detecting amyloid pathology due to Alzheimer's disease. Standardisation of assay methods and cut-off values validated in different populations are needed before routine use.

Ethics approval: Ethics approval was not required because the study is based on published data. The study protocol was prepared by the authors before data collection began.

Conflict of interest: The authors declare no conflict of interest.

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Author contributions: DA: concept, design, literature search, writing; OB: literature search, data extraction; MT: statistical analysis, critical review.

Data availability: The data extraction table is available from the corresponding author on reasonable request.

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