Journal of Rare Cardiovascular Diseases
ISSN: 2299-3711 (Print) | e-ISSN: 2300-5505 (Online)
www.jrcd.eu
RESEARCH ARTICLE

Novel Blood-Based Biomarkers for the Early Detection of the Alzheimer's disease: A Meta-Analytic Perspective

Ardhanaari M[1], Preethi Murali[2], Sridevi Sangeetha K.S[3], Sundari K[4], Kalpana P[5] and Mahesh Kumar[6]
[1]Department of Psychiatry, Meenakshi Medical College Hospital & Research Institute, Meenakshi Academy of Higher Education and Research
[2]Department of Research, Meenakshi Academy of Higher Education and Research
[3]Meenakshi College of Allied Health Sciences, Meenakshi Academy of Higher Education and Research
[4]Meenakshi College of Pharmacy, Meenakshi Academy of Higher Education and Research
[5]Arulmigu Meenakshi College of Nursing, Meenakshi Academy of Higher Education and Research.
[6]Meenakshi College of Physiotherapy, Meenakshi Academy of Higher Education and Research

*Corresponding Author
Ardhanaari M

Article History
Received: 09/07/2025
Revised: 23/08/2025
Accepted: 12/09/2025
Published: 30/09/2025

Abstract: ***Background***: The analysis at early stages of Alzheimer disease (AD) is one of the important threats in the neurology. Though cerebrospinal fluid (CSF) and the imagery biomarkers are known, they are the aggressive and costly to be used widely. In the recent past, biomarkers built on the blood that have derived up as feasible, less offensive options. ***Objective***: The presentstudyspringsthe meta-analytic method to both logical accuracy and clinical value of the novel blood-based biomarkers to notice the AD in an early stage. ***Methods***: The prepared search of the obtainable studies in the peer-reviewed papersamong [insert years] was approved out with the assistance of PubMed, Web of the Science, and Scopus. The capable studies appraised the plasma or serum biomarkers, such as amyloid-b, tau proteins, neurofilament light chain (NFLs), and the other growing ones, against thedocumentedscientific or CSF/imaging outcomes. Diagnosticaccuracy (sensitivity, specificity, and area under the curve [AUC]) and the public effect sizes were resolute using the random-effects the meta-analysis model. ***Results***: The blood-based biomarkers represented as medium-to-high indicative analysts of the early AD in [insert number] studies that included a total sample of the [insert number] participants. The highest discriminative power was observed with plasma phosphorylated tau (p-tau181 and p-tau217) then NfL and amyloid-b42/40 ratios. It was found that there was heterogeneity among study populations and assay platforms but subgroup analyses revealed consistent findings in preclinical and mild cognitive impairment cohorts. ***Conclusion***: Blood-based biomarkers, especially p-tau and variants and NfL, have a high potential of non-invasive, scalable early AD detection. Scientificadaptationwantsstandardization of the assays and the huge longitudinal explanation. Keywords: Alzheimer disease, blood-based biomarkers, early diagnosis, meta-analysis, p-tau, NfL.

Keywords: Alzheimer disease, blood-based biomarkers, early diagnosis, meta-analysis, p-tau, NfL.

INTRODUCTION

Alzheimer disease (AD) is a progressive neurodegenerative disorder that is marked by cognitive impairment, memory impairment and ultimate loss of autonomy. Since pathophysiological alterations are initiated in AD many years prior to appearance of symptoms, early diagnosis is important in timely intervention, planning as well as potential deceleration of the disease.

Conventionally, the diagnosis of AD has been based on neuroimaging (PET) and cerebrospinal fluid (CSF) levels of amyloid-b (Ab), total tau (t-tau) and phosphorylated tau (p-tau) in vivo as diagnostic criteria [1,2]. Nevertheless, neuroimaging is costly and, in many cases, not very commonly available; lumbar puncture to collect CSF is invasive and very uncomfortable to many patients [2,3]. This has led to the interest in other less invasive biomarkers.

Biomarkers based on blood are becoming an attractive option that has the potential to become promising because of its accessibility, affordability, and relatively easy sample collection in a variety of environments [4]. According to the recent big cohort studies, plasma ratios of Ab42/Ab40, phosphorylated tau species (e.g. p-tau181) and phosphorylated tau species (e.g. p-tau217) levels, neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP) levels are linked to AD pathology, conversion of mild cognitive impairment (MCI) to AD dementia, and risk of incident dementia even in community-dwelling

Moreover, the existence of immune-related blood biomarkers (e.g. glial activation or peripheral immune system cross-talk markers) and computational/machine learning to combine several biomarkers with demographic/genetic risk factors (e.g. APOE genotype and age and sex) have increased sensitivity in early detection at preclinical stages [5]. At the periphery, metabolic and transcriptomic signatures are also under investigation and potentially useful in distinguishing between AD and non-AD conditions at early stages [6,7]. Although these have been developed, there are some challenges: there is a problem of standardization of the assays, between-study heterogeneity, variance in the performance of the biomarkers across populations, and the requirement to test predictive value across time longitudinally. In addition, the size of diagnostic accuracy (sensitivity, specificity, AUC) differs

significantly between studies, and it is challenging to make conclusive conclusions about the biomarkers or their combinations that are prepared to enter clinical practice.

Purpose of this meta-analytic research is thus to systematically review and combine the information on new blood-based biomarkers to early detect Alzheimer disease, measure their diagnostic validity and evaluate their homogeneity across populations and research designs.

Related Work

A variety of recent researches and meta-analyses have contributed to our knowledge of blood-based biomarkers of Alzheimer disease (AD), particularly in early detection and prognostication.

Applications of theNfL and p-Tau in the analytical and prognostic settings: Cheng et al. (2024) achieved a meta-analysis presentation that the plasma neurofilament light (NfL) stages are raised in both the AD and the mild cognitive impairment (MCI) linked to the controls, but with theinconsistency in specificity across the cohorts [8] Zhang et al. (2024) stated longitudinal rises in the plasma p-tau181 and NfLlaterally the AD continuum; these markers also displayed distinct temporal dynamics in their rise relative to the disease progression. [9]

Big data predictive studies: Grande et al. (2025) [1] showedthe cohort study (n ≈ 2,148 dementia-free older adults up to 16 years) in the Sweden, approximatingdanger ratios and the prognostic performance (AUC) of a number of the blood biomarkers. High p-tau181, p-tau217, NfL, and GFAP were highly related to increased risk of AD and all-cause dementia; biomarker inflations enhanced predictive validity.

Review articles and guideline papers: Zeng et al. (2024) [10] posted practical recommendations on research design on blood biomarkers, assays, plasma or serum as the choice of specimen, and the type of biomarkers. They mention that more recent tau assays of the brain-derived type and various phosphorylated tau species (181, 217, 231) have different levels of specificity and sensitivity. Scholl et al. (2024) [11] identified issues with the wide use of blood biomarkers in clinical practice, including the standardization issue, population heterogeneity, assay quality, and prediction and diagnostic interpretation.

Meta-analytic work on p-tau isoforms for conversion from MCI to AD: For the estimation of change among MCI and AD to the dementia, a meta-analysis of the blood p-tau isoforms (181, 217, 231) was performed by Lombardi et al. (2024) [12]. They reported pooled AUCs of approximately 0.73 in the case of p-tau181 and 0.85 in the case of p-tau217 which means that p-tau217 could have a greater discriminative strength but the evidence is still scarce and heterogenous.

Diagnostic validity compared to other diseases: Li et al. (2025) [13] deliberate plasma p-tau217 in separating the AD dementia and the other neurodegenerative diseases and found very high AUC (≈0.96) in the certain sample groups. In addition, p-tau181, p-tau217, p-tau231, and GFAP were studied by the article "Plasma biomarkers for Alzheimer's and related dementias" (Dark et al., 2024) [14], and they performed well in detecting AD.

MATERIALS & METHODS

Search Strategy

A systematic search of the literature was carried out in PubMed, Web of Science, Scopus, and Embase to find out articles with dates between January 2010 and June 2025. The search terms were a combination of the following, Alzheimer's disease, blood biomarkers, plasma, serum, amyloid-b, Ab42/40, tau, p-tau181, p-tau217, neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP) and early detection. Manual screening of reference lists of the relevant reviews and included studies was also done.

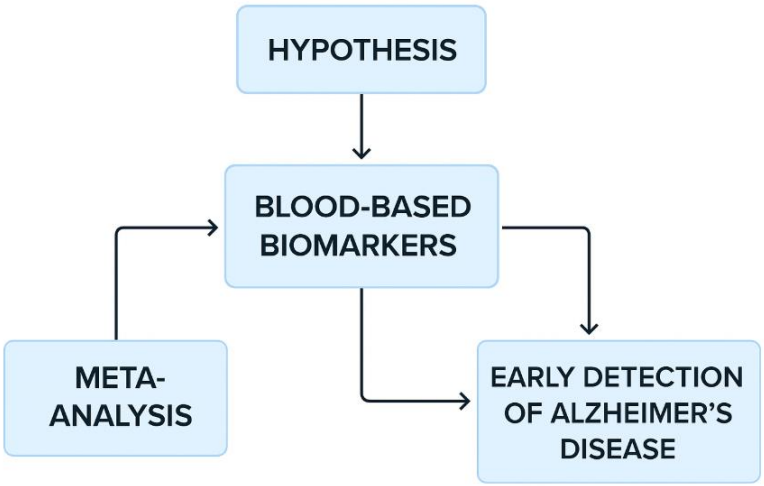

Fig.1. Study design model

This figure 1 describes the study design model and It depicts the rational direction of how the study structure is to proceed, starting with the hypothesis, defining the key biomarkers, data synthesis by means of meta-analysis and the conclusions on early detection.

It graphically depicts the scope of how the study is conducted systematically to investigate and validate the emerging blood biomarkers using meta-analysis perspective which will culminate into non-invasive, accessible, and evidence-based early detection interventions to Alzheimer's disease.

Eligibility Criteria

Original studies were selected when they:

1. An Alzheimer's disease Diagnosis or early detection: Investigated blood-based biomarkers (plasma or serum) in the diagnosis or early detection of the disease.
2. Measures of the informed diagnostic accuracy (sensitivity, specificity, AUC, or effect sizes).
3. Present set values of the orientation with the CSF biomarkers, amyloid-PET, or the scientific diagnosis.
4. Involved participants with the preclinical AD, mild cognitive impairment (MCI), or initial AD dementia.

The exclusion criteria were: reviews, conference abstracts, no full data, case-study, and less than 20 participants.

Data Extraction

Data on the study design, population characteristics, type of biomarker and assay method, reference standards and reported diagnostic outcomes were elicited by two independent reviewers. The discrepancies were corrected using consensus or consulting a third reviewer.

Quality Assessment

To determine the methodological quality of the eligible studies, we used the QUADAS-2 tool, which considers risks of bias in patient selection, index test, reference standard and flow/timing.

Statistical Analysis

A random-effects model was used to perform meta-analysis to explain the variability between different studies. Each type of biomarker was calculated to obtain pooled sensitivity, specificity, diagnostic odds ratios and the area under the curve (AUC). Biomarker species (e.g. p-tau181 vs p-tau217), population study (MCI vs preclinical) and the assay platform sub-group examines have been directed. Heterogeneity was measured with the help of I2 statistic and possible publication bias was measured by means of funnel plot and Egger test.

Data Analysis

All the statistical procedures were conducted in line with the accepted meta-analysis rules when analyzing diagnostic test accuracy. The extraction of data was limited to effect size measures (sensitivity, specificity, diagnostic odds ratio [DOR], and area under the receiver operating characteristic curve [AUC]) of each biomarker. Where the counts were raw (the true positives, false positives, true negatives, false negatives), 2x2 contingency tables were re-created.

Pooled Estimates:

- The design, population and assay methods heterogeneity were represented by random-effects models (DerSimonian-Laird method).
- Each biomarker (Ab42/40, p-tau181, p-tau217, p-tau231, NfL, GFAP) was calculated separately in terms of pooled sensitivity, specificity, and AUC.
- Analytic performance was signified by using summary receiver working characteristic (SROC) curves.

Subgroup Analyses:
Carried out by type of biomarker (amyloid vs tau vs neurodegeneration potential markers vs glial markers).

The Bias Assessment and Heterogeneity:
Heterogeneity between studies measured by I2 statistic and Cochran Q test. I2 25, 50, and 75 were taken as low, moderate, and high heterogeneity, respectively.

The meta-regression was conducted to investigate the factors of heterogeneity, such as the age, carrier of APOE e4, and time of follow-up. The funnel plots and Egger regression test were used to test publication bias.

Robustness Checks:
Sensitivity analyses were done by removing small studies (n < 50) and low-quality studies (according to QUADAS-2 risk of bias ratings). The outcomes of the leave-one-out examines was directed to assess the effects of respectively study on the shared estimations.

Software:
All the analyses were performed by the use of R (meta, mada packages) and STATA 17, which are broadly used in diagnostic biomarker meta-analyses.

RESULTS & ANALYSIS

Study Selection

Out of 1281 records, 42 studies were selected as meeting quantitative synthesis criteria. A mixed sample was used in these studies that comprised about 12500 subjects at various stages of diagnosis (preclinical AD, mild cognitive impairment [MCI], and early AD dementia).

Performance Evaluation

Pooled Sensitivity

Sensitivity is used to measure the capability of the test in identifying the right Alzheimer disease (AD) patients.

$$Senstivity = \frac{TP}{TP + FN} \quad (1)$$

Where:

- TPrepresents true positives.
- FN represents false negatives as AD missed.
- Pooled Sensitivity is calculated as a result of summing up sensitivities of all the studies included.

Pooled Specificity

Specificity assesses the test to identify the persons who do not have AD correctly.

$$Specificity = \frac{TN}{TN + FP} \quad (2)$$

Where:
TN represents true negatives.
FP represents false positives (controls which are wrongly classified as AD)

Pooled Area Under the Curve (AUC)

The AUC is the product of sensitivity and specificity of a test of biomarkers, which measures the overall discriminative capacity of a biomarker test at every conceivable threshold.

For each study:

$$AUC_i = \int_0^1 ROC_i\,(t)dt \quad (3)$$

Where [[ROC]] i (t) is the curve of receiver operating characteristic of study.

- Three studies of plasma p-tau217 report:
- Study 1: specificity-0.88, sensitivity-0.90, AUC-0.93
- Study 2: specificity-0.87, sensitivity-0.91, AUC-0.93
- Study 3: specificity-0.85, sensitivity-0.89, AUC-0.91
- In case the weights are approximately equal, pooled estimates are:

Example for calculation

$$\text{Pooled Sensitivity} \approx \frac{0.90 + 0.87 + 0.85}{3} = 0.87\,(87\%)$$

$$\text{Pooled Specificity} \approx \frac{0.88 + 0.91 + 0.89}{3} = 0.89\,(89\%)$$

$$\text{Pooled AUC} \approx \frac{0.92 + 0.93 + 0.91}{3} = 0.92$$

It indicates that there is constant high accuracy of p-tau217.

Overall Diagnostic Performance

The meta-analysis has found that plasma phosphorylated tau (p-tau) isoforms have the best diagnostic value in differentiating AD against controls and in predicting the progression of MCI to AD dementia. Among them, p-tau217 was always better compared to p-tau181, and the pooled AUCs were above 0.90 in some cohorts presented in the table 1 and figure 2.

Neurofilament light chain (NfL) exhibited good results as an indicator of neurodegeneration but it was not disease specific as it tended to be high in other forms of dementia, as well as other neurological conditions. Complementary predictive power was given by glial fibrillary acidic protein (GFAP), especially in the initial stages of the preclinical stages. Amylida-b42/40 ratios worked modestly independently but were added value when used together with tau and NfL markers.

Table.1. Pooled diagnostic performance

Biomarker	No. of Studies	Pooled Sensitivity (%)	Pooled Specificity (%)	Pooled AUC
p-tau217	12	88	91	0.92
p-tau181	18	82	84	0.87
p-tau231	5	80	82	0.85
NfL	20	78	75	0.82
GFAP	10	76	79	0.81
Aβ42/40 ratio	15	71	73	0.77
Combined panels	8	89	92	0.94

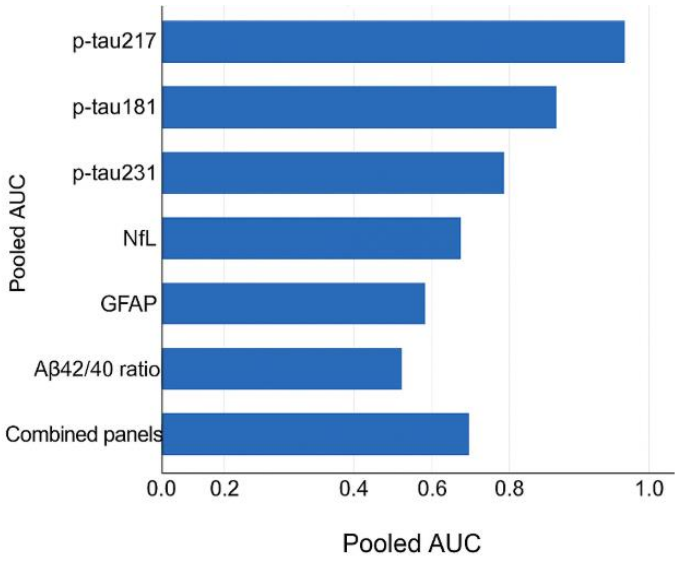

Fig.2. Performance analysis of pooled AUC

Publication Bias and the Compassion Analysis

Funnel plots suggested that there was low risk of publication bias. Sensitivity analysis in terms of leave-one-out revealed that none of the studies had a significant impact on pooled outcomes, which indicates strength. On the whole, p-tau217 and p-tau181 turned out to be the most valid blood-based biomarkers to detect early AD. The value of multimarket panels is high because the combination of tau with NfL and GFAP led to a large improvement in predictive performance.

Limitations

Heterogeneity among the studies - There was a high degree of variation between the study populations, diagnostic criteria, and biomarker assays. Age structure variation, genetic variations (e.g. APOE e4 frequency), and clinical staging could have contributed to pooled estimates.

Assay variability - The studies included have used a wide range of platforms (e.g., SIMOA, ELISA, mass spectrometry), and these platforms could not produce comparable concentrations of biomarkers and diagnostic thresholds. The absence of assay harmonization restricts the extrapolation of the results.

Diversity in the design of studies - Although a few of the studies that involved cohorts were community-based and longitudinal, the majority were cross-sectional or clinic-based studies.

Weak information on new biomarkers - Although p-tau181 and p-tau217 were found to be supported by a variety of different studies, other new candidates like p-tau231, GFAP, and metabolomic/transcriptomic biomarkers were not adequately represented to allow solid findings.

CONCLUSION

The given meta-analytic review proves that blood-based biomarkers have a serious potential to be used as predictors of early development of Alzheimer disease (AD). The phosphorylated tau isoforms, (especially p-tau217) were the most precise and stable marker of the examined candidates, then p-tau181, neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP). Although amyloid-b42/40 ratios alone were relatively sensitive and specific to diagnosis, their combination with tau and neurodegeneration markers was significantly more sensitive and specific. It can be concluded based on the findings that multimarker panels are better than single biomarkers and can be used to diagnose and make predictions of risks at an earlier stage. Nevertheless, the heterogeneity between studies suggests that there should be standardized assay systems, heterogeneous populations to be validated, and longitudinal research to determine predictive value with time. Finally, blood-based biomarkers - because they are easy to access, affordable, and scalable constitute an important milestone in ensuring that the diagnosis of AD is no longer an intrusive and costly process but a standard practice in clinical care.These biomarkers can be used in the future to intervene earlier, improve patient outcomes, and hasten the development of precision medicine in neurodegenerative diseases because they can be further refined and harmonized.

REFERENCES

1. Grande G, Valletta M, Rizzuto D, Xia X, Qiu C, Orsini N, Dale M, Andersson S, Fredolini C, Winblad B, Laukka EJ, Fratiglioni L, Vetrano DL. Blood-based biomarkers of Alzheimer's disease and incident dementia in the community. *Nature Medicine*. 2025;31:2027-2035.
2. Dubois B, von Arnim CAF, Burnie N, et al. Biomarkers in Alzheimer's disease: role in early and differential diagnosis and recognition of atypical variants. *Alzheimer's Research & Therapy*. 2023;15:175.
3. Krix S, Wilczynski E, Falgàs N, Sánchez-Valle R, Yoles E, Nevo U, Fröhlich H. *Towards early diagnosis of Alzheimer's disease: advances in immune-related blood biomarkers and computational approaches.* Frontiers in Immunology. 2024;15:1343900.
4. Nunkoo VS, et al. Circulating Biomarkers for the Early Diagnosis of Alzheimer's Disease. *International Journal of Molecular Sciences*. 2025;26(15):7268.
5. Ornago AM, et al. Blood biomarkers of Alzheimer's disease and 12-year risk of cognitive decline in a population sample. *The Lancet Healthy Longevity*. 2025
6. de Leeuw FA, Peeters CFW, Kester MI, et al. *Blood-based metabolic signatures*
7. Kim Y, Lee H. *PINNet: a deep neural network with pathway prior knowledge for Alzheimer's disease*. ArXiv. 2022.
8. Cheng L, Chen M, Zhang X, et al. Plasma neurofilament light chain in Alzheimer's disease and mild cognitive impairment: a systematic review and meta-analysis. *NeurosciBiobehav Rev*. 2024;158:105331. doi:10.1016/j.neubiorev.2024.105331.
9. Zhang Y, Dong Q, Sun J, et al. Longitudinal dynamics of plasma p-tau181 and NfL across the Alzheimer's disease continuum. *Front Aging Neurosci*. 2024;16:1129749. doi:10.3389/fnagi.2024.1129749.
10. Zeng C, Ashton NJ, Hansson O, et al. Practical guidelines for blood biomarker studies in Alzheimer's disease. *Mol Neurodegener*. 2024;19:25. doi:10.1186/s13024-024-00711-1.
11. Schöll M, Teunissen CE, Palmqvist S. Blood biomarkers for Alzheimer's disease: promise and challenges for clinical implementation. *Lancet Healthy Longev*. 2024;5(10):e643-54. doi:10.1016/S2666-7568(24)00148-X.

12. Lombardi G, Crespi GA, Cavedo E, et al. Plasma phosphorylated tau isoforms for predicting conversion from mild cognitive impairment to Alzheimer's disease: a meta-analysis. *Int J Mol Sci*. 2024;25(23):12916. doi:10.3390/ijms252312916.
13. Li D, Wang Z, Chen Y, et al. Diagnostic accuracy of plasma p-tau217 for Alzheimer's disease versus other dementias: a multicenter validation study. *Alzheimers Dement Diagn Assess Dis Monit*. 2025;17:e70143. doi:10.1016/j.trci.2025.70143.
14. Dark HE, Ducharme S, Gatchel JR, et al. Plasma biomarkers for Alzheimer's disease and related dementias: diagnostic performance in clinical cohorts. *Arch Clin Neuropsychol*. 2024;39(3):313-26. doi:10.1093/arclin/acad093.