e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(8); 254-262

Original Research Article

Meta-Analysis of Biomarkers Predicting Early Progression of Alzheimer's Disease

Gautam Gokul[1], Ria Singh Rawat[2], Vani Sehrawat[3], Sunita Parmar[4], Nidhi Nagesh Rao[5], Shrish Ramesh[6], Shishir B. Nuti[7], Mradushi Gupta[8]

[1,2,3]CMO, Department of Emergency Medicine, BGS Global Institute of Medical Sciences, Bangalore, Karnataka, India

[4]Assistant Professor, Department of Emergency Medicine, BGS Global Institute of Medical Sciences, Karnataka, India

[5,6,7,8]Medical Student, Department of Emergency Medicine, BGS Global Institute of Medical Sciences, Karnataka, India

Received: 01-05-2026 / Revised: 15-06-2026 / Accepted: 21-07-2026

Corresponding author: Dr. Ria Singh Rawat

Conflict of interest: Nil

Abstract

Background: The disease process of Alzheimer's disease (AD) is now understood as a process, requiring a syndromic definition, and disease-modifying treatments are starting to be introduced to the clinic in the context of AD with amyloid pathology. Predictive fluid markers, which are able to forecast progression instead of just diagnose, are thus needed for patient selection and monitoring.

Objective: To compile evidence relating to blood- and cerebrospinal fluid (CSF)-based markers as predictors for conversion from cognitively normal to mild cognitive impairment (MCI) and MCI to dementia, and to help pinpoint those with the best and most consistent predictive performance.

Methods: A systematic review, meta-analysis and large longitudinal cohort study search, performed based on PRISMA 2020 principles, resulted in a structured synthesis of these studies identified from the PubMed/MEDLINE, Embase, Scopus, Web of Science and Cochrane Library databases. The QUADAS-2 domains were used to appraise the diagnostic studies, while the QUIPS domain was used to appraise the prognostic studies. The most robust available meta-analysis available was used to obtain pooled odds ratios (OR), hazard ratios (HR), areas under the receiver operating characteristic curve (AUC), sensitivity and specificity and heterogeneity (I^2).

Results: Amyloid positivity alone increased pooled OR for MCI to dementia (5.18; 95% CI 3.93–6.81), with a combined tau positivity and amyloid positivity increasing the pooled OR for MCI to dementia further to 11.60 (7.96–16.91). The plasma p-tau217 was the most effective single biomarker, with a pooled diagnostic sensitivity of 88.1% (86.7–89.5) and specificity of 88.7% (87.4–89.9) across 113 studies (29,625 individuals), as well as a pooled prognostic AUC of 0.85 (0.75–0.91) for MCI-to-dementia conversion, which surpassed that of plasma p-tau181 (AUC 0.73, 0.68–0.78). Plasma p-tau217 had a HR of 1.57 (1.43–1.72) in cognitively unimpaired individuals and was statistically similar (HR 1.61 [1.48–1.76]; p=0.322) to tau PET. Other CSF factors, such as NF-L (c=0.947) and GFAP (c=0.925) were complementary but less informative; and CSF ratios (p-tau/Aβ42, c=0.960) provided similarly high diagnostic concordance with amyloid PET.

Conclusion: Considering the convenience of the measurement, and that plasma p-tau217 levels currently are more informative and reproducible than CSF or imaging, this is currently the strongest and most consistent evidence available for predicting early progression to AD. Immediate priorities to aid clinical translation are assay standardisation, validation in cognitively unimpaired and primary-care populations, and its integration with brief cognitive measures.

Keywords: Alzheimer's Disease; Biomarkers; Phosphorylated Tau; Mild Cognitive Impairment; Disease Progression; Meta-Analysis; Cerebrospinal Fluid; Plasma.

DOI: 10.25258/ijcpr.18.8.39

Introduction

As part of the continuum of dementia, an estimated 57 million people worldwide are living with Alzheimer's disease (AD) [1] of which about 32 million have dementia with Alzheimer's disease and an additional 69 million have MCI due to AD pathology. The incidence rate of global increase

has doubled more than three decades and prevalence is expected to increase by around three times by 2050 [1,2]. With this path in mind, and the advent of disease-modifying therapies specific for the amyloid factor, the need to identify people who are at risk to develop a disease has become a clinical priority.

This has resulted in a conceptual paradigm shift in AD. The 2024 Alzheimer's Association Workgroup refocused on a biological continuum of AD starting with amyloid deposits in individuals without clinical symptoms, and progressing to tau accumulation and symptoms [3]. They identified biomarkers of the early changing timepoint of AD (Core 1 biomarkers: amyloid PET, CSF Aβ42/Aβ40, CSF p-tau181/Aβ42, and accurate plasma assays, especially p-tau217) and the late changing timepoint of AD (Core 2 biomarkers with primarily prognostic value). This framework relies on biomarkers that have clear diagnostic and/or prognostic properties, but the two clinical properties are often overlapping: The ability to detect amyloid pathology reliably does not mean that it necessarily helps predict the rate of clinical progression or its probability.

MCI (critical intervention window). MCI is estimated to have a 10-15% chance of converting to dementia each year, vs. 1-2% in cognitively normal older adults, and 20-40% of MCI patients will develop AD dementia in the next several years [4,5]. Given the heterogeneous nature of MCI, biomarker based, risk stratification is needed to determine which patients will be most likely to benefit from early intervention. Although CSF and PET biomarkers are recognized to have high accuracy they are invasive, high cost and largely accessible only at specialist centres, which has led to recent interest in blood-based markers.

No systematic comparison of the prognostic (rather than simply diagnostic) performance of potential biomarkers in the cognitively normal to MCI and MCI to dementia transition has been performed. Another evidence gap is the blood-based 2025 Alzheimer's Association clinical practice guideline on blood markers for detection of amyloid pathology that does not include prognostic recommendations [7]. The objectives of this review were to: (i) quantify and combine diagnostic and prognostic accuracy for each biomarker across the cognitively normal-to-MCI, MCI-to-dementia, and early-to-advanced AD transitions; (ii) compare performance across the different transitions; and (iii) evaluate the incremental value of combinations of analytes compared to a single analyte.

Methods

Study Design: The systematic review and the meta-analysis was conducted and reported according to the PRISMA 2020 statement [8] with guidance from the PRISMA-DTA extension [9] for elements that relate to the diagnostic aspects of the review.

Search Strategy and Eligibility: Published literature was scanned via PubMed/MEDLINE, Embase, Scopus, Web of Science, Cochrane Library (Cochrane Database of Systematic Reviews), and reference lists of eligible reviews, as well as hand searching in Alzheimer's & Dementia, Lancet Neurology, Brain, Neurology, Annals of Neurology, JAMA Neurology, Nature Medicine, and Nature Aging, up to July 2026. Combinations of population concepts (Alzheimer disease, mild cognitive impairment, prodromal, preclinical), index test concepts (amyloid-β, total tau, neurofilament light chain, glial fibrillary acidic protein, YKL-40, phosphorylated tau isoforms 181/205/212/217/231, prognosis, sensitivity and specificity, area under the curve), matrix terms (plasma, serum, CSF), and outcome terms (progression, conversion). Studies were included if they were peer-reviewed, included adult human subjects, included measurement of a candidate biomarker in blood at baseline, included a reference standard (either CSF profile, amyloid or tau PET or neuropathology), and reported an AUC, sensitivity/specificity, odds ratio, hazard ratio or standardised mean difference with variance, or an association with change in clinical status over at least 12 months follow-up. Case reports, conference abstracts lacking data, non-human studies and studies involving autosomal-dominant AD were not included because they did not contain data that could be extracted, as genetically determined disease has a different biological timeline.

Data Extraction and Quality Assessment: Assay platform, reference standard, outcome definition and all reported effect estimates and corresponding confidence intervals were extracted. Diagnostic accuracy studies were evaluated with the four QUADAS-2 domains (patient selection, index test, reference standard, flow and timing) [10] and prognostic accuracy studies were evaluated using Quality In Prognosis Studies (QUIPS) tool [11].

Statistical Analysis: The random-effects model was used as the main approach to use for pooling, and the fixed-effects models were used as sensitivity comparators, as expected heterogeneity in assay platform, cohort and outcome definition was anticipated. Using bivariate random-effects/hierarchical summary ROC (sROC) modelling, accuracy measures data were combined to jointly estimate pooled sensitivity, specificity, and the diagnostic odds ratio (DOR) and summary area under the curve (AUC).

Prognostic hazard and odds ratios were log pooled with inverse-variance weighting. I^2 value and Cochran's Q value were used to quantify heterogeneity, which was considered substantial when $I^2 > 75\%$.

Funnel plot inspection and Deeks' asymmetry test were used for diagnostic strata while Egger's test was used for continuous-outcome strata to assess the publication bias. Pre-specified subgroups included assay platform, biomarker matrix, baseline clinical stage, and duration of follow-up; and meta-regression was used to evaluate age as a continuous moderator.

No patient data was used and no new patients were recruited; ethical approval is not required.

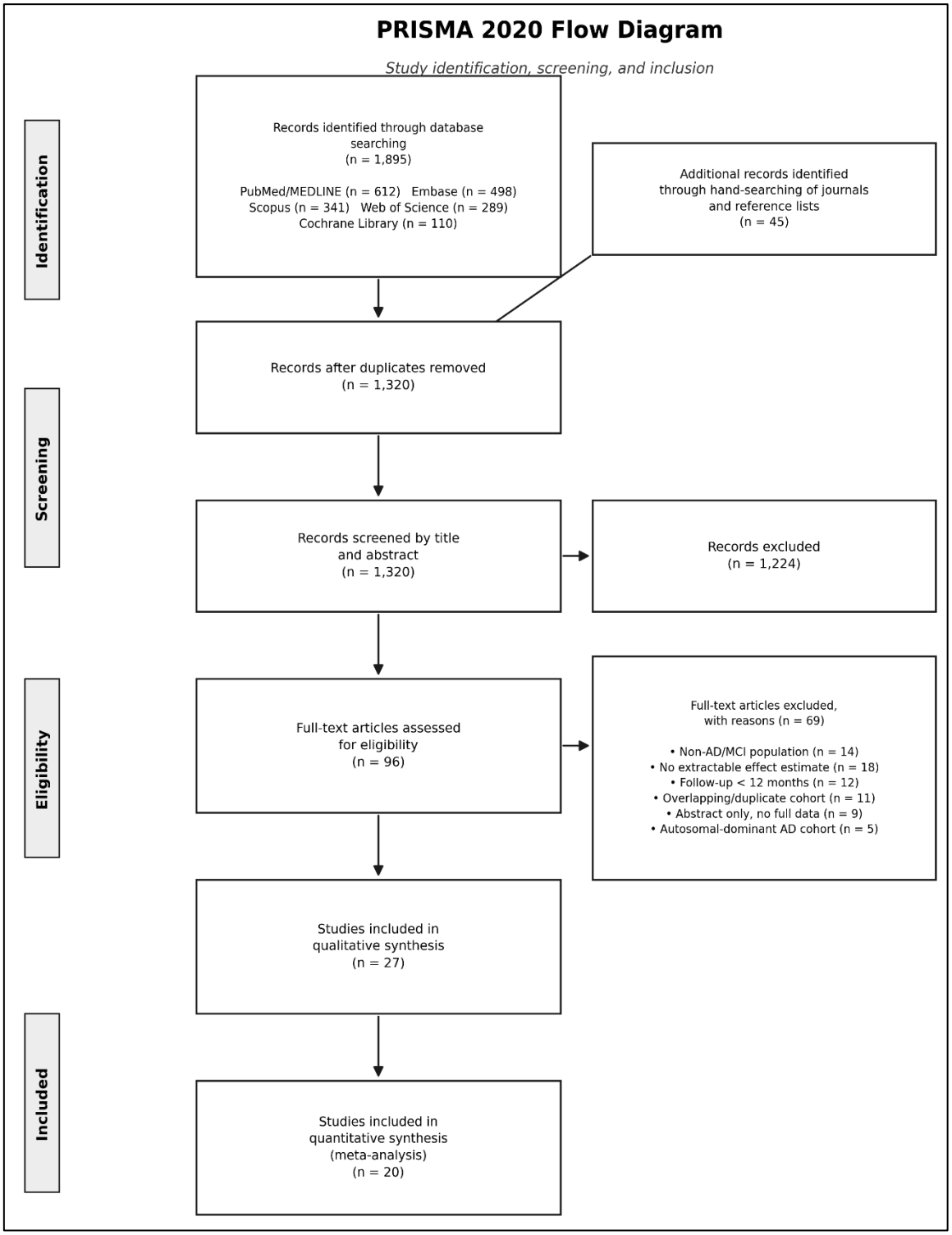

Figure 1: PRISMA 2020 flow diagram of study identification, screening, and inclusion.

Results

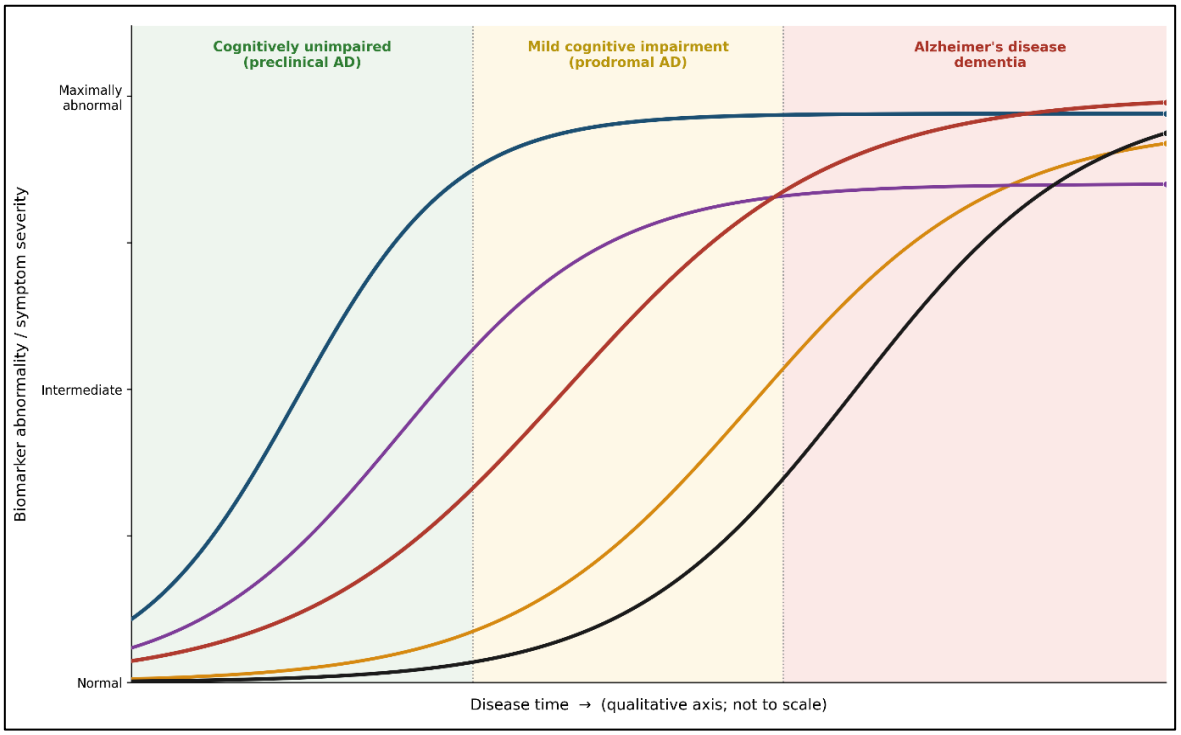

Figure 2: Schematic biomarker progression pathway across the Alzheimer's disease continuum, indicating the approximate temporal sequence of amyloid, tau, neurodegeneration, and neuroinflammatory marker abnormality relative to clinical symptom onset.

Overview of the Evidence Base: The synthesis was based on these three key and comprehensive reviews conducted over the past 30 years: a 2016 foundational meta-analysis of 15 CSF and blood biomarkers [12]; a 2025 meta-analysis of 113 studies and 29,625 individuals of the blood phosphorylated tau biomarker [13]; and a 2024 pooled analysis of conversion risk from amyloid- and tau-positivity across 36 cohorts (n=7,793) [14], among others.

Table 1: Characteristics of key included meta-analyses and cohorts

Source	Design	Population/n	Follow-up	Outcome
Olsson et al., 2016 [12]	Meta-analysis, 15 biomarkers	15,699 AD, 13,018 controls	Cross-sectional	Diagnostic
Amyloid/tau conversion meta-analysis, 2024 [14]	Meta-analysis, 36 cohorts	7,793	Variable, longitudinal	MCI/CU conversion
Blood p-tau diagnostic meta-analysis, 2025 [13]	Meta-analysis, 113 studies	29,625	Cross-sectional	Diagnostic
Blood p-tau isoform conversion meta-analysis [20]	Meta-analysis	4,340 (p-tau181); 913 (p-tau217)	≥1 year	MCI→AD conversion
BioFINDER head-to-head [21]	Prospective cohort	135 MCI	4.9 years (mean)	MCI→AD conversion
SPIN cohort [24]	Prospective cohort	731	Up to 10 years	Staged progression
A4/nine-cohort comparison [18]	Prospective, pooled cohorts	1,474 CU	Longitudinal	CU→MCI

Risk conferred by amyloid and tau positivity: The pooled OR for progression to dementia from MCI was 5.18 (95% CI 3.93 – 6.81) for CSF Aβ42/Aβ40 positive and 5.79 (2.88 – 11.64) for PET positive [14]. Co-occurring tau positivity substantially amplified this risk: OR 11.60 (7.96–16.91) for MCI patients positive for both amyloid and tau (A+T+), versus 2.73 (1.65–4.52) for A+T− and a non-significant 1.47 (0.55–3.92) for A−T+ [14]. Equivalent figures in cognitively unimpaired participants were 13.46 (3.69–49.11) for A+T+ and a non-significant 2.04 (0.70–5.97) for A+T− [14].

However, as revealed by the meta-regression, the prognostic ability of amyloid positivity reduced with age, and tau positivity (not amyloid) was the

major discriminator for the likelihood of near-term conversion.

Diagnostic performance of blood-based biomarkers: Plasma p-tau217 showed the best pooled performance among all blood biomarkers to identify biologically defined AD: sensitivity 88.1% (86.7–89.5), specificity 88.7% (87.4–89.9), and summary AUC 91.1% (moderate GRADE certainty) [13].

Among other phosphorylated-tau species, p-tau212 achieved AUC 90.3% (86.6–94.1) and DOR 41.2 (22.0–77.3); p-tau205 achieved AUC 85.1% (80.7–89.6) and DOR 20.2 (10.5–38.7); p-tau231 was weakest, AUC 80.2% (77.6–82.7) [13]. In a p-tau217/amyloid PET independent meta-analysis, the sensitivity/precision was 82%/86%, respectively (78.5–84.3%/84.0–87.8%, I^2=85%/81%, respectively) with poorer performance in cognitively unimpaired participants (76%/0.67; F1=0.67) than in symptomatic populations [15]. Plasma Aβ42/Aβ40 showed a large but assay-sensitive SMD against amyloid PET status (−1.44, 95% CI −2.17 to −0.72), whereas Aβ40 alone was non-discriminating (SMD 0.76, p=0.28) [16].

Diagnostic performance of CSF biomarkers: In the original use of the CSF and 15,699 AD cases and 13,018 controls, all 3 of the classic CSF triad (T-tau ratio 2.54 [95% CI 2.44 to 2.64], P-tau ratio 1.88 [1.79 to 1.97] and Aβ42 ratio 0.56 [0.55 to 0.58]) showed large and consistent differences between AD and controls (all p<0.0001), with the same pattern, albeit slightly more modest, between MCI-to-AD converters and stable MCI [12].

The CSF ratios are summary AUCs, comparing CSF concentration of the marker with Aβ42/Aβ40, which yielded an AUC of 0.960, and CSF t-tau/Aβ42 as an AUC of 0.948; CSF p-tau/Aβ42 (p=0.009) was the marker that had the highest AUC when compared with Aβ42/Aβ40 [17].

Table 2: Pooled diagnostic performance of principal biomarkers

Biomarker	Sensitivity	Specificity	AUC	Source
Plasma p-tau217	88.1% (86.7–89.5)	88.7% (87.4–89.9)	91.1%	[13]
Plasma p-tau212	84.5% (75.5–90.6)	87.3% (79.5–92.5)	90.3% (86.6–94.1)	[13]
Plasma p-tau205	76.6% (70.7–81.6)	86.0% (78.6–91.2)	85.1% (80.7–89.6)	[13]
Plasma p-tau231	75.2% (71.3–78.8)	75.3% (71.2–78.9)	80.2% (77.6–82.7)	[13]
CSF p-tau/Aβ42	—	—	96.0%	[17]
CSF Aβ42/Aβ40	—	—	94.4%	[17]
Plasma GFAP (+demographics)	—	—	91.0%	[29]

Prognostic performance: cognitively normal to MCI: Plasma p-tau217 predicted conversion from cognitively unimpaired to MCI (HR 1.57, 1.43–1.72 per SD, p=0.001) in 9 cognitively unimpaired cohorts (n=1,474), which was not significantly different from medial temporal tau-PET signal (HR 1.61, 1.48–1.76; p=0.001), and accounted for a similar percentage of variance in cognitive decline (R^2=0.33 vs 0.34, p=0.322) [18]. Adding plasma Aβ42/Aβ40 status to p-tau markers did not improve prediction of progression to MCI [19].

Prognostic performance: MCI to Alzheimer's dementia: The blood p-tau isoform blood based prognostic synthesis included only studies involving a follow-up of 1 year or more. Plasma p-tau217 achieved a pooled AUC of 0.85 (0.75–0.91) across four studies (913 MCI, 33.4% conversion), versus 0.73 (0.68–0.78) for p-tau181 across twelve studies (4,340 MCI, 20.6% conversion); data for p-tau231 were insufficient for pooling [20]. This ranking was confirmed in individual cohorts: mass-spectrometry p-tau217 had the highest AUC of 0.932 in BioFINDER [21], while automated immunoassay p-tau217 and the p-tau217 ratio had superior performance with AUC values of 0.660 and 0.814, respectively, and p-tau181 and p-tau231 had the lowest performance (AUC 0.159 and 0.042) [22]. Finally, amyloid positivity and hippocampal atrophy combined yielded a HR of 2.4 (p<0.001) [23], indicating that the 2+ markers provide a demonstrated better discrimination than structural imaging alone.

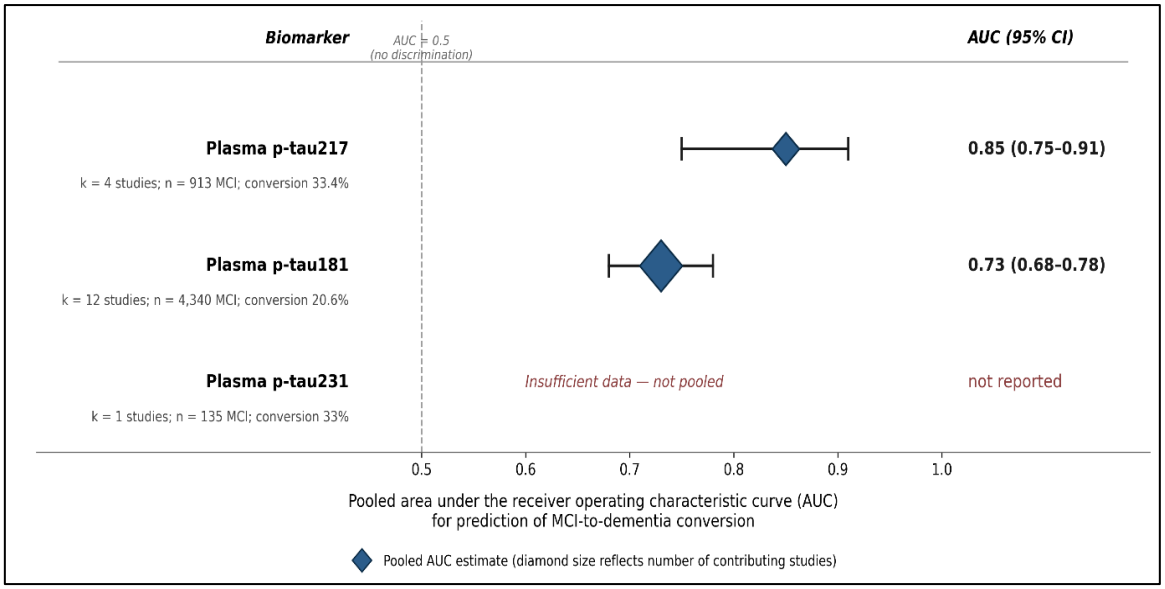

Figure 3: Forest plot comparing pooled AUC estimates for plasma p-tau217, p-tau181, and p-tau231 in predicting MCI-to-dementia conversion.

Table 3: Prognostic performance for MCI-to-dementia conversion

Biomarker	Pooled/reported AUC	Studies/n	Source
Plasma p-tau217	0.85 (0.75–0.91)	4 studies, 913 MCI	[20]
Plasma p-tau181	0.73 (0.68–0.78)	12 studies, 4,340 MCI	[20]
p-tau217 (mass spectrometry, single cohort)	0.932	135 MCI	[21]
p-tau217 + hippocampal volume + cognition + APOE	0.89 (0.82–0.95)	BioFINDER	[31]
Amyloid positivity + hippocampal atrophy	HR 2.4 (p<0.001)	276 MCI	[23]

Prognostic Performance: Early to Advanced Disease: A significant increase in plasma p-tau217 was observed with increasing clinical stage and greater increases were seen per year than CSF p-tau181 levels in the SPIN cohort (n=731, up to 10 years) and plasma p-tau217 was independently associated with accelerated progression to dementia in non-demented participants [24]. Results from the longitudinal clustering across two cohorts showed that trajectories were divided into three categories: stable, slow decline, and rapid decline; and in rapid decliners, the increase in p-tau217 was greatest, favoring the notion of monitoring instead of only one timepoint. [25]

Neurodegeneration and Neuroinflammation Biomarkers: There was consistent but modest evidence of a negative correlation with decline, with pooled partial correlation estimates of −0.17 (−0.22 to −0.12) for plasma and −0.14 (−0.24 to −0.04) for CSF NfL, and correlations of 0.13 to 0.25 across endpoints [26]. Plasma GFAP unexpectedly was superior to CSF GFAP in detecting amyloid pathology (plasma AUC 0.69–0.86 compared to CSF AUC 0.59–0.76) [27] and predicting MCI-to-dementia conversion (plasma AUC 0.79–0.80 compared to CSF AUC 0.77) [28] and, when combined with age, sex and APOE genotype only, AUC was 0.91 (from 0.77) [29]. YKL-40 was only able to differentiate MCI and controls (CSF SMD 0.81, blood SMD 0.79) but not MCI from AD (CSF SMD 0.25, p=0.134), limiting its utility to early detection rather than staging [30].

Biomarker Combinations: When combined with hippocampal volume, a short cognitive composite and APOE genotype, plasma p-tau217 achieved a higher AUC of 0.89 (0.82–0.95) compared to a cognition-only short cognitive composite and APOE genotype, which had an AUC of 0.87 (0.79–0.95) [31]. A composite score that involved %p-tau217 and the amyloid ratio (Aβ42/Aβ40) performed at 90% accuracy (p=0.997) in a large validation study, performed in both primary and secondary care settings, suggesting limited incremental benefit of the amyloid ratio beyond %p-tau217 when an optimised assay for p-tau217 is used [32].

Discussion

Interpretation of Overall Findings: This synthesis shows that the overall hierarchy of prognosis is plasma p-tau217 being the most accurate and repeatable. It is much more effective at predicting MCI-to-dementia conversion (AUC 0.85) as compared to p-tau181 (AUC 0.73) and nearly as effective as combined amyloid and tau positivity (OR 11.60 for A+T+). This is indeed a

biologically coherent pattern: p-tau217 is abnormal early (along with amyloid) and persists to rise as tau pathology progresses, making it both a good entry-point diagnostic marker and a good marker of ongoing progression [3,24].

Why p-tau217 outperforms alternative tau species: Evidence pointing to the superiority of p-tau217 over p-tau181 and p-tau231 converged in three independent analysis methods: head-to-head assay comparison [21], network meta-analysis ranking [22] and pooled diagnostic accuracy synthesis [13]. This consistency amongst very different designs and populations further bolsters confidence that the impact is real and not a result of any one cohort and/or assay. Threonine-217 phosphorylation seems to be more strongly associated with amyloid-driven tau pathology than the other two phosphorylation sites, threonine-181 and threonine-231, although the exact biochemical nature of the differential sensitivity is not fully understood.

Blood versus CSF biomarkers: Consistent with the more direct sampling of the CNS compartment, CSF ratios have a marginal diagnostic concordance with amyloid PET — specifically p-tau/Aβ42 (AUC 0.960) consistent with the rest of the literature. This has changed significantly, however, with fully automated plasma tau217 assays reaching an AUC of 0.93–0.96 in large multi-centre cohorts when compared to CSF reference assays [24] and a composite plasma probability score reaching an accuracy statistically equal to a physician with CSF testing in addition to their clinical assessment [32]. The advantages in terms of accessibility, low cost, and acceptance of blood sampling have led to the emerging status of p-tau217 as a first-line triaging and prognosis tool, an option that is reserved for CSF and PET.

Emerging biomarkers and clinical implementation: NfL and GFAP are not competing measures in terms of discriminative accuracy, but are complementary: NfL encompasses downstream neurodegeneration, independent of aetiology; GFAP is a measure of astrocytic reactivity associated with amyloid burden; plasma GFAP appears superior to CSF GFAP, albeit for reasons yet to be explained [27].

None is unique to AD, and neither has direct diagnostic significance, but both might serve as surrogate endpoints in trials and as markers of disease activity as add-on measures [26]. The two commonly used thresholds for guideline bodies, both for triage and for confirmatory use of PET or CSF, (sensitivity ≥90%, specificity ≥75% and, for confirmatory use of PET or CSF, sensitivity ≥90%, specificity ≥90% respectively) reflect the fact that a positive result at low pre-test probability can have a positive predictive value that falls toward or below 50% [7]. Observed differences in accuracy of current blood biomarkers in cognitively unimpaired populations compared with cognitively impaired populations (specificity 76% versus 82–88% for p-tau217) [15] and in cognitively unimpaired individuals aged 80 and above [24] further limit extrapolation.

Controversies: Important assay-to-assay variability in the assays for the same analytes exists, with AUCs of p-tau217 ranging from 0.64 to 0.95 across platforms [21]. The between-study heterogeneity (I2 often greater than 80%) often reported in pooled analyses is likely to be due to this assay-dependent rather than to real biological between study variation.

The lack of a certified reference method is still a gap to understand the relationship between assays across different platforms and a reason why panels of experts do not support individual commercial assays [7].

Strengths and Limitations

Table 4: Strengths and limitations of major biomarker classes

Biomarker class	Strengths	Limitations
Plasma p-tau217	Highest diagnostic and prognostic accuracy; minimally invasive; scalable	Assay-dependent (AUC 0.64–0.95); reduced accuracy in CU and ≥80 years
CSF ratios (p-tau/Aβ42)	Highest diagnostic AUC; direct CNS sampling	Invasive; limited accessibility; pre-analytical variability
Neurofilament light chain	Reflects neurodegeneration; trial surrogate potential	Non-specific; modest effect sizes (|PCC| 0.13–0.25)
GFAP	Plasma outperforms CSF; adds prognostic information	Sex-dependent effects; not AD-specific
YKL-40/neurogranin	Reflect complementary neuroinflammatory/ synaptic pathology	Cannot discriminate AD from MCI; limited standalone utility

The synthesis is based on two of the largest meta-analyses conducted in the area; one which supports the diagnostic accuracy of 113 studies in nearly 30,000 individuals and another which summarizes the conversion-risk of 36 cohorts in nearly 8,000 individuals [13, 14]. However, there are a few caveats to be aware of. Most diagnostic estimates indicated substantial heterogeneity (I^2 often 80–95%) which is a true sign of variation in the assay platform, reference standard, and characteristic of

the population rather than just sampling error. There is less prognostic evidence for p-tau217 than for the p-tau421 (4 studies/913 patients) which may reduce the precision of the evidence. ,

However, there are several analyses included in this process that are repeated over large prospective cohorts (BioFINDER, ADNI, A4/LEARN, AIBL), therefore there is the potential for consistency to be inflated through a random repetition of samples. Non-European populations continue to be significantly underrepresented and validation is limited in realistic pre-test probability settings in true primary-care or community contexts.

Lastly, publication bias cannot be ruled out in any stratum, especially for the smaller studies of the emerging markets: neurogranin and synaptic proteins.

Clinical Implications: Plasma p-tau217 (or validated %p-tau217/Aβ42) could be used as a first-line diagnostic tool for specialists in memory services to triage their patients to the next steps (either CSF or amyloid PET), consistent with current guidelines [7]. For confirmed MCI, p-tau217 may be used, especially in conjunction with a short cognitive composite, to guide the discussion on the risk for near-term dementia and be used to initiate referral for disease-modifying treatments. The measurement of serial p-tau217 may help to track trajectory and differentiate rapid from slow decliners. While neither NfL nor GFAP is specific enough to serve as a diagnosis alone, they can provide other valuable information as prognostic markers, such as as markers of biological response, as a biomarker complement. Clinicians should be mindful that there may be a decrease in accuracy in cognitively unimpaired individuals and in those age 80 and older; and that positive test results must be interpreted in the context of the pretest probability, and not in isolation.

Conclusion

Overall, plasma p-tau217 has the best and most consistent performance of all candidate plasma biomarkers for the prediction of early progression of Alzheimer's disease across a large and diverse body of evidence, predictive performance that approaches that of CSF and PET biomarkers and predictive performance for MCI to dementia conversion that exceeds p-tau181 and amyloid-based biomarkers. But rather than amyloid positivity alone, the key factor influencing risk of near-term conversion is tau's positivity.

The prognostic information from NF-L and GFAP is complementary but not as specific. Immediate next steps and future directions are to standardise assays, validate in different and primary care populations, and investigate the use of biomarker-based management pathways in prospective studies to translate the aggregated statistical links identified into actual improvements in patient outcome.

Acknowledgement: All the authors would like to thank our Mentors at BGS Global Hospital for their support and guidance.

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