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The Role of Blood Biomarker p-tau217 in the Early Detection of Alzheimer's Disease: A Systematic Review

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Abstract: *This systematic review sought to assess the function of the blood biomarker phosphorylated tau 217 (p-tau217) in the early identification of Alzheimer's disease. A systematic review was carried out adhering to the PRISMA 2020 protocols. Literature searches were executed in PubMed, ScienceDirect, and Scopus to locate original studies published between 2023 and 2026. Eligible studies assessed blood p-tau217 in individuals with mild cognitive impairment, suspected Alzheimer's disease, Alzheimer's disease, or at-risk populations and reported diagnostic performance or correlations with established Alzheimer's biomarkers. Study quality was evaluated utilizing QUADAS-2 for diagnostic accuracy studies and the Study Quality Assessment Tools for observational and longitudinal studies. A total of 328 records were retrieved, of which 18 studies met the inclusion criteria. Research consistently demonstrates that plasma p-tau217 serves as a highly accurate biomarker for identifying the biological pathology of Alzheimer's disease, specifically regarding amyloid and tau status. Numerous studies have reported impressive area under the curve (AUC) scores between 0.92 and 0.97. When p-tau217 is paired with Aβ42 or the Aβ42/40 ratio, its diagnostic precision improves significantly, particularly in patients who are cognitively normal or in the preclinical stages of the disease.*

Keywords: *Alzheimer's Disease; P-Tau217; Blood Biomarker; Early Detection; Systematic Review*

Introduction

Dementia is still one of the global health problems that continues to increase as the elderly population grows. According to the World Health Organization, the number of individuals affected by dementia reached approximately 57 million in 2021, with an incidence rate of nearly 10 million new cases annually. Among these, Alzheimer's disease stands as the leading cause of dementia, accounting for an estimated 60–70% of the total cases reported. This condition not only causes a decline in cognitive function, but also has an impact on patient independence, quality of life, family burden, and long-term health care needs (Organization, 2025).

The problem of dementia is also an important issue in Indonesia. The increase in life expectancy and the increasing number of elderly populations make the risk of neurodegenerative diseases, including Alzheimer's disease warrants growing attention, as some projections indicate that roughly 1.2 million individuals in Indonesia currently suffer from dementia a figure poised to quadruple by 2050. Such trends highlight the critical necessity for early Alzheimer's detection, which is vital to minimize diagnostic delays and

enhance therapeutic strategy development starting from the disease's nascent phase (Marsigit, 2025).

Alzheimer's disease is a neurodegenerative condition fundamentally characterized by a steady decline in memory, cognitive function, and the capacity to carry out daily tasks. This progression is driven by the buildup of beta-amyloid plaques and pathological tau proteins within the brain. While the gold standard for confirming a diagnosis typically involves either cerebrospinal fluid testing or amyloid PET imaging, these methods are not always practical for routine use. Their widespread implementation is hindered by several significant barriers, including the high financial burden, limited availability, the risks associated with radiation from PET scans, and the invasive nature of lumbar punctures required for cerebrospinal fluid collection. Consequently, these challenges make routine Alzheimer's screening difficult to implement on a broad scale, particularly in healthcare settings that operate with limited resources (Administration, 2025; Palmqvist et al., 2024).

In recent years, blood biomarkers have begun to gain attention as a simpler, minimally invasive, and potentially more accessible method to support the detection of Alzheimer's disease. One of the most researched biomarkers is phosphorylated plasma tau 217 or p-tau217. This biomarker is considered to have a strong relationship with Alzheimer's pathology, especially changes in amyloid and tau in the brain. Studies show that p-tau217 has high diagnostic accuracy in identifying Alzheimer's pathology, even in some studies showing performance close to cerebrospinal fluid and PET biomarkers (Ashton et al., 2024; Palmqvist et al., 2024).

The field of Alzheimer's diagnostics has seen a surge in interest regarding p-tau217, coinciding with significant breakthroughs in blood-based biomarker technology. A pivotal development occurred in 2025, when the U.S. Food and Drug Administration (FDA) granted authorization for the clinical use of the *Lumipulse G pTau217/β-Amyloid 1-42* plasma ratio assay. This diagnostic tool is intended for use in adults exhibiting symptoms of cognitive decline, marking a major shift toward more accessible testing. This regulatory approval highlights the growing recognition of p-tau217 as a vital, minimally invasive tool for facilitating the earlier identification and clinical diagnosis of Alzheimer's disease. The test is considered to help detect amyloid pathology by a method that is easier than PET or lumbar puncture, although it is not intended as a general population screening or a single examination without other clinical evaluation (Administration, 2025).

Although plasma p-tau217 shows great potential, results between studies may still vary due to differences in study design, population characteristics, disease stage, type of assay used, cut-off values, as well as comparative standards such as PET, cerebrospinal fluid, or clinical diagnosis. A recent systematic review and meta-analysis found that plasma p-tau217 achieved a pooled sensitivity of 88.1%, specificity of 88.7%, and an AUROC of 91.1% for detecting Alzheimer's disease, while highlighting the need for prospective real-world validation studies (Therriault et al., 2025).

In light of these developments, this research is crucial for providing a systematic review of p-tau217 as a blood-derived marker for the initial detection of this

neurodegenerative condition. The study aims to appraise existing evidence regarding the efficacy of this biomarker in identifying early-stage decline, particularly among individuals presenting with cognitive symptoms. By doing so, this review seeks to clarify the potential of p-tau217 as a highly accessible diagnostic tool while identifying critical knowledge gaps that warrant further scientific inquiry.

Methodology

This systematic literature review followed the PRISMA 2020 guidelines to evaluate the role of the blood-based biomarker phosphorylated tau 217 (p-tau217) in the early detection of Alzheimer's disease. A systematic literature search was performed across the PubMed, ScienceDirect, and Scopus databases to identify articles published between 2023 and 2026. This process utilized a targeted combination of keywords encompassing Alzheimer's disease, p-tau217, blood biomarkers, early detection, and diagnostic accuracy. The search conducted on May 3, 2026 resulted in 328 articles, which were then selected through a process of duplication, title and abstract screening, and complete text review until 18 articles were obtained that met the inclusion criteria and were worthy of analysis.

Inclusion criteria included original research articles that examined blood biomarkers of p-tau217 in individuals with mild cognitive impairment, suspected Alzheimer's, Alzheimer's disease, or at-risk populations, as well as reporting diagnostic parameters such as sensitivity, specificity, AUC, accuracy, predictive values, or association of p-tau217 with standard Alzheimer's biomarkers. Studies using comparative standards such as amyloid-PET, tau-PET, cerebrospinal fluid biomarkers, clinical diagnosis of Alzheimer's, or neuropathological examinations were also included. On the other hand, review articles, editorials, case reports, conference abstracts, articles without p-tau217 diagnostic data, or articles that do not clearly explain methods and outputs are excluded from the study.

Article quality assessment was carried out using the QUADAS-2 instrument for diagnostic accuracy studies and Study Quality Assessment Tools for observational and longitudinal studies. Articles are then classified into good, medium, or poor quality categories, with only good and medium quality articles included in the final synthesis. The extracted data included the characteristics of the study, the p-tau217 examination method, the comparative standard, and the main diagnostic results. Furthermore, the data underwent narrative synthesis to assess the effectiveness of p-tau217 in identifying early-stage Alzheimer’s, differentiating it from other cognitive conditions, and determining its correlation with amyloid and tau biomarkers. A meta-analysis was not conducted because of the inherent variability in study designs, participant populations, diagnostic methodologies, threshold values, and reference standards employed.

Result and Discussion

Scientific Article Selection

The results of the literature search yielded 328 articles from three databases, namely PubMed as many as 29 articles, ScienceDirect as many as 52 articles, and Scopus as many as

247 articles. After the elimination of duplication of 62 articles, there are 266 articles left which continue to the title and abstract screening stage.

At the title and abstract screening stage, as many as 218 articles were excluded because they were not in accordance with the focus of the research, such as review articles, conference proceedings, not p-tau217 biomarkers, not Alzheimer's population, or did not discuss early detection or diagnostic accuracy. A total of 48 articles were then continued to the full text assessment stage.

After a full text review, as many as 30 articles were excluded for the following reasons: review, meta-analysis, conference, or protocol as many as 8 articles; biomarkers that are not suitable or not p-tau217 as many as 9 articles; population or research focus is not suitable for as many as 5 articles; did not report external diagnostics in 5 articles; and full text is inappropriate or incomplete as many as 3 articles. In the final stage, 18 articles that met the inclusion criteria were obtained and analyzed in this systematic literature review. The article selection process is shown in Figure 1.

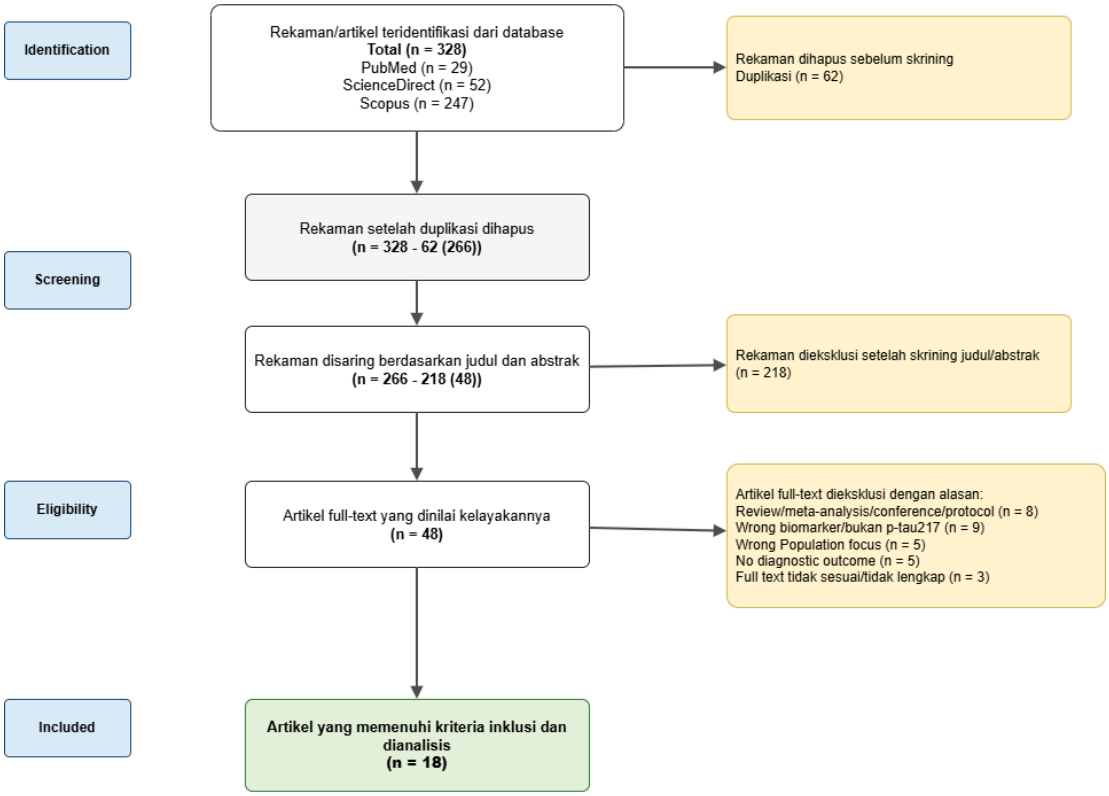

Figure 1. Article Selection PRISMA Flowchart

Table 1. Characteristics of the research analyzed

Yes	Researcher (Year)	Study design	Population/setting	Number of samples	Key biomarkers	Benchmark standards	Research focus
1	(Ashton et al., 2024)	Observational cohort	TRIAD, WRAP, and SPIN; subjects with and without	786	Plasma p-tau217	Aβ-PET, tau-PET, CSF	Accuracy of p-tau217 for detecting Aβ and tau

			cognitive impairment				Alzheimer's pathologies
2	(Wang, Huang, et al., 2025)	Clinical cohort and community	Clinical and community cohorts	234	Plasma p-tau217/Aβ42	Aβ-PET / clinical biomarker	Accuracy of the p-tau217/Aβ42 ratio for Alzheimer's diagnosis
3	(Kang et al., 2025)	Cohort retrospective	K-ROAD cohort; CU and CI	2.497	Plasma p-tau217, Aβ42/40, GFAP, NfL	Aβ-PET	Combined performance of p-tau217 and Aβ42/40 in clinical subgroups
4	Daniliidou et al. (2025)	Clinical cohort	Memory clinic	113	Blood biomarkers, including p-tau217	Clinical diagnosis / CSF	Effect of comorbidities on diagnostic precision of blood biomarkers
5	(Martínez-Dubarbie et al., 2025)	Cross-sectional	Memory clinic and healthy control	493	Plasma p-tau217, NfL	CSF biomarker	Diagnostic performance of p-tau217 using the Lumipulse platform
6	(Chang et al., 2025)	Cross-sectional	AD, non-AD, and cognitively unimpaired	371	pTau217, pTau181, GFAP, NfL, Aβ42/40, total tau	Amyloid PET	Plasma biomarker panel and machine learning for amyloid positivity identification
7	(Wang, Fan, et al., 2025)	Diagnostic cohort	Two independent cohorts	463	Aβ42/40, p-tau217, p-tau181, GFAP, NfL	PET or CSF	Blood biomarker performance of the internal jugular vein and median cubital vein
8	(Um et al., 2025)	Cross-sectional	Clinical cohort with Alzheimer's	262	Plasma p-tau217/Aβ42 ratio	Amyloid PET and neuroimaging	Automated assay performance of p-tau217/Aβ42

							and neuroimaging correlation
9	(Martínez-Dubarbie et al., 2024)	Longitudinal	Cognitively unimpaired healthy volunteers	209	Plasma p-tau217	ATN/amyloid and tau status	Longitudinal trajectory of p-tau217 in subjects without cognitive impairment
10	(Sim et al., 2025)	Community cohort	Dementia-free older adults	147	Plasma pTau-217, pTau-181, GFAP, NfL, Aβ42/40	CSF biomarkers and MRI	Correlation of p-tau217 with brain atrophy, cognition, and CSF
11	(Matsuura et al., 2026)	Diagnostic studies	AD, control, and non-AD	113	Plasma p-tau217 on three assays	Amyloid PET and tau PET	Comparison of three p-tau217 assays for detecting Alzheimer's pathology
12	(Rissman, Donohue, et al., 2024)	Diagnostic studies	Preclinical Alzheimer's disease	75	Plasma Aβ42/Aβ40 and p-tau217	Amyloid PET	Accuracy of plasma biomarker ratios for PET amyloid classification in preclinical Alzheimer's
13	(Niimi et al., 2024)	Cross-sectional	J-TRC and BioFINDER; Non-demented elderly	474 + 177	Plasma Aβ42/40 and p-tau217	Aβ-PET	Combination of Aβ and p-tau217 to detect brain amyloid
14	(Janelidze et al., 2024)	Longitudinal	CUs of BioFINDER-2, Knight ADRC, and BioFINDER-1	495 + 283 + 205	P-tau217 and Aβ42/40 plasma	Aβ-PET and CSF Aβ42/40	Prediction of early Aβ accumulation in people without cognitive impairment
15	(Aguillon et al., 2023)	Longitudinal	Autosomal dominant Alzheimer's disease; PSEN1 E280A	44	Plasma p-tau217	Amyloid PET, PET weather, cognition	Prediction of brain pathology and cognitive

							function in ADAD
16	(Salvadó et al., 2025)	Cross-sectional cohort	12 international cohorts; cognitively unimpaired	2.916	Plasma p-tau217	Aβ-PET or CSF	Preclinical Alzheimer's identification using p-tau217
17	(Vanderlip et al., 2026)	Trial data analysis	A4 Study; cognitively unimpaired amyloid-positive older adults	1.169	Plasma pTau217 + digital memory assessment	PACC, amyloid PET, tau PET	Enrichment strategies for preclinical Alzheimer's trials
18	(Rissman, Langford, et al., 2024)	Longitudinal	A4 and LEARN; high-risk asymptomatic individuals	345	Plasma p-tau217 ECL immunoassay	Amyloid PET	Prediction of amyloid PET positivity in asymptomatic individuals

Table 2. Key statistical results of research related to p-tau217 in early detection of Alzheimer's

Yes	Researcher (Year)	Key statistical results	Interpretation
1	(Ashton et al., 2024)	AUC for Aβ: 0.92–0.96; AUC for tau: 0.93–0.97. Plasma p-tau217 shows accuracy comparable to CSF biomarkers.	P-tau217 plasma has high accuracy for detecting Alzheimer's biological pathologies.
2	Wang et al. (2025)	The p-tau217/Aβ42 ratio showed diagnostic performance in both the clinical cohort and the community.	The p-tau217/Aβ42 ratio has the potential to improve the biological detection of Alzheimer's.
3	Kang et al. (2025)	In CU, the combination of p-tau217 and Aβ42/40 increased AUC compared to p-tau217 alone; in CI, the AUC increase is more limited.	The combination of p-tau217 and Aβ42/40 is more beneficial in the early stages or cognitively unimpaired.
4	Daniliidou et al. (2025)	Comorbidity can affect the interpretation of blood biomarkers, but p-tau217 remains a major discriminating biomarker.	Clinical factors and comorbidities need to be considered when using p-tau217.
5	Martínez-Dubarbie et al. (2025)	P-tau217 plasma has an AUC of 0.95 to distinguish subjects A+ and A-; p-tau217/Aβ42 has an AUC of 0.97.	P-tau217 performs very well in memory clinic settings.
6	Chang et al. (2025)	The plasma biomarker panel achieves an accuracy of >92%; pTau217 itself achieved >90% accuracy and became the highest biomarker in the model.	pTau217 may be a cost-effective single biomarker for amyloid positivity screening.
7	Wang et al. (2025)	Biomarkers of the internal jugular vein and median cubital vein were compared; IJV-Ab42/40 shows performance equivalent to p-tau217 and p-tau217/Aβ42.	The location of blood collection can affect the performance of biomarkers, especially Aβ42/40.

8	Um et al. (2025)	The automated p-tau217/Aβ42 assay demonstrated high biomarker performance against Alzheimer's neuroimaging.	The p-tau217/Aβ42 ratio has the potential to be used as an automated plasma test in clinical practice.
9	Martínez-Dubarbie et al. (2024)	A+ and T+ are associated with faster p-tau217 enhancement; APOE ε4 affects baseline and rate of p-tau217 change in healthy groups.	Plasma p-tau217 can be a dynamic marker in the preclinical stage.
10	Sim et al. (2025)	Plasma pTau-217 correlated with lower cognitive scores, lower cortical thickness, and pTau-217 CSF; plasma-CSF correlation pTau-217 R = 0.76.	p-tau217 may reflect early biological changes even though subjects are still cognitively healthy.
11	Matsura et al. (2026)	Three p-tau217 assays can distinguish amyloid-positive and negative with high accuracy; Lumipulse has a strong correlation with tau.	The difference in assay platforms needs to be noted in the interpretation of p-tau217 results.
12	Rissman et al. (2023)	The combination of Aβ42/Aβ40 and phospho-tau217 improved the classification of amyloid PET in preclinical AD.	The combination of plasma biomarkers may improve the efficiency of preclinical Alzheimer's screening trials.
13	Niimi et al. (2024)	J-TRC: AUC was highest at 0.936 in the p-tau217/Aβ42 + APOE + age + sex model; CDR 0: AUC 0.948; CDR 0.5: AUC 0.955.	The combination of p-tau217 with Aβ and clinical factors improves the detection of abnormal Aβ-PET.
14	Janelidze et al. (2024)	The combination of %p-tau217 and Aβ42/40 had an AUC of 0.949 for detecting abnormal CSF Aβ-status and was associated with a longitudinal increase in Aβ-PET.	The combination of p-tau217 and Aβ42/40 is useful for predicting the initial accumulation of Aβ.
15	Aguillon et al. (2023)	Baseline p-tau217 relates to amyloid PET, tau PET, and subsequent memory functions.	p-tau217 has diagnostic as well as prognostic value in familial Alzheimer's.
16	Salvadó et al. (2025)	p-tau217 has good accuracy for predicting Aβ positivity; PPV and accuracy are improved when combined with PET or CSF on a two-stage approach.	p-tau217 may be the initial test for preclinical Alzheimer's identification.
17	Vanderlip et al. (2026)	The combination of high pTau217 and low DMA showed the greatest cognitive decline; The need for trial samples decreased from 3,252 to 818 per group.	pTau217 may help select preclinical trial participants who are at risk of progression.
18	Rissman et al. (2024)	Plasma p-tau217 ECL immunoassay showed AUROC 0.87 for amyloid PET ≥20 CL and 0.89 for ≥33 CL.	Plasma p-tau217 is accurate for detecting amyloid PET positivity in asymptomatic individuals.

Table 3. Synthesis of the role of blood biomarker p-tau217 in the early detection of Alzheimer's disease

Yes	Categories of findings	Supporting articles	Direction of results	Conclusion
1	Single p-tau217 diagnostic accuracy	Ashton et al.; Martínez-Dubarbie et al.; Salvadó et al.	p-tau217 indicates a high AUC for detecting Aβ or tau pathology.	p-tau217 is effective as a major blood biomarker for the biological detection of Alzheimer's.

2	Preclinical Alzheimer's detection	Salvadó et al.; Janelidze et al.; Rissman et al.; Vanderlip et al.	p-tau217 can identify the risk of Aβ positivity in individuals without cognitive impairment.	p-tau217 is relevant for early detection before the onset of clinical dementia.
3	Combination of p-tau217 with Aβ42/40	Kang et al.; Niimi et al.; Janelidze et al.; Rissman et al.	The combination of p-tau217 and Aβ42/40 improved accuracy, especially in CU/preclinical.	The combination of biomarkers may strengthen early Alzheimer's screening.
4	Relationship with PET and CSF	Ashton et al.; Aguillon et al.; Sim et al.; Wang et al.	p-tau217 correlates with amyloid PET, tau PET, and CSF biomarkers.	p-tau217 reflects the biological pathology of Alzheimer's in the brain.
5	Prognostic value	Aguillon et al.; Vanderlip et al.; Martínez-Dubarbie et al.	p-tau217 is associated with biomarker progression, cognition, and risk of cognitive function decline.	P-tau217 is not only diagnostic, but it can also help predict progression.
6	Assay variations and clinical implementation	Matsura et al.; Martínez-Dubarbie et al.; Um et al.	The performance of p-tau217 was influenced by the assay platform, cut-off, and interpretation approach.	Standardization of assays and cut-offs is required before widespread application.
7	Clinical factors and comorbidities	Daniliidou et al.; Chang et al.; Wang et al.	Factors of age, APOE, BMI, kidney function, and sampling location may affect the interpretation of biomarkers.	The interpretation of p-tau217 should take into account the clinical characteristics of the patient.

Table 4. Quality assessment of the analyzed articles

Yes	Researcher (Year)	Assessment instruments	Quality	Reasons for assessment
1	Ashton et al. (2024)	QUADAS-2	Good	The population was clear, using multiple cohorts, *the* p-tau217 index test was described, the PET/CSF benchmark was clear, and the diagnostic results were reported to be complete.
2	Wang et al. (2025)	QUADAS-2	Good	Assess the p-tau217/Aβ42 ratio in clinical and community cohorts, have biological comparator standards, and report diagnostic performance clearly.
3	Kang et al. (2025)	QUADAS-2	Good	Large sample counts, using Aβ-PET as a comparator, and performing subgroup analysis and validation on different cohorts.
4	Daniilidou et al. (2025)	NHLBI	Medium	The purpose of the study was clear and assessed the influence of comorbidities, but the interpretation of biomarkers could be influenced by the heterogeneity of the patient's clinical condition.
5	Martínez-Dubarbie et al. (2025)	QUADAS-2	Good	Using a memory clinic cohort, the Lumipulse examination method is clear, CSF benchmarking standards are available, and AUC results are reported to be complete.
6	Chang et al. (2025)	QUADAS-2	Medium	It uses amyloid PET as a comparator and a complete biomarker panel, but *the cross-sectional* design and

				machine learning approach require further external validation.
7	Wang et al. (2025)	QUADAS-2	Good	Using two cohorts, comparing blood biomarkers from different vein locations, and using PET or CSF as the benchmark.
8	Um et al. (2025)	QUADAS-2	Good	Assess *p-tau217/Aβ42 automated assay with PET amyloid comparator and neuroimaging, making it relevant for clinical applications.*
9	Martínez-Dubarbie et al. (2024)	NHLBI	Medium	The longitudinal design in cognitively healthy subjects did not focus directly on diagnostic accuracy against clinical Alzheimer's cases.
10	Sim et al. (2025)	NHLBI	Medium	Using a community cohort and assessing the relationship of pTau-217 plasma to CSF, cognition, and MRI, but the number of subjects with paired CSF data was more limited.
11	Matsuura et al. (2026)	QUADAS-2	Medium	Using PET as a benchmark standard and comparing three *assays*, but the sample size is relatively small so generalizations are still limited.
12	Rissman et al. (2023)	QUADAS-2	Good	Assessing the combination of Aβ42/Aβ40 and p-tau217 against the classification of amyloid PET in preclinical Alzheimer's with clear diagnostic performance reporting.
13	Niimi et al. (2024)	QUADAS-2	Good	Using two different cohorts, involving non-dementia populations, using Aβ-PET as a comparator, and reporting AUC in detail.
14	Janelidze et al. (2024)	NHLBI	Good	Longitudinal design with multiple cohorts, assessing predictions of initial Aβ accumulation, and using PET and CSF as biological comparators.
15	Aguillon et al. (2023)	NHLBI	Medium	Assess autosomal dominant Alzheimer's disease with PET biomarkers and cognition, but the population is very specific and the sample count is relatively small.
16	Salvadó et al. (2025)	QUADAS-2	Good	Large sample counts from 12 international cohorts, using PET or CSF as comparators, and assessing p-tau217 as a self-test and a two-stage approach.
17	Vanderlip et al. (2026)	NHLBI	Good	Using trial data with a large sample number and long follow-up, and assessing the combination of pTau217 and *digital memory assessment* on cognitive progression and biomarkers.
18	Rissman et al. (2024)	QUADAS-2	Good	Using A4 and LEARN data, p-tau217 was assessed against PET amyloid, and reported AUROC and stability of repeated assays.

Based on the results of the quality assessment, as many as 12 articles were categorized as having good quality and 6 articles were of medium quality. No articles of poor quality were included in the final synthesis. Good quality articles generally have clear benchmarking standards such as *amyloid-PET*, *tau-PET*, or cerebrospinal fluid biomarkers, p-tau217 examination methods described, as well as complete reporting of diagnostic outputs. Medium-quality articles are still included because they are still relevant to the research objective, but have limitations such as smaller sample sizes, *cross-sectional* designs,

highly specific populations, or the need for further external validation. Some of the main articles support this assessment because they use PET/CSF as a benchmark and clearly report diagnostic performance such as AUC, PPV, accuracy, or biomarker correlation.

Research Characteristics

The articles analyzed primarily consist of original research assessing the utility of the p-tau217 blood biomarker in the context of Alzheimer's disease. These studies employ a diverse range of research designs, spanning longitudinal, cohort, and cross-sectional studies, as well as diagnostic investigations utilizing data from both clinical and community-based cohorts. The participant populations examined include cognitively unimpaired individuals, patients diagnosed with mild cognitive impairment or Alzheimer's disease, and subjects identified as being at preclinical risk for Alzheimer's.

Among the 18 studies included in this review, six (33.3%) were cohort-based studies, five (27.8%) were cross-sectional studies, four (22.2%) were longitudinal studies, two (11.1%) were diagnostic studies, and one (5.6%) was a trial data analysis. This distribution indicates that cohort-based and cross-sectional designs together accounted for more than 60% of the available evidence, while longitudinal and diagnostic studies provided additional evidence regarding disease progression and diagnostic performance.

Based on the study design distribution, the 18 included studies consisted of five cross-sectional studies, four longitudinal studies, six cohort-based studies, two diagnostic studies, and one trial data analysis. The cohort-based studies included observational cohort, clinical cohort, retrospective cohort, diagnostic cohort, and community cohort designs. The sample sizes varied widely, ranging from 44 to 2,916 participants. Most studies evaluated plasma p-tau217 using amyloid PET, tau PET, cerebrospinal fluid biomarkers, or clinical biomarker standards as comparators. This distribution indicates that the evidence included in this review was derived from heterogeneous study designs, with cross-sectional and cohort-based studies being the most commonly represented.

Most studies used plasma as the primary sample for p-tau217 examination. The most commonly used benchmarks are amyloid PET, tau PET, cerebrospinal fluid biomarkers, or a combination of clinical assessment and biological biomarkers. Some studies have also compared the performance of p-tau217 with other blood biomarkers, such as Aβ42/40, p-tau181, GFAP, NfL, and total tau.

The most commonly reported output parameters were area under the curve, sensitivity, specificity, positive predictive value, diagnostic accuracy, correlation with PET or CSF, and the ability of p-tau217 to predict biomarker progression and cognitive function. One study showed that plasma p-tau217 had high accuracy in identifying Aβ and tau pathologies, with an AUC for Aβ of 0.92–0.96 and an AUC for tau of 0.93–0.97.

The Role of p-tau217 in the Detection of Alzheimer's Pathology

The synthesis results indicate that plasma p-tau217 exhibits robust diagnostic capability in identifying Alzheimer's-related pathologies, particularly those involving amyloid and tau. Several studies demonstrated that p-tau217 has high diagnostic accuracy in distinguishing individuals with positive and negative amyloid or tau PET findings and

performs comparably to cerebrospinal fluid (CSF) biomarkers. Similarly, Ashton et al. reported that p-tau217 identified Aβ-PET abnormalities with an AUC of 0.92–0.96 and tau-PET abnormalities with an AUC of 0.93–0.97, highlighting its strong potential as a blood-based biomarker for Alzheimer's disease.

In the memory clinic population, p-tau217 also showed excellent performance. The Martínez-Dubarbie et al. study reported that p-tau217 plasma had an AUC of 0.95 in differentiating amyloid-positive and amyloid-negative subjects based on CSF biomarkers. The study also shows that the two-cut-off approach can reduce the need for confirmatory examinations such as lumbar puncture or PET.

The Role of p-tau217 in Early Detection and Preclinical Alzheimer's

Some of the articles analyzed assessed p-tau217 in populations without cognitive impairment or preclinical Alzheimer's populations. The results suggest that p-tau217 may help identify individuals at risk of amyloid pathology before the onset of clinical dementia. The study by Salvadó et al. involved 2,916 individuals without cognitive impairment from 12 international cohorts and showed that plasma p-tau217 can be used as a standalone test as well as part of a two-stage approach with PET or CSF to identify preclinical Alzheimer's.

The study by Rissman et al. also showed that p-tau217 plasma examination by the electrochemiluminescence method has a high diagnostic value in predicting amyloid PET positivity in asymptomatic individuals. The reported AUROC values were 0.87 for amyloid PET ≥20 centiloid and 0.89 for amyloid PET ≥33 centiloid.

Additional research indicates that pairing p-tau217 with the Aβ42/40 ratio can enhance the early identification of cerebral amyloid deposition. Specifically, Janelidze et al. observed that the combined use of plasma %p-tau217 and Aβ42/40 demonstrated strong efficacy in recognizing abnormal Aβ levels, achieving an AUC of 0.949 in one of their evaluations.

Combination of p-tau217 with Other Blood Biomarkers

Multiple investigations have demonstrated that pairing p-tau217 with additional blood biomarkers can enhance the efficacy of Alzheimer's pathology detection. The most frequent combination utilizes p-tau217 alongside Aβ42/40. Research by Niimi et al. found that integrating plasma Aβ and p-tau217 increased the identification of abnormal amyloid PET findings in non-demented elderly individuals. Predictive models incorporating p-tau217, Aβ42/Aβ40, APOE, age, and sex achieved high AUC values across preclinical and prodromal Alzheimer's cohorts. Similarly, Kang et al. reported that the dual use of p-tau217 and Aβ42/40 improved diagnostic precision for identifying Aβ-PET positivity in cognitively unimpaired subjects. Within this population, the combined approach yielded a superior AUC compared to utilizing p-tau217 in isolation.

Chang et al.'s study assessed a panel of plasma biomarkers with a machine learning approach. The results showed that pTau217 was the highest-ranked biomarker and single-handedly had an accuracy of more than 90% in identifying amyloid positivity, while the combined panel achieved an accuracy of more than 92%.

Relationship of p-tau217 with Cognitive Progression and Other Biomarkers

Some studies not only assessed the diagnostic ability of p-tau217, but also assessed its association with cognitive progression, biomarker changes, and changes in brain structure. The Vanderlip et al. study showed that the combination of digital memory assessment and plasma pTau217 could identify preclinical Alzheimer's individuals who are at higher risk of cognitive and biological progression. The group with high pTau217 and low memory performance showed faster cognitive decline as well as a greater increase in PET tau biomarkers.

Research by Aguillon et al. regarding autosomal dominant Alzheimer's disease demonstrated that plasma p-tau217 is linked to amyloid PET pathology, tau PET findings, and cognitive performance in later stages of life. These results reinforce the utility of p-tau217 as a minimally invasive biomarker, highlighting its value not only for diagnosis but also for prognosis.

Furthermore, a study by Sim et al. involving a cognitively healthy community cohort revealed that plasma pTau-217 concentrations were associated with reduced cognitive performance, decreased cortical thickness, and a robust correlation with CSF pTau-217 levels. These observations indicate that p-tau217 possesses the capability to identify biological alterations related to Alzheimer's during early phases, even prior to the onset of clinical dementia.

Clinical Implications and Research Limitations

The findings of this review indicate that the blood biomarker p-tau217 holds significant potential as an initial screening tool for the early detection of Alzheimer's disease, particularly for individuals experiencing mild cognitive complaints or those within at-risk populations. These tests can effectively assist in identifying patients who require subsequent diagnostic evaluations, such as amyloid or tau positron emission tomography (PET) or cerebrospinal fluid (CSF) biomarker analysis. The primary advantage of p-tau217 is its profile as a simpler, minimally invasive, and more reproducible alternative compared to PET scans or lumbar punctures.

The p-tau217 test also has the potential to be used as a clinical selection tool to improve diagnostic efficiency. Patients with high p-tau217 levels can be directed for confirmatory examination, while patients with low levels can be monitored periodically according to clinical conditions. This role is important because several studies show p-tau217 is related to the pathology of amyloid, tau, cognitive changes, and the biological progression of Alzheimer's. The limitation of this study lies in the heterogeneity of the articles analyzed, including differences in study design, population characteristics, type of *assay*, *cut-off* value, and comparative standards. Most of the evidence also comes from international cohorts, so generalizations to Asian populations, including Indonesia, still require further validation. This study also used narrative synthesis without *meta-analysis*, so it could not provide a combined estimate of the overall sensitivity, specificity, or diagnostic accuracy of p-tau217.

Conclusion

Plasma p-tau217 plays a significant role in the early diagnosis of Alzheimer's disease by accurately reflecting its underlying biological processes, particularly amyloid and tau

pathology. It has demonstrated excellent diagnostic performance in differentiating individuals with Alzheimer's-related pathology from those without the disease across clinical populations, including patients with mild cognitive impairment and cognitively unimpaired individuals. The combination of p-tau217 with Aβ42/40 may also improve detection ability, particularly in preclinical populations or at-risk individuals. The application of p-tau217 in clinical practice still requires standardization of examination methods, validation of cut-off values, and testing in more diverse populations, including Asian and Indonesian populations. Further research is recommended using a prospective, longitudinal, and multicenter design to strengthen the evidence regarding the benefits of p-tau217 as a diagnostic and prognostic biomarker of Alzheimer's disease.

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