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Clinical Value and Limitations of Plasma p-tau217 in the Supplementary Diagnosis of Early Alzheimer's Disease

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Abstract. Early and accurate diagnosis of Alzheimer's disease (AD) is necessary to enable timely intervention. Some of the traditional tests, such as positron emission tomography (PET) scans and cerebrospinal fluid (CSF) punctures, are too expensive or invasive and thus not been widely used. This review systematically evaluates the clinical progress of research on plasma phosphorylated tau 217 (p-tau217). The aim is to know if p-tau217 can be used as an early marker for the start of mild cognitive impairment (MCI) in brains of older adults. According to the current data, plasma p-tau217 have good diagnostic ability for early-stage Alzheimer's disease and can be used in a "two-cutoff" method at the clinic. Therefore, non-AD patients do not need to be included in the primary care area, and high-risk individuals in special memory clinics can be identified to reduce the number of expensive PET and CSF tests. However, it still has many problems in clinical use. In short, although plasma p-tau217 is a promising non-invasive early detection method, healthcare professionals should still consider all the circumstances in the overall health status of each patient before making any decisions.

Keywords: Alzheimer's disease, plasma p-tau217, supplementary diagnosis

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia worldwide and is an unprecedented challenge to global healthcare. Pathologically, it is characterized by the gradual deposition of extracellular beta-amyloid (Aβ) plaques and intracellular neurofibrillary tangles in the brain. Early diagnosis and treatment of AD could significantly improve clinical outcomes and reduce economic burden. Specialist centers misdiagnose AD in 20-30% of instances, and misdiagnosis rate in primary care is estimated at 40% [1].

Cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers for Aβ and tau are now increasingly used for the diagnosis of AD and are important for assessing eligibility for anti-Aβ treatment. While molecular imaging and CSF biomarkers that meet the criteria for disease detection and progression monitoring, their limited scalability, high costs and invasiveness represent major barriers to their widespread use in primary care and specialty clinics [2]. And that leads to looking for easier alternatives.

Blood biomarkers are promising for accessible and scalable diagnostic solutions for AD, as they are less costly and invasive than PET and CSF [3]. Of more than 15 phosphorylation sites

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investigated, p-tau217 has become one of the most promising candidates. Its elevation is related to the accumulation of Aβ plaques, which is the pathological feature of AD [4, 5]. A recent meta-analysis of 30 studies showed that plasma p-tau217 reached 82% sensitivity and 86% specificity in detecting amyloid pathology, similar to CSF-based tests [4]. Based on these results, p-tau217 has gradually been added to the diagnostic criteria and clinical guidelines of memory clinics. With the spread of test platforms for blood-based biomarkers, problems have arisen in the interpretation and comparison of these assays. Data from different studies and regions have not been integrated [6]. Circulating p-tau217 is expressed in both the central nervous system and peripheral organs, so it is not highly specific to people with common age-related diseases. A "gray zone" problem further complicates diagnostic triage [2, 7] . These gaps collectively indicate the need for further validation of its clinical utility in real-world settings. This paper thus will discuss the clinical applicability of early supplementary diagnosis and the current clinical deficiencies pointed out in recent studies. The clinical utility of plasma p-tau217 for the adjunctive diagnosis of early AD is reviewed, and the limitations preventing its translation into clinical practice are critically discussed.

2. Biological basis of tau and p-tau217 in AD pathogenesis

Tau is a protein associated with microtubules that helps organize and stabilize the assembly of axonal microtubules to maintain the structure of the neuronal cytoskeleton and support axonal transport. Under normal conditions tau is moderately phosphorylated which helps modulate its binding affinity for microtubules and maintain normal neuronal function [8]. Multiple sites of hyperphosphorylation of tau result in a reduction of its binding to microtubules in AD, destabilizing the neuronal cytoskeleton and promoting its self-aggregation into paired helical filaments that ultimately form neurofibrillary tangles, a major pathological hallmark of the disease [8]. This hyperphosphorylation mechanism is closely related to the accumulation of amyloid-beta, while abnormal tau phosphorylation and aggregation occurs simultaneously and subsequently to amyloid pathology in AD continuum [8]. One of the many tau phosphorylation sites known to be disease-relevant epitopes is Threonine 217 (T217) of the tau protein, which has a stronger and more specific association with AD pathology than many other phosphorylation sites, and phosphorylation at T217 is an indicator of concurrent presence of amyloid and tau pathologies rather than one or the other process alone [8]. This intimate mechanistic relationship between high levels of p-tau217 and the fundamental molecular pathology of AD provides the biological basis for its use as a blood-based biomarker that can track disease-related changes before the emergence of obvious clinical symptoms [8].

3. Diagnostic efficacy of p-tau217 in early AD

3.1. High accuracy with a stage-dependent gradient across the early-ad spectrum

The introduction of blood-derived biomarkers has revolutionized the diagnostic paradigm for AD, with plasma p-tau217 as the most accurate independent marker for early disease [8-10]. In response to the initial accumulation of Aβ plaques, its levels in the bloodstream start to increase significantly before the appearance of visible clinical symptoms, although whether this rise precedes or coincides with mature tau tangle formation is unknown. Plasma p-tau217 is a marker of the co-occurrence of amyloid and tau pathology, rather than non-specific neuronal damage [10]. Recent studies repeatedly demonstrate high diagnostic performance of plasma p-tau217 to distinguish early-stage AD from non-AD cognitive impairments [6, 11].

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This superiority is verified by a comprehensive meta-analysis of 113 eligible studies with a pooled AUC of 91.1% for p-tau217. And this diagnostic accuracy is reasonably robust regardless of the platform used [12]. However, this overall accuracy masks significant differences between stages. Plasma p-tau217 exhibits better diagnostic accuracy in symptomatic individuals, but reduced sensitivity in asymptomatic groups [12]. This attenuation is attributed to the fact that thresholds defined in symptomatic populations do not directly apply to earlier disease stages, where the biological signal is inherently weaker and harder to detect. So the clinical utility of p-tau217 is not primarily evaluated in severe dementia, where diagnosis is often obvious. Its real test, however, is to reliably detect pathology in the preclinical and prodromal stages such as subjective cognitive decline (SCD) and mild cognitive impairment (MCI) when intervention is of the greatest value.

3.2. Triage strategy in clinics

Researchers has shown that a risk-stratified two-threshold triage system is better, and plasma p-tau217 has now been added to the daily clinical worklist without increasing the risk of misdiagnosis [13]. This design directly addresses the stage-dependent accuracy gradient mentioned in Section 3.1. A single cutoff cannot optimize both sensitivity and specificity at all times in the early stages of AD.

Ashton and other colleagues put forward a two-threshold division of the three diagnostic groups for patients based on the level of plasma p-tau217 [5]. Metrics that are below a certain lower bound are added to the rule-out group and AD pathology can no longer be diagnosed [5]. This allows healthcare professionals to consider alternative causes of cognitive decline, such as vascular cognitive impairment, depression and metabolic disorders, by means of fewer tests. At the same time, those with a high value are also added to the rule-in group. This indicates a higher probability of underlying AD pathology [5], and further PET or CSF tests will be organized to confirm this diagnosis and determine if it is suitable for new medications. There is an intermediary, or "gray zone," category between the two limits for which the plasma assay outcomes are ambiguous and more confirmatory tests need to be carried out before a diagnostic can be made [5].

This stratification approach has been empirically shown to considerably reduce dependence on invasive or expensive confirmatory assessments. In a two-way workflow validated by two different memory-clinic cohorts (BioFINDER-1 and BioFINDER-2), this approach reduced the need for CSF tests by 61.2-85.9% with overall diagnostic precision of 88.2-92.0% [13]. It is important to acknowledge that this is a triage strategy prior to confirmatory testing for treatment eligibility and not a substitute. Current guidelines for donanemab specify that qualifying individuals must exhibit biomarker evidence of AD validated by PET or CSF, and both FDA-approved labeling for lecanemab and donanemab requires confirmation of amyloid pathology through PET or CSF before commencing treatment [14, 15]. Plasma p-tau217 is significantly elevated, but has not been established as a definitive marker for anti-amyloid treatment. The clinical utility in this context is thus not to replace a need for PET or CSF, but to efficiently identify those that are most likely to benefit from these confirmatory tests, optimizing the therapy pathway instead of bypassing it.

Taken together, implementing a plasma p-tau217 triage method offers significant therapeutic benefits. It reduces unnecessary PET and CSF utilization in the rule-out group, accelerates the diagnostic process for the rule-in group and allocates limited resources to those patients most likely to require and gain from them.

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4. Current limitations in clinical practice

Despite the significant promise of plasma p-tau217 in the supplementary diagnosis of early AD, its translation from well-defined research cohorts to complex, real-world clinical settings faces considerable obstacles. To realize its maximum utility as the first screening tool, three major classes of limitations must be addressed. They are diagnostic uncertainty within the triage framework, physiological variables from age-related comorbidities and the lack of cross-platform assay standardization.

4.1. The "gray zone" dilemma

The "gray zone" dilemma, introduced in Section 3.2, remains an inevitable obstacle in early clinical triage. Employing a two-cutoff strategy automatically produces an ambiguous interval where biomarker findings are intermediate. For about 15% to 20% of individuals in this category, plasma p-tau217 does not yield conclusive clinical direction, thus still requiring more costly and invasive confirmatory procedures such as amyloid PET or CSF testing. The prolonged diagnostic uncertainty may heighten psychological distress for patients anticipating a conclusive answer. To alleviate this constraint, scholars have investigated multi-modal frameworks combining plasma p-tau217 with p-tau181 [7]. Plasma p-tau217 independently serves as a highly sensitive continuous marker of Aβ-induced tau phosphorylation. However, within the limited concentration range that specifies the "gray zone", minor measurement fluctuations can cause a patient to pass an ambiguous biological threshold. Employing p-tau181 as an independent binary marker within this subgroup facilitates reclassification through an alternative and partly unique signal instead of depending on additional stratification of the identical underlying analyte. In a recent cohort trial at a memory clinic, our sequential model accurately classed 77.4% of previously ambiguous patients as either likely AD or non-AD, without necessitating further CSF or PET examinations [7].

4.2. Comorbidity-related confounding

The high prevalence of comorbidities among older adults introduces significant metabolic interference into blood test interpretation. The clearance of p-tau217 is partially influenced by renal function, suggesting that even mild chronic kidney disease (CKD) can increase plasma p-tau217 levels irrespective of actual brain pathology, with this discrepancy becoming disproportionately worse at lower estimated glomerular filtration rate (eGFR) and leading to elevated false-positive rates as kidney function deteriorates [16]. This risk is probably undervalued by current validation studies, which generally omit patients with significant renal impairment, thus inflating the accuracy in primary care and community environments where CKD frequently goes undetected. Ratio-based adjustments only somewhat mitigate this phenomenon by enhancing specificity at the expense of sensitivity, leading to minimal overall improvement of accuracy, especially when severe CKD is inadequately represented [17, 18]. Other age-related comorbidities, such as hypertension and type 2 diabetes, complicate interpretation by independently increasing p-tau217 levels or weakening its association with actual amyloid or tau burden [19]. Overall, these results suggest that plasma p-tau217, used without simultaneous evaluation of renal function and other comorbid conditions, may be untrustworthy for early Alzheimer's disease screening in elderly individuals.

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4.3. Lack of platform standardization

Finally, the lack of platform standardization represents a major barrier to commercialization and routine clinical adoption. Variations in antibody pairs, calibrators and detection chemistries among commercial platforms, such as Lumipulse and ALZpath, demonstrate that each assay targets p-tau217 with a distinct epitope specificity and binding affinity, so that absolute concentration values are not interchangeable across platforms; inter-platform correlations are less robust in amyloid negative and cognitively unimpaired groups compared to symptomatic populations [6]. Moreover, no certified reference method or material for p-tau217 currently exists, resulting in cutoffs that are specific to each assay and study [6]. Encouragingly, coordinated efforts to address this gap are already underway. The IFCC Working Group on Biomarkers of Neurodegenerative Diseases, with the backing of the Alzheimer's Association and the Alzheimer's Drug Discovery Foundation, has commenced the creation of a certified reference method and material for plasma p-tau217 [20]. Nonetheless, no such reference materials have been officially validated or broadly embraced at this moment, indicating that assay-specific thresholds will probably continue to be the standard in clinical practice for the near future.

5. Conclusion

This review summarized the clinical applicability of plasma p-tau217 as a supplementary diagnostic biomarker for early AD, drawing on evidence spanning its underlying biological mechanism, its diagnostic performance relative to CSF and PET and the limitations hindering its integration into routine practice. Collectively, the evidence indicates that the plasma p-tau217 offers a more accessible alternative to invasive AD testing. Rather than serving as an independent diagnostic tool, it is best understood as a first-line stratification tool reducing unnecessary referrals for confirmatory CSF and PET examinations. This distinction provides a practical benchmark for healthcare professionals and researchers aiming to integrate the biomarker wisely into diagnostic processes. However, the diagnostic performance of plasma p-tau217 is constrained by three factors including uncertainty within the gray zone, physiological variability associated with comorbidities and the lack of standardization across platforms. Among these limitations, the absence of harmonized reference standards appears the most urgent issue. This research combined results from studies that differed considerably in assay platform, cutoff methodology and demographic factors without formal heterogeneity assessment. Future research should focus on harmonizing assay systems, creating a common reference.

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