

The Role Of Phosphorylated Tau Protein In The Prognosis Of Patients With Mild Cognitive Impairment: A Systematic Review

Carolina Matté Dagostini¹, Taís Luise Denicol¹, Juan Sebastian Sanchez León¹, Luiza Périco Borges², Murillo Cesar Gionedis³, Raphael Machado de Castilhos¹

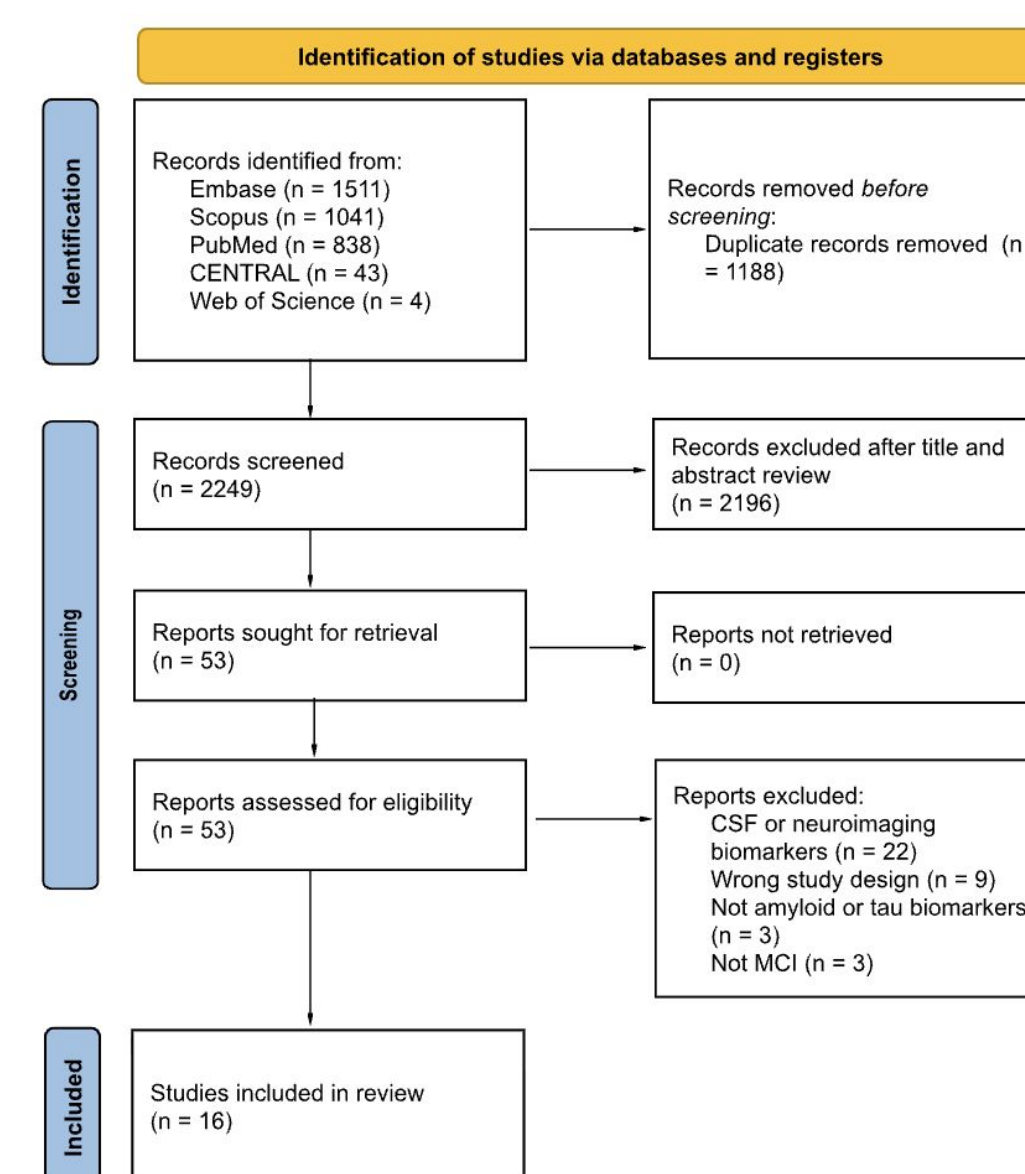
¹Neurology, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, ²Universidade do Vale do Rio dos Sinos, Porto Alegre, Brazil, ³Hospital Geral de Caxias do Sul, Caxias do Sul, Brazil

INTRODUCTION

Mild Cognitive Impairment (MCI) represents an intermediate stage between normal aging and dementia due to Alzheimer's Disease (AD). Early identification of individuals at high risk of progression is crucial, as current interventions cannot reverse deficits in moderate or advanced stages. While cerebrospinal fluid biomarkers, neuroimaging, and nuclear medicine techniques demonstrate high diagnostic accuracy, their widespread use is limited by high cost, limited availability, and invasiveness. Plasma biomarkers have therefore emerged as a promising, low-cost, and minimally invasive alternative, with potential for early detection, longitudinal monitoring, and broader clinical applicability, including in primary care settings. This systematic review aimed to assess the prognostic value of plasma phosphorylated tau (p-Tau) for cognitive decline and the conversion from MCI to AD.

METHODS

A systematic literature search was conducted in PubMed, CENTRAL, Web of Science, Embase, and Scopus. Clinical studies involving patients with MCI that investigated plasma p-Tau in relation to cognitive decline or MCI-to-AD conversion were included. Study quality was assessed using the Newcastle-Ottawa Scale (NOS) for cohorts. Figure 1 shows the PRISMA flowchart.



RESULTS

Of 3,427 studies identified, 16 met inclusion criteria, all cohort designs of good methodological quality. Sample sizes ranged from 85 to 2,266 participants. Fourteen studies assessed p-Tau181, four evaluated p-Tau217, and one investigated p-Tau231; nine studies used the SIMOA assay. Cognitive decline was evaluated in six studies using validated scales, all demonstrating an association between elevated plasma p-Tau and cognitive deterioration. Thirteen studies examined MCI-to-AD conversion, consistently reporting that higher plasma p-Tau levels predict both cognitive and functional decline and subsequent progression to AD.

Table 1. Association between plasma p-Tau and cognitive decline.

Author	Results
Shekhar, 2016	Statistically significant linear correlation ($p < 0.00001$) between plasma p-Tau181 concentration and MMSE ($r = -0.3899$) and MoCA scores ($r = -0.3962$).
Cullen, 2020	Plasma p-Tau181 showed a strong independent association with MMSE worsening ($\beta = -1.65$; $p < 0.0001$).
Karikari, 2020	Higher plasma p-Tau181 concentrations were strongly associated with MMSE decline after one year ($p = 0.0015$).
Simrén, 2021	Elevated plasma p-Tau181 levels predicted steeper MMSE decline over time ($\beta = -0.07$; 95% CI -0.28 to -0.05 ; $p < 0.001$).
Therriault, 2021	Higher plasma p-Tau181 levels predicted greater memory decline over 5 years ($\beta = -0.11$; SE = 0.01; $t = -7.37$; $p < 0.001$).
Grasset, 2024	Elevated plasma p-Tau181 was associated with a more pronounced MMSE decline ($\beta = -0.055$; 95% CI -0.067 to -0.043).

CONCLUSIONS

Elevated plasma p-Tau, particularly p-Tau181 and p-Tau217, is a robust predictor of cognitive decline and MCI-to-AD conversion. These findings support plasma p-Tau as a reliable, minimally invasive biomarker for prognostic assessment, with important implications for early detection, disease monitoring, and clinical decision-making.

Table 2. Association between plasma p-Tau and progression from MCI to Alzheimer's disease.

Author	Results
Cullen, 2020	Elevated plasma p-Tau181 was associated with increased risk of conversion from MCI to AD (OR = 5.87; HR = 2.52) over 4 years.
Janelidze, 2020	Each one-standard deviation increase in baseline log plasma p-Tau181 was associated with a higher risk of AD dementia (HR = 3.8; $p < 0.001$) over 5 years.
Palmqvist, 2021	Plasma p-Tau alone showed good accuracy for predicting conversion to AD (AUC = 0.83) over 4 years.
Simrén, 2021	Patients with MCI who converted to AD within 1 year had higher plasma p-Tau181 concentrations (17.13 ± 6.19 pg/mL vs. 12.26 ± 5.89 pg/mL; $p < 0.001$).
Therriault, 2021	Elevated plasma p-Tau181 levels were associated with a higher risk of progression to AD (HR = 2.06; 95% CI 1.55–2.74; $p < 0.001$) over 5 years.
Binette, 2022	Patients who progressed to AD within 3 years had higher baseline plasma p-Tau217 levels compared with non-converters (0.62 ± 0.36 vs. 0.25 ± 0.24 pg/mL; $p < 0.001$).
Xiao, 2022	High plasma p-Tau181 levels (>2.41 pg/mL) were independent predictors of progression from MCI to AD over 5 years.
Janelidze, 2023	Patients who progressed to AD within 5 years had significantly higher plasma p-Tau217 levels (AUC = 0.932; 95% CI 0.891–0.974; $P_{diff} < 0.027$).
Kivisäkk, 2023	Individuals with MCI who progressed to AD within 4 years showed 1.7-fold higher plasma p-Tau181 concentrations ($p < 0.001$).
Kwon, 2023	Conversion from MCI to AD within 3 years was associated with higher plasma p-Tau181 levels (OR = 1.355; 95% CI 1.015–1.809; $p = 0.040$).
Palmqvist, 2023	The combination of plasma p-Tau181, p-Tau217, and Aβ42/Aβ40 showed high predictive accuracy for MCI-to-AD conversion (AUC = 0.87; 95% CI 0.82–0.92) over 6 years.
Planche, 2023	Elevated plasma p-Tau181 predicted AD in patients with MCI (c-index = 0.731; 95% CI 0.694–0.768) over 5 years.
Silva-Spinola, 2023	Individuals who progressed to AD within 6 years showed a significant increase in plasma p-Tau181 levels ($p = 0.01$).

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CONTACT



cdagostini@hcpa.edu.br
[LinkedIn](#)
[Research Gate](#)
[Instagram](#)