

CSF eMTBR-tau243 – A candidate biomarker for diagnosis and disease staging in Alzheimer's Disease

Sara Riazi¹, Steen G. Hasselbalch^{1,2}, Tim West³, Philip Verghese³, Joel Braunstein³, Kristopher Kirmess³, Justine Coppinger³, Anja Hviid Simonsen¹, Kristian Steen Frederiksen^{1,2}

1: Danish Dementia Research Centre, Department of Neurology, Rigshospitalet, Copenhagen, Denmark. 2: Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark. 3: C2N Diagnostics, LLC, St. Louis, Missouri, USA

BACKGROUND AND AIM

In recent years, different tau species have gained substantial interest as biomarkers with high sensitivity and specificity for Alzheimer's Disease (AD). Research has identified a novel tau fragment that includes the endogenous microtubule binding region of tau, eMTBR-tau243, which reflects neurofibrillary tangle pathology closely.

This study aimed to assess the diagnostic value of eMTBR-tau243 and its ability to differentiate disease stages across the dementia spectrum in a real-world memory clinic cohort.

OBJECTIVES

- To assess the diagnostic accuracy of eMTBR-tau243 for the detection of cerebral amyloid positivity
- Investigate the value of eMTBR-tau243 as a singular biomarker to evaluate disease severity
- Prognostic value of combined %p-tau217 and eMTBR-tau243 measured by longitudinal MMSE scores in patients with and without cerebral amyloid deposition

Table 1. Subject Demographics

	Amyloid Positive	Amyloid Negative
N	188 (42.2%)	258 (57.8%)
Age, Mean (Range)	70.3 (7.3)	72.7 (7.6)
Sex, Female	110 (60.8%)	109 (41.1%)
MMSE		
Mean (Range)	23.7 (4.6)	25.4 (4.2)
Cognitive Status		
No Cognitive Impairment (CU)	4 (2.1%)	44 (17.1%)
Mild Cognitive Impairment (MCI)	56 (29.8%)	99 (38.4%)
Mild Dementia	96 (51.1%)	78 (30.2%)
Moderate Dementia	30 (16.0%)	31 (12.0%)
Diagnosis		
Alzheimer's Disease	126 (67.0%)	19 (7.4%)
Normal Pressure Hydrocephalus (NPH)	12 (6.4%)	82 (31.8%)
Frontotemporal Dementia	1 (0.5%)	20 (7.8%)
Other	47 (25.0%)	137 (53.1%)

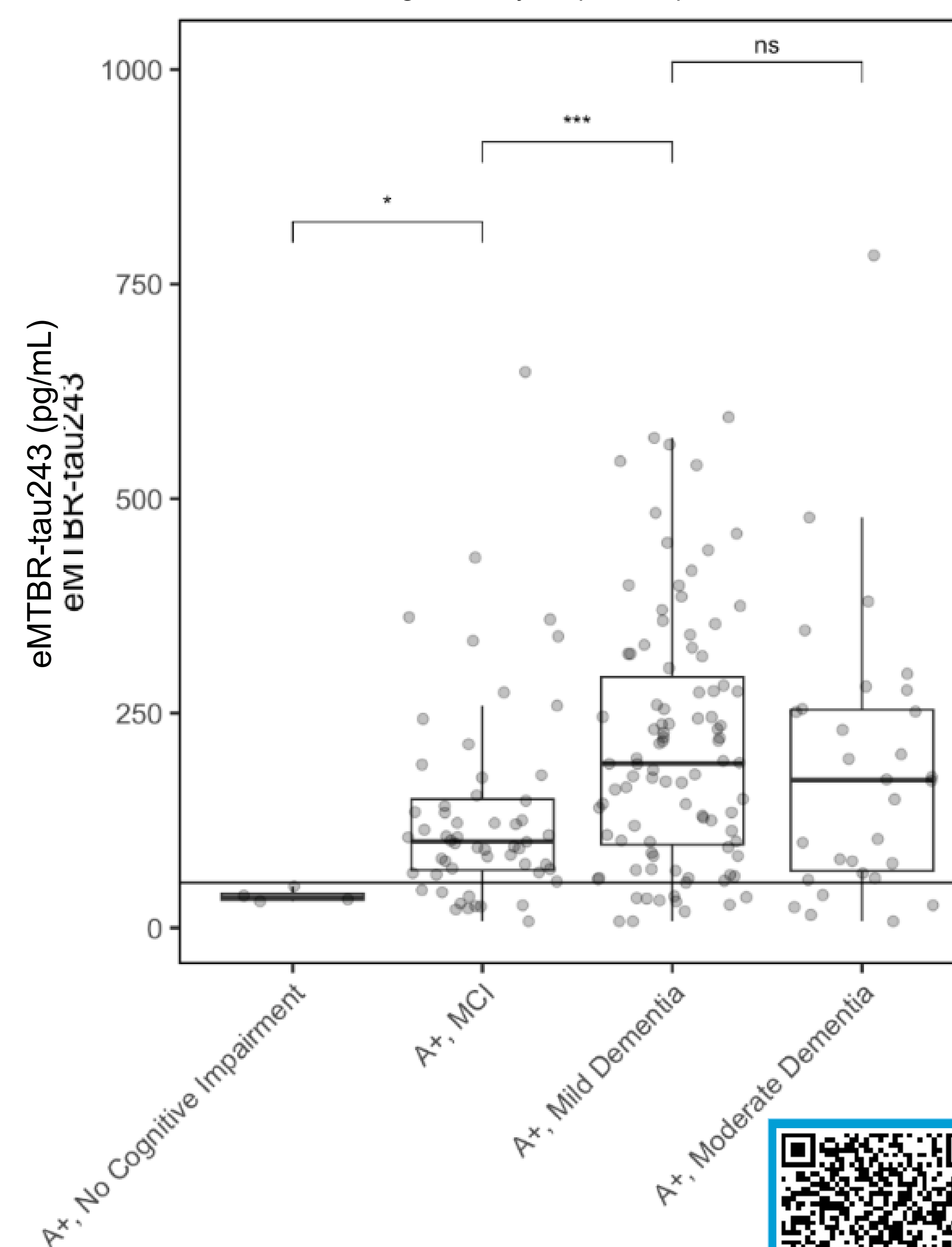
METHODS

In this **cross-sectional** cohort study, patients from the Danish Dementia Research Center were **consecutively** included. The cohort consisted of patients referred to the Memory Clinic at Rigshospitalet for diagnostic evaluation in 2021-2023 who had undergone lumbar puncture (n=403), or lumbar puncture combined with 11C-Pittsburgh Compound B-PET (11C-PiB-PET) scan (n=43). Amyloid positivity was determined using CSF p-tau181/Aβ42 or amyloid PET.

Additionally, blood plasma p-tau217 and non-phosphorylated p-tau217 (np-tau217) and CSF eMTBR-tau243 analyses were performed by LC-MS/MS (C2N Diagnostics).

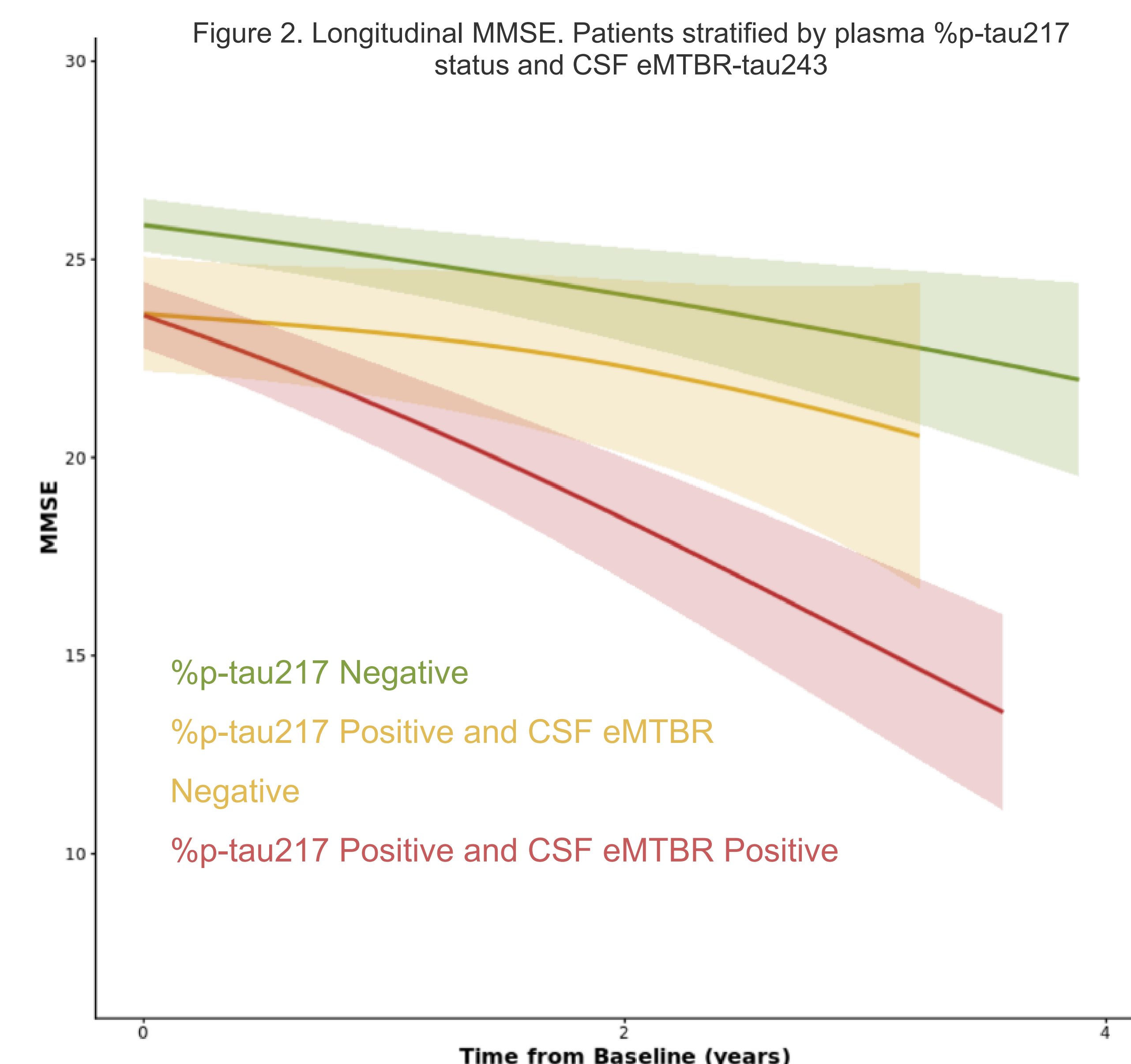
A subgroup of 258 (57.9%) patients were **followed for up to 4 years** with cognitive assessments (including MMSE).

Figure 1. Baseline eMTBR-tau243 levels across cognitive disease stages in amyloid positive patients



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RESULTS

A total of 446 patients were included.

CSF eMTBR-tau243 identified cerebral amyloid pathology with an ROC AUC of 0.923 (95% CI, 0.897-0.95); Using the Youden index, sensitivity was 84.5% (95% CI, 78.6-89), and specificity was 90.3% (95% CI, 86.1-93.4).

In A+ patients, eMTBR-tau243 showed incremental increases across disease stages (Cognitive unimpaired 37.4 (SD ± 7.7); MCI 135.0 (SD ± 118.7); Mild dementia 211.7 (SD ± 144.8); Moderate dementia 187.4 (SD ± 164.6).

Further, plasma %p-tau217 positive patients with high CSF eMTBR-tau243 levels declined faster, as measured by longitudinal MMSE measures, than %p-tau217 positive patients.

CONCLUSION

CSF eMTBR-tau243 shows strong potential as a biomarker for amyloid pathology, disease staging and cognitive decline in AD.