

Higher Diagnostic Latency in Early-Onset Alzheimer's Disease compared to Late-Onset Alzheimer's Disease in a Memory Clinic Setting

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Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease globally, with a distinction drawn between early-onset AD (EOAD), defined by an age of onset (AOO) below 65 years, and late-onset AD (LOAD), with AOO at or above 65 years. These two subpopulations differ not only in the age at which symptoms emerge, but potentially also in clinical presentation, disease trajectory, and psychosocial context. EOAD patients frequently present in mid-life, often while still professionally active and with family responsibilities, creating a distinct set of challenges that differ markedly from those faced by elderly LOAD patients. Atypical, non-amnestic presentations are more common in EOAD, which may complicate early recognition. Research on disease-specific differences between these subsets has so far yielded only mixed results: while some studies indicate faster progression in EOAD, others have found no meaningful differences in biomarker profiles or rates of decline. Differences in CSF biomarker levels between EOAD and LOAD have been reported inconsistently across the literature, with implications for detection and disease staging. Due to these divergent clinical and psychosocial contexts, patients with EOAD and LOAD may also differ in their pathways to diagnosis. Analyzing time to diagnosis across these subgroups can yield important insights into improving timeliness of diagnosis and treatment referral, particularly as new disease-modifying therapies with early-stage eligibility criteria become available.

Methods

A retrospective data analysis was conducted at the outpatient memory clinic of the Department of Neurology, Vienna General Hospital, Medical University of Vienna, including 72 patients treated

between 2017 and 2022 with biomarker-confirmed diagnoses of MCI or AD dementia according to the NIA-AA 2018 framework. Inclusion required either a positive amyloid PET scan or CSF Aβ42 below 500 pg/ml, with an INNOTEST Amyloid Tau Index (IATI) of ≤1. The study included an analysis of CSF biomarkers (Aβ42, total tau [t-tau], phosphorylated tau [p-tau]), analyzed using INNOTEST, alongside MMSE scores and demographic parameters obtained at the time of the first diagnostic visit. Age of onset was self-reported by patients or caregivers. Time to diagnosis was computed by subtracting self-reported age of onset from age at the first diagnostic visit, serving as a proxy for diagnostic latency. The cohort was stratified by age of onset into EOAD and LOAD subgroups for comparative analyses. Mann-Whitney-U tests were used for group comparisons of metric parameters, and Spearman's correlation analyses were performed to examine relationships between CSF biomarkers, demographic parameters, and MMSE. All analyses were performed using IBM SPSS Statistics (version 30.0), with a significance threshold of $p \leq 0.05$.

Results

At the time of the first diagnostic visit, patients had a mean MMSE composite score of 22 (SD=5.5), reflecting meaningful cognitive impairment already present at the point of initial clinical evaluation. The cohort was 52.8% female and included 43 patients (59.7%) with EOAD (mean AOO=55.1 years, SD=6.7) and 29 patients (40.3%) with LOAD (mean AOO=71.8 years, SD=4.7). Mean time to diagnosis was statistically significantly longer for EOAD patients (2.8 years, SD=1.8) than for LOAD patients (1.9 years, SD=2.6; $p=0.004$), indicating greater diagnostic latency in the early-onset group. In the exploratory correlation analysis, an inverse correlation was observed between AOO and time to diagnosis ($\rho=-0.257$, $p=0.03$), confirming

that lower age of onset was associated with a longer interval between symptom onset and clinical diagnosis across the full cohort. Mean MMSE scores were non-significantly lower in EOAD patients compared to LOAD patients, pointing to a trend toward more advanced cognitive impairment at the time of diagnosis in the younger-onset group, though this did not reach statistical significance. MMSE scores were significantly correlated with t-tau ($\rho=-0.593$, $p<0.001$), p-tau ($\rho=-0.418$, $p<0.001$), and IATI ($\rho=0.635$, $p<0.001$), with directionality consistent with more advanced disease stage, further supporting the utility of these biomarkers as indicators of disease progression at time of diagnosis.

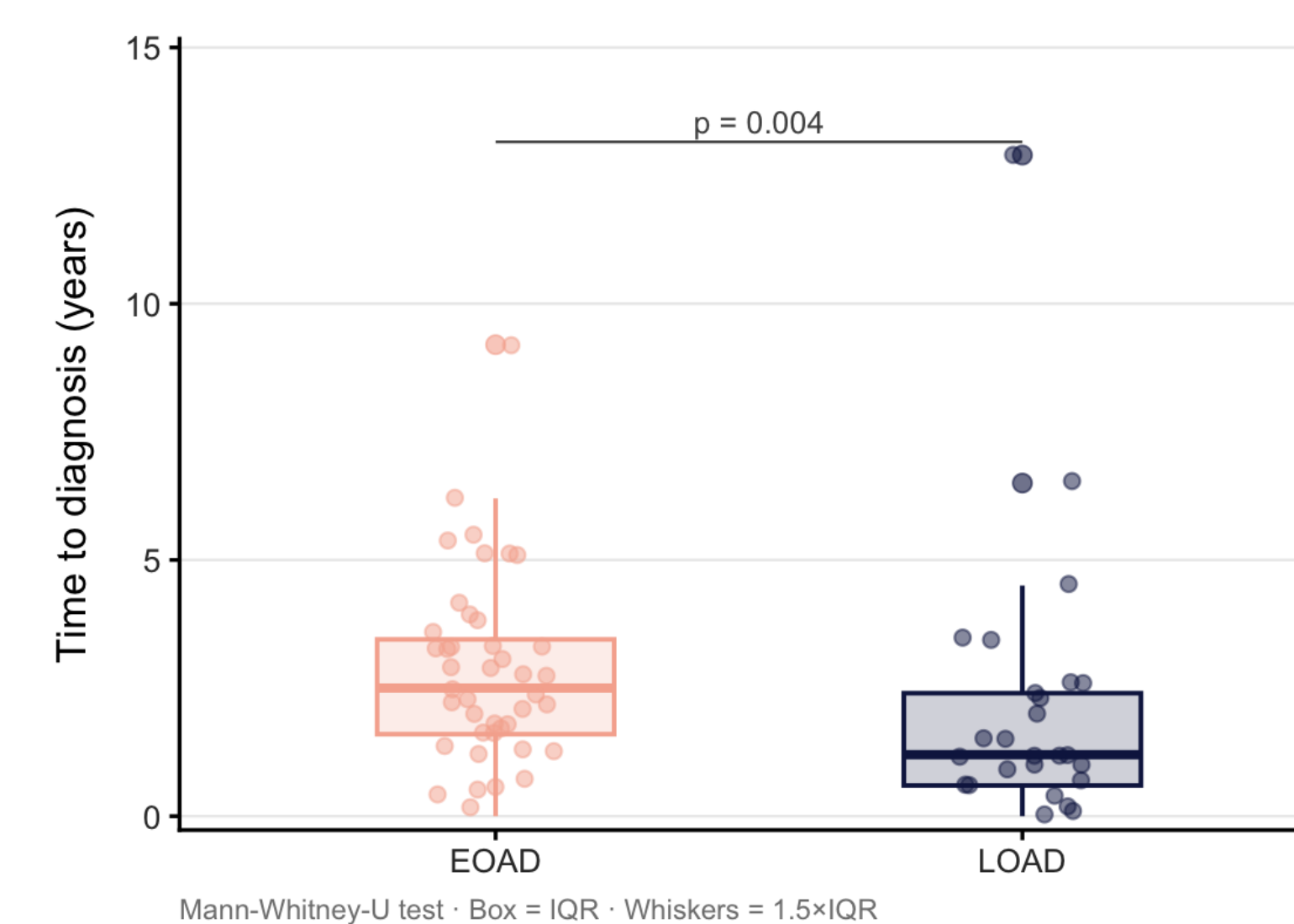


Figure 1. Time to diagnosis by onset group. EOAD (n=43) showed significantly longer diagnostic latency than LOAD patients (n=29; 2.8 vs. 1.9 years, Mann-Whitney-U, $p=0.004$). Box = IQR, whiskers = $1.5 \times \text{IQR}$, points = individual values.

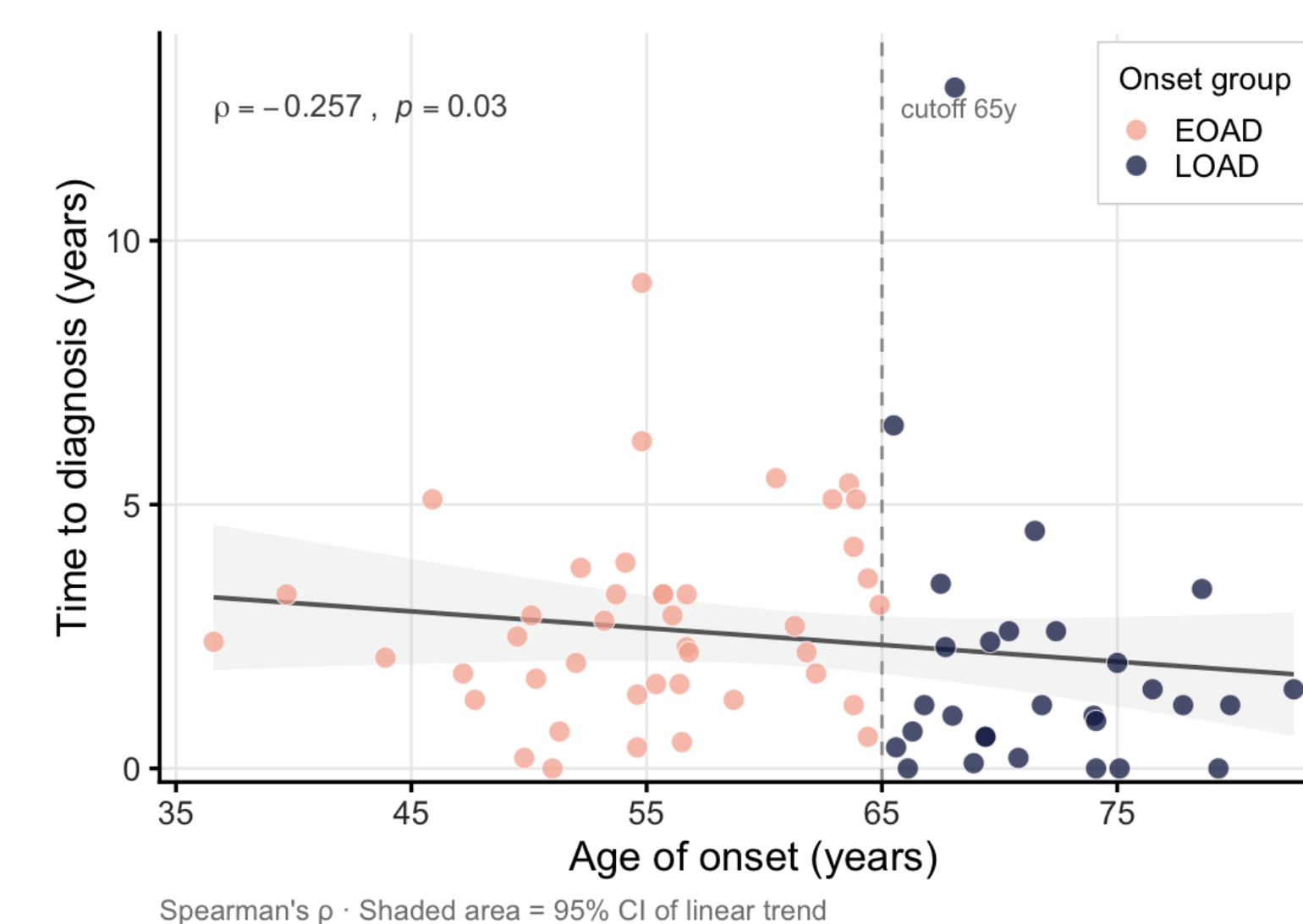


Figure 2. Scatter plot of age of onset versus time to diagnosis (n=72), colored by onset group. The regression line reflects an inverse correlation between younger age of onset and longer diagnostic delay (Spearman's $\rho=-0.257$, $p=0.03$). Dashed line indicates 65-year onset cutoff.

Conclusion

The findings presented here depict a pattern of higher diagnostic latency from AOO for EOAD patients, evidenced by a statistically significant longer time to diagnosis as well as non-significantly lower MMSE scores and biomarker levels trending toward more advanced disease stage at diagnosis compared to LOAD patients. These results suggest that by the time EOAD patients reach a tertiary memory clinic, their disease may be at a more progressed stage than that of their LOAD counterparts at the equivalent diagnostic timepoint. Possible interpretations of these findings may point to a lower awareness of disease vulnerability among younger individuals, who may attribute early cognitive symptoms to stress, burnout, or other causes before considering a neurodegenerative etiology. Additionally, structural and socio-cultural factors, including referral pathways less attuned to younger patients with cognitive complaints, and lower clinical index of suspicion for AD in working-age adults, may contribute to the observed delay. Improving awareness, screening protocols, and referral structures specifically for younger patients with potential EOAD warrants further attention, particularly given the growing importance of early diagnosis for access to disease-modifying therapies.

Key takeaways

- EOAD patients wait significantly longer for diagnosis than LOAD patients (2.8 vs. 1.9 years, $p=0.004$).
- Disease stage is already advanced at first presentation at a tertiary center across both subgroups.
- Earlier diagnosis in EOAD is an actionable target for improving access to treatment and care.

Contact information

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