

Diagnosis and prognosis of Alzheimer's disease using CSF: added value of Aβ40 and making use of all available biomarkers.

T. Claessen¹⁻³, I.M.W. Verberk^{1,3}, W.M. van der Flier³⁻⁶, A.W. Lemstra^{2,3}, Y.A.L. Pijnenburg^{2,3}, M.J.A. Koel-Simmelink^{1,3}, C.E. Teunissen^{1,3}, A.C. van Harten¹⁻³

¹ Neurochemistry Laboratory, Department of Laboratory Medicine, Amsterdam UMC, location VUmc, Amsterdam, the Netherlands, ² Alzheimer Center Amsterdam, Department of Neurology, Amsterdam UMC, location VUmc, Amsterdam, the Netherlands
³ Amsterdam Neuroscience, Neurodegeneration, Amsterdam, the Netherlands, ⁴ Alzheimer Nederland, Amersfoort, the Netherlands, ⁵ Epidemiology and Data Science, Vrije Universiteit Amsterdam, Amsterdam UMC, location VUmc, Amsterdam, the Netherlands, ⁶ Amsterdam Public Health, Amsterdam, the Netherlands

T.Claessen@amsterdamumc.nl



BACKGROUND

- Cerebrospinal fluid (CSF) pTau-181/Aβ42 and Aβ42/40 are widely used to detect Alzheimer's disease (AD) pathology.
- pTau-181/Aβ42 combines amyloid and tau biomarkers, limiting independent A-T(N) staging.
- Adding Aβ40 permits amyloid assessment with Aβ42/40 while preserving pTau-181 as an independent tau marker.

AIM

To investigate whether adding Aβ40 to Aβ42 and pTau-181 preserves concordance with amyloid positron emission tomography (PET) and improves prognostic stratification in a memory clinic cohort.

METHODS

Inclusion criteria

- Diagnostic: 448 individuals with available amyloid PET within one year of CSF collection (Table 1).
- Prognostic: 220 individuals with SCD and 290 with MCI and available longitudinal follow-up data (Table 2).

Biomarkers

- CSF Aβ40 was measured using the Elecsys® research-use-only assay, alongside Elecsys® Aβ42 and pTau-181 assays.

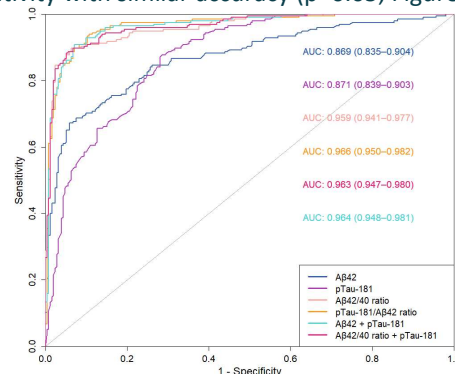
Analyses

- Diagnostic: Accuracy was assessed using receiver operating characteristic curves with amyloid PET status as reference.
- Prognostic: Clinical progression was analyzed using Cox proportional hazards models. Gaussian mixture modeling identified low, intermediate, and high pTau-181 stages to assess whether pTau-181 stratification predicted progression beyond amyloid positivity.

DIAGNOSTIC RESULTS

	Amyloid PET positive (n = 253)	Amyloid PET negative (n = 195)	Total sample (n = 448)
Psychiatric disorders	2 (0.8%)	19 (9.7%)	21 (4.7%)
SCD	22 (8.7%)	54 (27.7%)	76 (17.0%)
MCI	44 (17.4%)	41 (21.0%)	85 (19.0%)
AD dementia	173 (68.4%)	0 (0%)	173 (38.6%)
FTD	3 (1.2%)	27 (13.8%)	30 (6.7%)
LBD	6 (2.4%)	14 (7.2%)	20 (4.5%)
VaD	1 (0.4%)	9 (4.6%)	10 (2.2%)
Other dementias	2 (0.8%)	18 (9.2%)	20 (4.5%)
Neurological diseases	0 (0%)	13 (6.7%)	13 (2.9%)

Aβ42/40 and pTau-181/Aβ42 detected amyloid PET positivity with similar accuracy ($p > 0.05$, Figure 1).



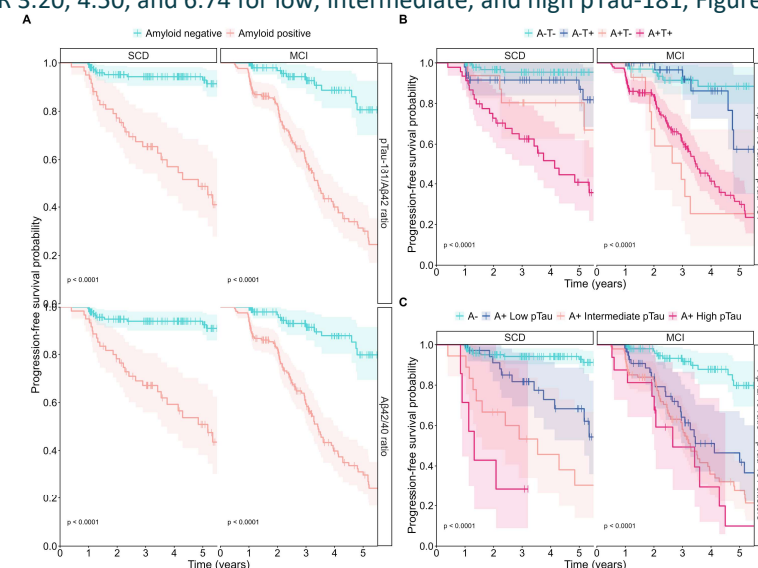
PROGNOSTIC RESULTS

	SCD (n=220)	MCI (n=290)	p
Female			
n (%)	83 (37.7%)	111 (38.3%)	0.52
Age (years)			
Mean (SD)	60.9 (7.46)	65.3 (7.08)	<0.001
CSF amyloid-positive			
n (%)	62 (28.2%)	170 (58.6%)	<0.001
MMSE			
Median [IQR]	29.0 [27.0, 29.0]	27.0 [25.0, 28.0]	<0.001
Education (years)			
Median [IQR]	13.0 [10.0, 13.0]	10.0 [9.0, 13.0]	0.171
Follow-up (years)			
Median [IQR]	4.17 [2.21, 6.12]	2.61 [1.52, 4.12]	<0.001
Clinical progression			
n (%)	44 (20.0%)	110 (37.9%)	<0.001

PROGNOSTIC RESULTS

pTau-181/Aβ42 (SCD HR 6.42, MCI HR 4.44) and Aβ42/40 (SCD HR 6.11, MCI HR 4.19, Figure 2.A) were similarly associated with clinical progression.

Among Aβ42/40-positive individuals, increasing pTau-181 stages were associated with increases in progression risk (SCD HR 4.40, 7.37, and 16.9; MCI HR 3.20, 4.50, and 6.74 for low, intermediate, and high pTau-181, Figure 2.C).



CONCLUSION

- The Aβ42/40 ratio and the pTau-181/Aβ42 ratio showed similar diagnostic performance for detecting amyloid PET positivity.
- Adding Aβ40 enabled separate amyloid and tau classification, supporting more granular prognostic stratification in amyloid-positive individuals with SCD and MCI.

ACKNOWLEDGEMENTS

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