

Automated Plasma pTau 217 Measurements for the Detection of Amyloid Pathology in Patients with Cognitive Decline

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Background

Tau phosphorylated at threonine 217 (pTau 217) has emerged as a highly specific blood-based biomarker for amyloid pathology associated with Alzheimer's disease (AD), demonstrating strong concordance with established cerebrospinal fluid (CSF) and amyloid-PET (positron emission tomography) imaging markers. The development of reliable plasma-based assays represents a major step toward less invasive and more accessible diagnostic pathways for AD. The Lumipulse® G pTau 217 Plasma (CE) assay, an automated chemiluminescent enzyme immunoassay, offers such a solution for routine clinical use.

Study Objective

This study aimed to evaluate the clinical performance of the Lumipulse G pTau 217 Plasma assay (Fujirebio Europe N.V.) to identify amyloid pathology in a European cohort of patients, aged 50 years and over, presenting with signs and symptoms of cognitive decline. The study included the determination and validation of diagnostic cut-off values and the establishment of reference ranges.

Method

The study included 592 patients aged ≥50 years who presented with cognitive complaints at a specialized memory clinic between September 2022 and February 2025 and underwent diagnostic lumbar puncture. The cohort encompassed a broad clinical spectrum, including Alzheimer's disease dementia (AD; n = 75), non-AD dementia (non-AD; n = 76), mild cognitive impairment due to AD (MCI-AD; n = 188), mild cognitive impairment due to other causes (MCI-other; n = 239), and subjective cognitive decline (SCD; n = 14) patients.

Participants were randomly assigned to a cut-off determination cohort (n = 300) or to an independent validation cohort (n = 292). Amyloid status was defined using the Lumipulse G Aβ1-42/Aβ1-40 ratio in CSF (cut-off >0.062), resulting in an overall prevalence of amyloid positivity of 50.8%. pTau 217 concentrations were measured from pristine K₂EDTA plasma samples using the Lumipulse G pTau 217 Plasma assay.

Diagnostic accuracy was assessed using receiver operating characteristic (ROC) curve analysis in accordance with CLSI EP24-A2 guidelines. Cut-off values were determined using two approaches. A single cut-off was derived based on the bootstrapped maximum Youden index, while a dual cut-off approach was defined to optimize sensitivity, specificity, and the size of an intermediate (grey) zone. In addition, reference ranges were established in amyloid-negative individuals using non-parametric methods, in accordance with CLSI EP28-A3c guidelines, with stratification by age decade and sex.

Results

Demographics

Table 1: Clinical and demographic characteristics of subjects in determination cohort.

		AD	Diagnostic Stage/Diagnostic Group		SCD	Amyloid status		Total
Total		35	40	92	128	5	150	300
Gender	Male	9 (25.7%)	18 (45.0%)	32 (34.8%)	70 (54.7%)	2 (40.0%)	52 (34.7%)	131 (43.7%)
	Female	26 (74.3%)	22 (55.0%)	60 (65.2%)	58 (45.3%)	3 (60.0%)	98 (65.3%)	169 (56.3%)
Age (years)	50 - 59	0 (0.0%)	4 (10.0%)	3 (3.3%)	15 (11.7%)	0 (0.0%)	3 (2.0%)	22 (7.3%)
	60 - 69	6 (17.1%)	9 (22.5%)	9 (9.8%)	30 (23.4%)	1 (20.0%)	19 (12.7%)	55 (18.3%)
	70 - 79	27 (77.1%)	21 (52.5%)	61 (66.3%)	76 (59.4%)	4 (80.0%)	105 (70.0%)	189 (63.0%)
	80 - 85	2 (5.7%)	6 (15.0%)	19 (20.7%)	7 (5.5%)	0 (0.0%)	23 (15.3%)	11 (7.3%)
	Average	74.2	72.1	74.9	71.0	72.4	74.6	72.8
	Median	75	74.5	76	73	73	75	74
	Min - Max	64 - 81	52 - 85	54 - 84	51 - 84	69 - 75	54 - 84	51 - 85
MMSE	<18	3 (8.6%)	6 (15.0%)	5 (5.4%)	1 (0.8%)	0 (0.0%)	12 (8.0%)	15 (5.0%)
	18 - 23	15 (42.9%)	9 (22.5%)	15 (16.3%)	11 (8.6%)	0 (0.0%)	31 (20.7%)	50 (16.7%)
	24 - 30	8 (22.9%)	18 (45.0%)	58 (63.0%)	93 (72.7%)	4 (80.0%)	81 (54.0%)	181 (60.3%)
	Unknown	9 (25.7%)	7 (17.5%)	14 (15.2%)	23 (18.0%)	1 (20.0%)	26 (17.3%)	54 (18.0%)
	Average	0.612	0.267	0.610	0.157	0.421	0.572	0.164
pTau 217 (pg/mL)	Median	0.512	0.175	0.516	0.116	0.168	0.454	0.116
	Min - Max	0.116 - 2.192	0.067 - 1.595	0.113 - 4.293	0.048 - 1.520	0.065 - 1.574	0.113 - 4.293	0.048 - 1.595

Table 2: Clinical and demographic characteristics of subjects in validation cohort.

		AD	Diagnostic Stage/Diagnostic Group		SCD	Amyloid status		Total
Total		40	36	96	111	9	151	292
Gender	Male	18 (45.0%)	15 (41.7%)	42 (43.8%)	43 (38.7%)	2 (22.2%)	61 (40.4%)	120 (41.1%)
	Female	22 (55.0%)	21 (58.3%)	54 (56.3%)	68 (61.3%)	7 (77.8%)	90 (59.6%)	172 (58.9%)
Age (years)	50 - 59	0 (0.0%)	5 (13.9%)	0 (0.0%)	11 (9.9%)	1 (11.1%)	0 (0.0%)	17 (5.8%)
	60 - 69	8 (20.0%)	9 (25.0%)	14 (14.6%)	26 (23.4%)	4 (44.4%)	27 (17.9%)	61 (20.9%)
	70 - 79	24 (60.0%)	18 (50.0%)	64 (66.7%)	64 (57.7%)	4 (44.4%)	96 (63.6%)	174 (59.6%)
	80 - 85	8 (20.0%)	4 (11.1%)	18 (18.8%)	10 (9.0%)	0 (0.0%)	28 (18.5%)	40 (13.7%)
	Average	75.3	70.9	74.7	71.4	68.9	74.8	72.9
	Median	76.5	72	76	73	67	76	72
	Min - Max	65 - 85	51 - 82	60 - 86	52 - 83	59 - 79	60 - 86	51 - 83
MMSE	<18	8 (20.0%)	2 (5.6%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	9 (6.0%)	11 (3.8%)
	18 - 23	19 (47.5%)	16 (44.4%)	22 (22.9%)	16 (14.4%)	0 (0.0%)	41 (27.2%)	73 (25.0%)
	24 - 30	7 (17.5%)	14 (38.9%)	62 (64.6%)	71 (64.0%)	9 (100.0%)	78 (51.7%)	163 (55.8%)
	Unknown	6 (15.0%)	4 (11.1%)	11 (11.5%)	24 (21.6%)	0 (0.0%)	23 (15.2%)	45 (15.4%)
	Average	0.761	0.235	0.602	0.133	0.092	0.589	0.166
pTau 217 (pg/mL)	Median	0.645	0.13	0.49	0.116	0.092	0.469	0.113
	Min - Max	0.204 - 2.294	0.042 - 1.765	0.153 - 2.505	0.030 - 0.469	0.050 - 0.142	0.077 - 2.505	0.030 - 1.765

Diagnostic accuracy

Lumipulse G pTau 217 Plasma demonstrated a high diagnostic accuracy for the detection of amyloid pathology. The area under the ROC curve (AUC) reached 0.91 (95% CI: 0.89–0.94), confirming a strong discriminative performance in this clinical population (Figure 1).

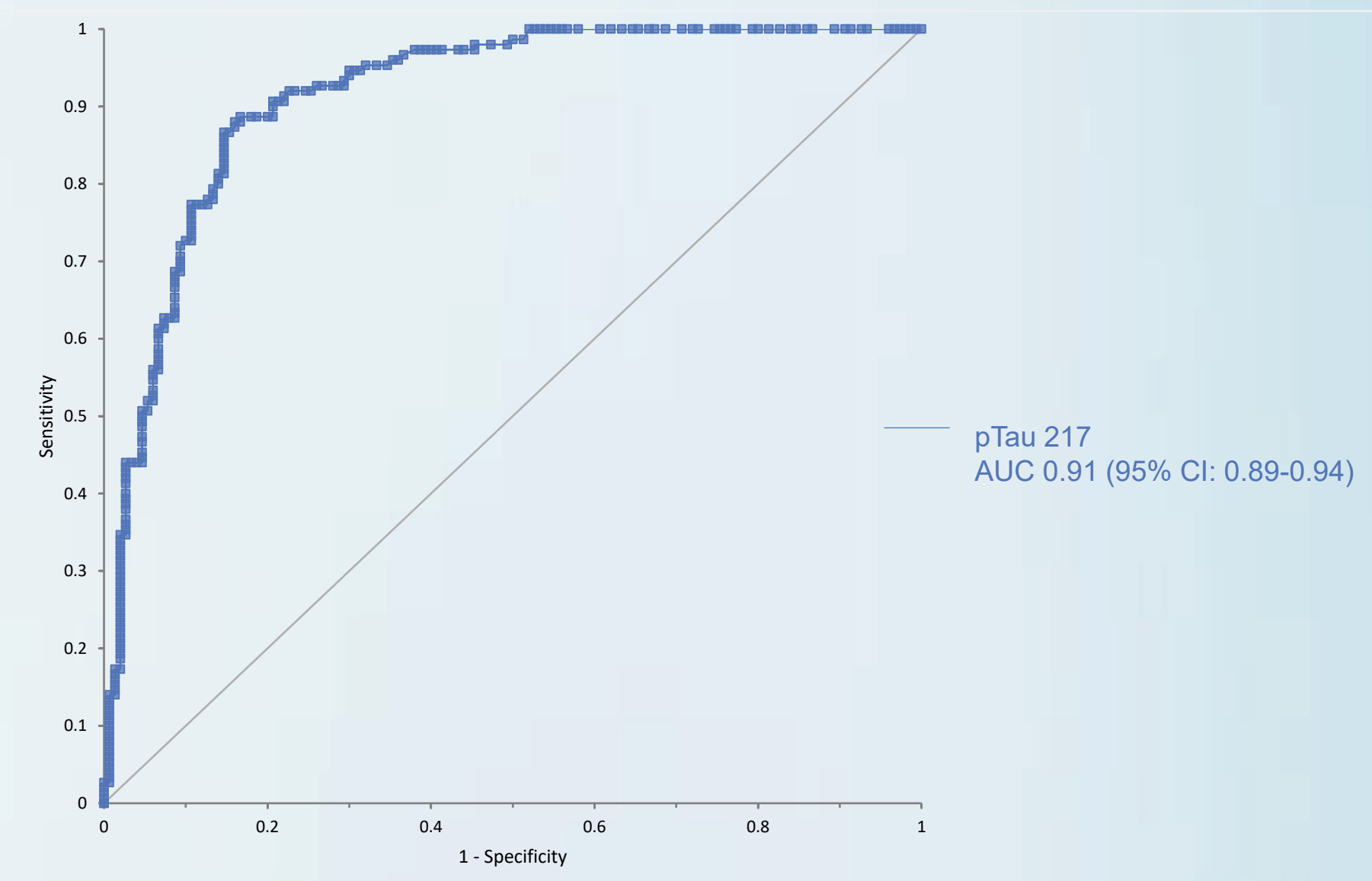


Figure 1: pTau 217 ROC curve for determination cohort (n = 300; prevalence Aβ-positivity = 50%).

Single cut-off approach

The single cut-off value determined according to bootstrapped maximum Youden index approach resulted in a cut-off value of:

- Result ≥ 0.201 pg/mL = Positive.

In the validation cohort, the single cut-off approach yielded a sensitivity of 0.881, 95%CI [0.828, 0.927] and a specificity of 0.851, 95%CI [0.787, 0.908], with an overall accuracy of 0.866 (253/292), 95%CI [0.825, 0.904]. Although these results indicate good diagnostic performance, predefined optimal acceptance criteria following the Global CEOi on AD (2024 Schindler, *et al*) were not fully met.

Dual cut-off approach

The optimal dual cut-off values were set considering sensitivity, specificity, and intermediate zone and were defined as:

- Result ≤ 0.162 pg/mL = Negative
- Result ≥ 0.278 pg/mL = Positive
- 0.162 pg/mL < Result < 0.278 pg/mL = Intermediate.

In the validation cohort, the dual cut-off approach significantly improved diagnostic performance, achieving both sensitivity and specificity of 0.908, 95%CI [0.854, 0.957] and 0.908, 95%CI [0.852, 0.957], respectively, as well as an overall accuracy of 0.908 (217/239), 95%CI [0.870, 0.943]. Importantly, this approach introduced an intermediate zone of 18.2%, allowing for improved clinical decision-making by distinguishing clearly positive and negative cases from intermediate results.

Reference ranges

Reference range analysis in Aβ-negative individuals (CSF Aβ42/Aβ40 ratio) included 291 subjects aged 51 to 85 years. Reference ranges were determined on all samples, and stratified by gender and age decade. The observed reference ranges (10th to 90th percentiles with 95% confidence intervals using a bootstrapped non-parametric method) are provided in Table 3. In this reference range population, 73.5% of the Lumipulse G pTau 217 Plasma assay results were consistent with a negative result and 8.9% with a positive result, while 17.5% fell within the intermediate zone.

Table 3: Reference ranges for Lumipulse G pTau 217 Plasma.

	10 th percentile	90 th percentile
All (n = 291)	0.070, 95%CI [0.065, 0.075]	0.259, 95%CI [0.215, 0.363]
Male (n = 138)	0.073, 95%CI [0.068, 0.079]	0.296, 95%CI [0.219, 0.482]
Female (n = 153)	0.065, 95%CI [0.054, 0.074]	0.256, 95%CI [0.198, 0.403]
50s (n = 36)	0.049, 95%CI [0.038, 0.055]	0.166, 95%CI [0.115, 0.272]
60s (n = 70)	0.062, 95%CI [0.054, 0.067]	0.184, 95%CI [0.141, 0.232]
70s (n = 162)	0.078, 95%CI [0.074, 0.083]	0.367, 95%CI [0.238, 0.490]
80s (n = 23)	0.088, 95%CI [0.080, 0.101]	0.495, 95%CI [0.226, 1.038]

Plasma pTau 217 concentrations demonstrated a gradual increase with age and were generally higher in males compared to females.

Conclusion

The Lumipulse G pTau 217 Plasma assay demonstrates strong capacity for detecting amyloid pathology in patients with cognitive decline.

The study highlights that a dual cut-off strategy is superior to a single cut-off approach, as it allows for improved sensitivity and specificity while maintaining an acceptable proportion of clinically meaningful intermediate results. Population-specific cut-off validation is essential to ensure optimal diagnostic accuracy. These findings support the use of plasma pTau 217 as a clinically actionable blood-based biomarker to aid AD assessment in specialized care settings.

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