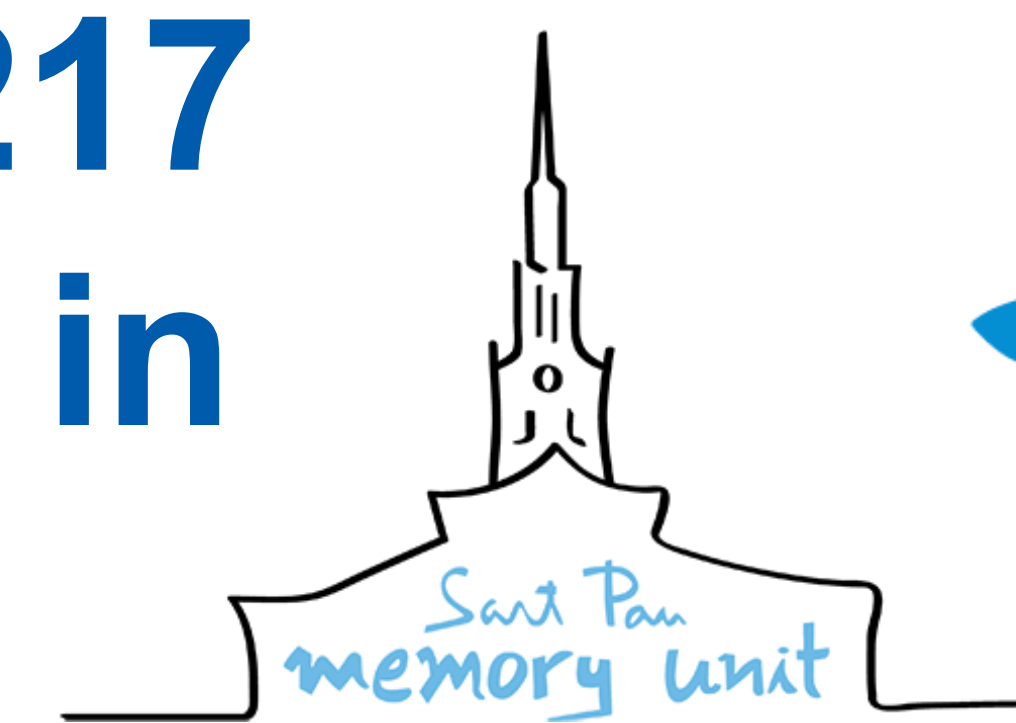


Performance of plasma pTau217/Aβ42 ratio and pTau217 to predict Aβ pathology status defined by CSF testing in SPIN cohort



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Background

- Early and accessible detection of amyloid pathology is central to Alzheimer's disease evaluation, yet CSF and PET testing remain limited by cost and invasiveness. Blood biomarkers, particularly plasma p-Tau217, have shown strong performance in identifying underlying AD pathology, and combining p-Tau217 with Aβ42 may enhance diagnostic accuracy.
- This study evaluated the performance of plasma p-Tau217 and the p-Tau217/Aβ42 ratio measured on the automated HISCL™-5000 / HISCL-800 immunoassay platform (Sysmex, Kobe, Japan) for predicting CSF-defined Aβ pathology in the SPIN (Sant Pau Initiative on Neurodegeneration) cohort.

Methods

- Plasma p-Tau217 and Aβ42 levels were measured by HISCL.
- The Mann-Whitney U test was applied to evaluate the differences of p-Tau217 and the p-Tau217/Aβ42 ratio between groups.
- The DeLong test was used to compare the performance of two models based on their AUC values.

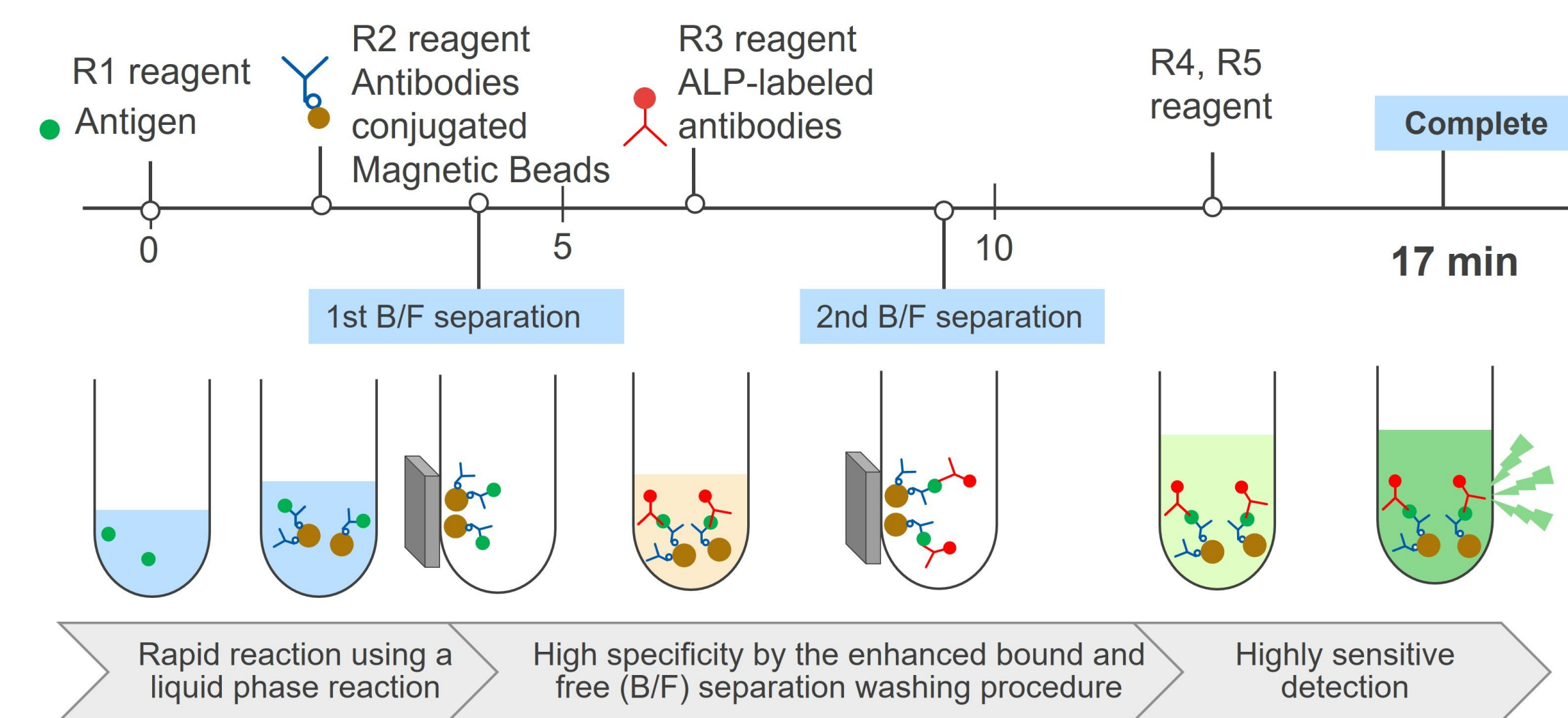


Figure 1. Principle of HISCL platform

Participant demographics

This study included 199 participants: 50 cognitively unimpaired (CU), 49 mild-cognitive impairment (MCI) due to Alzheimer's disease (AD), 49 MCI due to non-AD and 51 AD from The SPIN (Sant Pau Initiative on Neurodegeneration) cohort which was enrolled at Hospital de la Santa Creu i Sant Pau from 2013 to 2022³). The Aβ pathology was defined by CSF Aβ42/40 ratio measured by Lumipulse (Fujirebio-Europe).

Factor	Group	CSF Aβ-	CSF Aβ+	p value
	N	99	100	
Sex	Female / Male	44 / 55	63 / 37	0.011
Age (y/o), median [IQR]		65.00 [61.00, 71.00]	66.00 [64.00, 68.00]	0.392
MMSE, median [IQR]		29.00 [27.75, 30.00]	24.00 [21.00, 26.00]	<0.001
Family history	No / Yes / n.a.	21 / 47 / 31	29 / 31 / 40	0.048
Years of education		15.00 [9.00, 20.00]	11.00 [8.00, 13.75]	0.001
Clinical disease stage	CU / MCI-nonAD / MCI-AD / AD	50 / 46 / 0 / 3	0 / 3 / 49 / 48	<0.001
APOE ε4 status	- / + / n.a.	81 / 18 / 0	40 / 59 / 1	<0.001

Table 1. Participant demographics. Abbreviations: y/o; years old, IQR; Interquartile range, MCI-nonAD; MCI due to non-AD, MCI-AD; MCI due to AD, n.a.: not available, CSF Aβ-/+; Aβ negative/positive defined by CSF testing

Clinical performance of plasma pTau217 and pTau217/Aβ42 ratio

- Plasma p-Tau217 and the p-Tau217/Aβ42 ratio showed high performance in predicting Aβ pathology defined by the CSF Aβ42/40 ratio. The AUROC values were 0.947 (95% CI, 0.911–0.982) for p-Tau217 and 0.954 (95% CI, 0.920–0.987) for the p-Tau217/Aβ42 ratio.
- Plasma p-Tau217 and p-Tau217/Aβ42 ratio in Aβ+ group were distributed significantly higher than those of Aβ- group.

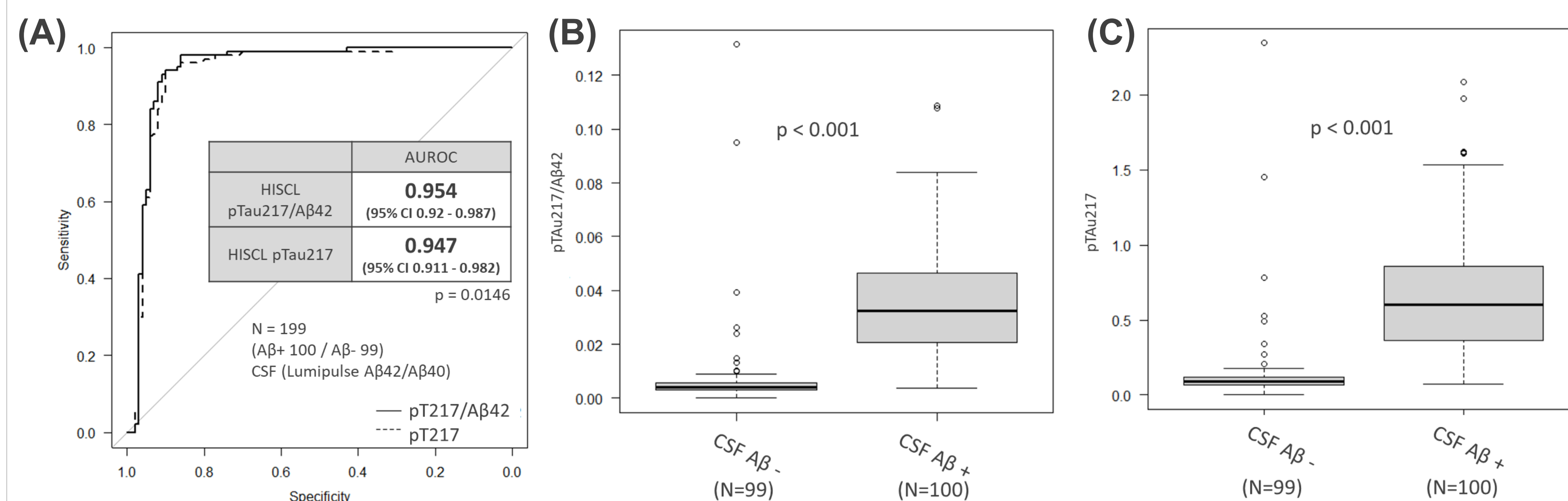


Figure 2. (A) ROC curve of plasma pTau217 and pTau217/Aβ42 ratio to predict CSF Aβ+/-, and the distribution of plasma pTau217/Aβ42 ratio (B) and pTau217 (C) in CSF Aβ+/- groups.

- Optimal cutoffs based on the Youden Index were 0.176 for p-Tau217 and 0.010 for the p-Tau217/Aβ42 ratio.
- At the p-Tau217 threshold of 0.176, diagnostic performance reached 93.0% sensitivity, 90.9% specificity, 91.2% PPV, 92.8% NPV, and 92.0% accuracy. At the p-Tau217/Aβ42 threshold of 0.010, sensitivity, specificity, PPV, NPV, and accuracy were 92.0%, 91.9%, 92.0%, 91.9%, and 92.0%, respectively.

pTau217 cutoff 0.176	CSF Aβ		HISCL	pos	neg	102
	pos	neg				
	93	9	pos	92	8	100
	7	90	neg	8	91	99
	100	99		100	99	199

sens	93.0%	≥ 90%
spec	90.9%	≥ 90%
PPV	91.2%	
NPV	92.8%	
Accuracy	92.0%	

pTau217/Aβ42 cutoff 0.01	CSF Aβ		HISCL	pos	neg	100
	pos	neg				
	92	8	pos	92	8	100
	8	91	neg	8	91	99
	100	99		100	99	199

sens	92.0%	≥ 90%
spec	91.9%	≥ 90%
PPV	92.0%	
NPV	91.9%	
Accuracy	92.0%	

- A two-threshold strategy designed to achieve both >95% sensitivity and specificity was also evaluated. Thresholds of 0.158 / 0.490 for p-Tau217 produced 94.2% accuracy with 21.6% intermediate zone, while thresholds of 0.007 / 0.024 for the p-Tau217/Aβ42 ratio yielded 96.1% accuracy with 23.1% intermediate zone.

pTau217 cutoff (positive) > 0.49	CSF Aβ		HISCL	pos	neg	65
	pos	neg				
Intermediate zone 0.159 - 0.49	61	4	pos	63	4	67
cutoff (negative) ≤ 0.158	34	9	gray zone	35	11	46
	5	86	neg	2	84	86
	100	99		100	99	199

Spec in positive group	96.0%	≥ 95%
Sens in negative group	95.0%	≥ 95%
Frequency of int. zone	21.6%	
Accuracy	94.2%	

pTau217/Aβ42 cutoff (positive) > 0.024	CSF Aβ		HISCL	pos	neg	67
	pos	neg				
Intermediate zone 0.008 - 0.024	63	4	pos	63	4	67
cutoff (negative) ≤ 0.007	35	11	gray zone	35	11	46
	2	84	neg	2	84	86
	100	99		100	99	199

Spec in positive group	96.0%	≥ 95%
Sens in negative group	98.0%	≥ 95%
Frequency of int. zone	23.1%	
Accuracy	96.1%	

- Overall, both single-threshold and two-threshold approaches achieved >90% sensitivity, specificity, and accuracy for predicting Aβ pathology.

Conclusions

Plasma p-Tau217 and the p-Tau217/Aβ42 ratio demonstrated high accuracy for identifying Aβ pathology defined by CSF Aβ42/40, with both markers achieving AUROC values >0.94 and strong diagnostic performance across sensitivity, specificity, and predictive values. The two-threshold strategy further enabled high accuracy while delineating a small intermediate zone suitable for confirmatory testing. These findings support the clinical utility of automated p-Tau217-based assays as scalable blood biomarkers for effective detection and triage of Alzheimer's disease-related amyloid pathology.

Reference

1) D Alcolea et al., Alzheimers Dement (N Y), 2019, 2) J Arranz et al, Alzheimers Res Ther, 2024

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