

Performance of plasma A β 42/40 ratio to predict A β pathology status defined by CSF testing in SPIN cohort

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Background

- The Amyloid status in the brain is currently examined by amyloid positron emission tomography (PET) or β -Amyloid (A β) 42 or the A β 42/40 ratio in cerebrospinal fluid (CSF)¹⁾. Predicting it by blood-based assays is useful for screening of Alzheimer's disease.
- Sysmex completed a declaration of conformity to the European IVD (CE-IVD) Directive for the assay kit that measures plasma A β using the Automated Immunoassay System HISCL™-5000/ Automated Immunoassay System HISCL-800 (HISCL) in 2022.
- The excellent performance of plasma A β 42/40 ratio measured by HISCL to predict A β pathology status defined by Amyloid PET was previously reported²⁾.
- In this study, we aimed to evaluate the performance of plasma A β 42/40 ratio to predict A β pathology defined by CSF testing in another cohort.

Methods

- Plasma A β 40 and A β 42 levels were measured by HISCL.

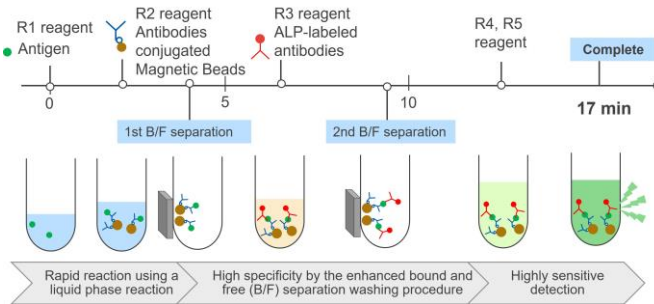


Figure 1. Principle of HISCL platform

- The Mann-Whitney U test was applied to evaluate the differences of A β 42/A β 40 ratio between groups.
- The DeLong test was used to compare the performance of two models based on their AUC values.

Participant demographics

This study included 200 participants: 50 cognitively unimpaired (CU), 49 mild-cognitive impairment (MCI) due to Alzheimer's disease (AD), 50 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 A β pathology was defined by CSF A β 42/40 ratio measured by Lumipulse (Fujirebio-Europe).

Factor	Group	CSF A β -	CSF A β +	p value
	N	100	100	
Sex	Female / Male	44 / 56	63 / 37	0.011
Age (y/o), median [IQR]		65.00 [61.00, 71.00]	66.00 [64.00, 68.00]	0.799
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 / 32	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 / 47 / 0 / 3	0 / 3 / 49 / 48	<0.001
APOE ϵ 4 status	- / + / n.a.	82 / 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 A β -/+; A β negative/positive defined by CSF testing

Clinical performance of plasma A β 42/40 ratio

- Plasma A β 42/40 ratio can predict the A β pathology determined by CSF A β 42/40 ratio at AUROC: 0.895 (95% CI 0.844 – 0.947). The calculated threshold determined by Youden Index was an A β ratio of 0.103 which is similar to the previously reported threshold 0.102²⁾.
- The sensitivity, specificity, PPV and NPV at the threshold 0.103 were 86.0%, 88.0%, 87.8% and 86.3%, while at 0.102 were 82.0%, 90.0%, 89.1% and 83.3%, respectively.
- Plasma A β 42/40 ratio in A β + group were distributed significantly lower than those of A β - group.
- There were significantly different distribution between disease stage groups except between CU and MCI-nonAD.

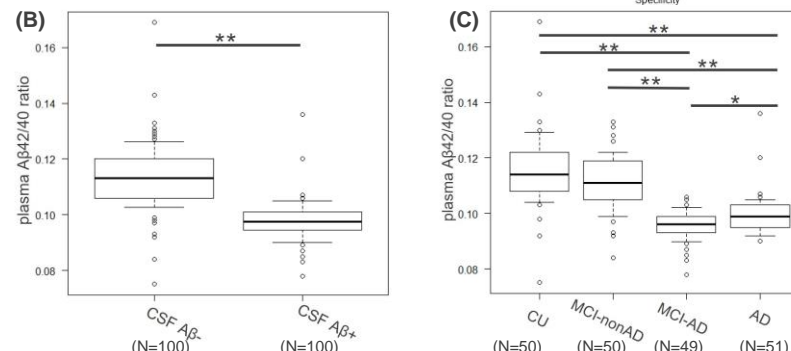


Figure 2. (A) ROC curve of plasma A β 42/40 ratio to predict CSF A β -/+, and the distribution of plasma A β ratio (B) in CSF A β -/+ groups, (C) disease stage groups. *p* values are indicated with asterisks: **p*<0.05, ***p*<0.001

Model with ApoE ϵ 4 and performance of plasma A β 42/40 ratio in MCI patients

- The addition of ApoE4 allele possession status didn't improve the performance significantly. (AUROC 0.903 (de Long's test *p*=0.519, compared to A β ratio only)).
- When analyzed only within MCI patients (due to AD and not due to AD), AUROC was 0.902 (95% CI 0.828 – 0.975). The sensitivity, specificity, PPV and NPV at the threshold 0.102 which was determined by Youden Index for this analysis were 88.5%, 87.2%, 88.5% and 87.2%, respectively.

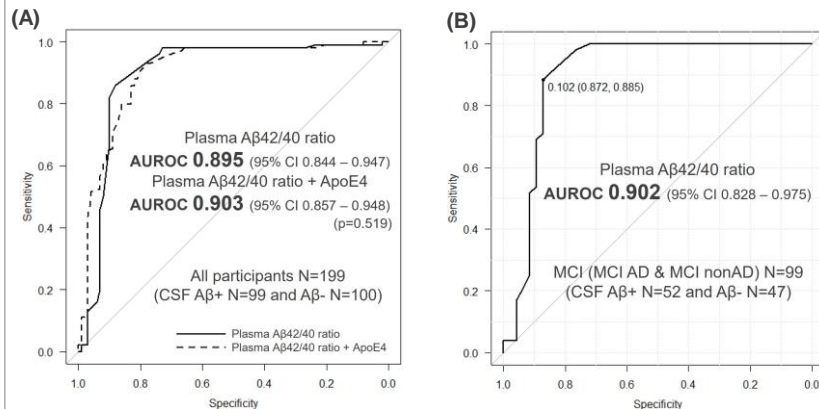


Figure 3. (A) ROC curves of plasma A β 42/40 alone compared with plasma A β 42/40 + ApoE ϵ 4 status to predict CSF A β -/+ in all participants whose ApoE ϵ 4 status are available (*n*=199 (99 CSF A β +, 100 CSF A β -)). (B) ROC curve of plasma A β 42/40 in MCI patients (MCI-AD and MCI-nonAD *n*=99 (52 CSF A β +, 47 CSF A β -))

Conclusions

- Plasma A β 42/40 ratio measured by HISCL achieved high accuracy in predicting A β pathology determined by CSF testing similarly to the previous report comparing with Amyloid PET in another cohort.
- This plasma assay may give a useful suggestion to detect A β positivity in brain in a less invasive way.

Reference

- CR Jack Jr et al., *Alzheimers Dement*, 2018
- K Yamashita et al., *Alzheimers Res Ther*, 2022
- D Alcolea et al., *Alzheimers Dement* (N Y), 2019