Three group classification of participants based on fully automated plasma β-amyloid measurements to achieve high positive and negative predictive values

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Background

- The accelerated development of disease-modifying therapies targeting β-amyloid (Aβ) for the treatment of Alzheimer's disease (AD) has increased the need for blood-based biomarkers to predict brain Aβ status.

- We reported that plasma $A\beta_{1-42}$ (Aβ42) to $A\beta_{1-40}$ (Aβ40) ratio measured by our fully automated immunoassay platform (HISCL™ series) predicted brain Aβ status defined by amyloid positron emission tomography (PET) as assessed by Centiloids (CL) with area under the curve (AUC) of 0.922.

- In the previous analysis, we determined a cut-off value of 0.102 using the Youden index. Using this cut-off value, we achieved high negative predictive value (NPV) of 94.0% and moderate positive predictive value (PPV) of 79.6%.

- In this study, we classified participants into three groups (plasma Aβ positive, intermediate, and negative groups) by their plasma Aβ42/Aβ40 ratio, in order to improve PPV of our plasma Aβ assay.

Rapid measurement
17 minutes per test

Small sample volume
30 μL per test

High throughput
100 or 200 tests per hour
(depending on the instrument)

Figure 1. Appearance and features of HISCL series.

Methods

- Plasma Aβ40 and Aβ42 were measured using a fully automated platform in a set of plasma samples sourced from participants in the screening period of the elenbecestat Phase 3 program.

- In this analysis, we included 172 amyloid PET positive and 199 negative participants.

- Brain Aβ status was determined by predefined Centiloid unit (CL) of amyloid PET (cut-off value defined previously as 32.21 CL).

- The AUC for plasma Aβ42/Aβ40 ratio for predicting brain Aβ status was obtained by performing ROC analysis using logistic regression.

- We determined the cut-off value of our plasma Aβ42/Aβ40 ratios that would result in a PPV of 90.0% or more. We then utilized this cut-off value and the prior reported cut-off value of 0.102 to divide participants into plasma Aβ positive, intermediate, and negative groups.
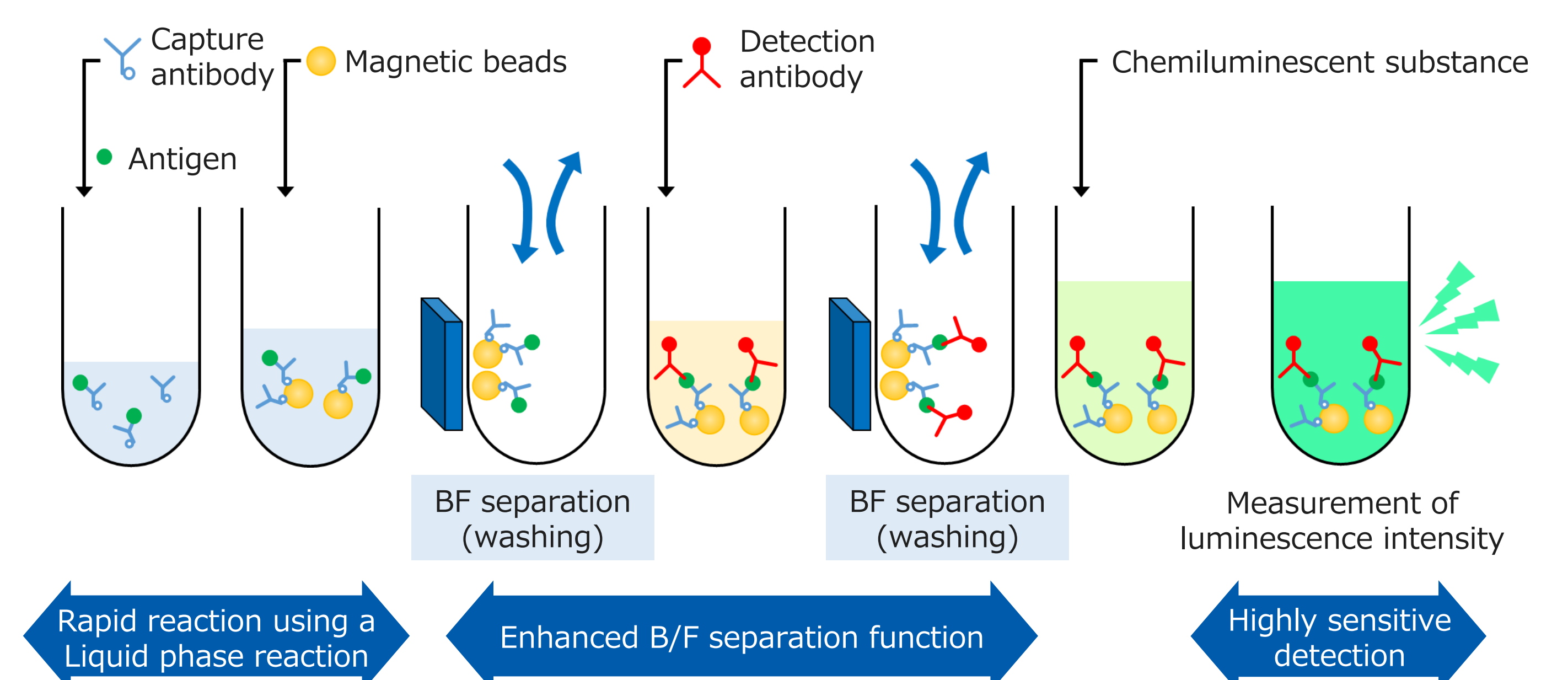

Figure 2. Assay principle of HISCL series.

Results

1. Participants demographics

- Amyloid PET positive group was significantly older, more often carried one or two *APOE* ε4 allele, and more often used florbetaben as an amyloid PET probe.

Table 1. Participants demographics

	Amyloid PET negative (n=199)	Amyloid PET positive (n=172)	*P* value
Age (y), mean ± SD	69.1 ± 8.8	72.8 ± 7.1	< 0.001
Sex, female/male	109/90	91/81	NS
Race, White/Japanese/Other	130/48/21	111/51/10	NS
APOE ε4 status, -/+/NA	160/38/1	68/103/1	< 0.001
Amyloid PET probe, FBB/FBP/FMM	138/16/45	100/28/44	0.024
MMSE, mean ± SD	26.4 ± 1.7	26.5 ± 1.9	NS
CDR-SB, mean ± SD	2.4 ± 1.0	2.5 ± 1.0	NS
Clinical disease staging, MCI due to AD/mild AD	40/159	35/172	NS

The differences between groups were evaluated using the Student's t-test for continuous measures and the χ^2 test for categorical variables.
Abbreviations: y, years; SD, standard deviation; NS, not significant; *APOE*, Apolipoprotein E; NA, not available; FBB, florbetaben; FBP, florbetapir; FMM, flutemetamol; MMSE, Mini-Mental State Examination; CDR-SB, Clinical Dementia Rating-Sum of Boxes; MCI, Mild Cognitive Impairment.

2. ROC analysis

- Plasma Aβ42/Aβ40 ratio measured using HISCL series predicted brain Aβ status defined by amyloid PET with an AUC of 0.93.

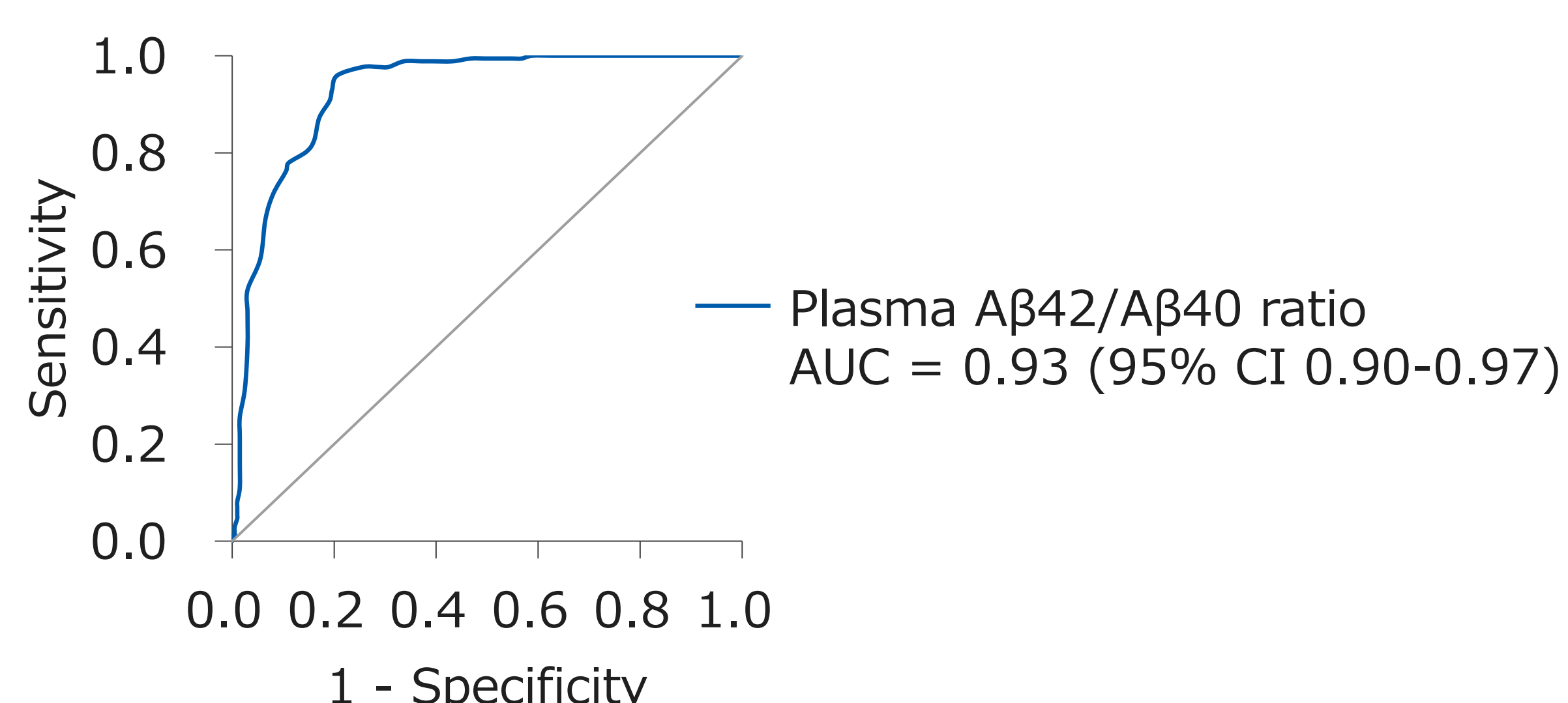Figure 3. Clinical performance of plasma Aβ42/Aβ40 ratio.
The AUC is described with 95% confidence interval (CI) which is calculated based on DeLong method.

3. Three group classification

- A cut-off value of 0.092 was determined as a value to achieve a PPV of at least 90.0%.

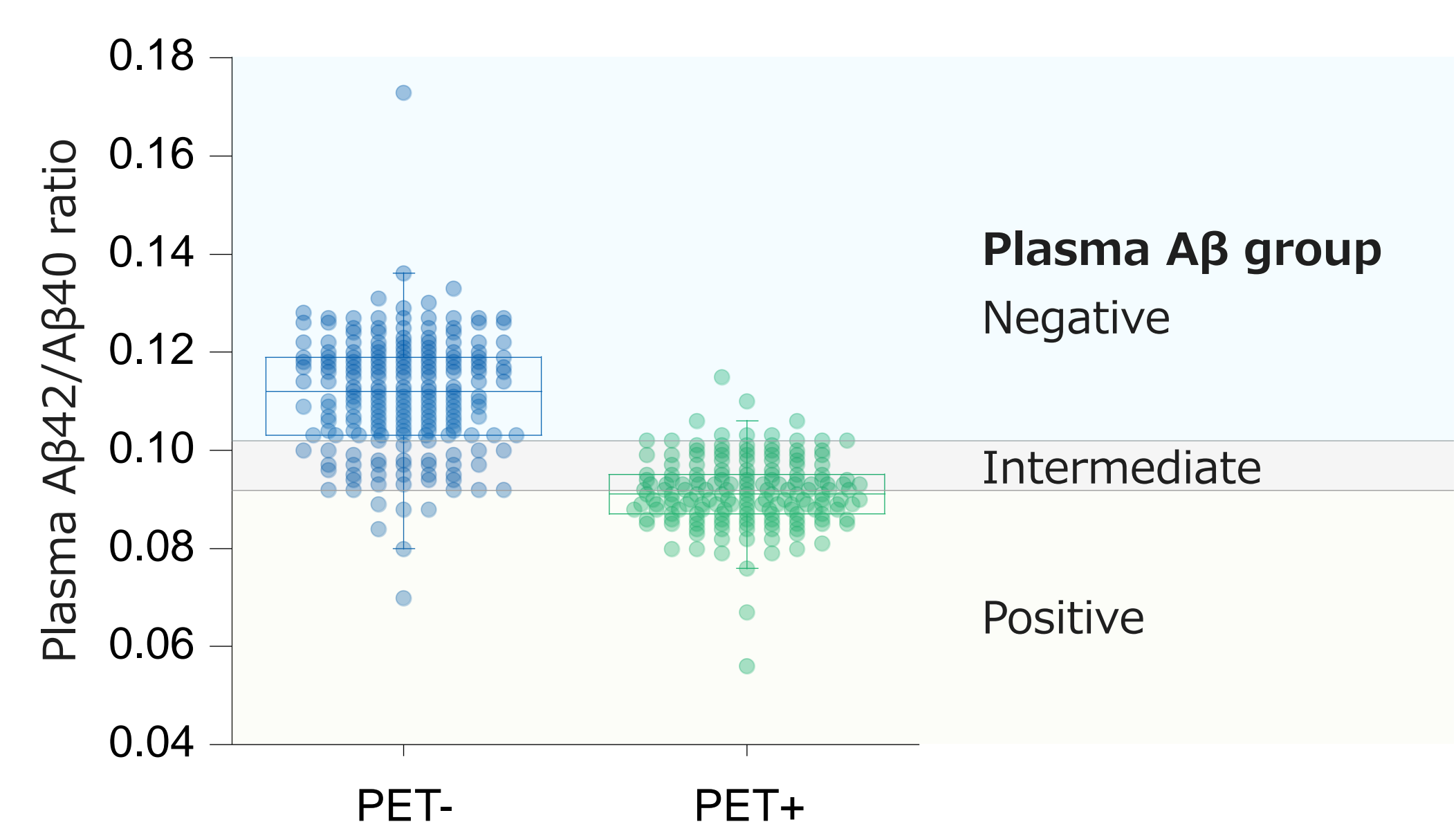- PPV in positive Aβ group was 90.1% while NPV in the negative Aβ group was 95.8%.

Figure 4. Three group classification using plasma Aβ42/Aβ40 ratio. Participants were classified into positive (≤ 0.092), intermediate (> 0.092 and ≤ 0.102), and negative (> 0.102) Aβ groups based on plasma Aβ42/Aβ40 ratio.

Table 2. Predictive values of plasma Aβ42/Aβ40 ratio.

		Amyloid PET		Predictive value	Frequency
		Negative	Positive		
Plasma Aβ group	Negative (Aβ42/Aβ40 > 0.102)	158	7	**95.8% (NPV)**	44.5%
	Intermediate (0.092 < Aβ42/Aβ40 ≤ 0.102)	30	65	68.4% (PPV)	25.6%
	Positive (Aβ42/Aβ40 ≤ 0.092)	11	100	**90.1% (PPV)**	29.9%

Conclusion

- Three group classification allowed our plasma Aβ assay to achieve PPV and NPV ≥ 90% with 74.4% of participants classifiable as Aβ positive or negative groups.

- This result indicated that our assay may contribute to reduce amyloid PET scan or CSF Aβ testing, which could be helpful in applications such as the recruitment step of clinical trials.

- However, it should be noted that predictive values and frequency will vary depending on the prevalence of amyloid PET positive participants.