Aβ42/Aβ40 ratio in plasma predicts amyloid-PET status in amnestic-MCI patients

María Pascual-Lucas, Leticia Sarasa, Elisabet Molina, Sergio Castillo, Pedro Pesini and José A. Allué

Araclon Biotech-Grifols, Zaragoza, Spain

alzheimer's association AAIC 21 ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE®

BACKGROUND

Previous studies have shown that the Aβ42/Aβ40 ratio in plasma predicts Aβ status reliably[1], suggesting that the assessment of plasma Aβ levels could be a useful screening tool for Alzheimer's disease clinical trials.

In this work, we explore the ability of Aβ42/Aβ40 plasma ratio as determined by a novel antibody-free, HPLC-MS/MS method (ABtest-MS), to predict the Aβ-PET status at the baseline visit in the ABvac40 (an active vaccine against Aβ40) phase II clinical trial, AB1601 (NCT03461276), that is being led and promoted by Araclon Biotech.

METHODS

A subpopulation of 73 amnestic-MCI (a-MCI) participants who had undergone [18F]Flutemetamol PET scans were considered for the present work. Aβ-PET status was assessed by visual reading.

Table 1. Demographic characteristics of the a-MCI patients from the AB1601 study at baseline.

		Aβ-PET (-)	Aβ-PET (+)	*p* value
Participants	*n (%)*	18 (24.7 %)	55 (75.3 %)	
Age, years	*median (IQR)*	68.0 (64.3-75.0)	70.0 (66.0-75.0)	0.530
Female	*n (%)*	7 (38.9 %)	38 (69.1 %)	0.045
APOE ε4 carriers	*n (%)*	7 (38.9 %)	36 (65.5 %)	0.087

Aβ40 and Aβ42 plasma levels were quantified using ABtest-MS, a novel antibody-free, HPLC-MS/MS method. Analytes were extracted directly from plasma and no immunoprecipitation procedure was followed. Intact Aβ1-40 and Aβ1-42 species were measured as no enzymatic digestion was performed. Levels of p-tau181 in plasma were measured with Simoa® p-tau181 V2 Advantage Kit (Quanterix, Billerica, MA, USA).

The ability of plasma Aβ42/Aβ40 ratio or p-tau181 levels to detect Aβ-PET positivity was assessed as the area under the ROC curve (AUC).

(1) Janelidze, S., et al., Detecting amyloid positivity in early Alzheimer's disease using combinations of plasma Aβ42/Aβ40 and p-tau. Alzheimers Dement, 2021.

RESULTS

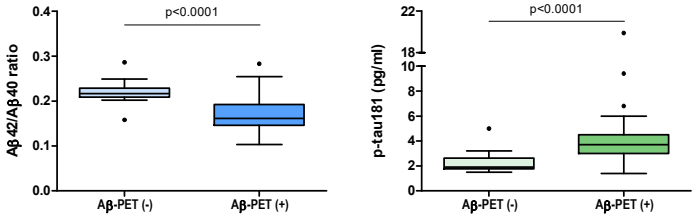
1. Distribution of Aβ42/Aβ40 ratio and p-tau181 levels in plasma between Aβ-PET groups

Aβ42/Aβ40 plasma ratio was significantly lower in the Aβ-PET (+) group than in the Aβ-PET (-) group (p<0.0001, Mann-Whitney test). The opposite was observed for p-tau181 plasma levels (p<0.0001, Mann-Whitney test).

Table 2. Plasma Aβ42/Aβ40 ratio and p-tau181 levels (median and interquartile range) in Aβ-PET (-) and Aβ-PET (+) groups.

	Aβ-PET (-)	Aβ-PET (+)	*p* value
Plasma Aβ42/Aβ40, ratio	0.217 (0.209-0.229)	0.161 (0.146-0.192)	< 0.0001
Plasma p-tau181, pg/ml	1.90 (1.78-2.63)	3.70 (3.00-4.50)	< 0.0001

Figure 1. Box and whiskers plots of plasma Aβ42/Aβ40 ratio (left graph) and p-tau181 levels (right graph) between Aβ-PET groups.



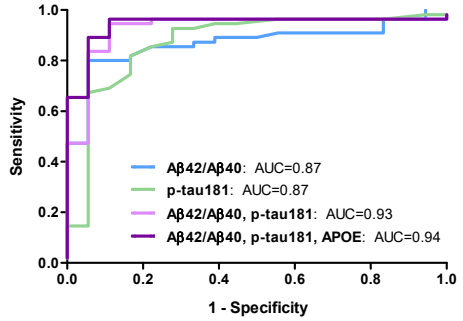
2. Discriminative ability of Aβ-PET status

ROC curve analysis for identifying Aβ-PET status revealed an AUC of 0.87 (95% confidence interval [CI] 0.78–0.95) for the Aβ42/Aβ40 ratio. Plasma p-tau181 levels performed identically with an AUC of 0.87 (95% CI 0.77–0.98).

The model combining plasma Aβ42/Aβ40 ratio and p-tau181 levels outperformed the models of both individual biomarkers alone with an AUC of 0.93 (95% CI 0.86–1.00; ΔAUC = 0.06).

A negligible increment in the AUC up to 0.94 (95% CI 0.88-1.00) was obtained after adjusting for APOE genotype.

Figure 2. ROC curves for discriminating Aβ-PET status.



The Youden cutoff of the plasma Aβ42/Aβ40 ratio (0.199) yielded a sensitivity of 80.0%, an specificity of 94.4% and an overall accuracy of 83.6%. These results were further improved in terms of sensitivity, NPV, accuracy and LR- when adding both plasma biomarkers and APOE genotype in the model.

Table 3. Agreement statistics between logistic regression models and Aβ-PET status.

Model	Se	Sp	PPV	NPV	Acc	LR+	LR-	1/LR-
Aβ42/Aβ40	80.0%	94.4%	97.8%	60.7%	83.6%	14.4	0.2	4.7
p-tau181	81.8%	83.3%	93.8%	60.0%	82.2%	4.9	0.2	4.6
Aβ42/Aβ40, p-tau181	94.5%	88.9%	96.3%	84.2%	93.2%	8.5	0.1	16.3
Aβ42/Aβ40, p-tau181, ApoE	96.4%	88.9%	96.4%	88.9%	94.5%	8.7	0.0	24.4

CONCLUSIONS

Aβ42/Aβ40 plasma ratio discriminates Aβ-PET positivity with high accuracy in this cohort of a-MCI individuals, performing as well as p-tau181.

The combination of both plasma biomarkers in addition to APOE genotype in the regression model yields an accuracy close to 95%, and could be used as a helpful tool for prediction of Aβ-PET status.