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【Overview presentation】

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Combination of Plasma Aβ42/40 and p-tau217 Measured Using Fully Automated Immunoassay System Accurately Predicts Amyloid Pathology Determined by Amyloid PET

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Overview presentation	**Background:** Prior to initiating anti-amyloidβ (Aβ) antibodies for Alzheimer's disease (AD), confirmation of amyloid pathology in the brain is required. Currently, positron emission tomography (PET) or cerebrospinal fluid (CSF) testing are mainly used. These tests are also useful for the differential diagnosis of atypical cases. However, these methods have limitations on their costs, burden, and invasiveness. Therefore, blood-based biomarkers have been highly sought after in clinical practice. Plasma Aβ42/40 ratio was first reported as candidate biomarkers, and more recently, p-tau217 has gained increasing attention. We previously reported that our plasma Aβ42/40, measured by a fully automated immunoassay system, can predict amyloid pathology as defined by amyloid PET [1]. Recently, Alzheimer's Association Clinical Practice Guideline on the use of blood-based biomarkers

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	has been published and they recommended that blood-based biomarker tests for triaging should have sensitivity of at least 90% and specificity of at least 75% [2]. Although further validation may be required, our plasma Aβ42/40 met these criteria in previous studies [1]. Measuring p-tau217 on the same platform may further improve diagnostic accuracy. On the other hand, in clinical practice, atypical cases may show exceptional values and affect accuracy. In this study, we evaluated the performance of our highly accurate Aβ42/40, p-tau217, and their combinations to predict amyloid pathology in a clinically heterogeneous cohort that includes atypical cases. **Methods:** Plasma samples from 45 Japanese patients registered in the TMIG Biobank were used in this study. All patients underwent amyloid PET using Pittsburgh Compound B (PiB) to support the differential diagnosis. PET positivity was determined by visual read. Plasma levels of Aβ40, Aβ42, and p-tau217 were measured using the Automated Immunoassay System HISCL™-5000 (Sysmex Corporation, Japan). The predictive performance for amyloid PET positivity was evaluated using each biomarker, their ratios, and combinations of biomarkers based on logistic regression. Receiver operating characteristic analyses were conducted, and cohort specific cut-offs were determined using Youden index. **Results:** Among the 45 patients, 22 were amyloid PET positive and 23 were amyloid PET negative. The median (interquartile range) ages of amyloid PET–positive and amyloid PET–negative groups were 62 (55 – 68) and 70 (60 – 75) years, respectively. Two patients in the amyloid PET–positive group and one in the negative group were younger than 50 years of age, and the remaining were 50 years or older. Both groups included 14 male patients, and the remaining patients were female. Clinical diagnoses were mainly symptomatic AD in the amyloid PET–positive group and non-AD mild cognitive impairment or dementia in the negative group. The amyloid PET–positive group showed significantly lower plasma Aβ42/40 (0.098 [0.094 – 0.103] vs 0.118 [0.110 – 0.121]) and higher plasma p-tau217 (0.669 [0.459 – 1.114] vs 0.073 [0.050 – 0.119]). Plasma Aβ42/40 and p-tau217 predicted amyloid PET positivity with area under curves (AUCs) of 0.859 and 0.925, and cut-offs in this cohort calculated by Youden index were 0.105 and

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	0.179, respectively. Based on these cut-offs, there were two patients in the amyloid PET–positive group with extremely high Aβ42/40 values, leading to false negative results. Both patients had early onset AD and were younger than 50 years of age. One patient had a family history of early-onset dementia compatible with autosomal dominant AD. Both showed increased values above the cut-off and were correctly identified as positive by p-tau217. For p-tau217, we observed two patients in the amyloid-PET-negative group showing high values above the cut-off leading to “false-positive” results. One of them showed Aβ42/40 in the normal range in concordance with amyloid PET. Both patients were in their 60s and had no significant family history of dementia. Both patients were suspected to have positive tau pathology based on high neocortical tau PET uptake using MK6240. Amyloid PET showed mild local uptake that did not reach the threshold of a positive binary reading (equivocal results). Predictive performance of p-tau217/Aβ42 was also evaluated and the AUC was 0.936. The combination of Aβ42/40 and p-tau217 yielded a slightly higher AUC (0.941) and better separation in typical cases. **Conclusions:** We confirmed that plasma Aβ42/40 and p-tau217 measured using our fully automated immunoassay system demonstrated high accuracy in predicting amyloid PET positivity. Although each of these biomarkers showed false-positive or false-negative results against amyloid PET, the results of other biomarkers were often useful in clinical interpretation. A previous study also showed that plasma Aβ42/40 can be increased in patients with autosomal-dominant AD [3] and may warrant further investigation. Patients with low Aβ PET and high neocortical tau PET results are the focus of debate and may or may not have AD [4, 5]. While combined biomarkers (i.e. p-tau217/Aβ42) can improve diagnostic performance, assessment of individual biomarkers may also be important in evaluating patients in a heterogenous cohort including rare but important cases such as those with early-onset familial AD or low Aβ and high neocortical tau PET cases. **References:** 1. Yamashita K, et al. *Alzheimers Res Ther* 2022; 14(1): 86. 2. Palmqvist S, et al. *Alzheimer's & Dementia* 2025; 21(7).

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