

Plasma Amyloid- β Oligomerization Tendency Predicts Amyloid PET Positivity

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Abstract

Background: Among other emerging amyloid-targeting blood-based biomarkers, Multimer Detection System-Oligomeric Amyloid- β (MDS-OA β) measures dynamic changes in concentration of oligomeric amyloid- β (OA β), which is considered the main pathogenic culprit of Alzheimer's disease (AD), in plasma after spiking with synthetic amyloid- β (A β). We aimed to investigate predictability of MDS-OA β on amyloid Positron Emission Tomography (PET) positivity.

Methods: A total of 96 subjects who visited Seoul National University Bundang Hospital for medical check-up complaining of cognitive decline and had undergone extensive medical assessment were recruited. Amyloid statuses were dichotomized into positive or negative based on visual assessment of amyloid PET. Plasma OA β concentration was measured by MDS-OA β . In the previous validation study, 0.78ng/ml was established as the cut-off value and the plasma OA β concentration higher than or equal to the cut-off value was defined MDS-OA β positive.

Results: MDS-OA β positivity could discriminate amyloid PET positivity with the AUC value of 0.855 (95% CI 0.776–0.933). Adding MDS-OA β positivity to prediction models including age, MMSE score, and APOE ϵ 4 status improved the performance up to the AUC value of 0.926 (95% CI 0.871–0.980).

Conclusions: The A β oligomerization tendency in plasma could predict amyloid PET positivity with high performance, and when it is combined with age, MMSE score, and APOE ϵ 4 status, the predictability was improved substantially. This suggests the potential of MDS-OA β as a useful initial stage test in clinical and research field of AD.

Background

Brain amyloidopathy is a hallmark of Alzheimer's disease (AD) and pathologic changes associated with amyloid- β (A β) is known to start 10–20 years prior to clinical manifestation [1,2]. Due to such long period of progressive pathological changes without symptoms, prediction of disease progression has always been a challenge. Also, as clinical trials on disease-modifying treatment have not shown satisfactory results, the necessity to advance the stage of therapeutic target population towards early AD stage as well as the importance of early detection of amyloidopathy have been emphasized.

Currently, brain amyloidopathy is assessed by amyloid positron emission tomography (PET) and cerebrospinal fluid (CSF) biomarker test [3]. However, their high cost and invasiveness limit their utility in spite of increased needs and hence, the development of an AD biomarker which could overcome such limitations has been long anticipated. There have been efforts to develop an amyloid-targeting blood-based biomarker in order to provide better accessibility in the research and primary care fields and blood-based biomarkers have shown promising potential in their utility in the prediction of amyloidopathy [4].

Multimer Detection System-Oligomeric Amyloid- β (MDS-OA β) is a modified atypical sandwich immunoassay for measuring A β oligomerization in plasma [5]. MDS was originally developed as a

means to detect prion oligomers in the blood of scrapie-infected animals, which selectively detect oligomers over monomers. The technique was further modified by spiking synthetic A β into plasma prior to the antigen-antibody reaction to measure oligomerization tendency of plasma A β . It measures the dynamic change of plasma oligomeric A β concentration which is higher in AD patients compared to normal healthy controls [5,6]. In previous studies MDS-OA β could differentiate AD from normal control group with high sensitivity and specificity [5,6].

In this study, we aimed to evaluate the predictability of plasma A β oligomerization tendency measured by MDS-OA β on brain amyloidopathy.

Methods

Subjects

We included subjects who visited the Neurocognitive Behavior Center of the Seoul National University Bundang Hospital, Republic of Korea, between May 2014 and May 2020 for medical check-up out of complaints on cognitive decline and had undergone extensive evaluation of cognitive function, that contained physical, neurological, neuropsychological, genetic (*APOE* genotyping) and biomarker analyses including brain magnetic resonance imaging, amyloid PET, and MDS-OA β . Patients who have not undergone amyloid PET or MDS-OA β were excluded from this study. Subjects consisted of 54 probable AD dementia patients according to the National Institute on Aging-Alzheimer's Association criteria [7], 27 mild cognitive impairment (MCI) patients according to the National Institute on Aging-Alzheimer's Association criteria [8], 7 subjective cognitive decline (SCD) patients according to the guideline by Jessen et al. [9], 8 other neurodegenerative diseases as a disease control group including 4 frontotemporal dementia (FTD) patients [10,11], 1 corticobasal syndrome (CBS) patient [12], 1 Parkinson's disease dementia (PDD) patient [13], and 2 progressive supranuclear palsy (PSP) patients [14]. Written informed consent was obtained from all subjects or their caregivers. This study was approved by the institutional review board of the Seoul National University Bundang Hospital (B-2004-604-305).

Blood sampling and MDS-OA β measurement

Blood was collected in 10-ml sodium heparin-containing tubes (BD-367874; BD Bioscience, San Jose, CA, USA) and centrifuged at 1500 \times g for 10 minutes at room temperature. The time interval between the blood sampling and centrifugation was maximal 3 hours. The plasma supernatant was aliquoted and stored in screw cap microtubes (polypropylene, SARSTEDT, Ref. number: 72.690) at -80°C until further analysis.

The MDS-OA β measurement was performed using the inBloodTM OA β test (PeopleBio Inc., Gyeonggi-do, Republic of Korea) with heparin-treated plasma samples. The inBloodTM OA β test is a modified sandwich Enzyme-Linked Immunosorbent Assay (ELISA) for measuring oligomerization tendency using two epitope-overlapping antibodies specific for the N-terminus of A β . The antibodies used are mouse monoclonal 6E10 (BioLegend, San Diego, CA, USA) and WO-2-HRP (Absolute Antibody Ltd, Oxford, UK) and the epitopes for these antibodies overlap at the N-terminus of A β . 6E10, the capturing antibodies are

coated on the wells of the 96-well plate to initially capture heterogeneous forms of A β . WO-2-HRP, the detection antibodies are added after the first antigen-antibody reaction and three rounds of washing to detect oligomeric forms of A β and produce signal via chemiluminescence.

Prior to the assay, plasma samples were thawed at 37°C for 15min. PBR-1 (synthetic A β made by PeopleBio Inc.) was then spiked into plasma and the mixture was incubated 37°C for 48 hours. The incubated plasma sample mixture and serially diluted standard samples were added to respective wells, and the plates were incubated at room temperature for 1 hour. Afterward, 100 μ l/well of enhanced chemiluminescence substrate solution (Rockland Immunochemicals Inc., Limerick, PA, USA) was added, and the Relative Luminescence Unit (RLU) signal was detected using Victor 3TM multi-spectrophotometer. Dilutions providing signal in the linear range of the standard curves were used for the conversion to RLU values to determine the concentration of oligomerized A β . All tests were completed in duplicate and the average was used. 0.78 ng/ml was established as the cut-off value in the previous validation study and the plasma OA β concentration equal to, or higher than the cut-off value was defined as MDS-OA β positive [6]. MDS-OA β tester was blinded to clinical information including demographics and diagnosis.

Amyloid status

Amyloid status was evaluated by amyloid PET. [18F]Florbetaben (n=82), [18F]Flutemetamol (n=6), [18F]Florbetapir (n=2), and [11C]Pittsburgh compound B (PiB; n=1) were used as ligands. Amyloid status was defined as positive (abnormal) or negative (normal) after visual assessment by one experienced nuclear medicine physicians and two neurologists.

Statistical analysis

Baseline characteristics between amyloid normal and abnormal group were compared using chi-squared tests, Mann-Whitney U tests as appropriate. The predictive ability of MDS-OA β and covariates on amyloid PET positivity was assessed by binary logistic regression models and presented as area under the curve (AUC) values by receiver operating characteristic (ROC) analysis. All statistical analyses were performed by R (version 4.0.0) and statistical significance was set at 0.05.

Results

Demographics and clinical characteristics

A total of 96 subjects were included in the study. The average age of total subjects was 71.50 \pm 9.73 years old, and 42 subjects (43.8%) were male. Among total cohort 68 (70.8%) subjects presented amyloid-positive and 28 subjects were amyloid-negative. Comparison of baseline characteristics between groups is demonstrated in Table 1. There was no significant difference in age, sex, education level, and frequency of APOE ϵ 4 carrier between groups. Amyloid-positive groups showed poor MMSE scores reflecting poor general cognitive function, and higher CDR and CDR-SOB indicating increased disease severity. Correspondingly, amyloid-positive group contained more AD patients than amyloid-negative group.

Amyloid-positive group presented significantly higher MDS-OA β value with plasma oligomeric A β concentration of 0.88 ng/ml than amyloid-negative group with 0.68 ng/ml (Figure 1).

Table 1. Demographics and clinical characteristics of subjects

	Amyloid-negative (N=28)	Amyloid-positive (N=68)	p value
Age, years	74.00 (70.50–79.00)	70.00 (61.00–75.50)	0.058
Male, n (%)	13 (46.43)	29 (42.65)	0.910
Education, years	16.00 (12.00–16.00)	16.00 (12.00–16.00)	0.783
<i>APOE</i> ϵ 4 carrier, n (%)	9 (36.0)	32 (55.17)	0.173
Diagnosis			<0.001
AD/MCI/SCD/OND*, n	4/11/6/7	50/16/1/1	
MMSE	24.00 (20.00–26.00)	19.00 (11.00–25.00)	0.016
CDR	0.5 (0.5–0.75)	1.0 (0.5–1.0)	0.003
CDR-SOB	3.0 (2.0–4.25)	6.0 (2.0–8.0)	0.014
MDS-OA β , ng/ml	0.68 (0.52–0.77)	0.88 (0.80–0.97)	<0.001

Data are presented as the median (interquartile range) unless otherwise specified.

* OND includes FTD, PSP, PDD, and CBS.

AD; Alzheimer’s Disease, CBS; Corticobasal Syndrome, CDR; Clinical Dementia Rating, CDR-SOB; Clinical Dementia Rating Sum of Boxes, FTD; Frontotemporal Dementia, MCI; Mild Cognitive Impairment, MMSE; Mini-Mental-State-Examination, MDS-OA β ; Multimer Detection System-Oligomeric Amyloid- β , OND; Other Neurodegenerative Disease, PDD; Parkinson’s Disease Dementia, PSP; Progressive Supranuclear Palsy, SCD; Subjective Cognitive Decline.

Figure 1. Concentration of plasma MDS-OA β according to groups

AD; Alzheimer’s Disease, MCI; Mild Cognitive Impairment, MDS-OA β ; Multimer Detection System-Oligomeric Amyloid- β , OND; Other Neurodegenerative Disease, SCD; Subjective Cognitive Decline.

MDS-OA β as a predictor of amyloid status

MDS-OA β positivity could differentiate amyloid-positive subjects from amyloid-negative subjects with sensitivity of 85.3% and specificity of 85.7% (AUC= 0.855, 95% CI = 0.776–0.933). Multivariate models with MDS-OA β positivity and other covariates including age, MMSE score, and *APOE* ϵ 4 status showed

much better performance with AUC values between 0.892 and 0.926 than multivariate models without MDS-OA β positivity (Table 2). Among various combinations of predictors, MDS-OA β positivity combined with age, *APOE* ϵ 4 status, and MMSE score demonstrated the highest AUC value of 0.926 (0.871–0.980).

MDS-OA β positivity alone presented better predictability than MMSE alone (AUC= 0.657, 95% CI = 0.545–0.769). Although, when combined with age and *APOE* ϵ 4 status, the AUC value for MMSE increased to 0.740 (95% CI = 0.626–0.853), this was not statistically significant compared with MMSE alone. However, when the combination of predictors were added with MDS-OA β positivity, predictive performance improved significantly (AUC= 0.926, 95% CI = 0.871–0.980) (Figure 2. A). When combining objective factors such as age and *APOE* ϵ 4 status with MDS-OA β positivity, the predictability on amyloid PET positivity was strengthened (Figure 2. B).

Table 2. Performance of predictors for amyloid PET positivity with and without MDS-OA β positivity

Predictors	AUC (95% CI)	Sensitivity (%)	Specificity (%)
MMSE	0.657 (0.545–0.769)	54.4	82.1
age + MMSE	0.681 (0.572–0.789)	47.1	89.3
age + <i>APOE</i> ϵ 4	0.684 (0.552–0.816)	77.6	60.0
age + <i>APOE</i> ϵ 4 + MMSE	0.740 (0.626–0.853)	56.9	84.0
MDS-OA β positivity	0.855 (0.776–0.933)	85.3	85.7
MMSE + MDS-OA β positivity	0.892 (0.820–0.963)	86.8	85.7
age + MMSE + MDS-OA β positivity	0.922 (0.863–0.981)	91.2	82.1
age + <i>APOE</i> ϵ 4 + MDS-OA β positivity	0.912 (0.844–0.980)	74.1	96.0
age + <i>APOE</i> ϵ 4 + MMSE + MDS-OA β positivity	0.926 (0.871–0.980)	74.1	96.0

AUC; area under the curve, CI; confidential interval, MMSE; Mini-Mental-State-Examination, MDS-OA β ; Multimer Detection System-Oligomeric Amyloid- β

Figure 2. Receiver Operating Characteristic analysis of MDS-OA β positivity with other predictors on amyloid PET positivity

1. Added MDS-OA β positivity to clinical information such as age, MMSE score, and *APOE* ϵ 4 status, predictability for amyloid PET positivity improves. B. Considered only objective factors such as age and *APOE* ϵ 4 status, combining with MDS-OA β positivity strengthened the predictability on amyloid PET positivity

MDS-OA β ; Multimer Detection System-Oligomeric Amyloid- β , MMSE; Mini-Mental-State-Examination.

Discussion

In this study, we found that MDS-OA β positivity could discriminate amyloid PET positivity with the AUC value of 0.855. Furthermore, adding MDS-OA β positivity to prediction models including age, MMSE score, and *APOE* ϵ 4 status improved the performance significantly up to the AUC value of 0.926.

Substantial effort to detect and measure amyloid- β in the blood has been made and several assays stood as promising candidates for blood-based biomarkers [4]. These assays principally aimed to quantify the concentration of A β ₄₂ and A β ₄₂/A β ₄₀. However, they have been employed in a limited capacity due to several unique characteristics of this protein, such as its scarcity in the blood [15] and tendency to self-aggregate [16] as well as of the blood matrix such as the abundance of various A β -binding proteins in the blood [17], which interfere the detection of A β .

MDS-OA β , on the other hand, takes a distinct approach to possibly overcome the said challenges. It measures the A β oligomerization tendency of plasma by implementing the spiking of synthetic A β [5], prior to selective detection of A β oligomers, reputedly the main pathogen of AD [18], over A β monomers using epitope-overlapping antibodies. It is highly anticipated that this technique shall bring the unprecedented solution to detection and monitoring of AD-related amyloid dynamics in the blood.

Discriminative performance of MDS-OA β between AD and normal control group was demonstrated in previous studies. In the study by An and his colleagues, MDS-OA β assay mechanism and its diagnostic performance were evaluated. AD group (n=27) was differentiated from age-matched normal control group (n=144) with AUC of 0.896 (sensitivity 83.3%, specificity 90.0%) [5]. A recent validation study with AD (n=52) and normal control (n=52) confirmed the diagnostic accuracy with AUC value of 0.999 (sensitivity 100%, specificity 92.31%) [6]. The current study was completed in more heterogeneous population including individuals with AD, MCI, SCD, or other neurodegenerative diseases, and predictability on amyloid PET positivity was comparable (AUC 0.855). In various combinations with age, MMSE scores, and *APOE* ϵ 4 status AUC values increased between 0.892 and 0.926. These are also comparable with or even better than performance of other amyloid-targeting blood-based assays

including immunoprecipitation followed by mass spectrometry [19,20], single-molecule arrays [21,22], and immune-infrared-sensor [23,24].

Another interesting finding was that the predictability on amyloid PET positivity was considerably enhanced when combining MDS-OA β positivity with age and MMSE scores with the AUC increasing to 0.922, whereas the predictability of age and MMSE scores combined had only AUC of 0.681 (95% CI 0.572–0.789). In clinical settings such as primary care, age and MMSE scores might be the only accessible information, and transfer of patients to specialized memory clinic for further work-up often rely on limited information based on MMSE score and age. A blood test such as MDS-OA β which has good predictability on amyloid PET positivity could be implemented as an early stage AD blood test to relieve such drawback and be utile in terms of screening the patients in advance of further diagnostic examination.

There were several limitations in this study. This study presented small sample size, especially for each diagnostic group. Additionally, our cohort showed relatively high prevalence of amyloid PET positivity and amyloid-positive group tended to be younger than amyloid-negative group. Younger patients with cognitive decline might have undergone amyloid PET more frequently than older patients during the diagnostic process, and this could have contributed to the characteristic of our cohort.

Conclusion

In summary, A β oligomerization tendency in plasma measured by MDS-OA β could predict amyloid PET positivity (AUC= 0.855, 95% CI = 0.776–0.933). Furthermore, when MDS-OA β positivity is combined with clinical information such as age, MMSE score, and APOE ϵ 4 status, predictability for amyloid PET positivity was improved (AUC= 0.926, 95% CI = 0.871–0.980). This suggests the potential of MDS-OA β as a useful initial stage test in clinical and research field of AD.

Abbreviations

AD; Alzheimer's Disease, CBS; Corticobasal Syndrome, CDR; Clinical Dementia Rating, CDR-SOB; Clinical Dementia Rating Sum of Boxes, FTD; Frontotemporal Dementia, MCI; Mild Cognitive Impairment, MMSE; Mini-Mental-State-Examination, MDS-OA β ; multimer detection system-oligomeric amyloid- β , OND; Other Neurodegenerative Disease, PDD; Parkinson's Disease Dementia, PSP; Progressive Supranuclear Palsy, SCD; Subjective Cognitive Decline

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of the Seoul National University Bundang Hospital (B-2004-604-305). Written informed consent was obtained from all subjects or their caregivers.

Consent for publication

Not applicable

Availability of data and materials

The study data are not publicly available for download, might be retrieved from corresponding author professor SangYun Kim.

Competing interests

All authors declare no competing interests.

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This study was not funded.

Authors' contributions

JMP analyzed, interpreted data and drafted the work. JSR and RL contributed to the acquisition of data and revision of the manuscript. KHS, YHP and YCY interpreted data and revised the manuscript. NR and SSAA revised the manuscript. SYK designed the work, interpreted data, and revised the manuscript. All authors read and approved the final manuscript.

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Figures

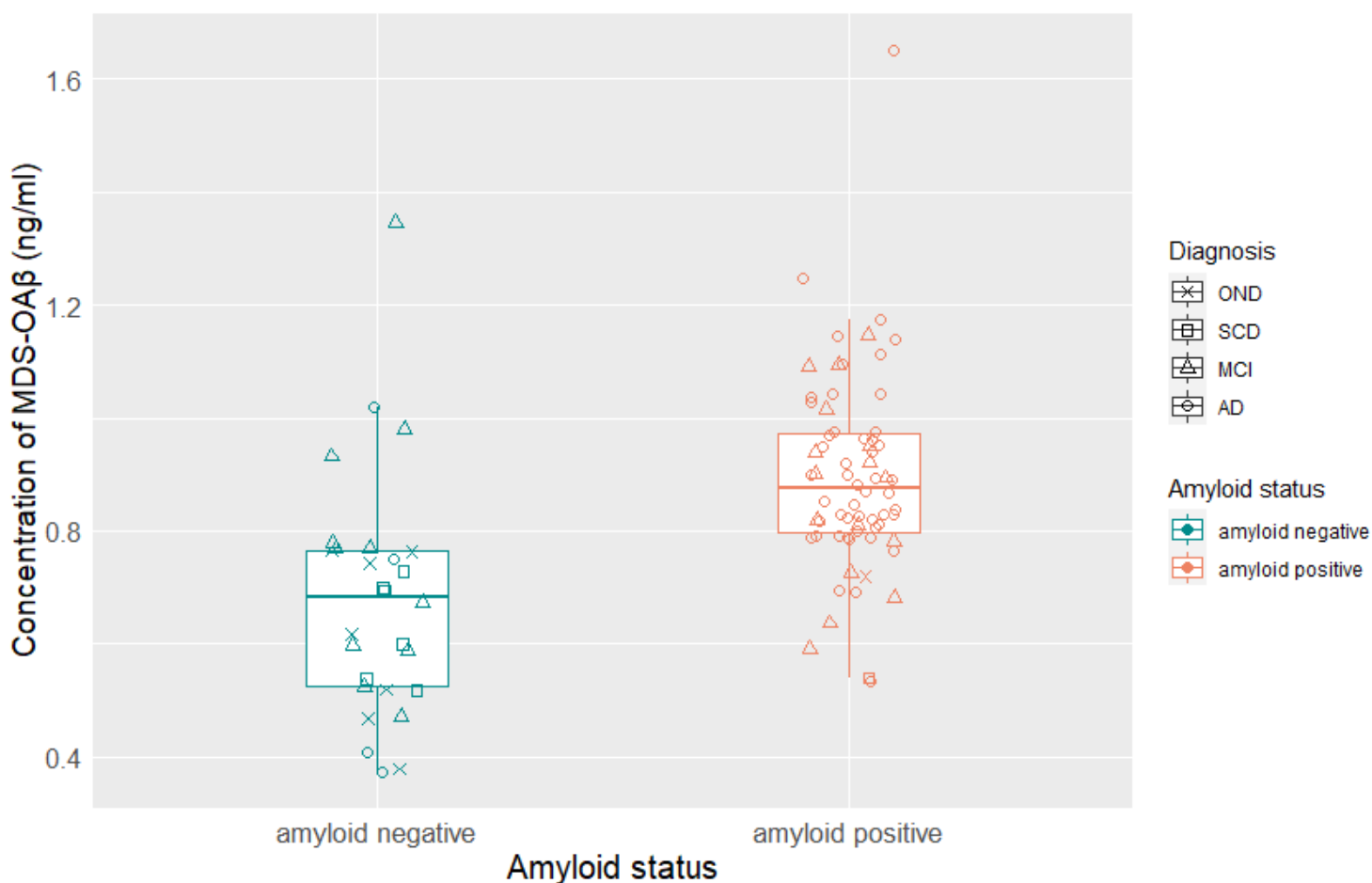


Figure 1

Concentration of plasma MDS-OA β according to groups AD; Alzheimer's Disease, MCI; Mild Cognitive Impairment, MDS-OA β ; Multimer Detection System-Oligomeric Amyloid- β , OND; Other Neurodegenerative Disease, SCD; Subjective Cognitive Decline. MDS-OA β as a predictor of amyloid status

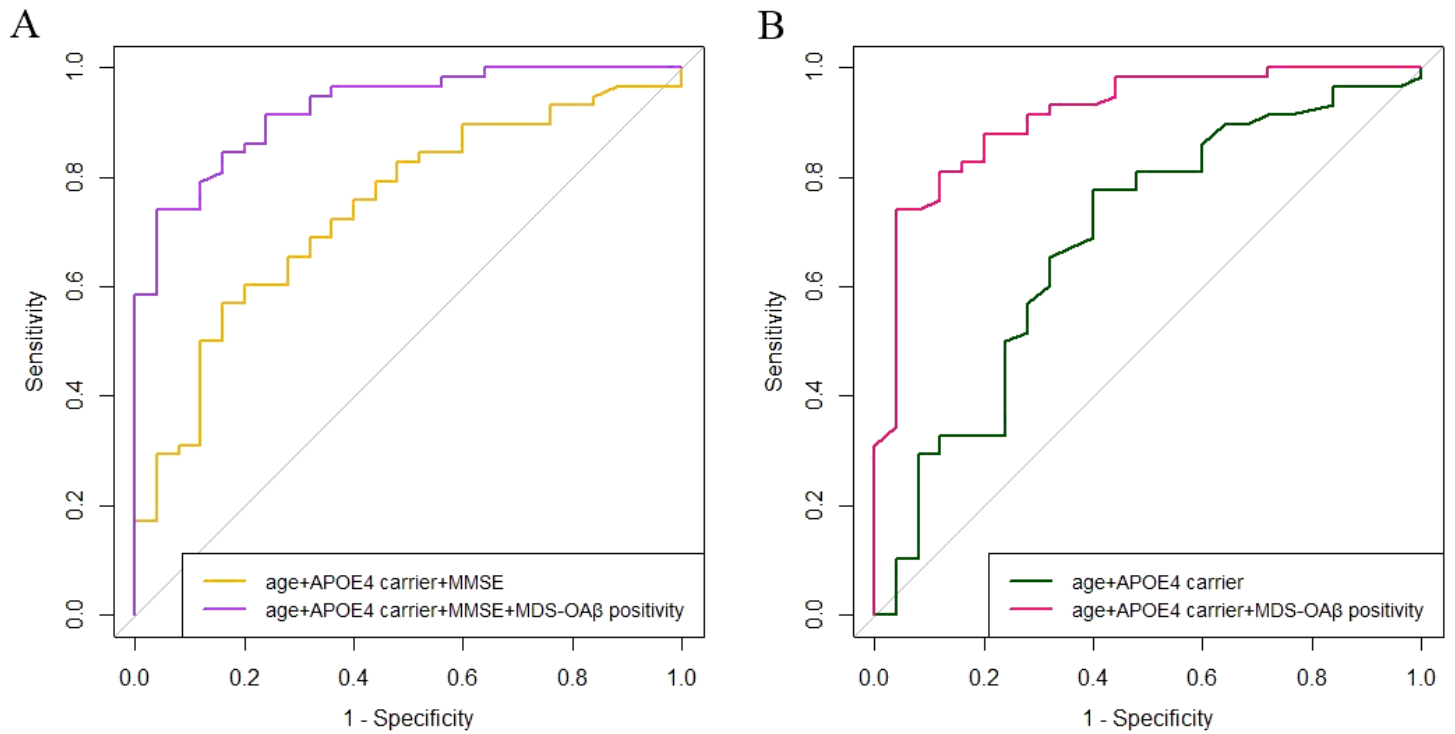


Figure 2

Receiver Operating Characteristic analysis of MDS-OA β positivity with other predictors on amyloid PET positivity A. Added MDS-OA β positivity to clinical information such as age, MMSE score, and APOE ϵ 4 status, predictability for amyloid PET positivity improves. B. Considered only objective factors such as age and APOE ϵ 4 status, combining with MDS-OA β positivity strengthened the predictability on amyloid PET positivity MDS-OA β ; Multimer Detection System-Oligomeric Amyloid- β , MMSE; Mini-Mental-State-Examination.