The associations of serum isoleucine with Alzheimer`s disease on assisting diagnosis, predicting conversion and assessing cognition

Running title: Isoleucine and Alzheimer`s disease

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Accepted

**Data used in preparation of this article were obtained from the Alzheimer's Disease N euroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators wit hin the ADNI contributed to the design and implementation of ADNI and/or provided d

ata but did not participate in analysis or writing of this report. A complete listing of A DNI investigators can be found at: http://adni.loni.usc.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Acknowledgments

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee

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organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

Conceptualization, XJJ, HZ; Data curation, YLX, SJR; Investigation, XJJ, ZYZ; Methodology, XJJ, XZ; Writing-original draft, XJJ; Writing-review & editing, HZ.

Ethical Statement

Compliance with Ethical Standards

The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

Funding

The authors report no funding.

Conflict of Interest

The authors claim no conflicts of interest.

Ethical approval and Institutional Review Board

The ADNI study was approved by the Institutional Review Boards of all the participating institutions.

Informed consent

Informed written consent was obtained from all subjects at each center and patient anonymity had been preserved.

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Associations of serum isoleucine with mild cognitive impairment and Alzheimer's disease

Running title: Isoleucine and Alzheimer's disease

Background: Advances in blood biomarker discovery have enabled the improved diagnosis and prognosis of Alzheimer's disease (AD). Most branched-chain amino acids, except isoleucine (Ile), are correlated with both mild cognitive impairment (MCI) and AD. Therefore, this study investigated the association between serum Ile levels and MCI/AD.

Methods: This study stratified 700 participants from the Alzheimer's Disease Neuroimaging Initiative database into four diagnostic groups: cognitively normal, stable MCI, progressive MCI, and AD. Analysis of covariance and chi-square analyses were used to test the demographic data.

Receiver operating curve analyses were used to calculate the diagnostic accuracy of different biomarkers and were compared using MedCalc 20. Additionally, Cox proportional hazards models were used to measure the ability of serum Ile levels to predict disease conversion. Finally, a linear mixed-effects model was used to evaluate the associations between serum Ile levels and cognition, brain structure, and metabolism.

Results: Serum Ile concentration was decreased in AD and demonstrated significant diagnostic efficacy. The combination of serum Ile and cerebrospinal fluid (CSF) phosphorylated tau (P-tau) levels improved the diagnostic accuracy in AD compared to T-tau alone. Serum Ile levels significantly predicted the conversion from MCI to AD (cutoff value = 78.3 μM). Finally, the results of this study also revealed a correlation between serum Ile levels and the Alzheimer's Disease Assessment Scale cognitive subscale Q4.

Conclusions: Serum Ile level may be a potential biomarker of AD. Ile had independent diagnostic efficacy and significantly improved the diagnostic accuracy of CSF P-tau in AD. Patients with MCI with a lower serum Ile level had a higher risk of progression to AD and a worse cognition assessment.

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Key Words: Alzheimer’s disease; isoleucine; mild cognitive impairment

Background

Alzheimer's disease (AD) is a prevalent form of dementia in older adults, affecting over 100 million individuals worldwide and imposing a significant burden on society.[1] Traditional biomarkers, such as cerebrospinal fluid (CSF) amyloid beta (Aβ), total tau (T-tau), and phosphorylated tau (P-tau), have been widely used in long-term research and are considered central to AD diagnosis and prediction. However, recent studies have identified novel blood biomarkers for AD, including serum P-tau, Aβ42/40, neurofilament light proteins, and glialfibrillary acidic protein,[2,3] which are easier to measure and contribute to the early diagnosis and long-time follow-up of AD.

Branched-chain amino acids (BCAAs) are the subset of amino acids that possess an aliphatic side chain with one branch.[4] Branched-chain aminotransferases can convert BCAAs to glutamate, a major excitatory neurotransmitter in the human brain that is related to hippocampal function and amnesia.[5] Additionally, glutamate can be converted to γ-aminobutyric acid after decarboxylation, which primarily functions as an inhibitory neurotransmitter. Thus, BCAAs contribute to balancing excitation and inhibition, making them potentially relevant to the pathology of neurodegenerative diseases such as AD.[6,7]

BCAAs comprise three amino acids: leucine, valine, and isoleucine (Ile). In 1990, Basun et al. reported significantly reduced CSF concentrations of leucine and valine in patients with AD compared with those in cognitively normal (CN) individuals.[8] Subsequently, González-Domínguez et al. observed decreased serum valine levels in patients with AD.[9] More recently, Xiong et al. reported similar results and further demonstrated that serum valine could predict the

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conversion of progressive mild cognitive impairment (pMCI) to AD.[10] However, the potential correlation between serum Ile level and mild cognitive impairment (MCI)/AD is unclear.

Therefore, this study explored the association between serum Ile level and MCI/AD, including its concentrations in various diagnostic groups, diagnostic efficacy, and potential to predict disease progression. Furthermore, we explored the correlation of serum Ile levels with various cognitive assessments, brain structure, and metabolism, as assessed by the Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), Alzheimer's Disease Assessment Scale cognitive subscales (ADAS-Cog 11, ADAS-Cog 13, and ADAS-Cog Q4), magnetic resonance imaging (MRI), and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET).

Materials and methods

Database description

This study analyzed data obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership led by principal investigator Michael W. Weiner, MD. ADNI participants have been recruited from more than 50 sites across the United States and Canada. The regional ethical committees of all participating institutions approved the ADNI and all study participants provided written informed consent. In this study, we profiled baseline serum samples from the ADNI-1 cohort. The extensive data for each patient included longitudinal assessments of cognitive decline and imaging findings, CSF marker levels, genetic information, and other omics data. Further information is available at http://www.adni-info.org.

From the database, we selected all participants who were aged 55–90 years; had completed at least 6 years of education; were fluent in Spanish or English; had no substantial neurological diseases other than AD; had baseline serum Ile samples from ADNI-1; and had complete lumbar puncture, MMSE, ADAS-Cog, and CDR data. Based on the clinical and behavioral measures provided by the ADNI-1, we classified these selected individuals as being CN (n = 221) or having stable MCI (sMCI, n = 120), pMCI (n = 179), or AD (n = 180).

Classification criteria

The criteria for CN included an MMSE score of ≥24 (range 0–30), where lower scores indicate more impairment and higher scores less impairment, and a CDR score of 0 (range 0–3), where lower scores indicate less impairment and higher scores more impairment.[11,12] The criteria for MCI included the presence of the subjective memory complaint, with an MMSE score of 24–30, CDR of 0.5, preserved activities of daily living, and an absence of dementia.[13] Patients with AD dementia fulfilled the National Institute of Neurological Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association criteria for probable AD, had MMSE scores between 20 and 26, and a CDR of 0.5 or 1.0.[14] We defined sMCI as patients with MCI who did not progress to AD during at least 24 months during follow-up and pMCI as patients with MCI who progressed to AD at any time during follow-up.[15] We excluded participants who were diagnosed with MCI at baseline but who reverted to CN during follow-up, as well as those who were diagnosed with AD at baseline but reverted to MCI during follow-up. Further information on the inclusion/exclusion criteria can be found at www.adni-info.org (accessed May 2023).

Serum Ile measurements

This study analyzed data from fasting morning blood samples collected at the baseline visit. Serum Ile levels were measured using a targeted metabolomics approach with the Absolute IDQ-p180 kit (BIOCRA TES Life Science AG, Innsbruck, Austria) and an ultra-performance liquid chromatography (UPLC)/mass spectrometry (MS)/MS system [Acquity UPLC (Waters), TQ-S triple quadrupole MS/MS (Waters)]. The Absolute IDQ-p180 kit was validated according to the European Medicine Agency Guidelines on Bioanalytical Method Validation. In addition, the plates underwent an automated technical validation to validate the run and verify the actual performance of the applied quantitative procedure, including instrumental analysis. Technical validation of each analyzed kit plate was performed using Met IDQ software based on the results obtained and defined acceptance criteria for blank, zero samples, calibration standards and curves, low/medium/high-level quality control samples, and measured signal intensity of internal standards across the plate.[16,17)]

CSF measurements

A lumbar puncture was performed in the morning after an overnight fast. CSF T-tau and P-tau levels were measured using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX, USA) and Innogenetics INNO-BIA AlzBio3 (Innogenetics, Ghent, Belgium) immunoassay reagents as described previously.[18)] All CSF data used in this study were obtained from the ADNI files "UPENNBIOMK5–8. csv" and "FAGANLAB_07_15_2015.csv" (accessed May 2023). Further details on the ADNI methods for CSF acquisition, measurements, and quality control procedures can be found at www.adni-info.org.

Cognitive assessments

Global cognitive performance was assessed using the Clinical Dementia Rating-Sum of Boxes (CDRSB), MMSE, ADAS-Cog 11, and ADAS-Cog 13. ADAS-Cog Q4 was also recorded, which is a subscale of ADAS-Cog 13 and reflects the delayed recall score of the word list. We selected the CDRSB, MMSE, and ADAS-Cog scores at five time points: baseline, and at 12, 24, 36, and 48 months. We obtained these data from the ADNI files "CDRSB.csv," "MMSE.csv," and "ADAS_ADNI1.csv" (accessed May 2023).

Neuroimaging methods

Structural brain images were acquired using 1.5-T MRI imaging systems with T1-weighted MRI scans using a sagittal volumetric magnetization-prepared rapid-acquisition gradient-echo sequence. We used hippocampal and ventricular volumes to represent neurodegeneration, and selected imaging data at five time points: baseline and at 12, 24, 36, and 48 months. We obtained these data from the ADNI files "FOXLABBSI_08_04_17. csv" and "UCSDVOL.csv" (accessed May 2023). Further details on the ADNI image acquisition and processing can be found at www.adni-info.org/methods.

FDG-PET

We used FDG-PET data to investigate cerebral glucose metabolism. The acquisition and processing of the PET imaging data in ADNI have been described in detail elsewhere. Briefly, we used the mean counts of the lateral and medial prefrontal, anterior, and posterior cingulate regions as well as those of the lateral parietal and lateral temporal regions to estimate the FDG standardized uptake value ratio for each participant. FDG-PET imaging data were acquired at baseline and at 12, 24, 36, and 48 months.

Statistical methods

We performed analysis of covariance and chi-square analyses to examine the significant differences in baseline demographics among the groups. The diagnostic accuracy of each biomarker was calculated using the receiver operating characteristic (ROC) curve and expressed as the area under the curve (AUC). We used MedCalc 20 to test the differences in AUCs among the biomarkers.

We evaluated the associations between serum Ile levels and AD incidence by calculating the hazard ratios (HRs) with 95% confidence intervals using Cox proportional hazard regression analysis based on two groups defined according to different Ile cutoff values, including median and quintile values,

We applied linear mixed-effects models to examine the relationship between serum Ile level and longitudinal cognitive assessment. The intercepts (baseline results) and slopes (ratio of changes) were then used as outcomes in linear regression models, with Ile as the predictor (adjusted for CDRSB, MMSE and ADAS-Cog with age, sex, and education; hippocampal and ventricular volumes with whole-brain volume) within diagnostic groups. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0, and GraphPad Prime 8.0.2. Statistical significance was defined as $p < 0.05$ in all analyses.

Results

Demographic results

The baseline characteristics of all the diagnostic groups are presented in **Table 1**. Compared with the CN group, the serum Ile level was significantly lower in the AD group (81.56 ± 17.17 vs.

88.23 ± 22.04 μM; p = 0.0049). We observed no significant differences in age or sex between the diagnostic groups. The AD group had significantly fewer years of education than the other groups. Regarding biomarkers, the prevalence of apolipoprotein (APOE) carriers was higher in the pMCI and AD groups. Similarly, the CSF T-tau and P-tau levels were higher in the pMCI and AD groups than in the CN and sMCI groups. Regarding cognitive assessment, CDRSB, MMSE, ADAS-Cog 11, ADAS-Cog 13, and ADAS-Cog Q4 scores differed significantly among the diagnostic groups, with the AD group showing the worst cognitive assessment score. Regarding brain structure, the whole-brain volume in the AD group was significantly smaller than those of the other diagnostic groups. This finding is consistent with the fact that the AD group had the highest ventricular volume and lowest hippocampal volume in this study. Finally, FDG-PET analysis showed significantly lower values in the pMCI and AD groups than in the CN and sMCI groups.

Diagnostic accuracy of serum Ile, CSF T-tau, and P-tau levels

We assessed the diagnostic efficacy of the biomarkers using ROC analyses. The results showed that serum Ile levels demonstrated significant diagnostic accuracy for AD but not for sMCI or pMCI **(Table 2)**. In contrast, CSF T-tau and P-tau levels showed significant diagnostic accuracy in all diagnostic groups **(Table 2)**. In the AD group, CSF T-tau and P-tau showed similar AUC values. However, the combination of serum Ile and CSF P-tau significantly increased the diagnostic efficacy compared with CSF T-tau alone **(Table 3)**.

Serum Ile levels to predict conversions from CN to MCI or AD and from MCI to AD

By May 2023, among the participants from the ADNI database, 25 participants who were CN had progressed to MCI or AD, and 180 participants with MCI had converted to AD during follow-up.

To investigate whether serum Ile could predict the conversion from CN to MCI or AD and from MCI to AD, we applied Cox proportional hazard models using serum Ile level as a continuous variable. We then calculated HRs for Ile as a dichotomized variable, using the median and quintile values as thresholds, respectively. The results are summarized in **Table 4.** While serum Ile levels did not significantly predict the conversion from CN to MCI or AD at any threshold, they did significantly predict the conversion from MCI to AD. Patients with MCI with lower serum Ile levels (≤78.3 μM) had a higher risk for progression to AD.

Relationship of serum Ile level with cognition

The baseline and longitudinal data are shown in **Fig. 1**. In the AD group, serum Ile level was negatively correlated with the ADAS-Cog Q4 score at baseline (β = −0.01529, p = 0.006) **(Fig. 1I)**, and positively associated with worsening ADAS-Cog Q4 over time (β = 0.00167, p = 0.022) **(Fig. 1J)**. In the other groups, serum Ile level was not associated with the baseline ADAS-Cog Q4 score **(Fig. 1I)** or the ratio of changes **(Fig. 1J)**. Serum Ile was not correlated with the baseline scores of the other cognitive assessments (ADAS-Cog 11, ADAS-Cog 13, MMSE, and CDR), **(Fig. 1A, 1C, 1E, and 1G)** or their changing rates **(Fig. 1B, 1D, 1F, and 1H)**.

Relationship of serum Ile levels with brain structure and metabolism

The baseline and longitudinal data are presented in **Figs. 2** and **3**, respectively. Serum Ile level was significantly positively correlated with baseline hippocampus volume in the CN (β = 4.58594, p = 0.037) and sMCI (β = 8.68655, p = 0.027) groups but not in the pMCI (β = −3.80666, p = 0.246) or AD (β = −1.14182, p = 0.751) (**Fig. 2C**) group. However, serum Ile levels were not correlated with the ratio of changes in hippocampal volume in any group (**Fig. 2D**). Furthermore,

serum Ile levels were not associated with baseline (**Fig. 2A**) or the ratio of changes (**Fig. 2B**) in ventricular volume. Finally, serum Ile level was not related to baseline brain metabolism (as measured using FDG-PET) at baseline (**Fig. 3A**) or its change rates (**Fig. 3B**).

Discussion

This study investigated the relationship between serum Ile levels, MCI, and AD. Our main findings are as follows. First, serum Ile concentration was significantly decreased in AD compared to that in CN participants. Second, serum Ile level alone had significant diagnostic accuracy for AD, while the combination of serum Ile and CSF P-tau significantly improved the diagnostic accuracy compared with CSF T-tau alone. Additionally, serum Ile levels could predict the conversion from MCI to AD. Finally, serum Ile level was negatively correlated with baseline ADAS-Cog Q4 and positively associated with the ratio of changes during follow-up in patients with AD.

Amyloid β-containing plaques and tau-containing neurofibrillary tangles are the central and traditional pathological features of AD. However, obtaining Aβ and tau samples requires lumbar puncture and CSF collection, which may cause patient discomfort and inconvenience. Serum amino acids have been extensively studied as new blood biomarkers in AD. P-tau quantification is based on the concentration of amino acids in serum.[19] In 1998, Molina et al. reported increased serum asymmetric dimethylarginine concentration in patients with AD.[20] In the same year, Fekkes et al. demonstrated the diagnostic and predictive value of the amino acid concentration ratio of serum to CSF in AD.[21] Several subsequent studies have also reported the relationship of levels of certain amino acids, including valine,[10] asymmetric dimethylarginine,[22] glutamic acid,[23]

and tryptophan, with AD.[24] Serum amino acids are a more convenient and less invasive option for detecting AD biomarkers from peripheral blood and could offer significant utility in clinical practice.

While previous studies have reported lower valine and leucine levels in individuals with AD compared with CN individuals, the association between Ile and MCI/AD remains unclear. For instance, a study on the impact of dietary intake on MCI/CN observed increased CSF Ile levels in the MCI group after 4 weeks of a high saturated fat/glycemic index diet compared with the CN group.[25] However, that study did not further investigate their potential correlation. Current research on Ile is mainly focused on nutritional preparation for athletes, animal husbandry, and critically ill patients.[26-29] Studies have also explored the relationship between Ile and metabolism, such as blood glucose, lipid, and insulin resistance.[30-32] Finally, Ile level is also reportedly related to the pathogenesis of maple syrup urine disease and is commonly used as a first-line therapy for this condition.[33,34]

Therefore, we investigated the association between serum Ile levels and MCI/AD in the ADNI-1 cohort. First, we confirmed that the serum Ile level was significantly lower in patients with AD compared with those who were CN. We demonstrated the diagnostic efficacy of serum Ile, which could predict AD prognosis. In this context, serum Ile level showed significant and independent diagnostic accuracy in AD. In addition, we observed the improved diagnostic efficacy of CSF P-tau compared with CSF T-tau in AD, especially in combination with the serum Ile level. This result is consistent with current research findings that CSF P-tau is an excellent biomarker for AD

diagnosis, as P-tau may better reflect tau tangle load.[35,36] In addition, serum P-tau may be another potent AD blood biomarker for AD diagnosis and for prognosis prediction.[37,38]

Regarding prognosis prediction, we observed a higher risk for AD conversion among patients with MCI with lower Ile levels (≤78.3 μM). To define the appropriate cut-off value, we searched recent studies for common standards, including 1) external reference value;[39] 2) median value;[40] 3) Youden Index;[41] 4) calculations such as Gaussian mixed modeling;[42] and 5) internal equal diversion points such as quintiles and quartiles.[43,44] Unfortunately, our search did not identify any specific external reference value, and recent studies generally reported trends rather than exact Ile values in patients with MCI.[25] In the present study, the p-value for Ile diagnostic accuracy was >0.05 in the pMCI group compared with the sMCI group, indicating that the Youden Index could not be used to differentiate pMCI from sMCI. Therefore, we used the median and quintile values as cutoff values for predicting conversion.

Patients with AD normally have worse cognitive assessment scores.[45] We observed that lower serum Ile levels were associated with a higher ADAS-Cog Q4 score at baseline and a more rapid decrease later in AD. ADAS-Cog Q4 is a subscale of ADAS-Cog 13 and reflects delayed word list recall. ADAS-Cog 13 is considered an excellent tool for dementia research and adds word list delayed recall and a maze task based on ADAS-Cog 11.[46,47] Thus, ADAS-Cog 13 consists of ADAS-Cog 11, ADAS-Cog Q4, and a maze task. Furthermore, Sano et al. observed increased ADAS-Cog 11 efficacy in diagnosing and predicting prognosis when combined with ADAS-Cog Q4.[48] Therefore, ADAS-Cog Q4 may be a useful subscale. Similarly, Grundman et al. also reported a significant difference in ADAS-Cog Q4 scores among CN, MCI, and AD groups.[49]

Yagi et al. identified ADAS-Cog Q4 and the other three subscales of ADAS-Cog 13 as prognostic factors in AD.[50] Therefore, ADAS-Cog Q4 plays an important role in cognition assessment. Due to its strong correlation with ADAS-Cog Q4, serum Ile levels could be used to assess the severity of cognitive impairment at baseline and predict cognitive changes in AD.

This study has several limitations, including the lack of CSF Ile data, which limited our ability to determine whether Ile levels are reflected in the brain. Additionally, this study only included participants with sMCI who were followed up for at least 2 years, potentially underestimating the number of participants who would progress to AD with a longer follow-up. Furthermore, the ADNI database includes highly educated individuals who have volunteered to participate in AD research; thus, a selection bias was possible as the study population is self-selected individuals who may have concerns about their cognition. Finally, the self-selectivity of our research population and relatively small sample size limit the generalizability of our findings to a wider community. Therefore, our findings require validation in a larger population-based cohort.

Conclusion

Serum Ile levels showed favorable diagnostic efficacy for AD, both as an independent biomarker and in combination with CSF tau. Serum Ile levels predicted the conversion of MCI to AD. Furthermore, serum Ile levels were related to the baseline ADAS-Cog Q4 score and reflected changes during follow-up in patients with AD. Therefore, serum Ile levels may be a potential and favorable blood biomarker for diagnosing and predicting the prognosis of AD.

Abbreviations

AD: Alzheimer's disease; Aβ: Amyloid beta; ADAS-cog: Alzheimer's disease assessment scale-cog; ADNI: Alzheimer's disease Neuroimaging Initiative; APOE: Apolipoprotein E; AUC: area under the curve; BCAAs: Branched-chain amino acids; CDR: Clinical Dementia Rating; CDRSB Clinical Dementia Rating-Sum of Boxes; CN: cognitively normal; CSF: cerebrospinal fluid; *FDG-PET* 18F-Fluorodeoxyglucose-PET; HR: hazard ratios; MCI: mild cognitive impairment; MMSE: Mini-Mental State Examination; pMCI: progressive MCI; ROC: receiver operating curve; T-tau: total tau; P-tau: phosphorylated tau.

Accepted