*Article*

# A Cost-efficient Model for Predicting Cerebral Aβ Burden Using MRI and Neuropsychological Markers in the ADNI-2 Cohort: Comparisons in Predictability among Machine Learning Models

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**Abstract:** Substantial studies have focused on early detection of Alzheimer's disease (AD). Cerebral amyloid beta (Aβ), is hallmark of AD, can be observed in vivo via positron emission tomography imaging using amyloid tracer or cerebrospinal fluid assessment, but costly expensive. The current study aims to identify and compared predictability in magnetic resonance imaging (MRI) markers and neuropsychological markers to predict cerebral Aβ status in AD cohort using machine learning (ML) approaches. The predictability in candidate markers for cerebral Aβ status was examined by analyzing 724 participants from the ADNI-2 cohort. Demographic variables, structural MRI markers, and neuropsychological test scores were used as input in several ML algorithms to predict cerebral Aβ positivity. Out of five combination of candidate markers, neuropsychological markers with demographics showed the most *cost*-efficient result. A feature selection model could distinguish abnormal levels of Aβ with the predictability of 0.85, indicating the same performance with MRI-based models. The result has first to identified the predictability in MRI markers using ML approaches, and secondary to demonstrate the neuropsychological model with demographics could predict Aβ positivity, suggesting a more cost-efficient method for detecting cerebral Aβ status compared to MRI markers.

**Keywords:** amyloid beta, neuropsychological assessment, machine learning, Alzheimer's disease

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## 1. Introduction

In 2010, 35.6 million people across the world were estimated to have dementia, which will approximately double to 65.7 million in 2030 [1]. With growing numbers of those with dementia, the cost of dementia can also be problematic. In the US the annual payment for dementia care was $ 236 billion in 2016, being expected to increase to more than $ 1 trillion in 2050 [2]. Alzheimer's disease (AD) is the most common cause of dementia, explaining about 70% of dementia population [3]. Consistently, the structural magnetic resonance imaging (MRI) has been used most frequently as a diagnostic modality for AD. It can help for clinician to allow for finding structurally pathological changes in the brain and the irreversible atrophy due to the neurodegeneration according to AD pathology [4]. A decade ago, the perspective about the disease was that either people with dementia had AD-related pathological changes, or those who were cognitively normal (CN) did not have such changes in their brains [5]. A view of the disease, however, has been reconsidered, in which both AD related pathological changes and clinical symptoms occur constantly, suggesting that the end state of that process indicate dementia, with accumulation of pathological and clinical changes. In this respect, the structural MRI (e.g., cortical atrophy) as clinical information on AD had no longer specific

evidence for AD, but the extent of cortical atrophy measured by structural MRI still associates well with Braak staging at postmortem autopsy evidences [6, 7].

Recently, it has been well established that beta-amyloid (Aβ) is essential component in AD and Aβ begins to accrue almost 10-15 years before the clinical onset of AD [8]. Advance in AD research and imaging method has made it possible to detect cerebral Aβ deposition in people without postmortem autopsy by using positron emission tomography (PET). Approximately 20-30% of CN elderly have AD-specific neuropathology in their brains as measured by carbon-11 labeled Pittsburgh compound-B ($^{11}$C-PiB) PET [9]. However, these techniques have a few limitations. Employing amyloid PET is expensive, not commonly available and causes exposure to radiation. Otherwise, cerebrospinal fluid (CSF) analysis also can be used to gauge Aβ 42, however, an invasive lumbar puncture, labor intensiveness, and poor inter-laboratory reliability made it difficult to be implemented [10].

Neuropsychological assessment, sensitive and cost-efficient measurement for diagnosing AD, can be an evaluation tool for AD related pathology without invasive method. Despite several advantages in applying neuropsychological assessment for evaluating AD pathology, only a few studies denoted the results using the assessment as a predictive tool [11, 12]. A recent study demonstrated the predictability based on neuropsychological assessment and demographics using a brief machine learning (ML) approach [13]. In the study, the result using ML suggested that neuropsychological tests with demographics could be used as a preliminary screening for detecting Aβ before undergoing neuroimaging such as amyloid PET. Excepts for several studies, the majority of the findings that applied ML were studies using structural MRI images in the AD-related research fields [14, 15]. Additionally, there were few studies that focused on applying ML techniques to AD studies to predict Aβ status [16, 17].

The goal of the current study was to propose models that can predict abnormal level of cerebral Aβ based on neuropsychological test scores and demographics using several ML algorithms. For comparing predictability performance with neuropsychological test derived models, two brain measures were considered which were well known to be related with the cerebral amyloid deposition [18, 19]: cortical thickness and volume. Finally, feature selection approaches were selected to provide the explainable and practical implications for results.

## 2. Materials and Methods

### 2.1. Ethics Statement

In this study, we used participant data from ADNI, a multicenter project with approximately 50 medical centers and university sites across the United States and Canada [20]. ADNI was launched in 2003 as a public–private partnership led by principal investigator, Michael W. Weiner, MD. Its primary goal is to test whether biological markers such as serial MRI, PET, and clinical and neuropsychological assessment can be combined to measure the progression of patients with mild cognitive impairment (MCI) and early AD. Participants were between 55 and 90 years old, and were able to undergo all assessment procedures, and consent to participate in longitudinal follow-up. Written consent forms were obtained from all participants and the study was conducted after approval from Institutional Review Board at each participating institution.

### 2.2. Participants

CN participants were the control group in ADNI study and showed no significant clinical symptoms such as depression, MCI, or dementia. Participants with significant memory concern (SMC) score within the normal range for cognitive function but reported concerns about their memory. Participants with EMCI and LMCI reported their SMC either autonomously via an informant or through clinicians. However, daily living activities were preserved and other cognitive domains showed no significant impairment without signs of dementia. The degree of MCI (early or late) was determined with Wechsler Memory Scale Logical Memory II [21]. Participants with AD

met National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable AD [22, 23]. A detailed description of the inclusion/exclusion criteria can be found at http://adni.loni.usc.edu/.

Data were downloaded from the ADNI database and included all subjects recruited in the ADNI-2 with complete baseline data available for cognitive assessment, APOE genotype processing and PET Aβ quantitation. Our study sample included 724 subjects (170 control subjects, 95 with SMC, 324 with MCI (169 with EMCI and 155 with LMCI), and 135 with AD) who were recruited between 2011 and 2013, each of whom had a baseline APOE genotype, structural MRI, and florbetapir session.

### 2.3. Amyloid PET data

Baseline Aβ deposition was visualized using florbetapir-PET. Amyloid PET results were downloaded from the latest available dataset "UCSF Berkeley – AV45 Analysis", Version: 2019-08-27 excel in the ADNI database. Detailed methods for PET acquisition and analysis can be found from the works by Landau and colleges [24, 25]. Florbetapir images consisted of 4 × 5 min frames acquired 50–70 min after injection. Images were realigned, averaged, resliced to a common voxel size (1.5 mm), and smoothed to a common resolution of 8 mm in full width at half-maximum [26]. Structural T1-weighted images were acquired concurrently with the baseline florbetapir images. The images were used as structural templates to define the cortical regions of interest (ROIs), and the reference regions in native space for each subject were obtained with FreeSurfer software (version 5.3.0), which is documented and freely available on online (http://surfer.nmr.mgh. harvard.edu/). Baseline florbetapir scans for each participant were co-registered to baseline structural T1-weighted images. Images were subsequently used to extract weighted cortical retention indices, standardized uptake value (SUV) from gray matter within four cortical ROIs (frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal) that were averaged to generate a mean cortical SUV as described online in greater detail(adni.bitbucket.org/docs/UCBERKELEYAV45/UCBERKELEY_AV45_Methods_12.03.15.pdf). Cortical SUV ratios (SUVR) were obtained by normalizing cortical SUV with the mean uptake in the whole cerebellum reference region. Participants were classified as cerebral Aβ positive if the florbetapir SUV ratio was greater than 1.1.

### 2.4. Structural MRI data

Structural MRI scans were obtained at baseline visit according to a standardized protocol (http://adni.loni.usc.edu/about/centers-cores/mri-core/). Briefly, all participants in the current study were scanned using the 3T-MRI scanning protocol (GE, Philips or Siemens). Cortical reconstruction and volumetric segmentation were performed with the same FreeSurfer image analysis suite. Cortical thickness and volume data was downloaded from "UCSF – Cross-Sectional FreeSurfer (5.1), Version: 2019-11-08" excel in the ADNI database. Further details for MRI scans are described in more detail elsewhere [27].

### 2.5. Neuropsychological assessment

The following measurements were considered: Mini-Mental State Examination (MMSE) [28]; Alzheimer's Disease Assessment Scale (ADAS-Cog 13) [29]; Rey Auditory Verbal Learning Test (AVLT) [30]; Logical Memory (LM) [21]; Clock Drawing Task [31]; Trail Making Test [32]; Category Fluency [33]; Boston Naming Test (BNT) [31]; and American National Adults Reading Test (ANART) [34].

*2.6. Statistical analyses*

Demographics were compared between groups using t-test. χ2 tests were used to compare dichotomous variables. For predictability estimation, the aforementioned features, cortical thickness and volume, and cognitive performances were used as input data for supervised learning ML algorithm. Algorithms used in current study works as follows: logistic regression (LR), support vector machine (SVM), boosted decision tree (BDT), and artificial neural network (ANN).

Next, to explain multivariate profiles with respect to input features that were accurately distinguished from Aβ positivity for participants, the adaptive least absolute shrinkage and selection operator (LASSO) ML algorithm were applied to the dataset [35]. The adaptive LASSO, which is a penalized regression method [36], is a popular technique for simultaneous estimation and consistent variable selection [35]. The regression coefficients of unimportant variables shrank to 0 by implementing the adaptive LASSO. In that regard, the adaptive LASSO algorithm provided interpretable results related to abnormal levels of cerebral Aβ status.

In order to evaluate generalizability of the results from the ML algorithms, 10-fold cross-validation was applied during the variable selection process. First, the data was randomly split into a training set (66.7% of the data) and a test set (33.4% of the data). All of the ML models were fitted using the training set and classifications were separately made on the test and training datasets. The optimal parameter, lambda, was determined across 1,000 iterations of 10-fold cross-validation to minimize the deviance of the model. Then, predictions were made on the test set based on the ML models trained in the training set.

The parameters used to compare predictability performances and validations of models were as follows: accuracy (ACC), precision (PRE), recall (REC), F1 score, the area under the curve (AUC) Analyses were performed using R, version 3.6.1 (http://www.r-project.org/).

## 3. Results

*3.1. Subject characteristics*

Demographic data for all participants are presented in Table 1. Of the 724 study participants, 339 (46%) were APOE ε4 carriers, and 400 (54%) were Aβ positive (Aβ+).

**Table 1.** Demographics of participants

| Characteristics | CN (N=170) | SMC (N=95) | EMCI (N=169) | LMCI (N=155) | AD (N=135) | Total (N=724) |
|---|---|---|---|---|---|---|
| Age, years | 73.9 (6.2) | 72.9 (5.7) | 71.6 (7.1) | 72.6 (7.6) | 74.9 (8.1) | 73.2 (7.1) |
| No. of females (%) | 91 (51%) | 55 (58%) | 71 (42%) | 71 (46%) | 56 (41%) | 344 (47%) |
| Education, year | 16.6 (2.5) | 16.7 (2.6) | 16.2 (2.7) | 16.6 (2.6) | 15.7 (2.6) | 15.7 (2.6) |
| No. of APOE ε4 carriers (%)[a] | 50 (28%) | 29 (31%) | 77 (46%) | 90 (58%) | 93 (69%) | 339 (46%) |
| Aβ positivity (%) | 53 (29%) | 33 (35%) | 84 (50%) | 108 (70%) | 122 (90%) | 400 (54%) |

Abbreviations: APOE ε4, apolipoprotein; Aβ, amyloid-beta; CN, clinically normal; SMC, subjective memory concerns; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, Alzheimer's disease. Data are presented as mean (SD) unless otherwise indicated. [a]APOE ε4 carriers are the percentage of individuals with at least one APOE ε4 allele.

*3.2. Feature combination*

In an attempt to compare the predictive performances of each model across combination of input features, we split the features into several subsets: 1) Whole dataset: Demographics (Demo) + neuropsychological assessment (NA) + cortical thickness (CT) + cortical column (CV); 2) Demo + CV + NA; 3) Demo + CT + NA; 4) Demo + CV + CT; 5) Demo + NA.

Performance of the ML models

The results from each ML model are presented in Table 2. With respect to structural MRI information, applying SVM algorithm to each subset was likely to demonstrate slightly better performances than others. However, there were a few differences in performance metrics over subsets and applied algorithms. We can see that the results of 5th combination (Demo+NA) were not much different from the results using structural MRI information. Thus, 5th combination (Demo+NA) was selected as further consideration due to its cost-efficiency compared to MRI methods. Unlike previous results, applying the ANN algorithm showed better performance than the BDT algorithm (Table 3).

*3.3. Feature selection from Adaptive LASSO*

The predictability from demographic (age, gender, and APOE ε4 status) and neuropsychological data was assessed for the performance to predict cerebral amyloid positivity. Figure 1 shows the multivariate profiles for cerebral Aβ positivity, revealed by adaptive LASSO algorithm. First, Aβ positivity was more prevalent in participants who were older, female, APOE ε4 carriers, and showed poor cognitive performance in several measures in the ADNI-2 population (worse delayed recall and global cognition: ADAS-Cog 13). The receiver operating characteristic (ROC) demonstrated AUC of 0.824 for distinguishing Aβ positivity using 6 of 20 features.

**Table 2.** Results on models including MRI markers

|  | ACC | RPE | REC | F1 | AUC |
|---|---|---|---|---|---|
| *WHOLE* |  |  |  |  |  |
| LR | 0.75 | 0.78 | 0.76 | 0.77 | 0.84 |
| SVM | 0.75 | 0.79 | 0.75 | 0.77 | 0.85 |
| BDT | 0.76 | 0.81 | 0.72 | 0.77 | 0.85 |
| ANN | 0.74 | 0.77 | 0.74 | 0.76 | 0.81 |
| *Demo+CV+NA* |  |  |  |  |  |
| LR | 0.76 | 0.80 | 0.76 | 0.78 | 0.84 |
| SVM | 0.76 | 0.80 | 0.74 | 0.77 | 0.85 |
| BDT | 0.75 | 0.81 | 0.71 | 0.76 | 0.84 |
| ANN | 0.73 | 0.77 | 0.73 | 0.75 | 0.81 |
| *Demo+CT+NA* |  |  |  |  |  |
| LR | 0.75 | 0.79 | 0.75 | 0.77 | 0.84 |
| SVM | 0.76 | 0.80 | 0.76 | 0.78 | 0.84 |
| BDT | 0.77 | 0.83 | 0.74 | 0.78 | 0.82 |
| ANN | 0.75 | 0.77 | 0.78 | 0.78 | 0.82 |
| *Demo+CV+CT* |  |  |  |  |  |
| LR | 0.77 | 0.82 | 0.76 | 0.79 | 0.84 |
| SVM | 0.74 | 0.80 | 0.72 | 0.76 | 0.84 |
| BDT | 0.75 | 0.83 | 0.70 | 0.76 | 0.83 |
| ANN | 0.71 | 0.85 | 0.58 | 0.69 | 0.81 |

Abbreviations: WHOLE; Demp+NA+CT+CV; Demo: demographics; NA. neuropsychological assessment; CT. cortical thickness; CV. Cortical volume; ACC. accuracy; PRE. precision; REC. recall; AUC. area under curve; LR. Logical regrension; SVM. support vector machine; BDT. boosted decision tree; ANN. artificial neural network.

**Table 3.** Results on models excluding MRI markers

|  | ACC | RPE | REC | F1 | AUC |
|---|---|---|---|---|---|
| *Deom+NA* | | | | | |
| LR | 0.75 | 0.79 | 0.74 | 0.77 | 0.83 |
| SVM | 0.75 | 0.80 | 0.73 | 0.76 | 0.83 |
| BDT | 0.71 | 0.76 | 0.70 | 0.73 | 0.79 |
| ANN | 0.75 | 0.83 | 0.70 | 0.75 | 0.83 |

Abbreviations: Demo: demographics; NA. neuropsychological assessment; CT. cortical thickness; CV. Cortical volume; ACC. accuracy; PRE. precision; REC. recall; AUC. area under curve; LR. Logical regression; SVM. support vector machine; BDT. boosted decision tree; ANN. artificial neural network.

**Figure 1.** Multivariate patterns of demographic information and neuropsychological markers predicting cerebral aβ burden: ADAS13, Alzheimer's disease assessment scale; APOE, ApoE ε4 positivity; AVLT _Del, Rey auditory verbal learning test delayed recall; LM_del, logical memory delayed recall.
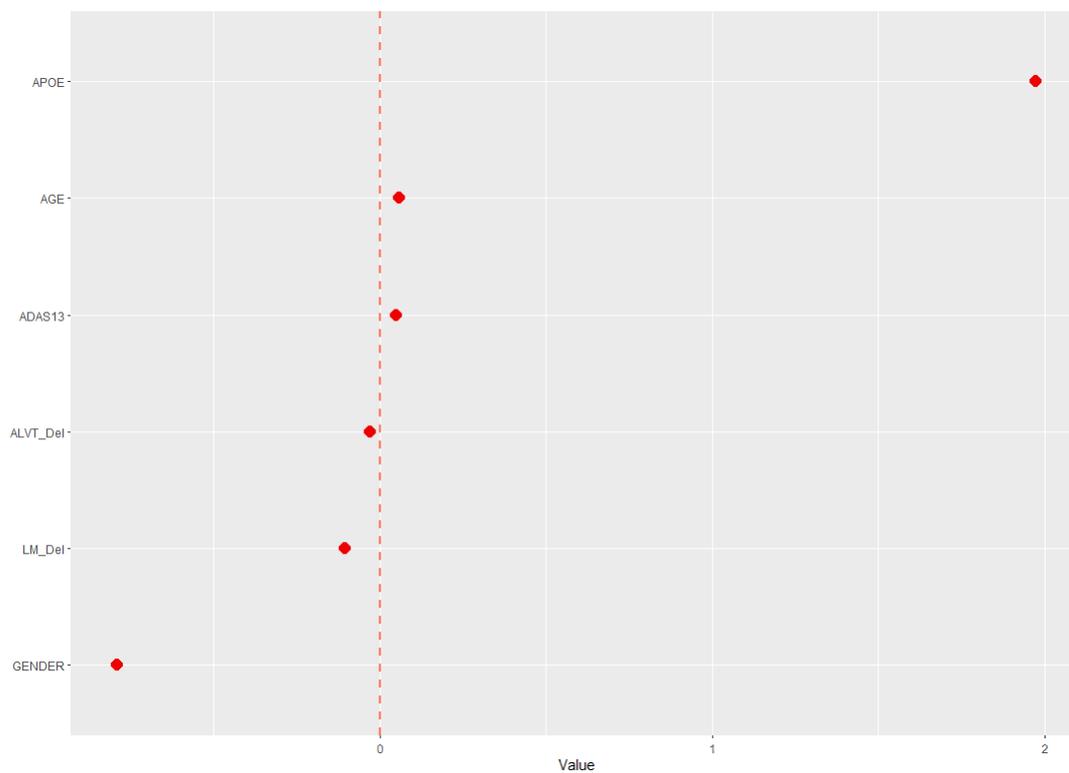
**Figure 2.** Receiver operating characteristic (ROC) curve based on the adaptive LASSO result.
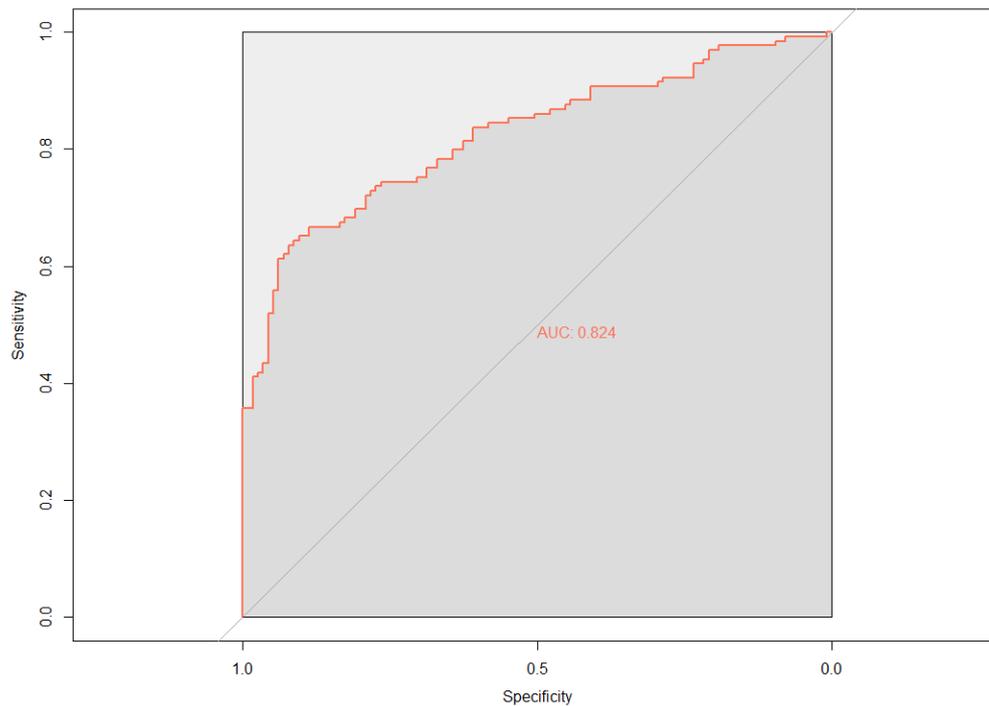


## 4. Discussion

Present study proposed a ML approach using various classifiers based on demographics, cortical thickness and volume, and neuropsychological performance data to predict cerebral Aβ deposition in the ADNI-2 cohort. The subset using demographics and neuropsychological assessment data demonstrated better cost-efficiency compared to other models including structural MRI data. Therefore, the cost-efficient model was chosen for further analysis, and the adaptive LASSO algorithm was adopted in feature selection process which can be the most predictive measure for cerebral Aβ positivity. Finally, multivariate profiles of cognitive performances and demographics were used to support explainability of the model.

Although some studies have reported high predictive accuracy for Aβ positivity based on ML methods, these studies were based on blood biomarkers or combined neuropsychological tests [16, 17]. Only one recent study showed the predictability for Aβ status using neuropsychological assessment based on ML [13]. To our knowledge, this is one of the first studies that evaluated relative performances using ML models predicting cerebral amyloid status based on several ML algorithms in the AD research.

Current findings demonstrate that including structural MRI markers can predict Aβ positivity with 85% predictability (Demo+CV+NA model using SVM, Table 2) in the ADNI-2 participants. The cost-efficient model (Demo+NA), however, shows similar results (Table 3), leading to the same result using adaptive Lasso model (AUC =0.85). Given these results, specific neuropsychological measures, even without neuroimaging markers, have practical implications for prediction of neuropathological biomarkers in AD without invasive methods (i.e. PET or CSF method).

In ADNI-2 cohort, age, gender, and APOE ε4 status are significant variables to predict Aβ positivity. However, education is not a significant indicator. These results are consistent with previous studies [37-39]. It is remarkable that certain cognitive measures show higher coefficient in predicting Aβ positivity compared to that of age, which is consistent with previous studies [13, 40].

As mentioned earlier, most of the studies using ML approaches have focused on diagnosis and progression of the disease based on limited biomarkers such as volumetric and/or surface-based brain measures, or blood proteins in AD research [14, 15, 41]. Based on the first study, our current work proposed the implication in ML-based models that can predict Aβ positivity, suggesting potential application of Aβ assessment through non-invasive MRI markers. Since the NIA-AA research framework has been updated, neuroimaging markers derived from structural MRI scans have been considered as non-specific information about neuronal injury and neurodegenerative changes in the AD course [42]. However, our results represented that MRI markers may still have beneficial information for AD specific pathology with combination of other layers of information such as demographics and neuropsychological assessments. Given the fact that employing amyloid PET scans has relatively limited accessibility than that of MRI scans, predicting cerebral Aβ status using MRI scans may provide potential implications in the health care system. First, progress of AD pathology can be predicted during assessment of other brain diseases with automated ML algorithm to on-line structural MRI analysis. Second, it could be an alternative modality for assessing AD specific pathology in case of the use of amyloid PET scans is limited.

More importantly, our findings demonstrate that the results based on neuropsychological data with several demographics is nearly accurate as the MRI markers in predicting cerebral Aβ status. This suggests the following benefits. Given that in most AD-related clinical trials, delayed recall and global cognition assessment are administrated as screening tools for participants' inclusion, a combination of these tests can be a preliminary tool in predicting Aβ status. There are financial advantages on detecting cerebral Aβ without Amyloid PET scans, considering the high cost of amyloid pet scan ($ 5,000 per person in the US; [43]). Moreover, the explainable profile from the adaptive lasso results can provide clinicians with reliable information about AD-specific pathology.

The current study has several limitations. First, ADNI population is not representative of the general population because the participants were deliberately selected based on robust inclusion criteria. Moreover, most participants in ADNI-2 cohort were recruited only from North America. Second, the results were only estimated in baseline visit, hence, the cross-sectional results are limited for causal assumptions of the input features and the outcome variables. In this regard, 10-fold-cross validation for out-of-sample generalization may support generalization of the results. Third, the use of limited structural MRI markers may not have enriched the results, suggesting that consideration of other MRI markers such as resting state fMRI, hippocampal volume, or T2-weighted image markers are needed to be considered for further analysis. Finally, although the results may cause an over-fitting problem regarding high dimensionality in structural MRI data, the process of dimension reduction is not implemented. Dimension reduction is not performed in order to prevent loss of information because it is pre-processed by Freesurfer suite rather than 2D image data. Undoubtedly, since the feature selection procedure for the final model serves as a dimensionality reduction, it is assumed that the cost-efficient model could have avoided over-fitting problems. Further research should be validated against various cohort studies.**5.**

## 5. Conclusions

In conclusion, our findings demonstrate that MRI markers using an ML algorithm might predict abnormal level of Aβ status in ADNI-2 cohort without invasive methods. Results also provide the same predictability using neuropsychological model based on the adaptive LASSO methods, which is cost-efficient than conventional neuroimaging methods. Application of these findings may give us opportunity to develop precise intervention for the patients who suffer from dementia.   The cost-efficient, non-invasive, and easily accessible aspects of the method can contribute to thorough recruitment for AD clinical trials and serve as an alternative method to patients who have difficulties in undergoing PET scans.

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