Can we improve prediction of Alzheimer's disease and Mild Cognitive Impairment by combining MMSE score and MRI-based imaging data?

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Abstract

BACKGROUND

This work aimed to find MRI-based markers for Alzheimer's disease (AD) and mild cognitive impairment (MCI) to improve diagnosis.

METHODS

The multinomial logistic regression was used to predict diagnosis status: AD, MCI, and normal control (NC) combined with the Bayesian information criterion for model selection. Several T1-weighted MRI-based radiomic features were considered as explanatory variables in the prediction model.

RESULTS

The best radiomic predictor was the relative brain volume defined as the ratio between the volume of the brain without cerebrospinal fluid and the volume of the whole brain multiplied by 100%. The model was trained on the ADNI dataset and tested on the independent EDSD dataset. The proposed method confirmed its quality by achieving a balanced accuracy of 95.18%, AUC of 93.25%, NPV of 97.93%, and PPV of 90.48% for classifying AD vs NC for the EDSD. The comparison of two models: with the MMSE score only as an independent variable, and corrected for the relative brain value and age, shows that the addition of an MRI-based biomarker improves the quality of MCI detection (AUC: 67.04% vs 71.08%) while maintaining quality for AD (AUC: 93.35% vs 93.25%). Additionally, among MCI patients predicted as AD inconsistently with original diagnosis, 56.25% from ADNI and 54.17% from EDSD were re-diagnosed as AD within a 48-month follow-up. It shows that our model can detect AD patients a few years earlier than a standard medical diagnosis.

CONCLUSIONS

The created method is non-invasive, inexpensive, clinically accessible, and efficiently supports the AD/MCI diagnosis.

1. Background

Alzheimer's disease (AD) is a progressive, neurodegenerative brain disease that causes memory loss, changes in behaviour, and problems with everyday tasks. Alzheimer's is the most common form of dementia, and it is responsible for 60–80% of dementia cases [1, 2]. The intermediate stage from normal cognition to dementia is a mild cognitive impairment (MCI). People suffering from MCI have a high rate of progression to dementia over a relatively short period, but not everyone will develop Alzheimer's disease [3]. Within a 3-year follow-up period, about 35% of patients with MCI status progress to AD or dementia [4]. A yearly conversion rate equals 5%-10% [4].

The main aim of this work is to find easily-accessible biomarkers for Alzheimer's disease (AD) and a mild cognitive impairment (MCI) to improve the diagnosis process. An additional challenge is to predict the diagnosis of Alzheimer's while a patient is still mildly cognitively impaired.

Many different methods to predict the diagnosis have been proposed in recent years. These methods are based on machine learning algorithms [5–13], regression models [4, 14–18], and other methods [19–24]. Many different biomarkers are used to classify AD and MCI. The first group of biomarkers is based on structural brain atrophy obtained from MRI imaging [7–9, 13]. The second group of biomarkers uses the evaluation of brain metabolic changes, which are measured by fluorodeoxyglucose positron emission tomography (FDG-PET) imaging [25, 26]. Fluid biomarkers are the third group, and this is connected with amyloid and tau obtained from cerebrospinal fluid (CSF) [6, 10, 27]. Moreover, diffusion tensor imaging (DTI) and functional MRI (fMRI) are also applied for the detection of AD and MCI [5, 6, 28, 29]. Most studies use multiple biomarkers in the early diagnosis of AD and MCI and are based on a combination of two or more following biomarkers: MRI-based biomarkers, fluid biomarkers or PET-based markers [5, 30, 6, 10, 24]. The availability of all three biomarkers (PET and CSF and MRI or DTI or fMRI) is limited due to the cost, time and invasiveness of the methods (PET and CSF) [31, 24].

This article presents a method that improves an MCI and AD's diagnosis process based on easily-accessible clinical biomarkers like age and Mini-Mental State Examination score (MMSE) [32], available in medical history for almost every patient with suspicion of dementia. We suggest using, in addition to those clinical predictors, the MRI-based disease progression radiological biomarkers to support the diagnosis. In patients suffering from Alzheimer's disease, the brain shrinks, and therefore the space filled with cerebrospinal fluid increases [33, 34]. Moreover, this brain shrinkage causes the brain to be more wrinkled. Because of that, we consider the relative brain volume and global measure of brain wrinkling as the imaging biomarkers.

2. Methods

2.1 MATERIALS

Data used in the study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu) and The European DTI Study on Dementia (EDSD). The ADNI was launched in 2003 as a public-private partnership led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org. The European DTI Study on Dementia (EDSD) is a multicenter framework created to study the diagnostic accuracy and inter-site variability of DTI-derived markers in patients with manifest and prodromal Alzheimer's disease [35].

The standard analysis dataset of the ADNI-1 project was used (collection name: ADNI1: Complete 1Yr 1.5T; subjects who have both 6- and 12-month scans available) to build a statistical model for predicting AD or MCI status [36]. This dataset was randomly split into and five subsets to conduct internal testing and 5-Fold Cross-Validation [37]. In the second stage, the final statistical model was built on the whole dataset, and that model was tested on the independent dataset from the EDSD database. The dataset of the ADNI-1 project includes MPRAGE T1- weighted 3D scans (1.5 T) and several clinical and neuropsychological measures acquired from healthy controls (NC), mild cognitive impaired (MCI) subjects and Alzheimer's disease (AD).

The second dataset used in the analysis comes from The European DTI Study on Dementia (EDSD) database [35]. The EDSD was started in 2010. The coordinator of this database is the German Center for Neurodegenerative Diseases (DZNE) in Rostock, Germany. Since 2013, the EDSD has also collected the data of subjects with MCI. Dataset used in the preparation of this article includes data of subjects who were marked as "not dropout". Our analysis was based on T1-weighted MRI.

ADNI dataset (dataset 1) is a reference dataset, and the EDSD dataset (dataset 2) is an independent validation dataset. Additionally, the EDSD dataset was divided into two subsets related to MRI scanning options: 1.5T and 3T.

ADNI provided intensity normalized and gradient un-warped TI image volumes [36]. The EDSD native data were used, and N4 bias field correction in N4ITK framework was applied [38]. For both datasets: ADNI and EDSD, skull stripping was achieved in the SPM 12 software package (https://www.fil.ion.ucl.ac.uk/spm/) [39].

2.2 STATISTICAL METHODS

The clinical characteristics of subjects from the ADNI and EDSD datasets were summarized by the diagnostic group (NC, MCI, AD) and presented in table 1. The following variables were considered at baseline: age, sex, mini-mental state exam (MMSE) and years of education. For quantitative measures, values of mean and SD were calculated, and for categorical variables, the percentage was presented. The comparisons between groups were conducted using the nonparametric Kruskal-Wallis test for quantitative measures (the Conover test was used in the post-hoc analysis), and the chi^2 test to compare proportions and *P*-value is presented in table 1. Additionally, table 1 contains effect size h^2 (eta-squared) with 95% confidence interval [40, 41].

Table 1. Clinical characteristics of the ANDI and EDSD dataset.

Characteristic	NC	MCI	AD	Unadjusted *P* value	Effect size h^2 [95%CI]
ADNI, n	194	311	133	-	-
Age, mean (SD) [years]	75.9 (5.08)	74.9 (7.06)	74.7 (7.59)	.4643 *	0.0053 [0; 0.0199]
Education, mean (SD) [years]	16.0 (2.79)	15.7 (3.00)	14.7 (3.11)	.0003 * .0004 † < .0001 ‡	0.0253 [0.0057; 0.0523]
MMSE score, mean (SD)	29.1 (1.03)	27.0 (1.78)	23.5 (1.91)	< .0001 * < .0001 † ‡ §	0.6023 [0.5581; 0.6387]
Female [%]	47.9	35.4	48.1	.0053	-
EDSD, n	194	152	136	-	-
Age, mean (SD), [years]	68.7 (5.90)	71.2 (6.76)	72.4 (8.28)	< .0001 * .0001 ‡ < .0001 §	0.0497 [0.0170; 0.0900]
Education, mean (SD), [years]	13.1 (3.67) n=173	12.4 (3.35) n=132	10.3 (3.33) n=134	< .0001 * < .0001 † ‡	0.1036 [0.0538; 0.1572]
MMSE score, mean (SD)	27.4 (6.49)	26.3 (3.14)	20.8 (5.36)	< .0001 * < .0001 † ‡ §	0.2198 [0.1569; 0.2793]
Female [%]	51.0	43.4	56.6	.07854	-

* Kruskal-Wallis rank sum test; † Conover test: AD vs MCI; ‡ Conover test: AD vs NC; § Conover test: MCI vs NC

Segmentation of cerebrospinal fluid (CSF) was conducted for each subject separately using the adjusted MiMSeg algorithm [42]. This procedure was based on the Gaussian mixture model and allowed us to separate CSF from the brain by finding the threshold on the greyscale.

Two additional descriptors were defined based on MRI scans to numerically represent the changes in the brain structure. The first variable (called 'relative brain volume' (RBV) and shown as a percentage) was defined as the volume of the brain without CSF (V_{-CSF}) divided by the volume of the whole brain (V) multiplied by 100%:

$$RBV = V_{-CSF}/V \cdot 100\%, \quad (1)$$

The second variable is a 'shrinkage factor' (SF). The shrinkage factor was defined as the surface of the brain without CSF (S_{-CSF}) with reference to a volume of the brain without CSF (V_{-CSF}) and multiplied by 100%:

$$SF=S_{-CSF}/V_{-CSF}\cdot 100\%, \quad (2)$$

The additional descriptor is the volume of lateral ventricles. The Automatic Lateral Ventricle delineatioN (ALVIN) algorithm was used to obtain the volume of lateral ventricles. ALVIN is a fully automated algorithm to segment the lateral ventricles from MRI images (ALVIN works within SPM8) [43].

The multinomial logistic regression was used to predict diagnosis status. The following independent variables were considered: age, sex, years of education, MMSE score, relative brain volume, shrinkage factor, and volume of lateral ventricles. The dependent variable was diagnosis status: Alzheimer's disease (AD), mild cognitive impairment (MCI) and normal control (NC) (reference status). Models with two-way interaction terms were also analyzed. A 5-fold cross-validation was executed. The Bayesian information criterion (BIC) was used to select the best model [44]. The comparison between two nested models was conducted using ANOVA, additionally the Bayes factor (exp(DBIC)) was calculated for two compared models. The parameters of a multinomial logistic regression (polytomous) model were estimated by a maximum likelihood estimation procedure. For values of coefficient, the adjusted odds ratio was calculated with its 95% confidence interval according to the method proposed by Woolf [45]. The receiver operating characteristic curve (ROC) together with the area under the curve (AUC) for the classification problem were estimated for both datasets [46].

The scheme of key steps conducted during data analysis is presented in Figure 1 (Figure S1 shows detailed information).

3. Results

The tests on ADNI clinical characteristics indicate that the differences between at least two medians are statistically significant for the following variables: years of education and MMSE score. For the independent EDSD dataset, the differences between at least two medians are statistically significant for all variables: age, years of education, and MMSE score. The effect size of age is very small for both datasets, ADNI and EDSD. The effect size of education is small for ADNI and medium for EDSD, and the effect size of the MMSE score is large for ADNI and very large for EDSD. Results of the chi^2 test inform that the null hypothesis "the proportion of the female is the same in NC, MCI and AD" should be rejected for ANDI but not for the independent EDSD dataset.

For all cross-validation analyses, the final model has the same structure. Diagnosis status was best predicted by the synergy of relative brain volume, MMSE score and age, where age has a corrective function. A comparison between the model without relative brain volume and age as a predictors (only MMSE was taken into account) and the model with the relative brain volume and age added showed the statistical significance of the differences ($p<0.00001$; BIC= 785.54 for the model with versus BIC= 809.68 for the model without relative brain volume and age). The value of Bayes factor for compared models is 132646731.7, which indicates very strong evidence for model. No interaction increases the model performance quality.

Table S1 presents average values of coefficients (with a 95% confidence interval) obtained in 5-fold cross-validation. Healthy controls (NC) is a reference group.

For each predictor, the adjusted odds ratio was calculated (see table S2). For each one percentage point decrease in relative brain volume, the odds of Alzheimer's disease increase by a factor of 1.35 (95% CI [1.27; 1.44]) and the odds of MCI disease increase by a factor of 1.19 (95% CI [1.15; 1.24]) in reference to healthy controls. Among subjects with mild cognitive impairment, for each one percentage point decrease in relative brain volume, the odds of Alzheimer's disease increase by a factor of 1.13 (95% CI [1.10; 1.16]). The decrease of 1 point in MMSE score multiplies the odds of Alzheimer's disease by 8.15 (95% [7.53; 8.81]) in reference to healthy controls. The odds of MCI disease are predicted to grow about 2.65 times larger (95%CI [2.52; 2.79]) for each reduction of point in MMSE score among healthy controls. For each 1 point decrease in MMSE, the odds of Alzheimer's disease increase by 3.07 (95% CI [2.99; 3.16]) for subjects with MCI.

Table 2 contains average values of statistics of prediction (with a 95% confidence interval) obtained in a 5-fold cross-validation for ADNI.

Table 2. Quality performance indices of prediction system (with 95% confidence interval).

Statistics	AD vs others	NC vs others	AD vs NC	MCI vs NC	AD vs MCI
ADNI (Model: Status of disease ~ Relative brain value + MMSE + Age)					
Sensitivity [%]	63.99 [48.61; 79.37]	70.08 [61.92; 78.24]	100	80.67 [75.63; 85.72]	63.99 [48.61; 79.37]
Specificity [%]	94.06 [90.93; 97.19]	87.84 [85.17; 90.51]	100	70.08 [61.92; 78.24]	88.22 [81.53; 94.9]
Positive Predictive Value [%]	74.41 [65.56; 83.26]	71.66 [67.12; 76.20]	100	79.84 [76.71; 82.96]	74.41 [65.56; 83.26]
Negative Predictive Value [%]	90.91 [87.34; 94.47]	87.13 [84.19; 90.07]	100	71.66 [67.12; 76.20]	82.71 [76.16; 89.26]
Prevalence [%]	20.84 [20.42; 21.26]	30.41 [30.05; 30.77]	38.51 [34.3; 42.73]	59.13 [57.50; 60.76]	34.11 [32.94; 35.29]
Balanced Accuracy [%]	79.02 [71.65; 86.4]	78.96 [75.23; 82.69]	100	75.38 [72.10; 78.65]	76.1 [68.52; 83.69]
AUC [%]	94.18 [92.09; 96.28]	90.01 [87.03; 92.99]	99.65 [99.18;100.00]	79.30 [74.35; 84.24]	90.78 [87.45; 94.11]
Cutoff point	0.16 [0.05; 0.26]	0.30 [0.20; 0.40]	8.38 [3.88; 12.87]	47.24 [35.28; 59.21]	30.13 [10.32; 49.95]
EDSD (Model: Status of disease ~ Relative brain value + MMSE + Age)					
Sensitivity [%]	69.85	73.20	96.94	75.78	71.43
Specificity [%]	90.17	88.19	93.42	77.17	80.17
Positive Predictive Value [%]	73.64	80.68	90.48	69.78	79.83
Negative Predictive Value [%]	88.39	83.01	97.93	82.08	71.85
Prevalence [%]	28.22	40.25	39.20	41.03	52.36
Balanced Accuracy [%]	80.01	80.70	95.18	76.48	75.80
AUC [%]	89.95	85.36	93.25	71.08	85.74
EDSD (Model: Status of disease ~ MMSE)					
Sensitivity [%]	71.32	69.59	97.98	77.78	72.39
Specificity [%]	89.6	89.58	93.10	73.37	79.03
Positive Predictive Value [%]	72.93	81.82	90.65	66.67	78.86
Negative Predictive Value	88.83	81.39	98.54	82.82	72.59

[%]					
Prevalence [%]	28.22	40.25	40.57	40.65	51.94
Balanced Accuracy [%]	80.46	79.59	95.54	75.57	75.71
AUC [%]	90.19	85.87	93.35	67.04	86.14

Abbreviations: AUC, the area under the ROC curve.

Values of areas under the ROC curve (AUC) were very high for classes AD vs others and NC vs others, and 5-fold cross-validation for ADNI resulted in 94.18% and 90.01%, respectively. The value of three classes (AD vs others, NC vs others, MCI vs others) of balanced accuracy is 76.10%. Specificity of 94.06% was gained for AD vs others, and it is the highest value; the sensitivity for this class is 63.99%. The value of Negative Predictive Value [%] (NPV) is 90.91% for AD vs others, while the value of Positive Predictive Value [%] (PPV) is 74.41%. The values of specificity, sensitivity, NPV and PPV for NC vs others are 87.84%, 70.08%, 87.13% and 71.66%, respectively. The pairwise analysis gave a very large value of AUC for the classification of AD versus NC (99.65%). The value of specificity, sensitivity, NPV and PPV for AD vs NC is 100%.

The multinomial logistic regression model was also trained on the whole ADNI dataset and tested on the independent EDSD dataset. Values of model coefficients are presented in table S3.

As before, for each predictor, the adjusted odds ratio was calculated (see table S4). One can notice that for each one percentage point decrease in relative brain volume, the odds of Alzheimer's disease increase by 1.35 (95% CI [1.25; 1.46]) in reference to healthy controls and the odds of MCI disease increase by a factor of 1.19 (95% CI [1.13; 1.26]) which is very similar to the estimates obtained in the first stage. Among subjects with mild cognitive impairment, for each one percentage point decrease in relative brain volume, the odds of Alzheimer's disease increase by a factor of 1.13 (95% CI [1.10; 1.16]). For each reduction of point in MMSE score, the odds are predicted to grow about 8.06 times larger (95%CI [6.48; 10.04]) for Alzheimer's disease and 2.64 (95% [2.27; 3.08]) for mild cognitive impairment in reference to healthy controls. The decrease of 1 point in MMSE score multiplies the odds of Alzheimer's disease by 3.05 (95% [2.85; 2.36]) among subjects with MCI status.

The obtained model was tested on the independent validation EDSD dataset, and table 2 presents the results. Additionally, Table S5 contains results for two subsets of EDSD: 1.5T and 3T.

The results of validation for the independent dataset (EDSD) have shown that values of areas under the ROC curve (AUC) for classes: AD versus others and NC vs others are 89.95% and 85.36%, respectively. The value of three classes (AD vs others, NC vs others, MCI vs others) of balanced accuracy is 76.83%. Specificity of 90.17%, sensitivity of 69.85%, NPV of 88.39%, and PPV of 73.64% were gained for AD vs others. The values of specificity, sensitivity, NPV and PPV for NC vs others are 88.19%, 73.20%, 83.01%, and 80.68%, respectively. The pairwise analysis confirmed the very large value of AUC for the classification of AD versus NC (93.25%). Specificity of 93.42% was gained for AD vs NC, and it is the highest value, the sensitivity for this class is 96.94%. The value of NPV is 97.93% for AD vs NC, while the value of PPV is 90.48%. Additionally, table 2 contains the results of validation for the independent EDSD dataset for the model built on the whole ADNI dataset with only independent variable MMSE score. Results confirm that adding the relative brain volume and age as a corrective function for natural brain aging improves the model. The value of AUC for MCI vs NC increases from 67.04% (for model with MMSE score only) to 71.08% (for model with the relative brain volume and age added).

The ROC curve was used to summarize the prediction of the model for ADNI and ESDS datasets (Figure 2).

During the follow-up, some subjects have converted from MCI status to AD. Table 3 contains the number and percentage of subjects with changes in diagnosis during 12 months of the follow-up in association with the prediction (ADNI datasets) and 48 months of follow-up (ADNI and the independent EDSD datasets). The prediction of the multinomial logistic regression model in 5-fold cross-validation of the ADNI dataset indicates that 32 subjects, who have MCI screening diagnosis, are predicted as AD status. Among these subjects, predictions are in line with 12 months of the follow-up diagnosis in 10 subjects (31.25%). A similar calculation was conducted for 48 months of follow-up. Table 3 contains the number and percentage of subjects with changes in diagnosis from MCI to AD during 48 months of the follow-up in association with the prediction (ADNI datasets).

Table 3. Compliance of the prediction with the change in diagnosis from MCI to AD.

Change from MCI to AD Number of subjects (%)	**Compliance of AD prediction with the follow-up diagnosis**	**No change in diagnosis from MCI to AD among AD predicted patients***	**AD prediction among subjects with MCI screen diagnosis**
ADNI – 12 months	10 (31.25%)	22 (68.75%)	32 (100%)
ADNI – 48 months	18 (56.25%)	14 (43.75%)	32 (100%)
EDSD – 48 months	13 (54.17%)	11 (45.83%)	24 (100%)

* Not for all subjects, follow-up diagnosis after 48 months is available, so “no change” or “missing information about change” occurs. This means that the outcome could improve if information about the change in diagnosis was available.

The prediction was consistent within 48 months of the follow-up diagnosis for 18 subjects (56.25%) among 32 subjects with MCI screening diagnosis and model prediction of Alzheimer's disease. One subject changed the diagnosis from AD to MCI during follow-up, and this diagnosis is compliant with the prediction. Three subjects developed MCI among NC subjects; the diagnosis is compliant with the prediction for one subject.

Prediction of the multinomial logistic regression model on the independent EDSD dataset shows similar results. Table 3 contains the number and percentage of subjects with changes in diagnosis from MCI to AD during four years of follow-up in association with the prediction (EDSD dataset). The multinomial logistic regression model on the independent EDSD dataset predicts Alzheimer's disease in 24 subjects with MCI screening diagnosis. Among these 24 subjects, 13 (54.17%) patients transited from MCI to AD status, and they confirmed the model prediction. The percentage may be even improved as some patients haven't follow-up on their diagnosis.

4. Discussion And Conclusions

Our aim was to improve classical diagnosis process based on MMSE score. We focused on finding the common available biomarker, which improves diagnostics. We obtained that the multinomial logistic regression model was of the same structure for all cross-validation analyses and based on the complete ADNI dataset. Diagnosis status was best predicted by the relative brain volume, MMSE score, and age. The results of comparison models with MMSE score only and the relative brain volume and age added shows that adding the relative brain volume (and age as an

adjustive factor for natural brain aging) improves model. The value of Bayes factor indicates strong evidence and we can notice that the quality of MCI detection increases (AUC: 67.04% vs 71.08%) while maintaining the quality for AD (AUC: 93.35% vs 93.25%). The average values of coefficients of the multinomial logistic regression models for 5-fold cross-validation and results for the whole ADNI dataset are very similar, which confirms the homogeneity of the training dataset and consistency of the diagnosis process. Average values of statistics of prediction obtained in 5-fold cross-validation for ADNI show that we have the outstanding results of classification AD vs NC and AD vs others, with AUC equaling 99.65% and 94.18%, respectively. Additionally, the values of AUC for AD vs MCI and for NC vs others are also very high (90.78% and 90.01%, respectively). The moderate value of AUC we have for MCI vs NC (79.30%) is still a very good result if we take into account that the MCI group is heterogeneous and some patients from this group develop AD, and some patients have stable MCI status. The average value of balanced accuracy for three classes (AD vs others, NC vs others, and MCI vs others) is 76.10% for 5-fold cross-validation. As we aim to develop a supporting diagnostic test, detecting patients with the disease is the most important, so Positive Predictive Value (PPV) and Negative Predictive Value (NPV) are the most important.

We have compared our classification results with results reported in the literature based on the ADNI dataset (11 studies used the ADNI dataset as a training dataset, one study used the internal locally dataset as a training dataset and ADNI dataset as an independent validation dataset; 6 studies among 12 used additionally independent validation dataset) (table 4).

Table 4. Overview of previous studies based on the ADNI dataset.

Studies	Sample size	Method	Input	Validation	Groups	Parameters	Results
Agostinho et al., 2022 [6]	The internal locally dataset (n=41): AD (n=20), NC (n=21).	SVM	MRI, PiB-PET and DTI	Internal locally dataset and external dataset (ADNI (n=330): AD (n=166), NC (n = 164))	AD, NC	AUC, ACC, SEN, SPEC, BACC	Dependent validation: AD vs NC: MRI: AUC=96%, ACC=92.05%, SEN=86.78%, SPEC=86.78%, BACC=92.05%; PiB PET: AUC=93%, ACC=90.53%, SEN=92%, SPEC=82, BACC=79.84%; DTI: AUC=86%, ACC=76.84%, SEN=76.17%, SPEC=82.09%, BACC=79.84%. Independent validation: AD vs NC: MRI: AUC=81%, ACC=78.02%, SEN=74.12%, SPEC=82.29, BACC=78.20%; PiB PET: AUC=81%, ACC=76.87%, SEN=87.9%, SPEC=68.33%, BACC=78.12%; DTI: AUC=69%, ACC=62.79%, SEN=54.31%, SPEC=71.98%, BACC=63.15%.
Gao et al., 2022 [7]	1134 subjects: AD (n=454), NC (n=680).	3DMgNet (multigrid and convolutional neural network)	MRI	10-fold cross-validation and external in-house dataset (AD (n=75), NC (n=59))	AD, NC	AUC, ACC, SEN, SPEC	Dependent validation: ACC=92.13%, AUC=94.43%, SEN=88.42%, SPEC=95%. Independent validation: ACC=87.91%, AUC=95.74%, SEN=79.73%, SPEC=98.31%.
Goenka et al., 2022 [8]	769 subjects: AD (n=70), MCI (n=224), NC (475)	CNN	MRI	633 scans from ADNI dataset	AD, MCI, NC	AUC, ACC	Dependent validation: AD vs NC: ACC= 97.83%, AD vs MCI: ACC=98.68%, NC vs MCI: ACC=99.10%, NC vs MCI vs AD: ACC=98.26%.

							AD vs NC: AUC=94%, AD vs MCI: AUC=97%, NC vs MCI: AUC=99%, NC vs MCI vs AD: AUC=98%.
Tang et al., 2021 [9]	560 subjects: AD (n=80), EMCI (n=230), LMCI (n=110), NC (n=140)	SVM, RF, DT	MRI	10-fold cross-validation	AD, EMCI, LMCI, NC	AUC, ACC, SEN, SPEC	RF: NC vs AD: ACC=96.14%, SEN=88.14, SPE=92.81%, AUC=92%. NC vs EMCI: ACC=77.45%, SEN=79.51%, SPE=33.54%, AUC=59%. NC vs LMCI: ACC=87.56%, SEN=64.71%, SPE=83.94%, AUC=81%. EMCI vs AD: ACC=90.15%, SEN=93.51%, SPE=92.43%, AUC=85%. LMCI va AD: ACC=84.54%, SEN=67.91, SPE=72.46%, AUC=89%.
Dyrba et al., 2021 [10]	633 subjects: AD (n=189), MCI (n=220), NC (n=254)	CNN	MRI and PET	1-fold cross-validation and three independent datasets: ADNI-3 (n=575), AIBL (n=606), DELCODE (n=474).	AD, MCI, NC	AUC, ACC, SEN, SPEC, BACC, PPV, NPV	Dependent validation: AD vs NC: BACC=88.9%, SEN=94.2%, SPE=83.6%, PPV=81.5%, NPV=95.2% AUC=94.9%. MCI vs NC: BACC=74.5%, SEN=65.5%, SPE=83.6%, PPV=78.1%, NPV=74.1%, AUC=78.5%. amyloid-positive AD vs amyloid-negative NC: BACC=94.9%, SEN=95.6%, SPE=94.3%, PPV=92.7%, NPV=96.6%, AUC=98.5%. amyloid-positive MCI vs amyloid-negative NC: BACC=86.7%,

							SEN=79%, SPE=94.3%, PPV=91.6%, NPV= 96.6%, AUC=92.5%. Independent validation DELCODE: AD vs NC: BACC=85.5%, SEN=94.2%, SPE=76.7%, PPV=66.2%, NPV=96.5% AUC=95.3%. MCI vs NC: BACC=71%, SEN=65.2%, SPE=76.7%, PPV=66.9%, NPV=75.3%, AUC=77.5%. amyloid-positive AD vs amyloid-negative NC: BACC=83.3%, SEN=95.9%, SPE=70.7%, PPV=73.4%, NPV=95.3%, AUC=96.8%. amyloid-positive MCI vs amyloid-negative NC: BACC=72.2%, SEN=73.7%, SPE=70.7%, PPV=71.2%, NPV= 73.2%, AUC=84%.
Marzban et al., 2020 [5]	406 subjects: NC (n=185), MCI (n=106), AD (n = 115)	CNN	MRI and DTI	10-fold cross-validation	AD,NC, MCI	AUC, ACC, SEN, SPEC	AD vs NC: AUC=94%, ACC=93.5%, SEN=92.5%, SPEC=93.9. MCI vs NC: AUC=84%, ACC=79.6%, SEN=62.7%, SPEC=89%
Li et al., 2020 [11]	404 subjects: NC (n=268), AD (n=136)	SVM	MRI	10-fold cross-validation and independent validation dataset (AD (n=41), NC (n=25))	AD, NC	ACC, SEN, SPEC	Dependent validation dataset: AD vs NC: ACC=93.07%, SEN=94.12%, SPEC=98.51. Independent validation dataset: AD vs NC: ACC=84.85%,

							SEN=85.36%, SPEC=84%
Bae et al., 2020 [12]	390 subjects: AD (n=195), NC (n=195)	CNN	MRI	5-fold cross-validation and independent validation dataset (AD (n=195), NC (n=195))	AD, NC	AUC, ACC, SEN, SPEC	Dependent validation dataset: AD vs NC: AUC=94%, ACC= 89%, SEN= 88%, SPEC=91%. Independent validation dataset: AD vs NC: AUC=88%, ACC= 83%, SEN= 76%, SPEC= 89%
Liu et al., 2020 [13]	449 subjects: AD (n=97), MCI (n=233), NC (n=119)	CNN	MRI	5-fold cross-validation and independent dataset (AD (n=45), MCI (n=46), and NC subjects (n=44)).	AD, MCI, NC	AUC, ACC, SEN, SPEC	Dependent validation: AD vs NC: ACC=88.9%, SEN=86.6%, SPE=90.8%, AUC=92.5%. MCI vs NC: ACC=76.2%, SEN=79.5%, SPE=69.8%, AUC=77.5%. Independent validation: AD vs NC: AUC=89.8% MCI vs NC: AUC=72.2%
Zhang et al., 2019 [24]	857 subjects: NC (n=322), MCI (n=322), AD (n = 213)	Graph Analysis	MRI	Data are randomly partitioned into 80% and 20% for training and testing.	AD, MCI, NC	AUC	AD vs MCI + NC: AUC=73%, NC vs AD + MCI: AUC=72%, MCI vs AD + NC: AUC= 69%.
Westman et al., 2012 [24]	369 subjects: AD (n=96), MCI (n=162) and NC (n=111).	Orthogonal Partial Least-Squares (OPLS)	MRI, PET, CSF	7-fold cross-validation	AD, MCI, NC	AUC, ACC, SEN, SPEC, PPV, NPV	AD vs NC: MRI with CSF: ACC= 91.8%, SEN=88.5%, SPEC=94.6%, PPV=93.4%, NPV=90.5% and AUC=95.8%. MRI only: ACC=87%, SEN=83.3%, SPEC=90.1%, PPV=87.9%, NPV=86.2%

							and AUC=93% CSF only: ACC=81.6%, SEN=84.4%, SPEC=79.3%, PPV=77.9%, NPV=85.4% and AUC=86.1%. MCI vs NC: MRI with CSF: ACC=77.6%, SEN=72.8%, SPEC=84.7%, PPV=87.4%, NPV=68.1% and AUC=87.6%. MRI only: ACC=71.8%, SEN=66.7%, SPEC=79.3%, PPV=82.4%, NPV=62.0% and AUC=81.5%. CSF only: ACC=70.3%, SEN=66.7%, SPEC=75.7%, PPV=80.0%, NPV=60.9% and AUC=74.9%.
Eskildsen et al., 2012 [47]	808 subjects: AD (n=194), NC (n=226), pMCI (n=161), sMCI (n=227)	LDA	MRI (cortical thickness and age)	leave-one-out (LOO) validation	AD, NC, pMCI, sMCI	AUC, ACC, SEN, SPEC	Independent feature sets: AD vs NC: ACC=85.5%, SEN=80.4%, SPEC=89.8%, AUC=92%. pMCI vs sMCI: ACC=67.8%, SEN=64.6%, SPEC=70%, AUC=68.2%. Dependent feature sets: AD vs NC: ACC=87.4%, SEN=82.5%, SPEC=91.6%, AUC=93.1%. pMCI vs sMCI: ACC=68.3%, SEN=67.7%, SPEC=68.7%, AUC=74.7%.

Abbreviations: AIBL, Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing; DELCODE, DZNE multicenter observational study on Longitudinal Cognitive Impairment and Dementia; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; pMCI, progressive MCI; sMCI, stable MCI; CNN, convolutional neural network; LDA, linear discriminant analysis; SVM, support vector machine; RF, random forest; DT, decision tree;

AUC, area under receiver operating characteristic curve; ACC, accuracy; SEN, sensitivity; SPEC, specificity; BAAC, balanced accuracy; PPV, positive predictive value; NPV, negative predictive value.

Table 4.

Our results for the independent validation dataset are not worse and, in many cases, even better than the results from previously published studies. Our model achieved the best balanced accuracy of 95.18% (balanced ACC) for the independent validation dataset when the highest value of balanced accuracy for AD vs NC from reported studies is 85.5% [10]. Although the highest reported value of AUC is 96.8, in this study, the decision is supported by the concentration of amyloid in CSF [10]. The second top reported AUC value is 95.74%, but this study focuses on only two categories: AD and NC, while we consider MCI as a third one [7]. The third value of AUC is 95.3%. This value is slightly bigger than ours, but other performance indicators like balanced accuracy, sensitivity, specificity, PPV, and NPV for AD vs NC are better in our approach [10]. The lowest value of AUC for AD vs NC among publications presented in table 4 is 69% [6]. The highest sensitivity value for AD vs NC is 95.6% for analysis based on the concentration of amyloid in CSF and 94.2% for analysis without amyloid data, while our estimated sensitivity is better and equal to 96.94% [10]. For the prediction specificity, the highest value observed is 98.31%, but this study focuses only on two categories: AD and NC, which means that it is easier to achieve better results than for three categories [7]. The second highest reported value of specificity is 89.8%, which is lower than ours (93.42%) [47]. The lowest value of specificity among publications is 68.33% [6]. Only one study from table 4 contains the results of NPV and PPV for AD vs NC, values of these indicators are 95.3% and 73.4% for analysis based additionally on amyloid data, and 96.5% and 66.2% for analysis without amyloid data, respectively [10]. Our results are again better; the value of NPV is 97.93% for AD vs NC, while PPV is 90.48%. The comparison of results for 5-fold cross-validation shows that our model achieves better results than all reported studies for the classification task of AD versus NC (table 4) [5, 6-13, 23, 24, 47]. The prediction results of AD vs NC from reported studies show that the highest AUC is 98.5% [10], when our result is 99.65%, the highest accuracy for AD vs NC is 97.83% [8], when our result is 100% (we have the balanced ACC). The highest values of sensitivity and specificity are 95.6% [10] and 98.51% [11], respectively, when our model achieved 100% for both parameters.

Additionally, among MCI patients predicted as AD inconsistently with original diagnosis, 56.25% from ADNI and 54.17% from EDSD were re-diagnosed as AD within a 48-month follow-up.

5. Conclusions

Our work shows that the proposed MRI-based biomarker, combined with MMSE score and adjusted for age, gives excellent AD status predictions. Moreover, our method, as based on MRI, doesn't require invasive and expensive laboratory tests and, as being a classical statistical learning model, doesn't require large calculation power.

In this paper, we proved that incorporating the radiological MRI-based biomarker into the standard clinical AD predictors leads to a handy model for daily clinical routine and improves the diagnosis process. Additionally, we demonstrated that our model detects some patients transitioning from MCI to AD as AD patients a few years earlier before regular medical diagnosis.

6. List Of Abbreviations

ACC - accuracy;

AD - Alzheimer's disease;

ADNI – Alzheimer's Disease Neuroimaging Initiative;

AIBL - Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing;

ALVIN - Automatic Lateral Ventricle delineatioN;

AUC – area under the curve;

BAAC - balanced accuracy;

BIC - Bayesian information criterion;

CI – confidence interval;

CNN - convolutional neural network;

CSF - cerebrospinal fluid;

DELCODE - DZNE multicenter observational study on Longitudinal Cognitive Impairment and Dementia;

DT - decision tree;

DTI - diffusion tensor imaging;

EDSD – European DTI Study on Dementia;

EMCI - early mild cognitive impairment;

FDG-PET - fluorodeoxyglucose positron emission tomography imaging;

fMRI - functional MRI;

LDA - linear discriminant analysis;

LMCI - late mild cognitive impairment;

MCI - Mild Cognitive Impairment;

MMSE – Mini-Mental State Examination score;

MRI - magnetic resonance imaging;

NC – Normal Control;

NPV – negative predictive value;

PET - positron emission tomography;

pMCI - progressive MCI;

PPV – positive predictive value;

RBV - relative brain volume;

RF - random forest;

ROC - receiver operating characteristic curve;

SEN - sensitivity;

SF - shrinkage factor;

sMCI - stable MCI;

SPEC - specificity;

SVM - support vector machine;

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: Data used in the analysis were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (https://adni.loni.usc.edu/) and The European DTI Study on Dementia (EDSD) (https://www.neugrid2.eu/ and https://neugrid4you.eu/).

Competing interests: The authors declare that they have no competing interests.

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Author's Contributions: Conceptualization, J. P.; methodology, J. P. and A. M.; software, A. M.; formal analysis, A. M.; writing—original draft preparation, A. M.; writing—review and editing, J. P. and A. M.; visualization, A. M.; supervision, J. P.; funding acquisition, J. P.

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at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

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Figures

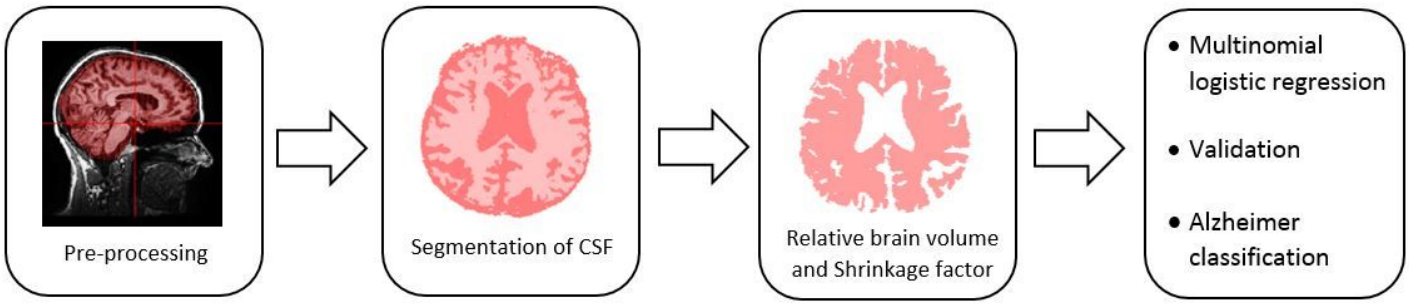

Figure 1

The scheme of key steps of data preprocessing and data analysis.

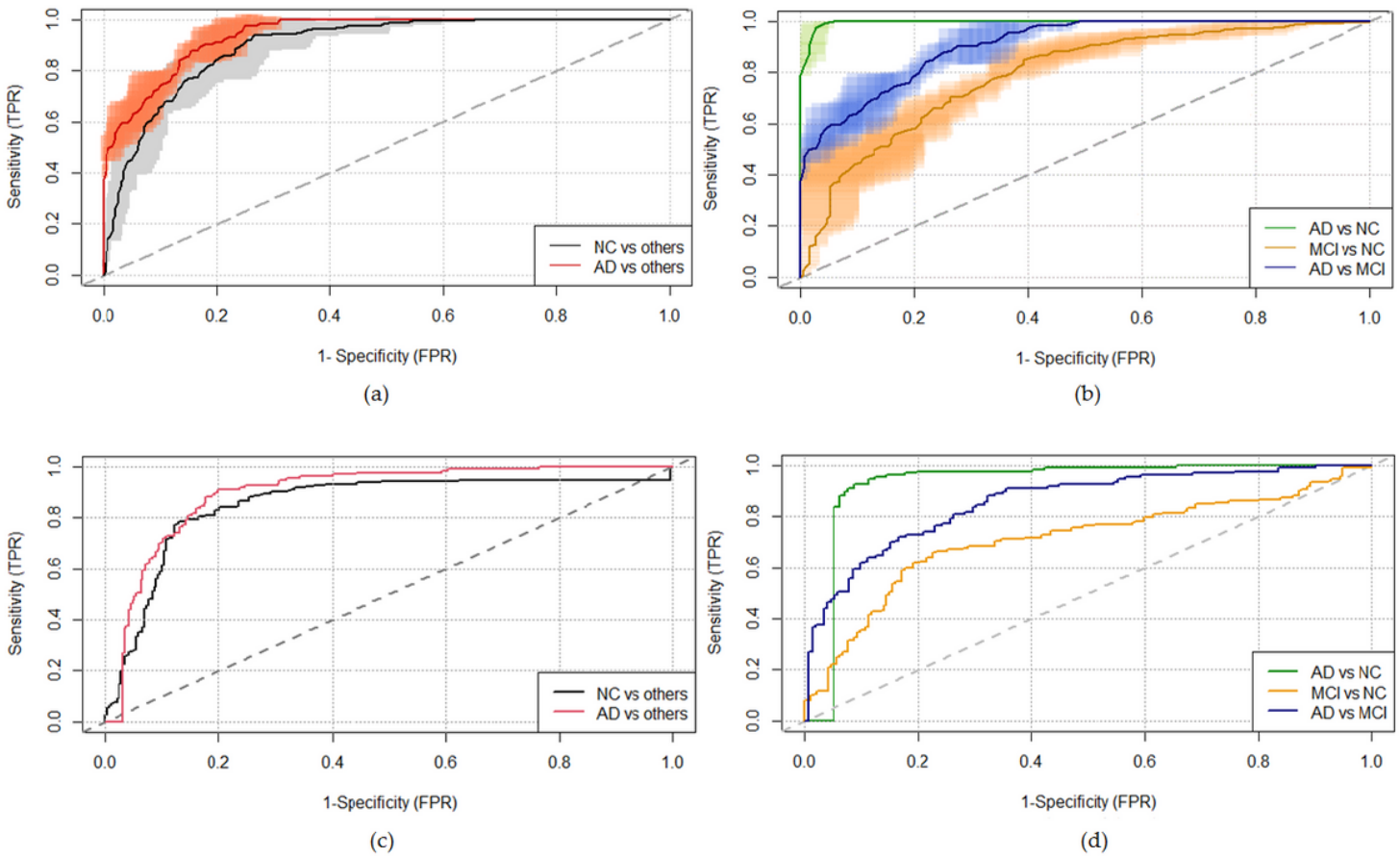

Figure 2

The ROC curve for classification between AD, MCI and NC: (a) The ROC curve for classification with average values of 5-fold cross-validation (ADNI data): AD vs others, NC vs others; (b) The ROC curve for classification with average values of 5-fold cross-validation (ADNI data): Ad vs NC, MCI vs NC, AD vs MCI; (c) The ROC curve for classification using ADNI data as training data and EDSD data (whole dataset) as test data: AD vs others, NC vs others; (d) The ROC curve for classification using ADNI data as training data and EDSD data (whole dataset) as test data: AD vs NC, MCI vs NC, AD vs MCI.

Supplementary Files

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