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Prediction of Alzheimer's Disease in the Pre-Clinical Phase using Machine Learning

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Diffusion tensor imaging; Decision tree algorithm; Machine learning; Computational intelligence; Alzheimer's disease

ABSTRACT

Recent advancements in neuroimaging methods, such as diffusion tensor imaging (DTI), have become a valuable resource for structural brain research, allowing for the detection of changes associated with severe neurodegenerative illnesses like Alzheimer's disease (AD). Simultaneously, computational tools based on machine learning for early diagnosis and the decision tree method are used to identify hidden patterns in data for phenotypic classification and identification of pathological scenarios. In this paper, we present a unique method for automatically discriminating between healthy controls and Alzheimer's patients using DTI values as predictive features. We demonstrate that this approach enhances classification performance (accuracy of 98%) compared to the comprehensive strategy of concatenating global features. Lastly, this type of method may be used in the feature selection phase of similar classification problems, allowing one to exploit the information richness of data while reducing the size of the feature space and, consequently, the computational effort required.

1. Introduction

Alzheimer's disease (AD) is the common form of dementia, caused by a neurodegenerative condition marked by memory loss and a progressive decline in cognitive abilities. Alzheimer's disease (AD), sometimes referred to as Alzheimer's, is a neurological condition that effects approximately 35,6 million individuals worldwide [2]. It is the most prevalent cause of dementia in the elderly population [1] of industrialized countries. Alzheimer's disease affects millions of people worldwide [3], according to the 2015 World Alzheimer's Report, and by 2050, dementia will affect 131.5 million people. Alzheimer's disease is characterized by gradual and irreversible neurologic degeneration, which results in a decline in cognitive abilities and eventual death [4]. The accumulation of two proteins, beta-amyloid and tau, in the brain kills cortical neurons, resulting in brain atrophy and white

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matter (WM) alterations [5-8]. The development of asymptomatic pathogenic alterations characterizes the Alzheimer's disease preclinical phase (preclinical phase), which is followed by Mild Cognitive Impairment (MCI) [5]. MCI is a pathological disease characterized by a symptom of broad spectrum. MCI can be the prodromal phase of AD, but it can also progress to other forms of dementia [9]. About half of MCI patients [10] could be classified as AD precursors. Particularly, the amnestic subtype of MCI appears to have a higher risk of developing AD [11,12]. Initial stages of (AD) are associated with grey matter (GM) atrophy and white matter (WM) alterations [13]. It is unclear, however, whether WM impairment is a fundamental early pathological indicator in MCI and AD [14].

Determining the cause of (AD) is extremely difficult due to the wide range of cognitive and behavioural symptoms that patients may exhibit. Like treatment responses, disease progression mechanisms are also subjective. Within this framework, the most challenging mission is to develop diagnostic tools that will aid in the early detection of the disease. (AD) and dementia research focuses primarily on identifying individuals in the prodromal phase. This is essential, as early therapies have been shown to delay clinical onset, halt disease progression, and reduce the number of individuals afflicted with the disease [15,16].

AD is still difficult to diagnose in vivo due to the vast array of symptoms demonstrated by patients. In this context, the development of innovative diagnostic tools based on computational intelligence that can aid physicians and specialists in early pathology detection and therapy plan selection is a challenging endeavour. Dementia and Alzheimer's disease have preclinical signs that are detectable several years prior to a clinical diagnosis [17].

2. Related Works

This section provides an overview of the existing techniques used in the identification and classification of AD, using ML methodologies, along with an examination of their respective characteristics.

Early detection is essential for effective treatment of Alzheimer's Disease, a common neurodegenerative condition in the elderly. By resolving missing data with cutting-edge approaches, this study evaluates the value of longitudinal data in predicting MCI-to-AD conversion prior to clinical diagnosis. Their study proves that it is possible to create AD staging and prognostic algorithms using longitudinal data, even in the face of missing values, by achieving an outstanding 71.16% accuracy [27]. The importance of early detection is underscored by the permanent harm Alzheimer's Disease (AD) does to memory and cognition. Their review of the literature highlights the growing significance of machine learning (ML) in the diagnosis of AD using 3D MRI scans and feature extraction methods. They set the stage for precise and effective AD prediction and categorization by measuring system performance with important indicators, providing promise for better patient care and research outcomes [28]. The urgent need for early diagnosis is underscored by the fact that AD is still a serious and incurable neurodegenerative illness. The integration of ML methods for diagnosing AD is explored in their literature review, with an emphasis on the fusion of data from diverse neuroimaging modalities and resolving related issues. They did not use ADNI dataset to perform the analysis. Their article greatly advances the development of computer-aided early diagnostic systems, thus enhancing AD research and patient treatment, by providing a thorough examination of feature extraction, selection, and fusion approaches [29].

Xiang *et al.,* [18] worked on how neuroimages and DNA information can be used together to better identify Alzheimer’s Diseases. Their study was not done using the ADNI dataset. Their combined model works well even with missing data and is better than the methods that have been used before. A machine learning method called JDINAC to look at gene expression data is used by

Chen *et al.,* [19]. This shows that interactions between pairs of genes are better at predicting AD than individual genes. In the field of neuro-imaging, a suggested AI tool by Koh *et al.,* [20] shows promise for diagnosing AD by using MRI brain pictures that have already been processed. Using methods like feature selection and classifiers, they got a very high level of precision. This systematic literature review (SLR) investigates the use of ML in estimating the risk of AD development using data from electronic health records. It analyses 64 relevant publications from 2010 to 2020 and finds an increasing trend in ML-based AD dementia research that emphasizes the use of neuroimaging and clinical data for individualized disease management and care planning. The results highlight the potential for ML to use structured and clinical notes data to enhance AD risk prediction, highlighting the significance of data sharing and repeatability for a broad effect. They conducted the study without using the ADNI dataset [30]. Deep learning also comes into play, as Liu *et al.,* [21] showed how stacked auto-encoders can help to improve the detection of (AD) and (MCI). This method works better for all diagnostic groups, even though it needs fewer identified samples. Tanveer *et al.,* [22] gave a detailed look at different machine learning methods, divided them into different types, and suggested future directions for research in early Alzheimer's Disease detection. Genetic data also plays a part. Oriol *et al.,* [23] looked at ML models to predict Late-Onset Alzheimer's Disease (LOAD) showed hopeful results, and found possible new genetic markers linked to the disease. The major cause of visual loss is diabetic retinopathy (DR), which necessitates early identification and diagnosis. The research uses an automated method, with MobileNetV2 proving to be the most successful model. The results show how automated CNN-based systems have the potential to transform DR diagnosis, relieving physicians' workloads and increasing productivity [31].

Belleville *et al.,* [24] talked about the importance of mixing cognitive, mental, and neural measures to improve how well they can predict the future. Lastly, cognitive patterns in juvenile Alzheimer's Disease are studied by Riley *et al.,* [25]. Their work showed that people with early-stage AD have different rates of cognitive decline than people without Alzheimer's Disease, which opens the door to non-invasive means for early diagnosis. In times of mental turmoil, a lot of people struggle and look for solace. In order to anticipate food preferences based on emotional states, their research uses machine learning models to dive into the relationship between emotions and comfort food preferences among students. The results show a strong correlation between emotional states and food preferences, and Nave Bayes is very accurate in predicting comfort food preferences, providing us with new understanding of how people manage their emotional health [32]. In this study, Hossain *et al.,* [26] MobileNetV2 and VGG16 deep learning models accurately diagnosed COVID-19 from chest X-ray images, showing promising potential for improving diagnostic accuracy over RT-PCR tests.

Mohamed *et al.,* review emphasizes the critical need for both early detection and continuous monitoring in addressing Alzheimer's disease. The proposed algorithm utilizing the Chan-Vese segmentation technique showcases a promising semi-automated model for quantifying hippocampal changes in MRI images, paving the way for further refinement and application in progression detection [33]. Ching *et al.,* shows highlights the crucial role of early detection in Alzheimer's disease using MRI images and emphasizes the efficacy of Transfer Learning, specifically the EfficientNet-B0 model, in achieving impressive classification accuracy, showcasing its potential to enhance diagnostic capabilities in the complex analysis of neurological disorders [34]. Exploring the intricate landscape of Alzheimer's Disease classification, Sanjay *et al.,* delves into the convergence of Deep Learning, Feature Extraction, and dataset-centric approaches, offering a comprehensive analysis of their efficacy in understanding and diagnosing the multifaceted stages of AD [35]. Integrating deep learning techniques, specifically concatenated CNN of DenseNet and MobileNet, with MRI data demonstrates a promising approach, achieving high accuracy (98.87%), precision (98.95%), and recall (98.99%) in multiclass classification of Alzheimer's disease, showcasing the potential of advanced

technology in neurodegenerative illness detection [36]. Azizan *et al.,* proposed method shows the impact of integrated exercise and reminiscence therapy on depression levels and quality of life in institutionalized older adults with mild-to-moderate Alzheimer's disease. Findings suggest that both reminiscence therapy alone and in combination with exercise effectively reduce depressive symptoms and enhance overall quality of life, providing valuable insights for healthcare practices in older adults' rehabilitation.

Together, these studies put light on new ways to identify and diagnose Alzheimer's Disease, which is moving the field toward more accurate and efficient methods [18-32].

3. Methodology

The proposed method used a variety of supervised classification ML algorithms based on the characteristics, such as K-Nearest Neighbors, Decision Tree, Naive Bayes, and others. Figure 1 represent the research method stages for our proposed method.

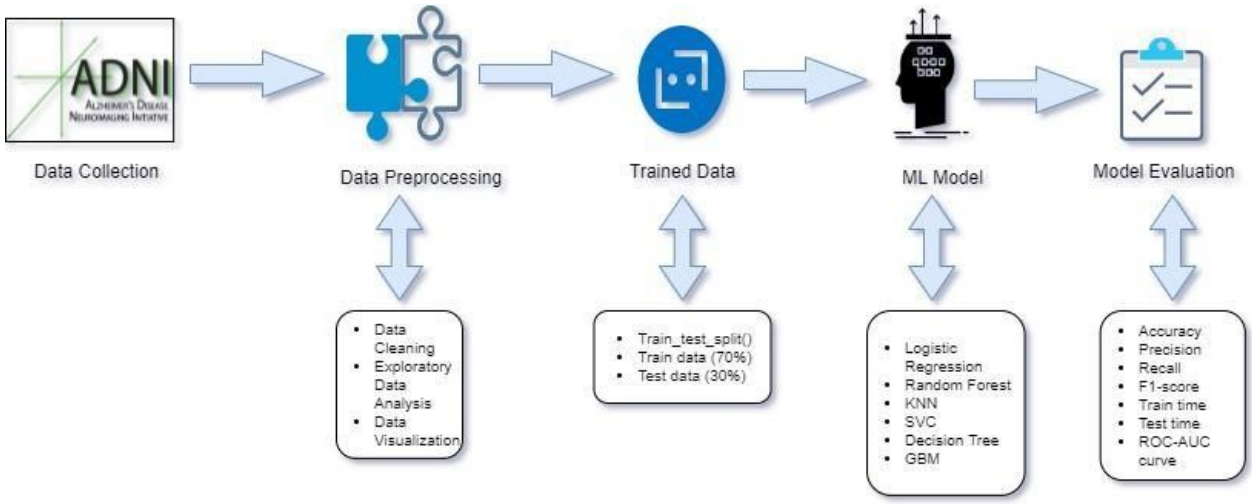


Fig. 1. Research Methodology Diagram

3.1 Data Description

This is based on data administration for the ADNI database (adni.loni.usc.edu). As a biomarker for Alzheimer's disease, Diffusion Tensor Imaging (DTI) provides information on the subtle microstructure changes of white matter integrity and is a more sensitive version of MRI imaging. The ADNI-2 and ADNI-3 projects acquire DTI Data for white matter regions of interest (ROI; see www.adni.org). The Laboratory of Neuro Imaging at UCLA generated DTI data. In accordance with the Helsinki Declaration, informed assent was obtained. After data cleaning, there are 177 individuals with DTI variables (228 continuous DTI variables) and they are all White.

3.2 Data Preparation

For Data Analysis, we prepared our dataset to eliminate disturbance during our exploration of the Alzheimer Disease data. It is a crucial component of EDA. We obtained data from the ADNI-2 and ADNI-3 initiatives and stored it in separate CSV files. Then, we merged the two CSV files together, and arranged the dataset sorted format and done category classification, and type modification.

We began by focusing only on DTI (Diffusion Tensor Imaging) factors in the dataset during the data processing stage of our research, removing extraneous columns and MRI variables to make the dataset more in line with the goals of the study. We experienced a little missing data problem of 18%, or 33 values, which we considered to be tolerable. In order to resolve this, we chose forward filling in order to keep the current data structure. We used Label Encoding to translate categorical variables into numerical representations and MinMax Scaling to provide uniform data scaling across all features while transforming the data. Fortunately, our dataset's class distribution was rather well distributed, eliminating the need for extra balancing methods. We used a heatmap to depict correlations in this subset of the data in order to investigate possible links between category variables. In order to simplify the dataset while keeping important data, we also used Principal Component Analysis (PCA) as a dimensionality reduction approach.

Finally, we utilized the model. feature importance technique to select the most important features, allowing us to highlight the key factors influencing the model's prediction performance. With the help of this extensive data processing pipeline, we were able to efficiently prepare the dataset for further analysis and modelling, which was in accordance with the main goals of our research.

3.3 Exploratory Data Analysis

After preparing our data, we began data-driven learning. To reach this objective, we utilized Exploratory Data Analysis (EDA). First, we obtained two hundred sixty-six features, none of which were entirely correlated to the AD prediction in the preclinical setting. Then, we eliminated the irrelevant and uninformative characteristics. It is determined from the dataset that there were five categories of patients evaluated. Table 1 shows the types of patients list of our dataset.

Table 1
Types of Patients

	Types	Number
EMCI	Early Mild Cognitive Impairment	52
AD	Alzheimer's Disease	36
CN	Cognitively Normal	33
LMCI	Late Mild Cognitive Impairment	31
SMC	Significant Memory Concern	25

After conducting an observation on our target feature, it was determined that approximately 35% of individuals exhibit preclinical Alzheimer's disease, while the remaining 65% exhibit non-preclinical Alzheimer's disease. It is worth noting that these proportions do not display a significant imbalance. Therefore, there was no requirement to carry out data balancing procedures. Figure 2 shows statistical chart to see the relation and aim in the dataset.

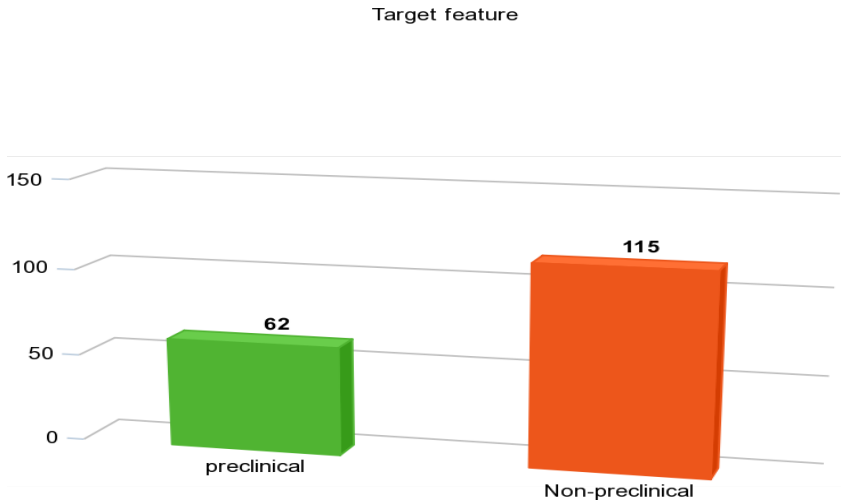


Fig. 2. Number of Preclinical Alzheimer's Disease Patients

Based on the findings presented in Figure 3, it can be observed that the variables exhibit a close approximation to a normal distribution. Since a normal distribution is present, there is no need to perform data scaling. There are also categorical variables present. The correlation between them provides valuable insights. Please refer to the following source for clear visibility: https://drive.google.com/file/d/1JryNJZd_4dRW3ml0ZcC2P1hfXZl--CNF/view?usp=sharing

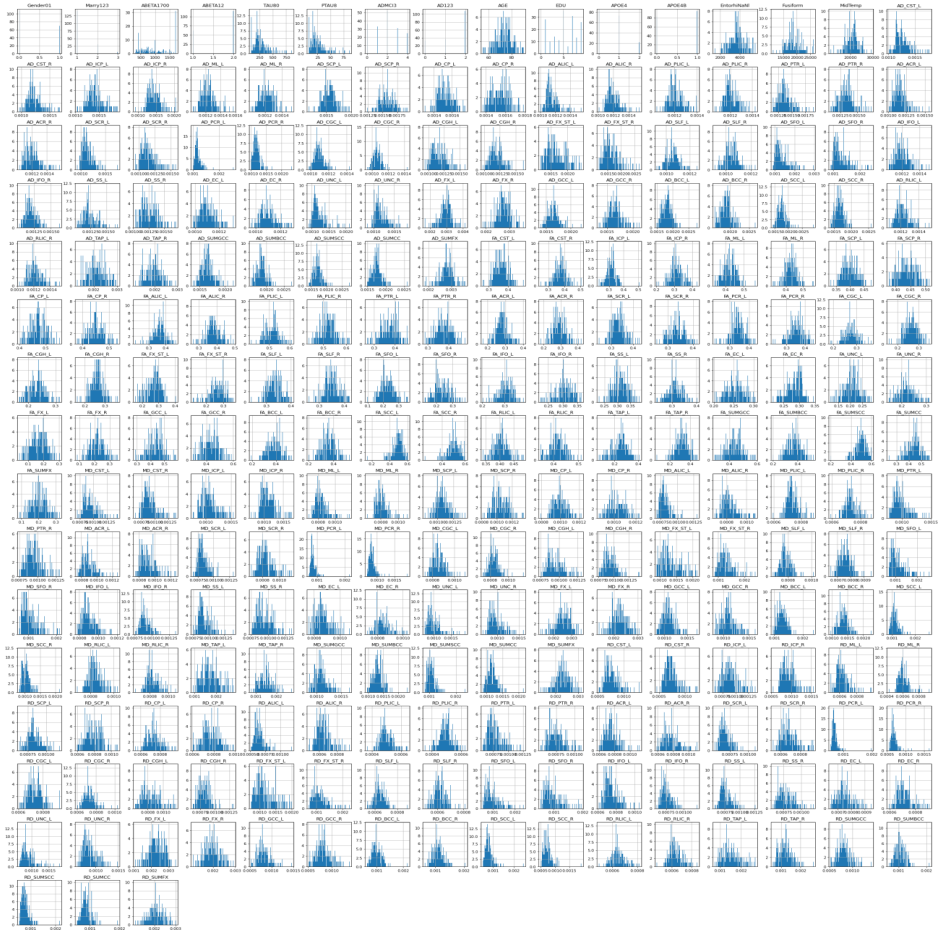


Fig. 3. Histogram of all Feature

The diagram in Figure 4 illustrates the categorical features present in the data. It is observed that there is a correlation between APOE4 and APOE4B, as well as between TAU80 and PTAU80. The APOE4 gene and Tau protein are known to have a substantial impact on Diffusion Tensor imaging.

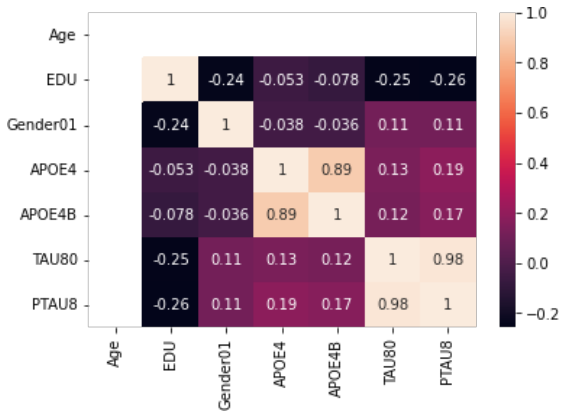
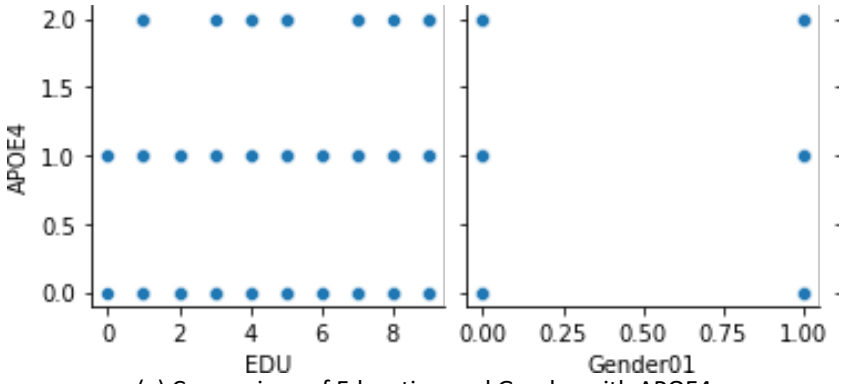
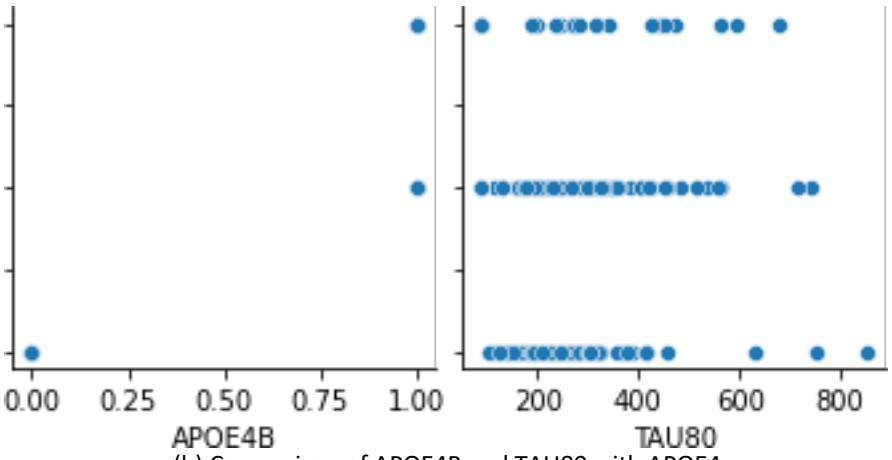


Fig. 4. Correlation of Categorical Variables

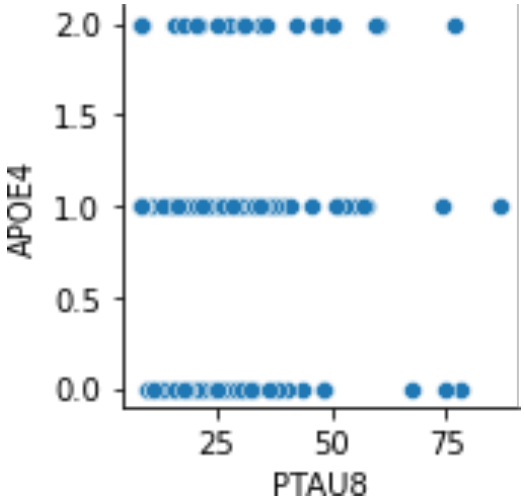
The distributions with categorical variables such as Education, gender, APOE4B gene, tau protein and Ptau protein. From the Figure 5, plots, it can be said that based on APOE4 gene, values of tau protein and Ptau protein are almost same scaled, equal number of males and females.



(a) Comparison of Education and Gender with APOE4



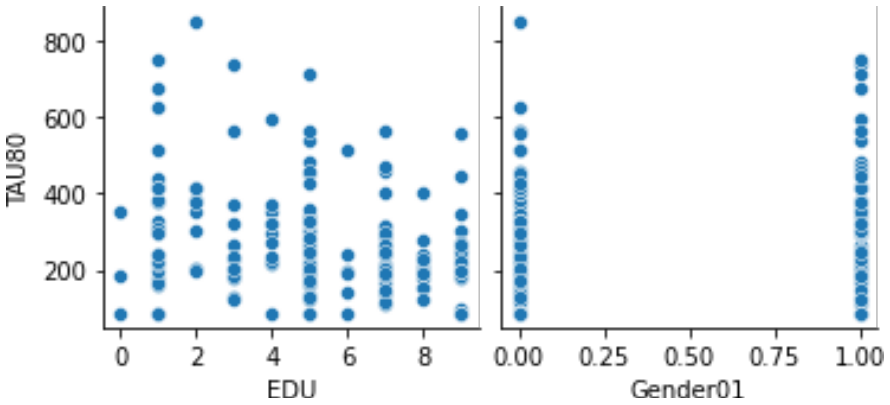
(b) Comparison of APOE4B and TAU80 with APOE4



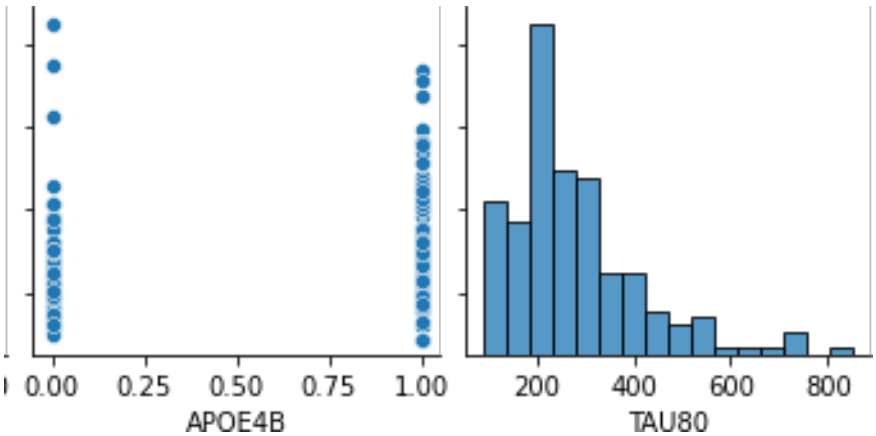
(c) Comparison of PTAU8 with APOE4

Fig. 5. Distributions of APOE4 with Other Categorical Features

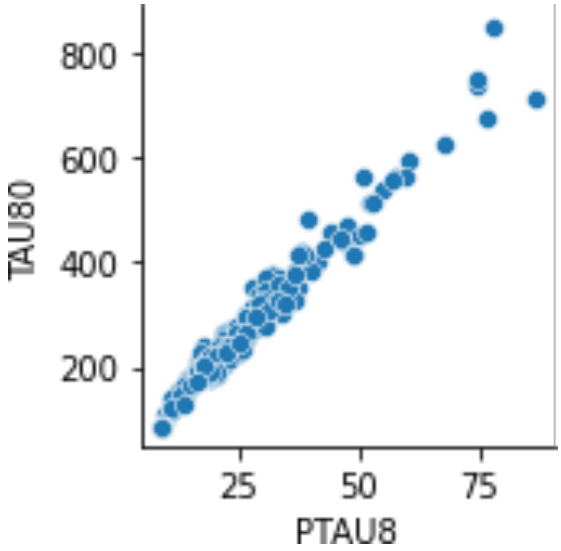
The distributions with categorical variables such as Education, gender, APOE4B gene, tau protein and Ptau protein. From the Figure 6 plots, it can be said that based on APOE4 gene, values of tau protein and Ptau protein are almost same scaled, equal number of males and females.



(a) Comparison of Education and Gender with TAU80



(b) Comparison of APOE4B and TAU80 with TAU80



(c) Comparison of PTAU8 with TAU80

Fig. 6. Distributions of TAU with Other Categorical Features

3.4 Resampling by Train-Test Split

We previously spoke about how we developed test-driven models for our experiments. When improving training for data science investigations, the major considerations are often computing the model's accuracy and lowering error. In our machine learning method, we have used one particular Re-Sampling approach for this purpose.

We partitioned the dataset into two sections and used the Train-Test-Split (TTS) resampling approach. The training dataset is the bigger portion (70–80%), while the test dataset is the smaller portion (20–30%). This is seen in the Figure 7 below:

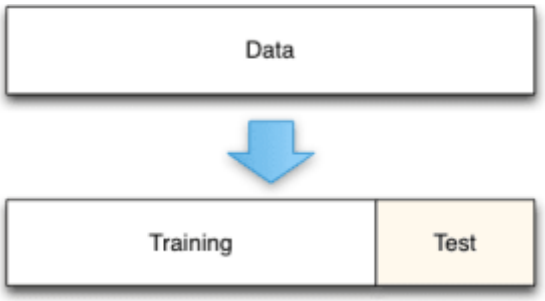


Fig. 7. Train Test Split Resampling

3.5 Evaluation

The last step we take before assessing and contrasting the models created in the preceding phases that employed the re sampling approaches outlined above. To do this, we have experimented with a number of assessment approaches that gauge the inaccuracies caused by prediction outcomes.

3.5.1 Accuracy

Accuracy is often described as the proportion or percentage of accurate predictions made on the test data. The calculation may be performed with ease by dividing the count of accurate forecasts by the total count of predictions made.

$$Accuracy = \frac{TP+TN}{TP+FP+TN+FN} \quad (1)$$

3.5.2 Precision

The accuracy and recall metrics are considered important markers for evaluating the performance of object identification algorithms. Precision is defined as the quantification of the proportion of correctly anticipated positive samples relative to the total number of positive samples. The mathematical expression representing accuracy is given by:

$$p = \frac{TP}{TP+FP} \quad (2)$$

3.5.3 Recall

Recall refers to the proportion of correctly predicted positive classes out of all the positive items included in the dataset. The mathematical expression representing the concept of recall is as follows:

$$R = \frac{TP}{TP+FN} \quad (3)$$

3.5.1 F1-score

The F1 score is used to assess the overall performance of a model by taking into account both precision and recall values. The formula for calculating the F1 score may be expressed as:

$$F1 = \frac{2P \times R}{P + R} \quad (4)$$

The number of classes that were successfully predicted to this particular class is shown by True Positive (TP). The symbol for accurate class count is True Negative (TN). False Positive (FP) is a statistic that represents the number of predicted classes that do not really fall within that category. The number of classes for which a false negative (FN) was found is shown.

4. Results

In our study, we have used six different ML algorithms to divide our dataset into two categories: Yes or No. The Decision Tree Algorithm achieved the highest accuracy of 98.15% out of these six machine learning techniques. A collection of figures that provide important details about the operation and results of our machine learning models serve as a visual representation of the conclusion of our study.

We show the Decision Tree model's Confusion Matrix in Figure 8 to demonstrate how well it can categorize data points. This matrix is an essential tool for assessing the model's precision, recall, and

overall prediction accuracy. The Confusion Matrix for our Gradient Boosting Machine (GBM) model is shown in Figure 9, providing a comparable assessment of its classification efficiency.

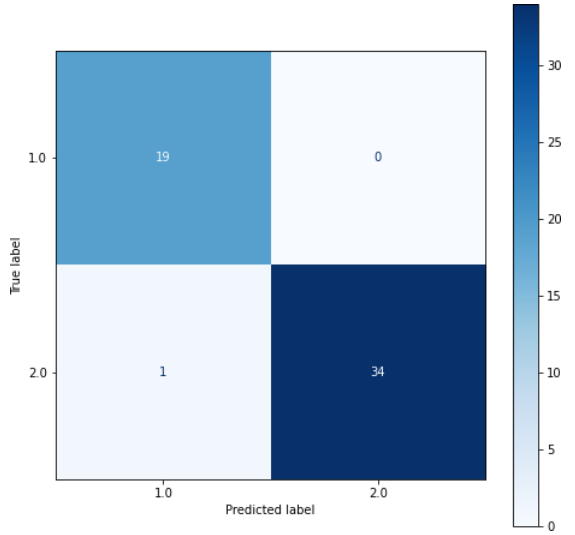


Fig. 8. Decision Tree's Confusion Matrix

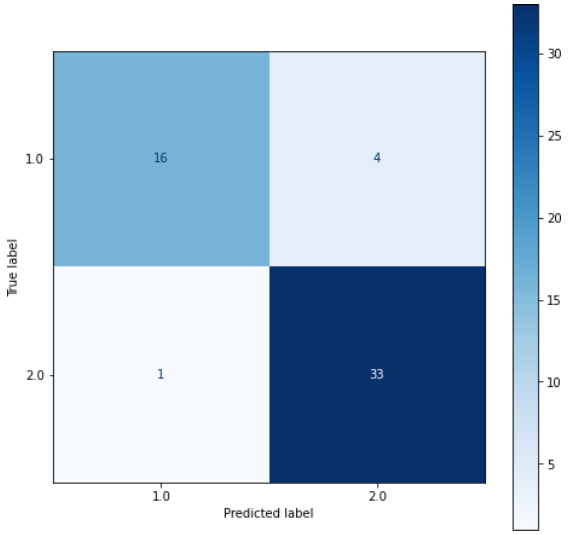


Fig. 9. GBM's Confusion Matrix

We can compare the classification outcomes of the K-Nearest Neighbors (KNN) and the logistic regression models using the confusion matrices shown in Figure 10 and Figure 11, respectively.

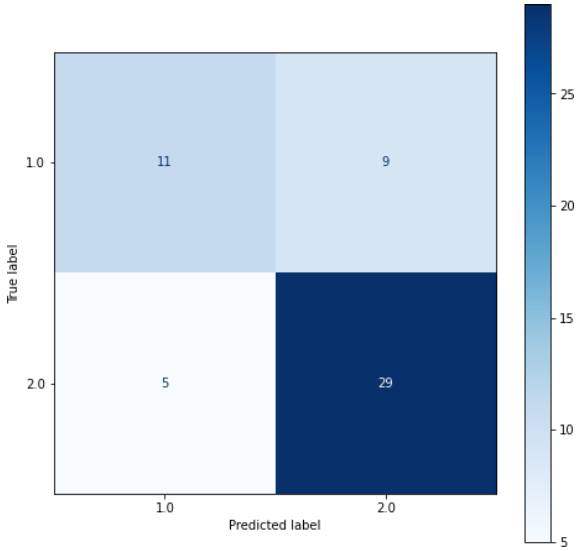


Fig. 10. KNN's Confusion Matrix

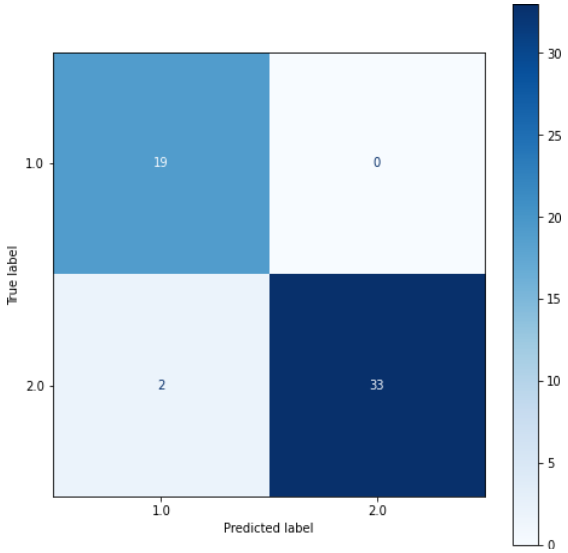


Fig. 11. Logistic Regression's Confusion Matrix

The Random Forest model's Confusion Matrix is shown in Figure 12, showcasing its classification performance and demonstrating its capacity to manage intricate data relationships. The Support Vector Classifier (SVC) model's performance is shown in Figure 13, which enables us to evaluate how accurate it is in classifying data points.

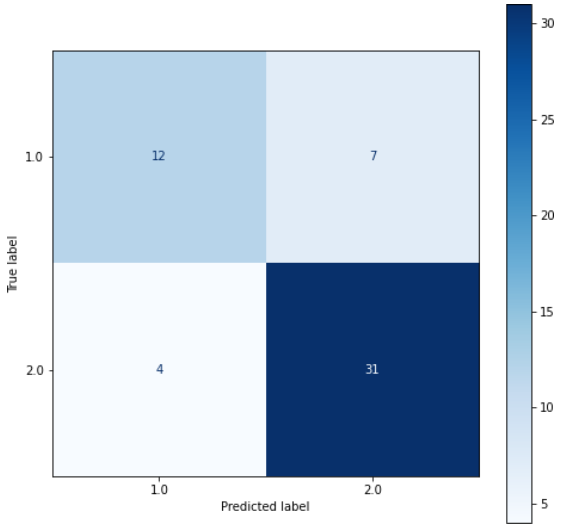


Fig. 12. Random Forest's Confusion Matrix

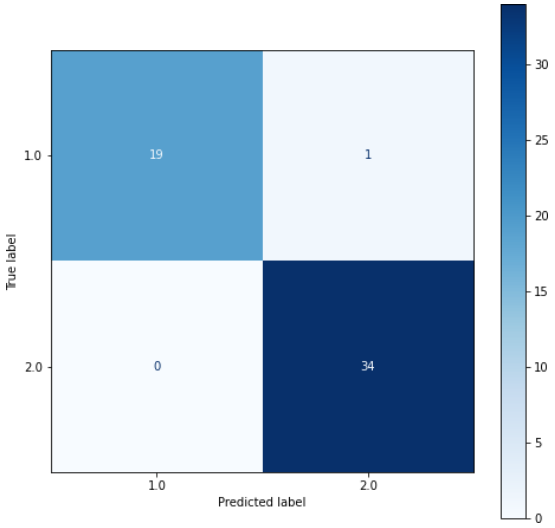


Fig. 13. SVC's Confusion Matrix

The AUC-Receiver Operator Characteristic Curve, a graphic depiction of the models' receiver operating characteristics and their capacity to distinguish between positive and negative classes, is shown in Figure 14.

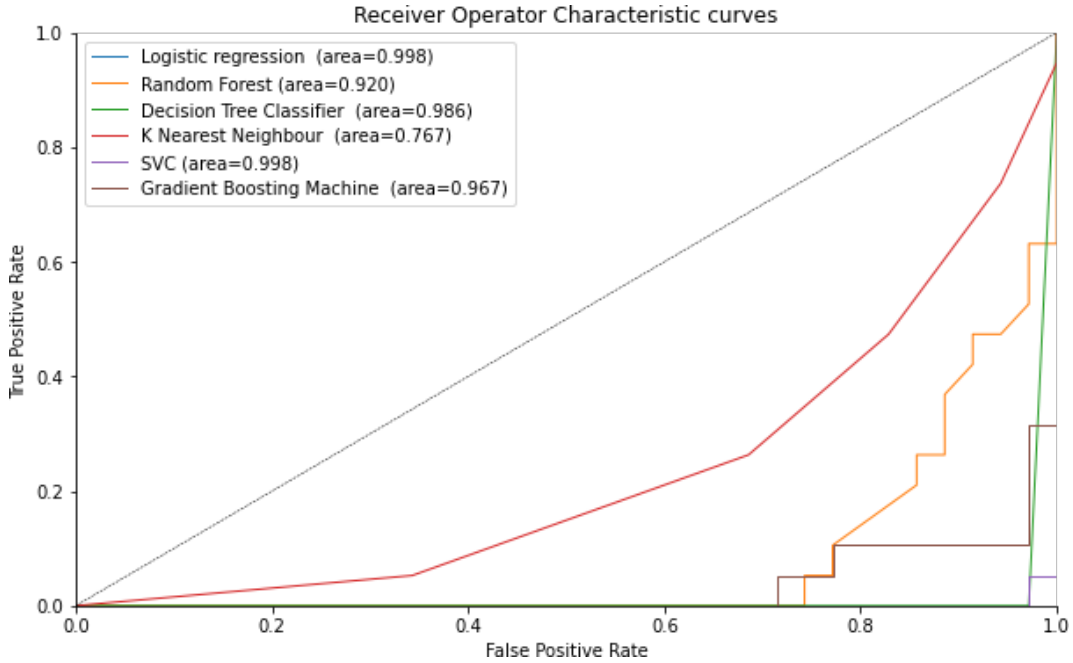


Fig. 14. AUC-Receiver Operator Characteristic Curve

The Precision-Recall curve, shown in Figure 15, illustrates the trade-off between precision and recall for different classification thresholds, which is essential for comprehending the model's performance in scenarios with unbalanced class distributions.

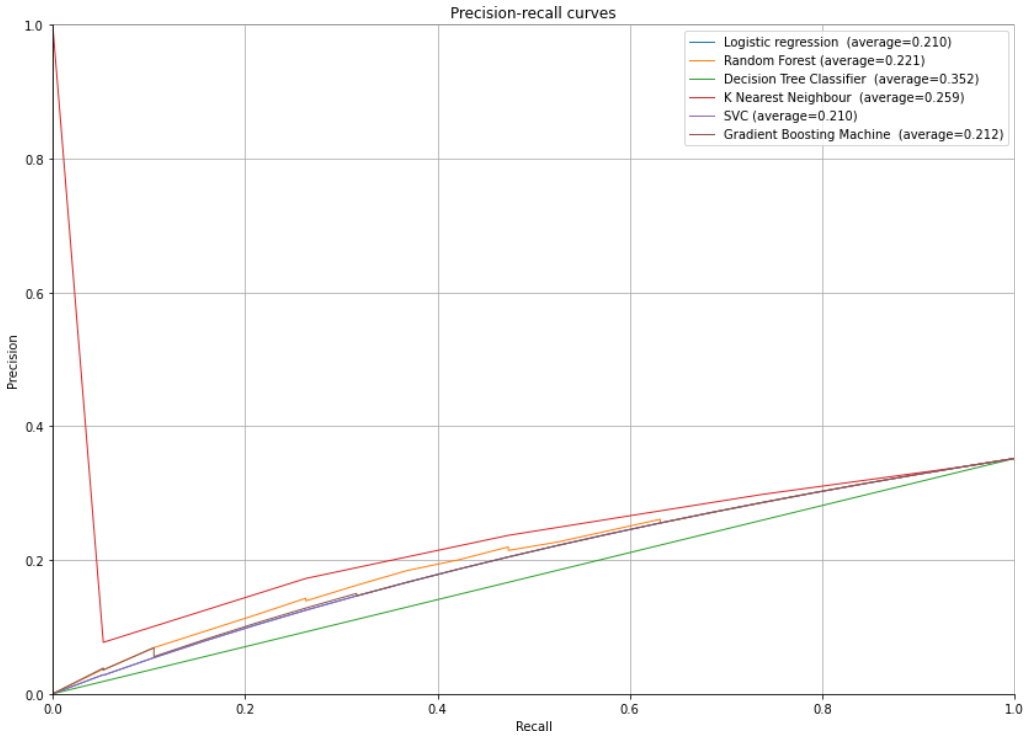


Fig. 15. Curve of Precision-Recall

Lastly, Figure 16 highlights the key characteristics that our models found, illuminating the key factors that significantly affect their predictions.

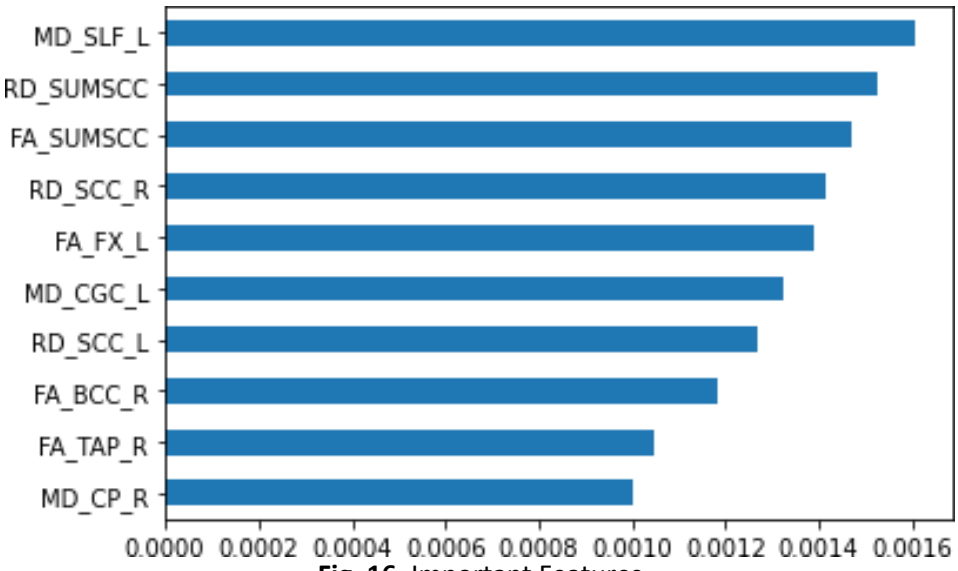


Fig. 16. Important Features

In addition to providing a visual narrative of the models' classification performance, their capacity to handle complicated data, and the primary characteristics influencing their forecast accuracy, these figures combined give a thorough summary of our study findings.

In terms of machine learning algorithms, we compared all the experiment results and visualization work we had done up to that point. Table 2 demonstrates that Decision Tree provides the most accurate predictions. KNN has both the lowest accuracy and recall values. Despite being inferior than the Decision Tree, the Logistic Regression model has greatly better performance.

Precision, Recall, and F1-score have all improved for the Decision Tree model. Table 2 demonstrates that Decision Tree outperforms the other methods and has the best parameter values.

Table 2
Comparison of performance of different methods used in this experiment

Models	Accuracy	Precision	Recall	F1-score
Decision Tree	98.15%	95%	100%	97.43%
Logistic Regression	96.27%	90.47%	100%	95%
KNN	72.22%	62.5%	52.63%	57.14%
Random Forest	79.63%	83.33%	52.63%	54.51%
SVC	96.23%	94.73%	94.73%	94.73%
GBM	90.74%	93.75%	78.95%	85.71%

4. Conclusions

This approach shows great potential in facilitating the early detection of (AD), thereby aiding in the phase of development and evaluation of drugs for (AD). During the course of our literature review, we have identified performance-related concerns as well as a range of studies that are pertinent to the (AD) diagnosis. We have conducted extensive experimentation by employing various methodologies and exploring different combinations of feature sets. Additionally, we have utilized resampling techniques, such as Train-Test-Split, in conjunction with diverse algorithms. Our objective in these endeavours is to optimize the accuracy of visual progression prediction. After conducting multiple experiments, we have determined that the Decision Tree algorithm is the most optimal prediction model for our dataset with highest accuracy of 98.15% out of these six machine learning techniques.

In this study, our objective was to determine the predictive factors of AD using preclinical data. It is evident that the provided information does not encompass the entirety of the outcome. Our dataset contains additional valuable metrics, such as factors based on MRI. In order to further enhance the research, it is advisable to conduct experiments using various ML, and DL algorithms. This will enable the measurement of additional performance indicators.

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