RAD Conference Proceedings, vol. 8, pp. 01-06, 2024
ISSN 2466-4626 (online) | DOI: 10.21175/RadProc.2024.01
www.rad-proceedings.org

USING MACHINE LEARNING FOR EARLY ALZHEIMER'S DETECTION IN COGNITIVE NEUROSCIENCE

Orrù Graziella*, Piarulli Andrea, Ciro Conversano, Angelo Gemignani

Department of Surgical, Medical and Molecular Pathology and of Critical Care Medicine, University of Pisa, 56126 Pisa, Italy

Abstract. *Alzheimer's disease (AD) is a leading cause of dementia, with early detection crucial for effective intervention. Machine learning (ML) has emerged as a promising tool for identifying AD-related biomarkers in neuroimaging and cognitive assessments. We reviewed literature from peer-reviewed journals and conference proceedings using PubMed, focusing on studies employing ML for early AD detection through neuroimaging and cognitive data. ML techniques show significant promise in early AD detection. Key studies demonstrate high accuracy in distinguishing between AD, mild cognitive impairment (MCI), and healthy controls. Notable, methods include MRI-based biomarkers, computer-aided diagnosis systems, and various ML algorithms. ML techniques can enhance early AD detection, leading to improved patient outcomes. Despite the promising results, this study did not conduct a systematic review, and further research is needed to address data availability and refine feature selection for better accuracy and generalizability.*

Keywords*:* *Alzheimer's disease, Alzheimer's detection, Cognitive neuroscience, Early Detection of Alzheimer's Disease, Machine learning*

1. Introduction

Alzheimer's disease (AD) is a degenerative neurological illness that progressively deteriorates over time. AD is the most common cause of dementia, affecting a significant number of individuals globally. It is estimated that by the year 2050, almost 1 in 85 people worldwide will be affected by this condition [1]. AD is classified as a subtype of dementia, a comprehensive term that encompasses a decline in cognitive abilities [2,3], such as memory, thinking, reasoning, and behavioral changes to the extent that it significantly disrupts everyday activities. It also involves the progressive decline and eventual death of nerve cells, resulting in the loss of brain tissue [4]. In this context, early detection of AD is crucial for timely intervention and treatment, enabling more effective symptoms management and potentially slowing the disease's progression [5]. However, early diagnosis of AD remains challenging due to the subtle and gradual nature of cognitive changes in the early stages.

In recent years, machine learning (ML) techniques have emerged as a promising avenue to evaluate brain imaging data and detect characteristics linked to different neurological or psychiatric conditions [i.e., 6-8] and it has been successfully applied in various fields, including forensic sciences [i.e., 9], mental health application [i.e., 10] and liver transplantation [i.e., 11], amongst others. ML is a broad area of artificial intelligence that focusses on creating algorithms that let computers use data to learn from and anticipate future events. Deep Learning (DL) is one of the many approaches and techniques used in this field.

DL is a specialized subset of ML that uses many-layered neural networks to model complex patterns in large datasets.

It is noteworthy that ML techniques have emerged as a viable approach to aid in the early detection and prognosis of AD [i.e., 12], as well. ML algorithms can analyze complex patterns and relationships (not immediately obvious) in neuroimaging data, cognitive assessments, and other biomarkers to identify individuals at risk of developing AD. Therefore, these techniques hold the potential to enhance the accuracy and efficiency of AD diagnosis, facilitating earlier intervention and leading to improved patient outcomes. In this regard, the objective of this study was to provide a brief overview of i) ML models; ii) key algorithms; iii) the performance metrics in ML and iv) the current state of research on the application of ML in cognitive neuroscience for the early detection of AD before concluding with the limitations and future directions. It is important to highlight that no systematic review was performed for this study given that the last review related to this topic was published this year [13].

2. Overview of Machine Learning Models and Key Algorithms

ML encompasses a wide range of models and algorithms designed for specific tasks and different types of data. Comprehending these methodologies enables researchers to make the right choices for

* E-mail of the corresponding author – graziella.orru@unipi.it

different applications, improving prediction performance in a variety of fields. Typically, ML models are typically distinguished in supervised and unsupervised models [14]. Supervised Learning entails training a model on a labelled dataset, wherein the algorithm learns to associate inputs with outputs based on given examples. Common applications are classification and regression tasks. Conversely, Unsupervised Learning deals with unlabeled data, wherein the model attempts to detect patterns or clusters within the data without prior knowledge of the outcomes. Clustering and dimensionality reduction techniques are characteristic.

Regarding Supervised Learning algorithms, it is crucial to mention (see: *Machine Learning in Psychometrics and Psychological Research*) [14]:

-Support Vector Machine (SVM): a classification technique that finds the optimal hyperplane to separate classes in a high-dimensional space.

-Random Forest (RF): an ensemble method that constructs multiple decision trees and merges their predictions for improved accuracy.

-Regularized Logistic Regression (RLR): an extension of logistic regression that includes regularization to prevent overfitting.

-XGBoost: an efficient gradient boosting algorithm that is widely used for supervised learning tasks.

-Gradient Boosting Algorithms: sequentially builds models that correct errors from previous models, applicable in both regression and classification.

-Decision Trees: a model that splits data into branches based on feature values, used for both classification and regression tasks.

-K-Nearest Neighbors (KNN): a non-parametric method that classifies based on the 'k' closest training examples.

3D-Convolutional Neural Networks (CNNs): these networks extend traditional convolutional neural networks by applying 3D convolutions, making them suitable for processing volumetric data.

-Voting Classifier: combines predictions from multiple models to improve overall classification accuracy.

In regard to Unsupervised Learning algorithms, for categorizing row data, it is important to cite:

-Clustering Algorithms (e.g., K-means): group similar data points together without labeled outcomes.

-Principal Component Analysis (PCA): a dimensionality reduction technique that transforms data into a lower-dimensional space while preserving variance. The core concept of PCA is to determine the directions (or main components) along which the data exhibits the greatest variance.

-Independent Components Analysis (ICA): can be used as a dimensionality reduction technique. Independent component analysis is a probabilistic technique for deriving a linear transformation of a stochastic vector. The objective is to identify components that are optimally independent and non-Gaussian.

-Hierarchical Clustering: builds a tree of clusters to represent data relationships without predefined labels. Hierarchical clustering strategies are primarily categorized into two types: agglomerative and divisive.

3. Performance metrics in machine learning

Before presenting the results of the studies considered, gaining a fundamental understanding of the most important metrics for assessing model performance in ML is crucial. These measurements include the area under the receiver operating characteristic curve (AUC), recall, accuracy, precision, and F1 score. Every metric offers important information about how well our prediction models work:

a) *Accuracy* measures the proportion of true results (both true positives and true negatives) among the total number of cases examined and it is calculated as:

$$\text{Accuracy}=\frac{TP+TN}{TP+TN+FP+FN}$$

where:

TP is the number of correctly predicted positive observations (True Positives).

TN is the number of correctly predicted negative observations (True Negatives).

FP is the number of incorrectly predicted positive observations (False Positives).

FN is the number of incorrectly predicted negative observations (False Negatives).

b) *Recall* also referred to as true positive rate or sensitivity; it measures how well the model can detect real positive cases:

$$Recall=\frac{TP}{TP+FN}$$

where:

TP is the number of correctly predicted positive observations (True Positives).

FN is the number of incorrectly predicted negative observations (False Negatives).

c) *Precision* assesses the accuracy of positive predictions, indicating how many of the predicted positive cases were actually positive:

$$Precision=\frac{TP}{TP+FP}$$

where:

TP is the number of correctly predicted positive observations (True Positives).

FP is the number of incorrectly predicted positive observations (False Positives).

d) *F1* score is the harmonic mean of precision and recall, offering a balance between these two metrics, particularly advantageous when addressing imbalanced datasets:

$$F1 = 2x\frac{Precision\ x\ Recall}{Precision + Recall}$$

e) *AUC* quantifies the overall performance of a binary classification model across all classification thresholds:

$$AUC = \int_0^1 TPR(FPR)dFPR$$

where:

TPR is the true positive rate and FPR is the false positive rate.

4. Methods

In order to reach our goal, we conducted a literature search of studies published in peer-reviewed journals and/or conference proceedings. The search was performed using PubMed database and additional records identified through other sources. We included some of the studies that applied ML techniques to neuroimaging data, cognitive assessments, or multimodal data to detect AD at an early stage.

5. Results

Extensive research has been undertaken on the application of ML algorithms for early detection of AD.

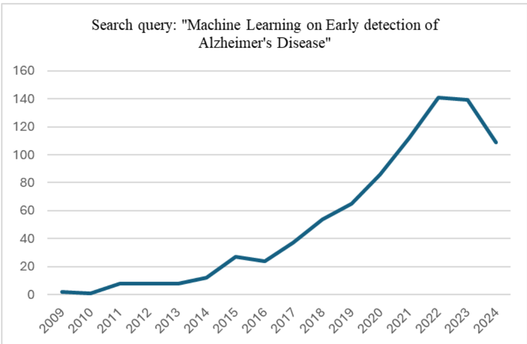

Figure 1. Research interest associated to the application ML techniques in the early detection of AD, based on Pubmed database (date: 1st August 2024)

Figure 1 depicts the growing interest in this topic over the last 15 years. The search query for "*Machine Learning on Early detection of Alzheimer's Disease*" yielded 777 results after applying filters based on publication dates (2009 to2024). Researchers have introduced novel methods for predicting the progression from mild cognitive impairment (MCI) to AD by using different ML techniques.

Table 1. Methodologies, variables considered, and key findings of each study analyzed

Notes: AD, Alzheimer's Disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; AUC, Area Under the Curve; CNNs, convolutional neural networks; LDS, Low Density Separation; MCI, Mild Cognitive Impairment; MCIc, MCI patients who will convert to AD; MCInc, MCI patients who will not convert to AD; MRI, magnetic resonance imaging; PCA, Principal Component Analysis; PLS, Partial Least Squares; RF, Random Forest; RLR, Regularized

Study	Machine Learning Techniques	Variables Used	Key Findings
Moradi et al.[13]	Semi-supervised learning based on LDS, SVM, RF, RLR	MRI data, age, cognitive assessments	Developed an aggregate biomarker with AUC of 0.9020 for distinguishing progressive MCI (pMCI) from stable MCI (sMCI); MRI biomarker alone achieved AUC of 0.7661
Khedher et al.[14]	Multivariate techniques (PLS, PCA) and SVM	Segmented MRI images	Achieved sensitivity = 85.11%, specificity = 91.27%, accuracy = 88.49% in differentiating AD and MCI
Uddin et al.[15]	Gaussian Naive Bayes, Decision Tree, RF, XGBoost, Voting Classifier, Gradient Boosting	OASIS dataset	Voting Classifier achieved 96% validation accuracy for predicting AD occurrence
Kavitha et al.[16]	Decision Tree, RF, SVM, Gradient Boosting, Voting Classifier	OASIS dataset	Validation average accuracy of 83%; RF and XGBoost were most effective
Salvatore et al.[17]	SVM	Structural brain MRI data	Discriminated between AD, MCIc, MCInc, and healthy controls with varying accuracies (AD vs healthy: 76%)
Nanni et al.[12]	Ensemble transfer-learning methods	Structural brain MRI data	AUC scores: AD vs healthy = 90.2%, MCIc vs healthy = 83.2%
Venugopalan et al.[18]	Deep learning models (3D-CNNs, stacked denoising auto-encoders)	ADNI dataset, MRI data, clinical and genetic data (SNPs)	Deep models outperformed shallow models (i.e., SVM, RF); multi-modality data integration yielded superior results

Logistic Regression; SNPs, single nucleotide polymorphisms; SVM, Support Vector Machine.

The findings presented above (Table 1) are not the result of a systematic review, as it briefly focuses on summarizing and discussing specific research findings rather than conducting a comprehensive analysis of all available literature on the topic.

Based on the analyzed studies, for example, Moradi et al., [15] introduced an innovative magnetic resonance imaging (MRI)-derived technique for forecasting the progression MCI to AD up to three years prior diagnosis. For this purpose, the authors have created a "novel MRI biomarker" using a combination of semi-supervised learning based on low density separation (LDS) and supervised learning algorithms such as SVM, RF and RLR. This biomarker when combined with age and cognitive assessments, resulted in a comprehensive biomarker, referred to as the aggregate biomarker. The aggregate biomarker demonstrated a 10-fold cross-validated AUC (area under the receiver operating characteristic curve) of 0.9020 in accurately distinguishing between progressive and stable MCI patients. In another study, Khedher et al., [16] have developed and introduced a computer-aided diagnosis (CAD) system for early AD detection based on ML techniques (SVM) applied to tissue-segmented MRI brain images. The proposed methodology seeks to differentiate between individuals with AD, MCI, and controls using multivariate techniques, including partial least squares (PLS) and principal component analysis (PCA). The system was able to achieve promising results in distinguishing AD and MCI patients from healthy controls, yielding the following accuracy values: sensitivity = 85.11%, specificity = 91.27% and accuracy 88.49%.

Interestingly, the study conducted by Uddin et al., [17] applied a ML model which included Gaussian Naive Bayes, Decision Tree, R, XGBoost, Voting Classifier, and Gradient Boost algorithms to accurately predict the occurrence of AD. The model was trained using the open access OASIS (Open Access Series of Imaging Studies) dataset with the purpose of assessing its performance based on different ML metrics such as accuracy, precision, recall, and F1 score (a metric that combines precision and recall measuring accuracy). Upon analysis, the results revealed that the Voting Classifier achieved the highest level of validation accuracy, reaching 96%, when applied to the AD dataset. In a prior study conducted by Kavitha et al., [18], the identical techniques indicated were used to the OASIS dataset, resulting in a notable validation average accuracy of 83% on the test data. The results confirmed that the most effective and optimal strategies, with excellent performance, were R and XGBoost. The accuracy of the Voting classifier model was comparable to that of the R and XGBoost models. The research emphasizes the potential of ML algorithms to assist clinicians in early diagnose AD, which can significantly impact lowering mortality rates associated with the disease.

Salvatore et al., [19] presented promising results. The authors demonstrated that ML algorithms applied to structural brain MRI data have yielded encouraging results in discriminating among AD patients, MCI patients who will convert to AD (MCIc) within 18 months, MCI patients who will not convert to AD (MCInc) within 18 months, and healthy controls. The SVM algorithm was employed in order to discriminate between the mentioned groups with the following accuracies: i) AD vs healthy controls: 76%; ii) MCIc vs healthy controls: 72%; iii) MCIc vs MCInc: 66%. Moreover, the most informative brain regions for classification, that aligns with several research, included pathologic changes in the following areas: temporal and parietal cortex, hippocampus, entorhinal cortex, entorhinal cortex, amygdala, thalamus, insula, anterior cingulate, precuneus and the cerebellum (which is not typically associated with AD-like atrophy).

The study conducted by Nanni et al. [12] attempted to assess the effectiveness of ensemble transfer-learning methods in predicting early diagnosis and prognosis of AD in comparison to a combination of conventional ML approaches based on SVM applied to structural brain MRI data. The results demonstrated that the ensemble transfer-learning approach effectively discriminated between AD and healthy controls, MCIc and healthy controls, and MCIc and MCInc, with AUC scores of 90.2%, 83.2%, and 70.6%, respectively. These scores were comparable or slightly worse than using a combination of conventional ML techniques (93.1% AUC; 89.6 AUC; 69.1% - 73.3%, respectively).

Venugopalan et al., [20] used DL models in conjunction with numerous datasets. The study employed MRI, single nucleotide polymorphisms, and clinical test data to classify individuals into three categories: AD, MCI, and healthy controls. In order to extract features from clinical and genetic data, the authors employed stacked denoising auto-encoders, while 3D-convolutional neural networks (CNNs) were utilized for processing imaging data. The study revealed that deep models had superior performance compared to shallow models (i.e., SVM, decision trees, RF, and k-nearest neighbors). Furthermore, the integration of multi-modality data yielded superior results compared to single modality models. The models found the hippocampus, amygdala brain areas, and the Rey Auditory Verbal Learning Test (RAVLT) as the most prominent aspects, consistent with existing research.

6. Conclusions

Early detection of AD is crucial for timely intervention and treatment, as it enables improved symptom management and potentially slows down the disease's progression. Based on the literature presented, ML algorithms and DL models have shown promising results in analyzing complex patterns in neuroimaging data, cognitive assessments, and other biomarkers to identify individuals at risk of developing AD. The research highlights the potential of ML algorithms to assist clinicians in early AD diagnosis, potentially leading to a significant reduction in associated mortality rates.

To summarize, ML models have proven effective in discriminating between AD patients, MCI patients, and healthy controls, showcasing the potential for enhanced patient outcomes through early detection. However, despite the substantial evidence found, the present study is subjected to several limitations. Notably, a systematic review or a meta-analysis was not conducted, thus preventing firm conclusions.

7. Limitations and future directions

Despite the promising results of ML techniques in the early detection of AD, there are still several limitations to be addressed. Firstly, the substantial constraint is that we did not conduct a systematic review, which limits firm conclusions. Secondly, the availability of datasets poses a significant challenge, therefore more extensive and diverse datasets are needed to improve the accuracy and generalizability of the ML models. To overcome this issue, *data augmentation*, for example, has become a popular strategy for increasing the size of a training dataset [21]. Data augmentation tries to generate new data that is used to train the model. It has been demonstrated to boost performance when validated on a different unseen dataset. Thirdly, the use of cognitive attributes for early detection is still in its infancy, thus warranting further investigation to validate the use of specific cognitive features. In this context, feature selection and feature extraction are important techniques in ML that identify the most relevant features from a dataset in order to improve model accuracy and interpretability. Alternative feature selection techniques to improve accuracy are represented by *dimensionality reduction* and *ensemble learning approaches*. *Dimensionality reduction* aim to reduce the number of input variables in a dataset while preserving critical information. This can lead to better model performance by removing noise and unnecessary features [22]; *ensemble learning methods* combined different classifiers to enhance overall performance and robustness (outperform single classifiers) [21]. They also provide insights into feature significance, facilitating feature selection.

Lastly, a significant challenge lies in determining which features are redundant or unnecessary, as this requires a deep understanding of the data and the characteristics of the condition. The trajectory of early AD detection using ML techniques will involve the removal of redundant and unneeded characteristics from existing feature sets, as well as the extraction and analysis of unique and distinctive aspects more conducive to detection. This strategy aims to enhance the precision of detection by optimizing the selection of features and integrating pertinent metrics.

As shown by a recent review (see Bazarbekov et al., 2024) [13], the application of ML in the early identification of AD holds substantial clinical implications that could revolutionize the traditional diagnostic methodologies. By using sophisticated algorithms to examine complex data sources including neuroimaging and neurophysiological data, biomarkers and sensor data, ML can improve the precision and the timing of AD diagnosis, allowing earlier interventions. Early identification is essential as it facilitates timely therapeutic measures possibly enhancing patient outcomes. Moreover, ML derived insights can enable personalized treatment strategies designed for specific patient profiles, thus enhancing resource distribution across healthcare systems. The implementation of ML technologies in clinical environments not only enhances diagnosis accuracy but also has the capacity to transform the standard of treatment for patients at risk to AD.

References

1. R. Brookmeyer, C. H. Kawas, N. Abdallah, A. Paganini-Hill, R. C. Kim, M. M. Corrada, "Impact of interventions to reduce Alzheimer's disease pathology on the prevalence of dementia in the oldest-old", *Alzheimer's & Dement.*, vol. 12, no. 3, pp. 225-232, 2016. https://doi.org/10.1016/j.jalz.2016.01.004
2. G. Orrù, S. Sampietro, S. Catanzaro, A. Girardi, M. Najjar, V. Giantin, G Sergi, E. Manzato, G. Enzi, E.M. Inelmen, A Coin, "Serial position effect in a free recall task: differences between probable dementia of Alzheimer type (PDAT), vascular (VaD) and mixed etiology dementia (MED)", *Archives of Gerontology and Geriatrics*, vol. 49, pp. 207-210, 2009. https://doi.org/10.1016/j.archger.2009.09.030
3. A. Coin, M. Najjar, S. Catanzaro, G. Orru, S. Sampietro, G. Sergi, E. Manzato, E. Perissinotto, G. Rinaldi, S. Sarti, A. Imoscopi, E. Ruggiero, A. Girardi, "A retrospective pilot study on the development of cognitive, behavioral and functional disorders in a sample of patients with early dementia of Alzheimer type", *Archives of Gerontology and Geriatrics*, vol. 49, pp. 35-38, 2009. https://doi.org/10.1016/j.archger.2009.09.010
4. G. McKhann, D. Drachman, M. Folstein, R. Katzman, D. Price, E.M. Stadlan, "Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease", *Neurology*, vol. 34, no. 7, p. 939, 1984. https://doi.org/10.1212/wnl.34.7.939
5. B. Dubois, A. Padovani, P. Scheltens, A. Rossi, G. Dell'Agnello, "Timely diagnosis for Alzheimer's disease: a literature review on benefits and challenges", *J. Alzheimers Dis.*, vol. 49, no. 3, pp. 617-631, 2016. https://doi.org/10.3233/JAD-150692
6. S. Vieira, W. H. Pinaya, A. Mechelli, "Using deep learning to investigate the neuroimaging correlates of psychiatric and neurological disorders: Methods and applications", *Neurosci. Biobehav. Rev.*, vol. 74, pp. 58-75, 2017. https://doi.org/10.1016/j.neubiorev.2017.01.002
7. D. B. Dwyer, P. Falkai, N. Koutsouleris, "Machine learning approaches for clinical psychology and psychiatry", *Annu. Rev. Clin. Psychol.*, vol. 14, pp. 91-118, 2018. https://doi.org/10.1146/annurev-clinpsy-032816-045037
8. R. Ferrucci, F. Mameli, F. Ruggiero, M. Reitano, M. Miccoli, A. Gemignani, C. Conversano, M. Dini, S.

Zago, S. Piacentini, B. Poletti, A. Priori, G. Orrù, "Alternate fluency in Parkinson's disease: A machine learning analysis", *PLOS ONE*, vol. 17, no. 3, pp. e0265803-1-12, 2022. https://doi.org/10.1371/journal.pone.0265803

9. G. Pace, G. Orrù, M. Monaro, F. Gnoato, R. Vitaliani, K. B. Boone, A. Gemignani, G. Sartori, "Malingering detection of cognitive impairment with the B test is boosted using machine learning", *Front. Psychol.*, vol. 10, pp. 1650-1-8, 2019. https://doi.org/10.3389/fpsyg.2019.01650
10. A.B. Shatte, D.M. Hutchinson, S.J. Teague, "Machine learning in mental health: a scoping review of methods and applications", *Psychol. Med.*, vol. 49, no. 9, pp. 1426-1448, 2019. https://doi.org/10.1017/S0033291719000151
11. A. Ferrarese, G. Sartori, G. Orrù, A. C. Frigo, F. Pelizzaro, P. Burra, M. Senzolo, "Machine learning in liver transplantation: a tool for some unsolved questions?", *Transplant Int.*, vol. 34, no. 3, pp. 398-411, 2021. https://doi.org/10.1111/tri.13818
12. L. Nanni , M. Interlenghi, S. Brahnam, C. Salvatore, S. Papa, R. Nemni, I. Castiglioni and Alzheimer's Disease Neuroimaging Initiative, "Comparison of transfer learning and conventional machine learning applied to structural brain MRI for the early diagnosis and prognosis of Alzheimer's disease," *Front. Neurol.*, vol. 11, p. 576194, 2020. https://doi.org/10.3389/fneur.2020.576194
13. I. Bazarbekov, A. Razaque, M. Ipalakova, J. Yoo, Z. Assipova, A. Almisreb, "A review of artificial intelligence methods for Alzheimer's disease diagnosis: Insights from neuroimaging to sensor data analysis", *Biomed. Signal Process. Control*, vol. 92, pp. 106023, 2024. https://doi.org/10.1016/j.bspc.2024.106023
14. G. Orrù, M. Monaro, C. Conversano, A. Gemignani, G. Sartori, "Machine learning in psychometrics and psychological research", *Front. Psychol.*, vol. 10, pp. 2970-1-10, 2020. https://doi.org/10.3389/fpsyg.2019.02970
15. E. Moradi, A. Pepe, C. Gaser, H. Huttunen, J. Tohka, and Alzheimer's Disease Neuroimaging Initiative, "Machine learning framework for early MRI-based Alzheimer's conversion prediction in MCI subjects", *NeuroImage*, vol. 104, pp. 398-412, 2015. https://doi.org/10.1016/j.neuroimage.2014.10.002
16. L. Khedher, J. Ramírez, J. M. Górriz, A. Brahim, F. Segovia, and Alzheimer's Disease Neuroimaging Initiative, "Early diagnosis of Alzheimer's disease based on partial least squares, principal component analysis and support vector machine using segmented MRI images", *Neurocomputing*, vol. 151, pp. 139-150, 2015. https://doi.org/10.1016/j.neucom.2014.09.072
17. K.M.M. Uddin, M.J. Alam, M.A. Uddin, S. Aryal, "A novel approach utilizing machine learning for the early diagnosis of Alzheimer's disease", *Biomed. Mater. Devices*, vol. 1, no. 2, pp. 882-898, 2023. https://doi.org/10.1007/s44174-023-00078-9
18. C. Kavitha, V. Mani, S. R. Srividhya, O. I. Khalaf, C. A. Tavera Romero, "Early-stage Alzheimer's disease prediction using machine learning models", *Front. Public Health*, vol. 10, p. 853294, 2022. https://doi.org/10.3389/fpubh.2022.853294
19. C. Salvatore, A. Cerasa, P. Battista, M. C. Gilardi, A. Quattrone, I. Castiglioni, and Alzheimer's Disease Neuroimaging Initiative, "Magnetic resonance imaging biomarkers for the early diagnosis of Alzheimer's disease: a machine learning approach", *Front. Neurosci.*, vol. 9, p. 307, 2015. https://doi.org/10.3389/fnins.2015.00307
20. J. Venugopalan, L. Tong, H. R. Hassanzadeh, M.D. Wang, "Multimodal deep learning models for early detection of Alzheimer's disease stage", *Sci. Rep.*, vol. 11, no. 1, p. 3254, 2021. https://doi.org/10.1038/s41598-020-74399-w
21. P. Chlap, et al., "A review of medical image data augmentation techniques for deep learning applications", *J. Med. Imaging Radiat. Oncol,* vol. 65, no. 5, pp. 545-563, 2021. https://doi:10.1111/1754-9485.13261
22. R. Zebari, A. Abdulazeez, D. Zeebaree, D. Zebari, J. Saeed, "A comprehensive review of dimensionality reduction techniques for feature selection and feature extraction", *JASTT*, vol. 1, no. 1, pp. 56-70, 2020. https://doi.org/10.38094/jastt1224