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Prediction of Medical Conditions Using Machine Learning Approaches: Alzheimer's Case Study

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Abstract: Alzheimer's Disease (AD) is a highly prevalent condition and most of the people suffering from it receive the diagnosis late in the process. The diagnosis is currently established following an evaluation of the protein biomarkers in cerebrospinal fluid (CSF), brain imaging, cognitive tests, and the medical history of the individuals. While diagnostic tools based on CSF collections are invasive, the tools used for acquiring brain scans are expensive. Taking these into account, an early predictive system, based on Artificial Intelligence (AI) approaches, targeting the diagnosis of this condition, as well as the identification of lead biomarkers becomes an important research direction. In this survey, we review the state-of-the-art research on machine learning (ML) techniques used for the detection of AD and Mild Cognitive Impairment (MCI). We attempt to identify the most accurate and efficient diagnostic approaches, which employ ML techniques and therefore, the ones most suitable to be used in practice. Research is still ongoing to determine the best biomarkers for the task of AD classification. At the beginning of this survey, after an introductory part, we enumerate several available resources, which can be used to build ML models targeting the diagnosis and classification of AD, as well as their main characteristics. After that, we discuss the candidate markers which were used to build AI models with the best results in terms of diagnostic accuracy, as well as their limitations.

Keywords: Alzheimer's disease; mild cognitive impairment; biomarkers; machine learning; deep learning; diagnosis

MSC: 68T07

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1. Introduction

Brain disorders are increasingly recognised as a significant cause of death and a global healthcare problem. They are broadly divided into two main categories, respectively *Neurodegenerative diseases* and *Neuropsychiatric disorders* [1].

Neurodegenerative Diseases are defined by progressive loss of neurons, which disrupts the function of the Central Nervous System (CNS) as well as the Peripheral Nervous System (PNS). Some common neurodegenerative diseases are Alzheimer's Disease (AD), Parkinson's Disease (PD), Prion Disease and Huntington's Disease (HD). These diseases cause the impairment of one or several particular functions contributing to one's daily experiences, such as movement, speech, memory and coordination. Therefore, patients with these conditions experience a significant reduction in social, work and day-to-day activities [2]. These limitations raised questions about the quality of life of both patients and caregivers. From this point of view, Clark outlined the importance of promoting well-being, such as to "add life to years rather than years to life" [3]. Several early reviews enumerated the risk factors associated with neurodegenerative diseases in general and AD in particular [4–9]. Aging has been identified as the primary risk factor for most neurodegenerative diseases [10,11]. More than one in nine individuals aged 65 and older were living with AD in 2021, with the prevalence of this condition continuously rising with the increasing age [12].

Neuropsychiatric Disorders are specific conditions in which an individual's thoughts, perceptions, emotions and behaviour cause suffering and interfere with the individual's daily functioning [13]. Bray et al. [14] provide a detailed survey illustrating several attempts of identifying susceptibility genes for neuropsychiatric disorders, enforcing the idea that these conditions are attributable to genetic factors. Recent epidemiological studies suggest that toxic stress converts this genetic susceptibility into actual neurological disorders [15,16]. Early-life negative events raise the risk for the development of the neuropsychiatric disorder. Childhood traumatic events are risk factors for developing bipolar disorders [17].

Multiple brain disorders occur after other life-threatening illnesses such as Acute Respiratory Distress Syndrome (ARDS). Sasanneja et al. [18] review pathophysiological mechanisms, epidemiology and risk factors underlying cognitive impairment following ARDS. In these cases, neurocognitive and neuropsychiatric problems persist for years after the lung injury, even when a clear and defined structural brain injury appears absent. The long-term sequelae prevent patients from regaining the quality of their lives before the illness. Kumar et al. [19] provide a comprehensive review of the brain pathologies and chronic neuropsychiatric sequelae associated with COVID-19 infection. In this context, multiply studies arise regarding the early diagnosis and the prevention of brain dysfunction in the critically ill [20–23].

Huang et al. [24] identify two highly important characteristics of the brain which contribute to recovery from brain injury. The first of them is the *redundancy*, which refers to the ability of intact brain areas to take over functions formerly performed by a damaged area. However, redundancy is reduced in older age [25], making the brain less capable of shifting functions from one area to another. Moreover, some functions of the brain, such as vision, can not be fulfilled by other brain areas [26]. As a result, direct harm to that areas may lead to permanent consequences. The second characteristic is the *plasticity*, meaning the ability of some nerve cells to change so that they can perform new functions. The level of plasticity experienced throughout life can be potentiated by genetic, cellular and molecular factors, as well as by environmental differences [27].

Alzheimer's Disease (AD) Overview

AD is an irreversible severe neurodegenerative disease that causes the deterioration of brain tissue and consequently, the loss of mental function. In 2019, AD was ranked as the sixth leading cause of death in the United States (US), accounting for 44.7% of all the dementia cases [28]. During 2020, COVID-19 has been added as a new cause of death and AD thus became the seventh leading cause of death in the US [29].

The causes of AD are not fully understood yet. However, significant progress is being made in this direction. Research shows that the AD brain is characterized by the extracellular amyloid plaques and intracellular tau tangles [30–33]. While it is not clear what causes this process to begin, it is known that it starts several years before symptoms occur. This is why significant efforts are being undertaken to find new biomarkers for the early identification of AD. While there is no drug or intervention which can successfully treat AD, the early detection of this condition involves several benefits. Firstly, the subject is more likely to be eligible for clinical trials, which most often address people in the early stages of AD. Secondly, Aducanumab, the first drug which attacks the underlying pathobiology of the disease and the first one approved in the last 18 years (in 2021), has been clinically tested on patients with early AD [34]. Therefore, if the disease was detected before the neurological symptoms arise, its evolution could be better controlled.

Younes et al. [35] attempted to identify change-points in measures based on brain imaging, cognitive tests and cerebrospinal fluids, in order to determine the risk of developing AD at least 10 years before the onset of the most prevalent symptoms. There have been distinguished minor changes in cognitive test scores 11 to 15 years before the start of cognitive impairment for the patients who later developed cognitive problems or dementia. Furthermore, increases in the rate of change of tau protein in cerebrospinal fluid have been discovered 34 years prior to symptom onset. An early and precise diagnosis of AD could

also save high amounts of money invested in medical and care expenses. According to [36], in 2020, the total amount of healthcare costs for the treatment of AD was estimated at $305 billion. It is an interesting fact that these costs are expected to increase to more than $1 trillion as the population ages.

Until now, several factors are known to increase the risk of developing this condition. The first and the most significant one is the age. According to [37], the probability of developing AD doubles every 5 years after reaching 65. The inherited genes can contribute to the risk of developing AD. It appears that this condition is one of the diseases with the highest level of heritability (more than 70%) [38]. Other factors include cerebrovascular diseases (the most consistently reported), diabetes, hypertension, smoking, obesity and dyslipidemia [39]. Silva et al. [40] provide a more in detail description regarding the association of the previous risk factors to AD development.

In the following, Section 2 enumerates several datasets and tools widely used in the state-of-the-art research, which prove to be highly relevant towards achieving the task of AD diagnosis. Section 3 presents the most recent findings regarding relevant biomarkers identification. The benefits of including each category of biomarkers, as well as their limitations are reviewed at the end of this section, next to references to the classifiers which employed them and led to the best diagnostic accuracy. Section 4 provides a detailed comparison of the latest ML approaches designed to predict conversion from MCI to AD and which had the best results in terms of diagnostic accuracy. Finally, Section 5 concludes and presents future directions of ML in the field of AD diagnosis and biomarkers identification.

2. Relevant Resources

In machine learning algorithms, data plays an essential role in terms of the quality of the solutions we obtain. Their size and the quality of the annotations they have are very important and that is why they are given special attention.

2.1. OASIS Datasets

The Open Access Series of Imaging Studies (OASIS) [41] is a project that made neuroimaging data sets of the brain available for free to the scientific community, with the aim to help the researchers that work in this field. Details about available OASIS datasets are presented in Table 1. These datasets are comprised of MRI data collected from both Cognitively Normal (CN) and AD subjects.

Table 1. OASIS Datasets [41].

Name	Dataset Type	Subjects Count	Scans Count per Patient	AD Subjects Count	Age & Gender for CN	Age & Gender for AD	References
OASIS-1	Cross-Sectional	416	3 or 4	100	18–96 years, 119 male, 197 female	60–96 years, 41 male, 59 female	[42]
OASIS-2	Longitudinal (two or more visits)	150	3 or 4	64 at initial visits and 14 at later visits	60–96 years, 22 male, 50 female	60–96 years, 36 male, 28 female	[43]
OASIS-3	Longitudinal (two or more visits)	>1000	not specified	489	42.5–95.6 years, 358 male, 487 female	42.5–95.6 years, 254 male, 248 female	[44]

2.2. ADNI Datasets

The Alzheimer's Disease Neuroimaging Initiative (ADNI) [45] is a study aimed at developing biomarkers for the early detection and tracking of AD. It comprises four distinct phases—ADNI1, ADNIGO, ADNI2 and ADNI3, in each of which new participants were recruited, while the existing ones from earlier phases continued to be monitored. A high level overview of the categories from this study is presented in Table 2.

Table 2. ADNI Datasets [45].

Data Type	Subcategories	References
Clinical Data	Recruitment Data, Demographics, Physical Examinations, Cognitive Assessment Data	[46–53]
Genetic Data	Genotyping and Sequencing Data	[51,54–57]
Medical Images	MRI and Positron Emission Tomography (PET) images	[48,51,58–66]
Biospecimen	Urine, Plasma and Serum from Blood, CSF	[48,61,67]

Details regarding gender, racial and age group distribution of subjects enrolled in ADNI studies are illustrated in Tables 3 and 4.

Table 3. Enrollment by Gender and Racial Categories.

	American Indian or Alaskan	Asian	Hawaiian	Black or African American	White	Multiple Reported	Not Reported	Total Subjects
Male	0	9	0	16	450	2	1	478
Female	1	5	0	23	314	1	0	344
TOTAL	1	14	0	39	764	3	1	822

Table 4. Enrollment by Age Group.

Age Group	Enrolled Subjects
Less than 55	4
55–60	22
61–65	56
66–70	85
71–75	244
76–80	229
81–85	137
86–90	44
91–95	1
TOTAL	822

As illustrated in Table 4, there are only 4 subjects less than 55 years old. Furthermore, 94% of male subjects and 91% of female subjects are white, which might lead to a classifier not generalising well to a larger and more diverse population. The distribution of subjects by diagnostic categories is represented in Table 5.

Table 5. Diagnostic Categories.

	Normal	MCI	AD	Total
Count	229	405	188	822
Percent	28%	49%	23%	100%

2.3. The Alzheimer's Project

The Alzheimer's Project [68] contains a detailed exploratory data analysis based on the ADNI dataset and several predictive models for AD diagnosis [69,70]. The authors used the ADNI1 dataset for both the cross-sectional and the longitudinal models. The choice of using only the ADNI1 phase was due to the fact that particular predictors were entirely missing across several phases of the ADNI study. A detailed comparison between these experiments is illustrated in Table 6. The baseline measurements refer to the ones retrieved at the first visit (both features and diagnosis). For each of the models, the best obtained results in terms of accuracy are illustrated in Table 6.

Table 6. Detailed comparison between Logistic Regression models developed in the Alzheimer's Project.

Model Type	Model Name	Features	Prediction Type	Training Accuracy Best Model	Test Accuracy Best Model	Train/Test Split
Cross-Sectional	Logistic Regression	All Baseline Features	Baseline Diagnosis Prediction	80.6%	78.3%	75%/25%
Cross-Sectional	Logistic Regression	MMSE, CDRSB scores	Baseline Diagnosis Prediction	93.4%	92.6%	75%/25%
Longitudinal	Logistic Regression	All Baseline Features & Time until last visit	Progression from Cognitively Normal to MCI/AD	75%	63%	80%/20%
Longitudinal	Logistic Regression	All Baseline Features & Time until last visit	Progression from MCI to AD	76%	63%	80%/20%

Limitations of this study:

- The youngest participant in the dataset is aged 55—therefore, the models can not be used to provide early diagnosis.
- The dataset has a large number of male participants, white and married - therefore, the models may not generalize well to the larger population.

Future directions concerning this study:

- The methodology should be extended to datasets involving younger patients.
- It should be tested whether the developed models predict well also on under-represented groups in the ADNI dataset.

3. Current Research Directions in Biomarkers Identification

AD is a complex neurodegenerative disease which has no effect and early diagnostic methods. The methods currently used to diagnose AD are based on cognitive tests, imaging techniques and cerebrospinal fluid (CSF) levels of amyloid-β1-42, total tau protein and hyperphosphorylated tau (p-tau).

3.1. Neuropsychological Tests

There is no single diagnostic test that can indicate if one has AD. However, as shown in Table 7, there are several mental cognitive status tests, which assess memory, thinking and simple problem-solving abilities.

Ref. [71] conducted several experiments on neuropsychological and cognitive data. They found out that traditional ML algorithms, such as Support Vector Machine (SVM), Random Forest (RF), Gradient Boosting (GB) and AdaBoost achieved similar classification performances with neuropsychological or cognitive data. The neuropsychological data gathered from participants included Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog), F-A-S Letter Verbal Fluency (F-A-S LVF) and Logical Memory subtest of the Wechsler Memory Scale (WMS-IV) scores. In addition, data with the Lawton Instrumental Activities of Daily Living Scale (IADL) and Neuropsychiatric Inventory (NPI) were collected and included in this study. IADL evaluates a person's ability to conduct daily tasks including using a telephone, doing laundry and handling finances. NPI consists of a brief interview with a family member or friend who can assess several behavioural areas that are frequently impaired in AD patients. The subjects having AD and MCI were part of the Memory Disorders Program cohort at Georgetown University Medical Center, while the CN individuals were recruited

from Washington DC metropolitan area. Employing all the features corresponding to nine neuropsychological test scores, the authors obtained the best results using GB, therefore obtaining an accuracy equal to 81.06%. Performing the same experiment, but this time applying Synthetic Minority Oversampling Technique (SMOTE) led them to an accuracy equal to 82.93% both with GB and RF algorithms. The Multilayer Perceptron (MLP) approach outperformed traditional algorithms when using neuropsychological test scores, the best result being equal to 88.46% in terms of diagnostic accuracy. Ref. [52] proposed an MLP based approach for the task of binary classification, with the data consisting of scores from three neuropsychological tests. More specifically, the data was retrieved from the ADNI datasets, containing the scores for the following tests: ADAS-Cog, MMSE and FAQ. For each of these tests, the baseline measurements were chosen (the ones from the first visit). The MLP models were trained to perform binary classification between distinct cognitive groups: AD vs. CN, AD vs. MCI, respectively MCI vs. CN. When using only one particular test, the best result was obtained by employing the MMSE scores for AD vs. CN and AD vs. MCI, with an accuracy equal to 96.92%, respectively 84.75%. In addition, for MCI vs. CN classification, the highest accuracy was obtained for the ADAS-Cog dataset, with a value equal to 81.54%. Finally, for AD vs. MCI vs. CN (3-way MLP) the best result was also reached when training on the ADAS-Cog related features, with an accuracy equal to 72.75%. The results considerably improved when the combined three tests were used as an input. The MLP model thus obtained an accuracy equal to 99.76% for AD vs. CN, 89.64% for AD vs. MCI, 90.81% for MCI vs. CN and 84.28% for AD vs. MCI vs. CN. Ref. [72] conducted a study to develop a DL algorithm for identifying a few top neuropsychological tests which could accurately classify the following groups: Early Mild Cognitive Impairment (EMCI), Late Mild Cognitive Impairment (LMCI), AD and CN. Besides these tests, the features also included demographics, genetic factors and blood biomarkers and were collected from 383 EMCI, 644 LMCI, 394 AD patients and 516 CN, all belonging to the ADNI dataset. The following five feature selection methods were used to identify the most predictive variables: Information Gain, Boruta Random Forest, Recursive Feature Elimination with the RF Classifier, Logistic Regression (LR) with LASSO/L1 regularization, and Permutation Importance. The neural network was an MLP with two fully connected dense layers for classification, followed by a dropout layer and ending with a fully connected dense layer. All five feature selection methods yielded the top classifiers to be the CDRS, LDELTOTAL, mPACCtrailsB, mPACCdigit and MMSE.

Table 7. Neuropsychological Tests for AD Diagnosis.

Name	Evaluated Skills	Score Range	Score Interpretation	References
Mini-Mental State Examination (MMSE)	Orientation, Attention, Memory, Language, Visual-Spatial Skills	0–30	The greater the impairment, the lower the score	[73–78]
Clinical Dementia Rating Scale (CDRS)	Memory, Orientation, Judgment, Problem Solving, Community Affairs, Home and Hobbies Performance	0–3	The greater the impairment, the greater the score	[79–84]
Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog)	Memory, Orientation, Language, Praxis	0–70	The greater the impairment, the greater the score	[85–89]
Functional Activities Questionnaire (FAQ)	Everyday Functional Abilities	0–30	The greater the impairment, the greater the score	[90–94]

Table 7. *Cont.*

Name	Evaluated Skills	Score Range	Score Interpretation	References
Everyday Cognition (ECog)	Everyday Functional Abilities	1–4	The greater the impairment, the greater the score	[95–100]
F-A-S Letter Verbal Fluency (LVF)	Verbal Fluency	Depends on the number of words created	The greater the impairment, the lower the score	[101]
Logical Memory subtest of the Wechsler Memory Scale	Memory Functions	Depends on the evaluated index (e.g., Visual Memory, Auditory Memory)	The greater the impairment, the lower the score	[102–107]
Delayed total recall (LDELTOTAL)	Ability to recollect information acquired earlier	Depends on the recalled amount of information	The greater the impairment, the lower the score	[72,108,109]
Modified Preclinical Alzheimer Cognitive Composite with Digit test (mPACCdigit)	Memory Functions	Depends on the recalled amount of information	The greater the impairment, the lower the score	[72,109]
Modified Preclinical Alzheimer Cognitive Composite with Trails test (mPACCtrailsB)	Processing Speed	-	The greater the impairment, the lower the score	[72,109]

3.2. Neuroimaging Biomarkers

One of the most important biomarkers studied for AD diagnosis is the structural change in the brain morphology measured from the Magnetic Resonance Imaging (MRI). MRI offers a direct measurement of brain structure in detail, facilitating the conversion of visible degeneration patterns into a biomarker score. This score can show how similar the individual's brain looks as compared to a CN brain or a clinically diagnosed AD brain.

According to [110], MRI-based measurements of atrophy are regarded reliable indicators of *disease state* and *progression*. Despite its convoluted structure, the boundaries of the hippocampus are easier to recognize by automated algorithms than *amygdala, entorhinal cortex* or *parahippocampal gyrus*. This is due to the fact that the anatomical boundaries of the hippocampus are distinct at high-resolution T1-weighted MRI scans. At the mild dementia stage of AD, hippocampal volume is already reduced by 10–15% [111]. A recent study estimated that MTA has 73% sensitivity and 81% specificity to predict whether patients with MCI will develop dementia [112]. However, there has been little research done for the diagnosis of AD using exclusively the hippocampal atrophy marker and machine learning methods for classification.

In order to perform an analysis of the brain tissue, accurate automated segmentation of brain structures needs to be done. Hippocampus segmentation in MRI is a problem in itself due to its small size, anatomical variability, low contrast and indistinct boundary. Ref. [113] shows that segmenting the hippocampus using conventional methods (based on the region growing technique) does not achieve acceptable results. Ref. [114] focus on an approach to detect AD from MRI scans using ML algorithms. In order to perform the experiments, there have been selected 235 MRI scans from the OASIS dataset corresponding to different AD stages. The preprocessing of the scans consists of the use of Contrast enhancement. For the feature extraction part, the texture, area and shape features are extracted using the Gray-Level Co-Occurrence Matrix and Moment Invariants from the hippocampus, which is selected as the Region of Interest (ROI). In addition, there are extracted features indicating the age, gender, education, socio-economic status and MMSE score. These are further fed to an Artificial Neural Network (ANN), which is trained to detect AD using the Scaled Conjugate Gradient (SCG) algorithm. The proposed system has an average accuracy of 86.8%.

Ref. [115] proposed an ensemble of three deep convolutional neural networks with slightly different configurations. These were fed with patches from three physical planes of

MRI images: horizontal, frontal and median. The MRI images belong to the OASIS dataset. As a preprocessing step, the scans are normalized (by shifting inputs to zero-mean and unit variance). Each individual CNN model has the same architectural pattern, consisting of convolution, batch normalization, rectified linear unit and pooling. The authors kept these layers very narrow with 12 filters per layer. Batch normalization speeds up the training process, by acting as a regularizer. The models were trained independently and the output classification labels were ensembled together using a majority voting technique. The accuracy of this model on the OASIS dataset was equal to 93.18%.

Ref. [116] proposed a CNN-based algorithm which uses MRI coronal slices covering the medial temporal lobe to classify AD vs. CN subjects. The authors used the Inception-v4 architecture [117] with slight modifications. This model was designed to take 2D images with three RGB channels as inputs. As a result, the gray-scale coronal slices were triplicated into three channels for consistency. After feeding the network with a single coronal slice, the output was a feature vector containing 1024 values. The authors added three additional values to the end of the vector: the age of the subject (because mild MTA is observed in CN elderly subjects), the sex and the number of coronal slices which were evaluated. The final concatenated vector contained 1027 values and was fed to the classifier module, a fully connected layer with 1027 input nodes and 2 output nodes. These were fed into a softmax output layer, which predicted the probability that a particular MRI image indicated the presence of AD. In terms of results, the accuracy of the models trained on the ADNI dataset was equal to 89%.

Ref. [118] also used a subset of the ADNI dataset, including 302 MRI images, for the task of AD classification. For the preprocessing step, the non-brain tissues were removed from scans by optimizing the fractional intensity threshold and reducing image bias and residual neck voxels. The brain-extracted images were further segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). In addition, GM images were registered to a standard template using linear affine transformation. Next, a convolutional architecture consisting of a set of learnable filters was used to extract low- to mid-level features. Feeding the obtained data to a GoogleNet classifier led to an overall accuracy rate equal to 98.84%.

Ref. [119] proposed a multistage classifier consisting of several CNN models, with the purpose of identifying subjects with MCI or AD using MRIs, as it follows: classification between AD and HC (Healthy Cognition), MCIc (MCI patients who will convert to AD) and HC, respectively MCIc and MCInc (MCI patients who will not convert to AD). For each of these binary classification tasks, multiple CNN models were trained using a set of sagittal, coronal and transverse MRI slices. These CNN models were further integrated into a single ensemble. Each base classifier based on 2D CNN models was trained using each set of the sagittal, coronal, or transverse MRI slices.

After building these base classifiers, the first five with the best generalization performance for each slice orientation were chosen. This resulted in three classifier ensembles based on single-axis slices, each of them containing the 5 best base classifiers. The output of an individual classifier ensemble was generated by combining the outputs of these 5 base classifiers. Finally, a majority vote scheme was used to combine the predictions of these three classifier ensembles. When tested on the ADNI dataset, the average classification accuracies were 84% for AD vs. HC, 79% for MCIc vs. HC, and 62% for MCIc vs. MCInc.

Table 8 summarizes the above-presented ML approaches, the employed preprocessing and classification algorithms, the used datasets and the accuracies of the best obtained models.

Table 8. Machine Learning Approaches using NeuroImaging Biomarkers.

Authors	Dataset Name	Data Type	Preprocessing	Classifier	Classification Accuracy
Raut et al., 2017 [114]	OASIS	MRI Data	Contrast enhancement	ANN	86.8%
Islam et al., 2018 [115]	OASIS	MRI Data	Image normalization	Ensemble of CNNs	93.18%
Bae et al., 2020 [116]	ADNI	MRI Data	Grayscale coronal slices were triplicated into 3 channels	Inception-v4	89%
Sarraf et al., 2017 [118]	ADNI	MRI Data	Removal of non-brain tissues from scans, Image Segmentation, Image Registration using Linear Affine Transformation	GoogleNet	98.84%
Pan et al., 2020 [119]	ADNI	MRI Data	Skull Extraction, Registration, Image Smoothing, Voxel-Based MRI Signal Intensity Normalization	Multistage classifier based on CNN	84.5%

3.3. Genome, Blood and Cerebrospinal Fluid Biomarkers

3.3.1. CSF Biomarkers

Methods relying on CSF biomarkers are both costly and invasive. In addition, the sensitivity and specificity of CSF amyloid-β1-42 and p-tau biomarkers have raised concerns in several studies about their clinical implications [120–122]. According to [120], CSF biomarkers are based on a quantitative interpretation. Even if standardization efforts are more advanced for CSF biomarkers than for other categories of biomarkers, their practical use must follow specific best-practice guidelines. Ref. [123] states that the sensitivity of CSF Aβ42 is between 0.69 and 0.81 and specificity between 0.44 and 0.89. These values imply a great risk of either overdiagnosis or underdiagnosed, misattributed or ignored symptoms. As a result, patients are frequently diagnosed late, placing a burden on the health systems. Ref. [124] proposed a classification model for AD diagnosis employing CSF biomarkers and the J48 algorithm, which led to an accuracy equal to 98.82%. The dataset was acquired from Kaggle and comprised 91 MCI patients and 242 CN subjects. The data consisted of protein level of amyloid—Aβ42, native Tau protein, phosphorylated form of Tau and Apolipoprotein E genotype. The feature selection step was accomplished using InfoGainAttributeEval from Weka (a data platform for ML tasks consisting of tools for data pre-processing, classification, and clustering).

Ref. [125] developed an ensemble model using a combination of CSF protein biomarkers to predict AD with an accuracy equal to 95.52%. The dataset employed in this approach was generated by Craig Schapiro et al. [126], comprising both demographic and CSF protein biomarkers. After applying Recursive Feature Elimination (RFE), three biomarkers proved to be the most informative: Cystatin C, Matrix metalloproteinases (MMP10) and tau protein. The classification model used a weighted average of an LR model and a linear SVM.

3.3.2. Genome Biomarkers

Several studies evaluated the potential of genetic biomarkers in AD diagnosis. According to [127], the following genes have been significantly involved in Early Onset AD (EOAD): Amyloid-β precursor protein (AβPP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2). Meanwhile, late-onset AD (LOAD) has been associated with other genes, including: apolipoprotein E-ϵ4 (APOE ϵ4), bridging integrator 1 (BIN1) region, clusterin (CLU), phosphatidylinositol clathrin assembly lymphoid-myeloid (PICALM), and complement receptor 1, identified in Genome-Wide Association Studies (GWAS) [128]. Among these associated genes for LOAD, the APOE ϵ4 allele proves to be a promising biomarker for AD diagnosis.

Booij et al. [129] used 1239 genes as features for a Partial Least Square Regression classifier to identify the presence or absence of AD. Data was collected from different health

institutions in the Oslo area of Norway between 2004 and 2005. The algorithm had an accuracy of 87% and managed to also discriminate AD from Parkinson's with an accuracy of 89%.

Lunnon et al. [130] used 48 genes, many of which were mitochondrial genes (associated with oxidative phosphorylation, mirroring changes known to occur in the brains of AD patients), together with an RF classifier to diagnose AD with an accuracy equal to 75%. Subjects employed in the experiment were from AddNeuroMed, a cross-European biomarker study.

Perera et al. [131] proposed a machine learning framework which identified 14 new candidate biomarker genes for AD, some of which are validated by biological research. The authors used GSE5281 [132] brain dataset, which contains 161 subjects and 24,438 unique gene symbols. After using feature selection algorithms such as RF, Extra Tree Classifier and Co-relation Matrix, the selected gene symbols are AC004951.6, MAFF, SLC39A12, PCYOX1L, CTD3092A11.2, RP11-271C24.3, PRO1804, PRR34-AS1, SST, CHGB, MT1M, JPX, APLNR, and PPEF1. Out of these, 4 genes have already been discovered as AD-related in the GeneCards [133], respectively: SST, CHGB, SLC39A12 and MT1M. In addition, using these 14 genes as features for an SVM classifier with a linear kernel led to an accuracy of 91.84% for the task of AD classification.

Sekaran et al. [134] identified 24 novel gene biomarkers using Rhinoceros Search Algorithm applied on the GSE1297 dataset retrieved from Gene Expression Omnibus (GEO). In addition, the authors applied an MLP classifier to these most informative features thus obtaining an accuracy equal to 100% in identifying the distinction between AD and normal genes. The data used for this experiment was extracted from the hippocampal region of the brain and contained 31 samples.

Sharma et al. [135] employed an ensemble of RF and LASSO to AD-associated gene expression datasets corresponding to four brain regions—Prefrontal Cortex (PC), Middle Temporal Gyrus (MTG), Hippocampus (H), and Entorhinal Cortex (EC), in order to identify new genetic biomarkers. The data was extracted from the GEO database. Few gene candidates were commonly identified by both feature selection methods. In addition, there were common gene candidates within different brain regions, such as e ZNF621, SLC25A46, RAE1, and ANKIB1, found in both H and EC regions. When using ElasticNet for the classification task, with both feature selection algorithms applied for the H and PC region data, the obtained prediction accuracy was 100%.

However, it is more difficult to collect genetic data from the patients, making this approach a more exclusive one.

3.4. Potential Novel Biomarkers

An important research direction in this field is represented by the identification and validation of novel biomarkers. From this point of view, Ref. [136] investigated how ML and novel biomarkers can be used for the diagnosis of AD. The authors studied the AD specialized journals and in addition to Aβ and tau-related biomarkers, they investigated other mechanisms of AD pathology, such as neurofiliament light (NFL), synaptic dysfunction and neuroinflammation.

NFL is a biomarker indicating neurodegeneration. Ref. [137] showed that blood NFL and CSF NFL concentrations correlate well, while NFL levels correlate inversely with MMSE scores. In addition, other CSF biomarkers including t-tau, p-tau, neurogranin and YLK-40 positively correlate with NFL.

Synaptic dysfunction is one of the earliest detected changes in AD. Nilsson et al. [138] investigated 17 synaptic proteins which might indicate synapse degeneration in AD. The results showed that beta-synuclein, gamma-synuclein, neurogranin, phosphatidylethanolamine-binding protein 1, 14-3-3 proteins and neuronal pentraxins are altered in AD compared to healthy controls, therefore acting as potential early indicators of the disease.

According to [123], biomarkers of neuroinflammation include sTREM2 and YKL-40, their elevated levels within the CSF indicating AD pathology. Gaetani et al. [139]

conducted research in order to identify protein biomarkers reflecting neuroinflammation in AD using multiplex proximity extension assay (PEA) testing. In addition, they applied ML approaches to identify biomarkers which discriminate between AD-MCI and other neurological diseases (OND). CSF samples belonging to the patients with AD-MCI and OND were collected over an 8-year period and further provided by the Laboratory of Clinical Neurochemistry, Department of Medicine and Surgery, University of Perugia. After performing a univariate analysis of the z-scores relative to the measured proteins, the most discriminatory proteins between AD-MCI and OND included SIRT2, HGF and MMP-10 and CXCL5. These tested proteins were also present after applying LASSO, showing promising performance in differentiating AD-MCI and OND.

Table 9 summarizes the benefits of including each category of biomarkers, as well as their limitations, providing references to the classifiers which employed them and led to the best diagnostic accuracy.

Table 9. Benefits and Limitations of Different Biomarker Categories.

Biomarker Category	Benefits	Limitations	Best Classifier References	Best Classifier	Best Classifier Dataset	Best Classifier Accuracy
Cognitive	Easy to conduct, Less expensive, Widely available, Noninvasive, Lack of pain	There is no single test which can indicate a diagnostic	[52]	MLP for AD vs. CN classification	ADNI	99.76%
MRI Data	Less expensive, Widely available, Noninvasive, Lack of pain	Decreased hippocampal volume is not AD-specific, Automatic segmentation of scans is challenging, Need expensive infrastructure	[118]	GoogleNet for AD vs. CN classification	ADNI	98.84%
CSF	Advanced standardization, High diagnostic performance	Expensive, Invasive	[124]	J48	Kaggle	98.82%
Genetic Data	Can help assess the risk of developing AD	Difficult to collect	[134,135]	MLP/ElasticNet	GEO	100%

4. Predicting Progression from MCI to AD with Machine Learning Approaches

Mild Cognitive Impairment (MCI) is an intermediate phase between healthy and AD. It is critical to identify MCI subjects who will convert to AD at an early stage to slow down the cognitive deterioration of AD patients. Conversion usually occurs in the first three years after being diagnosed with MCI and the conversion rate lowers considerably in the years that follow.

As seen above, several cross-section structural MRI-based methods were proposed to distinguish between healthy controls and AD patients, some of which report an average classification accuracy higher than 98% [118]. Even if these approaches do diagnose Alzheimer's, it is often too late for treatment, as most drugs approved by the Food and Drug Administration (FDA) seem to have a greater impact in the early stages of the disease. Moreover, anatomical development in the brain is due to both normal ageing as well as to AD progression, so it is difficult to discriminate between HC/MCI and AD at a single scan. Older subjects are more similar to AD, so to avoid such a bias, several approaches started to use longitudinal image information.

From this point of view, Ref. [140] provide a new way to discriminate between MCI patients that either convert to AD or remain stable, using longitudinal MRI. The dataset used in the paper is obtained from the ADNI collection. The scans are pre-processed by ADNI as follows: images from the Philips machine are intensity corrected by the N3 method [141], while images from Siemens or GE machines are grad-warped, followed by B1 bias field correction and N3 intensity non-uniformity correction. The anatomical development within the brain is represented by the Stationary Velocity Field (SVF) from registration between the baseline and follow-up images. A linear SVM is employed as a classifier. Using 36-month follow-up data and 10-fold cross-validation, this approach led to an accuracy equal to 92%. The authors also performed experiments on 6, 12 and 24-month follow-up images and concluded that similar classification performance can be obtained with each time interval, but 12 and 24-month follow-up provides slightly improved classification performance than 6 month follow-up.

Peixin et al. [142] proposed a two-stage classification model based on transfer learning and contrast learning for the prediction of development from MCI to AD. The authors used MRI scans from the ADNI dataset, which was further processed following the next three steps: bias field correction using N4 algorithm [143], affine linear alignment of scans onto the MIN152 atlas and skull stripping of each image for $129 \times 145 \times 129$ voxels. This study used the Med3D network [144] to initialize the model parameters and obtain general imaging features. In addition, training on unlabeled target datasets using contrastive learning (MoCo) was done to get target imaging features. Finally, the network was fine-tuned using the labelled target dataset, leading to a classification accuracy equal to 82%.

Gao et al. [145] also explored the use of transfer learning for the task of predicting conversion from MCI to AD. From this point of view, they proposed AD-NET (Age-adjust neural network), for which the pre-training model transfers not only features, but also an age prediction. The age-related information and the extracted features are further transferred in the fine-tuning model, where the risk of the subject converting to AD is predicted. The data used for this study is obtained from two sources: the ADNI dataset and the Information eXtraction from Images (IXI) public dataset, the second of which provides information about 581 cognitively normal subjects. In addition, the data used for MCI conversion prediction is obtained from ADNI. During the preprocessing step, the authors conducted rigid registration to the MNI152 atlas. This experiment led to a prediction accuracy equal to 83% for subjects with the age range between 75 and 90 years old and 79% for subjects with the age range between 55 and 75 years old.

Abrol et al. [146] conducted an investigation which evaluated the suitability of using ResNets with neuroimaging data for the task of predicting progression from MCI to AD. The input structural MRI images are part of the ADNI study. In the preprocessing step, they are segmented to identify the grey matter brain areas, which are further spatially normalized. Finally, they are smoothed using a 3D Gaussian kernel. The smoothed grey matter maps are fed to a ResNet model, which led to a prediction accuracy equal to 82.7%.

Table 10 summarizes the above-presented research, with a focus on the preprocessing and classification algorithms employed, as well as on the best results achieved. It is noticeable that the approach of Sun et al. [140] which used a linear SVM classifier performed best to distinguish progression from MCI to AD as compared to deep learning methods. While the dataset was common for all the mentioned approaches, we believe that this result was due to the preprocessing procedures employed.

Table 10. Comparison of studies on prediction of conversion from MCI to AD using MRI scans.

Authors	Dataset Name	Data Type	Preprocessing	Classifier	Classification Accuracy
Sun et al., 2017 [140]	ADNI	MRI Data	ADNI own preprocessings	SVM	92%
Peixin et al., 2022 [142]	ADNI	MRI Data	Bias Field Correction, Affline Linear Alignment onto MIN152 atlas, Skull Stripping	Med3D + MoCo	82%
Gao et al. [145]	ADNI & IXI	MRI Data	Rigid Registration to MNI152 atlas	3D CNN + Transfer Learning	83% for age 75–90, 79% for age 55–75
Abrol et al. [146]	ADNI	MRI Data	Segmentation, Spatial Normalization, Gaussian Smoothing	ResNet	82.7%

5. Conclusions and Outlook

This research article comprehensively examined the application of machine learning including deep learning to biomarker discovery and disease prediction in Alzheimer's disease. While there are significant improvements concerning biomarkers identification and early detection of AD, these subjects remain open to future enhancements.

The paper begins by defining the keywords most used in the paper. Afterwards, the most important datasets are detailed, respectively OASIS and ADNI, which contain data that can be fed to ML and DL algorithms to identify AD. The most consistent part of the paper is devoted to the presentation of the most important biomarkers and how they can be used to predict AD. Lately, we witnessed significant progress in research regarding new biomarkers for AD. MRI-based measures are among the most clinically validated biomarkers for the detection of AD, with [112] estimating that medial temporal atrophy (MTA) has 73% sensitivity and 81% specificity for predicting the conversion of patients with MCI to dementia. On the other hand, the results obtained by [134,135] emphasize the potential of genetic biomarkers in AD diagnosis. However, it is more difficult to collect genetic data from patients, as compared to clinical data and MRI based measurements. Meanwhile, collecting cognitive data about subjects using neurocognitive tests represents a convenient approach for retrieving possible indicators of AD. While there is no single diagnostic test which can identify if a person has this condition, several mental cognitive tests evaluate memory, as well as thinking and problem-solving abilities. Ref. [52] obtained an accuracy of 99.76% for AD diagnosis, using three MLP neural networks, trained using the results of the following cognitive tests: ADAS-Cog, MMSE and FAQ, with the data belonging to the ADNI dataset.

Some of the best-performing scientific works using these biomarkers have used neural networks such as ElasticNet (with an accuracy equal to 100%), MLP (with an accuracy equal to 99.76%), respectively GoogleNet (with an accuracy equal to 98.84%). These architectures were analyzed and detailed in the paper.

Future work will continue to be based on the resources and architectures presented in the paper, with a focus on identifying the most representative biomarkers and using them for the diagnosis of AD.

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Abbreviations

The following abbreviations are used in this manuscript:

AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale–Cognitive Subscale
ADIMO	Alzheimer's Disease In My Opinion
ADNI	Alzheimer's Disease Neuroimaging Initiative
AI	Artificial Intelligence
ANN	Artificial Neural Network
ARDS	Acute Respiratory Distress Syndrome
CDR	Clinical Dementia Rating
CDRSB	Clinical Dementia Rating Scale - Sum of Boxes
CNN	Convolutional Neural Networks
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CSFOP	Cerebrospinal Fluid Original Poster
DL	Deep Learning
ECog	Everyday Cognition
EL	Ensemble Learning
EMCI	Early Mild Cognitive Impairment
EOAD	Early Onset Alzheimer's Disease
FAQ	Functional Activities Questionnaire
FDA	Food and Drug Administration
GEO	Gene Expression Omnibus
HC	Healthy Cognition
HD	Huntington's Disease
IADL	Lawton Instrumental Activities of Daily Living Scale
IXI	Information eXtraction from Images
LDELTOTAL	Delayed total recall
LMCI	Late Mild Cognitive Impairment
LVF	Letter Verbal Fluency
MCI	Mild Cognitive Impairment
ML	Machine Learning
MLP	Multilayer Perceptron
MMP10	Matrix metalloproteinases
MMSE	Mini-Mental State Examination
mPACCdigit	Modified Preclinical Alzheimer Cognitive Composite with Digit test
mPACCtrailsB	Modified Preclinical Alzheimer Cognitive Composite with Trails test
MRI	Magnetic Resonance Imaging
NPI	Neuropsychiatric Inventory
OND	Other Neurological Diseases
PD	Parkinson's Disease
PEA	Proximity Extension Assay
PET	Positron Emission Tomography
PNS	Peripheral Nervous System
RFE	Recursive Feature Elimination
ROI	Region of Interest
SCG	Scaled Conjugate Gradient
SVF	Stationary Velocity Field
WMS	Logical Memory subtest of the Wechsler Memory Scale
WMS-IV	WMS – fourth edition
SVM	Support Vector Machine
RF	Random Forest

GB	Gradient Boosting
MTA	medial temporal atrophy

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