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Review

Review on Alzheimer Disease Detection Methods: Automatic Pipelines and Machine Learning Techniques

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Abstract: Alzheimer's Disease (AD) is becoming increasingly prevalent across the globe, and various diagnostic and detection methods have been developed in recent years. Several techniques are available, including Automatic Pipeline Methods and Machine Learning Methods that utilize Biomarker Methods, Fusion, and Registration for multimodality, to pre-process medical scans. The use of automated pipelines and machine learning systems has proven beneficial in accurately identifying AD and its stages, with a success rate of over 95% for single and binary class classifications. However, there are still challenges in multi-class classification, such as distinguishing between AD and MCI, as well as sub-stages of MCI. The research also emphasizes the significance of using multi-modality approaches for effective validation in detecting AD and its stages.

Keywords: Alzheimer disease; biomarker methods; automated pipeline methods; fusion based methods; machine learning methods

1. Introduction

Alzheimer's disease (AD) is a debilitating disease that affects millions of people worldwide, leaving them and their families struggling to cope with the devastating consequences. It is a progressive disorder that gradually destroys cognitive functions, including memory, language, and perception, making it a heart-breaking experience for both the patient and their loved ones [1]. Initially, those affected by AD may experience problems with memory, apathy, and difficulty performing everyday tasks [2]. Despite years of research, there is still no cure for AD, which is why early diagnosis and intervention are crucial for managing the symptoms and slowing down its progression. As the condition advances, the individual may experience difficulties with communication, thinking, behaviour, speaking, swallowing, and movement [3]. According to recent statistics, over 6.5 million individuals are affected by AD. People aged 65 or older living with AD are most common, with 2.41 million in the age range of 75–84 and 2.31 million aged 85 and over. Unfortunately, there is no definitive test to detect AD; it must be diagnosed during its early stages in order to be identified accurately. Machine learning and other AI-based approaches can be used to help detect the disease [4].

A number of biomarkers, such as sMRI, genetics, and clinical and biological specimens, are necessary to spot AD [5]. Biomarkers represent the raw information used to detect AD. It is essential to determine the right biomarker, as there is no definitive evidence as to which one is the most reliable [6]. Spatial features, such as CT measurements of the cortex, brain volume and brain surface area, can be discerned after processing, thereby increasing their diagnostic value [7]. Biomarkers are processed using both handcrafted and deep learning techniques for extraction, allowing these features to be extracted automatically. Commonly used Automatic Pipeline Methods, like FSL, Free Surfer, SPM12 and ANT, can be employed as handcrafted methods for processing biomarkers, whereas deep learning techniques, like CNN and Transfer Learning Methods, are usually used for Alzheimer's detection [8]. Deep learning-based methods use 2D T1-weighted MRI for accurate diagnosis

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and stratification of AD stages. Utilizing a shallow CNN architecture, the pipeline offers a fast and accurate diagnosis module and global (normal vs. MCI vs. AD) and local (VMD, MD, MoD) classifications [9]. The Ensemble method and ANN-based approach are also used for AD detection. The ANN achieves a sustainable accuracy as compared to Gradient Boosting & Voting Classifier [10]. Hybrid Deep Learning Approach with the Long Short-term Memory algorithm and magnetic resonance imaging aims to distinguish patients with cognitive normality from those with MCI and facilitate early detection and treatment [11]. In the Multimodality approach, MRI and PET scans are the most common biomarkers used to diagnose AD; Wavelet transform-based multimodality fusion of the two scans is utilised for early detection [12]. A hybrid deep-learning framework consisting of a 3D convolution neural network (3D CNN) and a bidirectional recurrent neural network (BRNN) to diagnose AD early explores the effect of fusing MRI with cross-sectional biomarkers [13]. This research looked into the numerous types of artificial neural networks (ANNs) that can be utilized to identify and anticipate AD based on the brain imaging of people with mild cognitive impairment (MCI) [14]. The most relevant articles were chosen based on an in-depth subject matter assessment. There are also other methods Like EEG deep learning (DL) architectures-modified convolution (CNN) and convolution auto encoder (Conv-AE) neural networks (NNs) for categorizing subjects into AD, MCI, and healthy control (HC) based on scalp EEG recordings [15]. Disease comprises various subtypes and stages, running from cognitive normal (CN) to MCI and from MCI to AD. The accuracy of a single class or binary class for detecting AD is quite high, particularly when distinguishing between AD and CN, AD and MCI, and CN and MCI [16]. However, multi-class detection, especially with three or four classes, as well as subclasses of MCI, can still be improved. Binary and multiple-class detection for the subtypes of MCI is still not satisfactory. Therefore, many research methods have been adopted to discover the appropriate pipeline for detecting these stages. Furthermore, some pipelines have demonstrated acceptable accuracy in recognizing AD across different classes. In this review, the most significant research works are screened and investigated significantly. The first part of the study involved a review of biomarkers to assess their effectiveness in detecting AD and its various classes. In the second part, the study investigated various handcrafted methods, such as automatic pipelines, to determine which could provide the best pre-processing approach for the different AD-oriented MRI scans and to determine their statistical features in terms of volume, area, max of the different cortical regions of the brain. In order to obtain the muti and hybrid range of features from the different scans, which pipelines were best for fusion and registration approach for the multimodality were considered. After the multimodality approaches, the classification techniques are analysed in the last section of the study, and various Ml and DL techniques are reviewed based on accuracy and binary and multi-class classification. Hence, the extensive research methodologies are outlined in Figure 1.

Therefore, Figure 1 describes the review organization. This organization uses biomarkers as indicators and methods for detecting AD. To understand its significance, Section 2 describes Biomarker methods for the detection of AD. In Table 1, some questions were framed to obtain the appropriate and sustainable mode or method for detecting AD and its stages.

Table 1. Research Question based on Contribution.

Question	Description
Q1	How can Medical Image Modalities be used for the detection of Alzheimer's disease and its various classes?
Q2	Does Multi-Modality Diagnosis approach improve the diagnosis accuracy of Alzheimer Disease?
Q3	Handcrafted features or deep learning-based solutions can be used to detect AD diseases. Which method provides the highest chance of detecting the disease?

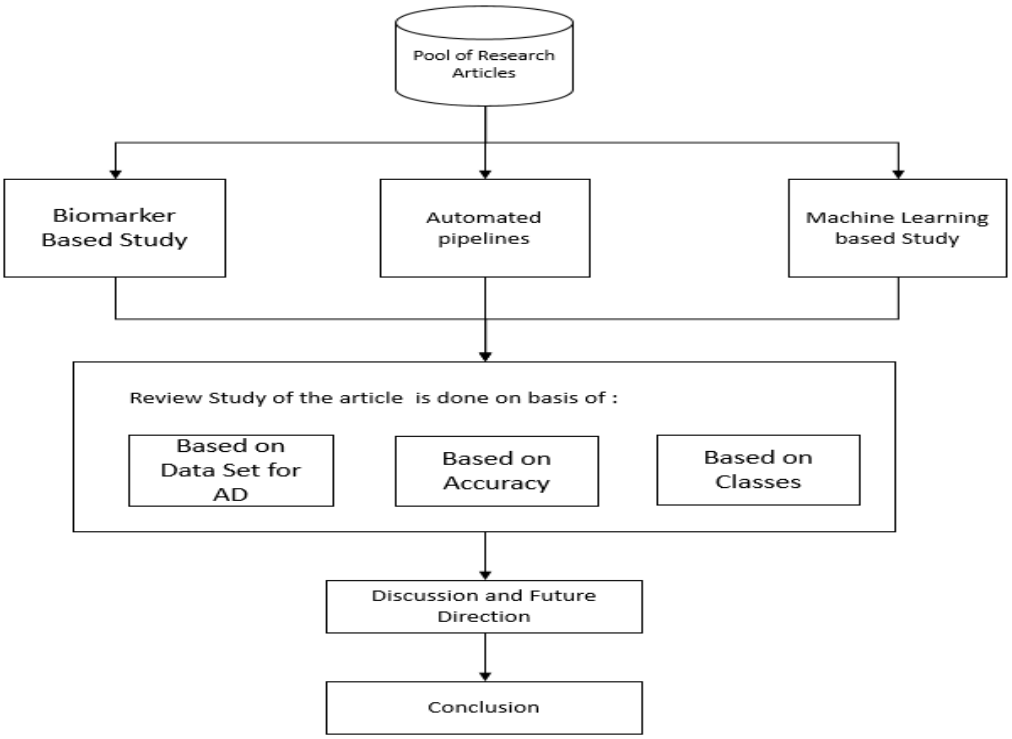

Figure 1. Review Methodologies.

To answer these questions, the segregation of different types of AD research articles is considered. This review process contains the analysis of 300 articles. Forty-five articles discuss the causes and factors of AD. Another 55 articles were used to understand the significance of biomarkers. In the fusion level and pure medical image processing analysis, 100 articles were used, while the remaining articles were taken into consideration for machine learning and deep learning-based analyses.

2. Biomarker Modalities

AD is a debilitating condition that affects millions of people worldwide. It is a progressive disorder that causes memory loss, cognitive decline, and behavioural changes. Biomarker-based research is one of the most important tools in the fight against AD. This innovative method of studying the disease allows researchers to identify patients with AD and track its progression through different stages. By using biomarkers, researchers can also identify other neurological defects that may be associated with the disease. Biomarker-based research is a critical step in the fight against AD, helping scientists better understand the disease and develop more effective treatments. In this article, we will explore the biomarker-based study of AD and its importance in e fight against this devastating condition. Different neuro defect can be identified by the different biomarkers available. These defects lead to a brain disorder, which was discovered to be responsible for abnormal behaviour in Alzheimer's patients [2]. In order to find the exact region in terms of biological reasoning, the Amyloid Precursor Protein (APP) is a small protein found in different neuro regions [4]. When certain disorders occur, the neurons that have been injured can regenerate, decompose, and recycle through Amyloid precursor protein (APP). A decrease in APP can lead to an increase in proteases in synapses, which leads to deficiency in the neuro region and causes interruptions in the brain. Brain synapses transmit signals from one neuron to another neuron. These neurons use the APP membrane to protect themselves from unwanted signals. Hence, inflammation can occur caused by proteases being bundled outside blood vessels. Inflammation is one of the major causes of AD and the different stages of the disease. The brain region efficiency levels can be understood through different biomarkers, Clinical Biomarkers, Genetic Biomarkers, Positron Emission

Tomography (PET), Biospecimen Biomarkers, Structural Magnetic Resonance Imaging (s MRI), Cerebrospinal Fluid (CSF), Positron Emission Tomography (PET), Fluid Attenuated Inversion Recovery (FLAIR), Diffusion Tensor Imaging (DTI), EEG (Electroencephalography). Medical professionals, scientists, and researchers use these methods for detecting AD and its different classes [17]. These biomarkers provide information such as grey matter content and white matter differences, which are indicative of brain disorders [18]. In order to determine this disorder, the presence of Amyloid in the brain, PET biomarkers are used [19]. Biomarkers can contain urine, plasma, serum, or cerebral spinal fluid [20] to detect diseases described in Table 2.

Table 2. Description of Different Biomarkers.

S.No	Biomarkers	Description
1	Clinical Biomarker	A clinical trial is an analysis of data, from the micro (patient care) to the macro (clinical trials), that are used in healthcare research (wide applications within a health system) [21]. Clinical trials collected this data for analysing patient outcomes. Novel pharmaceuticals, treatment approaches, devices, and other research are tested in clinical trials.
2	Genetic Biomarker	Genetic samples contain sensitive information about an individual's health and well-being. An individual's inherited or acquired genetic characteristics can be determined by DNA and RNA analysis [22].
3	Positron Emission Tomography (PET)	PET is required for analysing cholesterol levels and amyloid proportions in the brain. This biomarker allows for the measurement of glucose levels in various parts of the brain and the identification of different subjects with AD. A tesla scanner is capable of performing both Gamma Ray and PET imaging in patients with AD using the Amyloid detection method developed by [23].
4	Biospecimen Biomarker	The biospecimen data is information about the physical sample taken from an AD patient and prepared for sequencing analysis [24]. A structural quantification of the brain involves the collection of information from different parts of the brain that exhibit minor structural changes and mobility in. Using these biomarkers, one can track every function of the neuroanatomical structure when a patient suffers from any deficiency in their ageing process [25].
5	Structural Magnetic Resonance Imaging (s MRI)	MRI provides anatomical details about the brain. In AD patients, hydrogen atoms and resonance enable structural visualization through magnetic resonance imaging, both in static and magnetic fields Varghese et al. (2013). Structure analysis, volumetric analysis, cortical thickness measurement, voxel-based analysis, longitudinal analysis, and anatomical morphology are all performed by imaging techniques [26].
6	Cerebrospinal Fluid (CSF)	The proportions of proteins in CSF biomarkers determine whether a particular biomarker is applicable for AD detection. CSF analysis can be used to find differences between AD patients and healthy individuals based on the proportion of Aβ protein. Diagnoses are made by examining the reduction or increase in Aβ [27]. Aβ, Aβ40, Aβ42 proteins are found in the brain region as is phosphorylated tau (p-tau) and tau protein total (t-tau).
7	(APOE e4)	The neuro region, the lung region, and the heart region of the human body are influenced by genetic influences. This information is crucial to diagnosing and detecting AD patients [28]. A genetic biomarker assists in diagnosing the e4 allele of Apo lipoprotein E (APOE e4) in the brain which leads to the development of Alzheimer's symptoms and limits the production of amyloid in the brain.
8	Fluid Attenuated Inversion Recovery (FLAIR)	A flare image, also called a fluid-attenuated inversion recovery image, is a diagnostic method for AD detection. This biomarker can provide information regarding an unwanted lesion in the brain or a lesion which suppresses CSF's role in the brain [29]. The Flair Modality continues to use the T2 weighted proportion. It also contains information about the white matter remaining in the different parts of the brain affected by AD.
9	Diffusion Tensor Imaging (DTI)	The diffusion tensor imaging (DTI) technique uses isotropic diffusion to assess the brain's axonal (white matter) structure. Diffusion tensor imaging is utilized to determine the diffusivity of water molecules in tissue in order to identify the fibre bundles gathered in the affected region of the brain of AD patients [30]. Water molecules stagger communication between neurons when they do not flow regularly in the brain. This leads to progressive memory loss, eventually leading to AD.

Table 2. *Cont.*

S.No	Biomarkers	Description
10	EEG (Electroencephalography)	Brainwaves are measured by EEG. Routine EEGs have a regular frequency and shape. The electrical conductivity of AD patients' tissues varies between individuals and over time. Prolonged EEGs are used for detecting AD Marcel and del R [31]. Consequently, the detection of AD becomes smooth and provides a higher rate of precision than any other detection method.
11	PET (Positron Emission Tomography)	PET is a form of functional imaging technique that employs a radioactive tracer to evaluate the metabolic activity of diverse areas of the brain. PET scans can offer data on how different parts of the brain are performing, including how they react to different stimuli, and can be employed to identify ailments such as AD, Parkinson's disease, and epilepsy [32].
12	CT (Computed Tomography)	CT scanning is a type of imaging that uses X-rays to generate representations of the brain without any invasive measures. With CT scans, the size and shape of different sections of the brain, along with any irregularities, can be determined. This method is commonly used to detect conditions such as tumours, intracerebral bleeding, and stroke [33].

To make the most of the available biomarkers, pre-processing is a key step in refining the quality of biomarkers. In the case of neuroimaging biomarkers, volumetric-based pre-processing is the most widely used form of pre-processing. Volumetric biomarkers are becoming an increasingly important tool in the medical field for the diagnosis and treatment of various diseases. However, before these biomarkers can be used effectively, the data must be pre-processed to ensure accurate and meaningful results. In this article, we will explore the essential volumetric biomarkers that require pre-processing to prepare the data for feature extraction. We will discuss the importance of segmentation, bias field correction, and normalization in the pre-processing stage. Furthermore, we will delve into the different techniques used for each process and how they impact the quality of the data. A deeper understanding of the crucial role of pre-processing in volumetric biomarker analysis and how it can enhance the accuracy and effectiveness of medical research and diagnosis is given in Figure 2.

Prior to the utilization of Machine Learning and Deep Learning for feature extraction, a number of pre-processing techniques must be applied for structural MRI, PET and CT Modalities such as De-oblique, Field Inhomogeneity Correction, Non-Brain Tissue Removal, Bias Correction, Registration, and Segmentation. One of the most critical steps in medical image analysis is feature extraction, which involves identifying and extracting relevant information from the images. In the past, this was done using traditional pre-processing techniques, such as filtering, segmentation, and registration. However, with the advent of Machine Learning and Deep Learning, there has been a shift towards using these techniques for feature extraction. In this article, we will explore the importance of pre-processing techniques for structural MRI, PET, and CT modalities, and why they are still a crucial part of the feature extraction process. It is of the utmost importance that pre-processing is carried out correctly so as to enhance the detection accuracy of any AD classes. Additionally, when it comes to pre-processing PET images, registrations, motion corrections, delineation of volume interest, partial volume correction, and kinetic modelling are also required. Generally, registrations and bias corrections are executed before feature extraction for PET. Similarly, pre-processing is essential in Tractography, which entails a general description of the motion in the DTI modality, followed by FSL and EDDY current correction.

Table 3 outlines the pre-processing steps which must be completed prior to extracting features. The biomarkers detailed in the table elucidate their part in detecting AD and its associated classes. It is essential to determine which biomarkers are most pivotal in the detection methods of AD. In order to understand the uses of the different imaging modalities and what are the common data source which is taken for AD Detection are discussed. Table 4 elaborates on the application of the repository and biomarkers for AD detection in binary, multiclass, and one-class classifications.

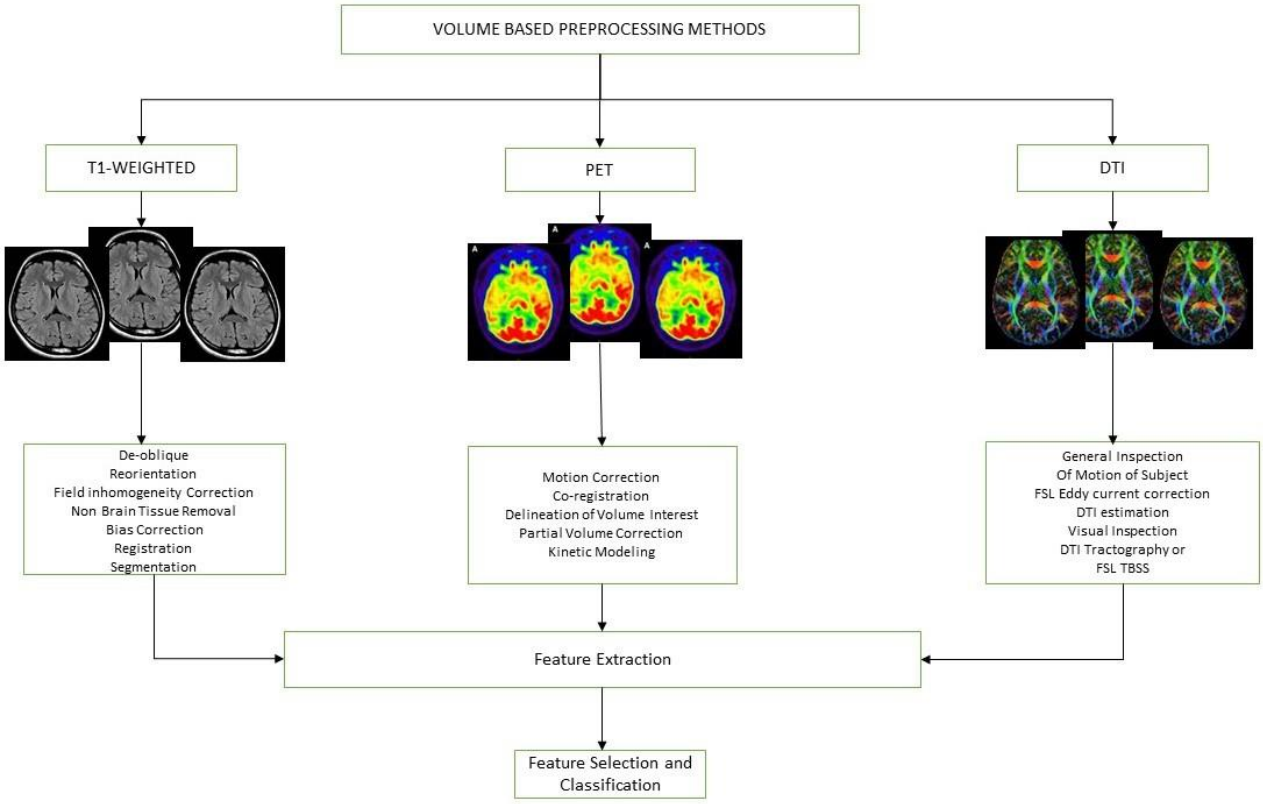

Figure 2. Volume Based Pre-processing Methods for different Biomarkers.

Table 3. General Pre-processing Methods used in Structural Biomarkers.

S.No	Preprocessing Methods	Description
1	De-Oblique	De-oblique pre-processing is a technique used to reduce the effects of perceptive distortion. This technique works by rotating the images, reducing any perspective distortion and allowing for easy interpretation.
2	Field Inhomogeneity Correction	This pre-processing method also helps in the removal of artifacts from the data. It helps remove the intensity of tissues not in the observed mean intensity.
3	Bias Correction	This method is used to correct the non-uniform shading in an image. In this technique, the low pass filter is used to remove the high frequency.
4	Non Brain Tissue Removal	This is the pre-processing of the removal of non-brain tissue from the captured image. Non-brain tissue removal is accomplished through a combination of techniques, including segmentation, morphological operations, and filtering.
5	FSL and Eddy Current	This FSL contain the approach to quantify the temporal dynamic of the Image, which is based on Fourier Transformation. Eddy Current pre-processing is used to identify the small changes in an image through the Eddy Current flows at the time the image is recorded.

Table 4. Identification of usability of AD biomarkers with reference to accuracy achieved in the different classifications.

S.No	Authors	Data Base	Year	Biomarker	Binary Class	Multi Class	Accuracy
1	[34]	OASIS DATABASE	2018	MRI	√	X	92% AD
2	[35]	HAVARD MEDICAL SCHOOL	2019	MRI	√	X	Multiclass 95.23

Table 4. *Cont.*

S.No	Authors	Data Base	Year	Biomarker	Binary Class	Multi Class	Accuracy
3	[36]	ADNI	2017	MRI	X	√	AD vs. NC 98.88
4	[37]	ADNI	2020	MRI	X	√	AD vs. NC 99.20
5	[38]	OASIS DATABASE	2019	MRI	√	√	92.85% AD
6	[39]	ADNI	2020	MRI	√	√	99% AD
7	[40]	OASIS	2013	MRI	√	X	90% AD
8	[41]	ADNI	2021	MRI	√	X	92% AD
9	[18]	ADNI	2019	BIO SPECIMEN	√	X	99.67% AD
10	[42]	GERAD1	2017	GENETIC	X	X	90% AD
11	[43]	ADNI, AIBL	2014	MRI	√	X	MCI to AD.86%
12	[44]	ADNI	2019	CSF, PET	√	X	CSF Abeta-42, Neuronal Pentraxin decreased
13	[45]	DIAN	2019	CSF	X	√	NLF rate changed to AD
14	[46]	ADNI	2013	AD, MCI	X	X	92% AD
15	[47]	ADNI	2013	CSF, MRI, PET	√	X	Misclassification 41.3% to 28.4%
16	[48]	ADNI	2019	PET, CSF	X	X	94% AD
17	[49]	ADNI	2003	FDG, PET	√	X	Detected AD
18	[50]	ADNI	2007	MRI	√	X	AD 86.8
19	[51]	ADNI	2017	MRI	√	X	AD-HC: 94.11%, MCI-HC: 83.77%
20	[52]	NICDS, ADRDA	2000	MRI	X	X	88.6% AD
21	[53]	PRIVATE HOSPITAL DATA	2006	MRI	X	X	MCI to AD 86%
22	[54]	PRIVATE Data Set	1993	CT, MR	X	X	91% AD
23	[55]	PRIVATE Data Set	2010	GENETIC	√	X	28 Score in AD
24	[56]	PRIVATE	2011	CLINICAL	X	X	CDE, MMSE score is high in AD
25	[57]	PRIVATE	2009	MRI	√	X	AD, HC
26	[58]	NINCDS-ADRDA	1997	MRCLINICAL	X	X	95% AD
27	[59]	PRIVATE	1996	CLINICAL	X	X	predicted AD
28	[60]	ADNI	2013	PET	√	X	64% MCI
29	[61]	ADNI	2020	MRI	√	X	96.8% AD vs. CN
30	[62]	OASIS Data Set	2020	MRI	√	X	97.75% AD vs. CN
31	[63]	MNIST Data Set	2021	MRI	√	X	AD vs. Healthy 96.8
32	[64]	ADNI	2021	MRI	√	X	AD vs. NC 98.73
33	[65]	OASIS	2022	MRI	√	X	AD vs. NC 98.99
34	[66]	ADNI	2022	MRI	√	X	AD vs. NC 85.12
35	[67]	OASIS	2023	MRI	√	X	AD vs. NC 95.48
36	[68]	ADNI	2023	MRI	√	X	77% ADNI, 76% OASIS

Several studies have been reviewed in Table 4 to create diagnostic models for AD by analysing various data types, including brain imaging (MRI, CT, PET), biomarkers, genetic data, and clinical data. The accuracy of these models varies depending on the type of data and classification task used, as indicated in the table. MRI is the most frequently used modality for diagnosing AD, followed by PET and CSF biomarkers. Some studies also used genetic data and clinical assessments for diagnosis. The classification tasks also varied, ranging from binary (AD vs. CN) to multi-class (MCI, AD, CN), and the accuracy ranged from 86% to 99.67%. Overall, the table highlights the diversity of approaches and data types used in AD diagnosis research and shows ongoing efforts to develop accurate models for early and accurate diagnosis of AD. Additionally, a multimodality approach may yield more accurate and reliable results in the detection of AD and its subtypes. Figures 3 and 4 describes the usability of the different biomarkers in different classes the referenced article.

Using biomarkers is a dependable means of detecting AD. By employing both handcrafted feature extraction methods and Deep Learning techniques to process these bio markers, we can better understand the role that Automatic pipelines (Handcrafted Feature Extraction Methods) play in detecting AD and its various stages. In Section 3, we highlight the significance of handcrafted feature extraction methods and their importance in the field of AD and the detection of AD.

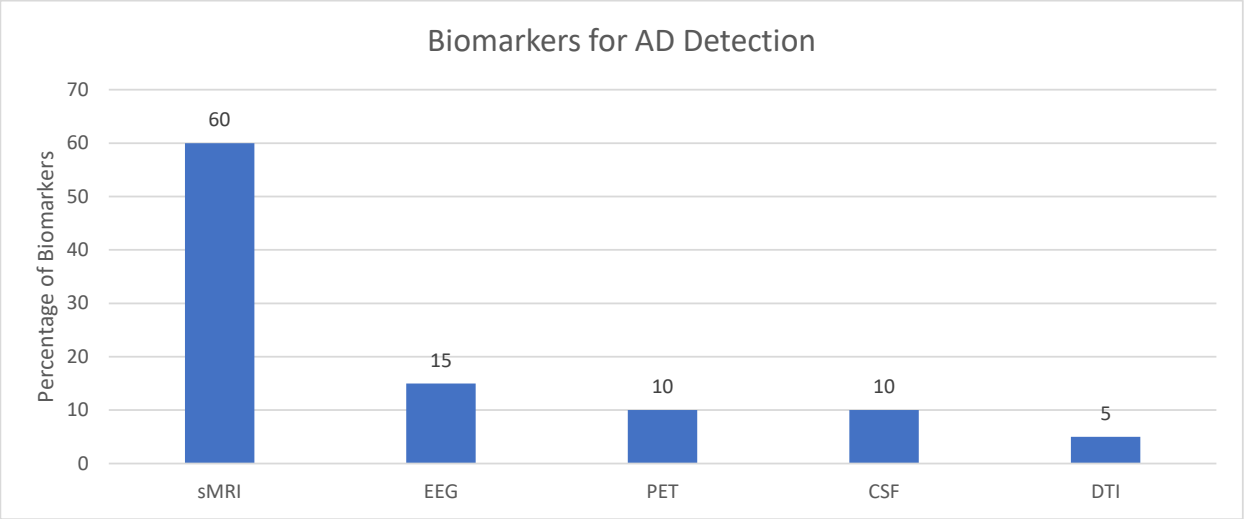

Figure 3. Description of most commonly used biomarkers for detecting AD.

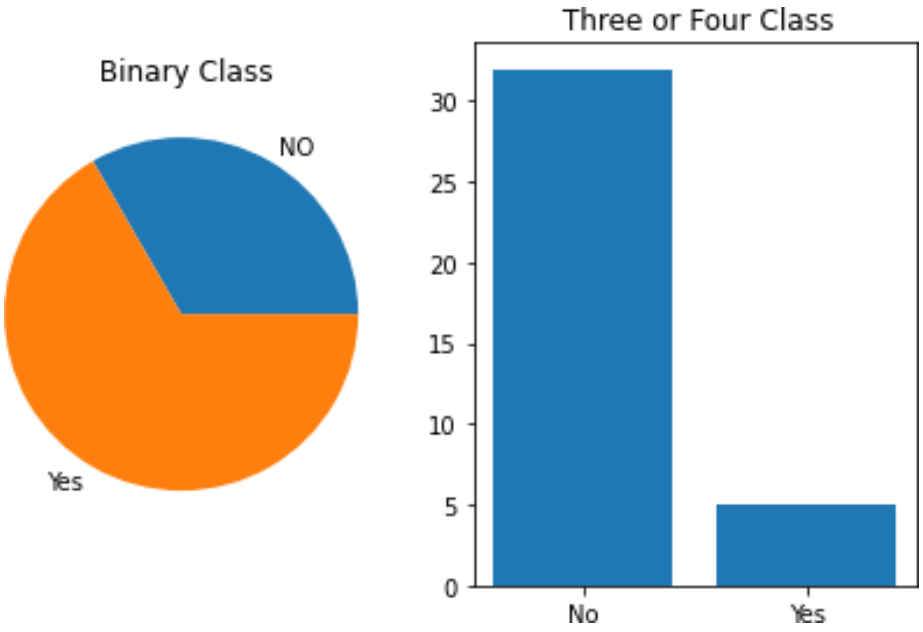

Figure 4. Analysis of binary class and multi class for AD and its stages detection.

3. Automated Pipeline

Automated Pipelines are techniques where various algorithms are packaged up to form the different pre-processing and operations for the neuro regions. Researchers commonly use Magnetic Resonance Imaging (MRI) for early and precise detection of structural and functional brain tissue abnormalities. These pipelines, such as Free Surfer, SPM, AFNI, FSL, DIPY, NIPYPE, AAL, fMRIPrep and Ants, are used to assess the different neuro regions of the brain. Through these methods, various areas can be identified by means of Handcrafted feature extraction techniques, which have significantly enhanced AD detection and treatment [69]. These strategies are based solely on image processing methods. They can distinguish the characteristics of AD patients and their subtypes from the Image Data Set [70]. These Automated tools are generally based on Image data sets which have 3D or 2D attributes. These automated tools are used for rectifying image abnormalities and recognizing significant features [71]. These methods require a large amount of computing power. Therefore, these approaches can better compute the features from the limited data set, including the areas, volumes, and thicknesses of the cortex at different stages of AD

and its subtypes [72]. Based on these computed features, a classification model can be generated to classify the classes. The classification of these methods is detailed below in Figure 5.

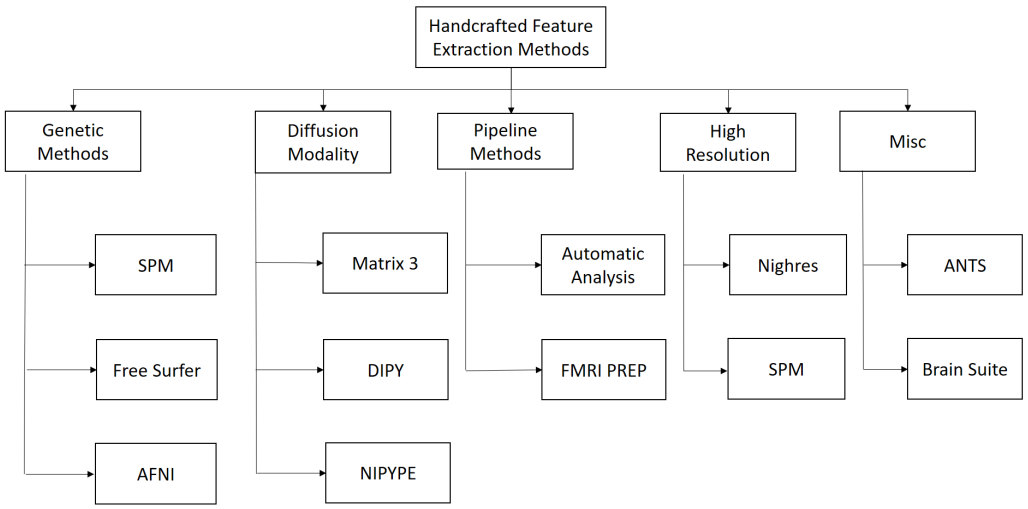

Figure 5. Organization for Handcrafted Feature Extraction Methods (Automated Pipeline methods).

Many of these techniques are frequently employed to analyse the grey matter and white matter in the brain that has the biological disorder. In the brain, several factors can help differentiate a deficient brain from a normal brain. Using this analysis, researchers looked at Free Surfer, SPM, and FSL, which are designed to better detect AD and its subtypes. Table 5 explains the automatic pipelines used for detection and their effectiveness.

Table 5. Analysis of the Automatic Pipelines for AD detection in the Single, Binary and Three or more class classification.

S.No	Author	Data Set	Year	Automated Pipelines	Multiple Class	Binary Class	Accuracy
1	[73]	ADNI	2016	SPM12 and VBM	X	√	AD vs. HC 99.93
2	[74]	NCRD	2020	SPM12	X	√	AD vs. CN 93.33
3	[75]	ADNI	2019	SPM12 and FSL	X	√	HC vs. mAD, $p < 0.001$, $p < 0.001$
4	[76]	ADNI	2019	ANT Tool and SPM12	X	√	AD vs. HC 98.33
5	[77]	ADNI	2016	FREE SURFER	X	√	MCnc vs. MCic = 73.91
6	[78]	ADNI	2015	FSL	X	√	CN vs. AD = 0.82
7	[79]	Private	2018	SPM	X	X	CSF parameter, AP ($p = 0.03$)
8	[77]	ADNI	2016	NON-Conventional	X	X	AD = 79.9%
9	[30]	ADNI	2018	FSL, ANOVA	X	X	Only CSF and Tau Comparison
10	[80]	ADNI	2017	SPM8	X	√	AD vs. NC = 88, AD vs. MCI = 75
11	[81]	ADNI	2018	FREE SURFER	X	√	MCI to AD $p = 1.07 \times 10^{-5}$
12	[82]	ADNI	2016	Verbal Learning Data	X	√	AD vs. MCI = R = 0.43, R = 0.050
13	[83]	ADNI	2017	FREE SURFER	X	X	NA
14	[84]	ADNI	2017	NON Conventional	X	X	NC to EMCI = 0.45
15	[85]	ADNI	2017	NEURO QUANT, NEURO READER	X	√	AD vs. MCI = 0.69
16	[55]	Private	2010	IBM SPSS	X	X	AD = 0.90
17	[86]	ADNI	2015	FSL	X	X	AD vs. NC = 90.2
18	[87]	ADNI	2017	FSL	X	√	NC vs. AD= 95
19	[88]	ADNI	2013	FSL	X	√	CN vs. AD = 90%
20	[89]	Klinikum Rechts-deisar	2012	FSL	X	√	AD vs. MCI = 95
21	[90]	ADNI	2012	SPM	X	√	AD (R = 0.51, $p = 2.2 \times 10^{-1}$)
22	[91]	ADNI	2017	Free Surfer	X	√	mAD vs. HC = 96.51
23	[92]	ADNI	2017	MMSE	X	X	NA
24	[93]	ADNI	2017	FSL	X	X	Changes in Hippocampus observed in EMCI
25	[94]	Private	2016	Free Surfer	X	√	AD ($p < 0.05$)

Table 5. *Cont.*

S.No	Author	Data Set	Year	Automated Pipelines	Multiple Class	Binary Class	Accuracy
26	[95]	ADNI	1920	FSL	X	X	AD = 0.98
27	[96]	ADNI	2016	MIPAV, SPSS	X	X	AD = 0.001, $p < 0.005$
28	[97]	ADNI	2023	SVM	X	√	AD vs. CN 0.92
29	[98]	ADNI	2023	Free Surfer	X	√	Changes in Hippocampus
30	[99]	ADNI	2023	Computer Assisted	X	√	AD 89%
31	[100]	Amsterdam Dementia Cohort (ADC)	2022	Free Surfer	X	√	AD vs. NC 98%
32	[101]	ADNI	2022	Free Surfer	X	√	EYO and white matter corelation
33	[102]	ADNI	2022	Free Surfer	X	√	Cortical Thickness Calculated

According to Table 5, ADNI is considered one of the most valuable open-source data sets for AD detection. The feature extraction method appears to work best for the free surfer.

With the FSL, FREE Surfer, over 95 percent accuracy was achieved in identifying AD, and its subtypes, shown in Figure 6. In multi-class analyses, there was a lack of accuracy when detecting AD at different stages, but in binary classifications, the accuracy was higher. Therefore, these automatic pipelines also include methods for identifying the various types of diseases using multi-modality approaches. These approaches involve the fusion of images that are registrations as well as the fusion of features in order to detect AD effectively.

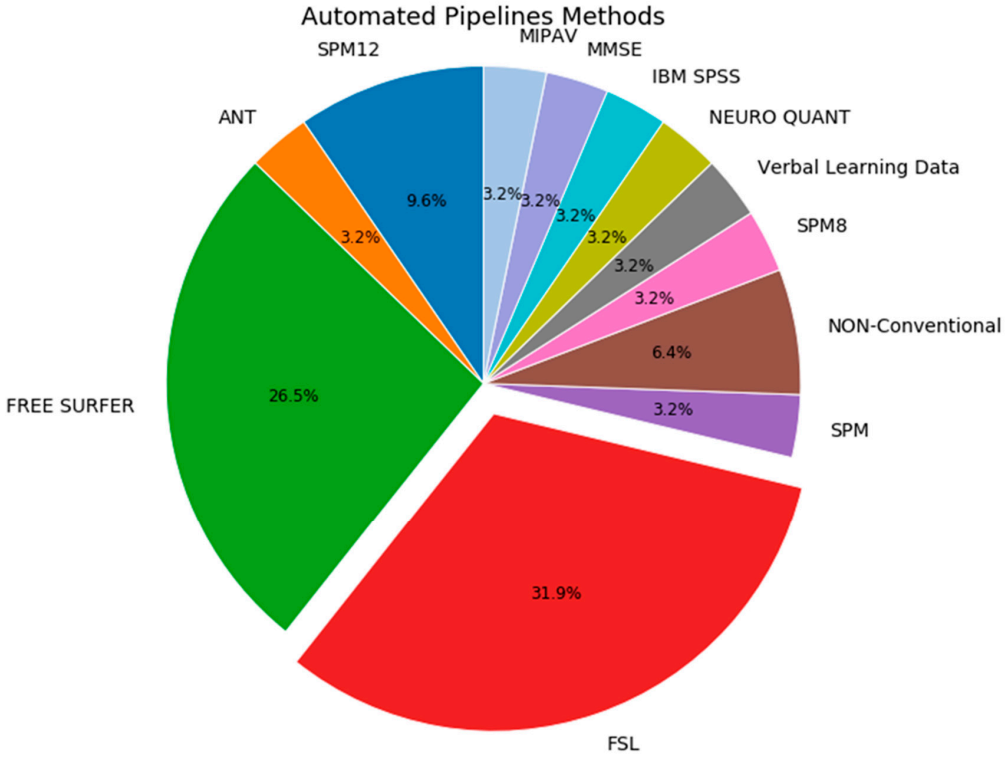

Figure 6. Automatic Pipelines for AD Detection.

Fusion Based Methods

Image registration is the act of adjusting two or more images of the same modality or object to one another, which have the same reference frame. The purpose of image registration is to identify the transformation that best fits the images, so that they can be compared or amalgamated for study. Image registration is one of the most significant steps of fusion, which helps to improve the detection rates of AD and its subtypes in Multimodality. Registration is the process of transforming data into a single coordinate system [103] Figure 7. Image fusion is the process of combining multiple Images of the

same modality or object into one image that contains all the data from the initial pictures. Image registration is a key factor in image fusion, as it ensures the input images are aligned before they are blended. By aligning the images, image registration decreases the effects of misalignment and distortion due to varied viewing angles, camera positions, or other aspects. This alignment can combine the images through several image fusion techniques, such as weighted averaging, maximum likelihood estimation, or multi-resolution analysis. Image registration is a critical step in many image-processing applications, including remote sensing, medical imaging, computer vision, and robotics. It is used to improve the accuracy and quality of image analysis, as well as to enhance the visualization and interpretation of image data. MRI (Magnetic Resonance Imaging) is a medical imaging technique that uses a strong magnetic field and radio waves to generate images of the body. MRI is commonly used to visualize soft tissues, such as the brain, spinal cord, and joints. The two different modalities are aligned with respect to the template image to ensure that the images are in the same spatial orientation and have the same resolution. After that, the specific ROI contains information of interest for further analysis. Then region matching is the process of identifying and aligning the corresponding regions of interest in multiple MRI images. This is important for comparing the same region across multiple images, such as tracking changes over time or between different patients. Then after ROI, a directional vector is calculated, a representation of the orientation and direction of an object or region within an MRI image. Directional vectors can be used to describe the orientation of structures such as nerves, blood vessels, or muscle fibres. Geometric transformation refers to the process of transforming the MRI image from one spatial orientation to another, such as rotating, scaling, or translating the image. Geometric transformation is used to align the MRI images, match the ROIs, and adjust for any distortions or variations in the image. Resampling refers to the process of changing the resolution or size of the MRI image. Resampling is necessary when geometric transformation is applied to ensure that the resulting image has the desired resolution and size. In summary, the steps involved in MRI image processing, from modality to resampling, include acquiring MRI images, aligning the images, identifying regions of interest, matching the ROIs, using directional vectors to describe the orientation of structures within the images, applying a geometric transformation to align the images and adjust for any distortions, and resampling the images to ensure the desired resolution and size. These steps are crucial for the accurate analysis and interpretation of MRI data in various medical applications.

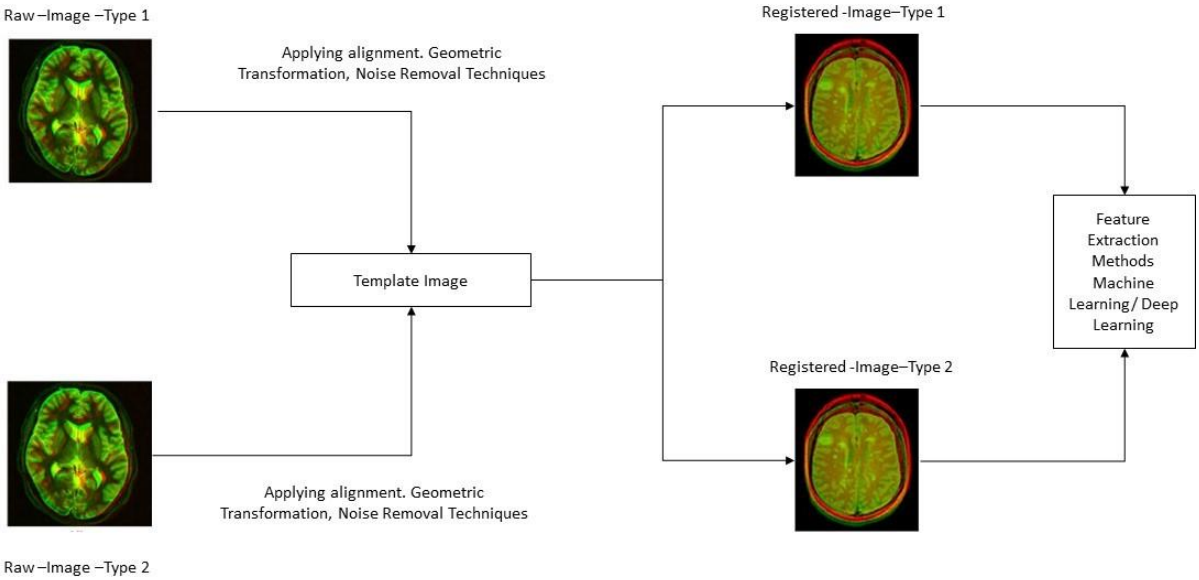

Figure 7. Before and After MRI image Registration [104].

In medical imaging, registration is used to combine data from several modalities, such as computed tomography (CT), magnetic resonance imaging (MRI), SPECT, and PET. Combining images reduces data while creating easier-to-process images more effective for detecting AD and its stages [105]. Hence, these registrations of the images contain the steps mentioned in Figure 8. This enables the creation of more appropriate models for detecting AD and its various subtypes. In this way, the detection rate of AD and the corresponding classes can also be improved. A number of factors need to be considered when choosing an appropriate registration method [106]. Due to the diversity of image registration tasks, there is no universal method. In order to extract the hybrid set of features, it is best to use the Hit and Trail method, which is both rigid and non-rigid. This approach also has a high success rate in detecting AD. The detailed analysis of the fusion and registration method is described in Table 6.

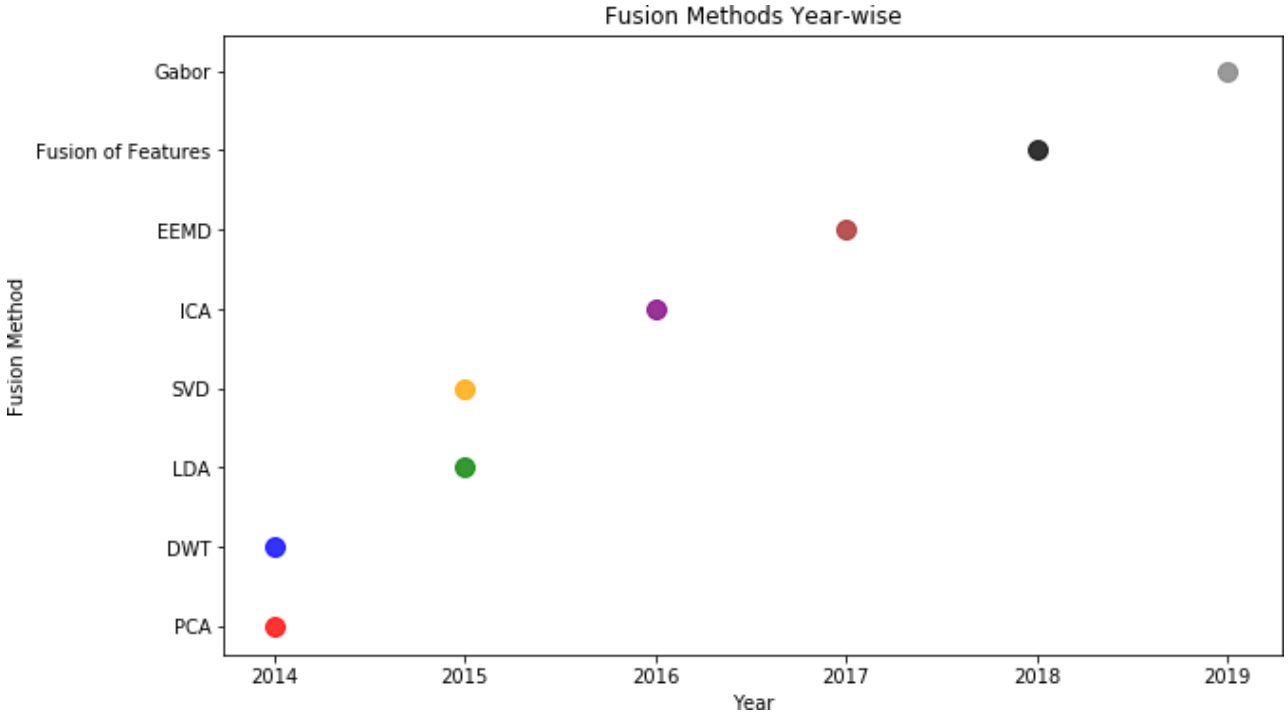

Figure 8. Fusion of Features Year Wise.

Table 6. Fusion and Registration methods for AD and Subtypes Detection.

S.No	Author	Date Set	Year	Subjects	Fusion Methods	Results	Feature Level Fusion	Pixel Level Fusion
1	[107]	ADNI	2014	ADNI AD, NC	fusion of classifiers	AD vs. NC = 92%	√	X
2	[108]	ADNI	2014	MRI and (FDG-PET), AD 204, MCI 76, 128 MCI, 101 NC	fusion of classifiers	AD vs. NC = 93.35%	√	X
3	[109]	ADNI	2016	93 AD, 204 MCI 76 MCI, (MCI-C), 128 MCI (MCI-NC), and 101 NC	Multi modal fusion MRI-PET	AD vs. NC, MCI vs. NC 96.93 and 82.75	X	√
4	[110]	ADNI	2016	CT and PET	Multispectral fusion for CT and PET Modalities	Multispectral fusion shows the Promising result	X	√
5	[111]	ADNI	2017	44 CN, 45 MCI and 45 AD, LCCN 52, 97 MCI, and 13 AD	Label Fusion	automatic segmentations	X	√
6	[112]	ADNI	2017	147 AD, 75 MCI and 35 (NC).	Multi-Modality Fusion	AD vs. NC 98 %	X	√
7	[113]	PRIVATE	2018	411 AD and 540 NC	Multi fusion	Effective ness of ITL was more	√	X
8	[114]	ADNI	2019	AD CT, MRI and SPECT	Fusion of features	Fusion approach of NCST and NSst provides better	√	X

Table 6. *Cont.*

S.No	Author	Date Set	Year	Subjects	Fusion Methods	Results	Feature Level Fusion	Pixel Level Fusion
9	[115]	ADNI	2019	AD	Fusion of Imaging Modalities	MRI + PET modality acceptable ACC	X	√
10	[116]	ADNI	2018	60 HC, 60 MCI, 60 cMCI, 60 AD	Fusion of Features	Modalities based Fusion	√	X
11	[117]	ADNI	2021	CT, MR	Multispetial Fusion	AD 702 ACC	X	√
12	[118]	ADNI	2021	419 CN, 473 MCI, 140 MCI	Decision Fusion	84.73 ACC	√	X
13	[119]	ADNI	2021	AD, CN, EMCI, LMCI	Decision Level Fusion	92.6 ACC	√	X
14	[120]	ADNI	2021	MRI, MCI, AD	Decision Level Fusion	80.9 ACC	√	X
15	[121]	ADNI	2021	AD, MCI	Multimodal Fusion	MRI + PET = 0.97 ACC	X	√
16	[122]	ADNI	2021	AD	Feature Level Fusion	90% ACC	√	X
17	[123]	ADNI	2021	AD	Adversely Hyper-graph Fusion	93.0 ACC	√	X
18	[124]	ADNI	2021	95 AD, 160 MCI	Image Fusion	94.11 ACC	X	√
19	[125]	ADReSS	2021	AD	Late Fusion	84–90 ACC	√	X
20	[126]	Private Data	2020	29 HC, 27 MCI	Attribute Level Fusion	94% HC vs. MCI	√	X
21	[127]	Private Data	2020	AD	Auto phagosome-lysosome fusion	Pathological intervention	X	√
22	[128]	ADNI	2023	MRI, PET and DTI	Feature Level Fusion	99% AD	X	√
23	[129]	ADNI	2023	MRI, PET	Feature Level Fusion	AD vs. CN 93.3	X	√

Multi modal imaging techniques typically incorporate hybrid level features as part of the detection process, primarily for the detection of MCI-AD [130], In comparison with feature level fusion and image level registration, both have acceptable accuracy for detecting Alzheimer's Subtypes. These steps constitute the process of pre-processing for the multimodality approach to detecting AD sub types. These features can be used in machine learning to generate models and this will classify the different types of AD. However, in Deep Learning no specific features are required. In addition, they can extract features and classify different types of AD. In order to bring more clarity, a systematic analysis is done in the Figure 8.

The Table 6 provides information about various fusion methods used for analysing medical data sets related to AD and Mild Cognitive Impairment (MCI). The fusion methods used in the studies include Adversal Hypergraph Fusion, Anchostic Fusion, Attribute Level Fusion, Autophagosome Lysosome Fusion, Decision Fusion, Feature Level Fusion, Fusion of classifiers, Fusion of Features, Fusion of Imaging Modalities, Gating Mechanism, Label Fusion, Multimodal Fusion, Multi-Modality Fusion, Multispectral fusion, Multispatial Fusion, and Multifusion of algorithm. The data sets used in the studies include ADNI, ADReSS, and Private Data. The years of the studies range from 2014 to 2021. The subjects in the studies include AD, CN, EMCI, LMCI, MCI, HC, and cMCI. Some studies have used multiple subjects. The accuracy achieved by the fusion methods ranges from 88% to 97%.

4. Machine Learning Methods

Machine learning and deep learning are used in research to categorize and evaluate patients, predict treatment outcomes, and assess risks. Researchers used deep learning and machine learning methods to classify neurodegenerative disorders caused by AD and their stages through imaging-based detection. Automatic pipelines utilize feature extraction techniques which are based on a variety of biomarker methods. As a result of Deep Learning, it can preprocess the biomarkers itself and extract the features, as well as develop a model to identify AD and its stages, SVM, ANN, and DNN are some of the most commonly used classification techniques for AD. The following table provides a brief of common classification methods. Therefore, researchers and scientists in the field of medical image processing commonly use these methods to detect AD at various stages. There are

also the various classification methods available which can also provide the subsequent analysis in the field. Figure 9 shows the different classification methods which used in the field of Alzheimer.

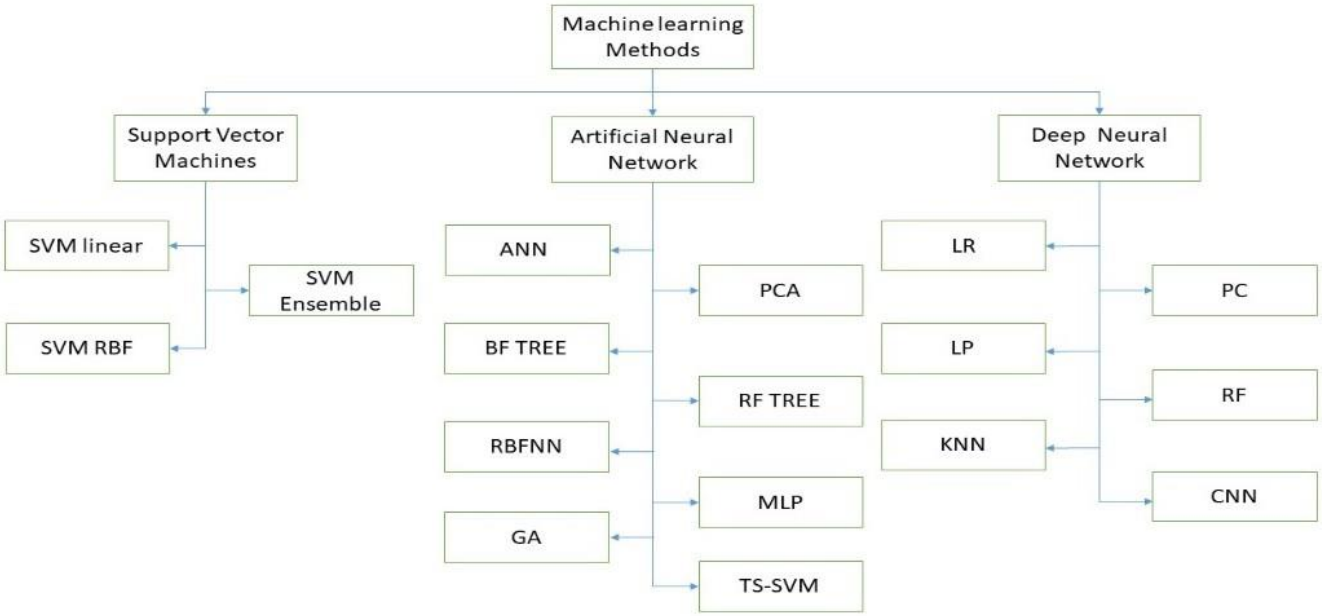

Figure 9. Classification methods based on machine learning.

In the detection of AD, these classification methods are widely used. A proper and systematic analysis of the Alzheimer detection is conducted in order to understand the significance of which methods provide the best classification of the different stages in Table 7.

Table 7. An analysis of the different classification methods for AD.

S.No	Article	Data Base	Year	Modality	F E Methods	Accuracy	Multi Class	Binary Class
1	[131]	AD, CN	2007	fMRI	ROI	81	X	√
2	[132]	CN, FTD	2008	MRI, PET	VBM	93	X	√
3	[133]	CN, AD	2009	sMRI	Morphometry	89	X	√
4	[134]	CN, AD	2010	SPECT	ROI	89	√	√
5	[135]	CN, AD	2012	sMRI	VBM	82	√	√
6	[136]	CN, MCI	2013	sMRI	SAE	89	X	√
7	[137]	CN, AD	2013	sMRI	Voxel	87	X	√
8	[138]	CN, MCI	2014	sMRI	ROI	91	X	√
9	[139]	AD	2017	sMRI	SVM	74	X	√
10	[140]	MCI CN	2019	sMRI	CNN	98	X	√
11	[141]	AD CN	2019	sMRI	CNN	97.52	√	√
12	[142]	AD ADNI	2009	MRI	SVM	97.13	X	√
13	[143]	ADNI	2015	MRI, PET	PCA	91.4	X	√
14	[144]	ADNI	2016	FMRI	Google Net	100	X	√
15	[145]	ADNI	2014	MRI	SVM	98.8	X	√
16	[146]	ADNI	2019	MRI	CNN, RNN	98	X	√
17	[147]	ADNI	2019	MRI	2D Convolution Network	98	X	√
18	[148]	ADNI	2019	MRI	3D CNN	94	X	√
19	[149]	EEG, ADNI	2019	MRI	Convolutional96 Deep Boltzmann Machine	96	X	√
20	[150]	ADNI	2020	sMRI	ADNet-DA	52.3	X	√
21	[151]	OASIS	2020	sMRI	12-Layer CNN	97.75	X	√
22	[152]	ADNI	2020	sMRI	Hog-CNN	98	X	√
23	[153]	ADNI	2022	sMRI	Res-NET, DenseNET	97	X	√
24	[154]	ADNI	2023	sMRI	JD-CNN	94.20	X	√
25	[155]	ADNI	2023	sMRI	RNN, Neural Network	90	X	√

Based on Table 7, The table shows the relation between the year and the feature extraction method accuracy in MRI studies. The accuracy is expressed as a percentage and ranges from 52% to 100%. The data includes various feature extraction methods such as

ROI, VBM, Morphometry, SAE, and CNN, among others, and covers a period of 17 years, from 2007 to 2023. From the bar chart at Figure 10, we can see that there are some notable trends in the accuracy of different feature extraction methods over time. For example, SVM and VBM had high accuracy in the earlier years but declined over time. In contrast, CNN-based methods had lower accuracy in the earlier years but have since become more accurate, with some achieving near-perfect accuracy in recent years. Overall, this data suggests that the accuracy of feature extraction methods in MRI studies has been steadily improving over time, with newer, more advanced methods showing promise for achieving even higher accuracy.

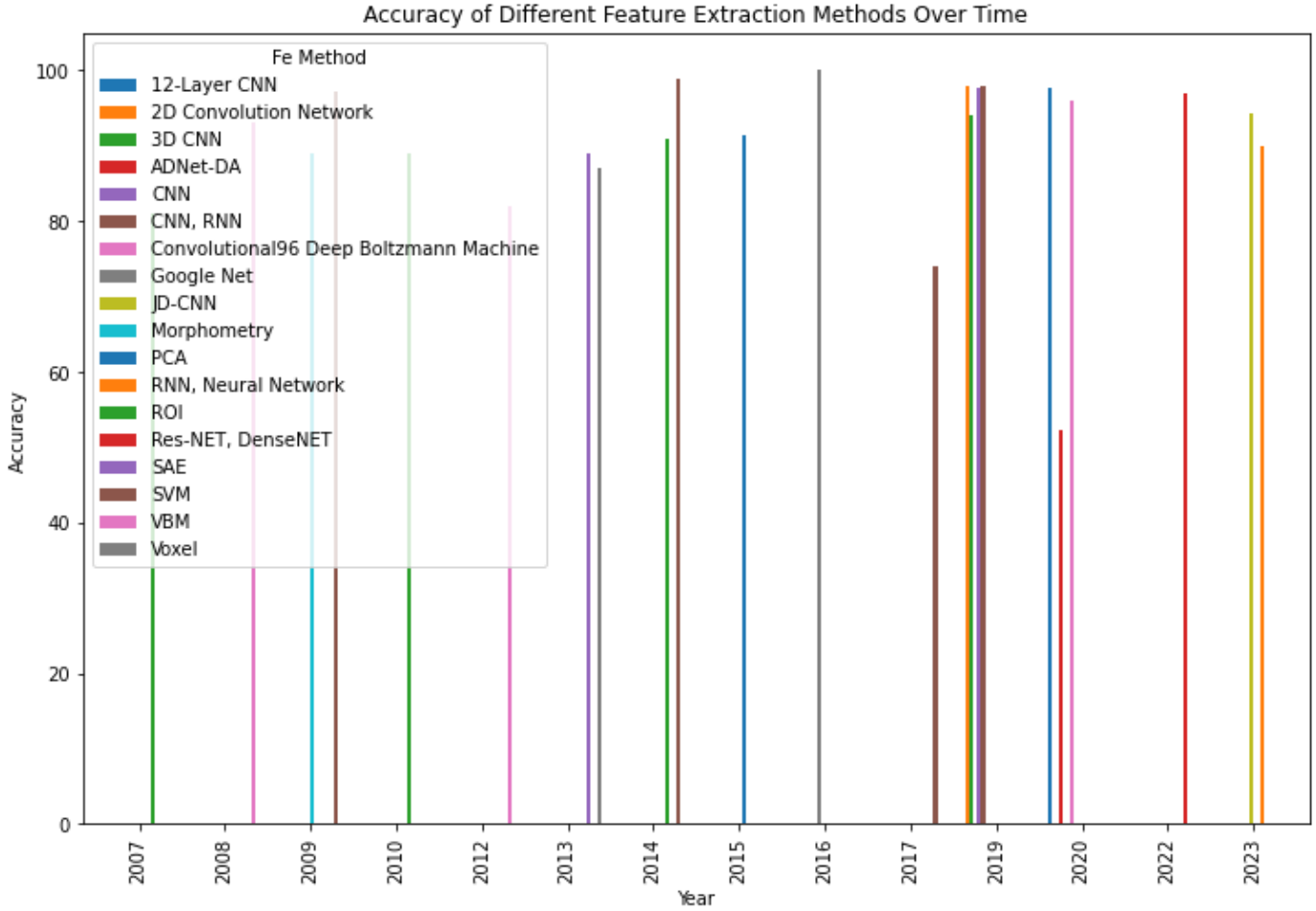

Figure 10. Feature Extraction Methods, year wise analysis.

However, it is worth noting that the accuracy of different methods can vary depending on the specific application and the quality of the data being used. Convolution neural networks provide the most accurate classification of ADs and their classes. The accuracy of the binary class is higher than that of all other types of AD. In the multi class classification of AD, the SVM outperforms other methods. However, there is still room for improvement in the detection of AD classes. Currently, the level of accuracy in the multi class is unacceptable. In order to classify and analyze MCI's sub classes, Deep Learning and Machine Learning methods still require improvement. According to a recent study, machine learning is more effective at detecting AD than deep learning and works on smaller data sets.

5. Discussion

Identification of structural differences in the brains of patients with neurological conditions versus healthy brains, neuroimaging is the most effective tool. The technique of analyzing biomarkers can provide both 2D and 3D structural information, which is

particularly helpful in understanding the dimensions of cortical regions affected by AD. Biomarkers such as Diffusion Tensor Imaging (DTI), which measures the amount of water molecules and fibers in various areas of the brain at different stages of AD, are useful for assessing brain conditions. Other biomarkers like PET modality, CSF analysis, and genetic biomarkers can also be used to differentiate between healthy brains and those with AD with good precision. However, MRI and PET biomarkers are the most commonly used and have an acceptable level of accuracy in detecting AD. Classifications are usually done at either a binary or multi-class level, with binary class accuracy being greater than 95%, but multi-class accuracy being less than 85%. While the accuracy of accessing from AD to CN and MCI to CN is acceptable, going deeper into stages shows unacceptable accuracy at MCI, AD to MCI.

After the Analysis of biomarker level we organized the systematic review in Automatic pipelines for detection of AD and there stages. Various studies used automated pipelines to classify patients with AD from healthy controls (HC) or mild cognitive impairment (MCI). The studies used different datasets, software, and classification schemes. Most studies reported high accuracy in binary classification, but there is a need for improvement in multiclass classification. Several studies reported significant differences in brain regions or biomarkers between AD and HC/MCI. Some studies used non-conventional methods or proprietary software, which may limit reproducibility. Overall, the studies highlight the potential of automated pipelines for AD classification and biomarker discovery but also indicate the challenges and limitations of this approach. Automated pipeline approaches like Free Surfer and FSL (FMRIB SOFTWARE LIBRARY) are additionally popular for the detection of AD and its stages. Generally, these techniques are more effective when the data sample is small. In general, the AD dataset is not very large for a particular population. These strategies employ multiple preprocessing techniques that are arranged in a pipeline for classifying subjects. The three or four classes of classification or the subgroups of MCI, require more improvement than the other categories.

Various studies that have used fusion techniques to improve the accuracy of AD diagnosis. The review utilized different data sets, including ADNI and private data, and different modalities such as MRI, PET, CT, and SPECT. Some analysis used decision-level fusion, where the results of different classifiers were combined, while others used feature-level fusion, where different features from different modalities were combined. There were also review that used both feature-level and decision-level fusion. The results showed promising accuracy rates ranging from 80.9% to 98%, depending on the fusion technique used. The combination of multiple modalities or features can significantly improve the accuracy of diagnosis, as demonstrated by the studies in the table. As more advanced deep learning techniques continue to be developed, it is likely that further improvements in diagnosis accuracy will be achieved in the future. However, it is important to note that more research is needed to validate the results of these studies and ensure that they can be applied in clinical practice. The result of fusion and registrations validation are totally depend upon the ml and dl methods. The details study of ML and DL methods where made. Various analysis conducted on the application of machine learning techniques for the diagnosis of AD using different imaging modalities such as MRI, PET, SPECT, and fMRI. The review also use different methods such as ROI, VBM, SVM, CNN, PCA, and deep learning networks for feature extraction and classification. The accuracy of the classification varies between them, with some achieving high accuracy rates above 90%, while others have lower accuracy rates. The fusion of multiple modalities and the use of deep learning networks, such as CNN and RNN, have shown promising results in achieving higher accuracy rates. Most of the studies have also applied the classification models to both binary and multi-class classification tasks. This review highlight the potential of using machine learning techniques for the early and accurate diagnosis of AD.

6. Future Directions and Challenges

AD is a growing concern worldwide, affecting millions of people and their families. Early detection of the disease is crucial for effective treatment and management, but current diagnostic methods can be costly and invasive. However, a recent review has uncovered exciting findings that could revolutionize the detection of AD. The review recommends the use of Handcrafted Feature Extraction, Fusion, and Machine/Deep Learning methods to detect AD and its stages. This approach combines the strengths of multiple techniques to create a more accurate and reliable diagnostic tool. As a highly skilled assistant specializing in digital marketing, I understand the importance of staying informed about the latest developments in technology and healthcare.

- Biomarker methods achieve high accuracy in binary classification for AD detection, they fall short in multi-group classification, indicating the need for improvement. To address this, handcrafted feature extraction and classification through Machine Learning Approaches are suggested. Multi-modality approaches require proper registration and preprocessing of the biomarker to overcome specific issues.
- In the recommendations, such as the Handcrafted Feature Extraction method, Fusion methods, and Machine/Deep Learning methods, for detecting AD and various classes of AD. Previous research has been conducted on Handcrafted Feature Extraction methods in binary or single modes to detect AD. However, fusion approaches have not been as successful researched or adopted in multi-modality and levels of investigation for AD detection is required. To improve fusion approaches, different image modalities can be used. Additionally, there have been significant advances in both conventional and non-conventional approaches to feature extraction and categorization strategies.
- Two approaches using Machine Learning Deep Learning can be employed to develop a model for detecting AD. The first method involves creating a model based on features, while the second method extracts features to build a model for detecting AD and their classes. Both of these methods have been used in several studies to detect AD. While binary classes have been accurately identified, non-conventional approaches are needed to improve accuracy for more than two classes. Structural bio markers in handcrafted feature extraction methods have shown promising results, but there is potential for multi-modal improvement in the classification of AD patients. Machine Learning approaches, particularly SVM, have enhanced the accuracy of classification and are increasingly utilized to automatically detect AD and its classes.

7. Conclusions

According to the results, the identification of AD and its different stages greatly relies on the use of structural MRI. Other methods like DTI, PET, and FLAIR can also be effective in detecting AD. These bio markers allow for the analysis of multiple classes and the use of various approaches to identify the different phases of AD, including CN vs. AD, MCI vs. AD, EMCI vs. AD, LMCI vs. AD, AD vs. LMCI vs. EMCI, and CN vs. AD vs. MCI. In addition, feature extraction methods that were manually imparted, which yielded the most suitable and optimal set of features in order to develop an improved model of AD and its various categories. The handcrafted feature extraction method demonstrated superior accuracy in identifying binary classes compared to models that identified multiple classes. The prominent techniques for feature extraction and 3D medical data preprocessing are primarily FREE Surfer and FSL.The research study aims to enhance the precision of identifying AD and its classes in both binary and multi-class classification. Fusion-based methods demonstrate substantial accuracy in feature-level and multi-modality level. The most effective approach for identifying AD and its classes is Machine Learning and Deep Learning. The research study reveals that Deep Learning Methods are more accurate in detecting AD and its classes. However, deep learning methods require a larger dataset compared to handcrafted feature extraction methods for the detection of diseases.

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