# Predicting Alzheimer's Disease Progression Using Multimodal Longitudinal Analysis: A Machine Learning Approach


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Biomedical Sciences

Supervisor: Dr. Ahmed Fuwad

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# THESIS ACCEPTANCE CERTIFICATE

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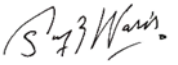
Name of Dean/HOD: Dr. Muhammad Asim Waris Signature: 

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***Dedicated to my extraordinary mother, whose constant support and unwavering cooperation propelled me towards this remarkable achievement.***

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# LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| AD | Alzheimer’s Disease |
| MCI | Mild Cognitive Impairment |
| RF | Random Forest |
| SVM | Support Vector Machine |
| LR | Logistic Regression |
| ADNI | Alzheimer's Disease Neuroimaging Initiative |
| CDR | Clinical Dementia Rating |
| MMSE | Mini-Mental State Examination |
| ADAS | Alzheimer's disease Assessment Scale |
| MRI | Magnetic Resonance Imaging |
| PET | Positron Emission Tomography |
| FDG-PET | Fluorodeoxyglucose-positron emission tomography |
| CSF | Cerebrospinal fluid analysis |
| EEG | Electroencephalography |
| ML | Machine Learning |
| KNN | k-nearest neighbors |
| ROC | Receiver operating curve |
| AUC | Area under the curve |
| SMOTE | Synthetic Minority Over-sampling Technique |
| CN | Cognitively normal |
| RAVLT | Rey auditory verbal learning test |

## ABSTRACT

Patients with Mild Cognitive Impairment (MCI) face an increased risk of developing Alzheimer's disease (AD), highlighting the importance of early diagnosis for effective interventions and management of the disease. In our study, we investigated the progression of AD in patients initially diagnosed with MCI using multimodal longitudinal data. A classification based framework was proposed for MCI prediction with baseline data of 569 stable MCI (sMCI) and 268 progressive MCI (pMCI) patients. Employing three supervised machine learning (ML) algorithms—support vector machine (SVM), logistic regression (LR), Random Forest (RF) and incorporating features such as cognitive function assessments, MRI, PET scans, CSF biomarkers, and genetic APOE status, the classification accuracies of 83.4%, 80.2%, and 80% were achieved respectively. Significant differences were observed in the performance of the models, with the SVM notably outperforming both LR and RF ($p < 0.05$). Impaired memory function and lower clinical tests scores were found as primary indicators of MCI patients progressing towards AD. Although the fusion of all modalities yielded accurate results for predicting MCI progression to AD, our analysis revealed less significant differences in evaluation metrics when only cognitive test results were used as features. This suggests that cognitive assessments alone are nearly as effective in predicting MCI progression, which can lead to more cost-effective strategies in clinical settings. This study underscores the need for further research aimed at developing new tools to assist clinicians in prognostic decision making.



**Keywords:** *Mild cognitive Impairment, Alzheimer's disease, early detection, machine learning, multi modal longitudinal analysis, classification*

# CHAPTER 1:INTRODUCTION

Alzheimer's disease (AD) is one of the most complex and prevalent neurodegenerative diseases, affecting millions of people around the world. This introduction aims to provide a comprehensive overview of AD, its progression, diagnostic challenges, the significance of early detection, the role of machine learning (ML) in disease prediction, and the specific problem statement addressed in this thesis.

## 1.1 Background

AD is a progressive neurodegenerative condition that mainly affects cognitive abilities and motor skills. It is the most common type of dementia, marked by the gradual deterioration of cognitive function, memory loss, and impairments in language, reasoning, and decision-making abilities. AD stands as a formidable challenge in contemporary healthcare, both in terms of its prevalence and the profound impact it exerts on individuals, families, and healthcare systems worldwide. AD is the leading type of dementia, affecting more than 50 million people globally and accounting for the majority of dementia cases. The prevalence of AD is expected to rise substantially in the coming decades due to aging populations and increasing life expectancy. Although some medications have been seen that are proven effective to lessen the symptoms of AD but there is no proper cure available for this disease [1]

Alzheimer's disease is a multifaceted disorder characterized by various factors contributing to neurodegeneration. Many hypotheses have been developed by researchers to figure out how neurodegenerative processes begin and progress to neuronal death, resulting in AD. The pathological hallmarks of Alzheimer's include the accumulation of amyloid-beta plaques and neurofibrillary tangles within the brain parenchyma. The amyloid beta peptide (Aβ) results from the proteolytic cleavage of a transmembrane protein called amyloid precursor protein (APP), which is mediated by enzymes β- and γ-secretases. Research has identified amyloid beta (Aβ) as the primary constituent of plaques found in AD. Amyloid beta protein contributes to the development of AD by creating abnormal clumps in the brain, known as amyloid plaques. These plaques disrupt

communication between brain cells, causing inflammation and brain tissue damage. Tau protein is a critical component of the neurofibrillary tangles that are characteristic of Alzheimer's disease. Under normal circumstances, tau protein aids in the assembly and stability of microtubules, which is essential for neuronal function. In Alzheimer's disease, however, the tau protein undergoes abnormal post-translational modifications such as acetylation and hyper phosphorylation, which affects its binding to microtubules. As a result, tau protein aggregates in the cytosol and form neurofibrillary tangles (NFTs). The exact mechanisms by which tau protein contributes to AD are still being studied, but it's evident that the abnormal aggregation of tau protein causes disruption of the normal functioning and signal transmission among neurons, leading to neuronal death and brain damage. The aggregation of abnormal proteins interferes with the normal functioning of neurons, leading to their degeneration and causing symptoms of AD, such as memory loss and cognitive decline. These aberrant protein aggregates precipitate a cascade of neurodegenerative processes, including neuronal dysfunction, synaptic loss, and eventually neuronal death. They tend to build up in the brain's parenchyma long before cognitive symptoms become apparent and significantly disrupt daily activities. As the disease progresses, widespread neuroinflammation further exacerbates neuronal damage, perpetuating the cycle of cognitive decline and functional impairment.[2]

An immune system's normal response to an injury or infection is inflammation. However, persistent inflammation in the brain can be damaging and aid in the emergence of AD. Inflammatory molecules are released by activated 'microglia,' the immune cells residing in the brain; which can harm neurons and encourage more inflammation. Furthermore, inflammation can make it more difficult for the brain to eliminate waste products and toxins, which promotes the aggregation of amyloid and tau proteins. To mitigate neuronal damage, researchers are putting forward therapy options that address chronic inflammation.

Neurons require a lot of energy, and there is a lot of ATP requirement and consumption in the brain, which is met by mitochondria, a cell's 'power house'. Neuronal function is dependent on mitochondrial integrity and well-functioning bioenergetics. However, with AD, a variety of variables, including elevated oxidative stress, impaired $Ca^{+2}$

homeostasis, and a disrupted mitochondrial genome, can impair mitochondrial function. Such defects cause mitochondrial dysfunction in neurons, resulting in a detrimental downturn that eventually leads to neuronal dysfunction, which is a characteristic of AD. Moreover, abnormal amyloid-beta levels can also induce abnormalities in mitochondria. According to studies, the size and number of mitochondria in AD patients are altered; additionally, there is uneven mitochondrial distribution in pyramidal neurons and poor mitochondrial protein import. This evidence indicates that mitochondrial dysfunction plays a central role in AD. Therapeutic strategies targeting mitochondria are currently being considered.

Two of the many factors that are linked to the onset of AD include oxidative stress and cholinergic stress. Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to counteract their harmful effects with antioxidants. Cellular components like DNA, lipids, and proteins may be harmed by oxidation as a result of this imbalance. Cholinergic stress arises from disruptions in cholinergic transmission and dysfunction within the cholinergic system. This system consists of a network of neurons that use the neurotransmitter acetylcholine (ACh) for communication. ACh is crucial for memory and learning and is often found to be compromised in AD. Both malfunctions in the cholinergic system and reduced cholinergic transmission can contribute to cholinergic stress, impacting cognitive functions such as memory and learning.

Recent studies suggest a connection between cholinergic stress and oxidative stress, which may contribute to AD progression via several processes. Cholinergic stress can facilitate oxidative stress by weakening the antioxidant defense mechanism and boosting the production of ROS. On the other hand, oxidative stress can also damage the cholinergic system by causing the deterioration of cholinergic neurons and decreasing the activity of the enzymes needed to produce acetylcholine. [3] [4]

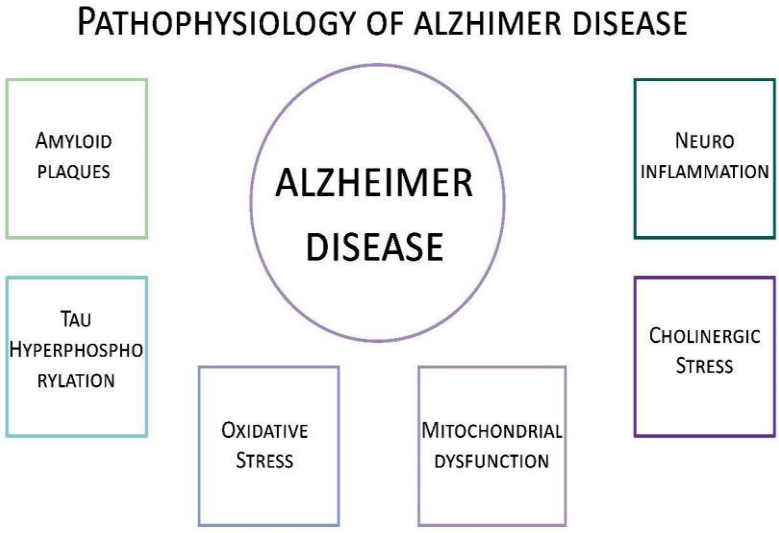



**Figure 1.1:** Figure describes various factors that can contribute to the onset and progression of AD[5]

Despite decades of intensive research, the exact etiology and pathogenesis of Alzheimer's disease remain elusive, highlighting the intricate nature of the disorder. Numerous hypotheses have been proposed to elucidate the underlying mechanisms driving Alzheimer's pathology, ranging from genetic predispositions and environmental factors to disruptions in neurotransmitter systems and immune dysregulation. However, a comprehensive understanding of the intricate interplay between these factors remains a central challenge in Alzheimer's research.

The pervasive impact of AD extends far beyond the realms of individual health, reverberating throughout society and imposing substantial economic and social burdens. The multifaceted challenges posed by Alzheimer's emphasize the pressing need for innovative strategies to address the disease comprehensively. From advancing our understanding of its pathophysiology to developing novel therapeutic interventions and enhancing support systems for affected individuals and caregivers, a multifaceted approach is essential to confront the complexities of AD effectively.

Looking ahead, collaborative efforts between researchers, clinicians, policymakers, and community stakeholders are imperative to tackle the multifaceted challenges posed by AD. By fostering interdisciplinary collaboration, promoting public awareness, and

investing in research infrastructure, we can strive towards a future where effective prevention, early detection, and treatment modalities mitigate the burden of AD and improve the quality of life for affected individuals and their families.[6]

### 1.2 Mild Cognitive Impairment: A Precursor to Alzheimer's

Before the onset of AD, individual often experiences subtle but noticeable changes in memory, thinking, and cognitive abilities that are beyond what would be expected for their age. These changes are not severe enough to affect daily life activities and are often ignored by individuals considering them as normal age related changes, overlooking their potential significance. This stage of disease is known as Mild Cognitive Impairment (MCI). MCI serves as a critical distinctive stage between normal cognitive aging and AD. This stage of cognitive decline needs to be evaluated and addressed.

MCI is characterized by subtle changes in memory, thinking, and cognitive abilities that are noticeable to the individual and may also be noticeable to others, yet these changes do not substantially disrupt daily activities. Common symptoms of MCI include difficulties in remembering recent events, challenges in concentrating on tasks, and a slower processing speed in decision-making.[7]

The crucial characteristic of MCI lies in its potential to progress to more advanced stages of cognitive impairment, including AD. While some individuals with MCI remain stable over time or even experience improvements in cognitive function, others face an increased risk of transitioning to AD or other forms of dementia. The transition from MCI to AD represents a pivotal moment in the trajectory of cognitive decline, marked by a gradual worsening of cognitive function and the emergence of additional symptoms such as disorientation, language difficulties, and impaired judgment. Neuroimaging studies have revealed progressive changes in brain structure and function during this transition, including atrophy of key brain regions involved in memory and executive function.

This transition is a focal point of concern, prompting the need for early detection, detailed assessment, and proactive intervention that may change the trajectory of cognitive decline. Longitudinal studies have demonstrated that a substantial proportion of individuals diagnosed with MCI will eventually develop AD, with annual conversion rates ranging from 10% to 15%. Early identification and monitoring of MCI are therefore essential for timely interventions and treatment planning to mitigate the risk of progression to AD and optimize patient's outcomes.

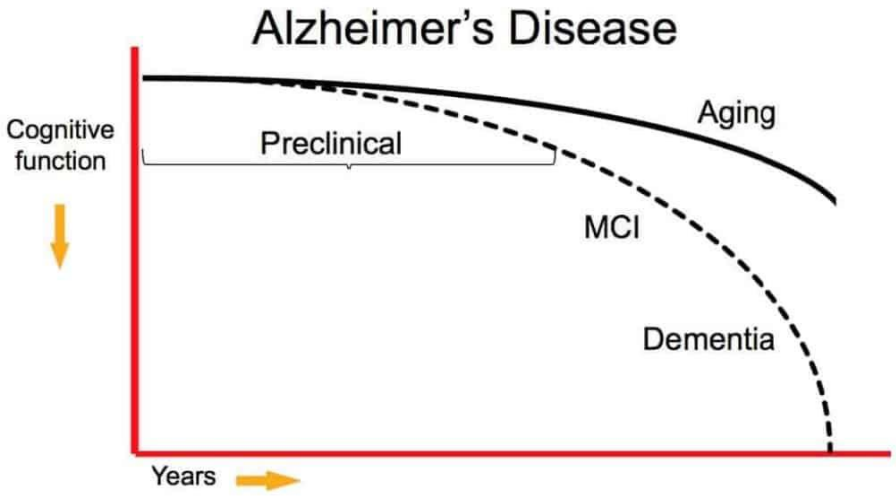



**Figure 1.2:** Shows comparison of Cognitive Decline: MCI to Dementia vs. Normal Aging.[7]

However, diagnosing MCI can be challenging due to the variability of symptoms, overlap with normal cognitive changes associated with aging, and the lack of definitive biomarkers. The uncertain prognosis of MCI further complicates the decision-making process for treatment options and long-term care for patients and their families. While some individuals with MCI may remain stable over time or even experience improvement in cognitive function, others face an increased risk of progressing to AD, which requires continuous monitoring and support. Therefore, it is advised for patients who notice symptoms of cognitive decline to visit doctor. A doctor can conduct tests related to memory, language, and other cognitive functions to determine if cognitive impairment exists, as MCI could be an early indicator of AD or another form of dementia. Although

there is currently no cure for MCI, there are strategies that can help individuals maintain their health and manage cognitive decline.[8]

## 1.3 Significance of Early Detection and Proactive Management

Early detection of AD and its precursor stages, such as MCI, holds immense significance for several reasons. Firstly, early diagnosis allows for timely interventions and treatments that may help slow down or even halt the progression of cognitive decline. While no treatment can reverse the damage caused by the disease, early intervention may halt or slow the disease. As some behaviors have been demonstrated to delay the advancement of the disease, early identification of the condition will also assist the patient in making the appropriate lifestyle modifications. Early detection will also help monitor different therapies and disease progression. Numerous studies have shown that early pharmacological and non-pharmacological interventions, such as cognitive training, physical exercise, and lifestyle changes, can delay the appearance of dementia symptoms and enhance overall quality of life.

Moreover, early detection allows individuals and their families to prepare for the future, make knowledgeable decisions regarding care choices, and utilize support services that can reduce the caregiving burden and improve patient outcomes.

### *1.3.1 Diagnostic Methods for Alzheimer's disease*

The diagnosis of AD can be challenging because of its complex pathology. It requires a multifaceted approach that encompasses various diagnostic methods aimed at evaluating cognitive function, detecting brain changes, and identifying biomarkers indicative of neurodegenerative processes. Integrating these diagnostic modalities into a comprehensive assessment framework enables clinicians to achieve an accurate and timely diagnosis of AD, facilitating early intervention and proactive management strategies aimed at optimizing patient outcomes. Moreover, such a rigorous diagnostic approach supports ongoing research and development of more effective treatments for AD.[6]

**Table 1.1:** Table shows different Diagnostic Methods for Alzheimer's disease

| **Diagnostic Method** | **Description** |
|---|---|
| Clinical Assessment | Medical history, cognitive tests (MMSE, CDR, ADAS), physical and neurological exams |
| Brain Imaging | MRI (Magnetic Resonance Imaging), PET (Positron Emission Tomography) scans |
| Biomarker Analysis | Cerebrospinal fluid analysis for Alzheimer's-associated biomarkers (e.g., amyloid-beta, tau proteins).Blood tests for emerging biomarkers of Alzheimer's disease. |
| Genetic Testing | APOE Genotyping for identification of genetic risk factors, such as the APOE ε4 allele, associated with Alzheimer's disease |
| Functional Imaging | Assessment of brain activity and connectivity patterns to elucidate functional changes associated with Alzheimer's disease (fMRI: Functional MRI) |
| Electroencephalography (EEG) | Measurement of brain electrical activity to detect abnormalities indicative of cognitive dysfunction (EEG: Electroencephalography) |

Clinical assessments play a crucial role in the diagnosis of AD, offering valuable insights into cognitive function and overall health status without the need for invasive procedures. These assessments are combination of physical examinations and standardized questionnaires which involve obtaining a detailed medical history, conducting cognitive tests such as the Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), and Alzheimer's disease Assessment Scale (ADAS), and performing physical and neurological examinations. They help to assess various aspects of cognitive abilities such

as memory, attention, language, and executive function. Furthermore, they enable the identification of subtle cognitive changes that may signal the MCI, a precursor to AD, allowing for early intervention and proactive management strategies. Additionally, these assessments are relatively non-invasive and well-tolerated by patients, making them accessible and widely applicable in clinical practice. [8]

**Table 1.2:** Table shows Neuropsychometric tests and cognitive domains

| **Neuro-Psychometric Tests** | **Cognitive Domains** |
|---|---|
| Mini-Mental State Exam (MMSE) | Orientation, attention, calculation, recall, language, and visual construction |
| Montreal Cognitive Assessment (MoCA) | Visuospatial and executive functions, naming, memory, attention, language, delayed recall, and orientation |
| Mini-Cog Test | Memory and executive function |
| AD Assessment Scale-Cognitive subscale (ADAS-Cog) | Memory, language, concentration, and attention |
| The sum of Boxes Clinical Dementia Score (CDR-SB) | Memory, judgment, orientation, community affairs, home hobbies, and personal care |
| Wechsler Logical Memory Subset | Immediate and delayed recall of verbal information |
| California Verbal Learning Test II (CVLTII) | Verbal learning and memory, attention, and visual recognition |
| Free & Cued Selective Reminding Test (FCSRT) | Verbal episodic memory |

Neuroimaging methods, such as magnetic resonance imaging (MRI) and positron emission tomography (PET), are vital for identifying structural and functional brain alterations linked to AD. PET scans that utilize radiotracers aimed at beta-amyloid and tau proteins can identify amyloid plaques and neurofibrillary tangles, respectively. PET is widely used in the diagnosis of AD because of its sensitivity in detecting the condition. However, the main drawback of this method is its prohibitively high cost. There are a few tracer elements available with the help of which clinicians can diagnose certain neurological conditions like AD. The tracer element mostly used for Alzheimer's

detection is 2-fluoro-2-deoxy-d-glucose (F-FDG). This tracer element can help to track the metabolism of glucose in the brain. Specific brain regions experience a decrease in the rate of brain glucose metabolism as AD progresses. The performance on cognitive tests is correlated with this decrease in brain glucose metabolism. The decline was observed years before any clinical signs associated with AD appear. The patient's frontal, parietotemporal, and posterior cingulate cortices show the most dramatic decrease. PET scans, particularly those employing 18F-FDG, offer a high sensitivity of up to 90% in detecting AD early on its advancement. However, the specificity of the imaging technique for differentiating AD from other dementias is very low. According to longitudinal studies, FDG-PET may both pinpoint MCI patients who will later acquire AD and predict when healthy persons would develop MCI.

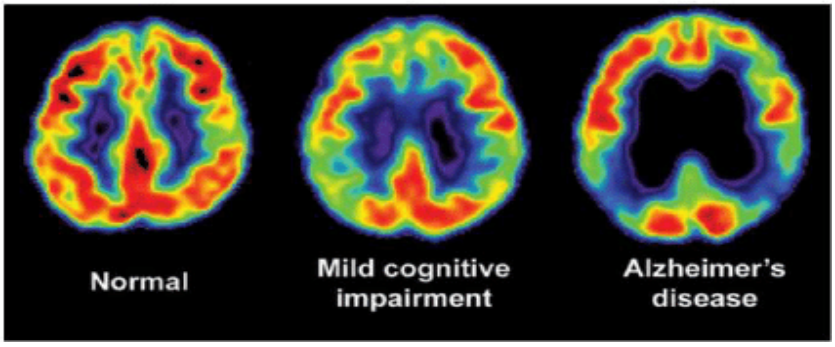



**Figure 1.3:** Shows PET scan images of different stages of AD [8]

MRI is a non-invasive imaging method extensively utilized for brain and spinal cord imaging. The images it produces are crucial for assessing cognitive health and identifying various brain-related disorders. MRI is particularly valuable in detecting AD, often before the onset of dementia symptoms. The most commonly used is structural MRI, which can observe changes in brain volume and structure, thus enabling the detection of numerous neurological conditions.

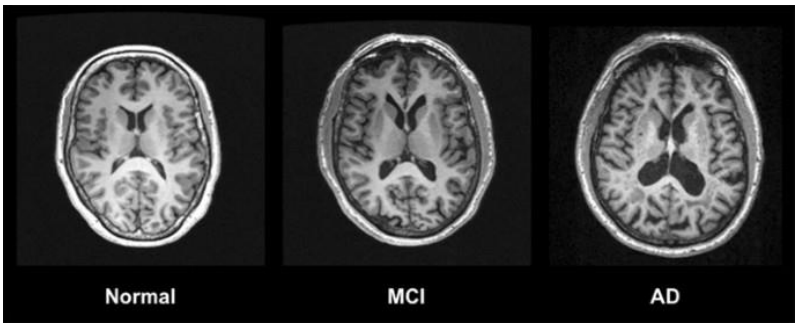



**Figure 1.4:** Shows MRI scan images of different stages of AD [9]

Functional MRI (fMRI) is a neuroimaging technique that is employed to assess brain function. This non-invasive method can track the progress of AD patients', treatments and examine functional impairments. It can also be used for early Alzheimer's detection and recent advancement in deep learning algorithms have shown great promise. During an fMRI scan, the oxygen levels in specific areas of the brain are measured as the person performs specific stimuli or cognitive tasks. The method includes recording brain activity while doing a task and while at rest, then subtracting the resting state from the task activity to find regions of increased blood flow. Advances in fMRI have made it possible to relate the neural underpinnings of cognitive and behavioral processes to neuroanatomical networks in the early stages of neurodegenerative illnesses. [9]

Cerebrospinal fluid analysis (CSF) is widely used to diagnose neurodegenerative diseases including various types of dementia. It provides valuable insights into the underlying pathophysiology of AD by measuring levels of beta-amyloid and tau proteins. Elevated levels of these biomarkers are indicative of AD pathology and can help in distinguishing between various types of dementia.

One of the drawback of CSF analysis for AD is its highly invasive nature which requires a spinal tap in the lumbar region. For the time being, it cannot be utilized as a screening procedure for AD, but novel biomarkers are being discovered which may change the perception about the procedure in the future. The CSF analysis though can be extremely helpful in drug development and evaluating drug performance.

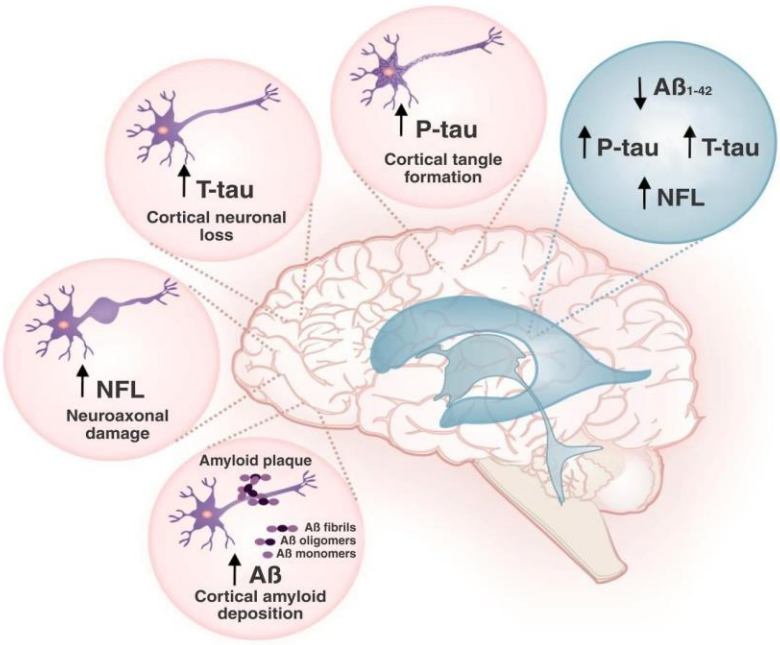



**Figure 1.5:** Shows Cerebrospinal Fluid Biomarkers for Detecting Alzheimer's[11]

AD is a complex disorder with a significant genetic element. Researchers have identified over 70 genetic variants associated with AD. Mutations in genes such as amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) have been linked to AD, as they encode proteins crucial in the development of the disease. In various genetic studies, the APOE gene has been repeatedly connected to sporadic late-onset AD. Even though several hundred families have these mutations, they only make less than 1% of all cases. Genetic testing is not frequently utilized to diagnose AD. However, asymptomatic individuals with a family history of dementia can consider getting tested to determine if they have a mutation linked to hereditary frontotemporal dementia or AD.

Electroencephalography (EEG), is a non-invasive method for determining brain electrical activity. EEG is often used in the clinical evaluation of individuals with MCI and AD. Whereas severe AD is characterized by an elevation in delta power, moderate AD is characterized by a rise in theta activity and a decline in beta and alpha activity. MCI patients display EEG features that fall between those of AD patients and healthy. The relative powers of alpha and theta waves derived from the left temporo-occipital region can effectively classify approximately 85% of MCI patients progressing towards AD. Patients with MCI and healthy brains have markedly different theta band power and coherence. However, traditional EEG amplitude and power spectral analysis may not be

sensitive enough to distinguish MCI patients from healthy controls. EEG is a helpful tool for identifying AD and MCI patients.

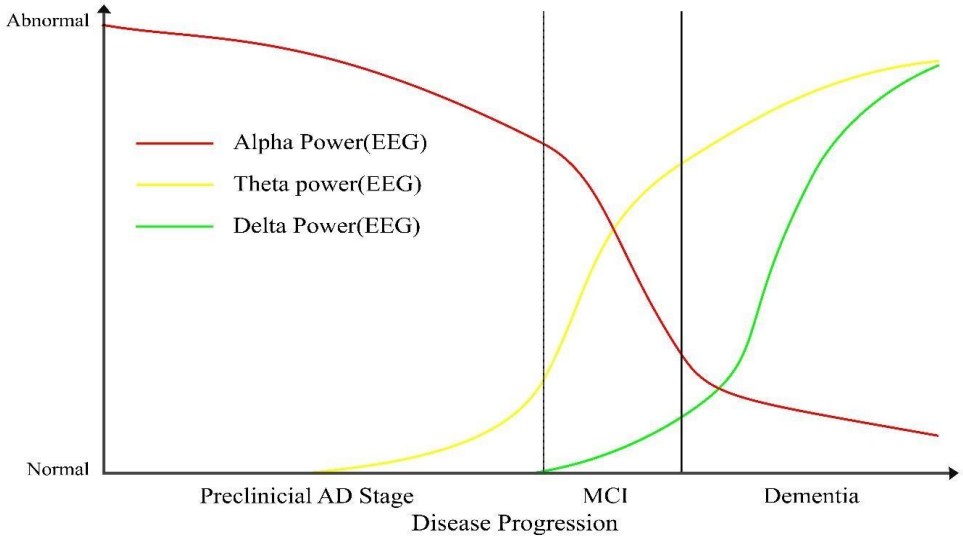



**Figure1.6:** Hypothetical model of EEG findings of Alzheimer patients [12]

### 1.4 Role of Machine Learning (ML) and Data Analysis

The scientific community now has access to extensive longitudinal neuroimaging datasets from healthy individuals, those with MCI, and AD patients. These datasets are supplemented with demographic, genetic, and cognitive measurements and are stored in public repositories like the Alzheimer's Disease Neuroimaging Initiative (ADNI) (http://adni.loni.usc.edu). By leveraging these resources, researchers can analyze and compare datasets to perform classification and automatic detection of AD and MCI progression. Advanced computer-aided techniques, notably machine learning (ML) algorithms, have emerged as potent tools for this purpose. ML algorithms are trained using neuroimaging results and other clinical variables to identify common features useful for classifying subjects based on specific criteria. This approach shows promising potential for improving early diagnosis and prognosis in clinical settings.

The insights gained from ML algorithms can be successfully integrated into clinical settings, helping healthcare professionals make better-informed decisions about early

diagnosis and prognosis. The ML paradigm is applicable not only to AD but also to any condition characterized by morphological changes or distinct neural patterns. Traditional statistical approaches often lack the capacity to integrate diverse data types effectively, hindering their predictive power. By contrast, machine learning algorithms offer the ability to analyze complex datasets and identify patterns that may not be apparent through conventional methods.

In recent years, the integration of machine learning and data analysis techniques has revolutionized the understanding of AD progression. ML algorithms, powered by large and heterogeneous datasets encompassing clinical, imaging, genetic, and biomarker data, have the capacity to uncover complex patterns and predictors of disease progression.

One of the primary advantages of machine learning in Alzheimer's research is its ability to handle high-dimensional and multimodal data, which traditional statistical methods may struggle to analyze effectively. Combining multimodal data with powerful machine learning algorithms contributes to the development of an accurate and reliable diagnostic tool. By leveraging advanced algorithms such as support vector machines (SVM), random forests, logistic regression, and neural networks, researchers can extract meaningful insights from complex datasets and develop predictive models for disease progression.

Machine learning approaches have been applied across various stages of AD, from early detection and diagnosis to prognosis and treatment planning. These models can forecast the probability of progression from MCI to AD, categorize patients according to their risk profiles, and guide personalized interventions tailored to the individual patient needs. Additionally, machine learning techniques facilitate the identification of novel biomarkers and imaging markers associated with Alzheimer's pathology, enhancing the understanding of underlying mechanisms of disease progression. It helps in early intervention and treatment planning. [13]

### 1.5 Research Objective

The problem addressed in this thesis revolves around predicting the progression of Alzheimer's disease in individuals with Mild Cognitive Impairment (MCI) using a

multimodal machine learning approach. This research aims to improve prediction accuracy and enable proactive interventions by combining clinical, imaging, biomarker, and genetic data.

The primary objectives of this research include:

i. With an aim to make results multimodal analysis, all the clinically relevant features were included. These features included demographic data, clinical tests scores from neuropsychological assessments, cognitive function assessment tests, MRI examinations which include volumes of different brain regions, PET examination which include FDG-PET analysis, CSF protein biomarkers which include ABETA and TAU and genotypic information about APOE4 status. They were then used to train supervised machine learning algorithms.

ii. Longitudinal analysis was performed to monitor disease progression over time and to classify two groups of patients initially diagnosed as MCI during their baseline examination:
   - ❖ Progressive MCI: Patients who progressed to AD during the observation period.
   - ❖ Stable MCI: Patients who retained MCI diagnosis during the observation period.

iii. Machine learning algorithms such as Support Vector Machine (SVM), Logistic Regression (LR) and Random Forest (RF) were employed to classify the two sets of patients using baseline data.

The primary aim of this research is to improve the management of AD by facilitating early prediction and proactive intervention, thereby enhancing patient outcomes and quality of life. By accurately identifying MCI patients who are at higher risk of progressing to AD, healthcare providers can initiate targeted interventions, including lifestyle modifications, pharmacological therapies, and enrollment in clinical trials for disease-modifying treatments. Furthermore, the identification of biomarkers associated with AD progression can lead to the development of innovative diagnostic tools and therapeutic targets, advancing our understanding of the disease mechanisms and facilitating personalized medicine approaches. Differentiating between cognitive changes associated with the sub-classes of MCI is therefore an essential endeavor in the field of

research and through interdisciplinary collaboration between clinicians, data scientists, and researchers, this study aims to enhance early identification of the disease.

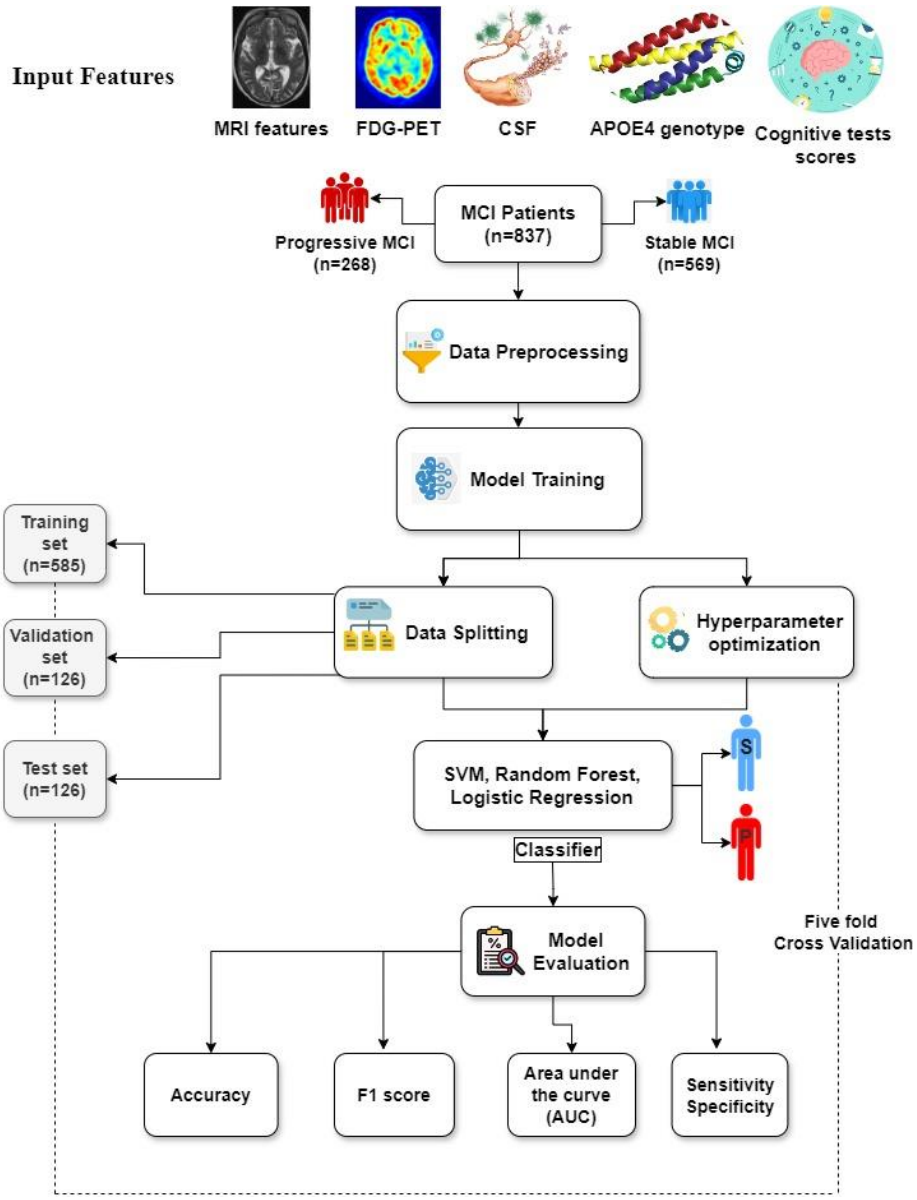



**Figure 1.7:** Illustrates an overview of the multimodal machine learning framework for predicting AD progression in MCI patients.

# CHAPTER 2: LITERATURE REVIEW

## 2.1 Introduction

This chapter provides a detailed review of the relevant literature related to the research question. It aims to establish a solid background and a robust framework for understanding the dynamics of AD progression, its prediction through multimodal longitudinal analysis and the potential benefits of machine learning techniques in addressing this challenge.

## 2.2 Alzheimer's disease: A Global Health Challenge

AD is a progressive neurological condition that often results in dementia. It is characterized by a decline in cognitive functions, loss of memory, and challenges in performing everyday tasks, posing substantial difficulties for individuals, their families, and health care systems worldwide. Consequently, understanding the progression of AD from MCI is essential for its early detection, intervention, and management.

### *2.2.1 Clinical Manifestations*

An individual experiencing AD passes through different stages of cognitive decline. In the early stages of disease, an individual experiences cognitive decline greater than expected age, yet not severe enough to disrupt daily activities. This phase is characterized by minor memory lapses and difficulties with concentration and problem-solving skills. As the disease progresses, memory loss becomes more pronounced, leading to language difficulties, disorientation, and changes in behavior and mood. In later stages, it becomes so severe that individuals may require assistance with basic activities of daily living.

The neuropathological hallmarks of AD include the accumulation of abnormal protein aggregates in the brain, such as amyloid beta plaques and neurofibrillary tangles. These pathological alterations interfere with neuronal communication, causing neuronal dysfunction and death, which in turn leads to progressive cognitive deterioration. Neuroimaging studies have demonstrated patterns of brain atrophy and functional

connectivity alterations associated with AD progression, providing insights into the underlying neurobiology of the disease. [6]

Early detection and accurate prediction of AD are critical for timely intervention and therapeutic planning. Advances in machine learning techniques enable the integration of multimodal data to develop predictive models for disease intervention, facilitating precision medicine approaches in disease care.

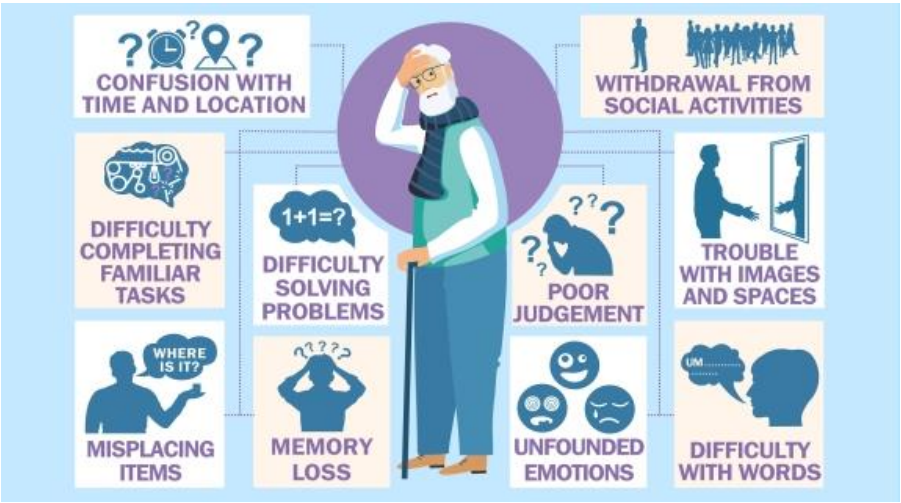


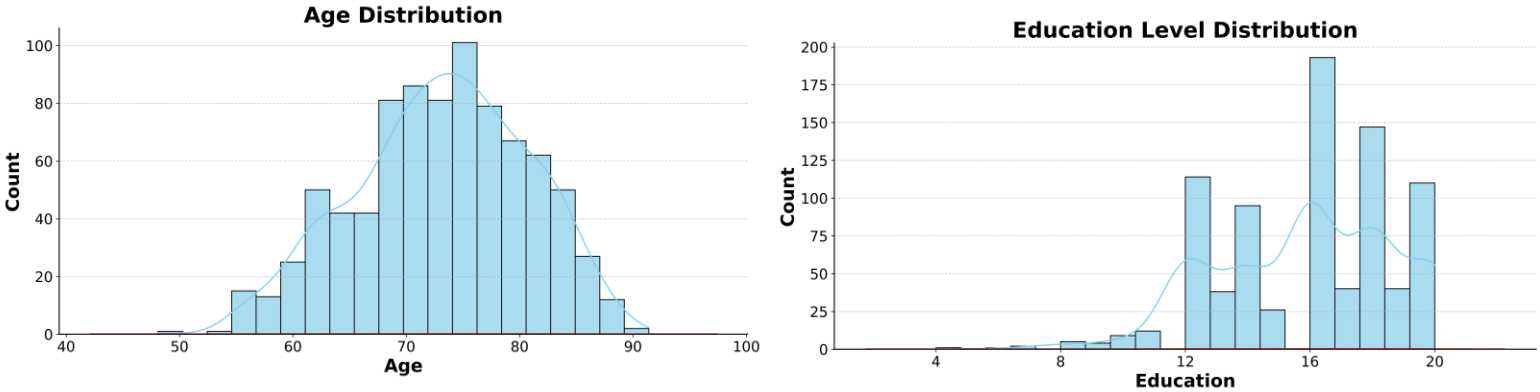

**Figure 2.1:** Shows symptoms of Alzheimer's disease [14]

### 2.3 Multimodal Approach in Alzheimer's disease Research

A multimodal approach for AD diagnosis involves using a combination of different features to assess cognitive function and internal brain structure. It involves integrating cognitive assessment tests, neuroimaging such as MRI and PET scans, genetic information, and CSF biomarkers. Each modality offers unique insights into the disease pathology and progression, allowing for a more precise identification of individuals at risk of progressing to AD. By leveraging a combination of sensitive biomarkers and imaging techniques, researchers can identify subtle changes in brain structure and function associated with preclinical or prodromal stages of AD, enabling early intervention strategies.[12]

*2.3.1 Demographic Information*

It involves gathering information about patient's age, sex, education level, and medical history which are considered important factors in AD research. They may influence disease risk, progression and response to treatment.




**(a)** **(b)**

**Figure 2.2**: (a) Shows age distribution of patients. (b) Shows education level of patients

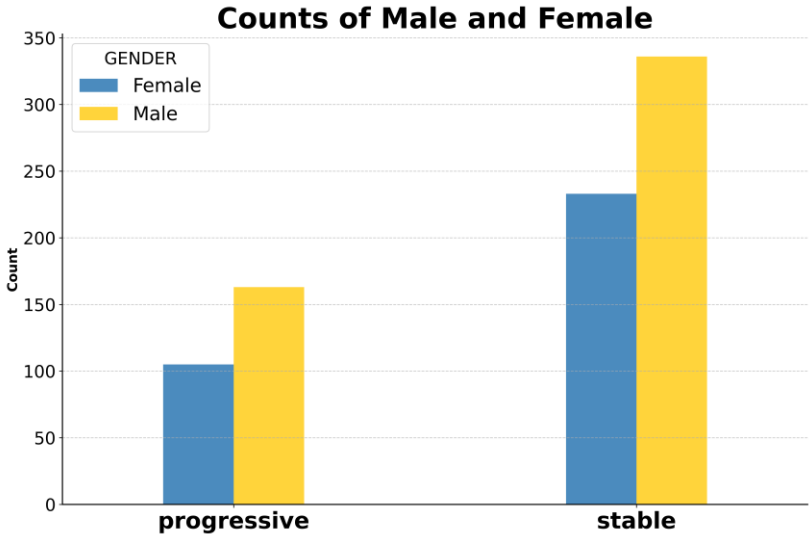



**Figure 2.3:** Shows counts of male and female in sMCI and pMCI groups

*2.3.2 Cognitive Assessments*

Cognitive evaluations consist of screening tests aimed at assessing abilities such as memory, attention, language, and other cognitive functions. Commonly employed standardized tests for gauging cognitive deficits in AD include: Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), Montreal Cognitive Assessment (MoCA), and the Alzheimer's Disease Assessment Scale (ADAS).

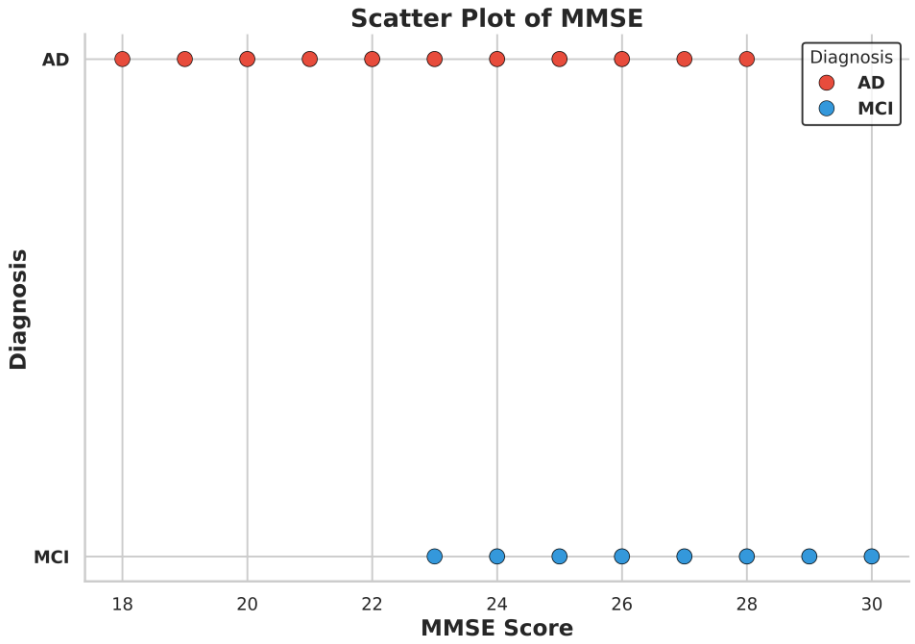



**Figure 2.4:** Shows scatter plot of MMSE against MCI and AD

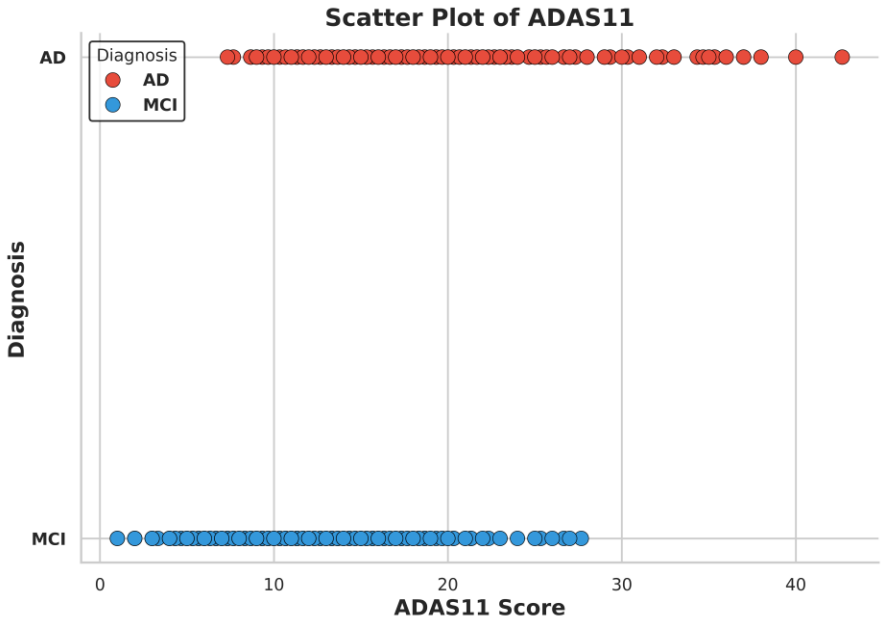



**Figure 2.5:** Shows scatter plot of ADAS11 against MCI and AD

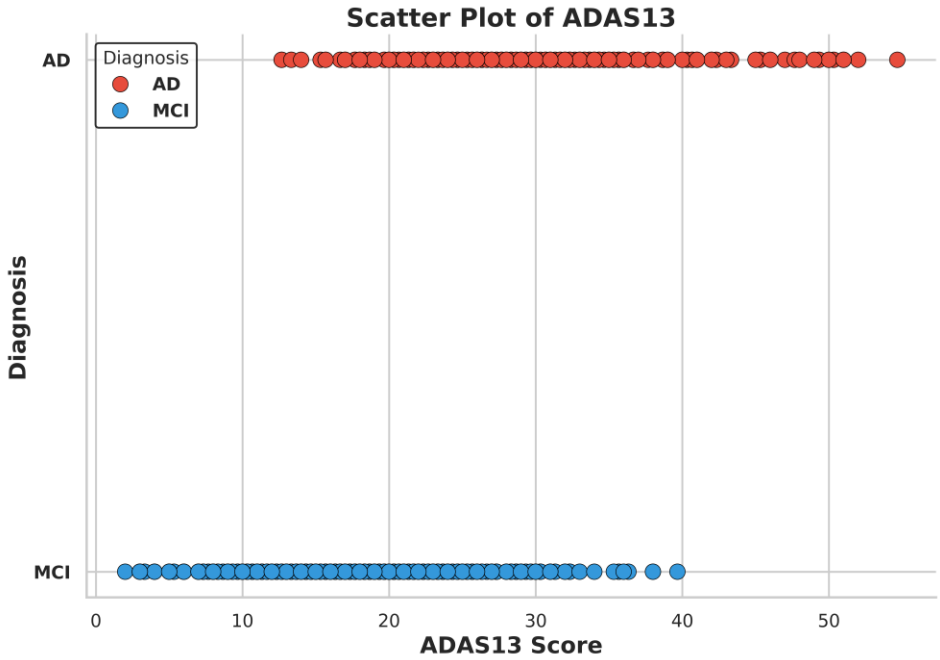



**Figure 2.6:** Shows scatter plot of ADAS13 against MCI and AD

*2.3.3 MRI (Magnetic Resonance Imaging)*

It is done to reveal structural changes in brain associated with AD. It uses magnetic fields and radio waves to create detailed images depicting the brain's anatomy and structure. Structural MRI can detect brain atrophy, white matter changes, and hippocampal volume loss associated with AD pathology.

*2.3.4 PET (Positron Emission Tomography)*

It is done to visualize the accumulation of specific proteins associated with AD. It can measure amyloid beta and tau deposition, neuroinflammation, and glucose metabolism abnormalities which are characteristic of AD.

*2.3.5 Genetic Information*

It is done to investigate the role of genetic variants, such as the Apolipoprotein E (APOE) gene in AD susceptibility and progression. Genetic testing is reserved for patients who have family history of AD and experience symptoms of cognitive decline at an early age.

*2.3.6 CSF Biomarkers*

Examining specific proteins in cerebrospinal fluid (CSF), such as amyloid-beta and tau, can signal the presence of AD. These CSF biomarkers are useful for early diagnosis, tracking the progression of the disease, and evaluating the response to treatment.

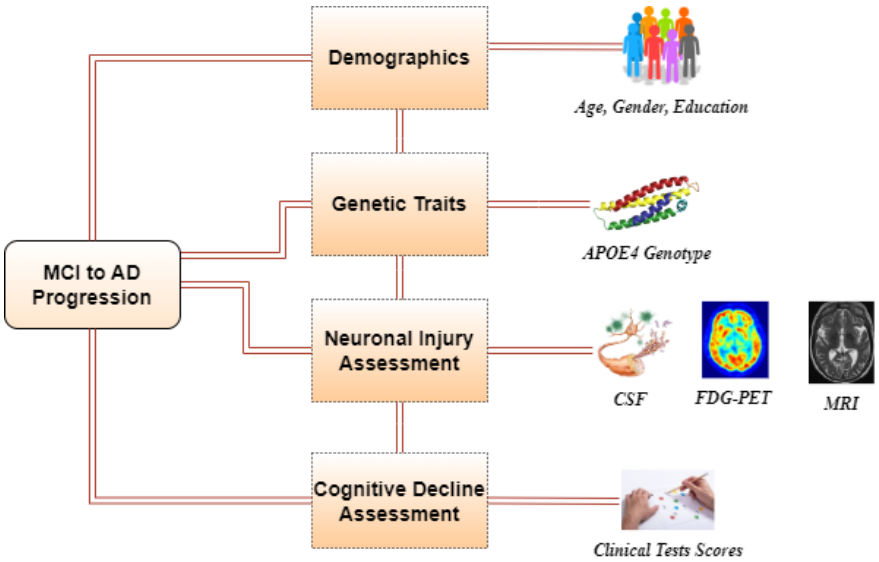



**Figure 2.7:** Predictive features for MCI to AD

## 2.4 Longitudinal Analysis

Longitudinal analysis involves tracking changes in patient's cognitive function and disease status over time. This approach differs from cross-sectional studies, which capture data at a single time point. Longitudinal analysis includes making multiple observations of the same individuals or populations across different time periods. This approach offers several advantages in investigating the progression and trajectory of AD pathology and its impact on cognitive function, brain structure, and biomarker profiles.

Advantages of longitudinal analysis include:

- It can help researchers to identify subtle changes in cognitive performance, neuroimaging biomarkers, and biomolecular profiles associated with different stages of AD.
- By examining how variables evolve over time within the same individuals, researchers can identify heterogeneity in disease trajectories, including variations in onset, rate of progression, and response to treatment.
- It can help to monitor cognitive decline, brain changes, and biomarker alterations over time, enabling researchers to identify preclinical and prodromal stages of AD, facilitating early intervention and preventive strategies.

Longitudinal analysis enables the development of predictive models and biomarkers for AD progression, facilitating personalized risk assessment and prognosis through large-scale data analysis.

## 2.5 Integration of Multimodal Longitudinal Analysis and Machine Learning

Machine learning utilizes algorithms to interpret data and forecast future outcomes. It has capacity to analyze data large and complex datasets to uncover hidden patterns and correlations. It can help in identifying patterns and factors indicative of AD progression at an early stage. This will ultimately help in timely interventions and proactive management and contributes to the development of accurate and reliable diagnostic tools.

In this study, the binary classification task involves distinguishing between two groups of patients: those who remained MCI during the observation period (stable MCI), and those

who progressed to AD during the observation period (progressive MCI). Leveraging machine learning models such as Support Vector Machine (SVM), Random Forest (RF), and Logistic Regression (LR), this approach aims to develop accurate predictive models for early detection and proactive management of the disease. Machine learning algorithms, including SVM, RF and LR, provide the computational tools necessary to analyze and extract meaningful patterns from the complex longitudinal dataset, enabling the development of accurate and reliable predictive models. [13]

*2.5.1 Types of Machine learning*

**i. Supervised Learning:**

In supervised learning, an algorithm is trained using labeled data that includes both input features and corresponding target labels. The objective is to establish a relationship between input features and output labels, enabling the algorithm to predict outcomes for new, unobserved data. Examples of supervised learning techniques include:

- Classification: Assigning discrete labels to data (such as binary or multi-class classification).
- Regression: Estimating continuous values (like forecasting real estate values or stock market prices).[14]

**ii. Unsupervised learning:**

In unsupervised learning, the algorithm discovers patterns and structures in unlabeled data, with no explicit target labels provided. The aim is to reveal underlying patterns, cluster like instances, or compress the dataset's dimensions. Examples of unsupervised learning methods include:

- Clustering: Organizing similar items into groups according to their attributes, such as with K-means or hierarchical clustering.[15]

### iii. Reinforcement learning:

In reinforcement learning, the algorithm improves its performance by interacting with a surrounding environment to accomplish a certain objective or to optimize total rewards. The agent learns by executing actions, receiving feedback in the form of rewards or penalties from the environment, and adapting its actions to enhance rewards over time. This type of learning is applicable in fields like robotics, gaming, and the navigation of autonomous vehicles.[16]

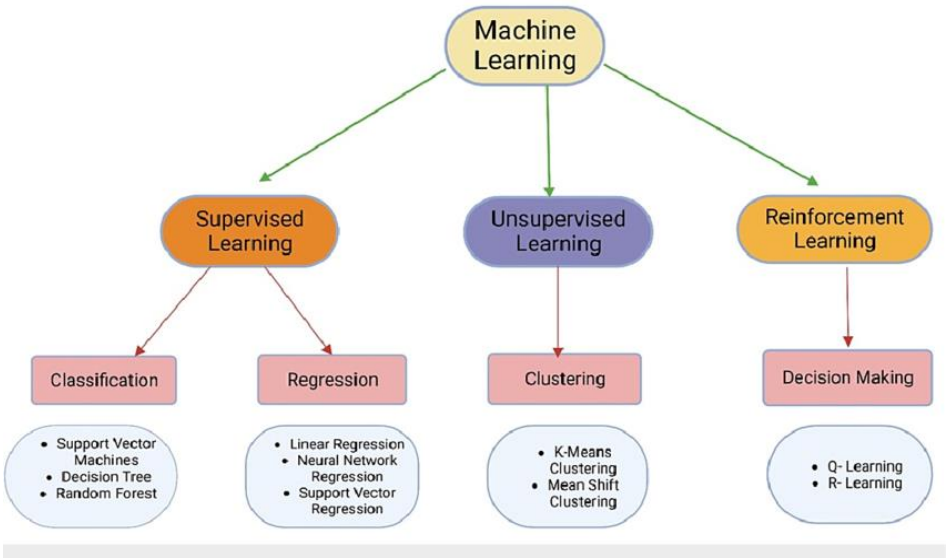



**Figure 2.8:** Shows types of machine learning [17]

*2.5.2 Framework of Machine Learning*

First step in machine learning framework was data curation. Then the data was cleaned by pre-processing steps to make it appropriate for a machine learning model. It includes data cleaning, missing value imputation, normalization, and feature engineering. Appropriate machine learning algorithms such as SVM, RF and LR were then chosen for the binary classification task. Then selected machine learning models were then trained using labeled data. Performance of machine learning models was then evaluated by using appropriate evaluation metrics such as accuracy, precision, recall, F1-score, and area under the receiver operating characteristic curve (AUC-ROC) on unseen test set. Hyper

parameter optimization with stratified cross validation was used to fine tune the machine learning models to optimize their performance and generalization capabilities. This framework offers a structured methodology for our study to categorize two patient groups and identify MCI patients who are at risk of progressing to AD.

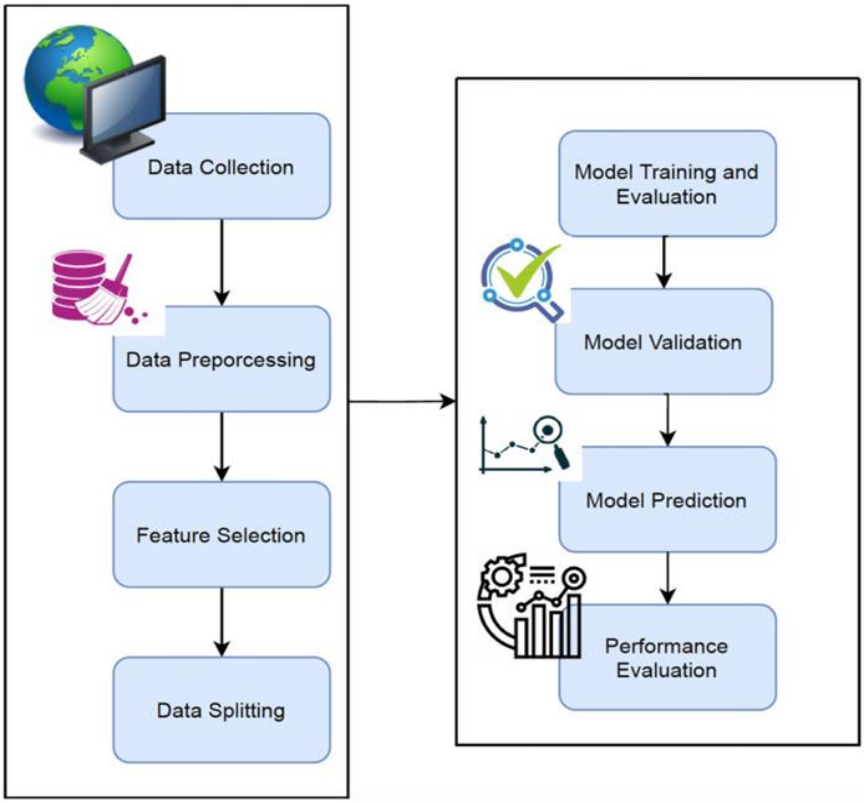



**Figure 2.9:** Shows classifcation framework of a machine learning model. [18]

*2.5.3 Support Vector Machine (SVM)*

A Support Vector Machine (SVM) is a type of supervised learning model mainly utilized for classification tasks. The fundamental concept of SVM involves finding the best hyperplane that can distinctly separate the classes in a dataset. The optimal hyperplane is selected to maximize the margin, or the distance, between the hyperplane and the closest data points from each class, known as support vectors. This approach helps improve the stability and precision of the model when classifying new examples.[17]

*2.5.4 Random Forest*

The Random Forest algorithm is a supervised learning technique that builds a collection of decision trees to enhance prediction accuracy. In this method, each decision tree is trained separately on a randomly chosen subset of both the training data and its features. For classification tasks, the ultimate prediction is made by combining the outcomes of all the trees through majority voting. This approach leverages the power of multiple decision trees, reduces the likelihood of overfitting that may occur with single trees, and boosts the general predictive capability of the model.[18]

### *2.5.5 Logistic Regression*

Logistic Regression is a supervised learning algorithm widely used for binary classification. It estimates the probability that a specific input belongs to a certain category by modeling the data using a logistic, or sigmoid, function. This function produces an output between 0 and 1, representing the likelihood of the input being classified into the default category. Due to its simplicity in implementation and interpretation, Logistic Regression is a favored option for predicting binary outcomes across diverse sectors like finance, healthcare, and social sciences.[19]

# CHAPTER 3: METHODOLOGY

## 3.1 Research Design

The primary objective of this study is to predict the progression of AD in individuals with MCI using a Machine Learning (ML) approach. Multimodal longitudinal analysis is employed to classify patients into two groups: Stable MCI, where patients retain MCI diagnosis during the observation period, and Progressive MCI, where patients progressed to AD during the observation period.

This study will help to determine the efficacy of multimodal longitudinal analysis in tracking disease progression, evaluation of machine learning algorithms for accurate classification and analysis of the most important features contributing to classification of two groups of patients.

## 3.2 Data source

The dataset for this study was sourced from the Alzheimer's disease Neuroimaging Initiative (ADNI), a renowned research initiative established in 2004. ADNI focuses on advancing research in AD and related disorders, aiming to enhance methods for early diagnosis and disease progression tracking. ADNI is an extensive platform having multimodal longitudinal data of Alzheimer's. It provides an opportunity to study diverse data aiming to enhance methods for early detection and proactive management. It helps scientists to explore various aspects of AD and contribute to the development of accurate diagnostic methods. The primary dataset used was named as ADNIMERGE, and additional CSF proteins biomarkers data were integrated into this file. Access to the data requires an online application, details of which are available at 'http: //adni.loni.usc.edu/data-samples/access-data/'.

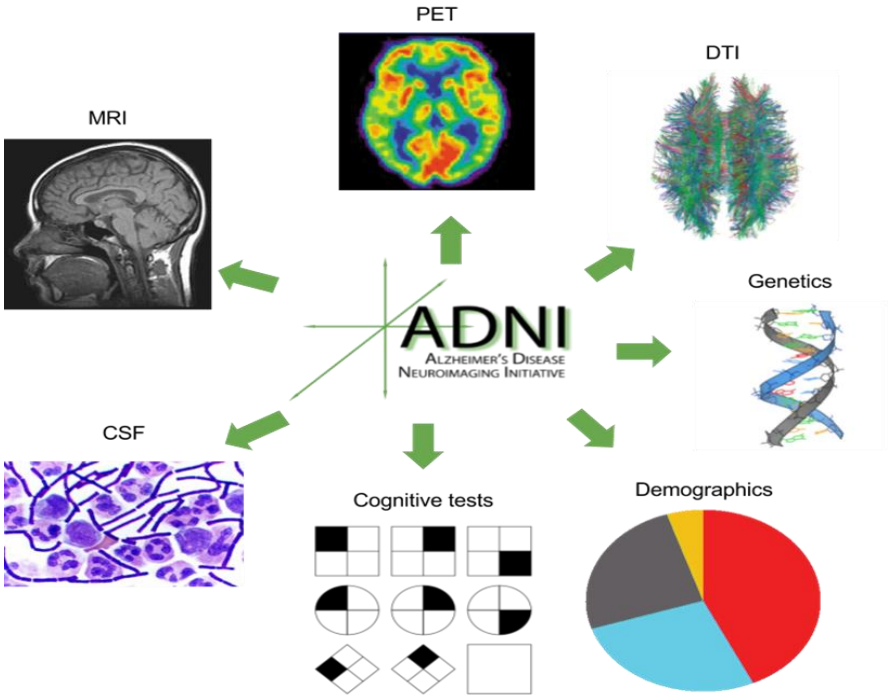



**Figure 3.1:** Illustrates data from ADNI offers insights into AD progression and understanding. [20]

### *3.2.1 Data selection*

The dataset was actually a longitudinal study including multiple follow up visits of a patient (5-10years). Longitudinal analysis was conducted, we saw the baseline and last visit diagnosis of a patient and based on that different groups were created. Out of all, we selected individuals who were identified as MCI at initial clinical examination and checked either they progressed to AD or remain MCI at their last visit. This leads to the inclusion of 837 patients divided into two groups: stable MCI who remain MCI during all visits (n=569, 68%, age range at baseline= 70-73), (male/female= 336/233) and progressive MCI who progressed to AD during observation period (n= 268, 32%, age range at baseline= 72-74), (male/female= 163/105).

### 3.3 Data Pre-Processing

Data pre-processing is carried out to ensure that the data is in a suitable format for a machine learning model and to improve the predictive performance of algorithms.

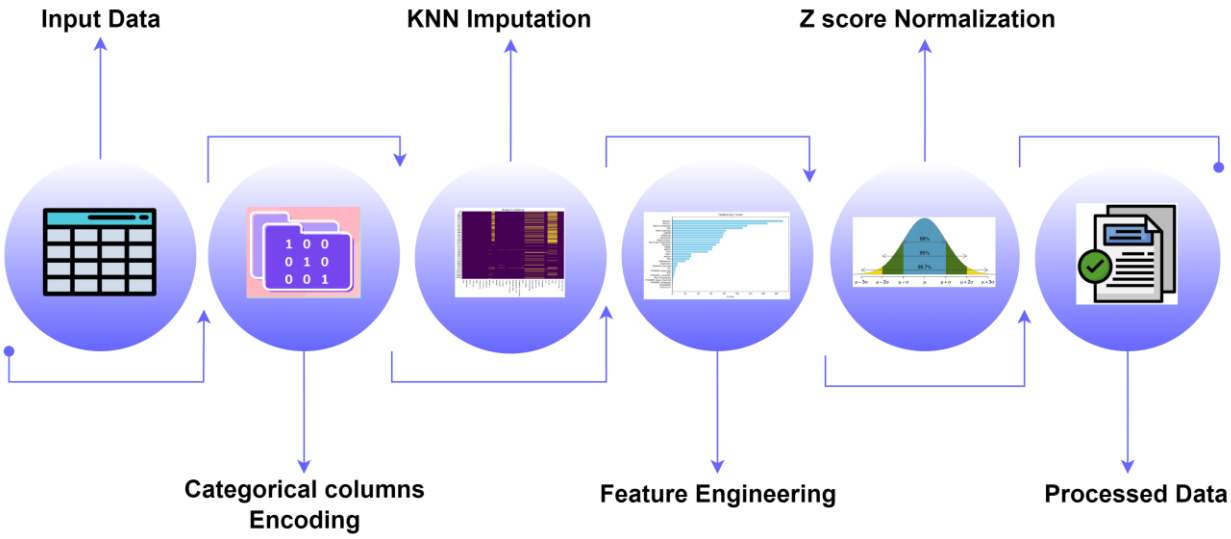



**Figure 3.2:** Illustrates main steps of data preprocessing

*3.3.1 Conversion of Categorical Data*

Initially, categorical columns in the dataset were transformed into numerical columns using one-hot encoding and label encoding, as for ML algorithm data must be in numerical format.

*3.3.2 Handling Missing Values*

Missing values in the dataset are imputed using the K-Nearest Neighbors (KNN) method to ensure data completeness. Missing values can adversely affect model performance, and imputation helps to retain valuable information from incomplete data.

*3.3.3 Data Scaling*

Finally, the dataset was then standardized using Z-score normalization to ensure that features have a mean of 'zero' and a standard deviation of 'one'. [20] By centering data,

outliers will have less influence on overall distribution of data. Calculation formula for Z-score is as follows:

$$z = \frac{x-\mu}{\sigma} \qquad (1)$$

*3.3.4. Feature Selection*

To improve classification accuracy, effective feature engineering was conducted, focusing on reducing dimensionality, minimizing redundancy and calculation reduction. F-score analysis was utilized to assess the importance of each individual variable in predicting the target variable, which is particularly effective for small data samples.[21] ANOVA-F value was employed to evaluate the feature importance between the target variable and each feature. A higher F-value indicates a greater discriminating power of the feature for prediction. Features with extremely low F-values were excluded to achieve feature selection objectives. To mitigate multicollinearity and prevent overfitting, highly correlated pairs were identified from the correlation matrix. Subsequently, one of the features within each pair, with somewhat lesser importance than the other, was removed based on the F-value.

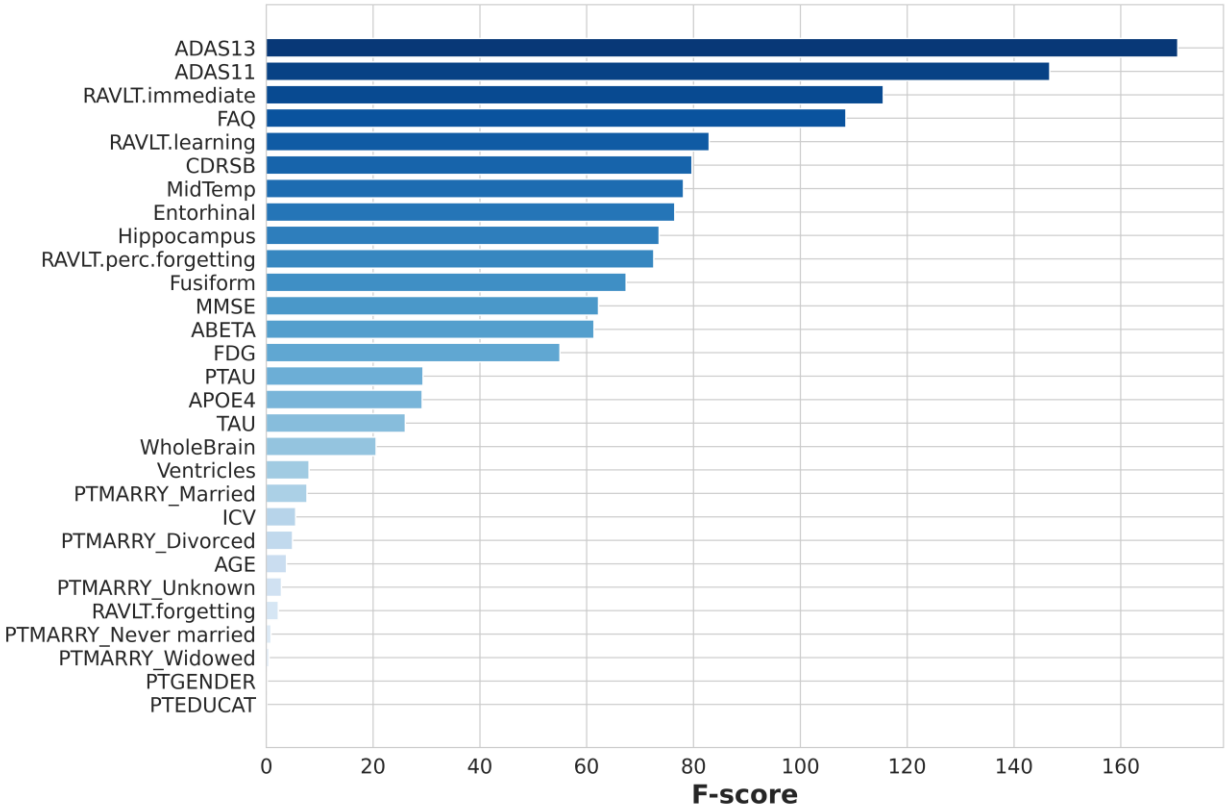



**Figure 3.3:** Feature Importance was determined using F-score. The dataset features are depicted on the y-axis, with their relative importance shown on the x-axis.

### 3.4 Class Imbalance Handling

Among the 837 patients, 569 patients are categorized as stable MCI and 268 patients as progressive MCI. Synthetic Minority Over-sampling Technique (SMOTE) is applied to address class imbalance. SMOTE, with the parameter 'sampling strategy' set to 'minority'. It was applied to tackle the problem of class imbalance, as 68% of the data belonged to one class and 32% to the other. It up samples the minority class by generating synthetic samples within training set, ensuring an equal class distribution so that the model can learn effectively.[22]

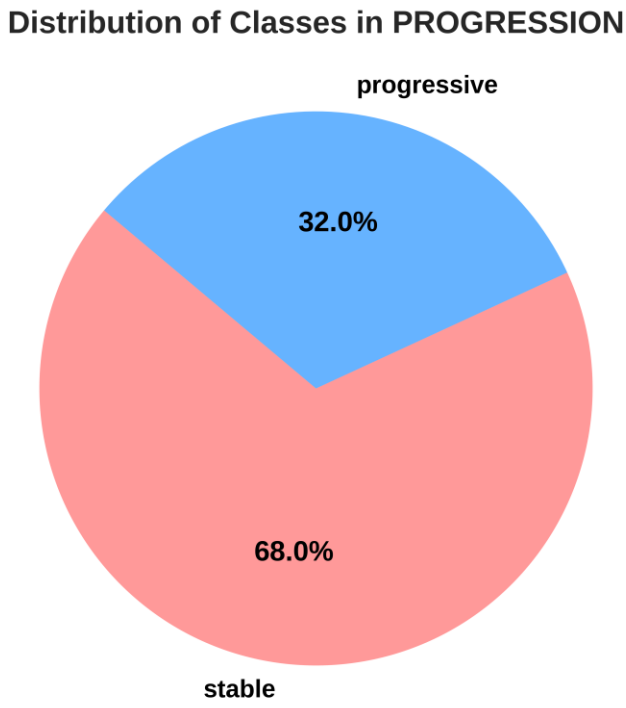



**Figure 3.4:** Shows distribution of classes in Target column

### 3.5 Model Training

This research study is designed to differentiate between two categories of patients: stable MCI and progressive MCI, by analyzing the characteristics of each group. To achieve this, we compared similarities and differences among the features provided. Machine learning algorithms were then trained using baseline data to identify patterns in the dataset for prediction purposes. The whole dataset was splitted into training, validation, and testing sets with proportions of 70% (n=585), 15% (n=126), and 15% (n=126) respectively. Three distinct machine learning models for the classification task: (1) Support Vector Machine (SVM), (2) Logistic Regression (LR), and (3) Random Forest (RF) were applied. The analysis was conducted using Python version 3.10.12 within the Google Colab environment. The 'RBF kernel' was utilized for SVM, penalty and solver parameter with 'l2' and 'lbfgs' were utilized for LR and parameter 'C' (regularization strength) was set to 1.0 because of their good performance on dataset. The best parameters for the RF model are: 'n_estimators'= 50, 'min_samples_split'= 10,

‘min_samples_leaf’= 20, ‘max_features’= 'sqrt', ‘max_depth’= 3, and ‘bootstrap’= ‘True’.

## 3.6 Performance Evaluation

Different evaluation metrics were used to predict the performance of models. We assessed classification accuracies across the training, validation, and testing sets to ensure an unbiased performance of model. The accuracy received on training set is used to assess how well model is trained using given data. Precision, recall, and F1 scores were calculated to assess the performance of classification approach on the test set. Furthermore, confusion matrices and ROC curve were used for all models to identify misclassifications and to determine the rates of true positives and true negatives for comprehensive model evaluation. The model performance was assessed on the test set to gauge its accuracy, precision, recall, and ability to handle class imbalance.

### *3.6.1 Hyper Parameter Optimization*

Hyper parameter Optimization was conducted to find the best hyper parameters for models and to maximum their performance on unseen test data. Random Search with Stratified Cross Validation (5 Folds) was used to enhance the model performance.

# CHAPTER 4: RESULTS

A total of 837 patients diagnosed as MCI at their first clinical examination were included for this study. Out of these, 569 patients maintained their MCI diagnosis throughout the observation period, while 268 patients progressed to AD. All necessary data pre-processing steps, as discussed in the previous section, were performed to optimize the data for effective model training, thereby facilitating robust predictions regarding disease progression.

Table 4.1 provides descriptive statistics that illuminates significant differences between two groups. It shows that individuals with progressive MCI exhibit notably lower scores on cognitive tests, indicating impaired memory function. In addition, they have reduced volumes of brain regions such as the hippocampus, whole brain, and entorhinal cortex. Furthermore, values for FDG-PET are lower for this group indicating lower metabolic activity in the brain and this group indicates higher percentage of APOE- ε4 allele carriers than stable MCI individuals. Additionally, these individuals demonstrate a higher accumulation of P-tau protein, which is indicative of neuronal damage and linked to Alzheimer's pathology. These findings are summarized and detailed in Table 4.1, highlighting the significant contrasts in clinical and biological markers between the two groups. This comprehensive assessment aids in understanding the intricate biomarker profiles and clinical presentations that characterize the progression of AD, underscoring the utility of a multifaceted approach in its diagnosis and monitoring.

**Table 4.1:** Demographic, cognitive and biological measures of sMCI and pMCI patients

| **Group** | **sMCI** | **pMCI** | **p value** |
|---|---|---|---|
| **Number of subjects(n)** | 569 | 268 | |
| **Demographics** | | | |
| Gender (M/F) | 336/233 | 163/105 | 0.627 |
| Education level | 15.8 ± 2.9 | 15.9 ± 2.7 | 0.708 |
| Baseline age (mean ± std) | 72.7 ± 7.8 | 73.8 ± 7.1 | 0.052 |
| **Cognitive function** | | | |
| Baseline MMSE (mean ± std) | 27.8 ± 1.7 | 26.8 ± 1.7 | <0.001 |
| Baseline ADAS11 (mean ± std) | 9.2 ± 4.0 | 12.9 ± 4.4 | <0.001 |
| Baseline ADAS13 (mean ± std) | 14.8 ± 6.1 | 20.8 ± 6.1 | <0.001 |
| Baseline CDRSB (mean ± std) | 1.3 ± 0.7 | 1.9 ± 0.9 | <0.001 |
| **Neuropsychological assessment** | | | |
| RAVLT.immediate (mean ± std) | 36.3 ± 10.6 | 28.5 ± 7.8 | <0.001 |
| RAVLT.learning (mean ± std) | 4.54 ± 2.5 | 2.8 ± 2.2 | <0.001 |
| RAVLT.perc.forgetting (mean ± std) | 55.2 ± 31.9 | 74.9 ± 29.1 | <0.001 |
| **Biological measures** | | | |
| Hippocampus volume (mean ± std) | 6990.0 ± 1091.2 | 6208.2 ± 1081.7 | <0.001 |
| Whole Brain volume (mean ± std) | 1.05e+06 ± 108539.2 | 1.0e+06 ± 114825.7 | <0.001 |
| Entorhinal volume (mean ± std) | 3644.1 ± 704.8 | 3129.0 ± 748.3 | <0.001 |
| FDG (mean ± std) | 6.3 ± 0.6 | 5.8 ± 0.6 | <0.001 |
| APOE4 (% positive) | 53% | 80% | <0.001 |
| PTAU (mean ± std) | 26.6 ±12.8 | 31.6 ± 12.0 | <0.001 |

### 4.1 Classification results

The performance of models were assessed on training, validation and test sets ensuring robustness against overfitting and to verify generalization ability to new, unseen data.

*4.1.1 Random Forest*

The results indicated that the model achieved an accuracy of 80%, demonstrating its effectiveness in accurately classifying two classes. Additionally, the model exhibited a high level of precision and recall, as evidenced by an F1 score of 85%. The mean cross-validation accuracy for the RF model was 79.3% ± 0.5%. Evaluation of model on all the three sets of data is depicted in table 4.2

**Table 4.2:** Performance evalution of RF model across training, validation and test set

| | **Accuracy (%)** | **Precision (%)** | **Recall (%)** | **F1 score (%)** |
|---|---|---|---|---|
| **Training set** | 80 | 84 | 74 | 79 |
| **Validation set** | 77 | 88 | 77 | 82 |
| **Test set** | 80 | 86 | 85 | 85 |

The 2 × 2 confusion matrix as illustrated in Figure 4.1 helps to visualize the performance by comparing the actual labels of the data with the predicted labels generated by the model. RF model misclassified 13/85 sMCI as progressive and 12/41 pMCI showing 85% sensitivity and a specificity of 70%.

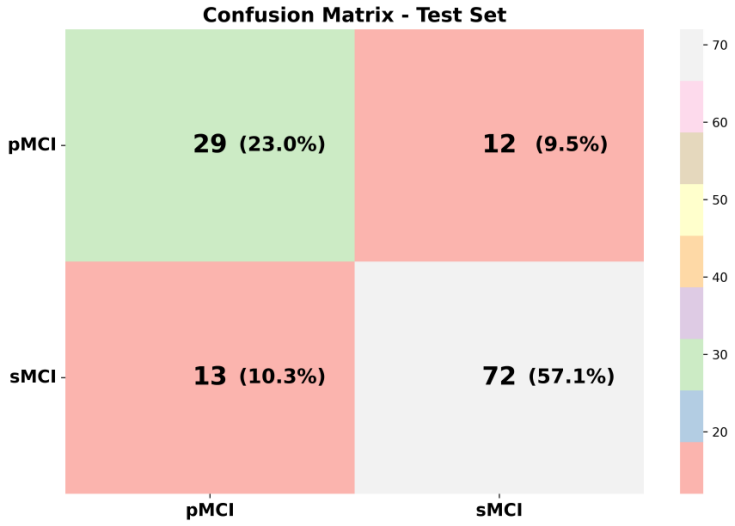



**Figure 4.1:** Confusion matrix returned from Random Forest

*4.1.2 Support Vector Machine*

The results demonstrated that the model attained an accuracy of 83.4%, effectively distinguishing the two classes. Furthermore, the model showed a commendable balance of precision and recall, which is reflected in the F1 score of 88%. The mean cross-validation accuracy for the SVM model was 82.1% ± 0.6%. The evaluation of the model across the three data sets—training, validation, and test is detailed in Table 4.3.

**Table 4.3:** Performance evalution of SVM model across training, validation and test set

| | **Accuracy (%)** | **Precision (%)** | **Recall (%)** | **F1 score (%)** |
|---|---|---|---|---|
| **Training set** | 89 | 93 | 84 | 88 |
| **Validation set** | 77 | 85 | 80 | 83 |
| **Test set** | 83.4 | 87 | 88 | 88 |

The 2 × 2 confusion matrix as illustrated in Figure 4.2 shows that SVM model misclassified 10/85 sMCI individuals as progressive and 11/41 pMCI as stable resulting in sensitivity of 88% and specificity of 73%.

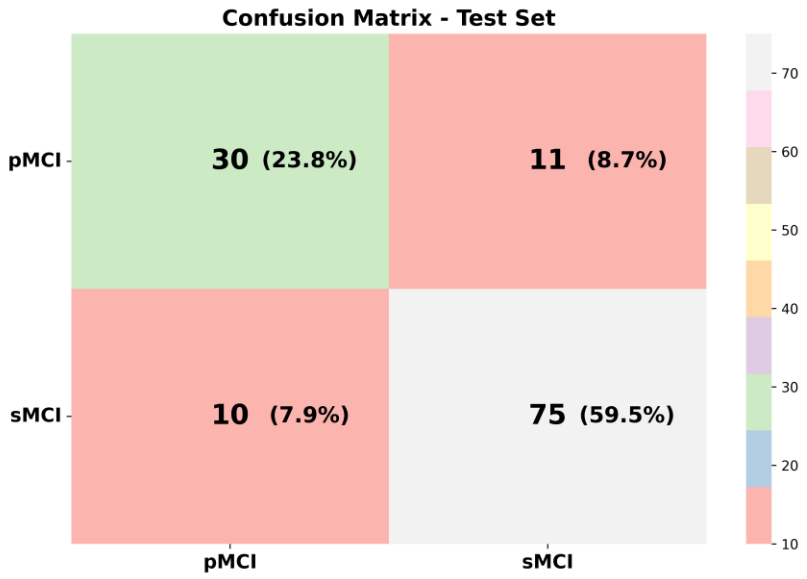



**Figure 4.2:** Confusion matrix returned from SVM

*4.1.3 Logistic Regression*

The results indicated that the model achieved an accuracy of 80.2%, successfully differentiating between the two classes. Moreover, it demonstrated a strong balance between precision and recall, as evidenced by an F1 score of 85%. The mean cross-validation accuracy for the SVM model was 79.2% ± 0.5%. The performance evaluation of the model on the training, validation, and test datasets is comprehensively detailed in Table 4.4.

**Table 4.4:** Performance evalution of LR model across training, validation and test set

| | **Accuracy (%)** | **Precision (%)** | **Recall (%)** | **F1 score (%)** |
|---|---|---|---|---|
| **Training set** | 79 | 81 | 76 | 78 |
| **Validation set** | 81 | 89 | 81 | 85 |
| **Test set** | 80.2 | 86 | 85 | 85 |

The 2 × 2 confusion matrix as illustrated in Figure 4.2 shows that LR model misclassified 13/85 sMCI individuals as progressive and 12/41 pMCI individuals as stable resulting in sensitivity of 85% and specificity of 71%.

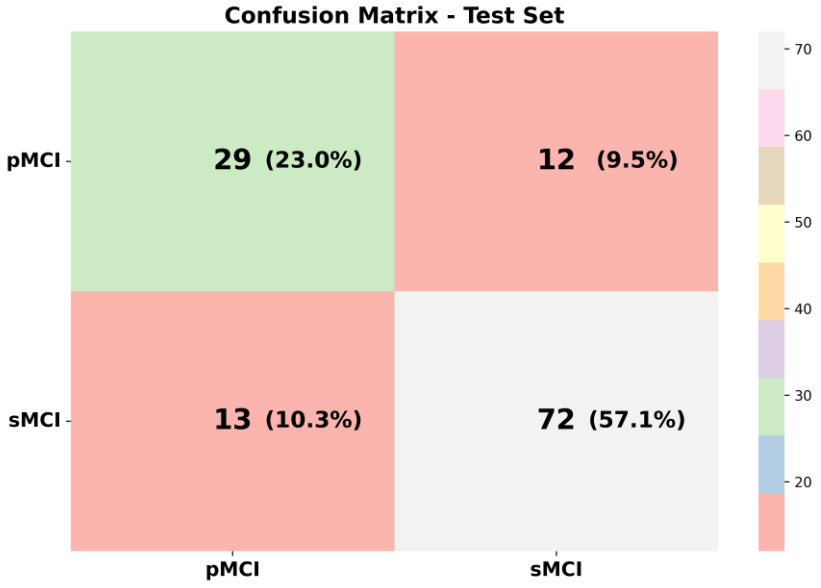
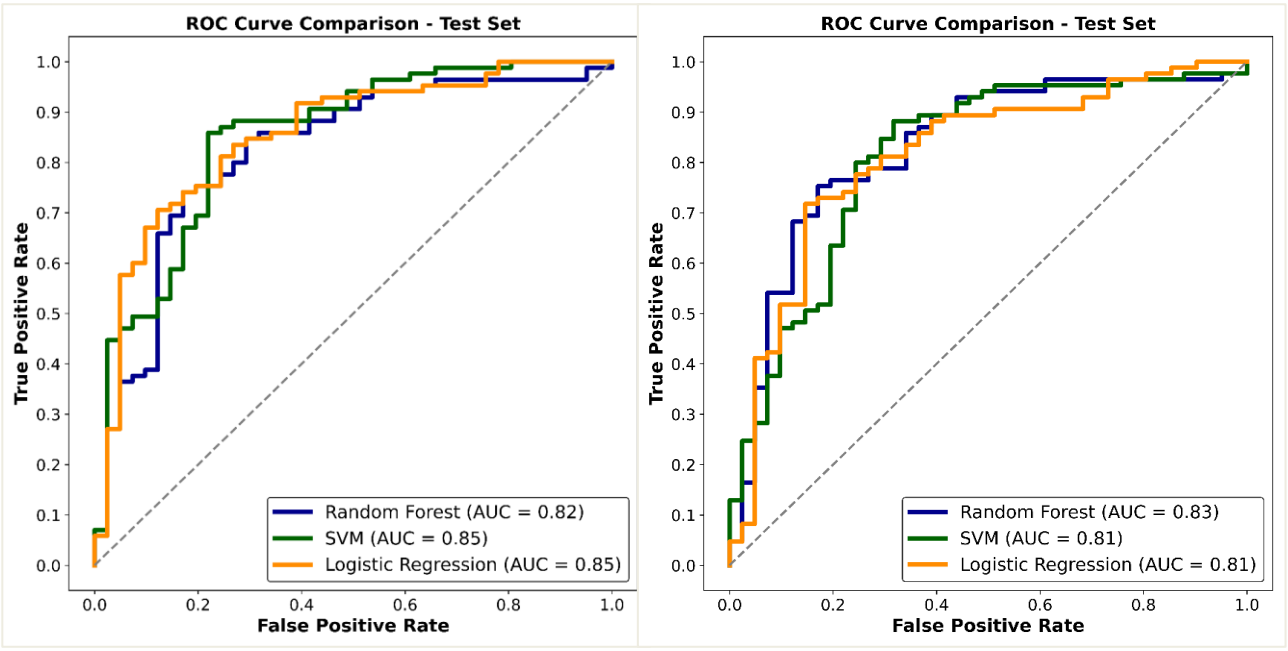



**Figure 4.3:** Confusion matrix returned from LR

The SVM model demonstrated significantly better performance compared to both the LR and RF models ($p < 0.05$). This result highlights the robustness of the SVM model, as evidenced by its superior performance on unseen test data and statistical validation through ANOVA.

Model performance was additionally evaluated using the Receiver Operating Characteristic (ROC) curve, which involved combining various modalities. This assessment aimed to analyze the impact of using a single modality versus a combined approach. Surprisingly when cognitive tests alone were used to train model, they did not show much differences among results indicating that cognitive tests alone can effectively classify between two classes making this approach cost effective. Figure 4.4 (a) displays the ROC curve for the proposed approach using all modalities to classify the two classes, while Figure 4.4 (b) presents the ROC curve when only cognitive tests were utilized.

Table 4.5 shows the comparison when different modalities were utilized as features suggesting that cognitive tests can classify between two classes, thus offering a cost effective prediction method.




**(a)** **(b)**

**Figure 4.4:** (a) ROC curve when all modalities were used. (b) ROC curve when only cognitive tests were used

**Table 4.5:** Models experiments on different modalities. The classification report of each model on different modalities showing accuracy, precision, recall, F1 score and AUC

| Classifier | Modalities | sMCI/pMCI | ACC (%) | Precision (%) | Recall (%) | F1 score (%) | AUC |
|---|---|---|---|---|---|---|---|
| **SVM** | Cognitive tests | 569/268 | 80 | 86 | 85 | 85 | 0.81 |
| | Cognitive tests, MRI,PET | 569/268 | 80 | 85 | 86 | 86 | 0.82 |
| | Cognitive tests, MRI, PET, CSF, APOE4 | 569/268 | 83 | 87 | 88 | 88 | 0.85 |
| **LR** | Cognitive tests | 569/268 | 78 | 85 | 81 | 83 | 0.81 |
| | Cognitive tests, MRI,PET | 569/268 | 79 | 86 | 83 | 84 | 0.84 |
| | Cognitive tests, MRI, PET, CSF, APOE4 | 569/268 | 80 | 85 | 86 | 85 | 0.85 |
| **Random Forest** | Cognitive tests | 569/268 | 79 | 83 | 87 | 85 | 0.83 |
| | Cognitive tests, MRI,PET | 569/268 | 79 | 84 | 88 | 86 | 0.83 |
| | Cognitive tests, MRI, PET, CSF, APOE4 | 569/268 | 80 | 86 | 85 | 85 | 0.82 |

# CHAPTER 5: DISCUSSION

Alzheimer's disease (AD) is a complex, multifactorial, and challenging neurological disorder affecting millions of individuals worldwide. It is characterized by cognitive decline, memory loss, and impairments in daily functioning, presenting significant challenges for affected individuals. Early detection and identification are crucial for disease management, making them a primary objective in the research field. Early diagnosis may help slow down or even halt the progression of cognitive decline .[11] [23] This study advances efforts in this area by classifying patients diagnosed with Mild Cognitive Impairment (MCI) at their first visit into two groups: those who progressed to AD during the observation period (pMCI) and those who remained MCI (sMCI). Multi-modal data, including cognitive test scores, MRI, PET, CSF biomarkers, and the APOE-ε4 allele, were used to run three supervised machine learning (ML) algorithms using baseline examination data. The results demonstrate the effectiveness of ML approaches in classifying patients between stable MCI and progressive MCI groups, with cross-validation accuracies of 83.4%, 80.2%, and 80% for SVM, LR, and RF, respectively.

Exploratory data analysis revealed that key indicators of MCI patients progressing to AD include impaired memory function, reduced hippocampal volume, diminished glucose metabolism, and increased accumulation of Tau protein in the brain. Additionally, a higher proportion of APOE-ε4 carriers (80%) was observed among individuals progressing to AD. The study population was predominantly educated, with an average of 16 years of education.

Most recent studies suggested that FDG-PET can help in the early detection of AD as glucose metabolism start decreasing in brain in the early stages of disease. [23], [24]When combined with other modalities, it helps in the confirm diagnosis of patient.[25] In the proposed approach, it has been noticed that all other modalities help in classifying individuals except of demographic characteristics. Feature importance from F-score revealed that cognitive test scores contributed significantly in predicting between two classes. Furthermore, when models were trained using only cognitive tests, they achieved comparable accuracy in discriminating between the two classes. It was noted

that although using all modalities achieved slightly greater accuracy, cognitive tests alone can also effectively classify between the two classes, making this approach more cost-effective. This cost-effective approach is particularly beneficial for individuals who cannot afford all the expensive tests. Moreover, it will assist in the early identification of the disease. Table 4.5 presents a comparison of the performance when various modalities are fed into a classifier. It was also noticed that MRI and FDG-PET have equal effect on performance of ML algorithm. So, individuals who cannot go for both of tests due to their expensive nature, can opt one of them to visualize the internal structures of brain. SVM performed better than other models in classification framework and achieved greater specificity and sensitivity as depicted by evaluation metrics of models. We also implemented fivefold cross validation to assess the model performance. The noted difference between sensitivity and specificity may stem from the smaller size of the pMCI group compared to the sMCI group, which likely led to reduced specificity relative to sensitivity.

The findings of this study have important implications for early detection, intervention, and management of Alzheimer's disease. Machine learning models can serve as valuable tools in identifying individuals at risk of disease progression, enabling timely interventions and personalized treatment strategies. However, it is important to acknowledge the limitations of this study. Although the proposed method yielded promising results in forecasting the progression from MCI to AD, it still holds some limitations. First is, its translation into clinical practice is very less because of scarcity of data. Patients should be encouraged to seek clinical evaluation as soon as they notice symptoms of cognitive decline, as our study indicates that cognitive tests can also aid in the identification of the disease. Data used in this study is mostly of educated people while studies suggest that less educated people who face socio-economic challenges are most likely to get AD because they have limited access to healthcare services and higher rates of chronic stress which leads to cognitive decline and neurodegenerative diseases. ADNI serves as an invaluable resource for AD research; however the data it collects comes exclusively from clinical sites in the US and Canada.[26] This geographical limitation may introduce bias into the dataset, potentially affecting the generalizability of findings to other populations worldwide. To improve the generalizability of research

findings in diagnosing AD, collaborative efforts are needed to gather data from more diverse populations across various regions.

Overall, this study contributes to advancing our understanding of AD progression and highlights the potential of machine learning approaches in predicting disease trajectory. By addressing the identified limitations and continuing to refine predictive models, researchers can further improve the accuracy and applicability of these tools in clinical practice and research settings.

# CHAPTER 6: CONCLUSION

The current research study suggests a multimodal machine learning based classification framework to categorize two groups of patients: one who remained stable MCI and the other who progressed to AD. By incorporating five modalities: PET, cognitive test scores, MRI, genetic data and CSF, models' achieved promising accuracies of 83.4%, 80.2% and 80% for SVM, LR and RF respectively. Furthermore, this study suggests that patients on a trajectory towards AD have lower clinical tests scores than MCI patients. The experimental findings suggest that this approach can effectively forecast the progression of the disease from MCI to AD based on baseline clinical examinations, facilitating early identification crucial for the treatment of this neurodegenerative disease. Additionally, our findings also highlight the importance of cognitive tests in disease identification, making this approach cost effective. Although we applied three ML algorithms, the achieved promising accuracy suggests potential for further exploration. We believe that the study can serve as a catalyst for developing additional ML algorithms and automated prognostic tools, ultimately aiming to design supportive aid to clinicians who provide prognostic information to individual patients.

The next chapter provides recommendations for future research paths as well as a full examination of the study's recommendations. This extensive discussion chapter includes key insights and a review of the study's findings, as well as information on any research gaps, consequences, limits, and potential future paths.

# CHAPTER 7: FUTURE WORK AND RECOMMENDATIONS

It’s imperative to expand the sample size of future studies. A larger and more diverse cohort would greatly enhance the predictive power and generalizability of machine learning models. Larger sample size will allow for better representation of variability in disease progression leading to more robust and reliable predictions. It will help to contribute the development of more accurate and clinically relevant predictive models for AD.

Moreover, future research should prioritize the inclusion of patients from diverse educational levels and cultural settings. While the ADNI dataset primarily consists of educated individuals, it's essential to account for the broader demographic landscape affected by Alzheimer's disease. By doing so, we can mitigate potential biases and ensure that predictive models accurately represent the diversity of patients affected by the condition.

Furthermore, efforts should be directed towards translating research findings into actionable clinical tools and guidelines. Findings from predictive models can assist healthcare providers in early detection, prognosis, and personalized treatment planning for patients with Alzheimer's disease. By addressing these recommendations, future research endeavours can contribute to advancing our understanding of AD progression and facilitate the development of more effective strategies for early detection, intervention, and management of this disease.

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