AI-Based Forecasting of Mild Cognitive Impairment to Alzheimer's Disease Using Multi-Modal Approach

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Supervisor: Dr. Ahmed Fuwad

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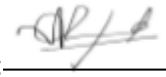
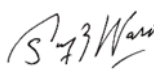
Supervisor Name: Dr. Ahmed Fuwad Signature: 

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

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I dedicate this thesis to all those who have shown kindness, support, and encouragement throughout my journey; your unwavering belief in me has been a source of strength and inspiration. A special nod goes to the makers of Panadol and Inderal, for easing the headaches and anxieties that came with this process!

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LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

AD	AD
CSF	Cerebrospinal Fluid
eMCI	Early Mild Cognitive Impairment
FDG	Fluorodeoxy Glucose
GB	Gradient Boosting
IBS	Integrated Brier Score
lMCI	Late Mild Cognitive Impairment
MCI	Mild Cognitive Impairment
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
RSF	Random Survival Forest
ST	Survival Tree
XST	Extra Survival Trees

ABSTRACT

With no medication currently available and a clinical trial failure rate of 99.6% for Alzheimer's disease (AD) , early diagnosis is crucial to prevent its progression. MCI has been identified as a transitional stage between healthy aging and AD, making it promising for early detection. In this study, we propose a machine learning (ML) based survival analysis approach to predict the time to AD conversion in early MCI and late MCI stages separately, as we found that the progression rate varies in both stages. Unlike typical ML classifiers, ML-based survival analysis models can provide information about the timing and likelihood of disease progression. We employed multiple ML survival models, including Random Survival Forest (RSF), Extra Survival Trees (XST), Gradient Boosting Survival Analysis (GB), Survival Tree (ST), Cox-net, and Cox Proportional Hazard (CoxPH), on 291 eMCI and 546 lMCI subjects. The study also compared different data modalities, such as cognitive tests, neuroimaging tests, and cerebrospinal fluid (CSF) biomarkers, both individually and in combination to identify the most influential features for the models' performance. The results show that RSF outperformed traditional CoxPH and other ML models used in this study. For the eMCI dataset, RSF trained on multimodal data achieved a C-Index of 0.96 and an IBS of 0.02. For the lMCI dataset, the C-Index was 0.82 and the IBS was 0.16. Additionally, the multimodal analysis highlighted the importance of cognitive tests, as they exhibited a statistically significant improvement over other modalities and multimodal data, demonstrating their reliability in predicting AD progression. Finally, individual survival curves were generated using RSF on baseline data to predict the probability of early onset of AD in patients. This facilitates clinical decision-making by assisting clinicians in developing personalized treatment strategies and implementing preventive measures to slow down or potentially stop the progression of AD during its early stages.

Keywords: AD, Early Prediction, Machine Learning, Survival Analysis.

CHAPTER 1: INTRODUCTION

Alzheimer's disease (AD) is a complex and multifaceted neurodegenerative disorder that has become a pressing global health concern. The staggering prevalence of AD and its profound impact on public health cannot be overstated. As the most common cause of dementia, AD affects millions of individuals worldwide, with devastating consequences for patients, caregivers, and society as a whole. According to the World Health Organization, dementia affects approximately 50 million people globally, with AD accounting for 60-70% of these cases. This translates to an estimated 30-35 million individuals living with AD worldwide [1]. The burden of this disease is expected to grow exponentially in the coming decades, with projections indicating that the number of people with dementia will nearly triple by 2050, reaching a staggering 152 million [2].

The prevalence of AD also highlights the urgent need for improved prevention, early detection, and effective treatments. Despite significant research efforts, currently, there is no cure for AD, and available therapies only provide temporary relief of symptoms or slow down the disease progression. The high failure rate of clinical trials, estimated at 99.6%, underscores the complexity of the disease and the challenges faced by researchers and healthcare professionals in developing new interventions [3]. Addressing the public health crisis posed by AD will require a multifaceted approach, including increased funding for research, improved access to diagnostic tools and support services, and the development of innovative strategies for prevention and treatment [4].

1.1 AD Pathophysiology

Alois Alzheimer, a German psychiatrist, published the first description of the illness that bears his name, in 1906. He identified neurofibrillary tangles and amyloid plaques in the brain that resulted in progressive degeneration [5]. Extensive research has been conducted since its discovery to have a better understanding of the causes, diagnosis, and finding treatment of AD. While numerous aspects remain unexplained, Alzheimer's is increasingly recognized as a complicated disorder influenced by a variety

of causes. The main causes of AD are often said to be the aggregation of amyloid and tau proteins, oxidative stress, and inflammation.

The Amyloid Precursor Protein (APP) plays an important role in the etiology of AD. This protein can combine and form plaques within the brain, resulting in decreased intercellular communication, inflammation, and brain tissue damage. Researchers identified beta-amyloid (Aβ) as the primary component of plaques associated with AD in 1984 [6]. In subsequent research conducted in 1991, investigations into genetics unveiled that mutations within the APP gene have the potential to generate abnormal forms of beta-amyloid; which, in particular family groupings, may be a factor in the early development of AD [7].

Based on such findings, numerous researchers believe that the aggregation of beta-amyloid (Aβ) initiates a chain reaction of detrimental events and functional disruptions in neurons, eventually leading to the onset of dementia [8]. Subsequent research provided further evidence supporting beta-amyloid's substantial role in the progression of AD, yet the precise underlying mechanisms remain unknown. As a result, the most promising treatment options try to prevent amyloid plaque formation. Treatment possibilities for AD include therapies that target beta-amyloid and its receptors. These methods include the use of vaccinations, and antibodies aimed against beta-Amyloid Modulators or inhibitors of gamma-secretase and beta-secretase, amyloid degrading proteases, microRNAs, and amyloid dyes are further potential therapy options [9].

The pathology of AD is significantly influenced by the tau protein. It typically participates in the organization and strength of microtubules. However, AD experiences abnormal deviations after translation and clumps together, forming neurofibrillary tangles (NFTs) [10]. The exact mechanisms by which tau protein contributes to AD are still being studied, but it is believed that the atypical aggregation of tau protein disrupts the regular functioning and signal transmission among neurons, leading to neuronal death and brain damage. Researchers are proposing new therapies to prevent tau protein

accumulation in AD, such as inhibiting aggregation, proteolysis, and tau phosphorylation, promoting tau clearance, and stabilizing microtubules.

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 [11].

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 ' powerhouse' [12]. Neuronal function is dependent on mitochondrial integrity and well-functioning bioenergetics. However, with AD, a variety of variables, including elevated oxidative stress, impaired Ca2+ homeostasis, and a disrupted mitochondrial genome, can impair mitochondrial function [13]. 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 suggests the pivotal role of mitochondria in AD, and therapeutical approaches that target mitochondria are under consideration [14].

1.2 Signs & Symptoms of AD

One of the initial and most noticeable symptoms of AD is memory impairment, especially difficulty in remembering newly acquired information. People with AD might repetitively ask the same questions, overlook significant dates or events, and frequently

misplace belongings. Such memory deficits can disrupt everyday tasks and social engagements, leading to frustration and anxiety for both the individuals affected and their family members. As the disease starts progressing, cognitive difficulties extend beyond memory loss. Patients with AD may experience challenges in planning, problem-solving, and completing familiar tasks, such as managing finances or following a recipe. They may also struggle with language, finding the right words to express their thoughts or understanding complex conversations [6]. These cognitive deficits can lead to confusion, disorientation, and difficulty navigating familiar environments. In addition to cognitive changes, AD can also impact an individual's mood and behavior. Patients may experience mood swings, depression, anxiety, or apathy, which can further complicate their daily lives and relationships. Behavioral changes, such as agitation, aggression, or wandering, are also common as the disease advances, often causing distress for both the patient and their caregivers. As AD advances, affected individuals may struggle with fundamental self-care activities like bathing, dressing, and eating. They might also face challenges in recognizing familiar faces, a condition referred to as agnosia. In the later stages, patients often become entirely reliant on others for their care and may undergo substantial physical deterioration, including issues with walking, swallowing, and controlling bodily functions [15].

Early symptoms of AD include cognitive decline which leads to memory impairment and frequent bouts of forgetfulness which eventually leads to dementia. This is followed by the progression of anomia which is the inability to retain and retrieve vocabulary. Anomia is followed by aphasia which is a language disorder that is caused by cognitive dysfunction in the part of the brain that controls linguistic expressions and comprehension. AD patients also experience semantic impairment, difficulty in problem-solving and concentrating on a particular task, and often feel disoriented. Patients suffering from AD also experience neuropsychiatric symptoms which include depression, apathy, auditory or visual hallucinations, delusions, irritability, and psychosis. In the final stages of AD, the patient suffers from ataxia and eventually loses mobility completely.

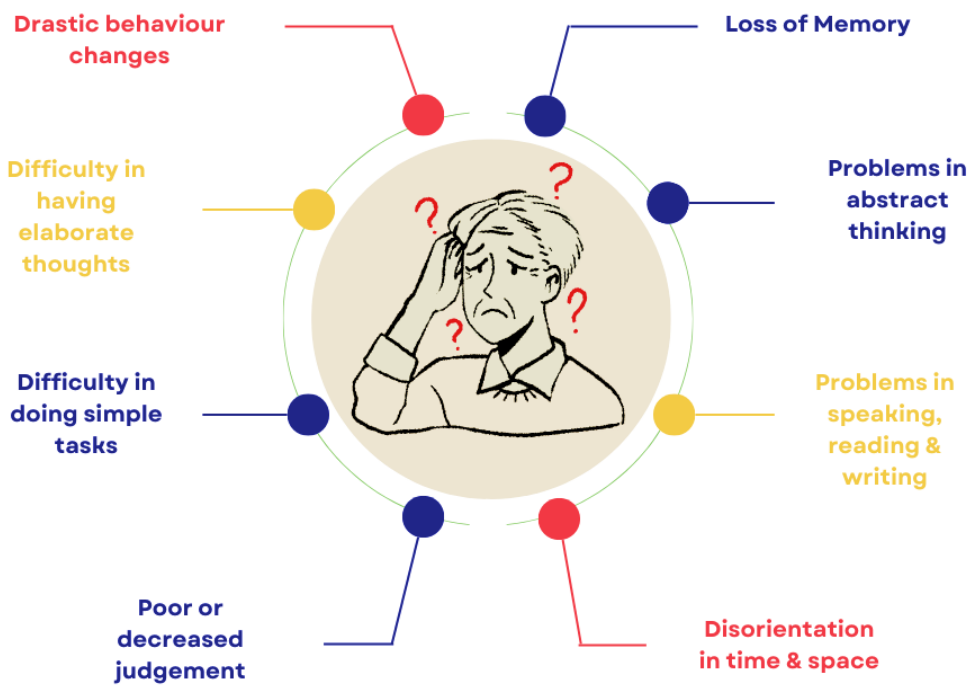


Figure 1.1: Signs and Symptoms of AD

1.3 Propagation of AD

Certain classes of neurons are more prone to the abnormalities present in AD. The infiltration is remarkably similar and shows minor variation from patient to patient. The spread follows a predictable pattern and starts in glutamatergic cells in the trans-entorhinal region and then slowly spreads into the entorhinal cortex before it spreads into the hippocampus. The neuron cells that were myelinated late during the development phase are the first ones the disease gets into and the ones that were myelinated first are the most resistant to AD. The spread follows an inverse pattern of cortical myelination. Based on the severity of encroachment, Alzheimer's can be classified into six distinct stages which are also called the Braak staging system. The trans entorhinal region is the first area affected by the disease [16]. This region develops late and is responsible for navigation and perception of time. During the first stage, the tau abnormality is only seen in the trans-entorhinal cortex which slowly spreads into the entorhinal and hippocampus in the second stage. The staging system shows a strong association with cognitive

impairment as well. Patients in stage 1 and 2 shows no manifestation of cognitive symptoms and are classified as CDR (Clinical Dementia Rating). Clinically this phase represents the pre-clinical phase of the disease [17].

During this stage, the transentorhinal and entorhinal regions are significantly impacted, with moderate alterations observed in the hippocampal formation, temporal and insular pro-neocortical areas, and some subcortical nuclei. At this point, the mature neocortex remains free of neurofibrillary tangles. Stage 4 starts with the damage spread from the entorhinal region to higher-order association areas. The first symptoms of the disease appear at this stage as the destruction is severe enough to hinder the flow of information between the higher-order limbic system and the prefrontal cortex. Asymmetrical affliction is also seen in certain patients occasionally [18]. The asymmetry of the disease in the hemisphere may be present, but it goes through its typical stages. One hemisphere may be lagging a stage but asymmetry with a hemisphere lagging 2 or more stages has not been observed so far. Due to initial clinical symptoms, stages 3 and 4 are considered the morphological counterparts of incipient Alzheimer’s. At stage 5, the symptoms are severe enough to hinder the patient's quality of life and that is why diagnosis is made usually at this stage. Although the disease may exhibit an asymmetrical pattern within the hemisphere, it follows its typical stages of progression. It is possible for one hemisphere to be slightly behind in a stage, but there have been no observations of a hemisphere lagging two or more stages behind. The staging system is also highly correlated with cognitive impairment. Stages 3 and 4 are considered to be the morphological equivalents of early-stage Alzheimer's due to their initial clinical symptoms. Diagnosis is typically made at stage 5, when the symptoms become severe enough to significantly impact the patient's quality of life. Stage 5 is associated with widespread destruction of the neocortex, especially brain-association areas and the infestation spread superolateral towards the motor areas in stage 6. The atrophy of the brain is macroscopically detectable in this stage [19].

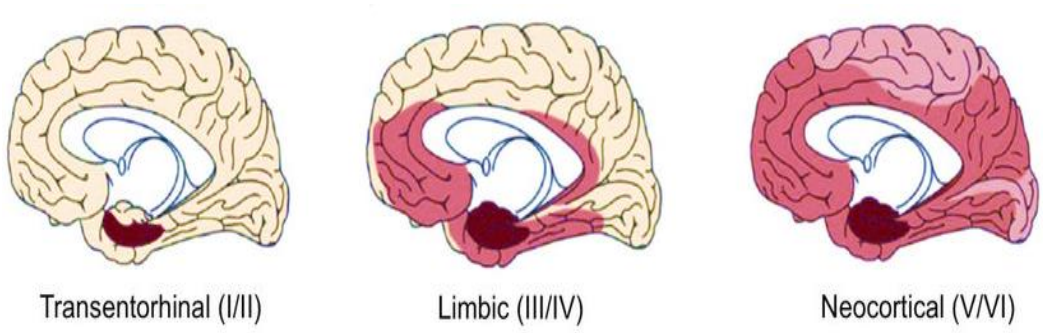


Figure 1.2: Braak Staging of AD.

1.4 Stages of AD

AD (AD) is a progressive neurodegenerative disorder that can be divided into several stages, each with its own set of characteristics and symptoms. These stages include preclinical AD, mild cognitive impairment (MCI) due to AD, and AD dementia.

1.4.1 Preclinical AD

Preclinical AD represents the earliest phase of the condition, marked by Alzheimer's-related changes in the brain, such as the buildup of amyloid-beta proteins and tau tangles, without any evident symptoms. This stage can persist for years or even decades before clinical symptoms appear. The NIA-AA criteria for preclinical AD outline three stages:

1. Stage 1: Cognitively normal individuals with abnormal amyloid markers
2. Stage 2: Cognitively normal individuals with abnormal amyloid and injury markers
3. Stage 3: Cognitively normal individuals with abnormal amyloid and injury markers and subtle cognitive changes

The proportion of individuals with preclinical AD increases with age and is higher in APOE-ε4 carriers. Studies have shown that the risk of progression to MCI or dementia increases with advancing preclinical AD stage.

1.4.2 Mild Cognitive Impairment

MCI due to AD is marked by slight alterations in memory, thinking, and other cognitive functions that are perceptible to the individual or their loved ones but do not greatly disrupt daily activities. Symptoms of MCI due to AD may include:

- Short-term memory loss
- Difficulty planning or performing familiar tasks
- Changes in speech
- Disorientation to time and place

MCI is recognized as a transitional phase between the cognitive variations associated with normal aging and the more severe cognitive impairment seen in AD [20]. While individuals with MCI may experience subtle memory lapses or other cognitive difficulties, these symptoms do not significantly impact daily functioning to the extent seen in dementia. The rate at which MCI progresses to dementia varies. Studies have found that between 32.7% and 70.0% of individuals with MCI due to AD develop AD dementia within 3.2 to 3.6 years of follow-up [21]. Research indicates that individuals with MCI are significantly more likely to develop AD compared to those without MCI.

1.4.3 Alzheimer's Disease Dementia

In the final stage of AD, individuals experience more pronounced cognitive and functional changes, such as severe memory loss, difficulty with basic activities of daily living, and changes in personality and behavior. Symptoms of AD dementia may include:

- Severe memory loss
- Difficulty with basic activities of daily living
- Changes in personality and behavior
- Difficulty with fine motor coordination and changes in gait

Individuals with severe dementia due to AD will require assistance with most normal activities and may experience a significant decline in cognitive and physical abilities.

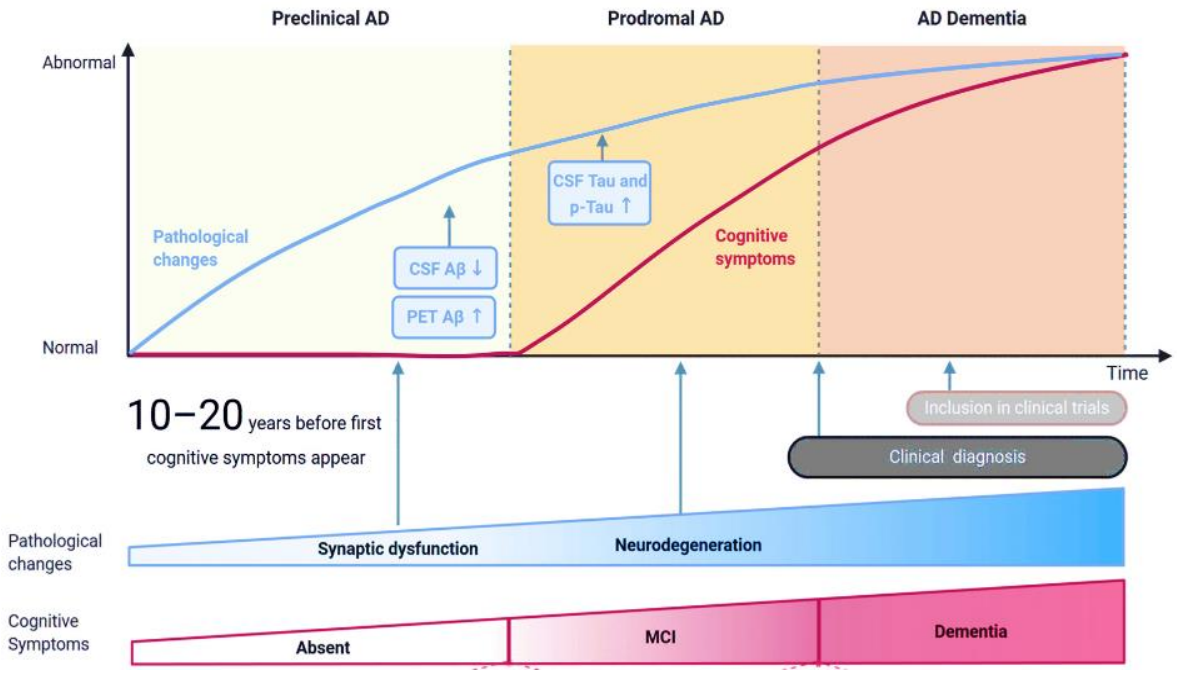


Figure 1.3: The three stages of AD: Preclinical AD, Prodromal AD, AD Dementia

1.5 Mild Cognitive Impairment as a Critical Stage

MCI is a critical phase in the spectrum of cognitive decline, acting as an intermediary between normal aging and AD. Those with MCI exhibit cognitive changes that are more severe than normal age-related decline but do not yet qualify for a dementia diagnosis. Recognizing and understanding MCI is essential as it often precedes the onset of AD, offering a window of opportunity for early intervention and management. MCI is recognized as a transitional phase between the cognitive changes associated with normal aging and the more severe cognitive impairment seen in AD. While individuals with MCI may experience subtle memory lapses or other cognitive difficulties, these symptoms do not significantly impact daily functioning to the extent seen in dementia [22]. However, the presence of MCI indicates an increased risk of progressing to AD, making it a critical stage for monitoring and intervention. One of the key features of MCI is its elevated risk

of progression to AD. Research has shown that individuals with MCI have a significantly higher likelihood of developing AD compared to those without MCI. The identification and monitoring of individuals with MCI are crucial for early detection and intervention, as timely measures may help delay or mitigate the onset of AD and its associated symptoms.

1.5.1 Subtypes of MCI: Early MCI (eMCI) and Late MCI (lMCI)

MCI can be further categorized into subtypes based on the severity and progression of cognitive impairment. Early MCI (eMCI) is characterized by mild cognitive deficits that are often subtle and may not significantly impact daily functioning. In contrast, Late MCI (lMCI) represents a more advanced stage of cognitive decline, with symptoms that are closer to those seen in early AD. Research has shown that individuals with lMCI have a higher likelihood of progressing to AD compared to those with eMCI. Studies have demonstrated varying conversion rates from MCI to AD, with lMCI showing a more rapid progression. Understanding the distinctions between eMCI and lMCI, as well as their respective conversion rates, is essential for predicting the course of cognitive decline and implementing appropriate interventions to support individuals at risk of developing AD. Research has indicated that individuals with lMCI are more likely to develop AD than those with eMCI. Conversion rates from MCI to AD have been found to vary in different studies, with lMCI showing a faster progression. It is crucial to comprehend the differences between eMCI and lMCI, as well as their respective conversion rates, in order to predict the trajectory of cognitive decline and implement suitable interventions for individuals at risk of developing AD.

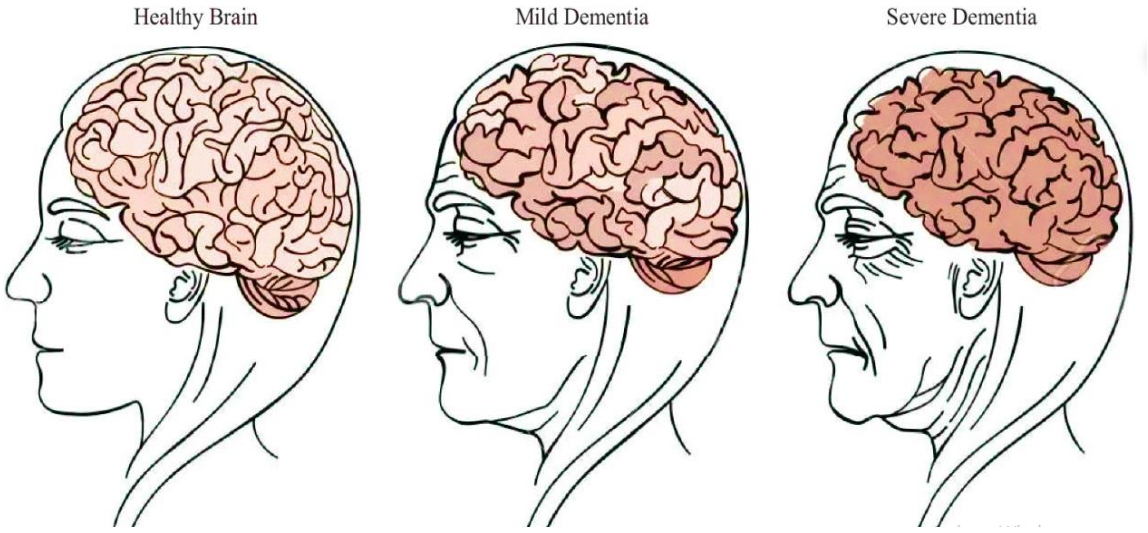


Figure 1.4: AD Progression.

1.6 Diagnostic Tools of AD

1.6.1 Neuropsychological Assessments

Neuro-psychometric tests are a simple and non-invasive way to detect cognitive impairment since they are typically brief, low-cost, and can be administered quickly, making them a useful tool in the therapeutic context.

Since 1975, Mini Mental State Exam (MMSE) developed by Folstein, has been a benchmark and extensively tested to asses cognitive impairment [23]. As advancements in research have shifted the emphasis to early identification of AD, numerous tests that are sensitive enough to detect AD in its early stages have been established. Nasreddine's Montreal Cognitive Assessment (MoCA) is a concise cognitive screening test that is highly sensitive and specific in diagnosing MCI [24]. In a study conducted on individuals with moderate AD, MMSE demonstrated 78% sensitivity, whereas MoCA achieved a perfect detection rate of 100%. Furthermore, research studies have shown that the Mini-Cog, which consists of a clock drawing activity and a three-item memory test, has a high

level of accuracy in identifying people with probable dementia ranging from 76% to 99%, with specificity rates ranging from 89% to 96%.

The AD Assessment Scale Cognitive subscale (ADAS-Cog), which was initially established to evaluate cognitive abilities in individuals with AD ranging from mild to moderate, has undergone modifications aimed at broadening its applicability in pre-dementia research [25]. These modifications have led to various ADAS-Cog variants with increased sensitivity and improved accuracy in predicting cases of dementia. The 'Clinical Dementia Rating' (CDR) scale, which is a diagnostic and staging test, is used to evaluate and categorize the extent of dementia in people with AD. Six distinct cognitive and functional domains are assessed by clinicians, and the sum of these domains' scores, or CDR-SB (Sum of the Boxes) score, has proven to have a strong predictive ability for identifying dementia and tracking the progression of cognitive or functional decline.

AD also impacts episodic memory, hence to assess episodic memory the 'Free and Cued Selective Reminding Test' (FCSRT), the 'California Verbal Learning Test II' (CVLT-II), and the 'Wechsler Logical Memory Subtest' is utilized. The Free and Cued Selective Reminding Test (FCSRT) is more predictive in identifying people with memory complaints who subsequently develop AD, but the California Verbal Learning Test (CVLT) displays increased sensitivity in detecting early-stage abnormalities in episodic memory. The FCSRT performs better than other tests in terms of sensitivity and specificity for identifying prodromal AD, according to studies. Furthermore, the FCSRT outperforms the Wechsler Logical Memory Delayed Recall in accurately forecasting the odds of cerebrospinal fluid (CSF) profile resembling AD in adults. Therefore, incorporating a neuro-psychometric test capable of detecting subtle cognitive impairments in patients becomes advantageous when constructing a screening battery to identify preclinical and early symptomatic AD.

1.6.2 Imaging Tests

MRI is a noninvasive imaging technique extensively used for brain and spinal cord imaging. The images can provide vital information about the person's cognitive health and detect many brain-related diseases. MRI is widely used in Alzheimer's detection and can detect Alzheimer's before the onset of dementia. The most commonly used is structural MRI which can detect changes in brain volume and structure and for this reason, can detect many neurological conditions. Medial temporal region brain shrinkage is a common observation in AD patients. Medial temporal lobe atrophy is another early symptom of AD and can be utilized to diagnose the disease early. The degree of brain atrophy in the medial temporal area, which includes the entorhinal cortex and the hippocampal tissue, can be assessed by structural MRI [26]. Additionally, it has been shown that medial temporal lobe atrophy is a reliable predictor of both the progression of cognitive symptoms in healthy people and the development of MCI into Alzheimer's. Earlier techniques of sMRI were manual in the volumetric analysis of the brain regions atrophied due to Alzheimer's and required a good knowledge of neuroanatomy and in also delineating parts of the brain. The more recent approaches use automatic methods for volumetry which are quick compared to manual-based volumetry and are easy compared to the previous manual methods. Voxel-based morphometry is an automated method for volumetry that makes use of specialized analysis-oriented software. By utilizing the voxel-based morphometry method, these software are specialized in differentiating between healthy and sick based on brain volume and region of interest [27]. MRI is a noninvasive imaging technique that is widely employed for the purpose of brain and spinal cord imaging. The resultant images can yield crucial insights into an individual's cognitive well-being and facilitate the identification of various cerebral disorders. Notably, MRI has found extensive application in the realm of AD detection, enabling its identification prior to the onset of dementia. Of particular prominence is the utilization of structural MRI, which is capable of detecting alterations in brain volume and structure, thereby rendering it highly effective in the identification of diverse neurological conditions.

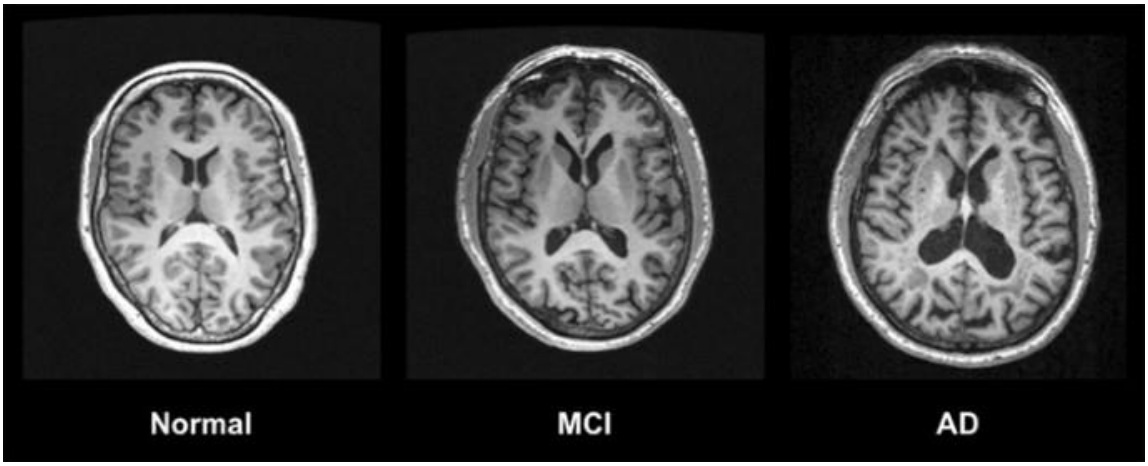


Figure 1.5: Changes in the brain of normal, MCI, and AD individuals, captured via MRI.

PET scan is a widely used method and is used extensively to detect many diseases. Brain scans using PET can be used to detect Alzheimer's. The method is widely used in the diagnosis of AD due to its sensitivity to detect the disease. Alzheimer's neuropathology precedes cognitive symptoms, and PET can identify the illness before symptoms appear, but the problem with this method is its exuberantly high cost. There are a few tracer elements available with the help of which clinicians can diagnose certain neurological conditions like AD [28]. The tracer element most used for Alzheimer's detection is 2-fluoro-2-deoxy-d-glucose (F-FDG). This tracer element can help 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. 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 Alzheimer's 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 will develop MCI [29]. Certain neurotransmitter systems are also impaired in AD and with the help of specialized tracers, we can detect the abnormality of

the neurotransmitter systems in AD patients. The affected neurotransmitter systems include cholinergic, serotonergic, and dopaminergic systems. Postmortem study reports show a reduction in the level of acetylcholine (ACH). Moreover, studies suggest a decrease in the activity of enzymes important for ACH production and metabolism while a reduction in butyrylcholinesterase activity which is localized in glial cells and amyloid plaques indicating an increase in the prevalence of amyloid plaques. The reduction in ACH activity is also seen in AD patients using certain radio ligands compared with same-age controls. MCI patients had an 8-15% drop in cortical ACH activity. Reduced ACH activity in MCI patients helped predict when MCI will turn into AD. Changes in dopaminergic as well as serotonergic systems have also been observed in AD patients during autopsy. Single photon emission CT(SPECT) using a tracer I-FP-CIT, showed a reduction in dopamine reuptake transporters in Lewy bodies dementia patients while no reduction in the case of AD. A multicenter clinical trial has demonstrated the effectiveness of I-FP-CIT SPECT in distinguishing between AD and dementia with Lewy bodies. Reduced levels of a 5-HT receptor were found in the hippocampus of AD patients after a PET scan, pointing to problems in their serotonergic systems. Some imaging techniques have also been developed that with the help of a tracer element, enable in vivo imaging of amyloid plaque. These imaging methods have been demonstrated to more accurately distinguish between moderate cognitive impairment in amnestic and non-amnestic individuals than the FFDG marker. Pittsburgh compound B(PIB) was among the first and the most studied radio ligands for amyloid imaging. The first research to make use of this tracer found that 16 Alzheimer patients retained more C-PIB in cortical and subcortical areas than healthy controls. In MCI and AD patients, a correlation between C-PIB retention and episodic memory quality has also been noted. However, autopsy investigations are necessary to validate the in vivo link between C-PIB retention and amyloid burden. Alterations in C-PIB retention and CSF amyloid beta can occur in the initial AD stages, Before changes in functional characteristics including cognition and cerebral glucose metabolism. Despite the sensitivity of the C-PIB to detect AD in the initial stage, F-FDG is a better tracer to track disease progression. Activated microglia is also a histopathological feature in AD and it can be seen by using a PET tracer 1C-(R)-

PK11195 which is a peripheral benzodiazepine receptor ligand. AD patients exhibited greater binding in the parietal, temporal, and hippocampus compared to healthy controls. Using the same PET ligand, researchers discovered low microglial activation levels in mild AD and MCI patients. To sum it all up, amyloid imaging using PET is more capable of detecting the disease in its initial stages while F-FDG is better suited to track disease progression while all the other tracers will help us understand the underlying pathophysiology of the disease.

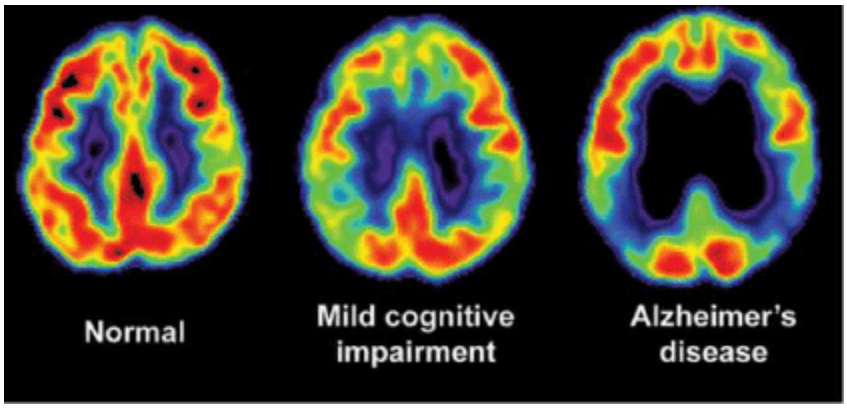


Figure 1.6: Functional changes in the brain captured via PET.

1.6.3 Cerebrospinal Fluid Biomarkers

Cerebrospinal fluid analysis (CSF) is widely used to diagnose neurodegenerative diseases including various types of dementia. Due to the CSF's proximity to the brain, alterations in the brain's biochemistry can be noticed in the CSF as well. Certain biomarkers in the fluid can be utilized to identify AD. Two different types of biomarkers exist which can be used to diagnose the disease. The basic biomarkers give us valuable information about the overall brain health and can be used to identify certain disorders which can help narrow down the diagnostic process. To rule out vascular dementia and conditions related to the cerebrovascular system, the ratio of CSF to serum albumin provides information on the blood-brain barrier. The CSF to serum albumin ratio in AD patients is normal, except for vascular dementia cases. The inflammation status can also be used to exclude certain chronic inflammatory and infectious conditions.

The ideal biomarkers for a disease should reflect its underlying pathology. For AD, some biomarkers have already been identified that have a direct connection to the disease and these neuropathological findings have been confirmed during an autopsy study. One of the most noticeable variations is the decrease in amyloid beta in cerebrospinal fluid, which is caused by the deposition of amyloid beta into plaques, which are not soluble and hence remain in the brain. With the help of C-PIB PET amyloid imaging, visualization of the fibrillary amyloid-beta load is possible in vivo. This reduction is also supported by certain studies that correlated high C PIB retention in amyloid PET ligands with low amyloid beta levels in CSF. Using several enzyme-linked immunosorbent tests (ELISA), the study found that the amyloid beta decrease in CSF was 50% lower than in age-matched healthy old adults. Total tau (t-tau) and phosphorylated tau (p-tau) levels in CSF can also be used to diagnose AD. It has been found that a quick transition from mild cognitive impairment to a fully developed AD is associated with elevated CSF t-tau levels. Additionally, it has been shown that increased CSF t-tau levels also signal a quick transition from mild cognitive impairment to fully developed AD. Using ELISA, studies have shown a 300% rise in the CSF total tau levels compared to age-matched healthy individuals. High neuronal degeneration, which is likewise positively linked with high t-tau levels in the CSF, is also found in Creutzfeldt-Jakob disease. The ratio of p-tau to t-tau is a differentiating factor that is seen to be normal in Creutzfeldt–Jakob disease but high in AD. Certain research implies that p-tau can be used to distinguish AD from dementia and other neurological conditions linked with high neuronal degeneration [30].

All these biomarkers have been found to diagnose Alzheimer's with good specificity and sensitivity ranging from 80-90% but there is a substantial improvement in the diagnostic accuracy when two or more of these biomarkers are considered together. For instance, one study discovered that combining amyloid beta 42 and t-tau increased the sensitivity of AD diagnosis from 78-84% using either biomarker alone to 86% and the specificity when using a single biomarker from 84-90% to 97% [31]. The CSF analysis can also be used to detect the disease in the prodromal stage but lacks accuracy considering p-tau and t-tau in detecting the disease at the preclinical phase of Alzheimer's. Although Amyloid beta was able to predict cognitive deterioration in a

healthy elderly group, the drawback to 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.

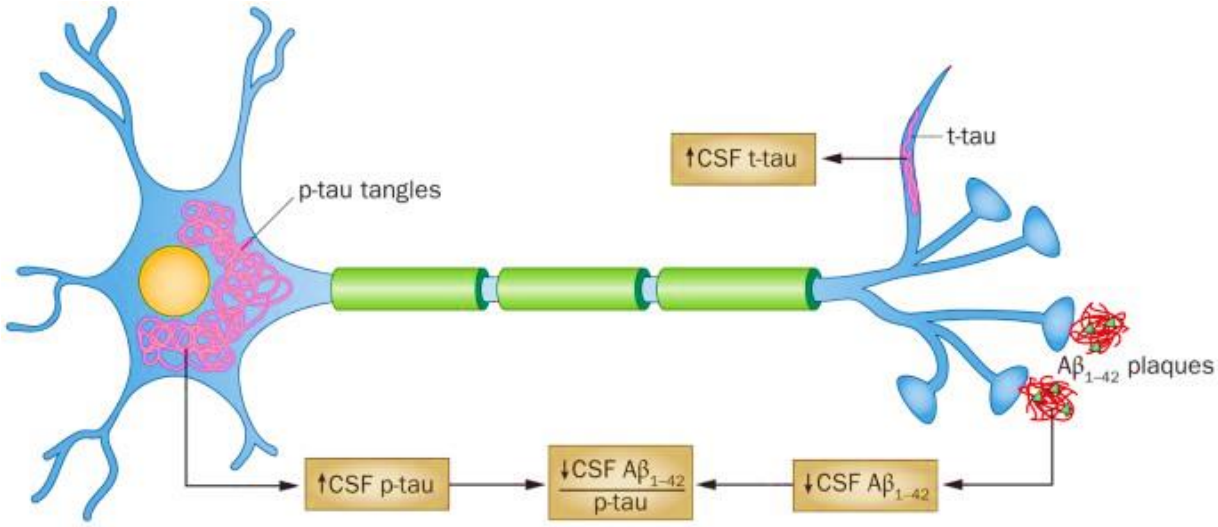


Figure 1.7: Cerebrospinal Biomarkers in Alzheimer's Detection.

1.6.4 Genetic Testing

Although most AD cases occur sporadically without a discernible genetic cause, a minor proportion is due to uncommon genetic mutations that directly trigger the disease. In these cases, genetic testing can serve as a valuable diagnostic tool, providing individuals and their families with important information about their risk and potential disease course. The apolipoprotein E (APOE) gene is the most recognized genetic risk factor for late-onset AD. There are three primary variants of the APOE gene: ε2, ε3, and ε4. People who inherit the ε4 allele face an elevated risk of developing AD, with the risk increasing further for those who inherit two copies of the ε4 allele [32]. However, the presence of the APOE ε4 allele does not guarantee the development of Alzheimer's, nor does its absence ensure immunity from the disease. Besides the APOE gene, researchers

have identified other genes that may contribute to AD's development, including APP, PSEN1, and PSEN2. These genes are linked to early-onset familial AD (FAD) and can cause an overproduction of amyloid-beta peptides, a key feature of AD's pathology. Individuals with FAD typically exhibit symptoms before age 65. While genetic testing can offer valuable insights into an individual's risk of developing AD, it is not a definitive predictor. Many factors, including age, lifestyle, and other genetic and environmental influences, can also play a role in the development of the disease. Additionally, the interpretation of genetic test results can be complex and should be done in consultation with a qualified healthcare professional, such as a genetic counselor or a physician specializing in AD [33]. Despite these limitations, genetic testing can be a useful tool in the diagnosis and management of AD. For individuals with a strong family history of the disease or those experiencing early-onset cognitive symptoms, genetic testing can help confirm a diagnosis and guide treatment and management strategies. Furthermore, as research into the genetic basis of AD continues to advance, the role of genetic testing in the prevention and treatment of disease may become even more important.

1.7 Challenges in AD Treatment

1.7.1 High Failure Rate of Clinical Trials

The development of effective treatments for AD has been a daunting challenge, with a staggering 99.6% failure rate in clinical trials. This high failure rate underscores the complexity of the disease and the difficulties faced by researchers in developing successful interventions. Despite significant investments and research efforts, the lack of progress in finding a cure for AD has been a major setback in the fight against this devastating condition.

1.7.2 Current Treatment Landscape

At present, there are limited treatment options available for individuals with AD. Existing therapies primarily focus on managing symptoms and slowing the progression of the disease, rather than addressing the underlying causes. Cholinesterase inhibitors,

including donepezil, rivastigmine, and galantamine, are frequently prescribed to address the cognitive symptoms of AD. These drugs function by boosting levels of acetylcholine, a neurotransmitter vital for memory and cognitive processes. Additionally, memantine is prescribed for moderate to severe AD, working by regulating glutamate, a neurotransmitter important for learning and memory. While these treatments can provide temporary relief and may slow the progression of AD, they do not halt or reverse the underlying neurodegeneration. Moreover, the benefits of these medications are often modest, and their effects diminish over time as the disease progresses. The limited efficacy of current treatments highlights the urgent need for more effective and targeted therapies that can address the root causes of AD.

1.7.3 Emphasis on Early Detection and Intervention

Given the challenges in developing effective treatments for AD, there has been a growing emphasis on the importance of early detection and intervention. By identifying individuals at risk for AD at an early stage, it may be possible to implement preventive measures and slow the progression of the disease. This approach is particularly relevant for individuals with Mild Cognitive Impairment (MCI), as research has shown that MCI has a high likelihood of progressing to AD [34]. Early detection of AD can be achieved through various methods, including cognitive assessments, biomarker tests, and neuroimaging techniques. Cognitive assessments, such as the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), are commonly used to evaluate an individual's cognitive function and detect signs of cognitive decline. Biomarker tests, which measure the levels of specific proteins in the blood or cerebrospinal fluid, can provide valuable information about the underlying pathological processes of AD. Neuroimaging techniques, such as positron emission tomography (PET) scans and magnetic resonance imaging (MRI), can visualize changes in brain structure and function associated with AD. By combining these various diagnostic tools, it may be possible to identify individuals at risk for AD at an earlier stage, allowing for timely interventions and the implementation of preventive strategies. This approach holds

promise in delaying the onset and slowing the progression of AD, potentially improving the quality of life for those affected by this devastating condition [35].

1.8 Role of Machine Learning in AD Research

The field of AD research has witnessed significant advancements with the integration of machine learning (ML) techniques. ML algorithms have the potential to uncover complex patterns and relationships within large, multidimensional datasets, making them invaluable tools for predicting the onset and progression of AD. By leveraging ML, researchers can develop more accurate and personalized predictive models, paving the way for early intervention and targeted therapies [21]. Machine learning algorithms, such as logistic regression, support vector machines, and neural networks, have been employed to predict the risk of developing AD at an early stage. These techniques analyze various biomarkers, including neuroimaging data, cognitive assessments, and genetic information, to identify individuals at high risk of progressing from Mild Cognitive Impairment (MCI) to AD [36]. By detecting subtle changes in brain structure and function, ML models can provide an early warning system, enabling timely interventions and potentially delaying the onset of the disease. One of the key benefits of using machine learning in AD research is the ability to develop personalized predictive models. Traditional risk assessment methods often rely on population-based averages, which may not accurately reflect an individual's unique risk profile. ML algorithms, on the other hand, can incorporate a wide range of individual-level data, such as genetic factors, lifestyle habits, and comorbidities, to generate more precise and tailored risk predictions. This personalized approach allows for targeted interventions and preventive strategies, optimizing the allocation of healthcare resources and improving patient outcomes.

1.9 Survival Analysis for Disease Forecasting

In addition to predictive modelling, machine learning techniques have also been applied to survival analysis in the context of AD research. Survival analysis focuses on estimating the time-to-event (e.g., disease onset or progression) and identifying factors

that influence the risk of an event occurring. This approach is particularly useful for studying the natural history of AD and predicting disease trajectories. Survival analysis employs statistical methods to analyze time-to-event data, taking into account the time at which an event occurs and the factors that influence the time-to-event [37]. In the context of AD research, survival analysis can be used to estimate the time to disease onset, progression from MCI to AD, or death. By incorporating covariates such as age, genetic factors, and biomarkers, survival analysis models can identify risk factors and predict individual disease trajectories. Compared to traditional methods that rely on cross-sectional data or simple time-to-event analysis, survival analysis offers several advantages in the context of AD research. First, survival analysis accounts for censored data, which occurs when the event of interest is not observed during the study period. This is particularly relevant in longitudinal studies of AD, where participants may drop out or be lost to follow-up. Second, survival analysis allows for the incorporation of time-varying covariates, which can change over the course of the study and influence the risk of the event [38]. This flexibility enables researchers to capture the dynamic nature of disease progression and identify time-dependent risk factors. Finally, survival analysis provides estimates of the cumulative incidence of an event, which can be used to inform healthcare planning and resource allocation. A fundamental concept in survival analysis is the survival function, represented as S(t), which indicates the probability that an individual will survive past a given time t. The survival function is defined as:

$$\boldsymbol{S(t) = P(T > t) S(t) = P(T > t)} \tag{1.1}$$

where T is the random variable that represents the time until the occurrence of the event of interest. The survival function offers insights into the probability of survival at various time points, playing a crucial role in interpreting time-to-event data. Another vital element of survival analysis is the hazard function, denoted as λ(t). This function represents the instantaneous rate at which the event occurs at time t, provided the individual has survived until that time. The hazard function is defined as:

$$\begin{aligned} \boldsymbol{\lambda(t) = \lim f_0 \Delta t \to 0 P(t \le T < t + \Delta t \mid \mathrm{T} \ge \mathrm{t}) \Delta t \lambda(t)} \\ \boldsymbol{= \lim \Delta t \to 0 \Delta t P(\, t \le T < +\Delta t \mid T \ge t\,)} \end{aligned} \tag{1.2}$$

The hazard function reflects the risk of an event happening at a particular time point, considering the individual's survival up until that moment. By analyzing the hazard function, researchers can identify factors that influence the risk of the event and assess how this risk changes over time. Survival analysis commonly involves the utilization of statistical models like the Cox proportional hazards model to assess time-to-event data. This model enables the calculation of hazard ratios, which measure the relative risk of an event happening across distinct groups or under different conditions. By incorporating covariates such as age, genetic factors, and biomarkers, the Cox model enables researchers to identify predictors of the event and assess their impact on the timing of the event. In summary, survival analysis offers a robust framework for examining time-to-event data. and understanding the factors that influence the occurrence of events. By utilizing survival functions, hazard functions, and statistical models like the Cox proportional hazards model, researchers can gain valuable insights into disease progression, prognosis, and risk factors in AD and other research areas [39].

1.9.1 Concept of Censored and Uncensored Subjects:

In survival analysis, researchers often encounter two key concepts: censored and uncensored subjects. These concepts are crucial for understanding how survival data is analyzed and interpreted. Censored subjects refer to individuals in the study whose outcomes are not fully observed or known at the time of analysis. This could happen due to various reasons, such as the end of the study period, loss to follow-up, or the occurrence of a different event that makes further observation impossible. Censoring, indicated by a vertical line on the survival curve, frequently occurs in longitudinal studies when the endpoint of interest has not been reached for all participants. On the other hand, uncensored subjects are those for whom the event of interest (such as death, disease progression, or failure) has been observed or fully recorded during the study period. These individuals contribute directly to the estimation of survival probabilities and the construction of the survival curve.

1.10 Multimodal Data Integration

1.10.1 Types of Data Used

The quest to understand and combat AD (AD) has led to the integration of diverse data modalities, each offering unique insights into the complex mechanisms underlying this debilitating condition. Neuropsychological tests, neuroimaging techniques, and cerebrospinal fluid (CSF) biomarkers are among the types of data used to create a comprehensive picture of AD. Neuropsychological tests, such as the Mini-Mental State Examination (MMSE) and the AD Assessment Scale-Cognitive (ADAS-Cog), provide valuable information about cognitive function and decline. These tests assess various aspects of cognition, including memory, attention, language, and executive function, allowing researchers to track changes over time and identify early signs of cognitive impairment. Neuroimaging techniques, including magnetic resonance imaging (MRI), positron emission tomography (PET), and functional MRI (fMRI), offer a window into the brain's structure and function. These imaging modalities enable the visualization of brain atrophy, white matter lesions, and alterations in brain activity, which are hallmarks of AD.CSF biomarkers, such as amyloid-β, tau, and phosphorylated tau, provide a direct measure of the biochemical changes occurring in the brain. These biomarkers are often used to diagnose AD and monitor disease progression, as they reflect the accumulation of amyloid plaques and neurofibrillary tangles, the pathological hallmarks of AD. These imaging modalities facilitate the observation of brain atrophy, white matter lesions, and alterations in brain activity, all of which are characteristic features of AD. These biomarkers are frequently employed for AD diagnosis and the monitoring of disease advancement, as they mirror the buildup of amyloid plaques and neurofibrillary tangles, recognized as the pathological hallmarks of AD.

1.10.2 Importance of Combining Multiple Modalities

The integration of diverse data modalities is a crucial aspect of AD (AD) research, as it allows for a more comprehensive understanding of this complex disorder. By

combining various types of data, such as neuropsychological assessments, neuroimaging scans, and cerebrospinal fluid (CSF) biomarkers, researchers can gain valuable insights that may not be apparent when analyzing individual data types in isolation [40]. One of the primary advantages of multimodal data integration is the enhanced predictive power it offers. When multiple data sources are combined, researchers can develop more accurate models of disease progression and improve the prediction of AD risk. This is particularly important for identifying individuals at high risk of developing AD, as it enables early intervention and potentially delays disease onset. For example, by incorporating cognitive test scores, brain imaging data, and CSF biomarkers into a single predictive model, researchers can more accurately identify individuals who are likely to progress from mild cognitive impairment (MCI) to AD. Furthermore, integrating multiple data modalities offers a more thorough understanding of the underlying mechanisms driving AD. By analyzing the relationships between cognitive decline, brain structure and function, and biochemical changes, researchers can gain insights into the specific pathways and processes involved in disease progression. This knowledge is crucial for developing targeted therapeutic strategies that address the root causes of AD, rather than simply managing symptoms. Another benefit of multimodal data integration is the ability to identify novel biomarkers and risk factors for AD. By examining patterns across different data types, researchers may uncover previously unknown associations or identify new targets for intervention. For instance, the combination of genetic data, neuroimaging findings, and clinical assessments may reveal novel genetic variants or brain regions that are linked to AD risk or disease progression. Furthermore, multimodal data integration allows for the personalization of treatment approaches. By considering an individual's unique combination of risk factors, cognitive profile, and biological markers, healthcare providers can tailor interventions to the specific needs of each patient. This personalized approach to AD management has the potential to improve patient outcomes and optimize the use of healthcare resources. In conclusion, the importance of combining multiple data modalities in AD research cannot be overstated. By integrating neuropsychological, neuroimaging, and CSF biomarker data, researchers can enhance predictive power, gain a more comprehensive understanding of disease mechanisms, identify novel biomarkers

and risk factors, and personalize treatment approaches. As the field of AD research continues to evolve, the integration of multimodal data will remain a critical component of efforts to prevent, diagnose, and treat this devastating disorder.

1.11 Research Objectives and Contributions

1.11.1 Aims of the study

The primary aim of this study is to develop stage-specific machine learning (ML) survival models to predict the progression of AD (AD) in patients diagnosed with Mild Cognitive Impairment (MCI). Given that MCI can be categorized into early MCI (eMCI) and late MCI (lMCI), this study seeks to conduct separate analyses for these subtypes to enhance prediction accuracy and clinical relevance. This differentiated approach is expected to provide clinicians with more precise tools for identifying patients at high risk of progression to AD. In doing so, it supports the implementation of more effective and timely interventions tailored to the individual patient's stage of MCI.

1.11.2 Development of Stage-Specific ML Survival Models

The focus is on creating ML survival models tailored to the distinct stages of MCI. By doing so, the models can capture unique progression patterns in eMCI and lMCI patients, allowing for more personalized predictions of disease progression. This approach aims to bridge the gap in current research, which often treats MCI as a homogeneous group despite the known differences between its early and late stages. Conducting separate analyses for eMCI and lMCI patients is crucial due to the varying rates of progression to AD between these groups. Research indicates that lMCI patients have a higher likelihood of progressing to AD compared to eMCI patients. By analyzing these subgroups independently, the study can develop more precise models that cater to the specific needs of each stage, potentially leading to better-targeted interventions.

1.11.3 Novel Contributions

This study makes several novel contributions to the field:

1. Use of Publicly Available Datasets: Utilizing publicly available datasets ensures that the findings are reproducible and can be validated by other researchers. These datasets include diverse data types such as neuropsychological tests, neuroimaging results, and cerebrospinal fluid (CSF) biomarkers.
2. Application of Cross-Validation and Techniques to Handle Data Issues: To enhance the reliability and generalizability of the models, the study employs cross-validation techniques. Additionally, methods to handle missing data and imbalanced datasets are implemented, addressing common challenges in medical data analysis.
3. Comparison of Data Modalities and Their Combinations: The study compares different data modalities, such as MRI, FDG, CSF biomarkers, genetic data, and cognitive tests, as well as their combinations. This comprehensive approach helps identify which modality or combination of modalities has the highest predictive power for each MCI stage.
4. Generation of Individualized Survival Curves: One of the unique aspects of this study is the generation of individualized survival curves. Unlike traditional models that provide population-level insights, these curves offer personalized predictions, helping clinicians tailor treatment plans to each patient's specific risk profile.
5. Stage-Specific Predictions for Better Clinical Interventions: By focusing on stage-specific predictions, the study aims to provide clinicians with tools to identify high-risk patients early. This can lead to timely interventions, potentially slowing down or preventing the progression of AD in MCI patients.

In summary, this research addresses a significant gap in the existing literature by developing and validating ML survival models tailored to the different stages of MCI.

The insights gained from this study have the potential to improve clinical outcomes through more accurate and personalized predictions of AD progression.

CHAPTER 2: DATASET AND FEATURE DESCRIPTION

2.1 Dataset and Feature Description

This study utilized data from the AD Neuroimaging Initiative (ADNI) database, which is a widely used resource in AD research. The ADNI database provides access to a wealth of clinical, imaging, and genetic data from hundreds of subjects, including individuals with AD, mild cognitive impairment, and healthy controls. Researchers can access this valuable resource through the ADNI website at adni.loni.usc.edu, where they can explore and analyze data to further their understanding of AD and improve diagnostic and treatment strategies.

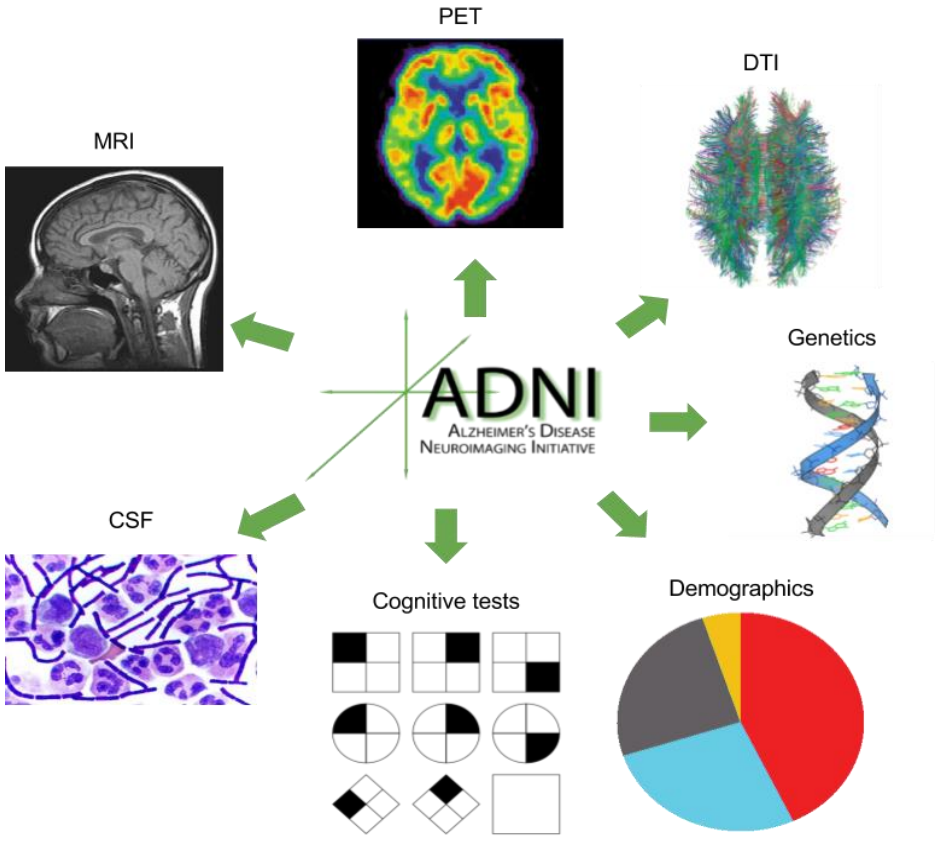


Figure 2.1: Types of data available on AD Neuroimaging Initiative Database.

2.2 Subject Selection

The study included a total of 837 patients diagnosed with Mild Cognitive Impairment (MCI). Among these patients, 291 were classified as having early MCI (eMCI) at baseline, while 546 were classified as having late MCI (lMCI). The decision to focus solely on baseline information and test results was made to train the machine learning models specifically for predicting the progression of AD. This approach ensured that the models were trained on the most relevant and representative data available at the initial stages of MCI diagnosis.

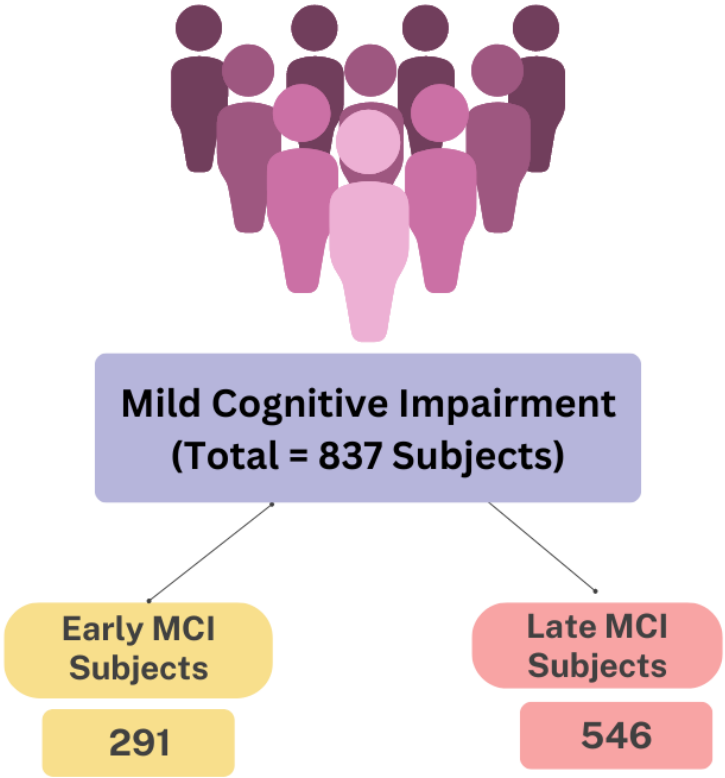


Figure 2.2: Number of MCI subjects included in the study.

2.3 Features Used in the Study

In this study, several features were included, from various data modalities. This section discusses the different modalities included and their respective features:

2.3.1. Demographic Information

1. Age (AGE): Age of the patient at baseline. Advanced age is a known risk factor for AD progression.

2. Patient Education (PTEDUCAT): Level of education attained by the patient. Higher education levels have been associated with a lower risk of developing AD.

3. Patient Gender (PTGENDER): Gender of the patient. Gender differences in AD prevalence and progression have been observed, with women being more susceptible.

2.3.2 Neuropsychological Tests

1. Clinical Dementia Rating Scale Sum of Boxes (CDRSB): Assesses the severity of dementia symptoms, including memory loss and daily functioning.

2. AD Assessment Scale - 11 items (ADAS11): Measures cognitive abilities such as memory, language, and orientation.

3. AD Assessment Scale - 13 items (ADAS13): Similar to ADAS11, evaluates cognitive functions with additional items.

4. Mini-Mental State Examination (MMSE): Screens for cognitive impairment by assessing memory, attention, and language skills.

5. Rey Auditory Verbal Learning Test - Immediate Recall (RAVLT.immediate): Measures the ability to recall a list of words immediately after hearing them.

6. Rey Auditory Verbal Learning Test – Learning (RAVLT.Learning): Assesses the ability to learn new verbal information over multiple trials.

7. Rey Auditory Verbal Learning Test – Forgetting (RAVLT.forgetting): Measures the rate of forgetting verbal information over a delayed period.

8. Rey Auditory Verbal Learning Test - Percent Forgetting (RAVLT.perc.forgetting): Indicates the percentage of forgotten words relative to the total learned.

9. Functional Activities Questionnaire (FAQ): Assesses the ability to perform daily activities independently, reflecting functional impairment.

2.3.3. Imaging Tests

1. FDG PET (Fluorodeoxyglucose Positron Emission Tomography): Measures brain glucose metabolism, which is altered in AD.

2. MRI Volumetric Biomarkers:

- Ventricles: Enlargement of brain ventricles is associated with brain atrophy and neurodegeneration.

- Hippocampus: Reduced hippocampal volume is a hallmark of AD and correlates with memory decline.

- Whole Brain Volume (WholeBrain): Total brain volume is a marker of overall brain health and atrophy.

- Entorhinal: The entorhinal cortex is an early site of pathology in AD, affecting memory and navigation.

- Fusiform: The fusiform gyrus is involved in facial recognition and may be affected in AD.

- Midtemporal (MidTemp): The midtemporal region is involved in memory and may show atrophy in AD.

- Intracranial Volume (ICV): Represents the total volume inside the skull, which can affect brain structure and function.

2.3.4. CSF Biomarkers

1. Total Tau Protein: Elevated levels indicate neuronal damage and are associated with AD progression.

2. Phosphorylated Tau Protein: Abnormal levels are indicative of tau pathology and are associated with cognitive decline.

3. Amyloid Beta Protein: Elevated levels or abnormal ratios of amyloid beta proteins are biomarkers for amyloid plaque accumulation, a hallmark of AD.

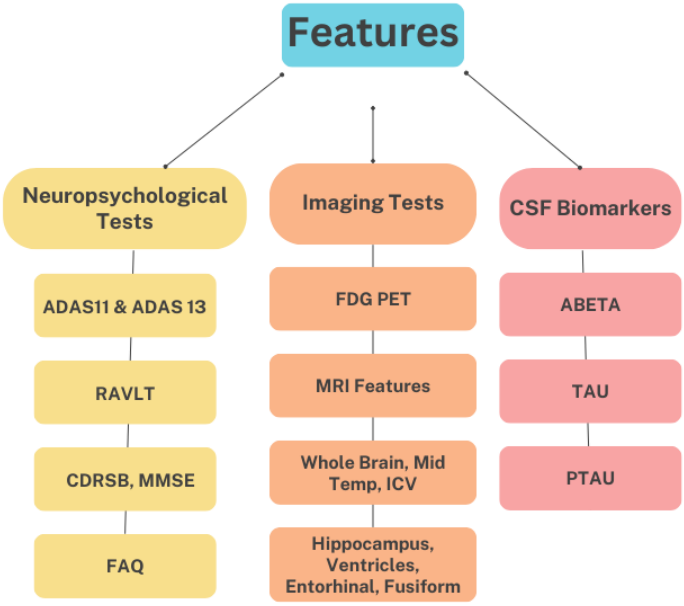


Figure 2.3: All features from different modalities that have been used in this study.

2.5 Target Variables

Survival analysis in this study relies on two crucial target variables: a binary event indicator and a time-to-event duration column. These variables play a fundamental role in understanding the progression of Mild Cognitive Impairment (MCI) to AD (AD). The binary event indicator serves to distinguish between patients with early MCI (eMCI) and late MCI (lMCI) who progress to AD. A value of "1" indicates progression to AD, signifying that the patient has converted from MCI to AD during the study period. Conversely, a value of "0" indicates that the patient remains in their respective MCI stage without converting to AD by the end of the study. Patients assigned the value of 1 are classified as uncensored, meaning their progression to AD has been observed or recorded. On the other hand, patients assigned the value of 0 are censored, indicating that their outcome (conversion to AD) has not been fully observed or documented during the study period. The time-to-event duration column provides information on the duration from the initial visit to the diagnosis of AD for uncensored patients. For censored patients, the time-to-event duration represents the period between their first and last visit that was documented for the study. This column allows researchers to track the progression of the disease over time and analyze the factors influencing the time to conversion from MCI to AD.

Table 2.1: Target Variables for eMCI and lMCI datasets

Diagnosis at Baseline	Outcome	PROGRESSION	Time
EMCI	AD (conversion)	1	Time till AD diagnosis
EMCI	EMCI (stable)	0	Time till the last observation of the study

Diagnosis at Baseline	Outcome	PROGRESSION	Time
LMCI	AD (conversion)	1	Time till AD diagnosis
LMCI	LMCI (stable)	0	Time till the last observation of the study

CHAPTER 3: METHODOLOGY

Figure 3.1 shows the workflow for the entire study process.

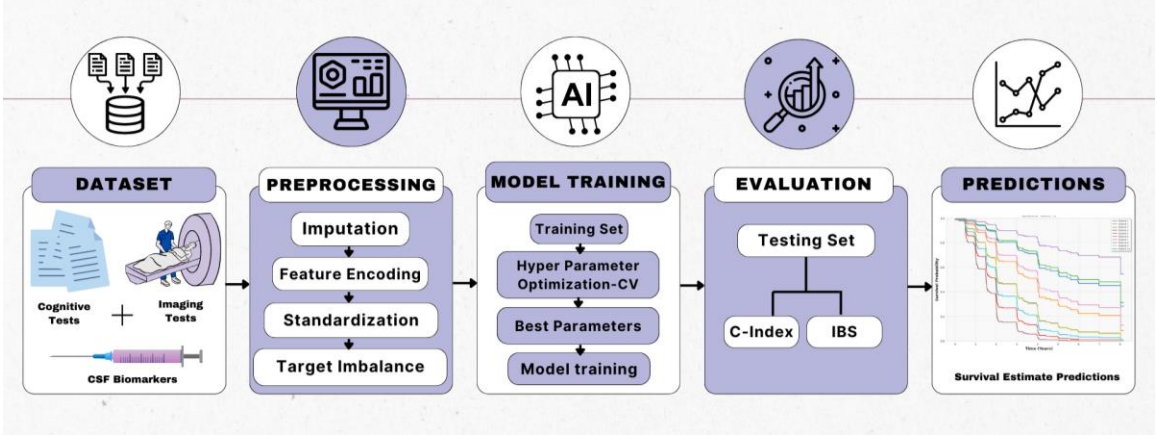


Figure 3.1: Machine learning pipeline for the prediction of AD conversion.

3.1 Statistical Analysis

In this study, our primary aim was to investigate potential differences in the progression of Mild Cognitive Impairment (MCI) to AD (AD) between its early and late stages. We employed several statistical techniques to achieve this goal:

3.1.1 Comparison between Features of eMCI and lMCI datasets

We initially used a *t*-test to identify significant differences in features between early and late MCI stages. This analysis helped us understand the baseline differences in key features between the two stages of MCI.

3.1.2 Kaplan-Meier Estimator

Subsequently, we utilized the Kaplan-Meier estimator to compare the probability of surviving without AD over time for each stage of MCI. The Kaplan-Meier estimator is a non-parametric statistic used to estimate the survival function from

lifetime data. It calculates the probability that an individual survives beyond a certain time point, taking into account the duration of follow-up for censored observations. In our study, we used the Kaplan-Meier estimator to estimate the survival curves for early and late MCI patients and compare their survival probabilities over time [41].

3.1.3 Log-Rank Test

Additionally, we applied the log-rank test to formally assess if there is a statistically significant distinction between the survival distributions of the two stages. It helps us determine whether the observed differences in survival between early and late MCI patients are statistically significant.

Further details of these analyses are presented in the results and discussion section. Based on these findings, we divided the MCI data into two separate datasets: one containing patients with early MCI at baseline and the other containing patients with late MCI at baseline. Data preprocessing and machine learning models were trained and evaluated on both datasets individually.

3.2 Data Preprocessing

3.2.1 Imputation

Missing values are a common challenge in medical studies, and our datasets were no exception, with several features containing missing values. Deleting entire rows with missing values can result in the loss of valuable information. Therefore, to make the most of the available data and ensure that our analyses are based on complete datasets, we employed KNN imputation. This technique estimates the missing value in a row by considering the values of its closest neighboring rows, which are likely to have similar characteristics. We chose an optimal k value of 5 for imputing missing values, balancing the need for accuracy with computational efficiency.

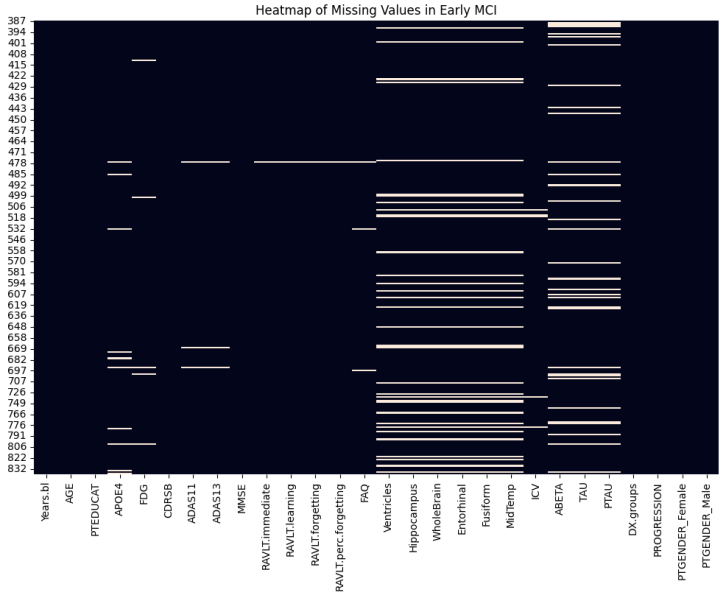


Figure 3.2: Heatmap of missing values in early MCI dataset.

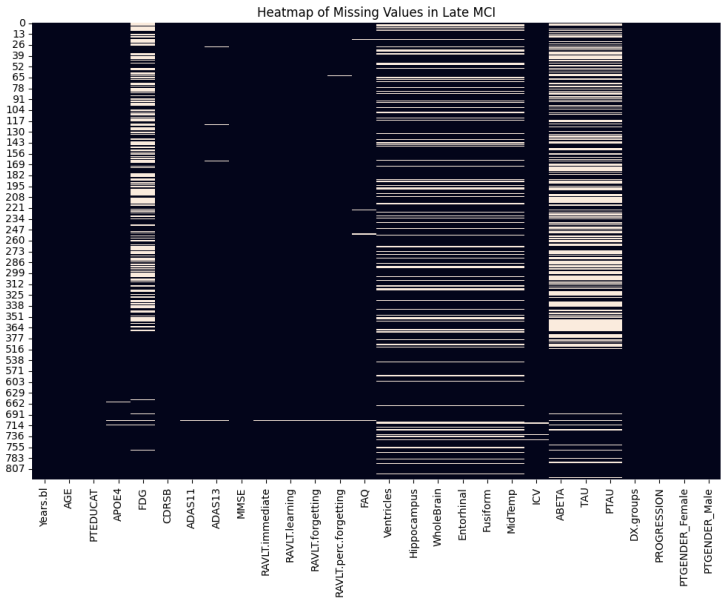


Figure 3.3: Heatmap of missing values in late MCI dataset.

3.2.2 Feature Encoding

To facilitate the accurate interpretation and utilization of categorical data by machine learning models, we used one-hot encoding for the categorical gender feature

'PTGENDER'. This transformation converts categorical data into a numerical format, enabling the models to effectively process this information in their calculations.

3.2.3 Standardization

For features with numerical values, we applied z-score normalization. This standardization technique ensures that all features have a mean of zero and a standard deviation of one, making them comparable and preventing any one feature from dominating the analysis. However, we excluded MRI volumetric biomarkers from this step. Instead, we scaled these biomarkers by dividing them by each patient's total intracranial volume (ICV). This scaling approach accounts for individual differences in brain size, ensuring that the biomarkers are comparable among patients regardless of their cranial size.

3.2.4 Target Imbalance

To address the imbalance in the prediction labels, we categorized patients into two groups based on their disease progression: those who showed progression of the disease (labeled '1') and those who did not (labeled '0'). The early MCI (eMCI) group exhibited a significant imbalance, with 268 patients who did not progress and only 23 patients who did progress. In contrast, the late MCI (lMCI) group had a more balanced distribution, with 301 non-progressive and 245 progressive patients. To mitigate this imbalance, we employed a method from the sklearn library to oversample the minority class (progressive patients), creating a more balanced dataset that would improve the performance of our machine learning models. Imbalanced datasets can lead to biased models that favor the majority class. By balancing the targets, the model can learn from a more representative sample of the data, leading to better generalization and performance on unseen data. Performance metrics like accuracy can be misleading on imbalanced datasets. For example, a model that always predicts the majority class could achieve high accuracy but would not be useful in practice.

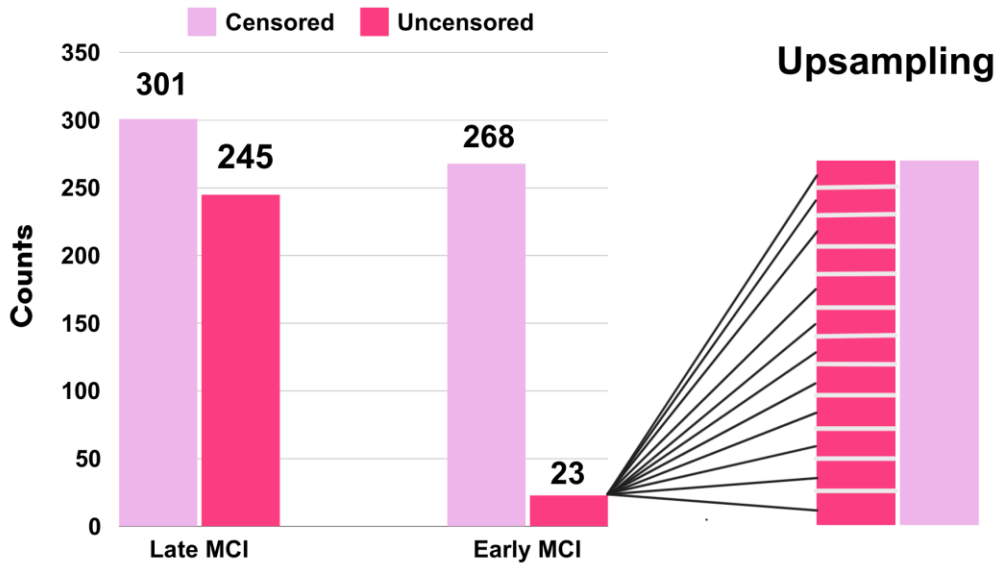


Figure 3.4: Distribution of censored and uncensored individuals in eMCI and lMCI datasets and upsampling of the minority class in eMCI dataset.

3.2.5 Train-Test Split

To ensure the robustness of our machine learning models, we split the data into training and testing sets using a stratified split based on the event indicator. We allocated 70% of the data to the training set and 30% to the testing set. This stratification helped maintain the distribution of the target variable across both sets, ensuring that the models were trained and evaluated on representative samples of the data.

Figure 3.5: Train-Test Split.

Table 3.1: Preprocessing of Features

Features	Type	Preprocessing
Age	Numeric	Standardization
PT EDUCATION	Numeric	Standardization
Gender	Categoric	One hot encoding
APOE4	Numeric	Standardization
CDRSB	Numeric	Standardization
ADAS11	Numeric	Standardization
ADAS13	Numeric	Standardization
MMSE	Numeric	Standardization
RAVLT.immediate	Numeric	Standardization
RAVLT.learning	Numeric	Standardization
RAVLT.perc.forgetting	Numeric	Standardization
RAVLT.forgetting	Numeric	Standardization
FAQ	Numeric	Standardization
FDG-PET	Numeric	Standardization
Ventricles	ICV	ICV
Hippocampus	ICV	ICV
Whole Brain	ICV	ICV
Entorhinal	ICV	ICV
Fusiform	ICV	ICV
Midtemp	ICV	ICV
ABETA	Numeric	Standardization
TAU	Numeric	Standardization
PTAU	Numeric	Standardization

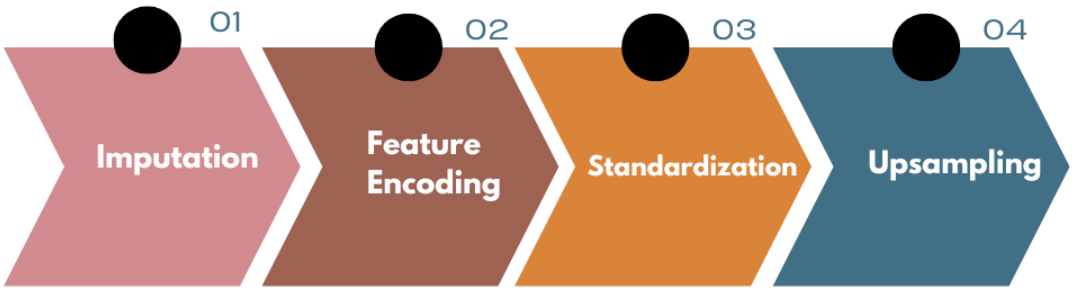


Figure 3.6: Preprocessing steps employed in this study.

3.3 Machine Learning Models For Survival Analysis

In this study, we utilized Python 3.10.12 and the sksurv module to apply multiple machine learning models. These models were chosen for their ability to handle complex data and their suitability for survival analysis, which is crucial for predicting time-to-event outcomes.

3.3.1 Ensemble Models

Ensemble models improve predictive performance by combining multiple decision trees, making them particularly effective for navigating intricate relationships within the data. The following ensemble models were employed in this study:

1. Random Survival Forest:

RSF is an extension of the conventional Random Forest algorithm, tailored to handle censored data where the event of interest has not yet occurred for certain individuals. It constructs an ensemble of decision trees, each trained on a random subset of the data with random feature selection. By aggregating the individual tree predictions, RSF makes more accurate survival predictions. RSF is highly effective in managing high-dimensional data and complex variable interactions, which are common in medical research. This model is particularly valuable for forecasting outcomes such as disease progression or patient survival.

2. Extra Survival Trees (XST)

XST adapts the principles of survival trees to handle censored data, a frequent occurrence in clinical research. It constructs numerous survival trees using a random subset of features and data for training. This randomization minimizes overfitting and enhances model performance. XST is computationally efficient, making it suitable for analyzing large datasets with complex survival patterns. Its robustness and efficiency are critical for accurately modeling the survival times of patients.

3. Gradient Boosting Survival Analysis

Gradient Boosting combines the predictions of multiple base learners, typically simple models slightly better than random guessing. These base models, known as weak learners, are added in an additive manner to progressively enhance the overall model's performance. Unlike RSF, which fits multiple survival trees independently and averages their predictions, gradient boosting builds the model stage by stage, with each new model correcting the errors of the previous ones. This iterative approach results in a strong predictive model capable of capturing complex data patterns.

3.3.2 Linear Models

Linear models are essential for understanding relationships between variables and time-to-event outcomes. The following linear model was used in this study:

1. Cox Proportional Hazards (CoxPH)

The CoxPH model is a well-known statistical approach for survival analysis. It examines the relationship between the survival time and predictor variables without assuming a specific distribution for the survival times. Instead, it calculates the hazard function, representing the probability of the event occurring at a particular time, given that the individual has survived up to that point. The CoxPH model is valuable for identifying risk factors and understanding how different variables influence the likelihood of an event, such as disease progression.

2. Cox-net

Cox-net is an extension of the CoxPH model that incorporates regularization techniques to handle high-dimensional data. This model applies penalties, such as Lasso (L1) or Ridge (L2), which help reduce the complexity of the model by shrinking the coefficients of less important variables toward zero. This regularization process prevents overfitting, especially in datasets with many predictors, by ensuring that the model does

not become too complex and overfit the training data. The Cox-net model is particularly beneficial for identifying the most relevant variables in predicting survival outcomes while controlling for the effects of less important variables. By penalizing less significant predictors, Cox-net effectively focuses on the most critical variables, improving the model's predictive power and interpretability.

3.3.3 Survival Tree

The Survival Tree model is another technique for handling censored data in survival analysis. It uses a decision tree approach, where the data is recursively partitioned into subsets that are increasingly homogeneous in terms of survival times. Each split in the tree is based on a predictor variable that best separates the data according to survival outcomes. Survival Trees are particularly useful for identifying complex interactions between variables and capturing non-linear relationships in the data.

3.3.4 Hyperparameter Optimization

A comprehensive strategy was used to deal with model overfitting and selection bias by including techniques such as tuning hyperparameters and using k-fold cross-validation. Hyperparameter tuning was performed using Grid Search with cross-validation (5 folds) on the training set, to determine the best hyperparameters. Grid Search CV exhaustively explores all the combinations to find the one that gives the best model performance. The models were then trained on the entire training set using the selected hyperparameters and evaluated on test sets.

3.4 Evaluation Metrics

3.4.1 Concordance Index (C-Index)

The Concordance Index, commonly referred to as the C-Index, is a pivotal performance metric in the realm of survival analysis. It is widely used due to its ability to provide a comprehensive assessment of a model’s predictive accuracy, particularly in the context of time-to-event data. At its core, the C-Index evaluates the model’s capability to

correctly rank the order of predicted event times. This ranking ability is crucial in survival analysis, as it directly relates to the model's effectiveness in predicting which individuals are more likely to experience the event (such as disease progression or failure of a mechanical component) sooner compared to others. Essentially, the C-Index measures the concordance between the predicted and actual event times. One of the primary advantages of the C-Index is its simplicity and interpretability. It provides a single numeric value that encapsulates the predictive performance of a model, making it an invaluable tool for comparing different models or tuning parameters. This single-number summary allows researchers and practitioners to quickly gauge which model is more effective in predicting the outcome of interest. The C-Index ranges from 0 to 1. A value of 0.5 indicates a model with no predictive power, equivalent to random chance. In contrast, a C-Index of 1 signifies perfect concordance, where the model accurately ranks all pairs of individuals in terms of their event times. Thus, a higher C-Index score denotes better model performance [42]. For example, a C-Index of 0.7 suggests that the model correctly ranks 70% of the pairs, indicating a good level of predictive accuracy. Moreover, the C-Index is particularly useful because it can handle censored data, which is a common characteristic of survival datasets. Censored data occurs when the event of interest has not been observed for some individuals during the study period. The C-Index appropriately accounts for these cases, ensuring that the metric accurately reflects the model's performance even in the presence of incomplete data.

3.4.2 Integrated Brier Score

The Integrated Brier Score (IBS) is a crucial metric in survival analysis, offering a thorough assessment of a model's predictive precision over the entire duration of the study. Unlike other metrics that might only provide a snapshot at a specific time point, the IBS captures the accuracy of predictions across the entire time spectrum, making it a comprehensive measure of model performance. Derived from the time-dependent Brier score, the IBS functions similarly to calculating the area under a curve. The Brier score itself measures the mean squared difference between the predicted probabilities of an event occurring and the actual outcomes, at various time points. By integrating these time-dependent Brier scores, the IBS consolidates these individual assessments into a

single, overarching value. This integration process essentially sums up the predictive errors across all time points, giving a holistic view of the model's performance. One of the significant advantages of the IBS is its ability to provide a single value that summarizes the model's predictive accuracy. This value ranges from 0 to 1, where lower values indicate better predictive performance [43]. An IBS close to 0 suggests that the model's predictions are highly accurate and align closely with the observed outcomes. Conversely, a higher IBS indicates poorer predictive accuracy, reflecting larger discrepancies between predicted and actual event times. The utility of the IBS lies in its ability to account for the entire follow-up period of the study, rather than focusing on a single moment in time. This makes it particularly valuable in survival analysis, where the timing of events is crucial, and the risk of events can change over time. By evaluating the model's performance over the entire study duration, the IBS provides a more nuanced and comprehensive picture of its predictive capabilities. Furthermore, the IBS is adept at handling censored data, which is a common feature in survival analysis. Censored data refers to instances where the event of interest has not occurred for some subjects by the end of the study period. The IBS appropriately incorporates these cases into its calculations, ensuring that the metric accurately reflects the model's performance even when some data points are incomplete. In practical terms, the IBS can be used to compare different predictive models, aiding in the selection of the most accurate model for survival analysis. It allows researchers to evaluate how well different models perform across the entire time frame of interest, facilitating a more informed and nuanced comparison. Additionally, the IBS can be instrumental in model tuning and validation, helping to identify and refine the parameters that yield the most accurate predictions.

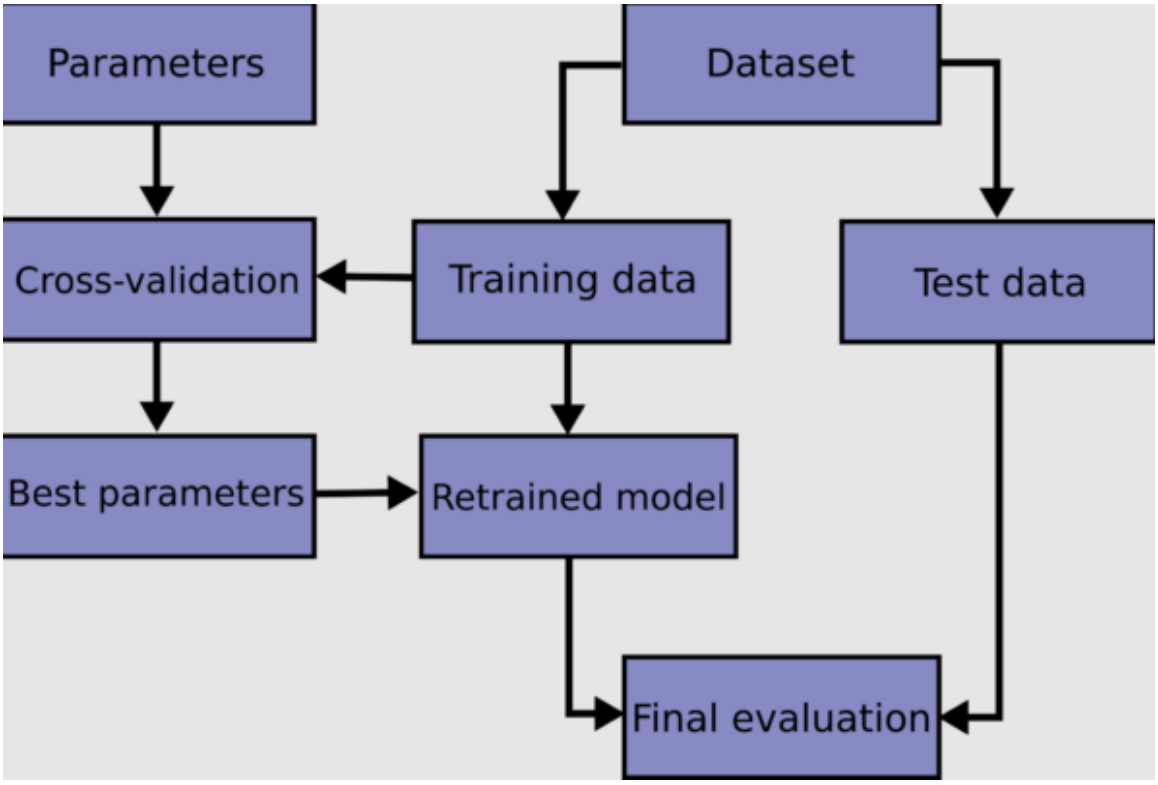


Figure 3.7: Machine learning workflow for eMCI and lMCI datasets.

CHAPTER 4: RESULTS

4.1 Statistical Analysis

The statistical results in Table 1 show statistically significant differences between almost all features of eMCI and lMCI datasets. Figure 3 shows the Kaplan-Meier (KPM) curves for both eMCI and lMCI highlighting varying probabilities of survival without AD over time. In this study, the median survival time for the eMCI group is 4.5 years, and 1.5 for the lMCI group. These results suggest that eMCI patients exhibit a slower disease progression, compared to the lMCI patients. The log-rank test further verified that the differences are statistically significant (p-value= 1.8 x 10^{-4}). These results confirm the existing understanding of how the progression rates differ between early and late MCI patients. As a result, we divided our dataset into two separate sets, one for each stage of MCI. Our goal was to make more precise predictions and create individual survival curves that are more accurate. By adopting this approach, ML models are better able to capture the unique patterns associated with each stage, ultimately enabling more personalized interventions for better patient outcomes.

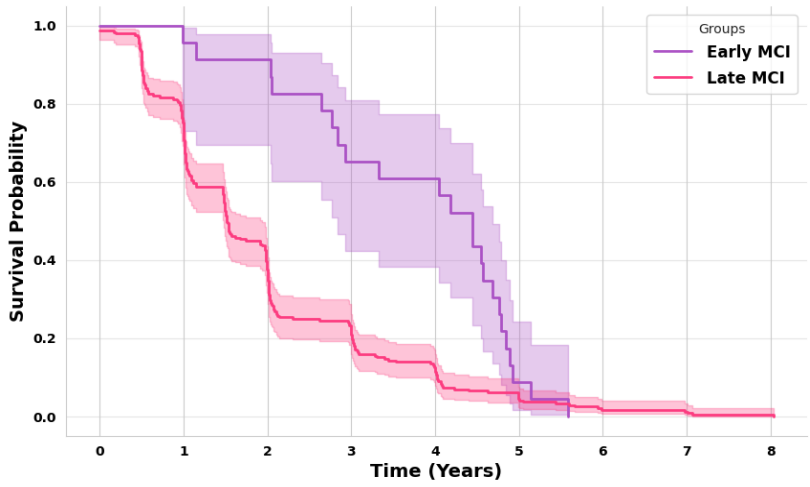


Figure 4.1: Comparison of survival curves of eMCI and lMCI groups showing varying survival probabilities.

Table 4.1: Data statistics of eMCI and lMCI groups in this study.

Features	eMCI (291)	lMCI(546)	*p*-value
Female, gender (n%)	127, (43.6%)	212, (38.8%)	0.17
Male, gender (n%)	164, (56.3%)	334, (61.1%)	0.17
Age	71 ± 1.2	74 ± 7.5	$p < 0.05$
Education	15.8 ± 2.7	15.8 ± 2.9	0.95
CDRSB	1.31 ± 0.75	1.66 ± 0.93	$p < 0.05$
ADAS13	12.9 ± 5.4	18.9 ± 6.4	$p < 0.05$
ADAS11	8.03 ± 3.5	11.6 ± 4.5	$p < 0.05$
MMSE	28.2 ± 1.6	27.2 ± 1.8	$p < 0.05$
RAVLT.immediate	39.2 ± 10	30.9 ± 9.2	$p < 0.05$
RAVLT.learning	5.21 ± 2.4	3.4 ± 2.4	$p < 0.05$
RAVLT.forgetting	4.3 ± 2.64	4.8 ± 2.3	$p < 0.05$
RAVLT.perc.forgetting	47.7 ± 30.5	69 ± 31	$p < 0.05$
FAQ	2.09 ± 3.2	3.9 ± 4.47	$p < 0.05$
FDG-PET	6.4 ± 0.6	6 ± 0.6	$p < 0.05$
Ventricles, $\times 10^3$	35.3 ± 20	43.1 ± 24	$p < 0.05$
Hippocampus, $\times 10^3$	7.2 ± 10	6.4 ± 11	$p < 0.05$
Whole Brain, $\times 10^5$	10.7 ± 1.1	10.1 ± 1.1	$p < 0.05$
Entorhinal, $\times 10^3$	3.7 ± 0.68	3.3 ± 0.74	$p < 0.05$
Fusiform, $\times 10^3$	18.7 ± 2.6	16.8 ± 2.5	$p < 0.05$
Mid Temporal, $\times 10^3$	20.6 ± 2.6	18.9 ± 2.9	$p < 0.05$
ABETA	1096 ± 450	844 ± 404	$p < 0.05$
TAU	259 ± 124	314 ± 141	$p < 0.05$
PTAU	24.6 ± 14	31 ± 15	$p < 0.05$

4.2 Performance of Machine Learning Models

To determine the best algorithm for AD predictions, we used six different models on two separate datasets each (eMCI and lMCI). These models included RSF, XST, and GB from scikit-survival's ensemble module, as well as ST from scikit-survival's tree module; CoxPH and Coxnet from scikit-survival's linear_model module. Hyperparameter optimization was done using grid search with 5-fold cross-validation, to obtain the best hyperparameters; which are presented in Table 2. Statistical significance was defined as a *p*-value less than 0.05. This section discusses the performance of ML models trained on multimodal data that includes all features. A detailed version of these results can be found in the Supplementary Materials. As compared to other models, RSF had the

highest accuracy on both datasets. All the ML models outperformed the traditional CoxPH model in both datasets. For eMCI group, among the ensemble-based models, RSF showed the best performance (C-Index= 0.96 ± 0.03, IBS= 0.02 ± 0.02), followed by Gradient Boosting (C-Index= 0.91 ± 0.03, IBS= 0.1 ± 0.02) and XST (C-Index= 0.89 ± 0.02, IBS= 0.1 ± 0.02). For the lMCI group, RSF showed the best performance here as well (C-Index= 0.82 ± 0.06, IBS= 0.1 ± 0.02), followed by XST (C-Index= 0.78 ± 0.06, IBS= 0.17 ± 0.03) and then Gradient Boosting (C-Index= 0.72 ± 0.04, IBS= 0.19 ± 0.02). In terms of linear models, Coxnet performed better than CoxPH in both eMCI and lMCI datasets. Coxnet achieved C-Index= 0.84 ± 0.04 and IBS= 0.05 ± 0.02 for eMCI; and for lMCI, it achieved C-Index= 0.68 ± 0.07, and IBS= 0.18 ± 0.03. CoxPH was the worst-performing model in both datasets and achieved a C-Index of 0.81 ± 0.03, and IBS of 0.2 ± 0.04 in the eMCI dataset. For lMCI dataset, CoxPH had a C-Index of 0.66 ± 0.07, and IBS of 0.2 ± 0.02. Furthermore, compared to the two tree-based models included in the study (RSF and XST), the Survival tree model's performance was worse for both eMCI (C-Index= 0.84 ± 0.04, IBS= 0.19 ± 0.02) and lMCI (C-Index= 0.68 ± 0.05, IBS= 0.23 ± 0.04).

In summary, RSF demonstrated superior performance in predicting conversion risk from eMCI and lMCI to AD outperforming other tree-based survival algorithms and statistical methods like CoxPH. The strong performance of RSF in our study shows that RSF is an effective predictor of survival outcomes in diseases such as AD. These results align with previous research, which has demonstrated the effectiveness of RSF in predicting time-to-event scenarios in both clinical and research settings [44], [36]. RSF possesses several key features that make it a reliable approach for disease forecasting, including robustness against outliers, lack of convergence issues, cross-validated prediction to prevent overfitting, and reliable inference of training data. Additionally, RSF gives a full nonparametric measure of variable importance, which helps identify the contribution of various factors in forecasting the survival function.

Table 4.2: Best performing hyperparameters obtained using Grid Search-CV

Models	eMCI	lMCI
RSF	min_samples_leaf = 1, min_samples_split = 2, n_estimators=100, max_features='sqrt'	min_samples_leaf = 2, min_samples_split = 2, n_estimators=150, max_features= 'sqrt'
XST	n_estimators = 100, max_depth = None, min_sample_split=5, min_samples_leaf = 5	n_estimators = 100, max_depth = None, min_sample_split =2, min_samples_leaf= 1
GB	learning_rate = 0.0001, max_depth = 5, min_samples_leaf = 5, min_samples_split = 5	learning_rate = 0.001, max_depth = 5, min_samples_leaf = 5, min_samples_split = 2
ST	max_depth = 5, min_samples_leaf = 5, min_samples_split = 10	max_depth = 10, min_samples_leaf = 3, min_samples_split = 4
Cox-net	L1_ratio = 0.0001	L1_ratio = 0.001
CoxPH	Alpha = 0.0001	Alpha = 0.0001

4.3 Multimodal Analysis

The results show that the models trained on a combination of features from various modalities (multimodal data) performed better than the models trained on a single modality in both datasets. Figure 4 provides a visual summary comparing the performance of different feature sets. Specifically, the ML models performed better on the eMCI dataset than on the lMCI dataset. RSF showed the best performance on both datasets when using both multimodal and individual modalities. When comparing results from single modalities (Cognitive, Imaging, and CSF), the cognitive modality performed well in both datasets across all models. For the eMCI group, RSF trained on cognitive features achieved a C-Index of 0.95 ± 0.03 and an IBS of 0.02 ± 0.02, compared to Imaging features (C-Index= 0.94 ± 0.03, IBS= 0.04 ± 0.02, $p<0.05$) and CSF biomarkers (C-Index= 0.95 ± 0.03, IBS= 0.02 ± 0.02, $p>0.05$). However, when RSF trained on multimodal data was compared to using cognitive features solely, there was no statistically significant improvement.

For the lMCI group, RSF trained on cognitive features achieved a C-Index of 0.78 ± 0.02 and an IBS of 0.17 ± 0.02, compared to Imaging features (C-Index= 0.71 ± 0.10,

IBS= 0.19 ± 0.02, $p<0.05$); and CSF biomarkers (C-Index= 0.57 ± 0.06, IBS= 0.22 ± 0.02, $p<0.05$). In this case, RSF trained on merging all modalities did not yield a statistically significant improvement over using cognitive features alone.

Our results suggest that different types of data contribute differently to predicting survival estimates. Although RSF trained on multimodal data achieved a higher C-Index compared to using cognitive tests alone in both datasets, the improvement was not statistically significant. This suggests that cognitive tests alone are robust predictors of AD progression for eMCI and lMCI subjects, with the additional modalities not contributing significantly to overall accuracy. Additionally, when comparing models trained on multimodal data to models trained on CSF biomarkers alone for eMCI dataset, no statistical improvement was observed. This indicates that for eMCI, CSF biomarkers and cognitive tests alone can yield good results. Given that CSF biomarker collection is a painful and invasive process, hence cognitive tests should be preferred, as they also provide similarly effective results.

To further understand the key predictors of the RSF's performance, a feature importance analysis using multimodal RSF models revealed that the top features differed between the two MCI stages. Figure 5 shows the feature importance of both datasets using the permutation feature importance method. The most significant features for the eMCI group were the CSF biomarkers, RAVLT.perc.forgetting, FAQ, and PTEDUCAT. In the lMCI dataset, the top contributing features were FAQ, ADAS13, ADAS 11, Mid temporal and CDRSB. Whereas, the model's performance was negatively impacted by CSF biomarkers, FDG, whole brain and MMSE. The feature importance analysis for both datasets showed that cognitive features ranked among the most influential predictors for model performance. The consistent best performance of the cognitive modality across all models and datasets highlights its importance as a key predictor of AD progression in MCI patients. Cognitive tests such as FAQ, ADAS13, and RAVLT can serve as reliable, non-invasive, and cost-effective alternatives for predicting AD conversion [45],[46]. These tests provide useful information about a patient's cognitive function and can be reliable predictors of disease progression and survival outcomes.

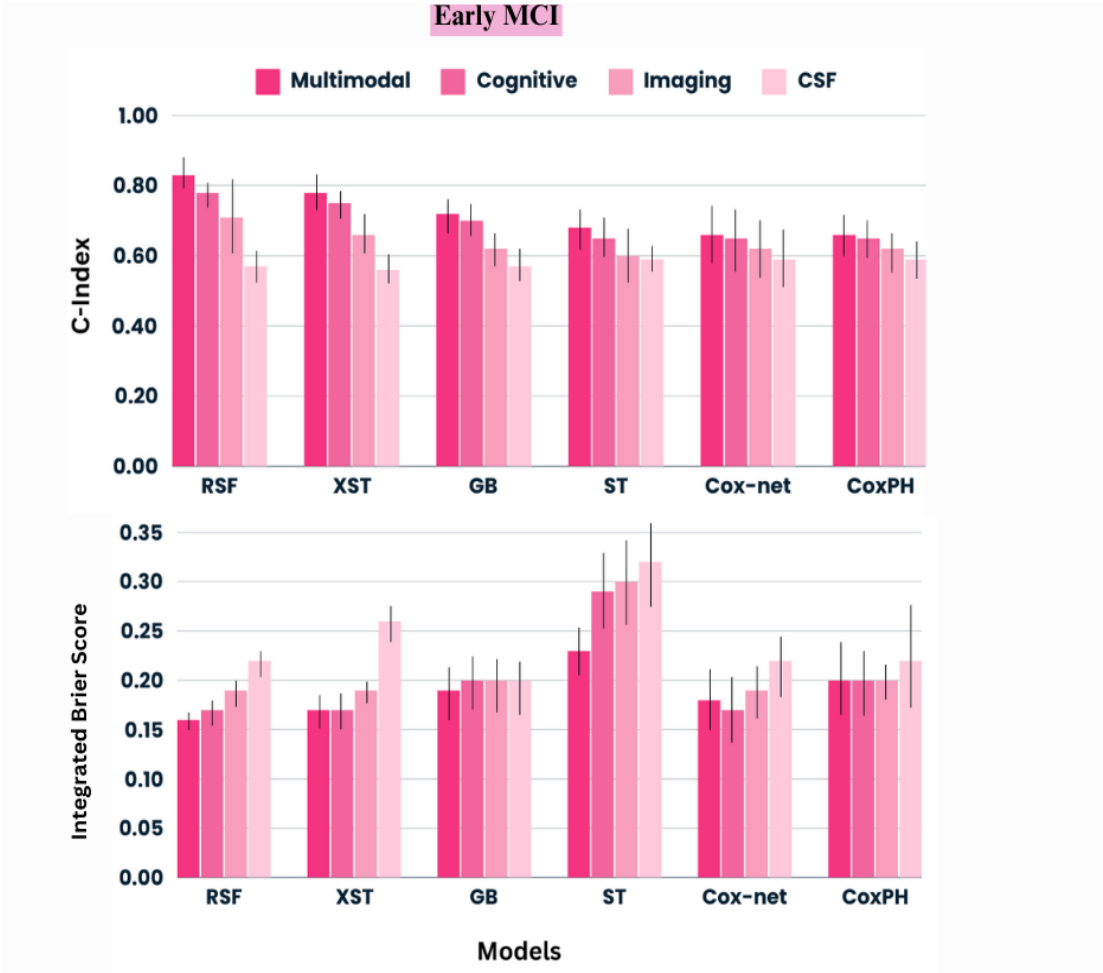


Figure 4.2: Performance of machine learning models in eMCI dataset.

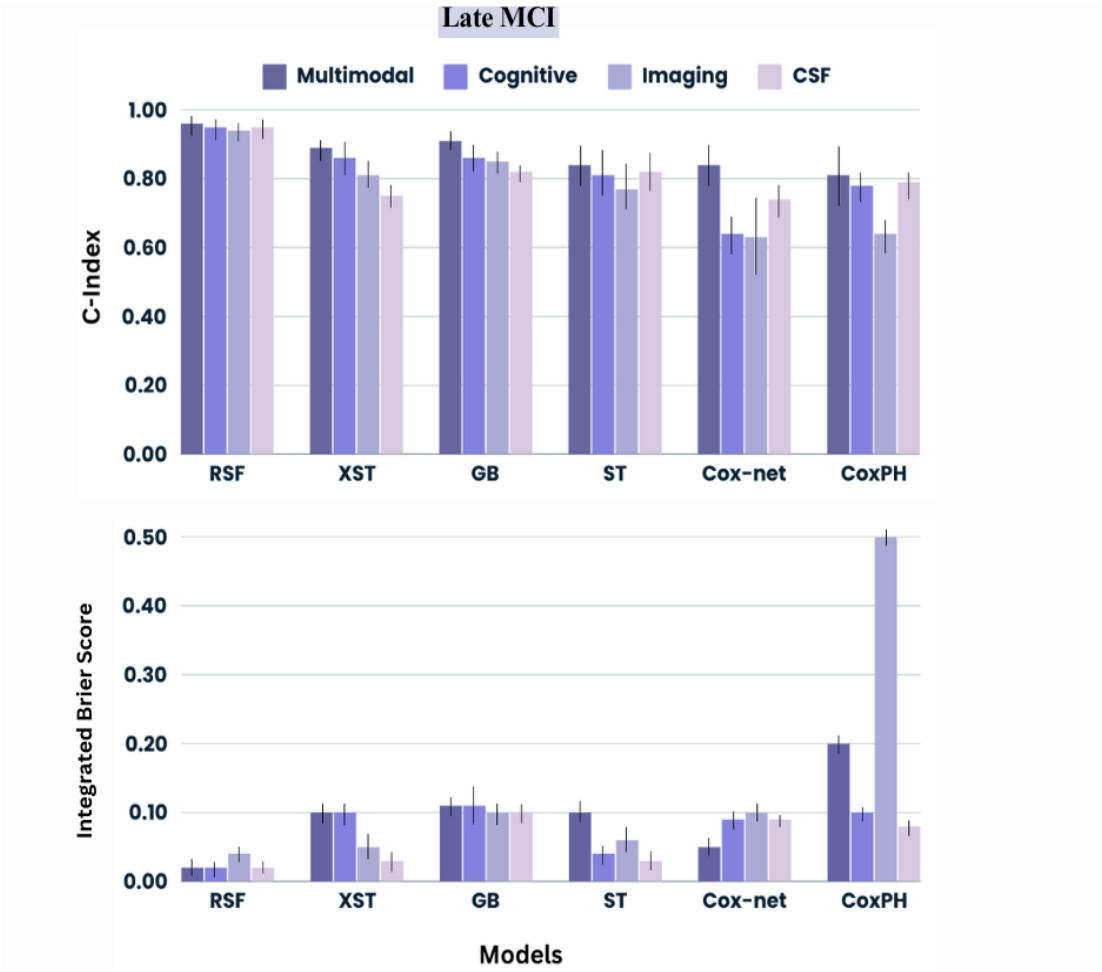


Figure 4.3: Performance of machine learning models in lMCI dataset.

Table 4.3: Performance of machine learning models across different feature sets

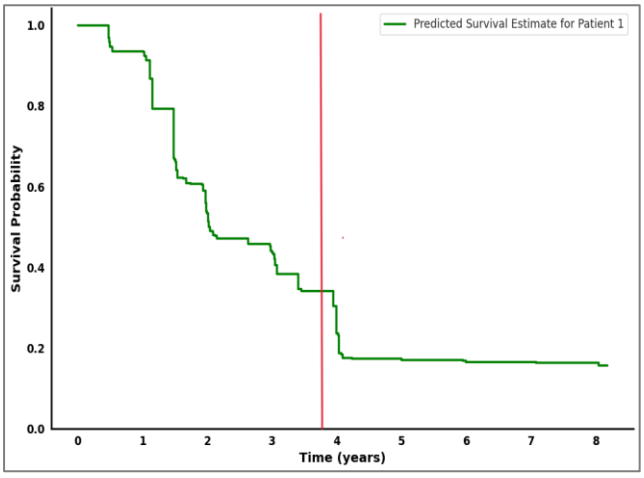
Early MCI					
MODELS	**Evaluation Metrics**	**Multimodal**	**Cognitive**	**Imaging**	**CSF**
RSF	C-Index	**0.96** ± 0.03	0.95 ± 0.03	0.94 ± 0.03	0.95 ± 0.03
	IBS	**0.02** ± 0.03	0.02 ± 0.02	0.04 ± 0.02	0.02 ± 0.02
XST	C-Index	0.89 ± 0.02	0.86 ± 0.05	0.81 ± 0.03	0.75 ± 0.02
	IBS	0.1 ± 0.02	0.1 ± 0.02	0.05 ± 0.02	0.03 ± 0.02
GB	C-Index	0.91 ± 0.03	0.86 ± 0.04	0.85 ± 0.03	0.82 ± 0.02
	IBS	0.11 ± 0.02	0.11 ± 0.01	0.1 ± 0.02	0.1 ± 0.02
ST	C-Index	0.84 ± 0.05	0.81 ± 0.06	0.77 ± 0.06	0.82 ± 0.06
	IBS	0.1 ± 0.02	0.04 ± 0.02	0.06 ± 0.03	0.03 ± 0.02
Cox-net	C-Index	0.84 ± 0.04	0.64 ± 0.06	0.63 ± 0.1	0.74 ± 0.06
	IBS	0.05 ± 0.02	0.02 ± 0.02	0.04 ± 0.02	0.02 ± 0.02
CoxPH	C-Index	0.81 ± 0.03	0.78 ± 0.06	0.64 ± 0.06	0.79 ± 0.04
	IBS	0.2 ± 0.04	0.1 ± 0.02	0.5 ± 0.04	0.08 ± 0.02
Late MCI					
RSF	C-Index	**0.83** ± 0.05	0.78 ± 0.02	0.71 ± 0.1	0.57 ± 0.06
	IBS	**0.16** ± 0.02	0.17 ± 0.02	0.19 ± 0.02	0.22 ± 0.02
XST	C-Index	0.78 ± 0.06	0.75 ± 0.04	0.66 ± 0.06	0.56 ± 0.04
	IBS	0.17 ± 0.03	0.17 ± 0.03	0.19 ± 0.02	0.26 ± 0.03
GB	C-Index	0.72 ± 0.04	0.70 ± 0.05	0.62 ± 0.04	0.57 ± 0.05
	IBS	0.19 ± 0.02	0.2 ± 0.02	0.2 ± 0.02	0.2 ± 0.02
ST	C-Index	0.68 ± 0.05	0.61 ± 0.07	0.59 ± 0.07	0.59 ± 0.04
	IBS	0.23 ± 0.04	0.29 ± 0.04	0.3 ± 0.05	0.32 ± 0.04

Cox-net	C-Index	0.68 ± 0.07	0.65 ± 0.07	0.60 ± 0.07	0.59 ± 0.01
	IBS	0.18 ± 0.03	0.18 ± 0.03	0.21 ± 0.02	0.22 ± 0.03
CoxPH	C-Index	0.66 ± 0.07	0.65 ± 0.07	0.52 ± 0.06	0.59 ± 0.07
	IBS	0.2 ± 0.04	0.2 ± 0.03	0.2 ± 0.02	0.22 ± 0.02

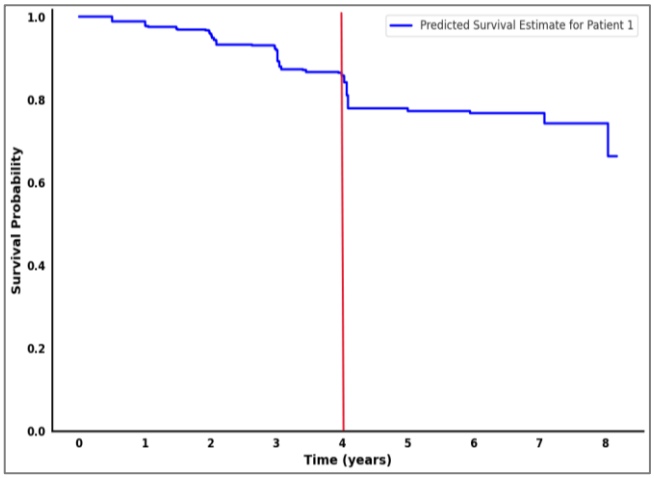
4.4 Individual Survival Curves

Survival curves visually summarize the time-to-event data, showing how the survival probability decreases as time progresses [47]. The Kaplan-Meier estimator is a non-parametric statistical tool that is commonly used for generating survival curves. However, it mainly represents survival distribution at a population level and has limited clinical usefulness. ML survival models can generate individual survival curves based on the characteristics of each subject. This capability is one of the strengths of using ML approaches in survival analysis, as they can provide patient-specific predictions, providing valuable insights into disease progression [41]. Incorporating individual survival curves allows clinicians to gather useful information, make informed therapeutic decisions, and allocate resources effectively. We used RSF trained on multimodal data, obtained on the baseline visit to generate individual survival distributions for four distinct patient scenarios: (a) Progressive eMCI, (b) Non-progressive eMCI, (c) Progressive lMCI, (d) Non-progressive lMCI. A reliable model should accurately predict high survival rates for individuals who do not progress to AD, and low survival rates for progressive cases. If the survival curve is close to 0 on the y-axis, it indicates a low probability of survival and a high risk of progressing towards AD. In contrast, a curve approaching 1 suggests a high probability of survival and a lower risk. Figure 6 shows individual survival curves for each selected scenario. The red line represents the actual progression time for progressive cases and the censored time for non-progressive individuals. Subjects (a) and (c), who have progressive eMCI and lMCI respectively,

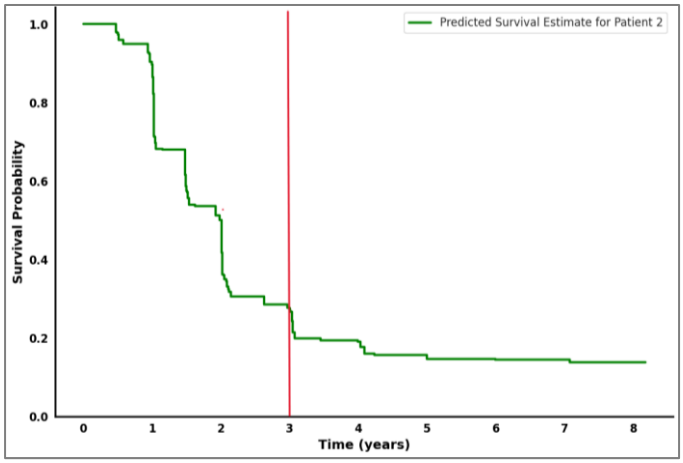
exhibit curves close to 0, indicating a high risk of AD development. Patients (b) and (c), who are classified as censored/non-progressive, show distinct patterns. Patient (b) was censored for 4 years after the initial visit, and the curve indicates a very low risk of developing AD over the years. Patient (d), censored for nearly 1.5 years, initially had a high probability of survival, but the curve shows a rise in risk after 3 years. The comparison between the predicted and actual survival probabilities in this study highlights the effectiveness of RSF in providing accurate predictions for all subjects. We utilized the information and test results available during the initial (baseline) visit to train the models. This approach aids clinicians in early-stage disease progression prediction, where only the test results and information from the patient's first visit are available. This not only conserves financial resources but also saves valuable time. Additionally, this approach holds immense value as family members and clinicians can plan for the future based on the patient's estimated survival probability. It highlights the significance of AI in supporting clinical decisions and assessing patient risk.



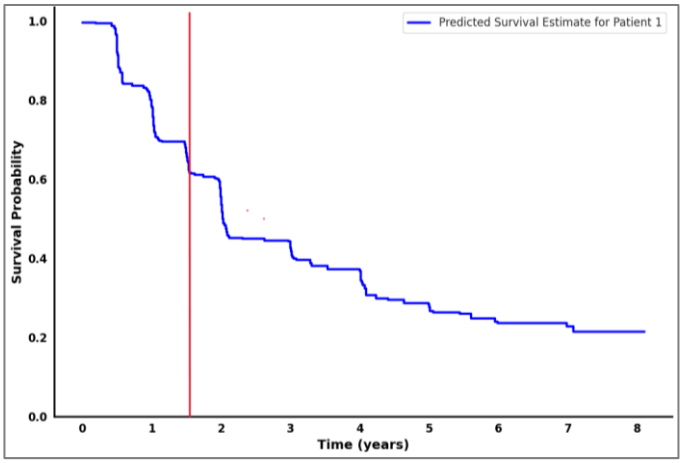
(a) Progressive eMCI subject



(b) Non-Progressive eMCI subject



(c) Progressive lMCI subject



(d) Non-progressive lMCI subject

Figure 4.4: Predicted survival estimates for subjects with progressive eMCI and lMCI as well as those with non-progressive eMCI and lMCI. The red line refers to the actual event times for progressive/uncensored patients and the actual censoring time for non-progressive/censored patients.

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CHAPTER 5: DISCUSSION

5.1 Performance of Machine learning Based Survival Models

The results of this study highlight the performance and effectiveness of various machine learning models in predicting the progression of MCI stages to AD. We utilized six different models on two separate datasets, representing early MCI (eMCI) and late MCI (lMCI) stages, to determine the most suitable algorithm for AD predictions. These models included RSF, XST, GB, ST, CoxPH, and Coxnet. Hyperparameter optimization was conducted using grid search with 5-fold cross-validation to ensure the best model performance.

5.1.1 Ensemble Models

Among the ensemble models, the RSF consistently showed superior performance across both datasets. For the eMCI group, RSF achieved a C-Index of 0.96 ± 0.03 and an IBS of 0.02 ± 0.02, outperforming other models significantly. Gradient Boosting followed with a C-Index of 0.91 ± 0.03 and an IBS of 0.1 ± 0.02, while XST showed a C-Index of 0.89 ± 0.02 and an IBS of 0.1 ± 0.02. These results indicate that RSF's ability to handle high-dimensional data and complex interactions between variables makes it particularly effective in predicting disease progression.

For the lMCI group, RSF also demonstrated the highest performance with a C-Index of 0.82 ± 0.06 and an IBS of 0.1 ± 0.02. XST and Gradient Boosting followed, with C-Indexes of 0.78 ± 0.06 and 0.72 ± 0.04, respectively, and IBS values of 0.17 ± 0.03 and 0.19 ± 0.02. The superior performance of RSF in both eMCI and lMCI datasets underscores its robustness and accuracy in survival analysis tasks.

5.1.2 Linear Models

The linear models, CoxPH and Coxnet, showed varying levels of effectiveness. Coxnet outperformed CoxPH in both datasets, highlighting the benefits of incorporating

regularization techniques to handle high-dimensional data. For the eMCI group, Coxnet achieved a C-Index of 0.84 ± 0.04 and an IBS of 0.05 ± 0.02, whereas CoxPH recorded a C-Index of 0.81 ± 0.03 and an IBS of 0.2 ± 0.04. In the lMCI group, Coxnet continued to perform better with a C-Index of 0.68 ± 0.07 and an IBS of 0.18 ± 0.03, compared to CoxPH's C-Index of 0.66 ± 0.07 and an IBS of 0.2 ± 0.02.

5.1.3 Survival Tree Models

The Survival Tree (ST) model, included in the study, demonstrated inferior performance compared to RSF and XST. For the eMCI dataset, ST had a C-Index of 0.84 ± 0.04 and an IBS of 0.19 ± 0.02. In the lMCI dataset, the C-Index was 0.68 ± 0.05 with an IBS of 0.23 ± 0.04. These results indicate that while ST models can be useful, they are generally less effective than ensemble models like RSF and XST in survival analysis.

5.1.4 Summary and Implications

In summary, RSF emerged as the best-performing model for predicting the risk of conversion from MCI to AD in both early and late stages. It outperformed other tree-based survival algorithms and traditional statistical methods such as CoxPH. The robust performance of RSF aligns with previous research, validating its effectiveness in time-to-event prediction scenarios within both clinical and research settings.

RSF's reliability can be attributed to several key features. It is robust against outliers and does not face convergence issues, which are common in other models. The use of cross-validated prediction prevents overfitting, ensuring that the model generalizes well to unseen data. Moreover, RSF provides a comprehensive nonparametric measure of variable importance, enabling researchers to identify the most significant factors contributing to the survival function. This capability is particularly valuable in medical research, where understanding the influence of different variables on disease progression can inform treatment and intervention strategies.

Overall, the findings from this study suggest that RSF is an effective and reliable tool for predicting survival outcomes in diseases like AD. Its superior performance across both eMCI and lMCI datasets underscores its potential as a valuable asset in medical research and clinical practice for forecasting disease progression and guiding decision-making processes.

5.2 Multimodal Analysis

The findings of this study highlight the significant role of multimodal data in enhancing the prediction of AD progression from MCI. Our results demonstrate that models trained on a combination of features from different modalities generally perform better than those trained on single modality datasets. This underscores the value of integrating diverse data types to capture the complex nature of disease progression.

5.2.1 Performance Comparison

A detailed analysis of model performance reveals that all machine learning models performed better on the eMCI dataset compared to the lMCI dataset. This may suggest that early-stage MCI features are more predictive of AD progression than those observed in later stages. The Random Survival Forest (RSF) consistently outperformed other models across both datasets, showcasing its robustness and effectiveness in handling survival analysis in medical research.

5.2.2 Multimodal vs. Single Modality

When evaluating the predictive power of single modalities (Cognitive, Imaging, and CSF biomarkers), cognitive features consistently ranked high in performance across all models and datasets. For instance, RSF trained on cognitive features achieved impressive results with a C-Index of 0.95 ± 0.03 and an IBS of 0.02 ± 0.02 for the eMCI group. In contrast, while RSF trained on multimodal data showed slightly higher C-Index values, the improvement over cognitive features alone were not statistically significant. This

suggests that cognitive tests alone are robust and reliable predictors of AD progression, especially in the early stages of MCI.

5.2.3 Cognitive Features as Key Predictors

The feature importance analysis revealed that cognitive features were among the top predictors for both eMCI and lMCI groups. In the eMCI dataset, key predictors included CSF biomarkers, RAVLT.perc.forgetting, FAQ, and PTEDUCAT. For the lMCI dataset, important predictors were FAQ, ADAS13, ADAS11, Mid temporal, and CDRSB. The consistent performance of cognitive tests highlights their utility as non-invasive, cost-effective, and reliable tools for predicting AD progression. These findings align with previous research emphasizing the importance of cognitive assessments in monitoring MCI and predicting its conversion to AD.

5.2.4 Clinical Implications

The lack of significant improvement with the inclusion of CSF biomarkers and imaging features in multimodal models suggests that cognitive tests alone may be sufficient for predicting AD progression in MCI patients. Given the invasive nature of CSF biomarker collection and the cost and complexity of imaging techniques, relying on cognitive tests could simplify clinical practice while maintaining high predictive accuracy. Cognitive assessments such as FAQ, ADAS13, and RAVLT are not only easier to administer but also provide crucial insights into a patient's cognitive function, which is directly relevant to the progression of AD.

5.3 Individual Survival Curves

The results of our study underscore the significant potential of the Random Survival Forest (RSF) model in generating individual survival curves, which can be immensely beneficial in clinical settings. Unlike traditional methods such as the Kaplan-Meier estimator, which provides a population-level survival distribution, RSF offers patient-

specific predictions. This capability is crucial for providing tailored insights into disease progression, particularly in conditions like AD (AD).

One of the key advantages of RSF is its ability to create individualized survival curves based on the unique characteristics of each patient. This feature is particularly useful in clinical settings where personalized treatment plans are necessary. By using multimodal data obtained during the baseline visit, RSF can predict individual survival distributions with a high degree of accuracy. This allows clinicians to make informed therapeutic decisions and allocate resources more effectively.

In our study, we used RSF to generate individual survival curves for four distinct patient scenarios: progressive eMCI, non-progressive eMCI, progressive lMCI, and non-progressive lMCI. The survival curves visually summarize the probability of survival over time, providing clear insights into the risk of progressing to AD. For example, subjects with progressive eMCI and lMCI showed survival curves close to zero, indicating a high risk of AD development. In contrast, non-progressive cases exhibited curves that suggested a higher probability of survival and a lower risk of progression.

These individualized survival curves are not just statistical tools; they have practical implications in clinical practice. For instance, a survival curve that shows a high probability of survival for a non-progressive patient can reassure both the patient and their family, reducing anxiety and stress. Conversely, a curve indicating a high risk of progression can prompt more aggressive intervention and closer monitoring, potentially altering the patient's treatment plan to mitigate the risk. Furthermore, the ability of RSF to accurately predict survival probabilities based on baseline visit data is particularly valuable. This approach conserves financial resources and saves time, as it relies solely on the information available during the initial patient visit. Early and accurate prediction of disease progression allows for better planning and more efficient use of healthcare resources.

In summary, the RSF model's ability to generate individualized survival curves enhances its utility in clinical settings. By providing precise, patient-specific predictions, RSF supports more informed decision-making, better resource allocation, and improved patient outcomes. The incorporation of AI in generating these curves highlights the growing importance of machine learning in clinical practice, offering significant benefits in predicting and managing disease progression.

SUMMARY OF RESEARCH WORK

This project delves into AI-based forecasting of AD (AD) progression in patients with Mild Cognitive Impairment (MCI) using a multi-modal dataset and various machine learning (ML) models. Given the staggering 99.6% failure rate of clinical trials for AD, early diagnosis becomes imperative for effective mitigation and prevention. ML models provide promising tools for predicting AD onset during the MCI stage, with ML-based survival analysis models offering insights into both the timing and likelihood of disease progression.

In this study, we employed ML-based survival models to predict the time-to-conversion to AD for early MCI (eMCI) and late MCI (lMCI) stages separately, recognizing that their progression rates differ. The models used included Random Survival Forest (RSF), Extra Survival Trees (XST), Gradient Boosting Survival Analysis (GB), Survival Tree (ST), Cox-net, and Cox Proportional Hazard (CoxPH). Our study involved 291 eMCI and 546 lMCI subjects. We compared various data modalities, including cognitive tests, neuroimaging tests, and CSF biomarkers, both individually and in combination, to determine which features most significantly influenced model performance.

Our results showed that RSF outperformed the traditional CoxPH and other ML models used in this study. For the eMCI dataset, RSF achieved a C-Index of 0.96 and an IBS of 0.02, while for the lMCI dataset, it achieved a C-Index of 0.82 and an IBS of 0.16. The multimodal analysis underscored the importance of cognitive tests, which showed a statistically significant improvement over other modalities, highlighting their reliability in predicting AD progression. Additionally, individual survival curves were generated using RSF on baseline data to predict the probability of early AD onset in patients. This enables clinicians to develop personalized treatment plans and take preventive measures, potentially slowing down or preventing AD progression in individuals with MCI.

The dataset for this study was multi-modal and longitudinal, including demographics (age, gender, education), neuropsychological tests (MMSE, CDR, ADAS, RAVLT, FAQ), genetic tests (APOE4), imaging tests (MRI and FDG), and CSF biomarkers (TAU, ABETA, PTAU). Our methodology involved data preprocessing, including initial data cleaning, selecting patients with baseline diagnoses of eMCI and lMCI, one-hot encoding for categorical data, feature scaling through standardization, and handling missing values using KNN imputation.

We utilized seven ML models to predict the time to conversion to AD and the probability of conversion over time: Random Survival Forest, Survival Trees, Extra Survival Trees, Cox-PH, Cox Regression, Gradient Boosting Survival Analysis, and Component-wise Gradient Boosting. Hyperparameter tuning was performed using k-fold cross-validation, and model evaluation was conducted using the Concordance Index and Integrated Brier Score. Feature importance was assessed through Permutation Feature Importance analysis to identify key predictive features.

The study revealed that lMCI patients had a higher risk of developing AD over time compared to eMCI patients. The use of ML models to predict the time to AD conversion demonstrates the potential of ML in aiding clinical intervention and improving patient outcomes. This research highlights the ability of ML models to provide early and accurate predictions of disease progression, which can inform clinical decision-making and contribute to the development of personalized treatment plans for MCI patients.

CHAPTER 6: CONCLUSIONS AND FUTURE RECOMMENDATION

This comprehensive study uses advanced machine learning approaches to predict the time-to-conversion to AD in early and late MCI individuals by analyzing multiple data modalities. Based on statistically significant differences in the progression rates of early and late MCI, we built separate machine-learning models for each stage to accurately capture the distinct patterns in those stages for prediction. Our research demonstrates that the RSF model consistently outperforms traditional methods in predicting the progression of early and late MCI to AD. We utilized baseline visit data from cognitive, CSF biomarkers, and imaging test results to train models for predicting time and individual survival curves. While combining various data types improves accuracy, cognitive tests alone are the most impactful in predicting outcomes for both early and late-stage MCI. This underscores the importance of cognitive tests, which are cost-effective, non-invasive, and time-saving. This approach is highly clinically relevant, enabling healthcare practitioners to identify high-risk patients earlier, allowing for timely interventions, and providing personalized treatment plans suited to each patient's specific needs; based on baseline data. The efficacy of machine learning-based survival analysis models in predicting disease outcomes demonstrates the potential value of AI in assisting clinical decisions and evaluating patient risks. A limitation of this study is its small sample size. Future studies may consider using larger sample sizes to validate our results and ensure their applicability to a wider population.

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LIST OF PUBLICATIONS

- A Review of Alzheimer's Pathophysiology, Diagnostic Methods, and Multimodal Techniques (under review)
- Early Prediction of AD in Early and Late Mild Cognitive Impairment Individuals: A Multimodal Machine Learning-Based Survival Analysis Approach (under review)