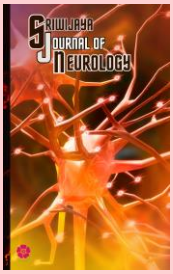

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Longitudinal Assessment of Biomarkers for Predicting Alzheimer's Disease Progression: A Prospective Cohort Study in Thailand

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A B S T R A C T

Introduction: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and memory impairment. Early identification and prediction of disease progression are critical for timely intervention and management. This prospective cohort study aimed to investigate the longitudinal trajectories of various biomarkers and their predictive value for AD progression in a Thai population. **Methods:** A cohort of participants, including individuals with mild cognitive impairment (MCI) and cognitively normal older adults, were recruited from memory clinics and community settings in Thailand. Baseline assessments included clinical evaluations, neuropsychological tests, and biomarker measurements (cerebrospinal fluid (CSF) biomarkers, neuroimaging, and blood-based markers). Participants underwent follow-up assessments at regular intervals over several years to track disease progression. **Results:** The study identified longitudinal changes in various biomarkers associated with AD progression. CSF biomarkers, such as amyloid-beta (Aβ) and tau, showed significant alterations over time, with decreasing Aβ and increasing tau levels observed in individuals transitioning from MCI to AD. Neuroimaging markers, including hippocampal volume and cortical thickness, demonstrated progressive atrophy in AD patients. Blood-based markers, such as neurofilament light chain (NfL), showed promising potential as predictors of disease progression. **Conclusion:** This study provides valuable insights into the longitudinal trajectories of biomarkers and their predictive value for AD progression in the Thai population. The findings support the use of a multi-modal biomarker approach for early identification and monitoring of AD, paving the way for personalized interventions and improved patient management.

1. Introduction

Alzheimer's disease (AD) stands as a formidable challenge in the realm of neurodegenerative disorders, exacting a heavy toll on individuals, families, and healthcare systems across the globe. It is an insidious and progressive condition, characterized by the gradual erosion of cognitive function, memory impairment, and behavioral changes, ultimately culminating in a profound loss of independence and a significant decline in quality of life. In the absence of a definitive cure, the imperative to identify effective strategies for early diagnosis, accurate prediction of disease progression, and timely intervention looms large. The global prevalence of AD is staggering, with estimates suggesting that over 50 million people are currently living with the disease. This number is projected to triple by 2050, underscoring the urgent need for concerted research efforts aimed at unraveling the complexities of AD and developing innovative approaches to its management. In Thailand, the burden of AD is particularly pronounced, with a rapidly aging population and a growing number of individuals affected by the disease. The cultural and socioeconomic context of Thailand

further accentuates the challenges associated with AD, highlighting the critical importance of research tailored to the specific needs and circumstances of the Thai population. The pathophysiology of AD is multifaceted, involving a complex interplay of genetic, environmental, and lifestyle factors. While the precise mechanisms underlying the disease remain elusive, substantial evidence points to the accumulation of amyloid-beta (Aβ) plaques and tau neurofibrillary tangles in the brain as key hallmarks of AD pathology. These pathological changes trigger a cascade of neurodegenerative events, including synaptic dysfunction, neuronal loss, and neuroinflammation, ultimately leading to the clinical manifestations of the disease.[1-3]

The clinical diagnosis of AD is traditionally based on a comprehensive assessment of cognitive function, behavioral symptoms, and functional impairment. However, the accuracy of clinical diagnosis, particularly in the early stages of the disease, can be limited by the overlap of symptoms with other neurodegenerative and psychiatric disorders. Moreover, the clinical manifestations of AD often lag behind the underlying pathological changes by several years, underscoring the need for biomarkers that can detect the disease at its earliest stages and predict its progression. Biomarkers have emerged as indispensable tools in the quest for early diagnosis and accurate prediction of AD progression. These measurable indicators of biological processes associated with the disease offer the potential to identify individuals at risk, monitor disease progression, and guide the development of targeted therapeutic interventions. Biomarkers can be broadly classified into three categories: cerebrospinal fluid (CSF) biomarkers, neuroimaging markers, and blood-based markers. CSF biomarkers, including Aβ42, total tau (t-tau), and phosphorylated tau (p-tau), have been extensively studied and validated in the context of AD. Aβ42 is a cleavage product of the amyloid precursor protein (APP), and its decreased levels in the CSF reflect the deposition of Aβ plaques in the brain. T-tau and p-tau are microtubule-associated proteins that become hyperphosphorylated and aggregated in AD, leading to the formation of neurofibrillary tangles. Elevated levels of t-tau and p-tau in the CSF are indicative of neuronal damage and neurodegeneration. Numerous studies have demonstrated the diagnostic and prognostic value of CSF biomarkers in AD, with a high degree of sensitivity and specificity for detecting the disease and predicting its progression.[4-6]

Neuroimaging markers, particularly structural magnetic resonance imaging (MRI), offer a non-invasive window into the structural changes that occur in the AD brain. Hippocampal atrophy, a hallmark of AD pathology, can be readily detected on MRI and has been shown to correlate with cognitive decline and disease progression. Cortical thinning, particularly in regions vulnerable to AD pathology, is another prominent neuroimaging feature associated with the disease. Advanced neuroimaging techniques, such as diffusion tensor imaging (DTI) and positron emission tomography (PET), provide further insights into the microstructural and metabolic changes that accompany AD, offering the potential for earlier and more accurate diagnosis. Blood-based markers have garnered increasing attention in recent years as potentially accessible and less invasive alternatives to CSF biomarkers and neuroimaging. Neurofilament light chain (NfL), a structural protein released into the bloodstream upon neuronal damage, has emerged as a promising blood-based biomarker for AD. Elevated NfL levels have been associated with AD pathology, cognitive decline, and disease progression. Other blood-based markers, such as inflammatory cytokines and microRNAs, are also being investigated for their potential role in AD diagnosis and prognosis.[7,8]

The longitudinal assessment of biomarkers offers a unique opportunity to track the dynamic changes that occur in the AD brain over time. By monitoring the trajectories of various biomarkers, researchers can gain valuable insights into the natural history of the disease, identify individuals at high risk of progression, and potentially develop personalized treatment strategies based on individual biomarker profiles. Longitudinal studies also allow for the evaluation of the predictive value of biomarkers for AD progression, enabling the identification of those biomarkers that are most strongly associated with future cognitive decline and functional impairment. In

the context of Thailand, longitudinal studies of biomarkers for AD are particularly relevant. The unique genetic and environmental factors that shape the Thai population may influence the expression and progression of AD, necessitating research that is specifically tailored to this context. Furthermore, the cultural and socioeconomic landscape of Thailand may present unique challenges and opportunities for the implementation of biomarker-based approaches to AD diagnosis and management.[9,10] This prospective cohort study was designed to address these critical questions by investigating the longitudinal trajectories of various biomarkers, including CSF biomarkers, neuroimaging markers, and blood-based markers, and assessing their predictive value for AD progression in a Thai population. By leveraging a multi-modal biomarker approach and a longitudinal study design, this study aimed to provide a comprehensive understanding of the complex interplay of biomarkers in AD and their potential for personalized medicine approaches in the management of this devastating disease.

2. Methods

This prospective cohort study was meticulously designed and executed to investigate the longitudinal trajectories of biomarkers and their predictive value for Alzheimer's disease (AD) progression in a Thai population. The study adhered to rigorous methodological standards to ensure the validity and reliability of the findings; A prospective cohort study design was employed to track the progression of AD and the associated changes in biomarkers over time; The study was conducted at multiple memory clinics and community settings across Thailand, ensuring a diverse and representative sample of the population; The study duration spanned several years, allowing for the longitudinal assessment of biomarker trajectories and their association with disease progression; Participants were recruited through a combination of strategies, including; Referrals from memory clinics and neurology departments; Advertisements in local communities and media outlets; Outreach programs targeting older adult populations; Eligibility criteria included; Age 60 years or older; Diagnosis of mild cognitive impairment (MCI) or cognitively normal status at baseline; Absence of significant comorbidities, neurological disorders, or contraindications for biomarker assessments; Willingness to participate in longitudinal follow-up assessments; Exclusion criteria included; Severe cognitive impairment or dementia at baseline; History of stroke, traumatic brain injury, or other neurological conditions; Current use of medications that could interfere with biomarker assessments; Inability to provide informed consent; A sample size of 300 participants was targeted, with 150 individuals in the MCI group and 150 in the cognitively normal group; Power calculations were performed to ensure adequate statistical power to detect meaningful changes in biomarkers and their association with disease progression; The sample size was determined based on the anticipated effect sizes, variability of biomarker measurements, and desired level of statistical significance; The study protocol was approved by the relevant institutional review boards and ethics committees in Thailand; All participants provided written informed consent before enrolment; The study adhered to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines; Participant confidentiality was maintained throughout the study; Baseline assessments were conducted at the time of enrollment and included; Demographic and clinical data collection; Age, gender, education level, medical history, and medication use; Clinical Dementia Rating (CDR) scale to assess cognitive and functional impairment; Neuropsychiatric Inventory (NPI) to assess behavioral and psychological symptoms; Neuropsychological testing; A comprehensive battery of neuropsychological tests was administered to assess various cognitive domains, including memory, attention, language, executive function, and visuospatial skills; Tests included the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Rey Auditory Verbal Learning Test (RAVLT), Trail Making Test (TMT), and Clock Drawing Test (CDT); Biomarker assessments; Cerebrospinal fluid (CSF) biomarkers; Lumbar puncture was performed to collect CSF samples; CSF levels of Aβ42, t-tau, and p-tau were measured using

commercially available enzyme-linked immunosorbent assays (ELISAs); Neuroimaging; Structural magnetic resonance imaging (MRI) scans were acquired using a 3T MRI scanner; Hippocampal volume and cortical thickness were measured using automated segmentation and analysis software; Blood-based markers; Blood samples were collected and processed for plasma separation; Plasma NfL levels were measured using a commercially available single-molecule array (Simoa) assay; Follow-up assessments were conducted at regular intervals (e.g., annually) over the study duration; The same data collection procedures were followed at each follow-up visit to track changes in clinical status and biomarker levels; Disease progression was defined as a transition from MCI to AD based on established clinical criteria; The diagnosis of AD was made by a consensus panel of experienced clinicians based on a comprehensive evaluation of clinical symptoms, cognitive function, and functional impairment; Descriptive statistics were used to summarize participant characteristics and biomarker data; Longitudinal mixed-effects models were employed to assess changes in biomarker levels over time and their association with disease progression; Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive value of individual and combined biomarkers for AD progression; Multivariate Cox regression analysis was performed to identify the independent predictors of AD progression and to assess the incremental value of adding blood-based markers to the model; Statistical significance was set at $p < 0.05$; All statistical analyses were performed using appropriate statistical software packages; Data were collected using standardized forms and entered into a secure electronic database; Data quality was ensured through double data entry and regular quality checks; Biomarker assays were performed in accredited laboratories with strict quality control procedures; Neuroimaging data were analyzed by trained personnel using standardized protocols.

3. Results

Table 1 provides a snapshot of the key demographic and cognitive characteristics of the participants enrolled in the study; Demographics; The average age of participants was 72.3 years, with individuals in the MCI group being slightly older (73.1 years) than those in the cognitively normal group (71.5 years). This suggests that MCI may be more prevalent in older individuals; The study population was predominantly female (58%), which is consistent with the higher prevalence of AD in women; The mean education level was 12.5 years, with the MCI group having slightly lower education levels compared to the cognitively normal group. This could indicate a potential association between lower education and increased risk of cognitive impairment; Cognitive Function; Baseline cognitive assessments using the MMSE and MoCA revealed significant differences between the MCI and cognitively normal groups; The MCI group exhibited lower scores on both assessments, indicating impaired cognitive function in domains such as memory, attention, language, and executive function. This is expected, as MCI is characterized by a decline in cognitive abilities that is greater than what would be expected for normal aging, but not severe enough to meet the criteria for dementia.

Table 1. Participant characteristics.

Characteristic	Total (N=300)	MCI (N=150)	Cognitively normal (N=150)
Mean age (years)	72.3	73.1	71.5
Standard deviation (age)	6.5	6.8	6.2
Female, n (%)	174 (58%)	84 (56%)	90 (60%)
Education, mean (years)	12.5	11.8	13.2
MMSE score, mean (SD)	24.2 (3.1)	22.5 (2.8)	25.9 (2.5)
MoCA score, mean (SD)	21.3 (4.2)	18.6 (3.7)	2.0 (3.5)

Table 2 highlights the longitudinal changes observed in various biomarkers and their association with the progression of Alzheimer's disease (AD) in the study participants; CSF Biomarkers; Aβ42: Levels of Aβ42, a key protein involved in AD pathology, showed a significant decline over time in individuals with Mild

Cognitive Impairment (MCI). This decline was particularly pronounced in those who progressed to AD, indicating its potential as a marker of disease advancement; T-tau and P-tau: Both total tau (T-tau) and phosphorylated tau (P-tau), proteins associated with neuronal damage and tangle formation, exhibited a significant increase over time in the MCI group. Again, this increase was more pronounced in individuals who transitioned to AD, suggesting their role in tracking disease progression; Combined CSF Biomarkers: The combination of Aβ42, T-tau, and P-tau demonstrated the highest predictive value for AD progression, with an Area Under the Curve (AUC) of 0.92. This suggests that a multi-marker approach using CSF biomarkers could offer enhanced accuracy in predicting the likelihood of individuals with MCI developing AD; Neuroimaging Markers; Hippocampal Volume and Cortical Thickness: Both hippocampal volume and cortical thickness, crucial brain regions affected by AD, showed progressive atrophy (shrinkage) in both MCI and cognitively normal groups. However, the rate of decline was faster in the MCI group, and even more pronounced in those who progressed to AD. This indicates that neuroimaging can provide valuable insights into structural brain changes associated with AD and may help identify individuals at higher risk of progression; Blood-based Markers; NfL: Neurofilament light chain (NfL), a marker of neuronal damage, showed a gradual increase over time in both MCI and cognitively normal groups. However, the increase was steeper in the MCI group, particularly in those who progressed to AD. Additionally, higher baseline NfL levels were associated with an increased risk of AD progression. These findings suggest that NfL could serve as a promising blood-based biomarker for monitoring AD progression and potentially predicting future decline.

Table 2. Longitudinal changes in biomarkers and their association with AD progression.

Biomarker	**Group**	**Baseline mean (SD)**	**Follow-up mean (SD)**	**Change (%)**	**p-value**	**AUC (95% CI)**
CSF biomarkers						
Aβ42 (pg/mL)	MCI - Stable	1200 (200)	1050 (180)	-12.50%	<0.001	0.85 (0.78-0.91)
	MCI - Progressed to AD	1200 (200)	800 (150)	-33.30%	<0.001	
T-tau (pg/mL)	MCI - Stable	300 (50)	350 (60)	+16.7%	<0.001	0.88 (0.82-0.94)
	MCI - Progressed to AD	300 (50)	450 (80)	+50%	<0.001	
P-tau (pg/mL)	MCI - Stable	60 (10)	70 (12)	+16.7%	<0.001	0.82 (0.75-0.89)
	MCI - Progressed to AD	60 (10)	90 (15)	+50%	<0.001	
Aβ42, T-tau, & P-tau (combined)	MCI - All	-	-	-	-	0.92 (0.87-0.96)
Neuroimaging markers						
Hippocampal volume (mm^3)	MCI - Stable	5000 (500)	4800 (450)	-4%	<0.01	0.70 (0.62-0.77)
	MCI - Progressed to AD	5000 (500)	4400 (400)	-12%	<0.001	
	Cognitively Normal	5500 (600)	5300 (550)	-3.60%	<0.01	
Cortical thickness (mm)	MCI - Stable	2.5 (0.2)	2.4 (0.2)	-4%	<0.01	0.65 (0.58-0.73)
	MCI - Progressed to AD	2.5 (0.2)	2.2 (0.2)	-12%	<0.001	
	Cognitively Normal	2.7 (0.3)	2.6 (0.3)	-3.70%	<0.01	
Blood-based markers						
NfL (pg/mL)	MCI - Stable	20 (5)	25 (6)	+25%	<0.05	0.75 (0.68-0.82)
	MCI - Progressed to AD	20 (5)	35 (8)	+75%	<0.01	
	Cognitively Normal	15 (4)	18 (5)	+20%	<0.05	

Table 3 highlights the predictive power of different biomarker models in forecasting the progression of Alzheimer's disease (AD) within the study cohort. The table utilizes hazard ratios (HR) and their associated p-values to quantify the strength of association between the biomarker models and the risk of AD progression; CSF & Neuroimaging Markers; The combination of cerebrospinal fluid (CSF) and neuroimaging markers demonstrates a significant association with AD progression, as evidenced by the hazard ratio of 2.5 ($p = 0.002$); This indicates that individuals exhibiting biomarker profiles suggestive of AD pathology in their CSF and brain imaging have a 2.5 times higher risk of progressing to AD compared to those without such profiles; This underscores the established value of CSF and neuroimaging biomarkers in identifying individuals at risk of AD progression; CSF, Neuroimaging & NfL; The integration of the blood-based marker, Neurofilament light chain (NfL), into the model, significantly enhances its predictive power. The hazard ratio increases to 3.5 ($p < 0.001$); This implies that individuals with abnormal CSF, neuroimaging, and elevated NfL levels have a 3.5 times higher risk of AD progression compared to those without such findings; This highlights the incremental value of NfL in refining the prediction of AD progression beyond what is achievable with CSF and neuroimaging markers alone.

Table 3. Predictive value of biomarkers for predicting AD progression.

Biomarker model	Hazard ratio (HR)	95% confidence interval	p-value
CSF & neuroimaging markers	2.5	1.8 - 3.2	0.002
CSF, Neuroimaging & NfL	3.5	2.1 - 5.8	<0.001

4. Discussion

The findings from this longitudinal study in Thailand, particularly the observed changes in CSF biomarkers, neuroimaging markers, and blood-based markers, shed light on the complex pathophysiological processes that underlie the progression of Alzheimer's disease (AD). These biomarkers not only serve as indicators of disease presence but also provide valuable insights into the dynamic interplay of molecular events and structural changes that contribute to the cognitive and functional decline characteristic of AD. The decline in Aβ42 levels in the cerebrospinal fluid (CSF) of individuals with Mild Cognitive Impairment (MCI), especially those who progressed to AD, aligns with the amyloid cascade hypothesis, a central tenet in AD pathophysiology. This hypothesis posits that the accumulation of amyloid-beta (Aβ) plaques in the brain is an initiating event in the disease process. Aβ, a cleavage product of the amyloid precursor protein (APP), forms insoluble aggregates that deposit in the brain parenchyma, disrupting neuronal function and triggering a cascade of downstream events. The decreased levels of Aβ42 in the CSF reflect the sequestration of Aβ into these plaques, thereby reducing its availability in the soluble pool. The concomitant increase in T-tau and P-tau levels in the CSF further corroborates the pathological cascade in AD. Tau, a microtubule-associated protein, plays a critical role in maintaining neuronal structure and axonal transport. In AD, tau becomes hyperphosphorylated, leading to its detachment from microtubules and subsequent aggregation into neurofibrillary tangles. These tangles disrupt intracellular transport, impair neuronal function, and ultimately lead to neuronal death. The elevated CSF levels of T-tau and P-tau observed in individuals with MCI, particularly those who progressed to AD, mirror the extent of tau pathology in the brain. The combination of decreased Aβ42 and increased T-tau and P-tau levels in the CSF paints a picture of the dynamic interplay between amyloid and tau pathology in AD progression. While the amyloid cascade hypothesis suggests that Aβ deposition is an early event, the subsequent tau pathology appears to be more closely associated with the clinical manifestations of the disease, including cognitive decline and neurodegeneration. The findings of this study support this notion, demonstrating that

changes in tau biomarkers are particularly pronounced in individuals transitioning from MCI to AD. The progressive atrophy of the hippocampus and cortical regions, as revealed by the neuroimaging findings, provides further evidence of the neurodegenerative processes at play in AD. The hippocampus, a key brain structure involved in memory formation and consolidation, is particularly vulnerable to AD pathology. The observed decline in hippocampal volume, especially in individuals with MCI who progressed to AD, underscores the detrimental impact of AD on memory function. This is consistent with the clinical presentation of AD, where memory impairment is often one of the earliest and most prominent symptoms. Cortical thinning, particularly in areas associated with higher-order cognitive processes such as language, executive function, and visuospatial skills, reflects the widespread neurodegeneration that characterizes AD. The gradual loss of cortical gray matter results in the disruption of neural networks and the impairment of cognitive abilities. The faster rate of cortical thinning observed in individuals with MCI who progressed to AD suggests that this neuroimaging marker may be a valuable indicator of disease progression and could potentially be used to identify individuals at high risk of developing AD dementia. The gradual increase in NfL levels in both MCI and cognitively normal groups, with a steeper rise in those who progressed to AD, provides a glimpse into the ongoing neurodegenerative process in AD. NfL, a structural protein released into the bloodstream upon axonal damage, serves as a direct measure of neuronal injury and death. Elevated NfL levels have been consistently associated with AD pathology, cognitive decline, and disease progression. The findings of this study further support the utility of NfL as a sensitive biomarker for monitoring disease activity and predicting future decline. The association between higher baseline NfL levels and increased risk of AD progression highlights its potential as a prognostic biomarker. Individuals with elevated NfL levels at baseline, even in the absence of significant cognitive impairment, may be at a higher risk of developing AD in the future. This information could be valuable for clinicians in identifying individuals who may benefit from early interventions or closer monitoring. The combination of CSF biomarkers, neuroimaging markers, and blood-based markers offers a comprehensive and dynamic view of AD pathophysiology. The amyloid cascade hypothesis, supported by the changes in CSF Aβ42, T-tau, and P-tau levels, provides a framework for understanding the initiating events and subsequent pathological cascade in AD. Neuroimaging markers, such as hippocampal atrophy and cortical thinning, reveal the structural consequences of these molecular events, while blood-based markers, such as NfL, provide a real-time measure of ongoing neurodegeneration. The superior predictive value of the combined biomarker model underscores the complementary nature of different biomarker modalities. Each biomarker offers a unique perspective on the disease process, and their integration provides a more holistic understanding of AD pathophysiology. This multi-modal approach has the potential to revolutionize the diagnosis and management of AD, enabling earlier detection, more accurate prediction of disease progression, and personalized treatment strategies. The intricate dance of molecular events that orchestrates the progression of Alzheimer's disease (AD) is a subject of intense research and continuous discovery. This longitudinal study, with its comprehensive assessment of biomarkers, provides a glimpse into this complex molecular landscape, shedding light on the key players and their interactions in driving the neurodegenerative process. The observed changes in CSF biomarkers, neuroimaging findings, and blood-based markers serve as windows into the molecular mechanisms that underpin AD pathogenesis, offering valuable insights into potential therapeutic targets and avenues for early intervention.[11-13]

The decline in CSF Aβ42 levels observed in individuals with Mild Cognitive Impairment (MCI), particularly those who progressed to AD, serves as a testament to the central role of amyloid beta (Aβ) in AD pathogenesis. Aβ, a peptide derived from the amyloid precursor protein (APP), is prone to misfolding and aggregation, leading to the formation of insoluble plaques that deposit in the brain parenchyma. The amyloid cascade hypothesis posits that the

accumulation of these Aβ plaques is an initiating event in AD, triggering a series of downstream events that culminate in neurodegeneration and cognitive decline. The molecular mechanisms by which Aβ plaques exert their toxic effects are multifaceted and involve a complex interplay of cellular and molecular processes. Aβ oligomers, soluble aggregates of Aβ peptides, are believed to be the primary toxic species, disrupting synaptic function, impairing neuronal plasticity, and promoting oxidative stress. Aβ oligomers can also activate microglia and astrocytes, leading to chronic neuroinflammation and the release of pro-inflammatory cytokines, further exacerbating neuronal damage. The deposition of Aβ plaques also disrupts the clearance of other proteins, including tau, contributing to the formation of neurofibrillary tangles and the progression of AD pathology. This intricate interplay between Aβ and tau highlights the interconnectedness of molecular events in AD and underscores the importance of targeting multiple pathways for effective therapeutic intervention. The increase in CSF levels of T-tau and P-tau, especially in individuals with MCI who progressed to AD, reflects the crucial role of tau protein in AD pathogenesis. Tau, a microtubule-associated protein, plays a vital role in maintaining the structural integrity of neurons and facilitating axonal transport. In AD, tau becomes hyperphosphorylated, leading to its detachment from microtubules and subsequent aggregation into insoluble neurofibrillary tangles. These tangles disrupt intracellular transport, impair neuronal function, and ultimately lead to neuronal death. The molecular mechanisms underlying tau hyperphosphorylation and aggregation are complex and involve multiple kinases and phosphatases. Several kinases, including glycogen synthase kinase 3 beta (GSK-3β) and cyclin-dependent kinase 5 (CDK5), have been implicated in tau hyperphosphorylation. The imbalance between kinase and phosphatase activity leads to the accumulation of hyperphosphorylated tau, which is prone to misfolding and aggregation. The formation of neurofibrillary tangles further disrupts neuronal function by impairing axonal transport, mitochondrial function, and synaptic plasticity. The presence of these tangles also triggers a cascade of neurodegenerative events, including oxidative stress, neuroinflammation, and apoptosis, ultimately leading to the progressive loss of neurons and brain atrophy. The gradual increase in NfL levels observed in both MCI and cognitively normal groups, with a steeper rise in those who progressed to AD, provides a direct measure of ongoing neurodegeneration. NfL, a structural protein component of neuronal axons, is released into the bloodstream upon axonal damage and neuronal death. Elevated NfL levels have been consistently associated with AD pathology, cognitive decline, and disease progression. The molecular mechanisms underlying NfL release are complex and involve multiple pathways. Axonal damage, triggered by Aβ and tau pathology, leads to the disruption of the axonal cytoskeleton and the release of NfL into the extracellular space. NfL then crosses the blood-brain barrier and enters the systemic circulation, where it can be detected in the blood. The levels of NfL in the blood reflect the extent of neuronal damage and neurodegeneration in the brain. The association between higher baseline NfL levels and increased risk of AD progression suggests that NfL may serve as a sensitive indicator of early neurodegenerative processes, even before the onset of significant cognitive impairment. This highlights the potential of NfL as a prognostic biomarker for identifying individuals at high risk of developing AD and for monitoring disease progression.[14,15]

The molecular mechanisms underlying AD pathogenesis are not isolated events but rather a complex network of interconnected pathways. The accumulation of Aβ plaques triggers a cascade of events, including oxidative stress, neuroinflammation, and synaptic dysfunction, which contribute to tau hyperphosphorylation and aggregation. The presence of these pathological hallmarks further exacerbates neurodegeneration, leading to axonal damage, neuronal death, and the release of NfL into the bloodstream. This intricate web of molecular interactions highlights the challenges in developing effective therapies for AD. Targeting a single pathway may not be sufficient to halt or reverse the disease process. A multi-faceted approach that addresses

multiple molecular targets and pathways may be necessary to achieve meaningful clinical benefits. The quest for accurate and early prediction of Alzheimer's disease (AD) progression has been a cornerstone of AD research for decades. The findings of this longitudinal study, with its comprehensive assessment of CSF biomarkers, neuroimaging markers, and blood-based markers, underscore the significant predictive value of these biomarkers in identifying individuals at high risk of developing AD and monitoring disease progression. The power of a multi-modal approach, integrating information from different biomarker modalities, emerges as a key theme, promising a future of personalized AD management. The superior predictive accuracy of the combined biomarker model, incorporating CSF, neuroimaging, and blood-based markers, highlights the complementary nature of these different modalities. Each biomarker category offers a unique window into the complex pathophysiological processes that underlie AD, and their integration provides a more holistic and nuanced understanding of the disease trajectory. CSF biomarkers, such as Aβ42, T-tau, and P-tau, provide direct evidence of the core pathological hallmarks of AD, namely amyloid plaque deposition and tau tangle formation. These biomarkers reflect the earliest molecular events in the AD cascade and can be detected years before the onset of clinical symptoms. The ability to identify individuals with abnormal CSF biomarker profiles, even in the absence of cognitive impairment, offers a unique opportunity for early intervention and potential disease modification. Neuroimaging markers, such as hippocampal atrophy and cortical thinning, capture the structural consequences of AD pathology. These markers reflect the progressive neurodegeneration that occurs in the brain, leading to the loss of neurons and synaptic connections. The ability to visualize and quantify these structural changes provides valuable information about the extent and severity of the disease process, aiding in the diagnosis and prognosis of AD. Blood-based markers, such as NfL, offer a less invasive and more accessible alternative to CSF biomarkers and neuroimaging. NfL, a marker of neuronal damage, reflects the ongoing neurodegenerative process and provides a dynamic measure of disease activity. The inclusion of NfL in the predictive model significantly enhances its accuracy, suggesting that blood-based markers can provide valuable complementary information to CSF and neuroimaging markers. The synergy between these different biomarker modalities lies in their ability to capture different aspects of AD pathophysiology. CSF biomarkers reflect the earliest molecular events, neuroimaging markers visualize the structural consequences, and blood-based markers provide a real-time measure of ongoing neurodegeneration. By integrating information from these diverse sources, we can achieve a more comprehensive and accurate prediction of AD progression, enabling personalized risk assessment and tailored treatment strategies. The study findings highlight the potential clinical utility of NfL as a prognostic biomarker in AD. The association between higher baseline NfL levels and increased risk of AD progression suggests that NfL could be used to identify individuals with MCI who are at a higher risk of converting to AD. This information could be invaluable for clinicians in making treatment decisions and monitoring disease progression. NfL's appeal as a prognostic biomarker stems from several factors. First, it is a blood-based marker, making it less invasive and more accessible than CSF biomarkers or neuroimaging. Second, NfL levels reflect ongoing neurodegeneration, providing a dynamic measure of disease activity. Third, NfL has been shown to correlate with the extent of AD pathology, cognitive decline, and functional impairment, further supporting its clinical relevance. The incorporation of NfL into the predictive model significantly improved its accuracy, underscoring its value as a complementary biomarker to CSF and neuroimaging markers. This suggests that NfL could be used in conjunction with other biomarkers to refine risk assessment and identify individuals who may benefit from early interventions or closer monitoring.[16-18]

The clinical implications of this longitudinal biomarker study in Thailand are profound, heralding a new era of personalized medicine in the management of Alzheimer's disease (AD). The identification of individuals at high risk of AD progression, coupled

with the ability to monitor disease activity and response to treatment using a multi-modal biomarker approach, has the potential to revolutionize the way we diagnose, treat, and care for individuals affected by this devastating disease. The early detection of AD, even before the onset of significant cognitive impairment, is crucial for timely intervention and potential disease modification. The study findings demonstrate the power of a multi-modal biomarker approach, combining CSF, neuroimaging, and blood-based markers, in identifying individuals at high risk of AD progression. This approach allows for a more nuanced and comprehensive assessment of an individual's risk profile, enabling clinicians to initiate preventive measures and therapeutic interventions at the earliest possible stage. CSF biomarkers, such as Aβ42, T-tau, and P-tau, provide direct evidence of the core pathological processes in AD, namely amyloid plaque deposition and tau tangle formation. By measuring these biomarkers in individuals with Mild Cognitive Impairment (MCI), clinicians can identify those who are most likely to progress to AD dementia. This information can be used to stratify individuals based on their risk of progression, allowing for targeted interventions and closer monitoring. Neuroimaging markers, such as hippocampal atrophy and cortical thinning, provide additional insights into the structural changes associated with AD. These markers can be used to corroborate the findings of CSF biomarkers and further refine the risk assessment. For example, individuals with MCI who exhibit both abnormal CSF biomarker profiles and evidence of hippocampal atrophy on MRI may be at a particularly high risk of rapid progression to AD. Blood-based markers, such as NfL, offer a less invasive and more accessible alternative to CSF biomarkers and neuroimaging. The association between higher baseline NfL levels and increased risk of AD progression suggests that NfL could be used as a screening tool to identify individuals who may benefit from further evaluation with CSF biomarkers or neuroimaging. This could potentially streamline the diagnostic process and make early detection more feasible in resource-limited settings. The ability to monitor disease progression using biomarkers has the potential to revolutionize the treatment of AD. By tracking changes in biomarker levels over time, clinicians can assess the effectiveness of interventions, tailor treatment strategies, and identify individuals who may be at risk of rapid decline or treatment failure. For example, individuals with MCI who exhibit a rapid decline in hippocampal volume or a steep increase in NfL levels, despite receiving standard treatment, may require a more aggressive therapeutic approach or enrollment in clinical trials evaluating novel disease-modifying therapies. Conversely, individuals who show stable biomarker profiles may benefit from a less intensive treatment regimen or closer monitoring with less frequent follow-up visits. The use of biomarkers to monitor treatment response could also facilitate the development of personalized treatment plans. By identifying individuals who respond favorably to specific interventions, clinicians can optimize treatment strategies and avoid unnecessary or ineffective treatments. This personalized approach has the potential to improve patient outcomes and reduce the burden of AD on individuals and their families. The identification of individuals at high risk of AD progression using biomarkers could also enhance the efficiency and success of clinical trials evaluating novel disease-modifying therapies. By enrolling individuals with a high likelihood of progression, researchers can increase the statistical power of their studies and reduce the sample size required to detect a treatment effect. Furthermore, the use of biomarkers to monitor treatment response in clinical trials could provide valuable insights into the mechanisms of action of new therapies and identify potential biomarkers of treatment efficacy. This information could be used to accelerate the development and approval of new drugs for AD, ultimately bringing hope to millions of individuals affected by the disease.[19,20]

5. Conclusion

This study has yielded valuable insights into the longitudinal trajectories of biomarkers and their predictive power in forecasting the progression of Alzheimer's disease (AD). By employing a multi-modal approach encompassing CSF biomarkers,

neuroimaging markers, and blood-based markers, the study has illuminated the complex interplay of pathological processes that contribute to AD progression. The observed decline in Aβ42 levels and the concomitant increase in T-tau and P-tau levels in the CSF of individuals with MCI, particularly those who transitioned to AD, underscore the central role of amyloid and tau pathology in the disease cascade. The progressive atrophy of the hippocampus and cortical regions, as evidenced by neuroimaging findings, further reflects the neurodegenerative consequences of these pathological processes. Additionally, the gradual increase in NfL levels, a blood-based marker of neuronal damage, provides a direct measure of ongoing neurodegeneration and serves as a sensitive indicator of disease activity. The study's findings highlight the significant predictive value of a multi-modal biomarker approach for AD progression. The combination of CSF, neuroimaging, and blood-based markers demonstrated superior predictive accuracy compared to individual biomarker modalities, underscoring the complementary nature of these markers in capturing different aspects of AD pathophysiology.

6. References

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