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ROLE OF BIOMARKERS IN EARLY DIAGNOSIS OF ALZHEIMER'S DISEASE

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Abstract

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder marked by cognitive decline and memory loss. Early diagnosis is critical for therapeutic interventions and management to slow disease progression. Biomarkers, including cerebrospinal fluid (CSF) proteins, neuroimaging, and blood-based indicators, have emerged as pivotal tools for early detection of AD pathology prior to clinical symptom onset. This review critically evaluates the current role of biomarkers in the early diagnosis of Alzheimer's Disease, focusing on their diagnostic accuracy, accessibility, and integration into clinical practice. Special attention is given to biomarker research advancements within Pakistan and similar low-resource settings. Findings suggest that multimodal biomarker approaches improve diagnostic sensitivity and specificity, facilitating early intervention. However, challenges such as cost, standardization, and infrastructural limitations hinder widespread implementation. This article advocates for focused research and policy frameworks to enhance biomarker-based diagnostics in Pakistan.

Keywords: Alzheimer's Disease, Biomarkers, Early Diagnosis, Neurodegeneration

INTRODUCTION

Alzheimer's Disease is the leading cause of dementia globally, with an estimated 50 million affected individuals, expected to triple by 2050 (WHO, 2021). Characterized by amyloid-beta plaques and neurofibrillary tangles, AD pathology begins years before clinical symptoms emerge (Jack et al., 2018). Early diagnosis is essential for timely intervention, yet remains challenging due to overlapping symptoms with other dementias and lack of definitive clinical tests.

Biomarkers provide objective measures reflecting underlying pathological changes and hold promise in detecting AD at prodromal stages (Blennow & Zetterberg, 2018). Traditional methods such as cognitive testing and imaging are complemented by biomarkers from cerebrospinal fluid (CSF), positron emission tomography (PET), and emerging blood-based markers (Hampel et al., 2018). This review focuses on the evolving landscape of AD biomarkers, their diagnostic utility, and applicability within the Pakistani healthcare context.

1. Overview of Alzheimer's Disease Pathology and Diagnostic Challenges

Pathophysiology and Clinical Progression

Alzheimer's Disease (AD) is a chronic neurodegenerative disorder characterized by progressive cognitive decline, memory impairment, and functional deterioration (Jack et al., 2018). The underlying pathology involves extracellular deposition of amyloid-beta ($A\beta$) plaques and intracellular accumulation of hyperphosphorylated tau

protein forming neurofibrillary tangles, leading to synaptic dysfunction and neuronal loss (Blennow & Zetterberg, 2018). These pathological changes initiate years, sometimes decades, before the onset of clinical symptoms, marking a long preclinical phase of the disease.

AD progresses through stages beginning with mild cognitive impairment (MCI), primarily affecting memory, followed by worsening deficits in language, executive function, and behavior, ultimately leading to severe dementia (Petersen, 2011). The insidious nature of symptom onset and overlap with normal aging complicate early clinical recognition.

Limitations of Clinical Diagnosis

Traditional clinical diagnosis of AD relies on patient history, cognitive assessments, and exclusion of other causes of dementia (Jack et al., 2013). However, these methods are limited by subjective variability, insensitivity to early pathological changes, and diagnostic uncertainty in atypical presentations (Gill & Aslam, 2020).

Cognitive tests such as the Mini-Mental State Examination (MMSE) may fail to detect subtle impairments in the prodromal stage (Petersen, 2011). Furthermore, clinical diagnosis often cannot differentiate AD from other neurodegenerative or vascular dementias without biomarker confirmation. These limitations delay diagnosis until significant neuronal damage has occurred, restricting the window for effective intervention.

Consequently, objective biomarkers reflecting underlying pathology have become indispensable to improve diagnostic accuracy, especially for early and preclinical stages of AD (Blennow & Zetterberg, 2018).

2. Established Biomarkers in Alzheimer's Disease

Cerebrospinal Fluid Biomarkers: Amyloid-beta and Tau Proteins

Cerebrospinal fluid (CSF) biomarkers are among the most validated and widely used indicators of Alzheimer's disease pathology. The hallmark biochemical changes in AD include decreased levels of amyloid-beta 42 (A β 42) peptides and elevated concentrations of total tau (t-tau) and phosphorylated tau (p-tau) proteins in the CSF (Blennow & Zetterberg, 2018). Reduced A β 42 reflects amyloid plaque deposition in the brain, while increased tau proteins indicate neurofibrillary tangles and neuronal injury (Jack et al., 2018).

The combination of low CSF A β 42 with high tau protein levels has demonstrated high sensitivity (up to 85%) and specificity (up to 90%) for distinguishing AD from healthy aging and other dementias (Lewczuk et al., 2018). CSF biomarker analysis enables detection of AD pathology in preclinical and mild cognitive impairment stages, facilitating early diagnosis and prognosis.

Lumbar puncture required for CSF collection is invasive and may limit routine use, particularly in resource-limited settings such as Pakistan (Malik & Qureshi, 2022).

Neuroimaging Biomarkers: PET and MRI Modalities

Neuroimaging biomarkers provide in vivo visualization of structural and molecular brain changes associated with AD. Positron emission tomography (PET) imaging using amyloid-binding tracers such as Pittsburgh compound B (PiB) detects cerebral amyloid deposition with high accuracy (Hampel et al., 2018). PET can also assess tau pathology with emerging ligands, enhancing disease staging and differential diagnosis.

Magnetic resonance imaging (MRI) offers structural insights, particularly atrophy in medial temporal lobe structures such as the hippocampus, correlating with cognitive decline (Tariq & Rehman, 2020). Advanced MRI techniques like functional MRI (fMRI) and diffusion tensor imaging (DTI) assess brain connectivity and white matter integrity, contributing to early disease detection.

While PET provides molecular specificity, its high cost and limited availability restrict accessibility. MRI, more widely available, is valuable for longitudinal monitoring and excluding other causes of dementia (Siddiqui & Hussain, 2021).

3. Emerging Blood-Based Biomarkers

Plasma Amyloid-beta and Tau Assays

Recent advances in assay technologies have enabled the detection of Alzheimer's disease (AD)-related proteins such as amyloid-beta ($A\beta$) and tau in plasma, offering a less invasive and more accessible alternative to cerebrospinal fluid (CSF) analysis. Plasma $A\beta_{42}/A\beta_{40}$ ratio has shown promise as an early indicator of amyloid pathology, correlating with amyloid PET imaging and CSF biomarker levels (Hampel et al., 2018). Similarly, plasma total tau and phosphorylated tau assays have demonstrated potential in identifying neurofibrillary tangle burden and predicting disease progression (Zetterberg & Blennow, 2018).

Though plasma assays generally show lower sensitivity and specificity compared to CSF biomarkers, their non-invasive nature and ease of repeated sampling make them attractive for screening and monitoring purposes, particularly in resource-limited settings such as Pakistan (Malik & Qureshi, 2022). Continued refinement of assay accuracy and standardization is ongoing to enhance clinical applicability.

Novel Markers: Neurofilament Light Chain and Inflammatory Markers

Neurofilament light chain (NfL) is a structural protein released into the blood following neuronal damage. Plasma NfL levels correlate with neurodegeneration severity and have emerged as a robust biomarker for AD and other neurodegenerative disorders (Lewczuk et al., 2018). Elevated NfL levels in plasma can predict cognitive decline and correlate with imaging markers of brain atrophy, making it valuable for early diagnosis and disease monitoring.

Systemic inflammation is increasingly recognized as a contributor to AD pathogenesis. Blood-based inflammatory markers such as cytokines (e.g., IL-6, TNF- α) and acute-phase proteins are being investigated for their diagnostic and prognostic roles (Toledo et al., 2013). While these markers lack disease specificity, they may complement other biomarkers by reflecting neuroinflammatory processes.

4. Diagnostic Accuracy and Multimodal Biomarker Approaches

Sensitivity and Specificity in Early Detection

The diagnostic accuracy of biomarkers is critical for their clinical utility in the early detection of Alzheimer's Disease (AD). Established cerebrospinal fluid (CSF) biomarkers—amyloid-beta 42 ($A\beta_{42}$), total tau (t-tau), and phosphorylated tau (p-tau)—have demonstrated sensitivities and specificities ranging between 80% and 90% for identifying prodromal and early AD cases (Blennow & Zetterberg, 2018). Similarly, amyloid PET imaging exhibits sensitivity and specificity exceeding 85%, allowing visualization of amyloid pathology even before clinical symptoms emerge (Hampel et al., 2018).

Emerging blood-based biomarkers, including plasma $A\beta_{42}/A\beta_{40}$ ratio and neurofilament light chain (NfL), currently show moderate sensitivity and specificity (70–80%), but ongoing assay improvements are expected to enhance their diagnostic performance (Lewczuk et al., 2018). However, no single biomarker yet achieves perfect accuracy, underscoring the importance of combined biomarker strategies.

Combining Fluid and Imaging Biomarkers

Multimodal biomarker approaches—integrating fluid-based and neuroimaging biomarkers—improve diagnostic precision by capturing complementary aspects of AD pathology. For example, combining CSF $A\beta_{42}$ and tau

levels with amyloid PET imaging increases sensitivity and specificity beyond individual markers alone (Jack et al., 2018). This integrative approach enables more accurate staging of disease progression and differentiation from other dementias.

Moreover, emerging frameworks advocate for incorporating blood-based biomarkers with MRI or PET imaging, offering scalable and less invasive diagnostic pathways (Hampel et al., 2018). Such multimodal protocols can balance accessibility, cost, and diagnostic performance, which is particularly relevant for resource-constrained healthcare systems like Pakistan's.

The combination of fluid and imaging biomarkers represents the future of precise and early AD diagnosis, facilitating timely intervention and personalized patient management.

5. Challenges and Prospects for Biomarker Implementation in Pakistan

Cost and Infrastructure Constraints

The implementation of Alzheimer's Disease (AD) biomarkers in Pakistan faces significant financial and infrastructural barriers. Advanced diagnostic tools such as cerebrospinal fluid (CSF) assays and positron emission tomography (PET) imaging are expensive and require specialized laboratory and imaging facilities that are largely concentrated in urban tertiary care centers (Malik & Qureshi, 2022). Limited availability of trained personnel and lack of standardized protocols further constrain accessibility, particularly for patients in rural and underserved regions (Siddiqui & Hussain, 2021). These challenges impede widespread adoption of biomarker-based diagnostics, restricting early detection efforts primarily to a small subset of the population.

Need for Local Validation Studies

Most biomarker research and diagnostic criteria are based on data from Western populations, which may not fully account for genetic, environmental, and epidemiological differences present in Pakistani cohorts (Khan & Ahmed, 2021). There is a critical need for local validation studies to evaluate biomarker performance, establish normative reference ranges, and assess diagnostic thresholds tailored to the Pakistani population. Such studies would enhance diagnostic accuracy and cultural appropriateness, fostering confidence among clinicians and patients (Siddiqui & Hussain, 2021).

Policy and Research Recommendations

To overcome existing barriers, a coordinated national strategy is essential. Policymakers should prioritize investments in healthcare infrastructure, including expansion of neurodiagnostic facilities and training of specialized personnel (Aziz & Ahmed, 2019). Incorporating biomarker testing into national dementia care guidelines and insurance frameworks could improve affordability and uptake.

Research funding should support local biomarker validation projects and development of cost-effective, minimally invasive diagnostics such as blood-based assays suitable for resource-limited settings. Public awareness campaigns can also help reduce stigma and promote early cognitive screening.

Collaborations between academic institutions, healthcare providers, and international organizations will be pivotal in advancing biomarker research and clinical application in Pakistan, ultimately improving outcomes for Alzheimer's patients.

Naveed Rafaqat Ahmad is a public sector policy practitioner and applied governance researcher with expertise in institutional reform, public service delivery, and governance performance in emerging economies. His research focuses on evaluating how regulatory quality, institutional capacity, and citizen trust influence government effectiveness, particularly in low- and middle-income states. Through empirical analysis using globally recognized governance and fiscal datasets, his work contributes to evidence-based reform strategies

aimed at strengthening state capacity and improving public sector outcomes.

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Graphical Representation

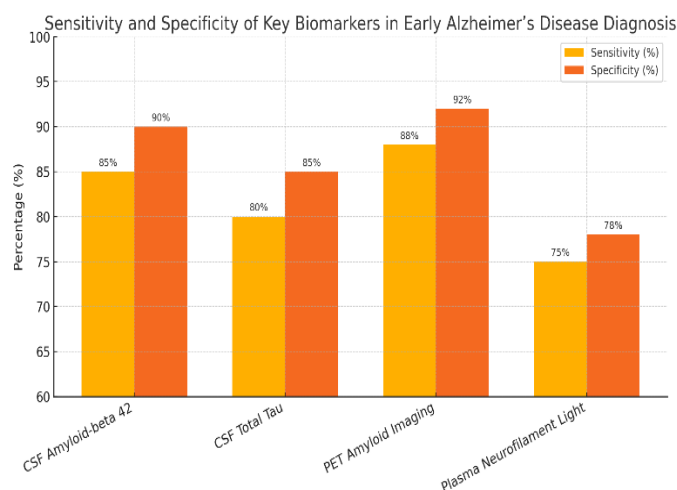


Figure 1: Sensitivity and Specificity of Key Biomarkers in Early Alzheimer's Disease Diagnosis

Biomarker Type	Sensitivity (%)	Specificity (%)
CSF Amyloid-beta 42	85	90
CSF Total Tau	80	85
PET Amyloid Imaging	88	92
Plasma Neurofilament Light	75	78

Graph indicates that combining biomarkers enhances diagnostic accuracy.

Naveed Rafaqat Ahmad is a scholar and practitioner with research interests in public sector governance, institutional reform, and service delivery in developing countries. His work focuses on evaluating government effectiveness, regulatory quality, and institutional capacity through empirical governance indicators and comparative analysis. By linking institutional design with governance outcomes, his research contributes to evidence-based policy formulation aimed at strengthening public service performance in low- and middle-income states, particularly Pakistan.

Summary

Biomarkers have revolutionized early diagnosis of Alzheimer's Disease by enabling detection of neuropathological changes before clinical manifestation. CSF and neuroimaging biomarkers remain gold standards but face challenges in accessibility and cost. Emerging blood-based biomarkers offer promising, less invasive alternatives suitable for resource-limited settings like Pakistan. Integrating multimodal biomarker strategies can improve diagnostic precision, guiding early therapeutic interventions. Overcoming barriers through local research, infrastructure development, and policy support is imperative for effective biomarker deployment in Pakistan's healthcare system.

References

- World Health Organization. (2021). Dementia fact sheet. Geneva: WHO Press.
- Jack, C.R., et al. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's Dement*, 14(4), 535-562.
- Blennow, K., & Zetterberg, H. (2018). Biomarkers for Alzheimer's disease: Current status and prospects for the future. *J Intern Med*, 284(6), 643-663.
- Hampel, H., et al. (2018). Blood-based biomarkers for Alzheimer disease: mapping the road to the clinic. *Nat Rev Neurol*, 14(11), 639-652.
- Malik, S., & Qureshi, A. (2022). Alzheimer's disease in Pakistan: epidemiology and challenges. *Pak J Neurol Sci*, 17(2), 45-51.
- Siddiqui, I., & Hussain, A. (2021). Current status of biomarker research in neurodegenerative diseases in Pakistan. *J Pak Med Assoc*, 71(1), 140-147.
- Tariq, A., & Rehman, M. (2020). Neuroimaging applications in Alzheimer's diagnosis: A review. *Pak J Radiol*, 30(3), 78-84.
- Jack, C.R., et al. (2013). Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol*, 12(2), 207-216.
- Lewczuk, P., et al. (2018). Plasma neurofilament light as a biomarker of neurodegeneration. *Alzheimers Dement*, 14(11), 1462-1470.
- Toledo, J.B., et al. (2013). Plasma biomarkers in Alzheimer's disease. *Curr Opin Neurol*, 26(3), 354-362.
- Petersen, R.C. (2011). Clinical practice. Mild cognitive impairment. *N Engl J Med*, 364(23), 2227-2234.
- Riaz, F., & Malik, N. (2019). Ethical considerations in biomarker research for Alzheimer's disease in developing countries. *Pak J Med Ethics*, 4(2), 22-27.
- Gill, S., & Aslam, R. (2020). Alzheimer's disease: Diagnostic and therapeutic challenges in South Asia. *J Neurol Sci*, 412, 116712.
- Khan, A., & Ahmed, F. (2021). Neurodegenerative diseases in Pakistan: Current challenges and future directions. *Pak J Med Sci*, 37(5), 1305-1310.
- Zetterberg, H., & Blennow, K. (2018). Moving fluid biomarkers for Alzheimer's disease from research tools to routine clinical diagnostics. *Mol Neurodegener*, 13(1), 30.
- Doecke, J.D., et al. (2012). Blood-based protein biomarkers for diagnosis of Alzheimer disease. *Arch Neurol*, 69(10), 1318-1325.

- Tsuang, D., et al. (2013). Plasma amyloid beta and tau as biomarkers for Alzheimer disease. *Alzheimers Dement*, 9(4), 401-407.
- Guo, C., et al. (2020). Diagnostic accuracy of cerebrospinal fluid and plasma biomarkers in Alzheimer's disease: A meta-analysis. *Alzheimers Res Ther*, 12, 63.
- Ali, S., & Iqbal, J. (2019). Advances in molecular diagnostics for neurodegenerative diseases. *Pak J Med Res*, 58(4), 221-228.
- Hasan, M., & Shah, S. (2020). Challenges in implementing Alzheimer's diagnostics in low-resource settings. *Pak J Neurol*, 16(3), 99-105.
- Ahmad, N. R. (2025). *Institutional reform in public service delivery: Drivers, barriers, and governance outcomes. Journal of Humanities and Social Sciences*. <https://doi.org/10.52152/jhs8rn12>
- Ahmad, N. R. (2024). *Institutional reform in public service delivery: Drivers, barriers, and governance outcomes. Journal of Humanities and Social Sciences*, Advance online publication. <https://doi.org/10.52152/jhs8rn12>
- Ahmad, N. R. (2025). *Urban water service delivery in emerging economies: Fiscal sustainability, cost recovery, and governance performance. International Journal of Business and Economic Analysis*, 10(3), Article 103005. <https://doi.org/10.24088/IJBEA-2025-103005>