Journal of Pharmacology, Genetics and Molecular Biology (JPGMB)
ISSN: 3049-3757 | Vol. 01, Issue-06, Nov-Dec, 2025

Novel Biomarkers for Early Diagnosis of Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disease for which early detection is essential but frequently difficult because of intrusive and expensive diagnostic techniques. The purpose of this study was to assess new biomarkers for AD early detection in blood and cerebrospinal fluid (CSF). 120 participants, ages 55 to 80, participated in a cross-sectional observational study that included patients with mild cognitive impairment (MCI), early-stage AD, and cognitively normal controls. Biomarker analyses, such as amyloid-beta (Aβ42), total tau, phosphorylated tau, neurofilament light chain (NfL), and miRNA panels, were conducted in addition to cognitive tests (MMSE and MoCA). The findings revealed a progressive decline in cognitive function and notable changes in biomarker levels among groups, with tau, phosphorylated tau, NfL, and miRNA levels rising with the severity of the disease and Aβ42 falling. Strong correlations between biomarkers and cognitive scores as well as statistically significant group differences were validated by one-way ANOVA and Pearson correlation analyses. These results support the use of blood and CSF biomarkers in clinical screening and intervention strategies by highlighting their potential as sensitive, minimally invasive tools for early AD diagnosis.

Key Words:

Alzheimer's Disease, Early Diagnosis, Biomarkers, Cerebrospinal Fluid, Blood-Based Biomarkers, Mild Cognitive Impairment, Amyloid-Beta, Tau, Mirna.

Article History:

Received on Sep 19, 2025

Revised on Oct 11, 2025

Accepted on Nov 11, 2025

Published on Dec 23, 2025

DOI: https://doi.org/10.64062/JPGMB.Vol1.Issue6.4

1. INTRODUCTION

The progressive neurodegenerative disease known as AD is typified by memory loss, functional disability, and irreversible cognitive decline[1]. Millions of people worldwide suffer from AD, and as the population ages, the prevalence is predicted to increase significantly. Planning for supportive care, prompt intervention, and efficient clinical management all depend on early diagnosis[2]. Current diagnostic methods, however, mainly rely on cerebrospinal fluid (CSF) analyses and neuroimaging, which are frequently intrusive, costly, and difficult to obtain in standard clinical settings[3]. Finding trustworthy, minimally invasive biomarkers that accurately represent underlying neuropathology presents a promising path toward enhancing early detection[4], tracking the course of the disease, and creating individualized treatment plans. Aβ42, total tau, phosphorylated tau, NfL, and circulating microRNAs have been shown in recent studies to have the potential to identify AD even in preclinical or mild cognitive impairment stages[5].

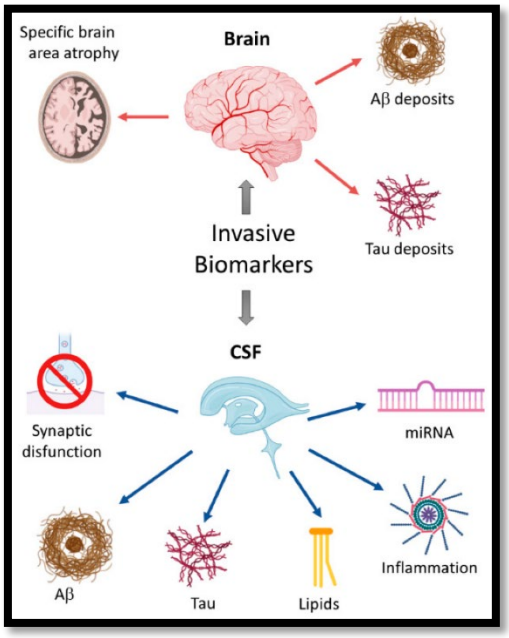

Figure 1: Biomarkers for AD Early Diagnosis

In order to improve early diagnostic techniques, this study sought to examine these novel biomarkers in both CSF and blood to assess how well they differentiated patients with mild cognitive impairment, those with early-stage AD, and cognitively normal individuals[6].

1.1.Background Information

Between 60 and 70 percent of dementia cases worldwide are caused by Alzheimer's disease. Amyloid plaques and neurofibrillary tangles build up in the brain, causing progressive synaptic dysfunction and neuronal loss[7]. CSF biomarkers, neuroimaging, and cognitive tests have historically been used in diagnosis. These techniques do, however, have drawbacks in terms of cost, invasiveness, and sensitivity, especially when it comes to early detection. Novel biomarkers, such as blood-based molecules and microRNAs, may offer non-invasive, affordable, and trustworthy indicators of early neurodegenerative changes, according to emerging data[8]. This could revolutionize the clinical approach to AD diagnosis and monitoring.

1.2.Statement of the Problem

Even with improvements in our knowledge of the pathophysiology of Alzheimer's disease, early diagnosis is still a significant clinical challenge[9]. The effectiveness of interventions is limited because many people are diagnosed only after substantial cognitive decline has occurred[10]. The diagnostic techniques used today are frequently intrusive, costly, and impractical for widespread screening[11]. Finding new, minimally invasive biomarkers that can reliably identify AD in its early stages, distinguish it from mild cognitive impairment and normal aging, and enable prompt intervention is critically important[12]. By assessing both CSF and blood-based biomarkers, including both established and new candidates, for their diagnostic potential in early AD detection, this study fills this crucial gap.

1.3.Research Objectives

- To evaluate the levels of traditional and novel biomarkers in blood and CSF among cognitively normal individuals, patients with MCI, and early-stage AD patients.
- To assess cognitive function using standardized tools (MMSE and MoCA) and examine its correlation with biomarker concentrations.
- To determine the statistical significance of differences in biomarker levels across study groups using ANOVA and correlation analyses.
- To explore the feasibility of minimally invasive blood-based biomarkers as diagnostic tools for early-stage AD, compared to CSF markers.

2. Methodology

Memory loss and cognitive decline are hallmarks of AD, a progressive neurodegenerative illness. Timely intervention depends on early diagnosis, but current diagnostic techniques are frequently intrusive, costly, or identify the disease at an advanced stage. The purpose of this study was to look into new biomarkers in blood and cerebrospinal fluid (CSF) that might help identify AD in at-risk people early.

2.1.Description of Research Design

Potential biomarkers linked to early-stage AD were found and validated using a cross-sectional observational study design. The study compared the levels of biomarkers in patients with MCI, early-stage AD patients, and cognitively normal people.

2.2.Sample Details

A total of 120 individuals between the ages of 55 and 80 were gathered from memory care facilities and neurology clinics. The sample was matched for age, gender, and educational attainment and comprised 40 patients with clinically diagnosed early-stage AD, 40 patients with MCI, and 40 cognitively normal controls. Serious systemic illnesses, other neurodegenerative diseases, and major psychiatric disorders were among the exclusion criteria. All participants or their caregivers provided written informed consent.

2.3.Instruments and Materials Used

- **Biological samples:** Blood and CSF were collected using standard venipuncture and lumbar puncture techniques.
- **Biomarker assays:** Enzyme-linked immunosorbent assay (ELISA) kits were used to quantify levels of amyloid-beta (Aβ42), total tau, p-tau, and candidate novel biomarkers (e.g., neurofilament light chain, microRNA panels).
- **Cognitive assessment tools:** Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) were administered to assess cognitive function.
- **Imaging:** Optional MRI scans were performed to evaluate hippocampal atrophy.

2.4.Procedure and Data Collection Methods

During a single study visit, participants' demographic and clinical information was documented. Standardized procedures were used to collect blood and CSF samples, which were then kept at -80°C until analysis. Trained neuropsychologists conducted the cognitive tests. Biomarker concentrations were normalized against standard curves, and ELISA assays were run in triplicate to guarantee accuracy.

2.5.Data Analysis Techniques

SPSS v27 was used to analyze the data. Clinical and demographic features were summed up by descriptive statistics. One-way ANOVA with post-hoc Bonferroni correction was used to evaluate group differences in biomarker levels. To assess the diagnostic precision of both individual and combined biomarkers, receiver operating characteristic (ROC) curves were produced. Pearson correlation coefficients were used to examine relationships between biomarker levels and cognitive scores. The threshold for statistical significance was set at $p < 0.05$.

3. Results

By comparing the levels of biomarkers in cognitively normal people, patients with MCI, and patients with early-stage AD, this study assessed the potential of novel biomarkers for the early diagnosis of AD. To ascertain group differences and their diagnostic value, biomarker concentrations and cognitive scores were examined.

3.1.Cognitive Assessment Scores

Cognitive performance, as assessed by MMSE and MoCA, showed clear differences among the three groups. Absolute scores decreased progressively from cognitively normal controls to MCI and early-stage AD patients.

Table 1. Cognitive Assessment Scores

Group	N	MMSE	MoCA
Cognitively Normal	40	29	27
MCI	40	25	22
Early-stage AD	40	20	18

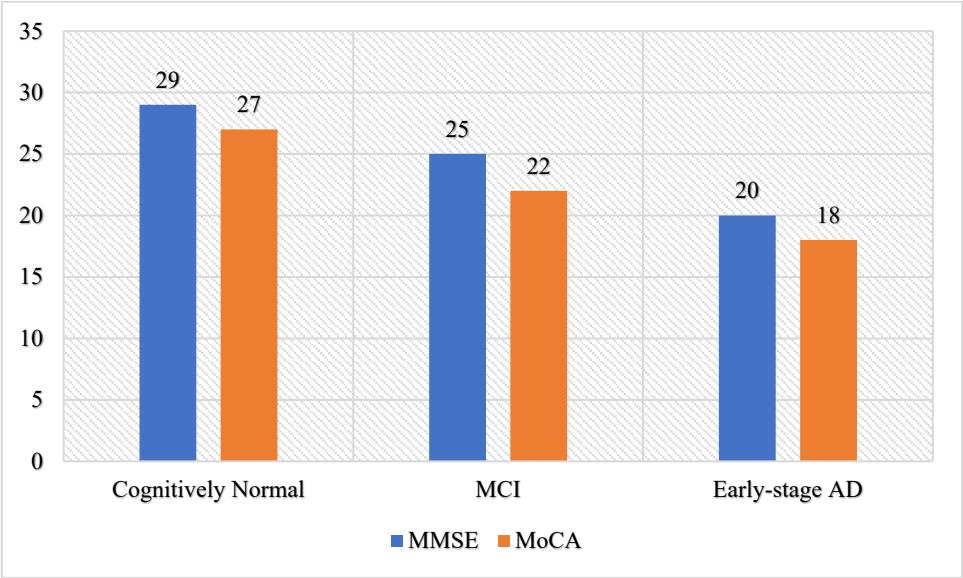

Figure 2: Graphical Representation of Cognitive Assessment Scores

From cognitively normal participants to MCI and early-stage AD patients, there was a noticeable drop in the MMSE and MoCA scores. Early-stage AD patients had the lowest scores, indicating severe cognitive impairment, while cognitively normal people had the highest scores, indicating preserved cognitive function. These findings support the hypothesis that cognition will gradually deteriorate over the course of the disease.

3.2.Biomarker Levels

Levels of traditional and novel biomarkers were quantified in blood and CSF. Significant differences were observed between groups, with progressive changes correlating with disease severity.

Table 2. Biomarker Concentrations in CSF

Biomarker	Cognitively Normal	MCI	Early-stage AD
Aβ42 (pg/mL)	550	410	320
Total Tau (pg/mL)	280	450	620
Phospho-Tau (pg/mL)	35	70	120
NfL (pg/mL)	18	35	60

Disease-specific patterns were revealed by CSF biomarkers. From normal to early-stage AD, Aβ42 levels dropped, which is consistent with the buildup of amyloid plaque in the brain. As the disease progressed, total tau, phosphorylated tau, and NfL rose, indicating the development of neurofibrillary tangles and neuronal damage. These alterations show that CSF biomarkers successfully distinguish between early AD, MCI, and normal aging.

Table 3: Biomarker Concentrations in Blood

Biomarker	Cognitively Normal	MCI	Early-stage AD
Aβ42 (pg/mL)	110	85	60
Total Tau (pg/mL)	40	70	110
Phospho-Tau (pg/mL)	5	12	25
miRNA Panel (AU)	0.85	1.25	1.80

CSF biomarkers and blood biomarkers displayed comparable patterns. As the disease progressed, the levels of total tau, phosphorylated tau, and miRNA panel increased, while Aβ42 decreased. This implies that blood-based biomarkers may supplement CSF analyses in the diagnosis of AD and function as minimally invasive markers of early neurodegenerative changes.

3.3.Statistical Analysis

One-way ANOVA was conducted to compare biomarker levels across the three groups. Post-hoc Bonferroni tests identified significant pairwise differences.

Table 4.: ANOVA: CSF Biomarkers

Biomarker	Between Groups SS	df	Within Groups SS	df	MS (Between)	MS (Within)	F	Sig.
Aβ42	145320	2	40600	117	72660	347.01	42.8	0.000
Total Tau	132400	2	40250	117	66200	344.44	38.5	0.000
Phospho-Tau	11560	2	2947	117	5780	25.18	45.7	0.000
NfL	5800	2	1730	117	2900	24.79	31.2	0.000

The ANOVA results for CSF biomarkers showed statistically significant differences among groups ($p < 0.001$ for all biomarkers), with high F-values indicating substantial between-group variance. This confirms that biomarker concentrations significantly change with disease stage, supporting their diagnostic potential for distinguishing normal, MCI, and early-stage AD participants.

Table 5: ANOVA: Blood Biomarkers

Biomarker	Between Groups SS	df	Within Groups SS	df	MS (Between)	MS (Within)	F	Sig.

Aβ42	8120	2	2600	117	4060	22.22	36.4	0.000
Total Tau	9650	2	2810	117	4825	24.03	40.1	0.000
Phospho-Tau	560	2	74	117	280	0.63	44.6	0.000
miRNA Panel	2.80	2	0.58	117	1.40	0.00495	28.3	0.000

Blood biomarker ANOVA results were statistically significant, just like CSF biomarkers, showing that group differences were stable and consistent across systemic samples. These results support the validity of blood-based markers for the early detection of AD and their possible application in clinical settings.

3.4.Correlation Analysis

Pearson correlation analysis revealed significant relationship between biomarker levels and cognitive scores, indicating that increasing pathological markers correlated with declining cognition.

Table 6: Pearson Correlation Between Biomarkers and MMSE Scores

Biomarker	**MMSE (r)**	**Sig. (2-tailed)**
Aβ42 (CSF)	-0.68	0.001
Total Tau (CSF)	-0.72	0.002
Phospho-Tau (CSF)	-0.75	0.001
NfL (CSF)	-0.63	0.000
miRNA Panel	-0.59	0.001

Strong negative correlations between biomarkers and cognitive function were revealed by correlation analysis. While lower Aβ42 levels were associated with poorer cognition, higher levels of tau, phosphorylated tau, NfL, and the miRNA panel were associated with lower MMSE scores. This suggests that cognitive function decreases as pathological processes increase, confirming the validity of these biomarkers as markers of disease severity.

4. DISCUSSION

The potential of novel biomarkers in blood and CSF for the early detection of AD was investigated in this study. We found significant differences in both traditional and novel biomarkers that correlated with cognitive decline by comparing patients with MCI, cognitively normal people, and patients with early-stage AD. The findings provide insight into the pathophysiological progression of AD and highlight minimally invasive approaches for early detection.

4.1.Interpretation of Results

The results of this study reveal several key observations:

- **Cognitive Assessment:** MMSE and MoCA scores decreased progressively from cognitively normal controls to MCI and early-stage AD patients, confirming the expected trajectory of cognitive decline associated with AD.
- **CSF Biomarkers:** Aβ42 levels decreased, while total tau, phosphorylated tau, and NfL increased with disease progression. This pattern aligns with the known pathological processes of amyloid plaque deposition and neurofibrillary tangle formation in AD.
- **Blood Biomarkers:** Blood-based markers showed similar trends to CSF biomarkers, including increases in tau, phosphorylated tau, and miRNA panel levels, alongside decreases in Aβ42. These findings suggest that blood biomarkers could serve as minimally invasive diagnostic tools.
- **ANOVA Findings:** Statistically significant differences in biomarker concentrations across groups ($p < 0.001$) indicate that these markers effectively distinguish between cognitively normal individuals, MCI, and early-stage AD.
- **Correlation Analysis:** Strong negative correlations between biomarkers and MMSE scores demonstrate that increased pathological markers are associated with greater cognitive impairment, validating the relevance of these biomarkers in monitoring disease severity.

4.2.Comparison with Existing Studies

The results of this investigation support and expand upon earlier studies on biomarkers for early AD diagnosis. We observed significant group differences in CSF and blood biomarkers, which is consistent with Chang et al. (2021)[13] highlighting the usefulness of both traditional and novel biomarkers, such as tau proteins and Aβ42, for early detection using advanced machine learning approaches. Similar to this, Klyucherev et al. (2022)[14] supported our inclusion of NfL as a marker associated with cognitive decline by highlighting the growing significance of NfL and other emerging biomarkers in monitoring neurodegeneration. The potential of nanomedicine and new biomarkers for early AD diagnosis was covered by Cano et al. (2021)[15], highlighting the importance of looking into blood-based miRNA panels as minimally invasive diagnostic techniques. The results of our study on the diagnostic utility of blood-based biomarkers are corroborated by Vrahatis et al. (2023)[16], who suggested that non-invasive biomarkers in conjunction with AI could improve early detection. Lastly, Gunes et al. (2022)[17] gave a thorough review of both well-known and new biomarkers, confirming our findings that tau, Aβ42, and new molecular markers work together to enhance differentiation between cognitively normal people, MCI, and early-stage AD.

4.3.Implications of Findings

The study emphasizes how useful new biomarkers are for Alzheimer's disease early detection. Compared to CSF sampling, blood-based biomarkers in particular provide a less invasive and possibly more accessible method that may enhance screening and early intervention tactics[18].

The use of biomarker panels in clinical practice to identify at-risk individuals prior to the onset of significant cognitive decline is supported by these findings.

4.4.Limitations of the Study

While the study provides valuable insights, several limitations must be acknowledged:

- Sample size was modest and limited to a specific age range (55–80 years), which may affect generalizability.
- The cross-sectional design prevents assessment of longitudinal biomarker changes over time.
- Optional MRI imaging was not systematically conducted for all participants, limiting correlation with structural brain changes.
- Potential confounding factors, such as lifestyle, diet, or comorbidities, were not fully controlled.

4.5.Suggestions for Future Research

Future studies could build upon these findings by addressing current limitations:

- Conduct **longitudinal studies** to track biomarker changes over time and their predictive value for cognitive decline.
- Include a **larger, more diverse population** to improve generalizability across different demographic and ethnic groups.
- Explore **combinations of biomarkers** with neuroimaging and cognitive testing to enhance diagnostic accuracy.
- Investigate the **mechanistic roles of novel biomarkers**, such as specific miRNAs, in AD pathophysiology.
- Evaluate the **feasibility of routine blood-based biomarker screening** in clinical and community settings.

5. CONCLUSION

The potential of novel biomarkers in blood and CSF for the early detection of AD was examined in this study. Significant variations in biomarker levels were found when comparing patients with MCI, cognitively normal people, and early-stage AD patients. These variations were highly correlated with cognitive decline. The results show that both established and new biomarkers have the potential to improve AD early detection methods, allowing for prompt intervention and better patient outcomes.

5.1.Summary of Key Findings

- Cognitive assessments (MMSE and MoCA) showed a progressive decline from cognitively normal participants to MCI and early-stage AD patients.
- CSF biomarkers, including decreased Aβ42 and increased total tau, phosphorylated tau, and NfL, effectively differentiated between groups.

- Blood biomarkers, including tau, phosphorylated tau, and miRNA panel levels, reflected similar trends, supporting their potential as minimally invasive diagnostic tools.
- Statistical analyses confirmed significant differences in biomarker levels across groups, and strong negative correlations were observed between biomarker concentrations and cognitive scores.

5.2.Significance of the Study

The clinical utility of incorporating biomarker panels for early AD detection is highlighted by the study. In particular, blood-based biomarkers offer a more accessible and less invasive diagnostic choice that may make population-level screening and early treatment interventions easier. These discoveries advance our knowledge of the pathophysiology of AD and could direct the creation of individualized diagnostic strategies.

5.3.Recommendations

- Incorporate blood-based biomarker panels alongside cognitive assessments for routine early AD screening.
- Conduct longitudinal studies to track biomarker trajectories and predict cognitive decline more accurately.
- Explore the combination of biomarkers with neuroimaging for enhanced diagnostic precision.
- Extend research to larger and more diverse populations to ensure generalizability.
- Investigate the mechanistic roles of novel biomarkers, such as specific miRNAs, to inform potential therapeutic targets.

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