International Journal of Nutrology
(Official Journal of the ABRAN - Brazilian Association of Nutrology)

ORIGINAL ARTICLE

DOI: 10.54448/ijn26S315

Serum p-Tau217 and apolipoprotein E as potential biomarkers for Alzheimer's disease severity: a case-control study

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DOI: https://doi.org/10.54448/ijn26S315
Received: 04-20-2026; Revised: 06-04-2026; Accepted: 06-06-2026; Published: 07-30-2026; IJN-id: e26S315

Editor: Dr. Ana Maria Ferreira Heyn, MD, Ph.D.

Abstract

Introduction: Alzheimer's disease (AD) is a chronic neurodegenerative illness characterised by aberrant protein accumulation and progressive cognitive decline. One of the most researched blood indicators of tau pathology is phosphorylated tau 217 (p-tau217), and apolipoprotein E (ApoE) is essential for lipid metabolism, amyloid removal, and neuronal maintenance. The severity of AD may be correlated with changes in these biomarkers. **Objective:** To compare serum levels of p-tau217 and ApoE in individuals with different severities of Alzheimer's Disease. **Methods:** The present case–control study consisted of 156 subjects aged between 55 and 85 years:106 patients with ad (and balanced frequency matched to healthy controls on age, international classification of diseases t63 diagnosis). The DSM-5 criteria classified the patients as mild (n = 12), moderate (n = 50), or severe (n = 44). Using the sandwich enzyme-linked immunosorbent assay (ELISA), the levels of circulating ApoE and p-tau217 were determined. The receiver operating characteristics (ROC) curve examination, Spearman's correlation, and the Kruskal-Wallis test were used in the statistical studies. **Results:** The mean serum p-tau217 and ApoE level were 165 ± 84.2 pg/mL and 75.5 ± 55.6 ng/mL, respectively. While serum p-tau217 significantly increased with severity of disease, ApoE levels decreased. We found a significant positive association of p-tau217 ($p<0.001$) and a negative association of ApoE ($p<0.001$) with disease severity by DSM-5 criteria. ROC analysis showed high diagnostic accuracy of CSF p-tau217 (AUC=0.916, sensitivity: 87.18%, specificity: 90.00%) and ApoE (AUC=0.992, sensitivity: 100.00%, specificity:98.00%). **Conclusion:** Increased serum p-tau217 and decreased ApoE levels were significantly associated with greater AD severity. Both biomarkers may serve as complementary noninvasive indicators of disease severity in Alzheimer's disease.

Keywords: Alzheimer's disease, p-tau217, apolipoprotein E, biomarkers, neurodegeneration, dementia.

Introduction

Alzheimer's disease is a gradual, irreversible neurological disorder that impairs behaviour, functioning, and cognition [1]. Alzheimer's disease is the primary cause of dementia and is rapidly emerging as one of the most costly, fatal, and burdensome diseases of this century [2]. represents the primary type of dementia, posing considerable and increasing global challenges. The etiology is complex and varied, arising from a combination of factors including aging, genetics, and environment. Current understanding of Alzheimer's disease pathogenesis encompasses multiple hypotheses, including cholinergic dysfunction, amyloid-β deposition, tau protein abnormalities, neuroinflammation, oxidative stress, metal ion dysregulation, glutamate excitotoxicity, alterations within the gut-brain-microbiota axis and impaired autophagy [3-7].

The molecular weight of tau is about 45–65 kDa and is composed of 352–441 amino acids. It assists with preserving the microtubule cytoskeleton's

structural integrity and appropriate operation, which is necessary for synaptic plasticity, neuronal morphology, and the axonal transport of organelles **[8,9]**. Phosphorylated tau (p-tau) is the most valuable blood biomarker for the pathophysiology of Alzheimer's disease (AD), with p-tau217 being the most specific. However, there hasn't been much access to p-tau217 tests for clinical and research purposes. For the wider evaluation and use of AD blood tests, it is imperative to increase access to this extremely accurate AD biomarker **[10]**. The most promising blood biomarker candidate is phosphorylated tau (p-tau), which has shown better disease specificity and diagnostic accuracy than other candidates **[11,12]**.

The current study deals with the assessment of distinct isoform of phosphorylated tau protein which is (p-tau 217) most accurate biomarker of Alzheimer's disease and versus other neuropathologies **[6]**. Most of the studies that encompasses Alzheimer's biomarkers, particularly Tau protein utilize total Tau protein as biomarker for Alzheimer's disease researches, as it shown in this Iraqi study **[7,13-18]**. APOE is widely distributed throughout the body, with the brain and liver producing a large amount of it **[19]**, under physiological states, ApoE is mostly made by astrocytes in the centralised nervous system (CNS) **[20]**. ApoE is a part of high-density-like lipoproteins in the CNS, providing them with stability and directing their transport and function **[21]**. Consequently, it is essential for the transfer of lipids and the metabolism of cholesterol. Although apoE also aids in lipid clearance **[22]**. Epidemiological data in Iraq, still limited; however, available studies suggest growing burden of cognitive disorders among the old age. According to research done in Baghdad, the prevalence rate of cognitive impairment among residents of an aged care facility was 24.2%, which is much higher than anticipated **[4]**, which is consistent with a study done in the USA was 22.2%. **[5]**.

Therefore, the present study aimed to evaluate serum phosphorylated tau 217 (p-tau217) and apolipoprotein E (ApoE) levels in patients with Alzheimer's disease and to investigate their association with disease severity according to DSM-5 criteria. In addition, the diagnostic performance of these biomarkers was assessed using receiver operating characteristic (ROC) curve analysis.

Materials and Methods

Study Design and Participants

The period of the case-control research was September 2024–August 2026, following the STROBE guidelines. A total of 156 individuals between the ages of 55 and 85 were enlisted, including 50 seemingly healthy controls and 106 patients with an Alzheimer's disease (AD) diagnosis. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) standards were used to split AD patients into three groups: light AD (n = 12), moderate AD (n = 50), and serious AD (n = 44). Participants were recruited from Ibn Rushd Hospital, Al-Rashad Hospital, and Al-Murjan Hospital. Clinical assessment and diagnosis were performed by a consultant physician using a structured interview based on DSM-5 diagnostic criteria.

Sample Size and Participant Recruitment

This was a consecutive sampling study. Inclusion Criteria: All eligible patients who were diagnosed with Alzheimer disease following the DSM-5 criteria during Stage 1 of the study period. Subjects with normal health controls or late during the same period were recruited. As a result, 156 individuals made up the final sample: 50 healthy controls and 106 AD patients. The obtained sample size was judged enough for identifying statistically significant variations in blood biomarker levels across the research groups.

Ethical Approval

The University of Babylon's College of Medicine Ethics Committee and the Hospital Ethics Committee approved the research after examining the informed consent form, participant information sheet, and study protocol. The research received ethical approval (IRB: 1870, February 27, 2025). The Declaration of Helsinki's tenets were followed in this investigation.

Informed Consent

Before being enrolled in the research, each subject provided written informed consent. Informed permission was sought from family members or legally designated representatives for individuals with cognitive impairments who were unable to provide consent on their own.

Reporting Guidelines

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) principles were followed in the execution and reporting of this case-control research.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) program, version 27, was used to input, code, and analyse the gathered data. The Shapiro-Wilk test was used to see if continuous variables were normally

distributed. The results were shown as mean ± standard deviation (SD) for normally distributed data or middle (range) for data that was not normally distributed. Percentages and rates were used to describe categorical factors. The Chi-square test or Fisher's exact test were employed to compare categorical variables when the expected cell count was less than five. When comparing continuous variables between more than two independent groups, the Kruskal-Wallis test was used. The correlations between age, serum biomarkers, and disease severity as defined by DSM-5 criteria were evaluated using Spearman's rank correlation coefficient. Receiver Operating Characteristic (ROC) curve analysis was used to evaluate the diagnostic effectiveness of serum biomarkers for Alzheimer's disease. We found the sensitivity, specificity, highest and lowest limit values, and 95% confidence intervals (CI). P-values less than 0.05 were used to define statistical importance.

Results

Age and Body Mass Index Distribution

Table 1. Anthropometric and Demographic Features of the Research Participants.

Variables	Total	Normal Group	Alzheimer's disease Group
Age, years	75 ± 6.3	74.2 ± 4.57	75.4 ± 6.96
Sex			
Male	60 (38.5%)	19 (12.2%)	41 (26.3%)
Female	96 (61.5%)	31 (19.9%)	65 (41.7%)
BMI group			
Healthy weight	6 (100%)	4 (66.7%)	2 (33.3%)
Overweight	118 (100%)	36 (30.5%)	82 (69.5%)
Obesity class I	28 (100%)	9 (32.1%)	19 (67.9%)
Obesity class II	3 (100%)	0 (0.0%)	3 (100.0%)
Obesity class III, severe obesity	1 (100%)	1 (100.0%)	0 (0.0%)
BMI: Body Mass Index; SD: Standard Deviation			

Source: Own authorship.

The data were divided into four subgroups based on an analysis of 156 participants: 50 healthy individuals, 50 participants with moderate Alzheimer's disease, 44 individuals with sever stage, and 12 participants with mild stage. The subjects' distribution into control, moderate, and sever stage is seen in Table 2.

Table 2. Clinical Status and Severity Distribution of Alzheimer's Disease.

Alzheimer disease Status		
Yes	106	67.90%
No	50	32.10%
Alzheimer disease Stage based on (DSM5)		
Mild	12	11.3%
Moderate	50	47.2%
Severe	44	41.5%
DSM5, Mean ± SD	**9.06 ± 3.94**	
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition SD: Standard Deviation		

Source: Own authorship.

The baseline serum biomarkers analysis showed that the mean tau level was 165 ± 84.2 pg /mL, while ApoE demonstrated a mean value of 75.5 ± 55.6 ng/mL (Table 3).

Table 3. Baseline serum levels of p-tau217 and ApoE in study participants (mean ± SD)

Variables	Mean	± SD
Tau (pg/mL)	165	± 84.2
ApoE (ng/mL)	75.5	± 55.6
SD: standard deviation; ApoE: Apo lipoprotein E.		

Source: Own authorship.

The scatter plots illustrate the relationship between serum p-tau217 levels (pg/mL) and Alzheimer's disease severity according to DSM-5 criteria (Figure 1).

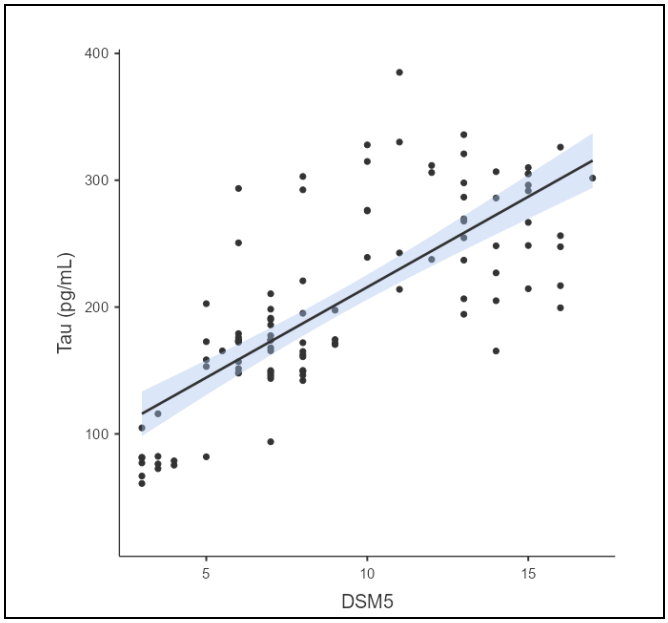

Figure 1. Scatter plots illustrating the relationship between serum p-tau217 levels (pg/mL) and Alzheimer's disease severity based on DSM-5 standards. Source: Own authorship.

Scatter plot showing the association between serum ApoE levels (ng/mL) and Figure 2 shows how Alzheimer's disease severity is categorised using DSM-5 criteria.

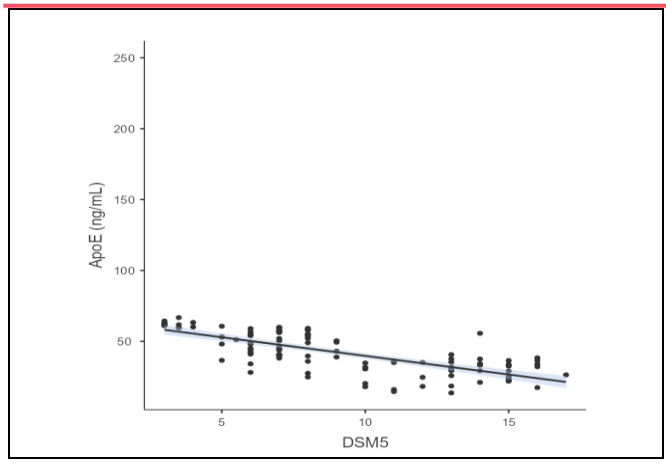

Figure 2. Scatter plots illustrating the relationship between serum apolipoprotein E (ApoE) levels (ng/mL) and Alzheimer's disease severity according to DSM-5 criteria. Source: Own authorship.

ROC curve analysis (Table 4, Figures 3 and 4) demonstrated that the evaluated serum biomarkers showed statistically significant diagnostic performance in predicting Alzheimer's disease progression ($p < 0.001$). At a threshold value of ≥137.071 pg/mL, serum p-tau217 demonstrated good diagnostic performance with an area under the curve (AUC) of 0.916, sensitivity of 87.18%, and specificity of 90.00%. ApoE, on the other hand, showed outstanding diagnostic accuracy at a cutoff value of ≤70.4675 ng/mL, with an AUC of 0.992, sensitivity of 100.00%, and specificity of 98.00%.

Table 4. Analysis of Receiver Operating Characteristic (ROC) Curves for Serum Biomarkers in Diagnosing Alzheimer's Disease Progression.

	Tau (pg/mL)	**ApoE (ng/mL)**
AUC	0.916	0.992
Confidence Interval	87.5%–95.7%	97.8%–100.0%
p- value	**<0.001**	**<0.001**
Cutoff	≥137.071	≤70.4675
Sensitivity	87.18%	100.00%
Specificity	90.00%	98.00%
AUC, area under the curve; ApoE, apolipoproteinE.		

Source: Own authorship.

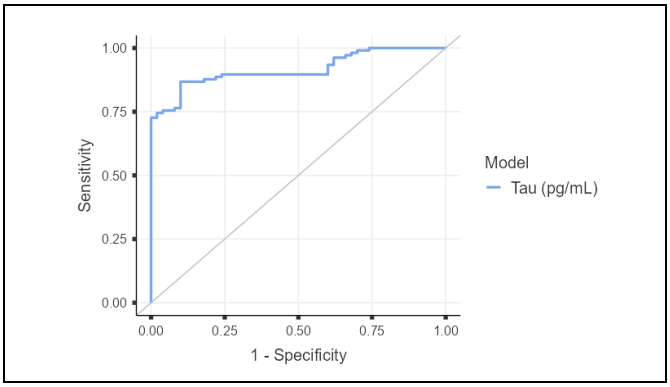

Figure 3. Analysis of the Receiver Operating Characteristic (ROC) curve and the area under the curve (AUC) for serum p-tau217 concentrations (pg/mL) about the severity of Alzheimer's disease as defined by DSM-5 criteria. Source: Own authorship.

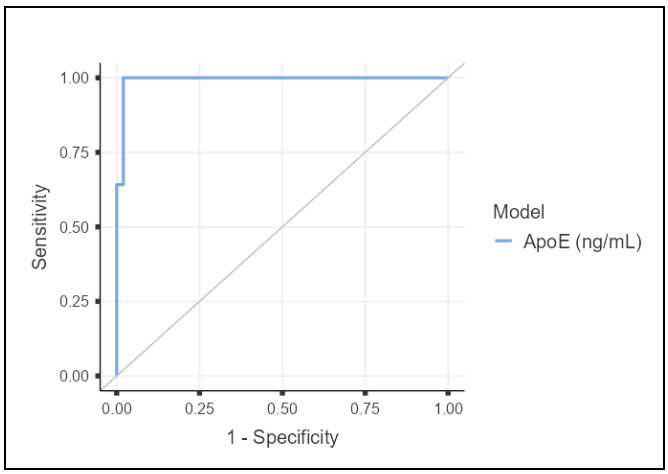

Figure 4. Blood apolipoprotein E (ApoE) concentrations (ng/mL) in connection to the severity of Alzheimer's disease according to DSM-5 criteria were analysed using the ROC curve and AUC.

Discussion

In the present study, p-tau217 levels significantly increased with increasing disease severity ($p<0.001$), thus confirming progressive neurodegeneration in Alzheimer's disease. Increased phosphorylated tau is an integral part of the pathway connecting amyloid-β (Aβ) pathology to hyperphosphorylated tau and neuronal injury. The build-up of Aβ seems to trigger the activity of kinases, such as the metabolites glycogen synthase kinase-3β (GSK3β) and cyclin-dependent kinase 5 (CDK5), which phosphorylates tau and releases phosphorylated tau fragments from neurones into the extracellular space before they enter the bloodstream **[13,14]**.

These findings align with the results presented by van der Kant et al **[15]**, indicating that tau pathology is progressive and tightly linked with neurodegeneration. Additionally, tau accumulation pathways independently of amyloid-associated ones have been shown to be valid progression biomarkers **[16]**. High tau concentrations correlate well with synaptic dysfunction, cortical atrophy and cognitive decline in AD as such, they are valuable biomarkers of neuronal damage and disease progression **[17]**. Thus, in clinical and scientific practice p-tau217 may represent a prognostic biomarker for ongoing neurodegeneration **[18]**.

In contrast, the current study showed that serum ApoE levels significantly decreased with progressing disease severity ($p<0.001$), indicating its implication in AD pathogenesis. Apolipoprotein E (ApoE), a central nervous system–specific lipid transport protein that is

secreted primarily by astrocytes, plays an important physiological role in cholesterol redistribution, synaptic repair, and amyloid-β clearance. During the progression of Alzheimer's disease, successive loss of neurons and astrocytic dysfunction could lower ApoE synthesis and secretion and decrease circulating levels.

Furthermore, ApoE interacts with amyloid-β and promotes its clearance by receptor-mediated processes; nevertheless, in late stage diseases, build-up of excessive amassed amyloid can also lead to the trapping of ApoE within insoluble assemblies leading to lower serum levels that can be measured **[23,24]**. ApoE mediates amyloid deposition and tau pathology as previously demonstrated in studies that support its role in the disease **[25]**. Moreover, ApoE has been shown to be an important regulator of amyloid and tau pathways **[26]**.

The decrease of ApoE shown in our study may reflect reduction in lipid transport and neuronal repair capacity or breakdown of cholesterol homeostasis within the CNS. ApoE is required for synapse maintenance, membrane repair, and amyloid clearance so its depletion may further contribute to increasing neurodegeneration and disease-related burden. Moreover, modified glial lipid metabolism is becoming acknowledged as a major player in neurodegenerative diseases **[27,28]**.

Study Limitations

There are many limitations to this research. First, the mild Alzheimer's disease group has a much smaller patient number than moderate and severe. Second, participants were recruited from only a handful of healthcare centers, this might restrict the results' external validity. Third, APOE genotype and neuroimaging biomarkers were not examined. The case–control design also limits potential causal implications between serum biomarker levels and disease progression.

Conclusion

Higher severity of Alzheimer's disease was associated with higher serum p-tau217 levels, and lower ApoE blood concentrations. The results show significant correlations between both biomarkers and disease progression as measured by DSM-5 status. These findings suggest that serum p-tau217 and ApoE may be complementary, non-invasive, clinical biomarkers for assessing Alzheimer's severity and monitoring changes in the neurodegenerative process in individual patients. To validate these results and assess their predictive efficacy, further extensive prospective investigations are required.

CRediT

Author contributions: The study's idea and design, data gathering, laboratory research, statistical analysis, and paper writing were all carried out by Ahmed Kadom Kalaf. Khawla A. Shemran Waleed Azeez AlAmeedy oversaw the study, analysed the information and made significant revisions to the article. She also handled participant recruiting, clinical evaluation, and manuscript review. All writers evaluated and approved the final content.

Acknowledgment

Author appreciate College of Pharmacy, Al-Nahrain University, Baghdad, Iraq for the help and support.

Ethical Approval

The University of Babylon's College of Medicine Ethics Committee and the Hospital Ethics Committee approved the research after examining the informed consent form, participant information sheet, and study protocol. The research received ethical approval (IRB: 1870, February 27, 2025). The Declaration of Helsinki's tenets were followed in this investigation.

Informed Consent

Informed consent was obtained from all participants involved in the study, with all procedures explained in detail before participation.

Funding

Not applicable.

Data Sharing Statement

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no competing interests.

Similarity Check

It was applied by Ithenticate[@].

Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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