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Association of Circulating Inflammatory Biomarkers with Early Cognitive Decline in Patients with Alzheimer's Disease: A Clinical Observational Study

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ABSTRACT

Background: Alzheimer's disease is a progressive neurodegenerative condition whereby the advancement of cognitive decline has a profound effect on the outcome of the patients. There is growing evidence that systemic inflammation plays a role in the pathogenesis of the disease, and inflammatory biomarkers in the blood may be indicators of early neurodegenerative alterations.

Objective: The study aims to evaluate the relationship between circulating inflammatory biomarkers and early cognitive deterioration in patients with Alzheimer's disease.

Methods: This was a clinical observational study done at Punjab Institute of Neurosciences (PINS), Lahore, Pakistan, between June 2024 and January 2025. Sixty patients were recruited with early-stage Alzheimer's disease through a consecutive sampling method. The cognitive capability was measured through the terms of the Mini-Mental State Examination (MMSE). Measures of serum interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) were taken with the help of enzyme-linked immunosorbent assays. The data were compared with SPSS version 26, and Pearson correlation and multiple linear analysis were carried out with SPSS.

Results: The mean age of the respondents was 65.8 years ± 7.2 years, and they comprised females. The high levels of IL-6, TNF-α, and CRP were found in the patients with low MMSE scores. There were significant negative correlations among the MMSE scores and IL-6 ($r = -0.52$, $p < 0.001$), TNF-α ($r = -0.44$, $p < 0.001$), and CRP ($r = -0.39$, $p = 0.002$). The strongest independent predictor of cognitive decline was IL-6.

Conclusion: The findings of the circulation of inflammatory biomarkers, especially IL-6, are strongly correlated with the cases of early cognitive decline in Alzheimer's disease and can be useful in identifying and monitoring the disease.

Keywords: Alzheimer's disease, cognitive decline, inflammation, IL-6, TNF-α, C-reactive protein, biomarkers

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INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia globally and has become a significant and increasing public health issue. It is a progressive neurodegenerative disease that is marked by slow deterioration of memory, cognitive functions, behaviour, and functional independence. As people are living longer, the burden of AD is growing at a disturbing rate worldwide, especially in less developed nations, like Pakistan, where medical facilities and early diagnosis tools are scarce [1].

The classical pathological characteristics of Alzheimer's disease are extracellular deposition of amyloid-beta plaques and intracellular deposition of neurofibrillary tangles fibrils made of hyperphosphorylated tau protein [2]. Though these mechanisms have always been viewed as central to the development of the disease, recent findings indicate that they are not sufficient in explaining the complexity of the disease development. There has been a

growing interest, consequently, in the role of neuroinflammation as a primary cause of early neuronal dysfunction and cognitive impairment [3].

The microglial cells and astrocytes are activated to mediate inflammation in Alzheimer's disease, which releases pro-inflammatory cytokines and chemokines [4]. This prolonged inflammatory reaction may interfere with synaptic communication, foster oxidative stress, and accelerate neuronal injury. Notably, inflammation is not limited to the central nervous system; the systemic processes of inflammation can also affect brain pathology due to the interaction with the blood-brain barrier and peripheral immune signalling pathways [5].

The inflammatory biomarkers (interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-a), and C-reactive protein (CRP) which circulate throughout the body, have become significant markers of systemic inflammation. Such biomarkers can be easily detected in the peripheral blood and could indicate the presence of neuroinflammatory activity. An increase in such markers has been linked to cognitive impairment, severity of the disease, and accelerated disease in Alzheimer's patients. The degree to which these circulating biomarkers are specifically related to early cognitive decline is a field that is yet to be explored [6,7].

Early detection of cognitive impairments is essential in administering therapeutic interventions in good time and managing the disease better. The need to employ available and affordable biomarkers may be one of the viable solutions in resource-limited clinical environments to conduct early-stage risk stratification and disease progression tracking. Discovering the association of systemic inflammation and initial cognitive alterations can also introduce new opportunities to apply specific anti-inflammatory treatment in Alzheimer's disease [8].

Thus, the current study was conducted to assess the correlation between circulating inflammatory biomarkers and early cognitive impairment in patients with Alzheimer's disease, and with the purpose of determining what potential biomarkers may be used to aid the prompt diagnosis and clinical decision-making [9].

MATERIALS AND METHODS

The present clinical observational study was undertaken in Punjab Institute of Neurosciences (PINS), Lahore, Pakistan, during eight months between June 2024 and January 2025. The study was initiated by getting ethical approval from the Institutional Review Board (IRB Ref No: IRB/2024/062). All the procedures were conducted according to the ethical principles suggested in the Declaration of Helsinki. All participants or their legally authorized representatives were asked to sign informed consent before enrolling.

Sixty participants with early-stage Alzheimer's disease were sampled through a non-probability sampling method of sequencing. The patients who fulfilled the set clinical diagnostic criteria of Alzheimer's disease between the ages of 55 to 80 years old were eligible to take part in the study. In the study, only those who presented with mild cognitive impairment or early cognitive decline were recruited in the study. Individuals with a history of acute infection, chronic inflammatory diseases, autoimmune disorders, malignancies, recent surgery, and use of corticosteroids, immunosuppressive therapy, or anti-inflammatory drugs were excluded to ensure that fewer confounding factors were involved in the determination of the inflammatory biomarker levels.

The structured data collection proforma was used to gather baseline demographic and clinical data, age, gender, duration of illness, comorbidities, and medication history. The cognitive status was assessed by the Mini-Mental State Examination (MMSE), which is a standardized and widely reputed instrument of cognitive status evaluation. The participants who scored between 18 and 26 based on MMSE were deemed to have early cognitive decline.

All the participants were sampled with venous blood under aseptic conditions after an overnight fast. About 5 mL of blood was then centrifuged to separate serum, which was then stored at −20 °C until analyzed later. Inflammatory biomarkers such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits based on the instructions of the manufacturer. Duplicity and repetition of all measurements were done to make them accurate and reproducible.

The Statistical Package of the Social Sciences (SPSS) version 26 was used to input and analyze the data. Continuous variables were given in the form of mean and standard deviation, and categorical variables were given in the form of frequencies and percentages. The Shapiro-Wilk test was applied to determine the normal distribution of data. The correlation of serum inflammatory biomarkers with MMSE scores was performed using the Pearson correlation analysis. Comparison of groups where suiting was by means of independent sample t-tests. Multiple linear regression analysis was done to come up with the independent predictors of cognitive decline, having taken into consideration possible confounding variables like age and gender. The p-value of 0.05 was taken to be statistically significant.

RESULTS

The study includes 60 patients with early-stage Alzheimer's disease. The mean age of the subjects in the study was 65.8 ± 7.2 years, with most of them belonging to the age range of 60–70 years. The percentage of females (56.7%) was slightly greater than that of males (43.3%). The study population had mild cognitive impairment, as the mean Mini-Mental State Examination (MMSE) score of the study subjects was 21.9 ± 2.5.

The demographics of the participants are presented in Table 1. A majority of the participants had at least one

comorbid condition, with the most common cases being hypertension and type 2 diabetes mellitus. The age and gender distribution represent the general clinical pattern of Alzheimer's disease; the increasing age and the prevalence of the disease among females are widely reported.

Inflammatory biomarkers showed an evident rising pattern in the level of serum in the patients who had a lower MMSE. The serum IL-6 level was 9.2 ± 2.6 pg/mL, TNF-α was 11.8 ± 3.0 pg/mL, and CRP was 6.8 ± 2.1 mg/L. The patients whose cognitive scores were relatively lower indicated higher levels of serum IL-6, TNF-α, and CRP, suggesting that there was a relationship between systemic inflammation and cognitive impairment.

Significant negative association between MMSE scores and all the inflammatory biomarkers measured was statistically significant. Table 2 indicates that IL-6 had the most significant negative relationship with cognitive performance ($r = -0.52$, $p < 0.001$), TNF-α ($r = -0.44$, $p < 0.001$), and CRP ($r = -0.39$, $p = 0.002$). These results indicate that an increase in the circulatory levels of inflammatory markers is linked with an increase in cognitive impairment in patients with Alzheimer's disease.

Additional multiple linear regression analysis showed that IL-6 was still a notable independent predictor of cognitive deterioration on age- and gender-adjusted analysis ($\beta = -0.45$, $p = 0.001$). TNF-α also exhibited a significant independent relationship, albeit with a low significance level ($\beta = -0.31$, $p = 0.008$), but CRP registered a borderline significance level in the regression analysis ($\beta = -0.22$, $p = 0.051$). Table 3 summarizes these findings.

Altogether, the findings suggest that there is a strong correlation between high levels of circulating inflammatory biomarkers and cognitive impairment in the initial period of Alzheimer's disease in patients. Of the biomarkers investigated, IL-6 showed the most reliable and the strongest association with cognitive impairment, and thus, its effect is a crucial signifier of early disease progression.

Table 1: Demographic and Clinical Characteristics of Study Participants (n = 60)

Variable	Frequency (%) / Mean ± SD
Age (years)	65.8 ± 7.2
55–60 years	18 (30.0%)
61–70 years	26 (43.3%)
>70 years	16 (26.7%)
Gender (Male)	26 (43.3%)
Gender (Female)	34 (56.7%)
MMSE Score	21.9 ± 2.5
Hypertension	28 (46.7%)
Diabetes Mellitus	24 (40.0%)

Table 2: Correlation Between Inflammatory Biomarkers and MMSE Scores

Biomarker	Mean ± SD	Correlation (r)	p-value
IL-6 (pg/mL)	9.2 ± 2.6	-0.52	<0.001
TNF-α (pg/mL)	11.8 ± 3.0	-0.44	<0.001
CRP (mg/L)	6.8 ± 2.1	-0.39	0.002

Table 3: Multiple Linear Regression Analysis for Predictors of Cognitive Decline (MMSE Score)

Variable	Beta (β)	Standard Error	p-value
IL-6	-0.45	0.09	<0.001
TNF-α	-0.31	0.11	0.008
CRP	-0.22	0.10	0.051
Age	-0.19	0.08	0.072
Gender	-0.12	0.07	0.114

DISCUSSION

The current study examined the connection between circulating inflammatory biomarkers and early cognitive decline in patients with Alzheimer's disease [10]. The results revealed that there was a high negative correlation between cognitive performance (MMSE scores) and serum concentration of IL-6, TNF-α, and CRP. These findings add to the accumulating body of study indicating that systemic inflammation is an essential factor in the initial phases of Alzheimer's disease [11].

Among the key findings of this study, there was a deep correlation between an increase in levels of IL-6 and the worsening of cognitive performance. One of the central cytokines in the processes of immune regulation is IL-6, which has been associated with neuroinflammatory mechanisms in the central nervous system [12]. Higher IL-6 concentrations could cause microglial stimulation, neuronal signaling impairment, and growth of oxidative stress, which could elevate neuronal degeneration. The presence of vibrant independent IL-6 predicting cognitive decline, even with the presence of confounding variables, indicates that it could find useful application as a viable biomarker of early disease progression [13,14].

Equally, TNF-α was found to have a negative correlation with MMSE scores. TNF-α has been associated with the effects of synaptic plasticity and neuronal survival of the brain, and a prolonged increase in the hormone can result in synaptic malfunctions and apoptosis. The concept

that chronic systemic inflammation may negatively influence cognitive functioning has been supported by the observed association in this study, even in the early stages of Alzheimer's disease [15,16].

The C-reactive protein was also significantly negatively correlated with the cognitive performance, though it is not as strongly associated as IL-6 and TNF-α. CRP is a long-established measure of systemic inflammation, which has been associated with inflammation of the vessels and endothelial dysfunction. It may have an indirect association with Alzheimer's disease, and this could be mediated by vascular effects on cognitive impairment. This evidence implies that neuroinflammatory and vascular inflammatory mechanisms may work together to increase cognitive impairment [17,18].

These study findings are in line with the inflammatory hypothesis of Alzheimer's disease, which postulates that chronic low-grade inflammation is associated with the onset and progression of the disease. The fact that the patients with the early cognitive decline have high levels of circulating inflammatory markers demonstrates that the processes of inflammation are already going on even before the neurodegeneration of a high severity. This has significant clinical implications since it implies that inflammation can be used as an early intervention [19,20].

Clinically, circulating inflammatory biomarker measurement is a viable and least invasive method of measuring disease activity. These biomarkers may be an alternative low-cost assessment of early risk stratification and monitoring in resource-limited areas like Pakistan, where access to state-of-the-art neuroimaging and molecular diagnostic tests may be limited. These markers could be included in the standard clinical assessment to enhance early diagnoses and be used in individual management [21,22].

Nonetheless, there are some weaknesses of this study that must be taken into consideration. The small sample size and the single center of the study can be a limitation to the extrapolation. Also, the cross-sectional design of the study does not allow for the development of any causal links between inflammation and cognitive decline. Further studies should be critical in longitudinal studies with more and greater samples to confirm these results and investigate the temporal dynamics of inflammatory biomarkers in Alzheimer's disease [23,24].

Irrespective of these restrictions, the study is an interesting contribution to the knowledge of the pathogenesis of early cognitive impairment in inflammatory mechanisms and the potential of inflammatory biomarkers as clinically usable markers of Alzheimer's disease [25].

CONCLUSION

The current study shows that there is a strong relationship between high levels of circulating inflammatory biomarkers and premature cognitive impairment in patients with Alzheimer’s disease. Of the examined markers, IL-6 was the most significant independent predictor of cognitive impairment, with TNF-α and CRP considered. All these indicate that systemic inflammation is an important factor in the early pathophysiological stages of diseases. The evaluation of the inflammatory biomarkers can be a useful non-invasive, early-detection, risk-stratification, and monitoring of Alzheimer's disease, especially when the diagnostic means are limited. Early screening of vulnerable people may enable intervention in time and may even prevent the progression of the disease. More extensive longitudinal, interventional, and large-scale studies are advised in order to gain more insight into the causal relationship between neurodegeneration and inflammation and to investigate the therapeutic potential of the inflammatory pathways in Alzheimer's disease.

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Authors’ Contributions: F.Q. conceived and designed the study, collected data, analyzed the results, and drafted the manuscript. M.N. contributed to study supervision, data interpretation, critical revision of the manuscript, and approved the final version. Both authors read and approved the final manuscript.

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Data Availability: The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request.

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