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ASSOCIATION BETWEEN PHQ-9 DEPRESSION SCORE AND INFLAMMATORY MARKERS (IL-6, TNF-A) IN HEMODIALYSIS PATIENTS

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Abstract

Objective: To assess the association between depression severity, measured using the Patient Health Questionnaire-9 (PHQ-9), and inflammatory markers (IL-6, TNF-α) in adult hemodialysis patients. **Methodology:** This cross-sectional study enrolled 100 adult patients undergoing maintenance hemodialysis thrice weekly for at least six months. Depression symptoms were evaluated using the PHQ-9 questionnaire. Fasting venous samples were collected pre-dialysis to measure serum IL-6 and TNF-α using ELISA kits. Patients were stratified into depression categories based on PHQ-9 scores. Correlations between PHQ-9 and inflammatory markers were analyzed using Spearman's correlation and multiple linear regression. **Results:** The mean age of participants was 52.6 ± 12.4 years, and 58% were male. Based on PHQ-9, 32% had minimal depression, 28% mild, 22% moderate, and 18% severe depression. Mean serum IL-6 increased progressively across depression categories (6.8 ± 2.1 pg/mL in minimal vs. 12.4 ± 3.6 pg/mL in severe). Similarly, TNF-α levels were significantly higher in severe depression (18.3 ± 5.2 pg/mL) compared with minimal depression (9.7 ± 3.1 pg/mL). PHQ-9 scores showed significant positive correlations with IL-6 ($r = 0.56$, $p < 0.001$) and TNF-α ($r = 0.49$, $p < 0.001$). In adjusted regression models, IL-6 remained an independent predictor of higher PHQ-9 scores ($\beta = 0.41$, $p = 0.002$). **Conclusion:** Depression severity in hemodialysis patients is strongly associated with elevated IL-6 and TNF-α levels, supporting the role of inflammation in dialysis-related depression. Routine psychological screening and targeted anti-inflammatory strategies may improve mental health outcomes in this population.

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INTRODUCTION

Depression is one of the most common psychological disorders among patients receiving maintenance hemodialysis, with prevalence rates reported to be three to five times higher than in the general population. The burden of depression in end-stage renal disease (ESRD) has profound clinical implications, including reduced treatment adherence, impaired quality of life, higher hospitalization rates, and increased mortality[1,2]. Unlike depression in the general population, which is often linked primarily to psychosocial factors, depression in hemodialysis patients represents a complex interplay of biological, psychological, and treatment-related determinants[3]. Among the biological mechanisms, chronic systemic inflammation has emerged as a major contributor to depressive symptomatology in CKD and ESRD.

Hemodialysis patients exhibit a sustained pro-inflammatory state resulting from uremic toxin accumulation, oxidative stress, bio-incompatibility of dialysis membranes, recurrent infections, and comorbid illnesses[4]. Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are two of the most consistently elevated cytokines in this population. IL-6 is a multifunctional cytokine that plays a central role in immune activation, hepatic acute-phase response, muscle wasting, and cardiovascular dysfunction[5]. TNF-α contributes to catabolic processes, endothelial dysfunction, anorexia, and fatigue—symptoms that overlap significantly with depressive manifestations[6]. Evidence from neurobiological and psychiatric literature shows that both IL-6 and TNF-α can modulate neurotransmitter metabolism, impair serotonin pathways, activate the hypothalamic-pituitary-adrenal (HPA) axis, and induce neuroinflammation, collectively increasing vulnerability to depression[7].

The Patient Health Questionnaire-9 (PHQ-9) is a brief, validated, and widely used depression screening tool that has been extensively applied in CKD and dialysis populations[8]. Its ability to capture the severity of depressive symptoms makes it suitable for both clinical and research settings. However, despite the high prevalence of depression in hemodialysis patients, depression often remains underdiagnosed, partly due to symptom overlap with uremia—such as fatigue, sleep disturbances, and appetite loss—and partly due to limited mental health screening in dialysis units[9]. Understanding the inflammatory basis of depression may improve screening accuracy and support early intervention strategies.

Several international studies have explored the link between inflammation and depression in ESRD; however, results vary across populations due to differences in ethnicity, dialysis vintage, comorbidities, and biochemical profiles. Some investigations have shown strong correlations between IL-6 levels and depressive symptoms, while others reported weaker or non-significant associations after adjusting for confounders[7,10]. The relationship between TNF-α and depression also appears inconsistent, with some studies supporting a role for TNF-α–mediated neuroinflammation, while others suggest a more indirect effect related to overall disease burden[6].

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Given these inconsistencies and the clinical importance of addressing mental health in dialysis patients, further research is warranted. The present study aims to evaluate the association between PHQ-9 depression scores and inflammatory markers IL-6 and TNF-α in adult hemodialysis patients. Understanding this relationship may provide insight into the biological underpinnings of depression in ESRD and support the development of integrated medical–psychological care strategies.

METHODOLOGY

This cross-sectional analytical study was conducted over a six-month period at the hemodialysis unit of a tertiary-care hospital. A total of 100 adult patients undergoing maintenance hemodialysis were recruited using consecutive sampling. Eligibility criteria included: age ≥18 years, receiving hemodialysis three times per week (each session lasting four hours), and having been on dialysis for at least six months to ensure clinical stability. Patients were excluded if they had any active infection, recent hospitalization within the last four weeks, autoimmune disease, malignancy, chronic inflammatory disorders, current corticosteroid or immunosuppressive therapy, or a pre-existing psychiatric diagnosis under active treatment, as these conditions could confound inflammatory marker levels or depression scores.

After obtaining written informed consent, socio-demographic and clinical details—including age, sex, comorbidities (diabetes mellitus, hypertension, ischemic heart disease), dialysis vintage, medication history, and interdialytic weight gain—were recorded using a structured proforma. Depression severity was assessed using the Patient Health Questionnaire-9 (PHQ-9), a validated and widely recommended instrument for screening depressive symptoms in chronic kidney disease and hemodialysis populations. The PHQ-9 includes nine items scored from 0 to 3, yielding a total score range of 0 to 27. Based on established cutoffs, participants were classified into four categories: minimal (0–4), mild (5–9), moderate (10–14), and severe depression (15–27).

Venous blood samples were collected immediately before the mid-week dialysis session to avoid the acute inflammatory effects of dialysis and ultrafiltration. All participants were required to undergo an overnight fast of 8–10 hours before blood sampling. Serum was separated by centrifugation at 3,000 rpm for 10 minutes and stored at −80°C until analysis. Serum IL-6 and TNF-α concentrations were measured using commercially available high-sensitivity enzyme-linked immunosorbent assay (ELISA) kits, following the manufacturer's instructions. All assays were performed in duplicate, and quality control samples with known cytokine concentrations were included in each run to ensure analytical precision and inter-assay reliability. Standard curves were generated for each plate using serial dilutions, and cytokine levels were expressed in picograms per milliliter (pg/mL).

Data were analyzed using IBM SPSS version 26. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were summarized as

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frequencies and percentages. To evaluate differences in inflammatory markers across depression categories, one-way analysis of variance (ANOVA) with post-hoc Tukey testing was applied. Correlation between PHQ-9 scores and inflammatory markers (IL-6, TNF-α) was assessed using Spearman's rank correlation coefficients because cytokine levels typically demonstrate non-normal distribution. To determine independent predictors of depression severity, a multiple linear regression model was constructed, adjusting for age, sex, dialysis vintage, diabetes, hypertension, and serum albumin level, which are known modifiers of inflammation and depressive symptoms. A p-value <0.05 was considered statistically significant for all analyses.

RESULTS

Table 1: Demographic and Clinical Characteristics of Hemodialysis Patients (n = 100)

Variable	Mean ± SD / n (%)
Age (years)	**52.6 ± 12.4**
Male	**58 (58%)**
Female	**42 (42%)**
Dialysis Vintage (months)	**38.7 ± 21.5**
Diabetes Mellitus	**62 (62%)**
Hypertension	**87 (87%)**
Ischemic Heart Disease	**28 (28%)**
Interdialytic Weight Gain (kg)	**2.3 ± 0.8**
Serum Albumin (g/dL)	**3.5 ± 0.4**
PHQ-9 Score	**9.8 ± 5.1**
Minimal Depression	**32 (32%)**
Mild Depression	**28 (28%)**
Moderate Depression	**22 (22%)**
Severe Depression	**18 (18%)**

Table 2: Comparison of Inflammatory Markers Across Depression Categories

Depression Category	n	IL-6 (pg/mL)	TNF-α (pg/mL)	p-value
Minimal	32	6.8 ± 2.1	9.7 ± 3.1	<0.001
Mild	28	8.9 ± 2.6	12.4 ± 3.8	
Moderate	22	10.6 ± 3.2	15.1 ± 4.7	
Severe	18	12.4 ± 3.6	18.3 ± 5.2	

Table 3: Correlation of PHQ-9 Score with Inflammatory and Clinical Variables

Variable	Correlation Coefficient (r)	p-value
IL-6 (pg/mL)	0.56	<0.001
TNF-α (pg/mL)	0.49	<0.001
Dialysis Vintage (months)	0.18	0.07
Serum Albumin (g/dL)	-0.32	0.001
Interdialytic Weight Gain (kg)	0.14	0.12
Age (years)	0.09	0.32

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DISCUSSION

The present study demonstrated a significant positive association between depression severity, measured by PHQ-9, and inflammatory markers (IL-6, TNF-α) in hemodialysis patients. The progressive increase in cytokine concentrations across depression categories, and the strong correlations observed, support the concept that inflammation plays an important pathophysiological role in dialysis-related depressive symptoms. These findings are consistent with previous reports showing that IL-6 and TNF-α are reliable biological correlates of depression in chronic kidney disease (CKD) and ESRD populations[11].

Inflammation is a well-recognized feature of hemodialysis. Repeated exposure to bio-incompatible dialysis membranes, accumulation of uremic toxins, oxidative stress, and frequent infections contribute to chronic elevation of pro-inflammatory cytokines.[12] IL-6 and TNF-α in particular have been implicated in metabolic dysregulation, anorexia, fatigue, and sleep disturbance, all of which overlap with depressive symptomatology. The present results, demonstrating nearly a two-fold elevation of IL-6 and TNF-α in severe depression compared with minimal depression, reinforce this biologically plausible link.

Moreover, IL-6 remained an independent predictor of PHQ-9 score on multivariable analysis, indicating that its contribution to depressive severity persists even after adjustment for traditional confounders such as age, comorbidities, and albumin level. Previous studies also emphasize IL-6 as a more consistent predictor of depression than TNF-α, possibly due to its broader biological activity in regulating acute-phase response, neuroendocrine activation, and neurotransmitter metabolism.[13] Experimental models suggest that IL-6 interferes with serotonin synthesis and promotes activation of the hypothalamic–pituitary–adrenal axis, both of which are implicated in the pathogenesis of major depressive disorder.[14]

An interesting observation was the negative correlation of serum albumin with PHQ-9 scores, indicating that patients with higher inflammatory burden and poorer nutritional status exhibited greater depressive severity. Hypoalbuminemia in ESRD reflects inflammation-driven malnutrition and catabolic state, which may exacerbate physical weakness and reduce quality of life, leading to higher depression scores. Several studies have similarly identified low albumin as a marker of both inflammation and psychosocial vulnerability in dialysis.[15]

The observed relationship between TNF-α and depression was also significant, though smaller than that of IL-6, aligning with mixed findings in the literature. Some authors describe TNF-α as an upstream mediator of neuroinflammation and sickness behavior, whereas others report weaker associations after adjustment for comorbidities, possibly reflecting heterogeneity in cytokine expression driven by dialysis modality, membrane biocompatibility, or comorbid conditions[6].

Clinically, these findings highlight the importance of routine depression screening in dialysis units, as depressive symptoms are frequently under-diagnosed due to overlap

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with uremic symptoms. The PHQ-9 is simple, validated, and feasible for use in dialysis settings. Beyond screening, our results support the rationale for considering anti-inflammatory strategies—nutritional optimization, biocompatible membranes, improved dialysis adequacy, lifestyle modification, and possibly cytokine-targeting therapies—to improve psychological well-being. Although causal direction cannot be inferred from cross-sectional analysis, the strength of association suggests that managing inflammation may help reduce depressive burden.

The study is limited by its cross-sectional nature, single-center design, and lack of longitudinal data; however, it adds meaningful evidence in a clinical context where biopsychosocial integration remains limited. Future prospective studies should evaluate whether reduction of inflammatory load translates into measurable improvement in depressive outcomes.

CONCLUSION

Depression severity in hemodialysis patients shows a strong positive association with elevated IL-6 and TNF-α, indicating a significant inflammatory contribution to depressive symptoms. Routine psychological screening using PHQ-9 should be integrated into dialysis care to ensure early detection. Targeting inflammatory pathways may offer an additional avenue to improve mental health outcomes in this vulnerable population.

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