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From Deficiency to Dysfunction: Exploring the Relationship between Serum Vitamin D and Inflammatory Indicators in Hemodialysis Patients

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Abstract

Background: Chronic kidney disease is frequently accompanied by vitamin D deficiency, especially due to impaired renal activation of vitamin D. In patients undergoing routine hemodialysis, vitamin D deficiency has been implicated in persistent systemic inflammation. Multiple inflammatory biomarkers are commonly used to assess inflammatory status in this population.

Objective: This study explored the prevalence of vitamin D deficiency in patients receiving maintenance hemodialysis and examined its association with key inflammatory biomarkers, including C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), serum albumin, and ferritin.

Methods: Adults aged 18-75 years with end-stage renal disease (ESRD) undergoing bi-weekly hemodialysis for at least three months were enrolled following informed consent. Serum concentrations of vitamin D and selected inflammatory markers were measured. Pearson's correlation was employed to evaluate associations ($p \leq 0.05$), and Kaplan–Meier analysis was applied to assess survival differences across vitamin D subgroups.

Results: Out of 94 participants, 86.2% were found to have insufficient vitamin D levels, with a mean value of 22.1 ± 21.3 ng/ml. An inverse correlation was observed between vitamin D and CRP ($r=-0.487$, $p<0.001$), NLR ($r=-0.320$, $p=0.002$), and ferritin ($r=-0.310$, $p=0.002$), whereas a positive relationship was identified with serum albumin ($r=0.405$, $p<0.001$). No statistically significant association was noted with PLR. Multivariate regression analysis reinforced the negative association between vitamin D and CRP. Survival analysis did not reveal significant differences among the vitamin D subgroups.

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Conclusion: Vitamin D deficiency is highly prevalent among patients undergoing hemodialysis and is significantly linked with increased systemic inflammation. These findings underscore the potential therapeutic value of vitamin D supplementation in attenuating inflammatory processes in ESRD patients.

Keywords: ***Vitamin D; Chronic inflammation; Hemodialysis; C- reactive protein; Neutrophil to lymphocyte ration; Platelets to lymphocyte ratio***

1. Introduction

Vitamin D deficiency is a widespread global health concern, affecting nearly one billion individuals, with around half of the world's population exhibiting suboptimal levels [1]. This issue is especially pronounced in individuals with end-stage renal disease (ESRD) receiving hemodialysis, where deficiency rates have been reported to surpass 80% [2]. Renal dysfunction significantly contributes to vitamin D deficiency due to decreased functional renal mass, impaired phosphate excretion, metabolic acidosis, and the accumulation of uremic toxins. These factors collectively reduce renal 1α-hydroxylase activity, diminishing production of calcitriol, the active form of vitamin D [3].

Vitamin D plays a pivotal role in maintaining calcium balance, regulating bone health, and modulating immune function. Its significance extends beyond musculoskeletal integrity, as deficiency in vitamin D has been associated with heightened systemic inflammation, an important contributor to the increased morbidity and mortality observed in patients with end-stage renal disease (ESRD). Acting as a key immunoregulatory molecule, inadequate levels of vitamin D have been linked to compromised immune defenses. A growing body of research highlights associations between vitamin D insufficiency and heightened susceptibility to infectious diseases, including COVID-19, as well as a range of autoimmune conditions such as inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and type 1 diabetes [4,5].

Numerous studies have examined the link between vitamin D deficiency and inflammatory status in individuals undergoing hemodialysis, often utilizing C-reactive protein (CRP) as the primary biomarker due to its cost-effectiveness and widespread availability. In recent years, interest has expanded to include alternative inflammatory indicators such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which offer similarly affordable yet informative insights into systemic inflammation. Among these, an NLR exceeding 3 is generally regarded as a dependable marker of heightened inflammatory activity [6].

Growing evidence highlights the immunoprotective effects of vitamin D, with supplementation shown to exert anti-inflammatory benefits that may modulate biomarkers such as CRP, NLR, and PLR. Despite global interest in this association, no prior research in Pakistan has specifically addressed the relationship between vitamin D status and inflammatory markers in patients with end-stage renal disease (ESRD). Addressing this knowledge gap, the current study seeks to assess the correlation between serum vitamin D levels and systemic inflammation in this population, thereby enhancing our understanding of vitamin D's immunomodulatory potential and its relevance to clinical management in ESRD.

2. Methodology

This retrospective, cross-sectional analytical study was conducted at the Dialysis Unit of the Department of Nephrology, Holy Family Hospital, Rawalpindi, Pakistan, from January to July 2025, and involved a total of 113 patients. Participants were selected using a purposive non-probability sampling method.

Eligible subjects included adults aged 18 to 75 years with end-stage renal disease (ESRD) who had been receiving bi-weekly hemodialysis for a minimum of three months and had provided informed consent. Patients were excluded if they were younger than 13 years, had active infections, experienced fever or focal symptoms within the preceding three months, had known bone-related conditions (such as osteoporosis or malignancy), had a prior diagnosis of vitamin D deficiency, or had recently undergone blood transfusions. Additionally, individuals who had recently changed dialysis centers or frequency were excluded to maintain uniformity and ensure reliable data. This strict selection protocol allowed for the inclusion of a homogenous patient cohort, facilitating a more accurate assessment of the relationship between vitamin D status and systemic inflammation.

Demographic data, comorbidities, vascular access type, catheter entry point condition, dialysis initiation indication, and dialysis duration were recorded. Vascular access types included arteriovenous fistula, permanent catheter, or temporary catheter.

Blood samples for serum vitamin D and inflammatory markers were collected pre-dialysis during the mid-week session. Vitamin D was analyzed using Chemiluminescent Microparticle Immunoassay (CMIA) and categorized per KDOQI guidelines: sufficiency (>30 ng/mL), insufficiency (16-30 ng/mL), mild deficiency (5-15 ng/mL), and severe deficiency (<5 ng/mL) [7].

Inflammatory markers measured included C-reactive protein (CRP), Neutrophil to Lymphocyte ratio (NLR), Platelet to Lymphocyte Ratio (PLR), serum ferritin, and albumin. Cutoffs for significant inflammation were CRP>10 mg/L, NLR>3, PLR>210, ferritin>300 ng/mL, and albumin<4.5 g/dL [8].

Data analysis was performed using IBM SPSS Statistics version 25. Continuous variables were presented as means ± standard deviations, while categorical variables were summarized as frequencies and percentages. Associations between categorical variables were evaluated using the Chi-square test, with a p-value ≤ 0.05 considered statistically significant. Independent t-tests were utilized to compare continuous variables between groups. The relationship between serum vitamin D levels and inflammatory markers was assessed using Pearson's correlation coefficient (r). Survival differences across vitamin D categories were analyzed using Kaplan-Meier survival curves, with the log-rank test applied to determine statistical significance.

3. Results

Of the initial 113 patients, 19 were excluded based on infection, comorbid bone disease, or loss to follow-up, resulting in a final sample of 94 patients (FIG. 1).

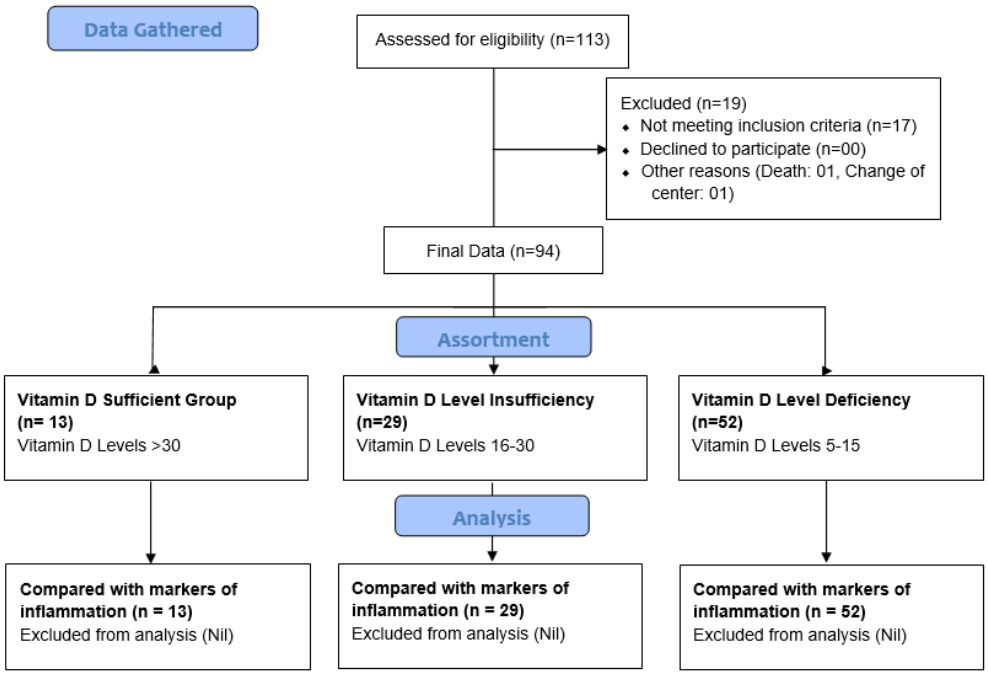

FIG. 1. **CONSORT 2010 Flow Diagram.**

The mean age was 41.8 ± 15.4 years; 57.4% were male. Comorbidities included diabetes and hypertension (29.8%), diabetes alone (18.1%), and hypertension alone (9.6%). Chronic liver disease was present in 19.1%, primarily due to hepatitis C (11.7%) (FIG. 2).

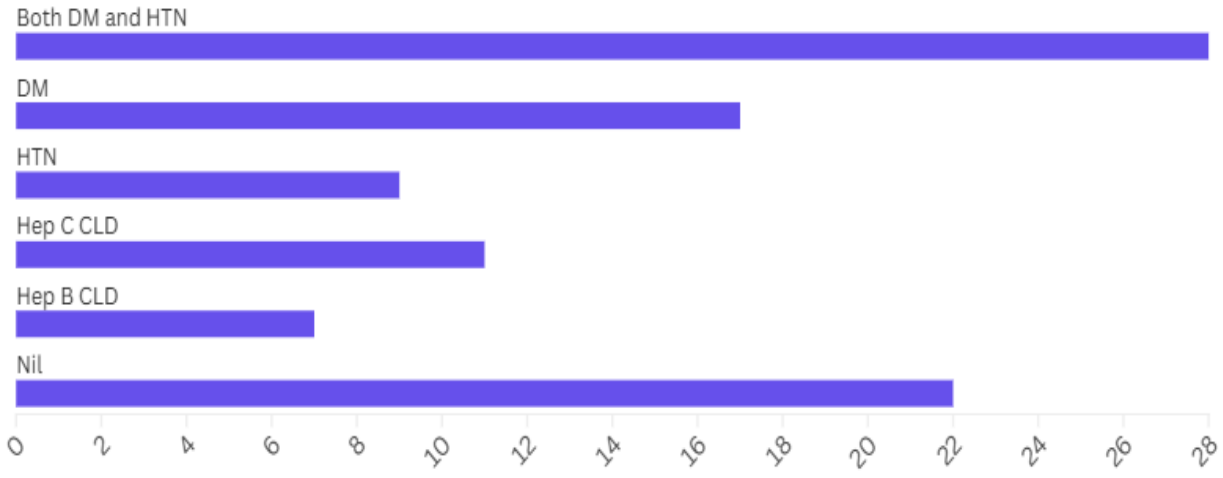

FIG. 2. **Co-Morbidities Data of the Study Population.**

Arteriovenous fistulas were the most common vascular access (59.6%), followed by permanent catheters (34.0%) and temporary catheters (6.4%). The mean dialysis duration was 122.5 ± 29.7 days. Hemodialysis initiation causes included

hypertensive nephropathy (29.8%), diabetic nephropathy (22.3%), chronic interstitial nephritis (19.1%), acute kidney injury progressing to ESRD (25.5%), and autosomal dominant polycystic kidney disease (3.2%).

Mean serum levels were as follows: vitamin D 22.1 ± 21.3 ng/mL, CRP 27.01 ± 37.80 mg/dL, NLR 3.15 ± 1.29, PLR 100.6 ± 42.72, ferritin 692 ± 681.5 ng/mL, and albumin 4.02 ± 0.56 g/dL. Based on vitamin D categorization, 86.2% had levels below 30 ng/mL, with 55.3% mildly deficient and 30.9% insufficient in vitamin D.

Statistically significant correlations were identified between serum vitamin D levels and several inflammatory markers. An inverse relationship was observed with C-reactive protein (CRP) ($r=-0.487$, $p<0.001$), ferritin ($r=-0.310$, $p=0.002$), and neutrophil-to-lymphocyte ratio (NLR) ($r=-0.320$, $p=0.002$). Conversely, serum albumin demonstrated a positive correlation with vitamin D levels ($r=0.405$, $p<0.001$).

No significant association was noted with platelet-to-lymphocyte ratio (PLR) ($p=0.544$) (FIG. 3). These associations remained significant even after adjusting for potential confounders in multivariate regression analysis, particularly the inverse link between vitamin D and CRP ($p<0.05$). Scatter plots were employed to visually illustrate the strength and direction of these correlations between vitamin D and the respective inflammatory biomarkers (FIG. 4).

Correlations

		VitaminDLevels	Albumin. Levels	Ferritin.Levels	CRP.Levels	PLR.Levels	NLR.Levels
VitaminDLevels	Pearson Correlation	1	.405**	-.310**	-.487**	-.063	-.320**
	Sig. (2-tailed)		.000	.002	.000	.544	.002
	N	94	94	94	94	94	94
Albumin.Levels	Pearson Correlation	.405**	1	-.264*	-.472**	.171	-.146
	Sig. (2-tailed)	.000		.010	.000	.099	.161
	N	94	94	94	94	94	94
Ferritin.Levels	Pearson Correlation	-.310**	-.264*	1	.374**	.127	.069
	Sig. (2-tailed)	.002	.010		.000	.221	.508
	N	94	94	94	94	94	94
CRP.Levels	Pearson Correlation	-.487**	-.472**	.374**	1	.073	.102
	Sig. (2-tailed)	.000	.000	.000		.486	.326
	N	94	94	94	94	94	94
PLR.Levels	Pearson Correlation	-.063	.171	.127	.073	1	.130
	Sig. (2-tailed)	.544	.099	.221	.486		.210
	N	94	94	94	94	94	94
NLR.Levels	Pearson Correlation	-.320**	-.146	.069	.102	.130	1
	Sig. (2-tailed)	.002	.161	.508	.326	.210	
	N	94	94	94	94	94	94

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

FIG. 3. **Table of Correlations.**

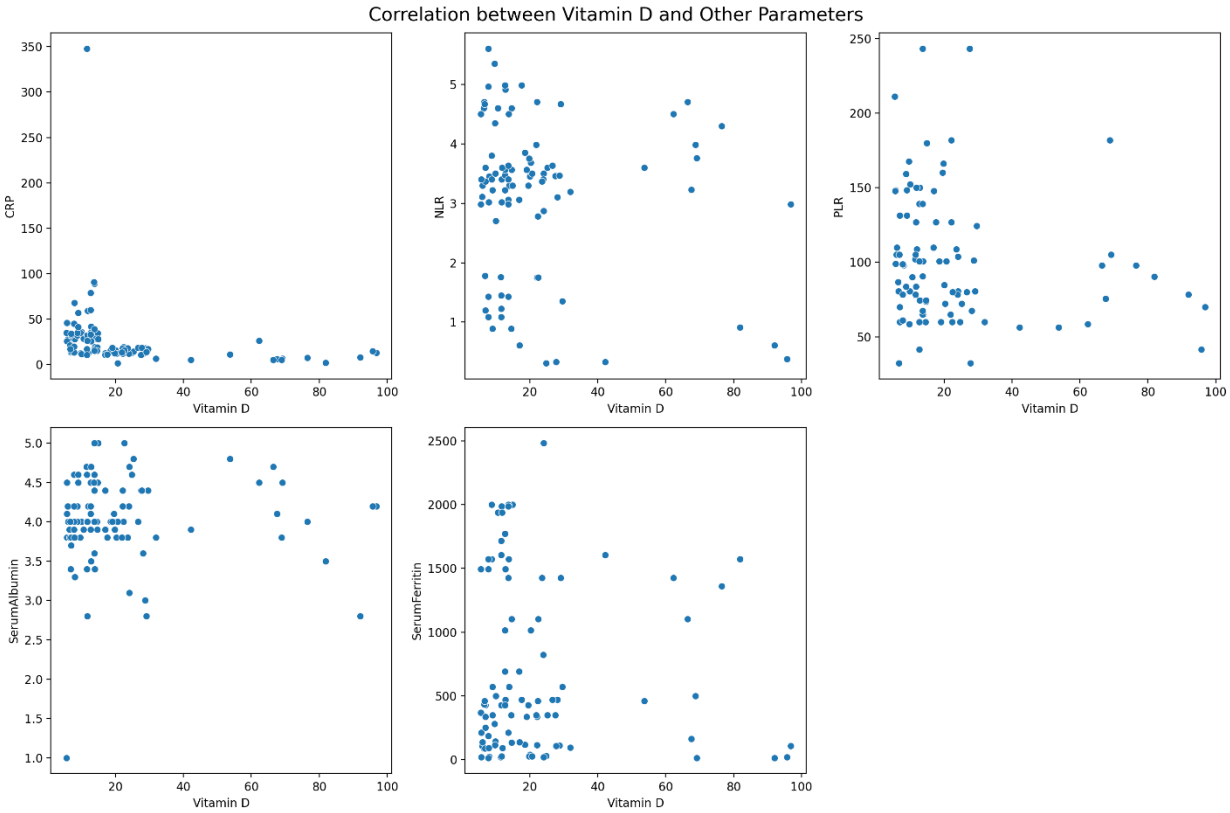

FIG. 4. **Scatter Plot for the Distribution of Data.**

Kaplan-Meier analysis showed borderline significant differences in survival between vitamin D-insufficient and sufficient groups (p = 0.070) and between insufficient and mildly deficient groups (p = 0.075), though none reached statistical significance (p < 0.05) **(Figure 5).**

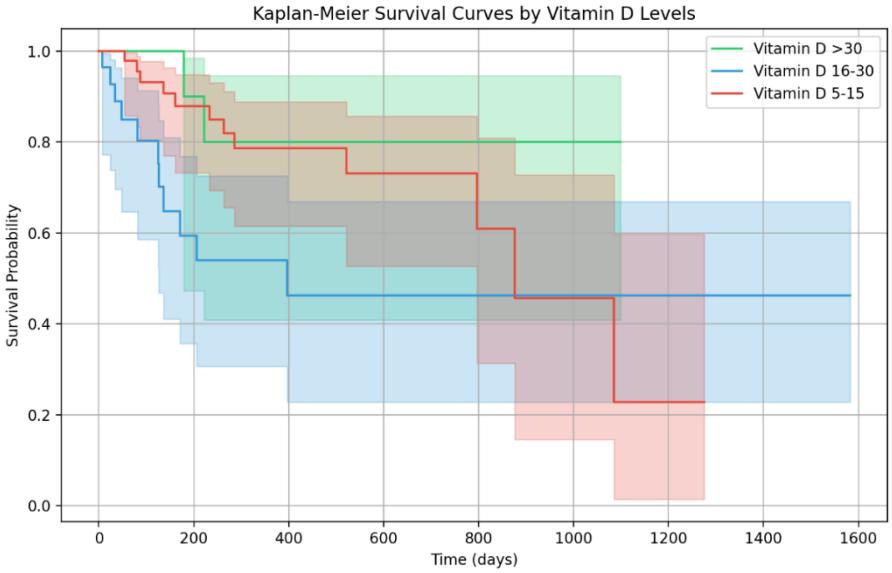

FIG. 5. **Kaplan- Meier Curves for Survival Analysis.**

4. Discussion

Vitamin D is a critical regulator of mineral balance and bone metabolism, and its role becomes even more pronounced in individuals with chronic kidney disease (CKD). Among patients undergoing hemodialysis, vitamin D deficiency is alarmingly common. Multiple factors contribute to this high prevalence, including impaired skin synthesis, limited dietary intake, reduced exposure to sunlight, and decreased activation of vitamin D receptors (VDR) in advanced stages of renal dysfunction. As renal function deteriorates, serum vitamin D concentrations tend to decline correspondingly. This trend was reflected in the current study, where 86% of participants were found to have insufficient vitamin D levels [9]. The mean serum level was 22.1 ± 21.3 ng/mL, with deficiency more common among males and those aged 45-60 years.

Hemodialysis patients often exist in a chronic pro-inflammatory state. This is exacerbated by dietary deficiencies, vascular access procedures, and immune system dysfunction. The resulting inflammation contributes significantly to the morbidity and mortality of patients with ESRD, manifesting in malnutrition, cardiovascular complications, and the so-called malnutrition-inflammation-atherosclerosis (MIA) syndrome [10]. Inflammatory status in these patients is often gauged using serum markers such as C-reactive protein (CRP), with levels above 6.2 mg/L linked to higher overall and cardiovascular mortality [11].

Recent studies increasingly recognize vitamin D as a pivotal immunomodulatory agent. Its biologically active form, calcitriol (1,25-dihydroxyvitamin D), exerts its effects by binding to vitamin D receptors (VDRs) expressed on various immune cells, including T lymphocytes, B lymphocytes, macrophages, and dendritic cells. This interaction enhances innate immune defenses while exerting regulatory control over adaptive immunity. Through these pathways, vitamin D stimulates the production of antimicrobial peptides such as cathelicidin and defensins, and influences cytokine profiles-suppressing pro-inflammatory mediators like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), while promoting anti-inflammatory cytokines such as interleukin-10 (IL-10) [12,13]. These immunomodulatory properties have positioned vitamin D as a promising therapeutic candidate in the management of a wide range of inflammatory and autoimmune disorders.

Despite growing interest, the relationship between vitamin D and inflammation in clinical populations remains multifaceted and, at times, inconclusive. While several studies have reported a significant inverse association between serum vitamin D concentrations and inflammatory biomarkers such as C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), findings across the literature are not uniformly consistent [14,15]. Conversely, others have failed to establish any meaningful correlations between vitamin D levels and CRP, ESR, or leukocyte counts in populations with and without CKD [16,17].

In our study, a general pro-inflammatory trend was observed, with CRP levels rising as vitamin D levels declined, supporting earlier findings by Muslimovic et al. that highlight a progressive rise in CRP and serum ferritin as renal function deteriorates [18]. With every 1 g/dL decrease in serum albumin, mortality increases by 47% in HD patients [10]. However, it is essential to interpret these markers with caution, since serum albumin and ferritin are influenced not only by inflammation but also by nutritional and iron status, limiting their specificity.

NLR and PLR have recently gained attention as cost-effective, easily accessible inflammatory markers in hemodialysis patients. Elevated NLR is associated with increased sensitivity for detecting systemic inflammation, while PLR may offer greater

specificity. Several studies support the utility of these ratios as reliable markers, suggesting that a composite assessment of multiple inflammatory indicators may be more informative than any single marker alone [19].

Beyond correlation, vitamin D supplementation has shown promising anti-inflammatory effects. It reduces the expression of pro-inflammatory mediators such as NF-κB and malondialdehyde, while upregulating antioxidant pathways including Nrf-2 and increasing levels of serum antioxidant enzymes [20]. Notably, for every 10 ng/mL increase in vitamin D, mortality risk in CKD patients is reduced by 14%, whereas levels below 18 ng/mL are associated with a 30% increase in mortality risk [21]. These findings underscore the potential of vitamin D optimization in improving not only bone health but also immune modulation and overall survival in hemodialysis patients.

Despite these findings, the study is limited by its cross-sectional design, single-center setting, and modest sample size, which restricts generalizability and prevents causal inference. Moreover, the influence of confounding factors, particularly nutritional and iron status, on traditional inflammatory markers highlights the need for more comprehensive evaluations. Future research should adopt longitudinal designs, incorporate broader inflammatory panels, and assess the impact of vitamin D supplementation to better understand its therapeutic potential.

5. Conclusion

A high prevalence of vitamin D deficiency is observed in patients receiving hemodialysis, and it shows an independent association with elevated CRP, NLR, and ferritin levels, reflecting a chronic inflammatory state. Optimizing vitamin D levels may offer metabolic and immunological benefits, supporting its consideration as part of comprehensive ESRD management strategies.

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This research received no external funding.

7. Ethical Considerations

Approval: The authors declare that approval was taken from the Ethical Review Board of Rawalpindi Medical University, Rawalpindi before study initiation.

Consent to Participate: The authors declare that all participants were included in the study only after written and verbal consent was given.

Protection of human and animal subjects: The authors declare that no experiments were performed on humans or animals for this research. The principles of beneficence and respect for human dignity were observed during data collection.

Confidentiality of data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent: The authors declare that informed verbal and written consent was taken from patients before data collection and no personal patient data appear in this article.

8. Data Access Statement

Research data supporting this publication are available with the corresponding author at reasonable request.

9. Conflict of Interest Declaration

The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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