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Evaluation of Systemic and Hematological Inflammatory Markers in Patients with Vitamin D Deficiency

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Abstract

Objective
This study aims to comprehensively examine the effects of vitamin D (VD) on systemic and hematological inflammatory markers.

Material and Method
A total of 2889 patients with albumin, C-reactive protein (CRP), creatinine and leukocyte values within the reference ranges were included in this retrospective study. Patients were divided into three groups based on their 25-hydroxy VD levels: group-1 (VD deficiency, VD<12 ng/mL (30 nmol/L)), group-2 (VD insufficiency, VD=12-20 ng/mL (30-50 nmol/L)) and group-3 (sufficient VD status, VD>20 ng/mL (50 nmol/L)) groups. CRP-albumin ratio (CAR), neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), and prognostic nutritional index (PNI) were calculated.

Results
The age of the groups did not differ significantly (p=0.094), while the percentage of females was significantly higher in group-1 than in group-2 and group-3 (p<0.05). CRP, CAR, and PLR values were significantly lower in group-2 and group-3 compared to group-1 (p<0.05 for all). Albumin and PNI values were significantly higher in group-2 and group-3 compared to group-1 (p<0.05 for all). In the multinomial multivariate logistic regression analysis, conducted using sex, CAR, PNI, NLR, PLR, and LMR parameters with group-3 as the reference category, significant odds ratios (OR) were observed for female sex, CAR, and PNI in relation to group-1.

Conclusions
These results show that there were increases in CAR and PNI, markers of inflammation and nutritional status, in the VD-deficient population, although routine laboratory parameters were normal.

Keywords: CRP-albumin ratio, inflammatory markers, prognostic nutritional index, Vitamin D deficiency

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Introduction

VD plays a key role in bone metabolism and maintenance of calcium and phosphorus balance by creating negative feedback with parathyroid hormone ts deficiency has been clearly demonstrated to be associated with rickets in children and with osteomalacia and osteoporosis in adults (3, 4). Besides bone metabolism, studies provide evidence for the protective role of VD in autoimmune conditions (e.g. multiple sclerosis (MS) and type 1 diabetes mellitus) and infectious diseases (e.g. respiratory tract infections) (5). Furthermore, VDD shows an increased risk of developing multiple malignancies and inflammatory diseases (e.g. MS, rheumatoid arthritis (RA) (6). Vitamin D deficiency (VDD) has become the most common micronutrient disorder worldwide, surpassing iron deficiency, and its frequency may exceed 50% in some countries (1). Vitamin D deficiency (VDD) is the most prevalent micronutrient disorder globally, surpassing iron deficiency, with a prevalence exceeding 50% in certain countries (1). The National Institutes of Health recommends using the 25-hydroxy (25-OH) vitamin D (VD) level to assess VD status (2).

The biological effects of VD are mediated by the nuclear VD receptor (VDR), which is present in various cell types including intestinal cells, osteoblasts, muscle cells, kidney cells, parathyroid epithelial cells, immune cells, adipocytes, nonparenchymal hepatic cells, and pancreatic ß-cells (7, 8). VDR is widely expressed in all immune cellular subsets, and binding of VD and VDR results in the activation of essential innate immune cells such as neutrophils, monocytes, and macrophages, leading to increased chemotactic, phagocytic, and bactericidal activities (9). Anti-inflammatory effects of VD also occur through upregulation of interleukin-10 (IL-10) (10).

The markers of the systemic inflammatory response are circulating white blood cells originating from lymphoid/myeloid tissues and acute phase proteins such as C-reactive protein (CRP) and albumin originating from the liver. CRP/Albumin ratio (CAR), determined by serum CRP and albumin levels, is a commonly used liver-related parameter in the follow-up of systemic inflammation. It has been shown that CAR is significantly higher in cancer (11), infection (12), inflammatory diseases (13) and DM with complications (14). In addition, markers such as neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), and platelet/lymphocyte ratio (PLR) obtained from hematological parameters have also been demonstrated as inflammatory markers (15). The prognostic nutritional index (PNI) serves as an indicator of both the nutritional and immune status of patients. It is calculated based on the serum albumin level and the peripheral blood lymphocyte count (16). Recently, it has been shown that it can be an important marker in predicting clinical outcomes in many diseases, such as COVID-19 disease (16), nasopharyngeal cancer (17), and gastric cancer(18).

Some studies demonstrate the protective effect of vitamin D (VD) in conditions associated with inflammation. To achieve a more comprehensive understanding, it is important to examine how systemic and hematological inflammatory parameters vary across different VD levels in patients without inflammatory diseases or infections. The aim of this study was to evaluate the impact of VD levels on systemic and hematological inflammatory markers in patients without inflammatory and infectious diseases.

Material and Method

In this retrospective study, we reviewed and recorded data from patients who had their 25-OH VD levels measured at AIBU Izzet Baysal Physical Treatment and Rehabilitation Training and Research Hospital Hospital between January 2021 and January 2022 during a general health check-up. Due to seasonal variations in vitamin D levels, data for an entire year were used to minimize the impact of these variations. The data included age, sex, 25-OH VD levels, whole blood results, and biochemistry test results (CRP, albumin, creatinine). Patients over 18 years of age were included in the study. Patients were excluded from the study if their CRP, albumin, hemoglobin, or white blood cell (WBC) values were outside the normal range, as abnormal levels of these biomarkers could indicate infection, inflammation, or malnutrition, which are factors associated with the inflammatory markers being evaluated in this study. Additionally, to exclude patients with renal failure, which can affect the kidneys' role in VD production, only those with creatinine levels within the reference range were included in the study. Patient files were analyzed, and patients with diabetes mellitus, hypertension, cancer, liver disease, renal disease and inflammatory diseases (ankylosing spondylitis, RA, MS, Behçet's disease, etc.) were excluded. Also, CAR, NLR, PLR, LMR, and PNI values were calculated using the obtained data. PNI values were calculated as albumin(gr/L) + 5xlymphocyte (109/L), and other parameters were calculated as ratios: CAR (CRP/Albumin), NLR (Neutrophil/Lymphocyte), PLR (Platelet/Lymphocyte), and LMR (Lymphocyte/Monocyte).

Patients were divided into three groups according

to their 25-OH VD levels (2): group 1 (VDD group, patients with VD level <12 ng/mL (30 nmol/L)), group 2 (VD insufficiency group, patients with a VD level of 12-20 ng/mL (30 - 50 nmol/L)) and group 3 (sufficient VD status group, patients with VD level >20 ng/mL (50 nmol/L)).

Statistical Analysis

Statistical analysis was performed using the SPSS statistical software for Windows (version 21, released in 2012, IBM, Armonk, NY, USA).

The distribution of continuous variables was assessed for normality using the Kolmogorov–Smirnov test and visual inspection of distribution histograms. For normally distributed variables, three-group comparisons were conducted using one-way analysis of variance (ANOVA) followed by Bonferroni post-hoc tests. Descriptive statistics for these variables are presented as mean ± standard deviation. Non-normally distributed variables were analyzed using the Kruskal-Wallis test, followed by post-hoc pairwise comparisons using the Dunn-Bonferroni method. For these variables, the descriptive statistics were shown as the median (1st-3rd quartile value). Categorical variables were compared using Pearson's Chi-square test. Correlation analysis was performed with Pearson's correlation test for parametric variables or Spearman's rank correlation test for non-parametric variables. Multivariate regression analysis was used to evaluate predictive factors, with results presented as odds ratios (OR) and 95% confidence intervals (CI). A p-value of less than 0.05 was considered statistically significant.

Results

A total of 2889 patients were included in the study. When compared in terms of sex distribution, there were more females in group 1 (N=875 (73.0%)), group

Table 1 Comparison of demographic and laboratory parameters of patients

	Group 1 (n=1199)	Group 2 (n=898)	Group 3 (n=869)	p
Sex, females	875 (73.0%)	523 (58.2%)†	427(53.9%)†	<0.001
Age	48 (36-58)	48 (36-58)	50 (40-58)	0.094
25-Hidroksi Vitamin D	8.2 (6.5-9.9)	15.7 (13.6-17.7)†	25.5 (22.8-30)†,‡	<0.001
WBC	6.99 (6.04-8.16)	7.09 (6.08-8.17)	6.83 (5.88-8)†,‡	0.008
CRP	1.4 (0.6-2.6)	1.2 (0.5-2.4)†	1.1 (0.4-2.5)†	<0.001
ALB	46 (43.0-48.0)	46.7 (44.0-49.0)†	47.0 (44.3-49.0)†	<0.001
LYM	2.03 (1.64-2.48)	2.05 (1.7-2.5)	2.08.(1.66-2.52)	0.377
MONO	0.61 (0.48-0.76)	0.62 (0.51-0.76)	0.59 (0.49-0.74)‡	0.024
NEU	4.04 (3.36-4.93)	4.06 (3.31-4.96)	3.88 (3.19-4.7)†,‡	0.001
PLT	274 (236-318)	265.5 (229-306)†	263 (224.3-308.0)†	0.001
CAR	0.031 (0.014-0.058)	0.026 (0.011-0.052)†	0.023 (0.010-0.054)†	<0.001
PNI	56.3 (53.1-59.4)	57.1 (54.1-60.5)†	57.5 (54.3-60.7)†	<0.001
NLR	2.031 (1.552-2.648)	1.938 (1.501-2.561)	1.862 (1.443-2.486)†	<0.001
PLR	134.0 (107.2-168.0)	129.2 (103.7-158.6)†	128.1 (101.2-164.3)†	0.002
LMR	3.259 (2.473-4.481)	3.294 (2.513-4.37)	3.443 (2.571-4.478)	0.139

Values are given as median (1st-3rd quartile) values and compared with the Kruskal-Wallis Test. Sex parameter was given as number (%) and compared with Pearson Chi-Square test. †: Significantly different from Group 1 based on the Dunn-Bonferroni pairwise comparison test (adjusted p-value < 0.05) ‡: Significantly different from Group 2 based on the Dunn-Bonferroni pairwise comparison test (adjusted p-value < 0.05), WBC: white blood cells, CRP: C-reactive protein, ALB: Albumin, LYM: Lymphocyte, MONO: Monocyte, NEU: Neutrophil, PLT: Platelet, CAR: C-reactive protein-albumin ratio, PNI: Prognostic nutritional index, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, LMR: Lymphocyte-monocyte ratio. The "Sex, females" parameter represents the proportion of female participants in each group, with all other participants being male. All parameters are reported as follows: Age in years; 25-Hydroxy Vitamin D in ng/mL; WBC, LYM, MONO, NEU, PLT in 10^9/L; CRP in mg/L; ALB in g/L.

Table 2 Multinominal multivariate logistic regression analysis of parameters.

Model 1: Reference category = Group 3; Nagelkerke R^2 = 0.052					
	Parameters	**B (SE)**	**Wald**	**p value**	**OR (95% CI)**
Group 1 vs Group 3	CAR	3.693 ± 1.602	5.312	0.021	40.178 (1.738-928.914)
	PNI	-0.039 ± 0.012	11.485	0.001	0.962 (0.94-0.984)
	NLR	0.082 ± 0.064	1.642	0.200	1.086 (0.957-1.231)
	PLR	-0.002 ± 0.001	1.724	0.189	0.998 (0.996-1.001)
	LMR	-0.021 ± 0.035	0.351	0.554	0.979 (0.914-1.049)
	Sex (Female vs. Male)	0.828 ± 0.101	66.808	<0.001	2.288 (1.876-2.79)
Group 2 vs Group 3	CAR	0.587 ± 1.717	0.117	0.733	1.798 (0.062-52.072)
	PNI	0.007 ± 0.012	0.379	0.538	1.007 (0.984-1.032)
	NLR	0.145 ± 0.067	4.657	0.031	1.156 (1.013-1.318)
	PLR	-0.003 ± 0.001	4.825	0.028	0.997 (0.995-1.000)
	LMR	-0.079 ± 0.038	4.171	0.041	0.924 (0.857-0.997)
	Sex (Female vs. Male)	0.263 ± 0.103	6.495	0.011	1.301 (1.063-1.593)
Model 2: Reference category = Group 1; Nagelkerke R^2 = 0.052					
Group 2 vs Group 1	CAR	-3.107 (1.525)	4.152	0.042	0.045 (0.002-0.888)
	PNI	0.047 (0.011)	17.624	<0.001	1.048 (1.025-1.071)
	NLR	0.063 (0.058)	1.167	0.280	1.065 (0.95-1.193)
	PLR	-0.001 (0.001)	1.185	0.276	0.999 (0.996-1.001)
	LMR	-0.058 (0.036)	2.639	0.104	0.944 (0.88-1.012)
	Sex (Female vs. Male)	-0.565 (0.098)	33.092	<0.001	0.569 (0.469-0.689)
Group 3 vs Group 1	CAR	-3.693 (1.602)	5.312	0.021	0.025 (0.001-0.575)
	PNI	0.039 (0.012)	11.485	0.001	1.04 (1.017-1.064)
	NLR	-0.082 (0.064)	1.642	0.200	0.921 (0.813-1.044)
	PLR	0.002 (0.001)	1.724	0.189	1.002 (0.999-1.004)
	LMR	0.021 (0.035)	0.351	0.554	1.021 (0.953-1.094)
	Sex (Female vs. Male)	-0.828 (0.101)	66.808	<0.001	0.437 (0.358-0.533)

B: Beta, SE: Standard error, OR: odd ratio, CI: Confidence Interval, CAR: C-reactive protein-albumin ratio, PNI: Prognostic nutritional index, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, LMR: Lymphocyte-monocyte ratio.

2 (N=523 (58.2%)) and group 3 (N=427 (53.9%)) (p<0.05 for both). There was no significant difference between the groups in terms of age (p=0.094).

Table 1 shows the comparison of CRP, albumin, hemoglobin, WBC, neutrophil, lymphocyte, platelet, CAR, PNI, NLR, PLR, and LMR values between groups. CRP, CAR, and PLR values were significantly lower in group 2 and group 3 compared to Group 1, and NLR values were significantly lower in group 3 compared to group 1 (p<0.05 for all). Albumin and PNI values were significantly higher in group 2 and group 3 compared to group 1 (p<0.05 for all). When neutrophil and WBC parameters were evaluated, no significant difference was found between group 1 and group 2 (p>0.05); they were significantly lower in group 3 than both group 2 and group 1 (p<0.05 for both).

The multinominal multivariate logistic regression analysis was performed with using the sex (female vs

Table 3 Correlation analysis of parameters with vitamin D levels.

		CAR	PNI	NLR	PLR	LMR
25-hidroxy vitamin D	rho	-0.082	0.122	-0.081	-0.070	0.032
	p value	<0.001	<0.001	<0.001	<0.001	0.089

rho: Spearman's correlation coefficient, CAR: C-reactive protein-albumin ratio, PNI: Prognostic nutritional index, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, LMR: Lymphocyte-monocyte ratio.

male), CAR, PNI, NLR, PLR and LMR parameters, with group 3 as the reference category. OR of female sex (OR: 2.288 (95% CI:1.876-2.790)), CAR (40.178 (95% CI:1.738-928.914)) and PNI (0.962 (95% CI:0.964-0.984)) were significant for group 1. For group 2, NLR, PLR, LMR, and female sex were significant ($p<0.05$ for all, Table 2). In the second model, group 1 was used as the reference category, OR of the female sex, CAR, and PNI for group 2 and 3 were significant ($p<0.05$ for all, Table 2). Other parameters were not statistically significant ($p>0.05$ for all, Table 2). Overall, female individuals, with elevated CAR levels, and lower PNI values were more inclined to belong to group 1 compared to group 2 and group 3. Table 3 shows the correlation analysis between VD and inflammatory markers.

Discussion

In the present study, VDD patients showed higher CRP, CAR, PLR, and NLR values and lower albumin and PNI values. Furthermore, in the multinomial multivariate logistic regression analysis, conducted with sex, CAR, PNI, NLR, PLR, and LMR parameters, significant OR were observed for female sex, CAR, and PNI in relation to VDD.

A review reported that some studies found a negative association between VD and inflammatory markers, while others found no significant association (19). Kruit et al. observed a negative correlation between serum VD and CRP levels in elderly patients with both inflammatory and non-inflammatory diseases, with a stronger correlation observed in the former group (20). Similarly, Lopez-Munoz et al. reported a negative correlation between serum VD and CRP levels in patients with ulcerative colitis but not those with Chron's disease (21). In a study conducted in patients with COVID-19, significant inverse correlations were found between 25-OH VD levels and interleukin-6 (IL-6), CRP, tumor necrosis factor-α (TNF-α), D-dimer, and IL-10 levels. Among these patients, it was shown that those with hypovitaminosis D (25-OH VD ≤ 20 ng/ml) had higher IL-6, CRP, TNF-α, D-dimer, and IL-10 values than those without hypovitaminosis D (22). In a Mendelian randomization analyses study, it was found that genetically predicted serum 25-OH VD had an L-shaped association with serum CRP (23). The relationship between VD and CRP levels has been extensively researched; however, some studies have failed to demonstrate a correlation (24, 25). While some studies have not established a connection between VD and CRP levels, the majority of literature, including our study, indicates that inflammatory parameters are generally elevated in individuals with VDD, thereby reinforcing the association between VD and inflammatory markers. The possible explanations for these differences may be variations in sample size, population demographics, or methodological approaches.

Albumin, is synthesized by the liver and acts as a negative acute phase reactant. A study has shown a linear relationship between albumin and VD levels in patients with COVID-19. (26). Along with its many other functions, albumin also plays a role in the transport of VD along with the VD binding protein. Albumin-bound vitamin D and free vitamin D yield the bioavailable form of vitamin D. However, it is free VD that plays a more direct role in biological processes (26). Hence, assessing variations in albumin levels along with CRP may allow the evaluation of the anti-inflammatory effects of VD and its bioavailable levels together. Furthermore, the CRP and albumin ratio, referred to as the CAR ratio, serves as a systemic inflammatory marker associated with the severity of inflammation and prognosis across various diseases such as malignancies, chronic inflammatory conditions, and sepsis (27). This ratio could potentially be utilized as an indicator of inflammation linked to VDD in patients exhibiting normal CRP and albumin values. For instance, a study on cerebral venous sinus thrombosis in pregnant women found that the CAR ratio was significantly elevated in those with venous

sinus thrombosis and severe vitamin D deficiency, highlighting its potential as a marker for inflammation related to VDD (28). In our study, higher CAR values were obtained in the VDD group (group 1) compared to the VD insufficient (group 2) and sufficient VD status (group 3) groups. Also, despite CRP and albumin values falling within the reference range, CAR values, serving as a systemic inflammatory marker, were elevated in patients with VDD compared to those with insufficient and sufficient VD status. This observation suggests that CAR can serve as an indicator of inflammation associated with VDD even in patients with normal CRP and albumin values. Furthermore, being female, having a higher CAR and lower PNI were found to be a predictor of being in the VDD group in our study, suggesting that there may be a cause-effect relationship between VD and inflammatory markers.

NLR, LMR, and PLR were hemogram-derived, easily available non-specific markers of inflammation (29). Studies have shown that patients with VDD exhibit significantly higher NLR levels (30) and increased PLR values, with decreased LMR in children with VDD (31).

Likewise, our study revealed higher levels of NLR and PLR in the VDD group compared to those with sufficient VD status. Furthermore, PLR values, obtained from the hemogram and serving as another inflammatory marker, were also elevated in the VDD group compared to both insufficient and sufficient VD status groups. In addition, NLR, PLR, and LMR values were found as significant predictors in the insufficient VD group compared to the sufficient VD status in our study (Table 2), which indicates that these parameters were more affected by the decrease in the VD level rather than CAR or PNI. The relationship between VDD and non-specific inflammation markers such as the NLR, LMR, and PLR has garnered significant attention in recent research. VD is known to play a crucial role in modulating the immune response, influencing both innate and adaptive immunity. It has been observed that VDD correlates with increased levels of inflammatory markers such as IL-6, TNF-α, and CRP (32, 33). For instance, reported that lower levels of 25-OH VD were associated with higher NLR and PLR, suggesting that VD may exert an anti-inflammatory effect that could help in regulating these ratios (32).Similarly, found that patients with VDD exhibited significantly higher NLR and PLR, indicating that chronic systemic inflammation might adversely affect VD metabolism, potentially leading to conditions such as osteoporosis (33). The mechanisms by which VD influences inflammatory markers are multifaceted. VD is believed to modulate the expression of various cytokines and inflammatory pathways. For example, it has been shown to inhibit the NF-kB and p38 MAPK pathways, which are critical in the inflammatory response (34). This inhibition can lead to a reduction in the production of pro-inflammatory cytokines, thereby lowering the levels of inflammatory markers such as IL-6 and TNF-α (34, 35). Furthermore, VD's role in macrophage polarization is significant; it promotes the M2 (anti-inflammatory) phenotype while inhibiting the M1 (pro-inflammatory) phenotype, thereby contributing to a balanced immune response (36). In addition to its direct effects on immune cells, VD may also influence the inflammatory milieu indirectly through its impact on metabolic processes. For instance, VDD has been linked to insulin resistance and obesity, both of which are associated with chronic low-grade inflammation (37). This connection suggests that VD may help mitigate inflammation by improving metabolic health, which in turn could influence NLR, LMR, and PLR. While there is a correlation between vitamin D deficiency and elevated non-specific inflammation markers such as NLR, LMR, and PLR, the direct and indirect mechanisms through which vitamin D exerts its effects are complex and multifactorial. Future research should focus on elucidating these mechanisms to better understand the therapeutic potential of vitamin D in managing inflammation.

PNI is both an inflammatory and nutritional status biomarker calculated from albumin and lymphocyte counts (38). It was shown that VDD and PNI were significantly associated with all-cause mortality, and there was a relationship between VDD and PNI (39). Similarly, we found that PNI levels were lower in patients with VDD than in patients with insufficient VD and sufficient VD status, and PNI was a significant predictor of VDD. Also, there was a weak but significant positive correlation between VD and PNI levels. Our study indicates that the PNI, serving as both an inflammatory and nutritional biomarker, was reduced in cases of VDD and exhibited a correlation with VD levels. This suggests that VD levels might contribute to heightened inflammation or be linked to a decline in nutritional status. Moreover, PNI values, which have been shown to be an indicator of the nutritional and immune status of individuals, were found to be lower in patients with VDD than in other groups, suggesting that it may be a marker that can be used in the evaluation of increased risk such as infectious and inflammatory diseases in patients with VDD.

This study has some limitations. First, the retrospective design of the study limits the ability to establish causality between vitamin D levels and the observed clinical outcomes. Second, the reliance on electronic health records introduces the possibility of

incomplete data. Also, we did not measure vitamin D supplementation or sun exposure, both of which could have influenced the results. Lastly, we only included patients whose routine laboratory parameters, except for VD, were within reference values. Therefore, any potential inflammatory effects of VD levels exceeding the reference range may not have been demonstrated.

Conclusion

Results of current study shows that there were increases in CAR and decrease in PNI, markers of inflammation and nutritional status, in the VD-deficient population, although routine laboratory parameters were normal. It is suggested that maintaining adequate VD levels may help improve inflammatory profiles. Further longitudinal prospective studies with patients with VDD may better isolate the cause-and-effect relationship between VD and the inflammatory markers CAR and PNI.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
The study was approved by the Bolu Abant Izzet Baysal University Clinical Researches Ethics Committee (No: 2021/295, date: 21/12/2021) and the Declaration of Helsinki for research on humans was followed.

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Availability of Data and Materials
Data available on reasonable request from the authors.

Authors Contributions
TA: Conceptualization; Data curation, Formal analysis; Investigation; Methodology; Resources; Validation; Writing- original draft, review & editing.

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