



Serum Vitamin D Levels as a Prognostic Biomarker in Patients Receiving Immune Checkpoint Inhibitors

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ABSTRACT

Objective: Vitamin D exerts pleiotropic effects on tumor biology and immune regulation, including modulation of T-cell function and antigen presentation. Preclinical evidence suggests that optimal vitamin D status may enhance immune checkpoint inhibitor (ICI) efficacy; however, data are limited among ICI-treated patients. We aimed to evaluate the prognostic significance of baseline serum 25(OH)D levels in patients receiving ICIs.

Material and Methods: A retrospective cohort of 244 patients with advanced solid tumors treated with ICI. Baseline serum 25(OH)D concentrations, obtained within 30 days prior to ICI initiation, were categorized as sufficient (>20 ng/mL), insufficient (12-20 ng/mL), or deficient (<12 ng/mL).

Results: The median age of the patients was 63 years; 65.2% were male. The most common tumor types were non-small cell lung cancer (32.8%), renal cell carcinoma (18.9%), and melanoma (14.3%). Vitamin D status was sufficient in 36.5%, insufficient in 34.8%, and deficient in 28.7% of patients. In multivariable analysis, vitamin D deficiency independently predicted shorter overall survival (OS) [hazard ratio (HR): 2.264, 95% confidence interval (CI): 1.553-3.300; p<0.001] compared with the vitamin D-sufficient group. Both vitamin D insufficiency (HR: 1.494; 95% CI: 1.067-2.092; p=0.019) and vitamin D deficiency (HR: 2.0; 95% CI: 1.411-2.833; p<0.001) were independently associated with inferior progression-free survival (PFS).

Conclusion: Baseline vitamin D deficiency is an independent adverse prognostic factor for OS and PFS in ICI-treated patients. Integrating vitamin D assessment into pretreatment evaluation may facilitate risk stratification and inform supportive care strategies, warranting prospective validation.

Keywords: Vitamin D; immune checkpoint inhibitors; prognostic biomarkers; survival

INTRODUCTION

Cancer cells create an immunosuppressive microenvironment in their vicinity, and its development is paramount to cancer progression.¹ Recently, it has been demonstrated that cell surface receptors called immune checkpoints, located on the surfaces of T-lymphocytes, play a crucial role in cancer progression and orchestrate immune evasion and exhaustion of anti-tumor T-cells.² Monoclonal antibodies targeting these checkpoints, known as immune checkpoint inhibitors (ICIs), have been developed and introduced into clinical practice over the last decade.³ The ICIs became the foundation of modern immunotherapy and significantly changed the cancer treatment landscape.⁴

Although ICIs have improved outcomes in several tumor types, many patients still do not respond to ICIs.⁵ In addition, toxicities, including class-specific adverse events, and the financial burden are concerning.⁶ Biomarkers are urgently needed to identify patients who are most likely to benefit. There are several tumor- and microenvironment-based biomarkers. While microsatellite instability (MSI) status, tumor mutational burden, and tumor programmed death-ligand 1 (PD-L1) expression are well-established predictive biomarkers, they require invasive tissue sampling, are costly, and may not fully capture the dynamic interaction between host immunity and tumor biology.⁷ These issues led to increased interest in peripheral blood-based biomarkers that evaluate various

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aspects of tumor-host interactions. From this perspective, simple biomarkers retrieved from the routine complete blood count and chemistry tests may be valuable and provide clues about the host's immune and nutritional status.

Vitamin D is an essential nutrient for bone health and also exerts antitumor effects, including the regulation of apoptosis, tumor-cell proliferation, invasion, angiogenesis, and metastasis.^{8,9} Vitamin D is a key immunomodulator, with its receptors prevalent on most immune cells.¹⁰ Its active metabolite, 1,25-dihydroxyvitamin D [$1,25\text{-(OH)}_2\text{D}$], modulates immunity through effects on antigen-presenting cell differentiation, lymphocyte proliferation, and cytokine secretion.¹¹ Experimental studies indicate that Vitamin D may enhance tumor immunotherapy by activating natural killer (NK) cells and T-cells, mitigating immunosuppressive factors such as pro-inflammatory cytokines and PD-L1, and favorably altering the TME.^{12,13} Preclinical models have shown improved immune-mediated tumor control and response to ICIs with higher vitamin D availability.¹⁴ Despite these mechanistic rationales, clinical evidence remains limited and inconsistent, often stemming from small sample sizes and single-center studies.^{15,16}

Based on the immunomodulatory role of vitamin D and emerging evidence suggesting its interaction with antitumor immune responses, we hypothesized that baseline serum vitamin D status may be associated with survival outcomes in patients treated with ICIs. Consequently, we aimed to evaluate the association between baseline vitamin D levels and survival outcomes among ICI-treated patients at our institution.

MATERIAL AND METHODS

Patients and Study Design

This retrospective cohort study included patients with metastatic or unresectable cancer who were treated with ICIs between September 2016 and August 2024. Exclusion criteria included participation in clinical trials or expanded access programs, absence of a baseline serum 25(OH)D measurement within 30 days prior to ICI initiation, incomplete clinical or survival data, and loss to follow-up within the first month after treatment initiation. Baseline serum 25(OH)D measurements were available for all patients and were obtained within 30 days prior to ICI initiation. Baseline patient demographics, Eastern Cooperative Oncology Group (ECOG) status, primary tumor type, metastasis sites, line of immunotherapy, type of ICI, survival outcomes, and baseline serum 25(OH)D levels were obtained from patient files and the electronic hospital registry. Serum 25(OH)D levels were obtained from blood samples drawn within 30 days prior to

ICI initiation as part of routine clinical practice. Measurements were performed in the institutional biochemistry laboratory using a standardized chemiluminescent immunoassay. Vitamin D status was categorized into three groups according to baseline 25(OH)D concentration: deficiency (<12 ng/mL), insufficiency (12-20 ng/mL), and sufficiency (>20 ng/mL). These cut-offs were selected to ensure clinical relevance, biological interpretability, and comparability with prior literature.¹⁷

The authors state that they have obtained Hacettepe University Health Sciences Research Ethics Committee approval (date: 26.08.2025, approval number: SBA 25/743).

Statistical Analyses

We reported continuous data as medians with interquartile range (IQR), and categorical variables as frequencies with percentages. For categorical variables, comparisons between vitamin D categories were conducted using the chi-square test or Fisher's exact test; for continuous variables, the Kruskal-Wallis or Mann-Whitney U test was employed, as appropriate. The Kaplan-Meier approach was used to examine the influence of prognostic factors on survival. Univariable Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for potential prognostic factors. Variables yielding a p-value of less than 0.10 in the univariable analysis were subsequently included in a multivariable Cox regression to control for confounding effects. Statistical analyses were performed using SPSS version 24; p-values <0.05 were considered statistically significant.

RESULTS

A total of 798 patients with metastatic or unresectable solid tumors were treated with ICIs at our institution. Of these, 123 patients were excluded due to participation in clinical trials or expanded access programs. The remaining 675 patients were evaluated for eligibility. Among them, 349 patients did not have an available baseline serum 25-hydroxyvitamin D measurement obtained within 30 days of ICI initiation; 54 patients had incomplete clinical or survival data; and 28 patients were lost to follow-up within the first month after treatment initiation. After applying these exclusion criteria, 244 patients were included in the analyses (Figure 1).

The median age of patients was 63 years (IQR, 55-69); 65.2% of patients were male. The most common primary tumors were non-small cell lung cancer (NSCLC) (32.8%), renal cell carcinoma (18.9%), and melanoma (14.3%). Most patients (77.5%) had an ECOG performance status (PS) of 0-1, and 40.6% received ICIs in the second-line setting. Nivolumab was the most frequently administered agent (80.3%), followed by atezolizumab (8.6%) and pembrolizumab (7.4%).

Baseline vitamin D status was sufficient in 89 patients (36.5%), insufficient in 85 (34.8%), and deficient in 70 (28.7%). The baseline demographic and clinical characteristics are detailed in Table 1.

When patients were stratified by vitamin D status, no statistically significant differences were observed in age, sex, ECOG PS, primary tumor type, treatment line, or presence of liver or lung metastases (Table 2).

In univariable analysis of overall survival (OS), ECOG PS ≥ 2 (HR: 1.670, 95% CI: 1.178-2.369; $p=0.004$) and lower vitamin D levels were associated with worse outcomes. Compared with patients with sufficient vitamin D levels, those with insufficiency had an HR of 1.462 (95% CI: 1.012-2.113; $p=0.043$) and those with deficiency had an HR of 2.315 (95% CI: 1.606-3.337; $p<0.001$). In multivariable analysis, vitamin D deficiency remained an independent predictor of shorter OS (HR: 2.264, 95% CI: 1.553-3.300; $p<0.001$), whereas vitamin D insufficiency was not significantly associated with OS (HR: 1.380, 95% CI: 0.944-2.017; $p=0.096$) compared with the vitamin D-sufficient group (Table 3). Median OS was 19.1 months (95% CI: 11.0-27.1) in the sufficiency group, 12.0 months (95% CI: 8.8-15.1) in the insufficiency group, and 7.1 months (95% CI: 4.6-9.5) in the deficiency group (Figure 2). Additional sensitivity analyses stratified by tumor type

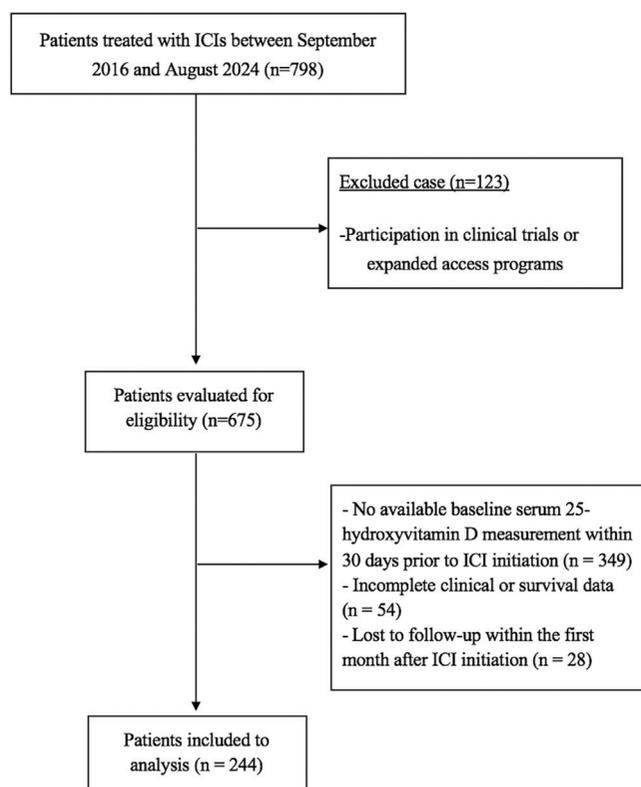


FIGURE 1: Flow diagram of patient selection process.

ICI: Immune checkpoint inhibitor

TABLE 1: Baseline patient characteristics of study cohort (n=244).

Clinical feature	n, (%)
Age at ICI treatment, median (IQR)	63 (55-69)
Sex	
Female	85 (34.8)
Male	159 (65.2)
ECOG PS	
0	109 (44.7)
1	80 (32.8)
2	39 (16.0)
3	16 (6.6)
Primary tumor	
NSCLC	80 (32.8)
RCC	46 (18.9)
Melanoma	35 (14.3)
HNC	22 (9)
SCLC	6 (2.5)
HCC	6 (2.5)
Urothelial cancer	6 (2.5)
Sarcoma	5 (2)
Others	38 (15.6)
Treatment line	
1	45 (18.4)
2	99 (40.6)
3	55 (22.5)
4 or later	45 (18.4)
Type of ICI	
Nivolumab	196 (80.3)
Nivolumab-Ipilimumab	8 (3.3)
Pembrolizumab	18 (7.4)
Atezolizumab	21 (8.6)
Avelumab	1 (0.4)
Liver metastases	
Absent	183 (75)
Present	61 (25)
Lung metastases	
Absent	105 (43)
Present	139 (57)
25-hydroxyvitamin D level	
Vitamin D sufficiency (>20 ng/mL)	89 (36.5)
Vitamin D insufficiency (12-20 ng/mL)	85 (34.8)
Vitamin D deficiency (<12 ng/mL)	70 (28.7)

ECOG PS: Eastern Cooperative Oncology Group performance status; HNC: Head and neck cancer; ICI: Immune checkpoint inhibitor; RCC: Renal cell carcinoma; NSCLC: Non-small cell lung cancer; SCLC: Small cell lung cancer; HCC: Hepatocellular carcinoma; IQR: Interquartile range.

TABLE 2: Comparison of baseline characteristics according to vitamin D status (n=244).

Characteristics	Vitamin D sufficiency (n=89)	Vitamin D insufficiency (n=85)	Vitamin D deficiency (n=70)	p-value
Age				0.687
<65 years	49 (55.1)	52 (61.2)	42 (60)	
≥65 years	40 (44.9)	33 (38.8)	28 (40)	
Sex, n (%)				0.776
Male	57 (64)	54 (63.5)	48 (68.6)	
Female	32 (36)	31 (36.5)	22 (31.4)	
ECOG PS, n (%)				0.115
0-1	68 (81.9)	62 (77.5)	46 (67.6)	
2-3	15 (18.1)	18 (22.5)	22 (32.4)	
Primary tumor, n (%)				0.759
NSCLC	26 (29.2)	29 (34.1)	25 (35.7)	
RCC	17 (19.1)	19 (22.4)	10 (14.3)	
Melanoma	12 (13.5)	12 (14.1)	11 (15.7)	
HNC	6 (6.7)	9 (10.6)	7 (10)	
SCLC	2 (2.2)	1 (1.2)	3 (4.3)	
HCC	4 (4.5)	0 (0)	2 (2.9)	
Urothelial cancer	3 (3.4)	1 (1.2)	2 (2.9)	
Sarcoma	1 (1.1)	2 (2.4)	2 (2.9)	
Others	18 (20.2)	12 (14.1)	8 (11.4)	
Treatment line, n (%)				0.779
1-2	50 (56.2)	51 (60)	43 (61.4)	
3 or later	39 (43.8)	34 (40)	27 (38.6)	
Liver metastases				0.520
Absent	65 (73)	62 (72.9)	56 (80)	
Present	24 (27)	23 (27.1)	14 (20)	
Lung metastases				0.761
Absent	39 (43.8)	34 (40)	32 (45.7)	
Present	50 (56.2)	51 (60)	38 (54.3)	

ECOG: Eastern Cooperative Oncology Group performance status; HNC: Head and neck cancer; RCC: Renal cell carcinoma; NSCLC: Non-small cell lung cancer; SCLC: Small cell lung cancer; HCC: Hepatocellular carcinoma.

demonstrated that vitamin D deficiency (HR: 2.23, 95% CI: 1.53-3.24) remained independently associated with shorter OS.

For progression-free survival (PFS), univariable analysis showed that ECOG PS ≥2 (HR: 1.504, 95% CI: 1.095-2.065, p=0.012) and lower vitamin D levels were associated with inferior outcomes. Compared with vitamin D sufficiency, insufficiency was associated with an HR of 1.610 (95% CI: 1.159-2.235; p=0.004), and deficiency was associated with an HR of 2.178 (95% CI: 1.549-3.064; p<0.001). In the multivariable analysis, both vitamin D insufficiency (HR: 1.494, 95% CI:

1.067-2.092; p=0.019) and vitamin D deficiency (HR: 2.0, 95% CI: 1.411-2.833; p<0.001) remained independent predictors of shorter PFS (Table 4). Median PFS was 10.4 months (95% CI: 7.0-13.7) for the vitamin D sufficiency group, 5.5 months (95% CI: 4.1-6.9) for the vitamin D insufficiency group, and 3.5 months (95% CI: 2.0-4.9) for the vitamin D deficiency group (Figure 3). Additional sensitivity analyses stratified by tumor type demonstrated that both vitamin D insufficiency (HR: 1.56, 95% CI: 1.11-2.19) and vitamin D deficiency (HR: 2.06, 95% CI: 1.45-2.92) remained independently associated with shorter PFS.

TABLE 3: Univariable and multivariable analyses for OS.

Variable	Univariable			Multivariable		
	HR	95% CI	p	HR	95% CI	p
Age (≥ 65 vs. <65)	0.999	0.738-1.351	0.994			
Sex (male vs. female)	1.107	0.808-1.515	0.527			
ECOG status (≥2 vs. <2)	1.670	1.178-2.369	0.004	1.570	1.101-2.238	0.013
Liver metastases at baseline (yes vs. no)	1.231	0.885-1.714	0.217			
Lung metastases at baseline (yes vs. no)	1.319	0.975-1.785	0.072	1.292	0.944-1.770	0.110
ICI treatment line (1-2 vs. 3 or later)	1.010	0.750-1.360	0.948			
ICI agent (nivolumab vs. others)	1.297	0.914-1.841	0.146			
Tumor type	1.099	0.975-1.261	0.182			
Vitamin D status (vitamin D sufficiency)	Ref			Ref		
Vitamin D insufficiency	1.462	1.012-2.113	0.043	1.380	0.944-2.017	0.096
Vitamin D deficiency	2.315	1.606-3.337	<0.001	2.264	1.553-3.300	<0.001

ECOG: Eastern Cooperative Oncology Group; ICI: Immune checkpoint inhibitor; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval.

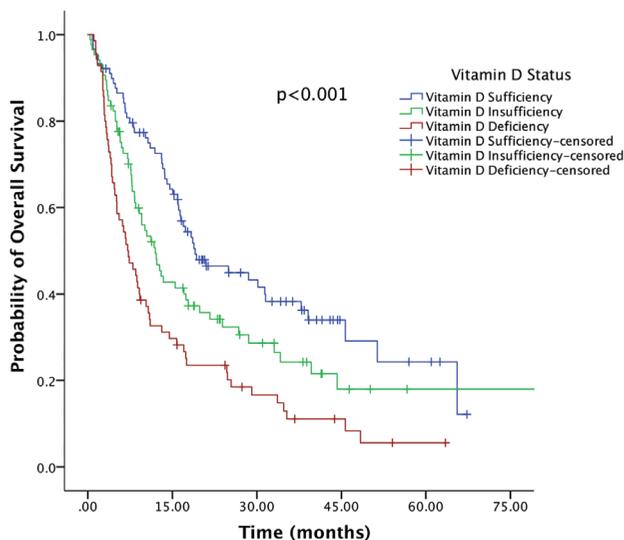


FIGURE 2: Overall survival of patients according to vitamin D status.

TABLE 4: Univariable and multivariable analyses for PFS.

Variable	Univariable			Multivariable		
	HR	95% CI	p	HR	95% CI	p
Age (≥ 65 vs. <65)	0.984	0.748-1.293	0.906			
Sex (male vs. female)	0.979	0.739-1.296	0.880			
ECOG status (≥2 vs. <2)	1.504	1.095-2.065	0.012	1.432	1.042-1.968	0.027
Liver metastases at baseline (yes vs. no)	1.260	0.931-1.705	0.134			
Lung metastases at baseline (yes vs. no)	1.250	0.951-1.644	0.110			
ICI agent (nivolumab vs. others)	1.119	0.800-1.566	0.510			
Tumor type	1.060	0.934-1.202	0.368			
ICI treatment line (1-2 vs. 3 or later)	1.143	0.872-1.499	0.334			
Vitamin D status (vitamin D sufficiency)	Ref			Ref		
Vitamin D insufficiency	1.610	1.159-2.235	0.004	1.494	1.067-2.092	0.019
Vitamin D deficiency	2.178	1.549-3.064	<0.001	2.000	1.411-2.833	<0.001

ECOG PS: Eastern Cooperative Oncology Group; ICI: Immune checkpoint inhibitor; PFS: Progression-free survival; HR: Hazard ratio; CI: Confidence interval.

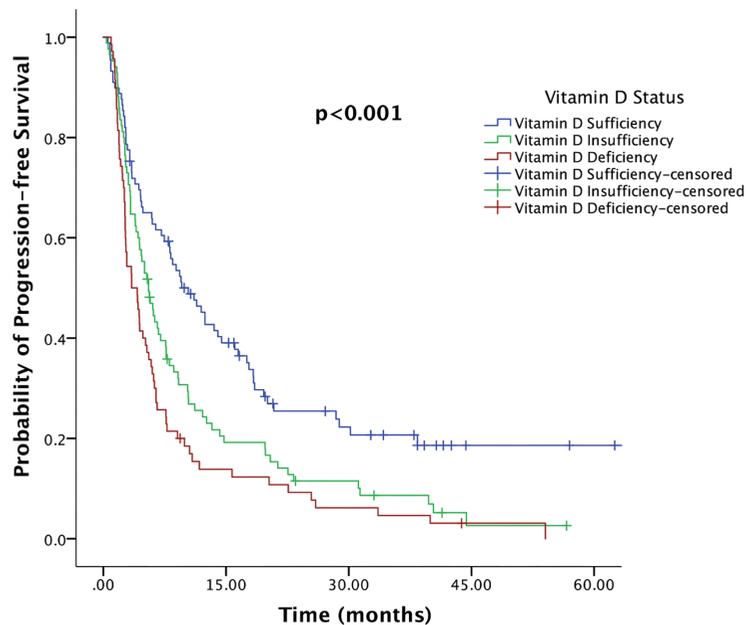


FIGURE 3: Progression-free survival of patients according to vitamin D status.

DISCUSSION

In this study, we observed that baseline serum vitamin D deficiency was independently associated with shorter PFS and OS in patients with advanced malignancies receiving ICIs. These results indicate that profound vitamin D deficiency may represent a clinically relevant biomarker of poor clinical outcomes in the immunotherapy setting, potentially reflecting impaired antitumor immunity and host nutritional-inflammatory status.

The prevalence of vitamin D deficiency varies across cancer populations but remains consistently high. In a prospective cohort of 77 patients with advanced NSCLC receiving ICIs, You et al.¹⁸ reported vitamin D sufficiency (>20 ng/mL) in only 33.8% of patients, insufficiency (10-20 ng/mL) in 55.9%, and deficiency (<10 ng/mL) in 10.4%. In a recent cohort of 120 prostate cancer patients in a sun-rich climate, Hasan et al.¹⁹ reported a median serum vitamin D level at diagnosis of 35.4 ng/mL (range: 7.8 to 120 ng/mL); vitamin D deficiency, defined as less than 20 ng/mL, was present in 12.5% of patients. In a cohort largely comprising patients with advanced disease and multiple prior lines of therapy, the observed prevalence of vitamin D deficiency (<12 ng/mL) was 28.7%. This exceeds rates reported in previous studies, implying that vitamin D deficiency may be especially common in heavily pretreated, advanced-stage patient groups and may hold prognostic importance.

Numerous investigations have focused on vitamin D's potential anticancer effects. Lower serum 25(OH)D is

associated with higher incidence and mortality from lung cancer, according to two meta-analyses.^{20,21} In another study, which included 4038 patients with 11 different malignancies and a median follow-up of 15.6 years, higher prediagnostic serum 25(OH)D concentrations were associated with improved OS (HR: 0.83, 95% CI: 0.70-0.98 for highest vs lowest quintile) and lung cancer-specific survival (HR: 0.63, 95% CI: 0.44-0.90).²² However, evidence on the prognostic role of vitamin D in the immunotherapy era is limited. In advanced melanoma, Galus et al.²³ reported that patients who maintained normal vitamin D levels, either at baseline or through effective supplementation during anti-PD-1 therapy, achieved significantly higher objective response rates (56% vs. 36.2%, $p=0.0111$) and longer median PFS (11.25 vs. 5.75 months, $p=0.0378$) compared with those with persistently reduced levels, although no statistically significant difference in OS was observed (31.5 vs. 27 months, $p=0.39$). In a prospective NSCLC cohort, higher baseline 25(OH)D levels were associated with improved OS; the vitamin D-sufficient group demonstrated a significant benefit compared with the insufficient and deficient groups (HR: 0.45, 95% CI: 0.25-0.81). Median PFS was longer in vitamin D-sufficient patients (606 days vs. 326 and 308 days), although these differences were not statistically significant ($p=0.12$). Perhaps most compellingly, a large multi-center analysis of over 3,000 ICI-treated patients (across various tumor types) found that baseline vitamin D deficiency was independently associated with significantly shorter OS (HR: 2.06, 95% CI: 1.21-3.52), whereas pre-treatment vitamin D supplementation was

associated with improved survival outcomes (HR: 0.69, 95% CI: 0.52-0.92), regardless of the season of ICI initiation.²⁴ Our results are consistent with emerging evidence showing that baseline vitamin D deficiency independently predicted poorer OS, while both insufficient and deficient vitamin D levels predicted shorter PFS. Collectively, these findings suggest the potential prognostic value of baseline vitamin D status in patients receiving ICIs, highlighting that either insufficient or deficient levels may adversely affect survival outcomes.

The biological mechanisms underlying this association are an active area of research. Vitamin D inhibits tumor growth primarily by inducing cell-cycle arrest via upregulation of the CDK inhibitors p21 and p27 and downregulation of cyclins.²⁵ Vitamin D also promotes apoptosis by increasing pro-apoptotic BAX and decreasing anti-apoptotic BCL2 and BCLXL, suppresses angiogenesis by reducing vascular endothelial growth factor and other pro-angiogenic factors, and mitigates DNA damage by enhancing DNA repair.^{26,27} Vitamin D also serves as a key immunomodulator in the antitumor immune response, enhancing the cytotoxic activity of macrophages, neutrophils, and NK cells, as well as modulating cytokine secretion to create a tumor-suppressive immune microenvironment. Vitamin D can also influence the gut microbiome, particularly the abundance and metabolic activity of *Bacteroides fragilis*, which have been linked to improved responses to ICIs.¹⁴ The vitamin D receptor (VDR), expressed on most immune cells, regulates transcription of numerous target genes; a low VDR-related gene signature (vitamin D-VDR sign) has been associated with worse outcomes in multiple cancers.^{28,29} Furthermore, vitamin D levels correlate with immune checkpoint regulation, as serum levels have been linked to PD-1 expression on CD8⁺ T-cells in NSCLC, suggesting a potential mechanistic basis for its interaction with immunotherapy.³⁰

Study Limitations

Despite the intriguing findings, our study has several important limitations. First, the retrospective and single-institution nature of our study may introduce selection biases and unmeasured confounding variables. Second, we used only one baseline measurement of 25(OH)D taken prior to ICI initiation, without serial monitoring. Vitamin D levels can fluctuate with seasonal exposure, supplementation, and acute-phase reactions; therefore, a single measurement may not reflect the patient's vitamin D status throughout therapy. Moreover, information regarding vitamin D supplementation during follow-up, including dose, duration, and adherence, was not systematically available and could not be analyzed. We also did not record the number of vitamin D-deficient patients

who subsequently received vitamin D supplementation, which could have partially mitigated the deficiency during follow-up. Finally, we did not collect detailed data on other potential confounders, such as nutritional intake, body mass index, sarcopenia, systemic inflammation, and malnutrition, or on concurrent medications that could influence vitamin D levels. Furthermore, established predictive biomarkers for immunotherapy efficacy, such as PD-L1 expression, tumor mutational burden, and MSI status, were not routinely available and could not be incorporated into the analyses. Given these limitations, our findings should be considered hypothesis-generating and require additional validation in larger, prospective studies.

CONCLUSION

In conclusion, our study results suggest that baseline serum Vitamin D level may serve as a prognostic marker in ICI-treated patients. Given its potential influence on immune function and treatment outcomes, integrating vitamin D assessment into pretreatment evaluation may facilitate risk stratification and inform supportive care strategies. We think that the prognostic value of baseline serum Vitamin D levels as a candidate prognostic biomarker should be evaluated in prospective clinical studies.

Ethics

Ethics Committee Approval: The authors state that they have obtained Hacettepe University Health Sciences Research Ethics Committee approval (date: 26.08.2025, approval number: SBA 25/743).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: T.K.Ş., S.A., B.Y.A., D.C.G., Design: T.K.Ş., D.C.G., Data Collection or Processing: T.K.Ş., O.B., G.K., N.G., F.Ş., S.A., Z.A., N.K., Ö.D., M.E., Ş.Y., S.A., B.Y.A., D.C.G., Analysis or Interpretation: T.K.Ş., B.Y.A., D.C.G., Literature Search: O.B., G.K., N.G., F.Ş., Writing: T.K.Ş., S.A., Z.A., N.K., Ö.D., M.E., Ş.Y., S.A., B.Y.A., D.C.G.

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