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Serum Vitamin D as a Predictor of Immunotherapy Response in Advanced Non-small Cell Lung Cancer

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ABSTRACT

Aim: Vitamin D is known to exert immunomodulatory effects and may influence the therapeutic efficacy of immune checkpoint inhibitors in patients with non-small cell lung cancer (NSCLC). This study aimed to evaluate the relationship between baseline serum vitamin D levels and survival outcomes in NSCLC patients treated with nivolumab.

Methods: In this retrospective study, we analyzed patients with stage IV NSCLC who received nivolumab as second-line therapy at a single tertiary center between October 2022 and September 2024. Patients were stratified based on baseline serum 25-hydroxyvitamin D levels into sufficient (≥20 ng/mL) and insufficient (<20 ng/mL) groups. Progression-free survival (PFS) and overall survival (OS) were assessed using the Kaplan-Meier method and compared using the log-rank test.

Results: A total of 39 patients were included in the final analysis. Of these, 16 (41.0%) had sufficient vitamin D levels, whereas 23 (59.0%) were classified as insufficient. Median PFS was longer in the sufficient group than in the insufficient group (10.1 vs. 4.6 months), although this difference was not statistically significant (p=0.292). Similarly, median OS favored the sufficient group (17.3 vs. 11.7 months), although this difference did not reach statistical significance (p=0.823).

Conclusion: Baseline vitamin D status may be associated with survival outcomes among patients with NSCLC receiving nivolumab. Although statistical significance was not achieved, the observed trends suggest a potential prognostic role of vitamin D. Further prospective studies are warranted to confirm these findings.

Keywords: Non-small cell lung cancer, immunotherapy, nivolumab, vitamin D, prognosis

Introduction

Non-small cell lung cancer (NSCLC) represents the most frequently diagnosed subtype of lung cancer and continues to be a major contributor to cancer-related mortality on a global scale [1]. Despite ongoing improvements in systemic treatment approaches, outcomes in advanced-stage disease remain limited [2].

The development of immune checkpoint inhibitors (ICIs), particularly those targeting the PD-1/PD-L1 pathway, has improved treatment options for patients with advanced NSCLC by enhancing anti-tumor immune activity [3]. However, not all patients benefit from these therapies, and considerable variability in treatment response persists. Although biomarkers such as PD-L1 expression and tumor mutational burden are commonly used in clinical practice, their predictive capacity remains incomplete [4].

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Beyond tumor-related characteristics, patient-related factors may also influence treatment outcomes. Vitamin D has been increasingly recognized for its role in immune regulation in addition to its classical functions in bone metabolism [5]. Its active metabolite, calcitriol, interacts with the vitamin D receptor, which is expressed in various immune cells, including T lymphocytes, dendritic cells, and macrophages [6]. Through these interactions, vitamin D may affect both innate and adaptive immune responses, potentially influencing anti-tumor immunity [7,8].

Low vitamin D levels are frequently observed in oncology patients and have been linked to less favorable clinical outcomes across different malignancies [9,10]. However, the relationship between vitamin D status and survival remains inconsistent across studies. While some reports have not identified a clear association [11], others have demonstrated improved outcomes in patients with higher circulating levels of 25-hydroxyvitamin D [25(OH)D] [12].

More recently, attention has focused on the potential interaction between vitamin D and immunotherapy outcomes. Some studies suggest that sufficient vitamin D levels may be associated with improved survival in patients receiving ICIs [13]. In addition, evidence from melanoma indicates that vitamin D supplementation may enhance response to PD-1 inhibition [14].

Given the limited data specifically addressing patients with NSCLC treated with ICIs, the present study aimed to evaluate the association between baseline serum vitamin D levels and survival outcomes, including progression-free survival (PFS) and overall survival (OS) in patients with advanced NSCLC receiving nivolumab.

Methods

This retrospective, single-center study, conducted at a tertiary oncology center, included patients with stage IV NSCLC who received nivolumab as second-line treatment between October 2022 and September 2024. Clinical data were retrospectively collected from electronic medical records.

Patient eligibility was determined based on the availability of key clinical information. Patients were eligible if they were aged ≥18 years, had histologically confirmed metastatic NSCLC, received at least one cycle of nivolumab, and had available baseline serum 25(OH)D measurements obtained before treatment initiation. Cases with missing essential data or insufficient follow-up were excluded from the analysis.

The study was approved by the Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee (approval no: AEŞH-BADEK-2024-931, date: 27.11.2024). The research was conducted in line with accepted ethical principles, and patient identities were not disclosed at any stage of data handling.

Relevant clinical details were retrieved from hospital records. These included demographic characteristics, disease-related variables, and treatment timelines. Information regarding disease status and follow-up was also reviewed.

Patients were followed during routine clinical visits and underwent radiological evaluations performed according to institutional practice standards.

Disease progression was determined based on radiological and clinical evaluation according to institutional practice.

Vitamin D status was assessed using baseline serum measurements. For analytical purposes, patients were grouped according to a predefined threshold into those with sufficient vitamin D levels and those with insufficient levels.

PFS was defined as the interval between nivolumab initiation and documented disease progression or death from any cause. OS was defined as the interval from nivolumab initiation to death from any cause or to the last follow-up.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics software (version 26.0; IBM Corp., Armonk, NY, USA). Survival analyses were conducted using the Kaplan-Meier method and compared using the log-rank test. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. A two-sided p value <0.05 was considered statistically significant.

Results

Patient Characteristics

The analysis included 39 patients who met the study criteria. According to baseline serum vitamin D levels, 16 patients (41.0%) were classified as vitamin D sufficient (≥20 ng/mL), whereas 23 patients (59.0%) were categorized as vitamin D deficient (<20 ng/mL). The median baseline vitamin D level was 17 ng/mL (range: 4-45 ng/mL).

The clinical and demographic characteristics of the cohort are summarized in Table 1. The proportion of male patients was similar in the two groups (81.3% in the sufficient group vs. 78.3% in the deficient group; p=0.820). Patients in the sufficient vitamin D group were more frequently aged ≥65 years compared to those in the deficient group (81.3% vs. 47.8%, p=0.035).

The groups were comparable in terms of ECOG performance status (p=0.514), histological subtype (p=0.440), and extent of metastatic disease (p=0.357).

Survival Outcomes

Patients with sufficient baseline vitamin D levels had a longer median PFS compared with those with deficient levels [10.1 months [95% confidence interval (CI): 0.1-20.8] vs. 4.6 months (95% CI: 2.9-6.2)]. However, this difference was not statistically significant (p=0.292; Figure 1).

A similar pattern was observed for OS. The median OS was 17.3 months (95% CI: 3.8-30.9) in the vitamin D sufficient group and 11.7 months (95% CI: 0.1-23.5) in the vitamin D deficient group, and this difference was not statistically significant (p=0.823; Figure 2).

Given the limited sample size, multivariable Cox regression analysis was not performed.

Table 1. Baseline clinical and demographic characteristics of patients with advanced NSCLC receiving nivolumab, according to serum vitamin D status

Characteristic	Sufficient vitamin D (≥20 ng/mL) n (%)	Insufficient vitamin D (<20 ng/mL) n (%)	p value
Sex			0.820
- Female	3 (19%)	5 (22%)	
- Male	13 (81%)	18 (78%)	
Age			0.035
- < 65 years	3 (19%)	12 (52%)	
- ≥ 65 years	13 (81%)	11 (48%)	
ECOG performance status			0.514
- 0	3 (19%)	5 (22%)	
- 1	11 (69%)	12 (52%)	
- 2	2 (12%)	6 (26%)	
Histological subtype			0.440
- Squamous cell carcinoma	5 (31%)	10 (44%)	
- Adenocarcinoma	11 (69%)	13 (56%)	

ECOG: Eastern Cooperative Oncology Group, NSCLC: Non-small cell lung cancer

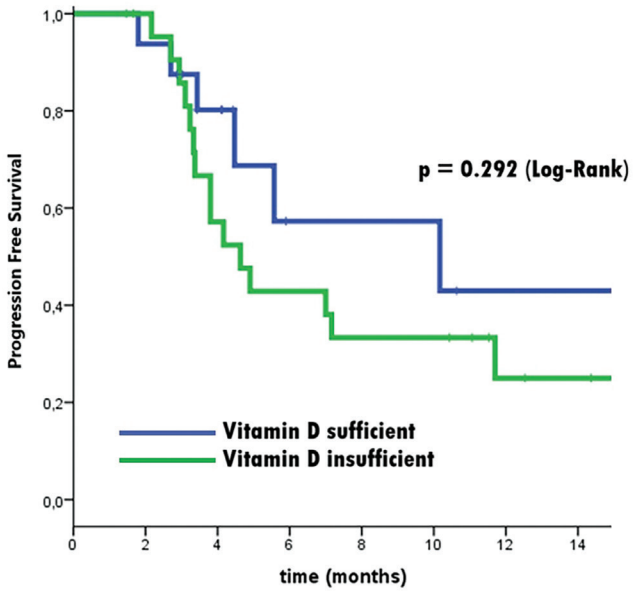

Figure 1. Kaplan-Meier curve for progression-free survival according to baseline serum vitamin D status (p=0.292, log-rank test)

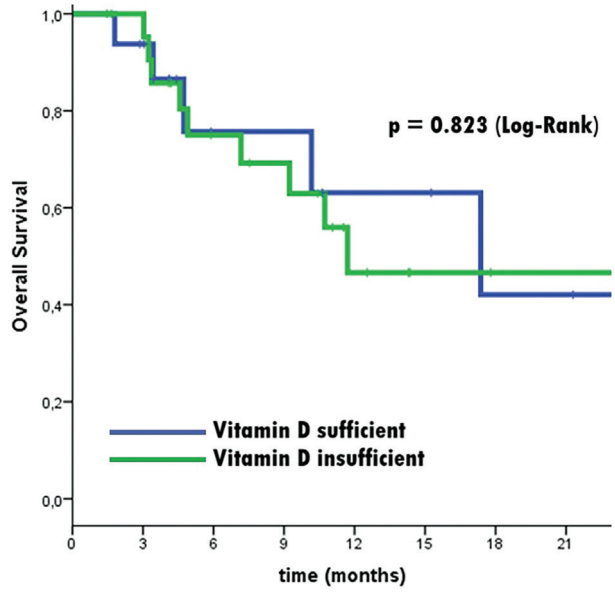

Figure 2. Kaplan-Meier curve for overall survival according to baseline serum vitamin D status (p=0.823, log-rank test)

Discussion

The findings of this study indicate a trend toward improved survival in patients receiving nivolumab who had higher baseline vitamin D levels. Although these differences did not reach statistical significance, the direction of the findings suggests that vitamin D status may still have clinical relevance in patients receiving ICIs.

The lack of statistical significance is likely attributable to the limited sample size and the inherent variability of retrospective cohort studies. Small patient numbers reduce the ability to detect modest differences, even when a consistent pattern is present. Despite this limitation, our observations are in line with previous reports suggesting that adequate vitamin D levels may be associated with improved outcomes and reduced treatment-related toxicity in patients receiving immunotherapy [13-17].

Rather than acting through a single pathway, vitamin D appears to contribute to overall immune balance. It may support a more controlled immune response by influencing inflammatory signaling and maintaining equilibrium between immune activation and regulation. In the setting of cancer, such an effect could help sustain anti-tumor activity while preventing excessive immune reactions. This broader

perspective may partially explain the differences observed between patient groups.

An additional finding in our cohort was that patients with sufficient vitamin D levels tended to be older, yet had numerically better survival outcomes. This observation suggests that vitamin D status may have prognostic value beyond age alone. Considering that aging is associated with gradual decline in immune function, adequate vitamin D levels may help preserve immune competence in older individuals [18-20].

Vitamin D status is also influenced by individual biological variability. Differences in metabolism, distribution, and binding proteins may affect circulating 25(OH)D levels and their functional impact. These factors indicate that vitamin D biology is complex and may not be fully reflected by a single baseline measurement [21].

Although vitamin D deficiency has been associated with poorer outcomes in various malignancies, data specific to NSCLC patients receiving ICIs remain limited. Our findings contribute to this field by suggesting that vitamin D status may represent a relevant host-related factor influencing treatment outcomes [9,22,23].

From a clinical perspective, vitamin D is a potentially modifiable parameter. Given its accessibility, low cost, and favorable safety profile, assessing and correcting deficiencies may represent a simple supportive strategy in oncology practice. However, whether supplementation directly improves immunotherapy efficacy requires further investigation.

Study Limitations

Several limitations should be considered when interpreting these results. The retrospective single-center design introduces potential selection bias, information bias, and unmeasured confounding, which should be considered when interpreting the findings. The relatively small sample size limits statistical power. In addition, factors such as nutritional status, comorbidities, and vitamin D supplementation were not fully evaluated. The absence of longitudinal vitamin D measurements also prevents assessment of dynamic changes during treatment. The limited sample size may have reduced the ability to detect statistically significant differences in survival, despite the observed numerical trends favoring patients with sufficient vitamin D levels.

Future Directions

Larger prospective studies are needed to confirm these findings. Future research integrating clinical, molecular, and immunological parameters may provide a more comprehensive understanding of the relationship between vitamin D and immunotherapy. In addition, interventional studies evaluating vitamin D supplementation could help clarify its potential therapeutic role.

Conclusion

Baseline vitamin D levels may be associated with clinical outcomes in patients with advanced NSCLC receiving nivolumab. Although statistical significance was not observed, the consistent trend toward improved outcomes supports further investigation in larger prospective studies.

Ethics

Ethics Committee Approval: The study was approved by the Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee (approval no: AEŞH-BADEK-2024-931, date: 27.11.2024).

Informed Consent: This is a retrospective study, therefore patient consent was not required.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.Ç., Ö.A.İ., B.Ö., D.M.K., Concept: S.Ç., O.S., K.B., S.D.Ş., B.Ö., D.M.K., Design: S.Ç., O.S., Ö.A.İ., A.T.A., B.Ö., D.M.K., Data Collection or Processing: S.Ç., K.B., S.D.Ş., Ş.E., D.M.K., Analysis or Interpretation: S.Ç., A.T.A., D.M.K., Literature Search: S.Ç., S.K., E.Z., Ş.E., D.M.K., Writing: S.Ç., S.K., E.Z., D.M.K.

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