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Research Article

Vitamin D Efficacy on Prognosis of Bladder Cancer Patients

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Abstract

Objectives: This study aimed to investigate the predictive value of vitamin D levels in patients with bladder cancer before systemic treatment.

Methods: A total of 125 bladder cancer patients were included in the study. The Kaplan–Meier method was used to estimate overall survival (OS) and progression-free survival (PFS), and the long-rank test was used for comparison. Univariate and multivariate Cox proportional hazards models were used to determine the association vitamin D and OS.

Results: The measured PFS and OS of the patients were 260.7 weeks and 323.6 weeks, respectively. Receiver operating characteristic analysis revealed that vitamin D level <12.5 ng/dl was determined as the optimal cutoff value for OS prediction with the sensitivity of 62.5% and specificity of 58.5% (AUC:0.633, p=0.01). After adjustment for the number of covariates, multivariate Cox regression analysis identified a lower vitamin D level as an independent predictive factor of worse OS (hazard ratio: 2.774, 95% confidence interval: 1.486–5.178, p=0.001).

Conclusion: Our results suggested that vitamin D level might function as an independent predictor in patients with bladder cancer before systemic treatment.

Keywords: Bladder cancer, overall survival, prognostic factors, progression-free survival, vitamin D level

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Bladder cancer (BC) is the world's tenth most common type of cancer.[1] Environmental, demographic, and genetic factors are all known to play a role in the development of BC.[2] Vitamin D is a highly active steroid prohormone converted into biologically active metabolites that bind to its nuclear receptors and influence various physiological processes.[3] It has been known for over a century to have a critical function in calcium metabolism and the skeletal system. On the other hand, vitamin D has been shown in preclinical studies to regulate tumor cell angiogenesis, invasion, and metastasis and diminish oxidative stress, which causes cell damage.[4]

The serum 25 (OH) D level is the most accurate indicator of vitamin D status in the human body.[5] Vitamin D deficiency, although most researchers disagree on the optimal level of vitamin D, is defined as a blood level of 20–30 ng/dL and is common throughout the world. One in every seven people globally suffers from vitamin D insufficiency, a level of less than 20 ng/dl.[6] Vitamin D insufficiency is more common in cancer patients. Numerous epidemiological studies have discovered a link between vitamin D deficiency and the chance of acquiring numerous types of cancer, including BC.[7] However, there was no agreement among them. In addition, in vitro and animal studies indicate that vitamin

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D may be beneficial against various cancers. Colorectal, prostate, and breast cancers are the cancers that have been studied the most intensively concerning vitamin D deficiency. Currently, research is examining the link between serum vitamin D levels and cancer prognosis in various cancer types.[8] Vitamin D has also been shown to play a role in human BC pathogenesis through cell culture, *in vivo*, and genetic studies.[9]

We conducted a retrospective cohort study to determine the predictive vitamin D level cut-off value associated with improved survival outcomes in patients diagnosed with locally advanced and metastatic BC before systemic treatment and to examine the effect of vitamin D deficiency on the disease process.

Methods

Patients

This retrospective observational study included 125 consecutive BC patients admitted to Pamukkale University Medical Oncology Department before receiving systemic therapy between January 2017 and April 2020 (Denizli, Turkey). We documented the baseline clinicopathologic characteristics. The majority of patients had high-grade uroepithelial carcinomas pathologically. Patients who were lost to follow-up had comorbidities (acute or chronic inflammatory diseases), or brain metastasis, or had a prior history of cancer were excluded. Patients had bladder cancer that was either locally advanced or distant metastatic.

The serum 25 (OH) D, parathyroid hormone (PTH), thyroid-stimulating hormone (TSH), calcium, albumin, hemoglobin, C-reactive protein (CRP), carcinoembryonic antigen (CEA), and lactate dehydrogenase (LDH) levels from routine biochemistry reports were obtained before treatment. Serum 25 (OH) D levels were determined using the immune measurement principle, which is based on an antigen-antibody reaction, in roche cobas 801 autoanalyzers. Throughout the study period, the measurement methodology remained constant. The ages, BCG treatment histories, cystectomy histories, radiotherapy histories, smoking histories, ECOG performance status, and bone metastasis status of patients were retrospectively analyzed from the files.

All procedures in this study were conducted per the Institutional and National Research Committee's ethical standards, the 1964 Helsinki Declaration, and its subsequent amendments. The Local Ethics Committee approved the study, and all research participants or their relatives provided written informed consent.

Statistical Analysis

Descriptive statistics were presented using the median and interquartile range, and categorical variables were presented using frequency and percent. The Chi-square test was used to evaluate categorical data, the Student's t-test was used to analyze numerical continuous data, and the Pearson test was used to determine correlation. Receiver operating characteristic (ROC) analysis was used to determine the cut-off values for serum vitamin D, TSH, calcium, albumin, LDH, and CRP levels. Survival analysis was performed using the Kaplan–Meier method and the log-rank test. The overall survival (OS) period was defined as the time interval between diagnosis and death, and the progression-free survival (PFS) period as the time interval between diagnosis and disease progression, metastasis, or death for any reason. Hazard ratios (HR) and confidence intervals (CI) were calculated using the Cox proportional hazards model to assess the effect of parameters on survival. $P<0.05$ was considered significant. SPSS 25 version (Chicago, IL, USA) was used for statistical analysis.

Results

Baseline Patient Characteristics

This cohort study consisted of 125 patients diagnosed with BC (Male/Female: 114/11) who have no prior systemic therapy after exclusion of patients with malnutrition, inflammatory diseases, and acute infectious that can affect the vitamin D values, and patients who were lost to follow-up. Table 1 summarizes the demographic and clinicopathologic characteristics of the study population stratified by vitamin D levels. All patients had locally advanced or metastatic BC with transitional cell carcinoma pathogenesis and received platinum-based chemotherapy (platinum + gemcitabine). In 64 patients, progression occurred (51.2%). During the median follow-up period of 147 weeks, a total of 53 (42.4%) deaths were recorded (minimum-maximum: 4–700).

The median vitamin D level of the group as a whole was 12.7 (3–75) ng/mL. ROC analysis was used to determine the cutoff values for all parameters. ROC analyses revealed that a vitamin D concentration of 12.5 ng/mL was the optimal cutoff point for predicting OS, with a sensitivity of 62.5% and specificity of 58.5% (AUC:0.633, 95% Confidence interval [CI] =0.534–0.732). Table 2 shows the ROC analysis results for risk factors affecting OS. ROC analysis determined p values for serum calcium, CEA, and creatinine levels to be non-significant. PTH levels were not included in the ROC analysis, because not all patients had PTH levels recorded. Table 3 summarizes the OS and PFS values for patient characteristics. Patients receiving BCG and having bone metastases significantly affect OS and PFS.

Table 4 summarizes the results of ROC analyses used to determine the OS values according to the cutoff values.

Table 1. Baseline clinicopathologic characteristics of the patients stratified based on Vitamin D level cut-off

Characteristics	All patients (n=125, (%))	Vitamin D level <12.5 ng/ml (n=58, (%))	Vitamin D level >12.5 ng/ml (n= 67, (%))	p-value
Median age (years)	65.2 ± 10.1	66.5 ± 10.1	64.1± 10.0	0.18
Gender				
Male	114 (91.2)	50 (86.2)	64 (95.5)	0.06
Female	11 (8.8)	8 (13.8)	3 (4.5)	
BCG treatment history				
Yes	21 (16.8)	9 (15.5)	12 (17.9)	0.45
No	104 (83.2)	49 (84.5)	55 (82.1)	
Cystectomy history				
Yes	58 (46.4)	22 (37.9)	36 (53.7)	0.06
No	67 (53.6)	36 (62.1)	31 (46.3)	
Definitive Radiotherapy				
Yes	15 (12)	8 (13.8)	7 (10.4)	0.36
No	110 (88)	50 (86.2)	60 (89.6)	
Bone metastasis				
Yes	21 (16.8)	7 (12.1)	14 (20.9)	0.14
No	104 (83.2)	51 (87.9)	53 (79.1)	
Smoking history				
Smoker	89 (71.2)	39 (67.2)	50 (74.6)	0.23
Non-smoker	36 (28.8)	19 (32.8)	17 (25.4)	
Progression				
Yes	64 (51.2)	34 (58.6)	30 (44.8)	0.08
No	61 (48.8)	24 (41.4)	37 (55.2)	

Continuous variables were given as median with interquartile range. Dichotomous variables were given as percentages. BCG treatment: 'Bacillus Calmette-Guerin' treatment.

Table 2. Cut-off values of risk factors affecting OS by ROC analysis

Risk factors	Area (95% CI)	Cut off	p-value	Sensitivity (%)	Specificity (%)
Vitamin D (ng/ml)	0.633 (0.534-0.732)	12.5	0.01	62.5	58.5
Albumin (g/L)	0.732 (0.643-0.822)	3.85	0.000	66.0	61.0
CRP (mg/L)	0.773 (0.689-0.856)	1.05	0.000	67.9	69.4
Hemoglobin (g/dL)	0.782 (0.695-0.870)	11.9	0.000	69.8	80.6
Age (years)	0.667 (0.572-0.762)	64.5	0.001	62.3	52.8
TSH (mU/L)	0.609 (0.504-0.714)	0.95	0.04	64.0	55.4
LDH (U/L)	0.634 (0.533-0.755)	185	0.008	62.3	54.2

The Impact of Vitamin D Level on Survival Outcomes

The study population's median PFS and OS were 260.7 (95% CI=200.8-320.5) and 323.6 (95% CI=258.1–389.1) weeks, respectively. Using Kaplan–Meier survival analysis, we discovered that patients with a higher vitamin D level had a longer PFS and OS than those with a lower vitamin D level (PFS: 309.2 weeks vs. 196.1 weeks, p=0.01; OS: 391.2 weeks vs. 242 weeks, p=0.002, respectively) (Figs. 1 and 2).

As shown in Table 5, multivariate Cox analysis revealed that low vitamin D status at treatment initiation was associated with poor OS (HR: 2.774, 95% CI=1.486–5.178, p=0.001, Table 5). Along with vitamin D levels, age (>65) (HR: 1.994, 95% CI=1.079–3.686, p=0.028), the absence of a history of BCG treatment (HR: 2.983, 95% CI=1.216–7.319, p=0.017), and high serum CRP level (HR: 1.072, 95% CI=1.027–1.120, p=0.002) were revealed to be independent predictors of OS.

Discussion

Even though epidemiologic evidence for vitamin D's effect on the risk and prognosis of locally advanced and metastatic BC is limited, in vitro and animal studies have dem-

Table 3. OS and PFS values of patients characteristics

Charecteristics	OS (weeks) (95% CI)	PFS (weeks) (95% CI)
All patients	323.65+33.42 (258.14–389.15)	260.72+30.52 (200.87–320.55)
Male	326.14+36.05 (255.47–396.82)	263.48+31.93 (200.88–326.08)
Female	241.62+51.29 (141.09–342.14)	171.44+54.80 (64.01–278.86)
	p=0.94	p=0.60
Definitive radiotherapy		
Yes	285.176+44.71 (197.54–372.80)	230.61+48.83 (134.89–326.33)
No	311.84+34.91 (243.40– 380.28)	254.77+31.49 (192.98–316.44)
	p=0.36	p=0.67
BCG history		
Yes	457.45+72.39 (315.55–599.35)	365.27+49.76 (267.73–462.80)
No	287.99+38.91 (211.72–364.25)	259.85+37.70 (185.96–333.75)
	p=0.010	p=0.023
Cystectomy history		
Yes	369.47+50.19 (271.08–467.86)	326.91+48.70 (231.45–462.38)
No	289.88+43.13 (205.34–374.43)	217.74+34.01 (151.10–284.39)
	p=0.30	p=0.163
Smoker	197.66+30.52 (137.83–257.41)	152.48+29.22 (95.20–209.71)
Non–smoker	357.86+40.73 (278.02 – 437.70)	203.82+37.34 (158.63–289.15)
	p=0.100	p=0.33
Bone metastasis		
Yes	166.05+36.36(93.77– 236.34)	137.39+32.51 (73.67–201.11)
No	366.36+37.58 (292.70– 440.02)	297.00+36.47 (255.51–368.49)
	p=0.010	p=0.011

Table 4. OS values according to cut off values of ROC analysis

Parameters	OS (Weeks) (95%CI)
Vitamin D <12.5ng/ml	242.01+46.30 (151.25–332.75)
Vitamin D >12.5ng/ml	391.27+45.96 (301.19–481.36)
	p=0.002
Albumin <3.85g/L	143.05+34.96 (74.51–211.59)
Albumin >3.85g/L	422.61+42.21 (339.87–505.35)
	p=0.000
CRP <1.05 mg/L	453.27+26.85 (91.45–196.72)
CRP >1.05 mg/L	144.09+45.80 (363.49–543.04)
	p=0.000
Hemoglobin <11.9 g/dL	139.75+21.04 (98.50–180.99)
Hemoglobin >11.9 g/dL	480.34+44.24 (393.61–567.7)
	p=0.000
Age >64.5 years	246.28+46.67 (154.79–337.77)
Age <64.5years	387.92+42.07 (295.67–480.18)
	p=0.035
TSH <0.95 mU/L	409.09+47.84 (315.31–502.87)
TSH >0.95 mU/L	194.55+24.52 (146.49–242.628)
	p=0.001
LDH >185 U/L	296.872+41.57 (215.38–378.35)
LDH <185 U/L	309.50+42.01 (227.16–391.84)
	p=0.08

onstrated that vitamin D has antineoplastic properties in cancer, including BC. Locally advanced and metastatic BC has a poor prognosis for various reasons, and it is critical to identify prognostic and predictive variables for this patient population. In this cohort study, circulating vitamin D levels before platin-based chemotherapy was associated with improved OS in patients with locally advanced or metastatic BC.

Dietary and skin-derived vitamin D is transformed in the liver to 25 hydroxyvitamin D3 (25 [OH] D3), which is then hydroxylated to form calcitriol (1,25 [OH] 2 D3) by the cytochrome P450 enzyme CYP27B1 in the kidneys.[10] Calcitriol is also locally synthesized by extrarenal CYP27B1, including many cancer cells, and acts in an autocrine, intracrine, or paracrine manner.[11] Both renal and extra-renal synthesized calcitriol bind to the nuclear vitamin D receptor in the cell and participate in signaling pathways by transcriptional regulation of anticancer genes involved in cell proliferation,[12] differentiation, apoptosis,[13, 14] inflammation,[15] angiogenesis,[16] and invasion-metastasis,[17] all of which contribute to the formation and progression of cancer. Calcitriol has been chiefly demonstrated to have cellular effects via genomic pathways, but it has also been shown to have cellular effects through non-genomic path-

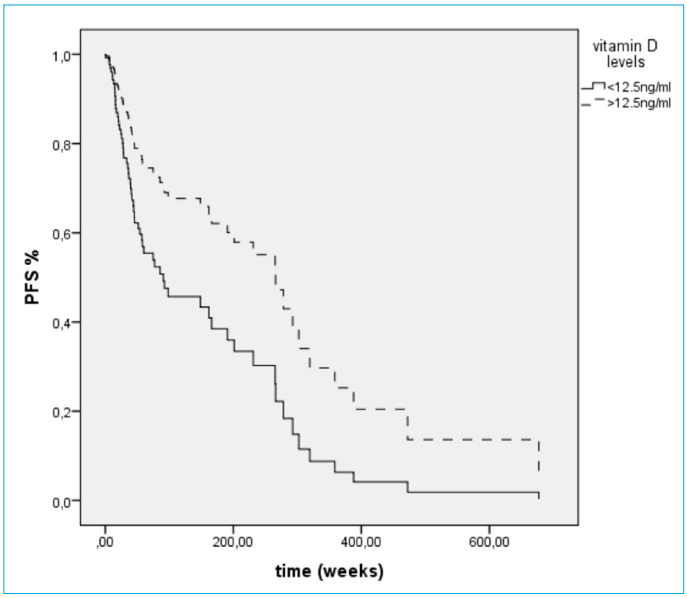

Figure 1. Demonstration of Kaplan–Meier curve stratified according to vitamin D for progression-free survival.

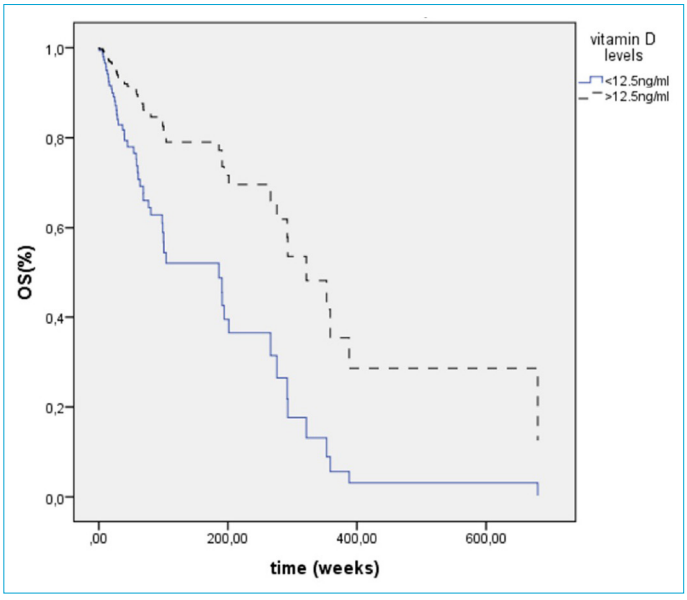

Figure 2. Demonstration of the Kaplan–Meier curve stratified according to vitamin D for overall survival.

ways.[18] The platinum-based chemotherapy regimen that is presently used to treat locally advanced and metastatic BC is the gold standard. Although the cisplatin-based combined regimen effectively treats BC, the low response rate and drug resistance appear significant clinical problems.[19] As a result, novel approaches to BC treatment are favorable. Cisplatin (cis-diammine-dichloro-platinum (II), cDDP) is a DNA-damaging drug that causes apoptosis in tumor cells by forming platinum-DNA adducts.[20] Calcitriol alters the antitumoral effects of chemotherapeutic drugs like cisplatin through a variety of mechanisms. Several studies have

Table 5. Multivariate Cox regression models analyzing the potential parameters for OS prediction

OS	HR			p-value
Age	1.994	1.079	3.686	0.028
BCG treatment				
No	2.983	1.216	7.319	0.017
Yes	Reference			
Albumin				
<3.85 g/L	Reference			
>3.85 g/L	0.555	0.272	1.131	0.105
TSH				
<0.95 mU/L	Reference			
>0.95 mU/L	1.019	0.995	1.042	0.121
CRP				
<1.05 mg/L	Reference			
>1.05 mg/L	1.072	1.027	1.120	0.002
LDH				
>185 U/L	Reference			
<185 U/L	0.999	0.998	1.001	0.303
Vitamin D				
<12.5 ng/ml	2.774	1.486	5.178	0.001
>12.5 ng/ml	Reference			
Hemoglobin				
<11.9 g/dL	Reference			
>11.9 g/dL	0.906	0.773	1.063	0.227

shown that calcitriol can benefit from cisplatin-based chemotherapy and has an anti-tumor effect in multiple malignancies.[21-24]

The results of a preclinic study indicate that pretreatment vitamin D levels enhance cisplatin-gemcitabine-induced apoptosis in BC cells, and this enhancement involves the activation of caspases 8, 9, and 3.[25] In a recent study, combined therapy (calcitriol and cisplatin-based chemotherapy) reduced P-glycoprotein (P-gp), associated with drug resistance, and advantageously altered apoptosis in BC cells.[26] According to these preclinical studies, calcitriol is effective in treating BC, and adding calcitriol to platinum-based chemotherapy might be beneficial.

The effect of vitamin D on various types of cancer arouses interest. In most epidemiological studies,[7, 27-29] the risk of developing BC was inversely related to vitamin D levels. Grant et al.[8] discovered that the evidence for the UVB-vitamin D-cancer hypothesis is generally robust.[7] This review cites two studies that discuss BC; a New Hampshire study found a strong correlation between vitamin D intake and the risk of developing BC.[30] Another study, which was done in Finland and had a 15-year follow-up, found that male smokers with lower serum vitamin D levels at the start of the study had a much higher risk of developing BC.[28]

In a meta-analysis of 2238 patients with homogeneously distributed BC, increased vitamin D levels reduced the risk of developing BC (Relative risk=0.75, 95% CI 0.65–0.87, p<0.001).[31] The relationship between vitamin D levels and cancer prognosis has garnered attention. According to a meta-analysis, vitamin D levels at diagnosis and cancer outcomes were significantly related. There was a 35% reduction in the risk of cancer-specific mortality in patients with colorectal cancer (pooled HR=0.65, 95% CI=0.47–0.88, p=0.005), a 35% reduction in patients with breast cancer (pooled HR=0.65, 95% CI=0.44–0.98, p=0.04), and a 50% reduction in patients with lymphoma (pooled HR=0.50, 95% CI=0.36–0.68, p=0.001). In addition, vitamin D levels at the time of diagnosis were associated with cancer outcomes in a limited number of prostate, head and neck, leukemia, melanoma, gastric, or Merkel cell cancer studies.[32]

In light of the results of these epidemiologic and preclinical studies, we planned to elucidate the possible effect of serum vitamin D levels in patients with locally advanced and metastatic BC before platin-based chemotherapy in this investigation. Numerous factors may influence the variation in circulating vitamin D levels; the most important of these are sunlight exposure and vitamin D intake. We did not collect information about the season of the blood test or the patient's sun exposure behaviors or outdoor activities. Regardless of the season, we established a cutoff value of 12.5 ng/ml for vitamin D level in patients with locally advanced and metastatic BC and demonstrated that vitamin D is an independent predictor of OS in multivariate analysis.[33] We observed improved OS in patients with vitamin D levels higher than 12.5 ng/ml (HR: 2.774, 95% CI: 1.486–5.118, p=0.001). Age (>65) (HR: 1.994, 95% CI: 1.079–3.686, p=0.028), BCG treatment history (HR: 2.983, 95% CI: 1.216–7.319, p=0.017), and CRP level (1.05 mg/L) (HR: 1.072, 95% CI: 1.027–1.120, p=0.002) were also identified as independent predictors of OS.

In summary, this cohort study reports that circulating vitamin D levels before first-line platin-based chemotherapy was related to poor survival outcomes in BC for the first time in the literature. However, our study has some limitations. First, our current study is a single-center and retrospective study. Second, our study did not examine factors that may affect vitamin D levels, such as sun exposure, body-mass index of the patient, and drugs used. Third, we could not collect PTH levels from all patient's records, so we could not evaluate another vitamin D-related disease. Even though our study strongly implies the importance of vitamin D in determining the prognosis of BC, the results should be confirmed by additional independent research and randomized clinical trials.

Conclusion

In our study, we evaluated our patients in terms of disease prognosis after being diagnosed with BC. We emphasized that low serum vitamin D levels may be a predictive value in our patients with BC by showing the relationship of poor survival. Due to the missing data from our study, such as PTH levels, seasonal vitamin D levels, and body mass index, it is possible to plan additional independent research and randomized clinical trials.

Disclosures

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was taken from Pamukkale University Ethical Comittee: 002.03.2021; Number 05.

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Conflict of Interest: None declared.

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