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Low Plasma 25-Hydoxyvitamin D at Diagnosis Predicts Poor Outcomes in Patients with Bladder Cancer: A Prospective Cohort Study

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ABSTRACT

This study aimed to investigate whether plasma 25-hydroxyvitamin D (25-OHD) at diagnosis predicts poor outcomes in patients with urothelial bladder cancer. A total of 177 patients with non-muscle-invasive bladder cancer (NMIBC) were prospectively followed up over a period extending beyond 6 years. Data on poor outcomes (ie., recurrence, progression, and mortality) were collected. Plasma 25-OHD was measured by immunoassay. Cutoff-Finder web application was used to determine the best 25-OHD cutoff point to predict a specific poor outcome. Cox-hazard models were applied to test how plasma 25-OHD affect patients outcome while adjusting for potential confounding factors. During the follow-up period, tumor recurrence and progression occurred in 40.7% and 14.1% of patients, respectively and 11.3% of patients died. Baseline 25-OHD was lower in patients who experienced poor outcome (12.2 ± 7.44 *vs.* 16.7 ± 10.6 ng/mL; $p < 0.001$). Multi-adjusted HR (95% CI) for vitamin D deficiency (25-OHD $<$ 12 ng/mL) was 2.09 (1.27-3.44) for recurrence, 2.63 (1.06-6.49) for progression and 2.93 (1.04-8.25) for mortality in patients with NMIBC. Low plasma 25-OHD in NMIBC patients is associated with higher risk of poor outcome. Future work is required to test whether correction of vitamin D deficiency will improve quality of life and extend survival in these patients.

Abbreviations: 1,25-di-OHD: 1,25 dihydroxyvitamin D; 25-OHD: 25-hydroxyvitamin D; BCG: Bacillus Calmette-Guerin; IOM: Institute of Medicine; MNIBC: muscle-invasive bladder cancer; NMIBC: non-muscle-invasive bladder cancer; TURBT: transurethral resection of the bladder tumor; UBC: urothelial bladder cancer; VD: vitamin D

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Introduction

Bladder cancer is a common urinary tract malignancy with frequent recurrence and treatment failure (1). Its incidence and mortality rates decreased in most Western countries but increased in developing countries (2). Urothelial bladder cancer (UBC) is the most common histological type accounting for 90% of bladder cancer cases (3). It is mainly diagnosed as non muscle invasive bladder cancer (NMIBC), with tumor confined to the epithelium or the sub epithelial connective tissue (1). NMIBC has an overall good prognosis, but a high likelihood of recurrence of 50–70% (4). It is also prone to progress to muscle-invasive bladder cancer, a potentially life threatening malignancy with a survival rate of only 30-50% (5). The most common treatment remains surgery, specifically transurethral resection of the bladder tumor (TURBT). Intravesical Bacillus Calmette-Guerin (BCG) immunotherapy is used as an adjuvant therapy for preventing recurrence in patients with noninvasive high grade or large tumor, or multiple tumors (6). BCG instillation induces a complex immune response with activation of immune cells and release of various cytokines resulting in antitumor activity (7). The management of UBC patients is considered to be the most expensive cancer in terms of lifetime cost per patient. Indeed, high recurrence rate of NMIBC require a lifelong surveillance by regular cystoscopic follow up and treatment of recurrences (8). Host factors including age, gender, tumor characteristics, and genetic profile are the main factors that affect UBC prognosis (9).

Vitamin D (VD) is a hormone-like micronutrient involved in several biological activities including cell

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proliferation, apoptosis, angiogenesis, and immune response, which makes it a candidate anticancer agent (10–12). VD originates mainly from skin synthesis following incidental skin exposure to sunlight with little derives from the diet (13). In the body, the molecule undergoes two-sequential hydroxylation; the first occurs in the liver resulting in 25 hydroxyvitamin D (25-OH). The second hydroxylation occurs in most tissues, but mainly in the kidneys giving 1,25 dihydroxyvitamin D (1,25-di-OHD). The latter form is the most active form of VD metabolites. However, circulating 25-OHD is the most suitable surrogate marker for body stores and the most used as marker for VD status (13). Evidence from systematic reviews and meta-analyses suggests that higher circulating 25-OHD levels are associated with better prognosis in patients with colorectal and breast cancer, while evidence is inconclusive for cancers in other sites (14–16). This highlights the need for studies evaluating the prognosis value of VD in other types of cancer. Data from recent meta-analyses suggest that low circulating 25-OHD levels are associated with a higher risk for developing UBC (17–19). However, plasma VD as a prognosis marker for UBC is unknown. In a prior report, low plasma 25-OHD was associated with higher risk of UBC occurrence in Tunisia (20), a region of high UBC incidence and mortality rates (21) and where hypovitaminosis D is common (22). The present study aimed to evaluate whether plasma 25-OHD at diagnosis predict poor outcomes in patients with UBC. For this purpose, we followed up patients with NMIBC and collected data on tumor recurrence, progression, and related mortality over a period extending beyond 6 years.

Subjects and Methods

Study Design and Participants

A prospective cohort study included consecutive patients who were diagnosed with NMIBC at the Department of Urology of Rabta Hospital (Tunis, Tunisia) between January 2012 and June 2014. Eligibility criteria to be enrolled in the study were being free of muscle or loco-regional invading or metastatic UBC, past/current cancer in other site, chemotherapy, other urogenital disease, intestinal, renal and liver disease, and current pregnancy. A surgical resection (ie., TURBT) was performed and the specimens were examined histopathologically. Patients with tumor of high grade or larger than 2 cm of size, or multiple tumors received intravesical BCG therapy. Histopathological examination allowed the determination of tumor characteristics (ie., histologic subtype, stage, grade, size, and number). Pathological stage was assigned according to the 2009 American Joint Committee on Cancer TNM staging system (23) and tumor grade according to the 1973 WHO grading system (24). Data on socio-demographics, medical history, skin phenotype, smoking status, and professional occupation were collected. Patients who smoked at least 100 cigarettes in their lifetime were considered as ever-smokers and those who never smoked or smoked less than 100 cigarettes were regarded as never-smokers. Occupational exposure was defined as having exerted for at least one-year-period one of the following professional occupations; building and painting, vehicles maintenance and repair, driving, plumbing and air-conditioning, farming and mining.

A total of 177 NMIBC patients responding to the criteria of eligibility were enrolled. They were followed until death or last follow-up visit, whichever occurred first. The primary endpoint was UBC recurrence, and tumor progression and UBC-related mortality were secondary endpoints. Recurrence was defined as the first time of tumor relapse regardless of tumor stage and grade. Progression was defined as muscle or loco-regional invasion, or metastasis. Outcome information was collected from medical records review or came from phoned patients or families. All patients gave their written informed consent prior to enrollment in the study. The study was approved by the institutional review board of Rabta Hospital. It was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Plasma 25-Hydroxyvitamin D Measurement

Fasting blood samples were collected from patients into EDTA-containing tubes and the plasma was separated and stored at −80 °C until analyzed (within 6 mo,). Blood was collected throughout the year and the time of blood sampling was ranked as high-sunshine season (May to October) or low-sunshine season (November to April). Plasma 25-OHD concentrations were measured by a competitive chemiluminescence immunoassay using the Liaison Analyzer and specific reagent kit (DiaSorin Inc., Stillwater, MN). Assay precision was tested with unmasked QCs and assay accuracy was checked using an external QCA program. The inter-assay CV was of 9.7%. According to The Institute of Medicine (IOM), vitamin D deficiency, insufficiency and sufficiency are defined as plasma 25-OHD concentration <12, 12–20, and ≥ 20 ng/mL, respectively (25).

Statistics

Statistical analysis was conducted using SPSS software (SPSS Inc., Chicago, IL). Cutoff Finder, a web application, enabling rapid biomarker cutoff optimization (26), was used to detect the optimal cutoff of plasma 25-OHD concentration for selected outcomes and to calculate the corresponding unadjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for NMIBC recurrence, progression, and related mortality and to map corresponding overview plots. Optimal cutoff is defined as the point with the most significant (log-rank test) split. Multivariable Cox-hazard models were applied to estimate survival curves with multi-adjusted HRs and their 95% CIs for NMIBC recurrence, progression, and related mortality by plasma 25-OHD classified as clinical categories (IOM criteria), season-specific tertiles, or Cutoff Finder outcome-specific thresholds. Adjustment was made for age (continuous), body mass index (continuous), gender (female/male), skin phenotype (fair/brown dark), tobacco smoking (never/ever) and occupational exposure (no/yes), BCG immunotherapy (no/yes), and tumor stage (pTa/pT1), grade (G1/G2/G3), number (single/multiple), and size (<1/1-3/≥3). Further adjustment for season of blood draw (low sunshine/high sunshine) was made for Cox-hazard model based on IOM criteria. Season-specific tertiles were calculated based on the distribution of plasma 25-OHD in all NMIBC patients and combined into a same variable.

Table 1. Baseline patients and tumors characteristics ($n = 177$).

Variable		UBC patients
Age , yr (mean ± SD)		64.8 ± 11.9
Sex ratio, male/female		154/23
Body mass index, Kg/m^2 (mean ± SD)		24.2 ± 3.81
Tobacco smoking, n (%)	Ever	140 (79.1)
	Never	37 (20.9)
Occupational exposure, n (%)	Yes	82 (46.3)
	No	95 (53.7)
Season of blood draw,[a] n (%)	Low sunshine	106 (59.9)
	High sunshine	71 (40.1)
Skin phenotype, n (%)	Fair	82 (46.3)
	Brown/Dark	95 (53.7)
Tumor stage, n (%)	pTa	99 (55.9)
	pT1	78 (44.1)
Tumor grade, n (%)	G1	89 (50.3)
	G2	70 (39.5)
	G3	18 (11.2)
Number of tumors, n (%)	Single	87 (49.1)
	Multiple	90 (50.9)
Tumor size, n (%)	<1 cm	23 (12.9)
	1 to 3 cm	33 (18.7)
	≥3 cm	121 (68.4)
Intravesical BCG therapy, n (%)	No	63 (35.6)
	Yes	114 (64.4)
Plasma 25-OHD, n (%)	<12 ng/mL	87 (49.2)
	12 to 20 ng/mL	55 (31.1)
	>20 ng/mL	35 (19.7)

25-OHD, 25-hydroxyvitamin D; BCG, Bacillus Calmette-Guerin; UBC, urothelial bladder cancer.
[a]High-sunshine season, May to October; low-sunshine season, November to April.

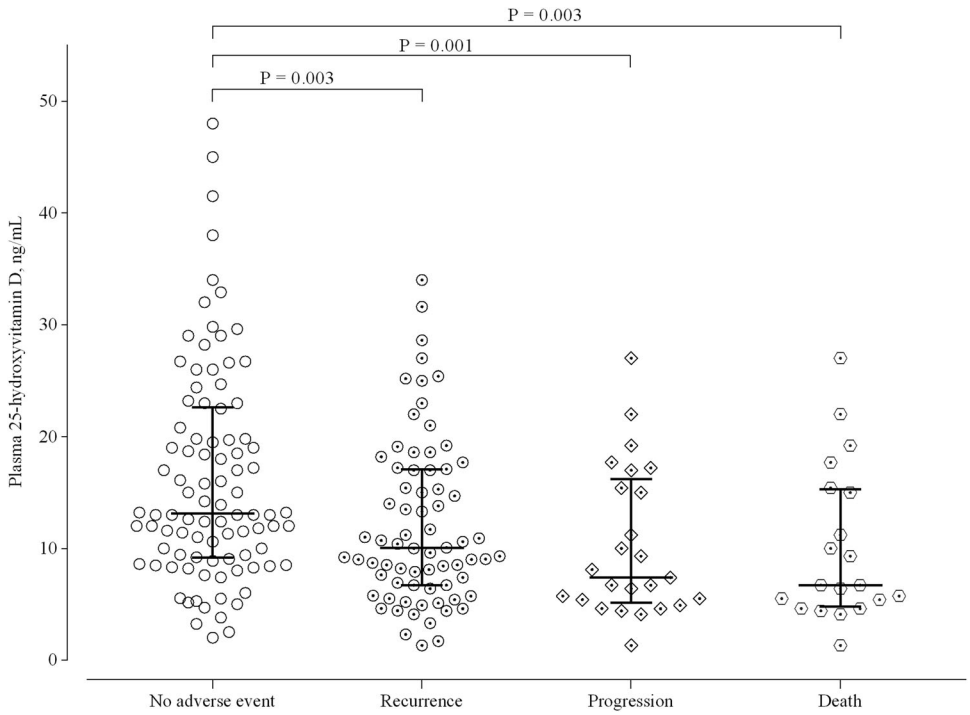

Figure 1. Comparative distribution of plasma 25-hydroxyvitamin D in patients with non-muscle invasive bladder cancer according to the outcome. The band inside the scatter dots plot is the median. The ends of the whiskers are the 25th and the 75th percentiles.

Results

Baseline characteristics of patients and tumors are listed in Table 1. At enrollment, most patients were males, current or former smokers, and exhibited VD deficiency/insufficiency (plasma 25-OHD< 20 ng/mL). During the follow-up period, 11 patients (6.21%) were lost, 72 patients (40.7%) experienced tumor recurrence, 25 patients (14.1%) showed tumor progression, and 20 (11.3%) patients died due to bladder cancer. The overall follow-up duration ranged from 10 to 78 mo, with a median of 66 mo,. For survivors, the follow-up duration was over 3 years for all patients and over 5 years for 123 patients (84.2%). Baseline plasma 25-OHD concentrations were significantly lower in patients who experienced recurrence, progression, or UBC-related death (Fig. 1). Univariate HRs and 95% CIs for UBC recurrence, progression and related mortality in dependence of plasma 25-OHD are depicted in Fig. 2. According to Cutoff-Finder application, the best plasma 25-OHD cutoff points to predict recurrence, progression, and mortality are 11.2, 7.39 and 6.80 ng/mL, respectively (Fig. 2). Risk of recurrence, progression, and UBC-related mortality was higher in patients with the lowest plasma 25-OHD category, regardless of the classification considered. Table 2 shows multi-adjusted HRs with 95% CIs for UBC recurrence, progression, and related mortality by plasma 25-OHD clinical categories (ie., IOM guidelines), season-specific tertiles and Cutoff Finder outcome-specific thresholds. Multi-adjusted survival curves for UBC recurrence, progression, and related mortality by plasma 25-OHD season-specific tertiles are depicted in Fig. 3.

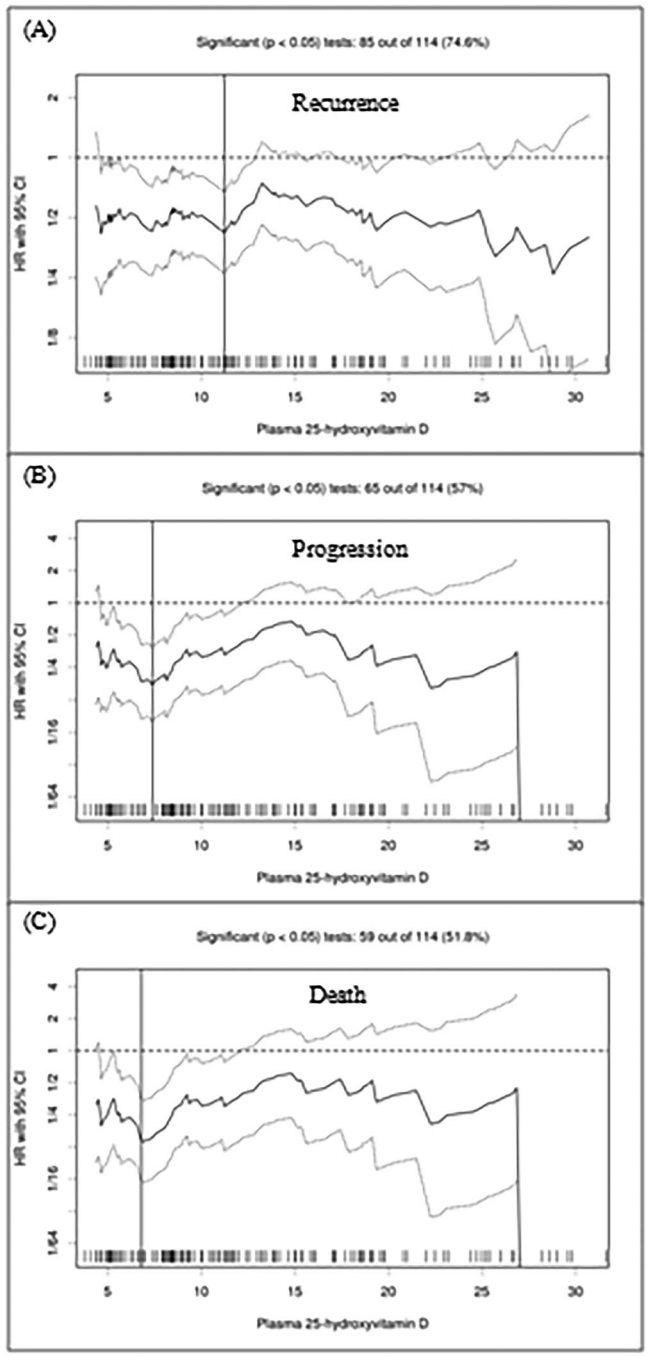

Figure 2. Overview of unadjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for non-muscle invasive bladder cancer recurrence (A), progression (B) and related death (C) in dependence of plasma 25-hydroxyvitamin D. The distribution of plasma 25-hydroxyvitamin D is shown as rug plot at the bottom of the figure. Two dashed lines represent upper and lower limits of 95% CIs, respectively, and the solid line between the two dashed lines represents HR. The optimal cutoff is marked by a vertical line. The percentage of significant cutoffs out of all investigated cutoffs is displayed at the top of the figure.

Discussion

This study showed that lower plasma 25-OHD concentrations are associated with higher risk of recurrence, progression, and death in NMIBC patients. Consistent with these findings, experimental data suggest that VD impacts UBC prognosis. Intra bladder 1,25-di-OHD therapy in animal model of UBC resulted in fewer tumors, which are less likely to be multifocal, invasive or of high grade (11). Likewise, co-treatment of 1,25-di-OHD with BCG resulted in prolonged survival in carcinogen-induced bladder cancer mouse model (27). In patients with UBC, expression of vitamin D receptor (VDR) positively correlates with survival (28) and various VDR gene polymorphisms are associated with tumor recurrence (29). Ecological studies have concluded that exposure to solar ultraviolet radiation, the primary source of VD, reduces bladder cancer mortality (30). In a retrospective analysis in veterans with bladder cancer, higher plasma VD levels were associated with prolonged

Table 2. Multi-adjusted hazard ratios with 95% confidence intervals for non-muscle invasive bladder cancer recurrence, progression, and related mortality by categories of plasma 25-hydroxyvitamin D concentrations defined according to different criteria.

Criteria	Plasma 25-OHD category	Multi-adjusted hazard ratio (95% confidence interval), P value		
		Recurrence	Progression	Mortality
Institute of Medicine[a]	≥12 ng/mL	1.00 (referent)	1.00 (referent)	1.00 (referent)
	<12 ng/mL	2.09 (1.27–3.44), 0.004	2.63 (1.06–6.49), 0.037	2.93 (1.04–8.25), 0.043
Season-specific tertiles[b]	2[d] and 3[d] tertiles	1.00 (referent)	1.00 (referent)	1.00 (referent)
	1[st] tertile	2.80 (1.70–4.63), <0.001	4.37 (1.77–10.8), 0.001	4.70 (1.69–13.1), 0.003
Cutoff Finder[a,c]	≥ specific threshold	1.00 (referent)	1.00 (referent)	1.00 (referent)
	< specific threshold	2.27 (1.37–3.75), 0.001	4.34 (1.70–11.1), 0.002	5.92 (2.14–16.4), 0.001

[a]Hazard ratio adjusted for age, gender, body mass index, skin phenotype, tobacco smoking, occupational exposure, season of blood draw, BCG immunotherapy, and tumor stage, grade, number and size.
[b]Hazard ratio adjusted for the same variables minus season of blood draw; plasma 25-hydroxyvitamin D (in ng/mL) tertiles (T) were: T1, <8.27; T2, 8.27 to 15 and T3, >15 for low-sunshine season (November to April), and T1, <10.7; T2, 10.7–18.4 and T3, >18.4 for high-sunshine season (May to October).
[c]Plasma 25-hydroxyvitamin D Cutoff Finder thresholds for recurrence, progression and death were 11.2, 7.39 and 6.80 ng/mL, respectively.

survival and better outcomes (31). The present study is the first prospective study that investigated prognosis value of plasma 25-OHD in UBC patients. Its findings along with literature data suggest that VD protects from UBC progression and that VD-based therapies may be an adjuvant strategy for UBC management.

VD was shown to modulate prognosis of cancer in other sites. A recent meta-analysis of 64 studies including 44 165 cancer patients provided evidence that high plasma 25-OHD is associated with better overall survival and decreased disease progression for all cancers, as well as for breast, hematological and skin cancers (32). Mechanisms by which VD could inhibit cancer progression include inhibition of tumor growth, induction of differentiation, apoptosis and antioxidant enzymes, regulation of immune function and metabolism of proteins involved in DNA repair, synthesis of prostanoids, promotion of autophagy and anti-inflammatory effects (33).

In this study, plasma 25-OHD at the bottom category was associated with higher risk for poor outcomes, but no differences were found between the middle and upper 25-OHD categories. This suggests that low VD status predicts poor outcomes rather than that high VD status predicts better outcomes. Being common in Tunisia (20, 22), VD deficiency could be an additional factor responsible of the high rates of UBC recurrence and mortality in our region (21). Thus, correction of low VD status could help to reduce UBC poor outcomes and related costs. Maintaining adequate VD status could be considered as a safe and economical therapeutics to avoid the social and economical burden of the disease.

BCG immunotherapy influences NMIBC recurrence/progression (6) and thus it is a potential confounder for patients' outcome. In this study, 64.4% of patients had received BCG immunotherapy as adjuvant therapy. However, it is unlikely that this treatment has confounded the effect of 25-OHD on outcomes in these patients since the association remained significant while adjusting for this variable.

The study covered a large number of participants. It focused on a biomarker (ie., plasma 25-OHD), which is superior to dietary intake estimates as it integrates both VD exogenous supply and endogenous synthesis (13). It is also independent from the participant interviewed, who for lack of memorization or appreciation may direct to erroneous estimates (34). Data derive from multivariate analyses while adjusting for potential confounders that could affect UBC prognosis or VD status. The results remain firm regardless the criteria considered for low VD status definition. Finally, the study has acceptable follow-up period and completeness and detailed clinical information. All these specifics strengthen and make trusty the findings. The study has also limitations; plasma 25-OHD concentrations were assessed at or near the moment of diagnosis, but hadn't been reexamined during the follow-up. VD status could have changed after cancer diagnosis and thus the outcome could have been affected by the variation over time. However, diagnosis of NMIBC in a patient doesn't generally provoke significant nutritional and life style changes. Also, no patient had received VD supplements or fortified food that could had influenced the outcome. Finally, plasma 25-OHD early in the course of UBC was shown to be more strongly related to outcomes than follow-up levels (31). The study was conducted in Tunisian population that is characterized by high rates of UBC and hypovitaminosis D and in which VD supplementation is uncommon. The findings are relevant for populations sharing similar characteristics.

Low VD status was associated with higher risk of recurrence, progression, and mortality in patients with NMIBC. This suggests that plasma 25-OHD at diagnosis may predict UBC outcome. Thus, patients with NMIBC would be screened for VD deficiency and any

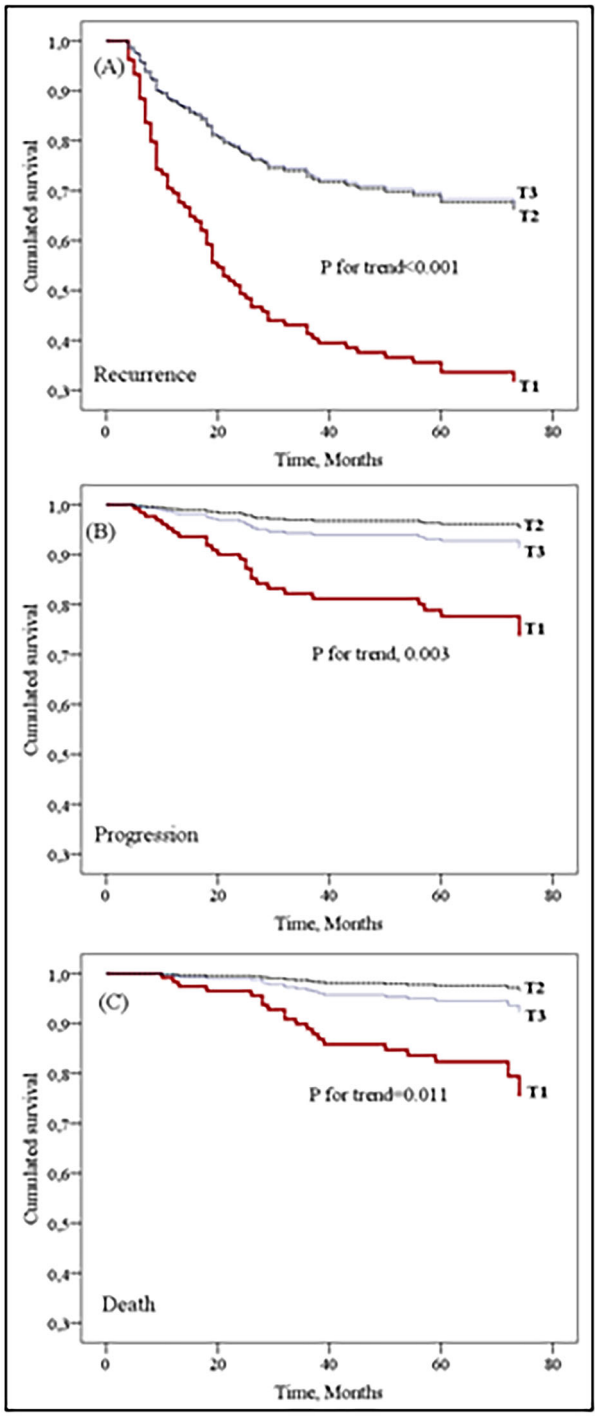

Figure 3. Multivariable* Cox model survival curves for non-muscle invasive bladder cancer recurrence (A), progression (B) and related death (C) by plasma 25-hydroxyvitamin D season-specific tertiles. The bold line refers to the 1st tertile (T1), the dashed line refers to the 2d tertile (T2) and the thin line refers to the 3d tertile (T3); *, adjusted for age, gender, body mass index, skin phenotype, tobacco smoking, occupational exposure, BCG immunotherapy, and tumor stage, grade, number and size; low-sunshine season tertiles cut-points (25-hydroxyvitamin D in ng/mL), 1st tertile, <8.27; 2d tertile, 8.27 to 15; 3d tertile, >15, and high-sunshine season tertiles cut-points (25-OHD in ng/mL): 1st tertile, <10.7; 2d tertile, 10.7 to 18.4; 3d tertile, >18.4.

deficiency should be corrected. Such strategy may contribute to reduce poor outcomes, improve quality of life, and extend survival in patients. However, before being adopted in routine practice, this should be evaluated in well-designed randomized controlled trials. Future work is needed to test the impact of VD supplementation in NMIBC patients.

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Declaration of Interest

Authors declare no conflicts of interest.

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