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Vitamin D deficiency and its association with fatigue and quality of life in advanced cancer patients under palliative care: A cross-sectional study

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Abstract

Background: A normal vitamin D status is required for bones and muscles to maintain their function and structure, but it also contributes to the functional integrity of other multiple physiologic systems in the body.

Aim: To assess the relationship of Vitamin D deficiency with health-related quality-of-life issues, fatigue, and physical functioning in advanced cancer patients.

Design: This is a cross-sectional study.

Patients/settings: Adults under palliative care, having a locally advanced or metastatic or inoperable solid cancer.

Results: Among 30 patients in palliative care with advanced solid cancer, 90% were vitamin D deficient. Serum Vitamin D concentration was positively correlated with patient-reported absence of fatigue ($s = 0.49$), and physical and functional well-being ($s = 0.44$ and $s = 0.41$, respectively, $p < 0.01$). Fatigue was the symptom with the highest median impact on their lives and was the only one associated with serum vitamin D ($p = 0.031$), with lower fatigue in patients with vitamin D concentrations in the third tertile. There was no evidence of a direct association between health-related quality of life and vitamin D status.

Conclusion: The 90% frequency of advanced cancer patients with vitamin D deficiency, together with the positive correlation of vitamin D status with the absence of fatigue and improved physical and functional well-being, points to vitamin D supplementation as a potential therapy to enhance the patient's quality of life.

Keywords

Advanced cancer, palliative care, vitamin D, quality of life, fatigue

Introduction

Background and rationale

Vitamin D can be nutritionally obtained from fortified foods, a few unfortified foods, or in the form of a dietary supplement. It is also produced endogenously, when ultraviolet rays from sun light interact with the skin. Vitamin D is a fat-soluble vitamin and becomes active through two hydroxylations, the first one occurring in the liver (converting vitamin D to 25-hydroxyvitamin D, also called 25(OH)D or calcidiol) and the second one in the kidney where 25(OH)D is transformed into 1,25-dihydroxyvitamin D, also called 1,25(OH)2D or calcitriol, the hormonal form of vitamin D, and consequently, the most active endogenous vitamin D metabolite.[1–3]

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Serum 1,25(OH)2D has a short half-life of 7–8 h. Its synthesis is tightly regulated by serum parathyroid hormone, fibroblast growth factor 23 (FGF23), and calcium and phosphate concentrations, and its circulating level does not typically decrease until vitamin D deficiency is severe,[1–3] resulting in a bad indicator of the status of vitamin D.[4] In contrast, serum 25(OH)D has a relatively long circulating half-life of 15 days.[4] Because vitamin D conversion to 25(OH)D is loosely regulated, it better reflects the circulating level of vitamin D that a person obtains through the aforementioned sources.[1–3] Due to the difficulties in measuring vitamin D levels, measurements of 25(OH)D are used to evaluate the status of vitamin D. The optimal serum 25(OH)D concentration is controversial, but for skeletal health, experts agree that levels lower than 20 ng/mL (i.e. 50 nmol/L) are suboptimal.[1–4]

Normal bone mineralization and growth are both promoted by a normal vitamin D status, which protects children from developing hypocalcemic tetany and rickets and adults from osteomalacia and osteoporosis, the so-called classical vitamin D actions.[1–3] Normal circulating vitamin D also exerts non-classical actions as those required to maintain the integrity of structure and function in muscle cells,[5] the modulation of cell growth (proliferation, differentiation, and apoptosis), neuromuscular and immunological functions, and in reducing inflammation.[1–3,6,7] Furthermore, epidemiologic data agree that vitamin D may have a protective effect against colon cancer, although the evidence is not as strong for a protective effect against prostate, breast, and cancers at other sites.[3] As indicated earlier, the adverse impact of vitamin D deficiency in maintaining the health benefits of classical and non-classical actions is not the result of lower circulating 1,25(OH)2D, as they occur in individuals with normal calcitriol levels.[3] The epidemiological association between vitamin D deficiency and higher risk of mortality for all causes results from the reduced local conversion of the low circulating 25(OH)D to 1,25(OH)2D by bone, muscle, and immune cells. Similar to cells of the kidney proximal tubules, numerous cell types can convert 25(OH)D to calcitriol,[8] the most potent endogenous metabolite for vitamin D biological actions that improve local function with minimal, if any, impact on calcium homeostasis.[9]

Due to (1) the significant fatigue, physical, and functional impairment in patients with advanced cancer, (2) the very limited therapeutic measures currently available to reduce them, and (3) the benefits of a normal vitamin D status on the functional integrity of multiple physiologic systems in the body, we hypothesized that a significant proportion of patients with advanced cancer in palliative care has vitamin D deficiency, that is, 25(OH)D $<$ 20 ng/mL, and that there is an association between serum vitamin D levels and the patient's self-assessment of quality of life (QL), as well as with the patient's capacity to perform daily living activities.

Objectives

Our objectives are to estimate the proportion of patients with advanced cancer in palliative care who present with serum vitamin D deficiency and to establish the relationship between serum vitamin D levels and patient-perceived QL, as well as physical condition, functional capacity, and fatigue.

Methods

Study design and setting

This study was designed as a cross-sectional study in palliative care cancer patients.

Participants were inpatients and outpatients who satisfied inclusion and exclusion criteria and were consecutively visited at the Hospital Universitari Arnau de Vilanova (HUAV), in the city of Lleida, Spain, from March 2013 to August 2014.

Participants

Eligible patients were adults having a locally advanced or metastatic or inoperable solid cancer under palliative care, upon signed informed consent. Since this study includes patient-perceived outcomes, exclusion criteria were having a Karnofsky $<$ 30%, a cognitive deterioration (more than 5 mistakes in Pfeiffer test), or suffering from significant pain, dyspnea, nausea, or vomiting (more than 6 out of 10 in the corresponding Numerical Rating Scale 0:10). The rest of the exclusion criteria included pregnant or breast-feeding females, undergoing severe liver or renal (glomerular filtration rate (GFR) $<$ 60) failure, having received chemotherapy or radiation therapy within the last 3 weeks prior to inclusion, or having the possibility of initiating a new cycle of chemotherapy or radiation therapy within a period of 6 weeks after their inclusion date to avoid the potential impact of chemotherapy or radiation therapy on fatigue.

Variables

Data collection was performed prospectively after approval of the study protocol by the hospital's ethics committee.

Vitamin D. Quantification of serum levels of 25-hydroxyvitamin D (i.e. 25(OH)D) were measured in ng/dL using the Chemiluminescence-Immunoassay on the LIAISON XL Analyzer (DiaSorin) in the Central Laboratory at the HUAV.

Primary and secondary end-points. Health-related quality of life (HRQoL) was considered the primary outcome and was assessed using the global health status/QL item from EORTC QLQ-C15-PAL,[10] a questionnaire developed for palliative care cancer patients. Scores range from 0 (poor) to 100 (excellent).

Cancer-related fatigue was considered a secondary outcome and was assessed using the fatigue subscale of the Functional Assessment of Cancer Therapy (FACT) questionnaire.[11] This is a widely used 13-item fatigue subscale where each item is a 5-point Likert self-reported scale ranging from 0 = "not at all" to 4 = "very much so." The total score varies from 0 = "worst condition" to 52 = "best condition."

Other patient-reported secondary outcomes included rates on (1) the impact of fatigue, pain, dyspnea, constipation, appetite loss, nausea/vomiting and insomnia; (2) physical functioning (PF) and emotional functioning (EF); (3) physical well-being (PWB) and functional well-being (FWB); and (4) functional capacity in the activities of daily living. The rates on the impact of symptoms were assessed using the questionnaire EORTC QLQ-C15-PAL, with scores ranging from 0 (none) to 100 (the highest) for negative impact on daily life. This questionnaire also includes the assessment of physical and emotional functions, both expressed as scores from 0 (poor) to 100 (excellent). PWB and FWB were assessed using the FACT questionnaire with scores varying from 0 = "worst condition" to 28 = "best condition." The addition of these two scores to the FACT estimation of fatigue is known as "Trial Outcome Index." Finally, the patient-reported functional capacity in the activities of daily living was assessed using the Barthel Scale (BS),[12] an ordinal scale that measures performance from 0 (completely dependent) to 100 (independent). Clinician-reported patient's performance status was assessed with the Karnofsky Performance Scale (KPS)[13] and the Palliative Performance Scale (PPS).[14] Both provide a score from 100 to 0, where 100 indicates no evidence of disease (normal performance) and 0 indicates death.

Covariates. Patients' socio-demographic characteristics (age, gender, and educational level), anthropometric characteristics (height, weight, body mass index, and tricipital skinfold thickness), primary tumor (coded according to the International Statistical Classification of Diseases and Related Health Problems–10th Revision (ICD-10)), tumor stage, standard serum chemistries (25(OH)D, hemoglobin, leukocytes, lymphocytes, platelets, triglycerides, total cholesterol, total proteins, albumin, liver transaminases alanine transaminase (ALT) and aspartate transaminase (AST), C-reactive protein, phosphorus, creatinine, calcium), and urinary chemistries (creatinine, calcium, and microalbumin).

Sample size

Sample size was established to estimate a correlation coefficient between 25(OH)D serum levels and self-perceived QL equal to or greater than 0.5, with 95% confidence (bilateral) and 80% statistical power. Based on these considerations, a minimum of 30 patients is required.

Statistical methods

A descriptive analysis of the study sample was performed using the usual summary measures for qualitative and quantitative variables. The proportion of vitamin D deficiency, with 95% confidence interval (CI), was estimated with the exact Binomial distribution. The relationship of 25(OH)D serum levels with the quantitative end-points was assessed graphically (scatterplots) and by estimating the Spearman's rank correlation coefficients to assess a monotonously increasing or decreasing trend, not restricted to linear relationships. Associations between quantitative end-points and 25(OH)D were also checked by grouping patients according to 25(OH)D tertiles. These associations were assessed graphically (boxplots) and statistically by using the Kruskal–Wallis test. A significance level of 5% and the statistical software R[15] were used.

Results

Participants

The participants' characteristics are shown in Table 1. A total of 30 patients were consecutively included after checking eligibility criteria. The study participants were primarily men (76.7%), had low educational levels (60.1%), were in average 63.3 years old (standard deviation (SD) = 10.97 years), and had an average body mass index of 24.4 (SD = 5.07). The distribution of primary tumors was heterogeneous, being the most frequent in the digestive system (14, 46.7%), followed by those from the respiratory (6, 20.0%), reproductive (5, 16.7%), urinary (2, 6.7%), and nervous (2, 6.7%) systems. Patient's disease stage was, mainly, metastatic. Regarding blood test results, the study patients had clinically significant low levels of hemoglobin and lymphocytes and high levels of C-reactive protein, with medians and interquartile intervals of 10.4 (9.3, 11.7) mg/dL, 11.0% (6.1%, 13.4%), and 22.9 (7.05, 63.8), respectively (Table 2). None of the patients was taking vitamin D supplements of any kind.

Vitamin D distribution

The vast majority of patients showed vitamin D deficiency, and the three subjects with levels over 30 ng/dL stand out as outliers, with a clearly asymmetric distribution. The proportion of patients with vitamin D deficiency was 90%, with an estimated 95% CI of (73%, 98%). The two tertiles were 7.6 and 10.5 ng/dL. Based on these values, the sample was partitioned into patients with values lower than 8 ($n = 12$), from 8 to values lower than 11 ($n = 9$), and patients with concentrations of 11 or higher ($n = 9$).

Clinician-reported performance status

Both performance status scales scores, KPS and PPS, showed a median of 60.0, and interquartile intervals of

Table 1. Description of the patients ($N = 30$).

	Summary measure
Men	23 (76.7%)
Age (years)	60.5 (55.5, 71.0)
Educational level ($n = 27$)	
Illiterate	2 (6.7%)
Primary-High school	22 (83.3%)
College	3 (10.0%)
BMI ($n = 27$)	24.3 (21.1, 27.7)
Tricipital skinfold thickness, TST (cm) ($n = 28$)	1.5 (1.0, 2.0)
Malignant neoplasma of	
Hypopharynx (C13)	2 (6.7%)
Esophagus (C15)	2 (6.7%)
Colon (C18)	4 (13.3%)
Rectum (C20)	1 (3.3%)
Anus/anal canal (C21)	1 (3.3%)
Gallbladder (C23)	1 (3.3%)
Pancreas (C25)	2 (6.7%)
ill-defined digestive organs (C26)	1 (3.3%)
Larynx (C32)	1 (3.3%)
Bronchus and lung (C34)	5 (16.7%)
Breast (C50)	1 (3.3%)
Corpus uteri (C54)	1 (3.3%)
Uterus (C55)	1 (3.3%)
Prostate (C61)	3 (10.0%)
Kidney (C64)	2 (6.7%)
Brain (C71)	2 (6.7%)
Tumor stage	
3	2 (6.5%)
4	28 (93.5%)

BMI: body mass index.
Qualitative characteristics are described as absolute number and relative frequency (%). Quantitative characteristics are described as median (first and third quartile).

Table 2. Chemistries.

	Summary measure
S.Creatinine (mg/dL)	0.72 (0.57, 0.83)
S. Calcium (mg/dL)	8.44 (7.94, 8.83)
S.Phosphorus (mg/dL)	2.97 (2.37, 3.44)
S.Total cholesterol (mg/dL)	160.5 (131.3, 184.8)
S.Triglycerides (mg/dL)	144.0 (94.3, 203.0)
S.Total proteins (g/dL)	5.61 (5.19, 6.19)
S.Albumin (g/dL)	3.10 (2.83, 3.38)
S.Aspartate transaminase, AST (U/L)	19.0 (15.3, 26.5)
S.Alanine transaminase, ALT (U/L)	18.5 (14.0, 26.5)
S.C-reactive protein, CRP (mg/L)	22.9 (7.1, 63.8)
S.25(OH)D (ng/mL)	8.5 (6.7, 12.6)
U.Creatinine (mg/dL) ($n=19$)	47.8 (32.5, 84.6)
U.Calcium (mg/dL) ($n=19$)	6.60 (3.10, 9.65)
U.Microalbumin (mg/L) ($n=18$)	5.77 (1.9, 22.3)
S.Leukocytes (x10x9/L)	10.2 (7.9, 13.2)
S.Hemoglobin (g/dL)	10.4 (9.3, 11.7)
S.Platelets (x10x9/L)	275.0 (232.3, 346.0)
S.Lymphocytes (%)	11.0 (6.1, 13.4)
S.Lymphocytes (x10x9/L)	1.09 (0.78, 1.46)

Values represent median (first, third quartile). S and U indicate serum and urinary chemistries.

(50.0, 60.0) and (52.5, 60.0), respectively. Thus, an average participant required occasional assistance but was able to care for most of his/her personal needs (Table 3).

Patient-reported outcomes

Patient-reported outcomes are summarized in Table 3. Overall QL showed a median of 50.0, with quartiles 33.3 and 62.5. EF showed the same median score but more variability. In contrast, PF showed much lower scores.

The median performance of daily living activities according to BS was estimated to be 85 out of 100, with first and third quartiles 61.3 and 98.8, denoting autonomy.

The median of patient's fatigue (Fatigue Score (FS)) assessment (using FACT-F subscale) was 20.3 out of 52 (52 being equivalent to absence of fatigue). PWB and FWB were scored with a median of 15.0 and 10.0, respectively, out of 28 (28 being the value denoting the best condition).

The patient's impact of symptoms score ranged from 0 (none) to 100 (the highest impact). Among all the symptoms, fatigue demonstrated the highest impact, with a median 41.7, followed by pain, dyspnea, sleep, appetite loss, and constipation, with a median of 33.3. By contrast, more than 50% of patients reported no impact of nausea/vomiting.

Vitamin D relationships

The results of blood and urine tests showed some statistically significant relationships with serum concentration of 25(OH)D (Table 4). Specifically, serum phosphorus and calcium showed positive and statistically significant Spearman's rank correlations of 0.41 and 0.40, respectively, whereas triglycerides showed a negative and statistically significant Spearman's rank correlation of −0.43. All these correlations were confirmed when partitioning participants according to the tertiles of serum vitamin D levels. In addition, a significant association was found for serum ALT concentration, with significantly higher values for the second tertile of 25(OH)D.

Clinician-reported performance status showed a positive Spearman's rank correlation with 25(OH)D serum concentration according to both performance scales (0.37 for KPS and 0.40 for PPS). Both correlations were confirmed when partitioning participants according to the tertiles of serum vitamin D levels (Table 5).

Among the patient-reported outcomes, those positively correlated with 25(OH)D were FS (0.49), PWB (0.44), and FWB (0.41). It was confirmed when partitioning participants according to the tertiles of serum vitamin D levels (Figure 1). A statistically significant negative Spearman's

Table 3. Physical performance and patient-reported outcomes.

	Summary measures
KPS (Karnofsky Performance Scale), +	60.0 (50.0, 60.0)
PPS (palliative Performance Scale), +	60.0 (52.5, 60.0)
Barthel, +	85.0 (61.3, 98.8)
PWB (physical well-being), +	15.0 (11.5, 20.0)
FWB (functional well-being), +	10.0 (6.00, 12.0)
FS (FACIT fatigue score), +	20.3 (14.0, 34.8)
TOI (PWB + FWB + FS), +	45.0 (32.3, 68.3)
Pain impact, −	41.7 (4.17, 95.8)
Dyspnea impact, −	33.3 (0.00, 66.7)
Insomnia impact, −	33.3 (0.00, 66.7)
Appetite loss impact, −	33.3 (0.00, 91.7)
Constipation impact, −	33.3 (8.33, 100)
Fatigue impact, −	66.7 (47.2, 100)
Nausea/vomiting, −	0.00 (0.00, 16.7)
Physical functioning, +	33.3 (13.3, 60.0)
Emotional functioning, +	50.0 (41.7, 79.2)
Overall quality of life, +	50.0 (33.3, 62.5)

FACIT: Functional Assessment of Chronic Illness Therapy; TOI: trial outcome index.
Values represent median (first, third quartile). Symbols + and − indicate that high scores mean better or worse health state in reference to the patient-measured outcome.

rank correlation was observed with nausea/vomiting (−0.39), although it was due to the high score reported by patients in the first tertile of 25(OH)D. Statistically significant associations were also found for the Barthel index, due to the low score reported by patients in the first tertile of 25(OH)D, and for the PF score and the fatigue symptom impact, both of them with a significantly better score for the third tertile (lower fatigue impact and higher PF). No statistically significant association was found for overall QL or other symptoms impact assessments or EF.

Discussion

Our study shows that vitamin D deficiency is highly present in patients in palliative care with an advanced solid cancer who, although not being severely disabled, are not candidates to receiving chemotherapy or radiotherapy. It is estimated to be 90%, with 95% CI of (73%, 98%). Fatigue is the most prevalent symptom in advanced cancer patients[16-19]. The self-assessment of symptoms placed fatigue as the one with the greatest impact in their lives when pain, dyspnea, and nausea/vomiting are under control. Fatigue was also the only symptom with a perceived impact significantly correlated with 25(OH)D serum concentrations, which in turn was significantly correlated with physician's assessment of patient's performance status and with patient-reported PF, perceived fatigue, as well as PWB and FWB. A significant association of 25(OH)D levels with patient-reported overall QL or with EF could not be established.

The main limitation of our findings is the scarce number of patients. Given the high heterogeneity of primary tumors included in our study, it does not permit the performance of subanalyses for each of the primary tumor families. A plausible hypothesis would be that vitamin D deficiency or even the impact of it on self-perceived QL could depend on the type of primary tumor, but the sample size available does not allow the testing of it. However, the goal was not to provide results according to the type of tumor, but to establish a first measure of vitamin D deficiency in these patients as a whole, and the relationship of this impairment to QL, functional capacity, and fatigue.

Another limitation is the single-center nature of the results, which precludes any further extrapolation of our findings. Indeed, geographical locations determine marked differences in dietary vitamin D intake, and more importantly, in sun exposure, which can greatly influence serum 25(OH)D concentration in the general population. However, its influence in advanced cancer patients under palliative care is likely to be minor because of their illness, which limits not only sun exposure (contraindicated before receiving chemo or radiotherapy) but also a regular food intake, as they are often malnourished. The last limitation, linked to the study design, is its cross-sectional nature, which avoids any causality interpretation. Even though in an observational study reverse causality cannot be fully ruled out, as suggested by a recent meta-analysis,[20] the well-delineated mechanisms underlying the benefits of a normal vitamin D status on muscular strength,[21] the renal levels of the anti-aging klotho gene,[22] and the attenuation systemic inflammation[8,23] support a direct adverse impact of vitamin D deficiency on the parameters examined rather than reversed causality.

Other studies in cancer patients have reported a variety of estimates of vitamin D deficiency. The most recently published vitamin D deficiency estimation was measured in 44% of patients with non-hematological cancer coming from oncological and palliative care (not only advanced cancer patients) in Brisbane, Australia.[24] Among advanced cancer patients, vitamin D deficiency (defined as <20 ng/dL) estimates vary between 47%[16] and 64%.[25]

Recently, a significant positive correlation (measured by Kendall's rank correlation test) of vitamin D serum levels with the Australia-modified Karnofsky Performance Status (AKPS) has been reported,[24] in agreement with our finding of a significant positive correlation of 0.37 with KPS and 0.40 with PPS as estimated by Spearman's rank correlation coefficients.

In conclusion, our study underscores the fact that patients with higher serum 25(OH)D levels show significantly higher scores in patient's reported FS, PF, PWB, and FWB scales and very low scores of fatigue impact when compared with patients with lower serum 25(OH)D concentrations. This is a new finding, not reported by previous publications, pointing out that fatigue is the

Table 4. Association between serum 25(OH)D concentrations and patient's age, body mass index, tricipital skinfold, and chemistries.

	Spearman rho	25(OH)D < 8	25(OH)D (8.0,11.0)	25(OH)D ⩾ 11	K-W
Age (years)	−0.13 (0.480)	70.0 (58.5, 76.8)	59.0 (55.0, 62.0)	58.0 (54.0, 71.0)	0.180
BMI (kg/m^2)	−0.14 (0.490)	24.3 (20.9, 26.4)	26.0 (24.2, 29.3)	23.6 (20.4, 26.5)	0.596
TST (cm)	0.25 (0.207)	1.30 (1.03, 1.58)	1.10 (1.00, 2.00)	1.90 (1.00, 2.10)	0.471
S.Creatinine (mg/dL)	−0.07 (0.718)	0.78 (0.58, 1.01)	0.66 (0.50, 0.77)	0.72 (0.59, 0.78)	0.657
S.Calcium (mg/dL)	0.40 (0.031)	8.04 (7.60, 8.58)	8.51 (8.40, 8.83)	8.71 (8.33, 8.84)	0.127
S.Phosphorus (mg/dL)	0.41 (0.023)	2.52 (2.13, 3.00)	3.03 (2.59, 3.31)	3.35 (3.22, 3.94)	0.071
S.Total cholesterol (mg/dL)	−0.13 (0.481)	160.5 (145.3, 180.8)	175.0 (142.0, 185.0)	130.0 (116.0, 188.0)	0.452
S.Triglycerides (mg/dL)	−0.43 (0.019)	162.5 (126.0, 224.5)	180.0 (122.0, 208.0)	93.0 (83.0, 113.0)	0.040
S.Total proteins (g/dL)	0.23 (0.212)	5.57 (4.99, 6.23)	5.68 (5.52, 6.10)	5.50 (5.40, 6.53)	0.674
S.Albumin (g/dL)	−0.02 (0.911)	3.15 (2.90, 3.43)	2.90 (2.80, 3.10)	3.20 (2.80, 3.30)	0.647
S.AST (U/L)	−0.24 (0.210)	21.0 (14.8, 25.8)	20.0 (18.0, 37.0)	16.0 (15.0, 17.0)	0.100
S.ALT (U/L)	−0.01 (0.957)	17.5 (14.0, 20.5)	27.0 (20.0, 64.0)	14.0 (12.0, 25.0)	0.013
S.CRP (mg/L)	0.05 (0.782)	22.9 (6.35, 30.8)	23.0 (9.30, 68.2)	14.7 (9.00, 134.0)	0.963
U.Creatinine (mg/dL)	0.02 (0.951)	61.4 (32.5, 74.8)	62.5 (42.9, 87.8)	45.9 (22.4, 69.9)	0.579
U.Calcium (mg/dL)	0.25 (0.297)	1.80 (1.15, 7.95)	6.60 (4.94, 10.7)	8.00 (5.70, 9.65)	0.239
U.Microalbumin (mg/L)	−0.33 (0.188)	22.8 (15.3, 39.4)	11.3 (1.89, 42.0)	2.32 (1.88, 4.00)	0.118
S.Leukocytes (x10x9/L)	−0.17 (0.361)	11.31 (8.11, 15.8)	9.86 (8.78, 11.4)	9.28 (4.55, 13.2)	0.619
S.Hemoglobin (g/dL)	0.20 (0.298)	10.55 (9.60, 11.3)	9.70 (8.50, 11.6)	11.1 (10.2, 13.7)	0.251
S.Platelets (x10x9/L)	−0.34 (0.069)	288.0 (248.0, 325.0)	350.0 (230.0, 381.0)	233.0 (180.0, 279.0)	0.256
S.Lymphocytes (%)	−0.08 (0.677)	9.95 (6.55, 13.43)	11.8 (8.10, 12.20)	11.0 (4.10, 13.70)	0.792
S.Lymphocytes (x10x9/L)	−0.15 (0.433)	1.25 (0.89, 1.43)	0.95 (0.78, 1.45)	0.87 (0.44, 1.46)	0.829

BMI: body mass index; TST: tricipital skinfold thickness; AST: Aspartate transaminase; ALT: Alaline transaminase. CRP: C-reactive protein.
S and U indicate serum and urinary chemistries. Spearman's rank correlation coefficient with serum 25(OH)D concentrations (in ng/mL) and its *p* value in parentheses are shown in the second column. Columns from third to fifth represent the median, (first and third quartiles) for each of the 25(OH)D tertiles. The last column shows the Kruskal–Wallis test *p* value for the differences between the three groups for each of the analyzed parameters.

Table 5. Association between serum 25(OH)D concentrations and either performance status or patient's reported outcomes.

Table 5	Spearman rho	25(OH)D < 8	25(OH)D (8.0,11.0)	25(OH)D ⩾ 11	K-W
Barthel, +	0.34 (0.069)	65.0 (53.8, 85.0)	90.0 (85.0, 95.0)	100.0 (70.0, 100)	0.083
KPS (Karnofsky Performance Scale), +	0.37 (0.043)	50.0 (50.0, 60.0)	60.0 (50.0, 60.0)	60.0 (60.0, 70.0)	0.092
PPS (palliative Performance Scale), +	0.40 (0.031)	55.0 (50.0, 60.0)	60.0 (60.0, 60.0)	70.0 (60.0, 80.0)	0.031
PWB (physical well-being), +	0.44 (0.014)	14.5 (10.5, 15.3)	13.0 (10.0, 14.0)	22.0 (20.0, 24.0)	<.001
FWB (functional well-being), +	0.41 (0.026)	6.50 (4.00, 10.5)	7.00 (6.00, 11.0)	12.0 (11.0, 18.0)	0.021
FS (FACIT fatigue score), +	0.49 (0.006)	17.0 (8.8, 23.4)	17.0 (14.0, 22.0)	38.0 (28.0, 43.0)	0.004
TOI (PWB + FWB + FS), +	0.50 (0.005)	36.8 (25.5, 47.0)	37.0 (32.0, 45.0)	75.0 (55.0, 82.0)	0.001
Pain impact, −	0.08 (0.679)	33.3 (0.00, 87.5)	83.3 (66.7, 100)	16.7 (0.00, 33.3)	0.204
Dyspnea impact, −	−0.14 (0.474)	33.3 (0.00, 75.0)	50.0 (0.00, 75.0)	33.3 (0.00, 66.7)	0.906
Insomnia impact, −	−0.14 (0.461)	33.3 (0.00, 66.7)	33.3 (0.00, 66.7)	0.00 (0.00, 33.3)	0.380
Appetite loss impact, −	−0.22 (0.233)	50.0 (25.0, 75.0)	33.3 (0.00, 100)	0.00 (0.00, 33.3)	0.312
Constipation impact,−	0.03 (0.863)	33.3 (25.0, 100)	66.6 (33.3, 100)	33.3 (0.00, 100)	0.581
Fatigue impact, −	−0.32 (0.087)	94.4 (58.3, 100)	88.9 (66.7, 100)	55.6 (33.3, 66.7)	0.031
Nausea/vomiting, −	−0.39 (0.031)	16.7 (0.00, 25.0)	0.00 (0.0, 16.7)	0.00 (0.00, 0.00)	0.025
Physical functioning, +	0.36 (0.052)	16.7 (6.67, 36.7)	33.3 (20.0, 46.7)	73.3 (33.3, 93.3)	0.037
Emotional functioning, +	0.07 (0.712)	50.0 (41.7, 70.8)	41.7 (41.7, 50.0)	66.7 (50.0, 83.3)	0.482
Overall quality of life, +	0.13 (0.489)	41.7 (29.2, 54.2)	33.3 (16.7, 50.0)	50.0 (50.0, 66.7)	0.108

FACIT: Functional Assessment of Chronic Illness Therapy; TOI: trial outcome index.
Spearman's rank correlation coefficient with serum 25(OH)D concentrations (in ng/mL) and its *p* value in parentheses are shown in the second column. Columns from third to fifth represent the median, (first and third quartiles) for each of the 25(OH)D tertiles. The last column shows the Kruskal–Wallis test *p* value for the differences between the three groups for each of the analyzed parameters.

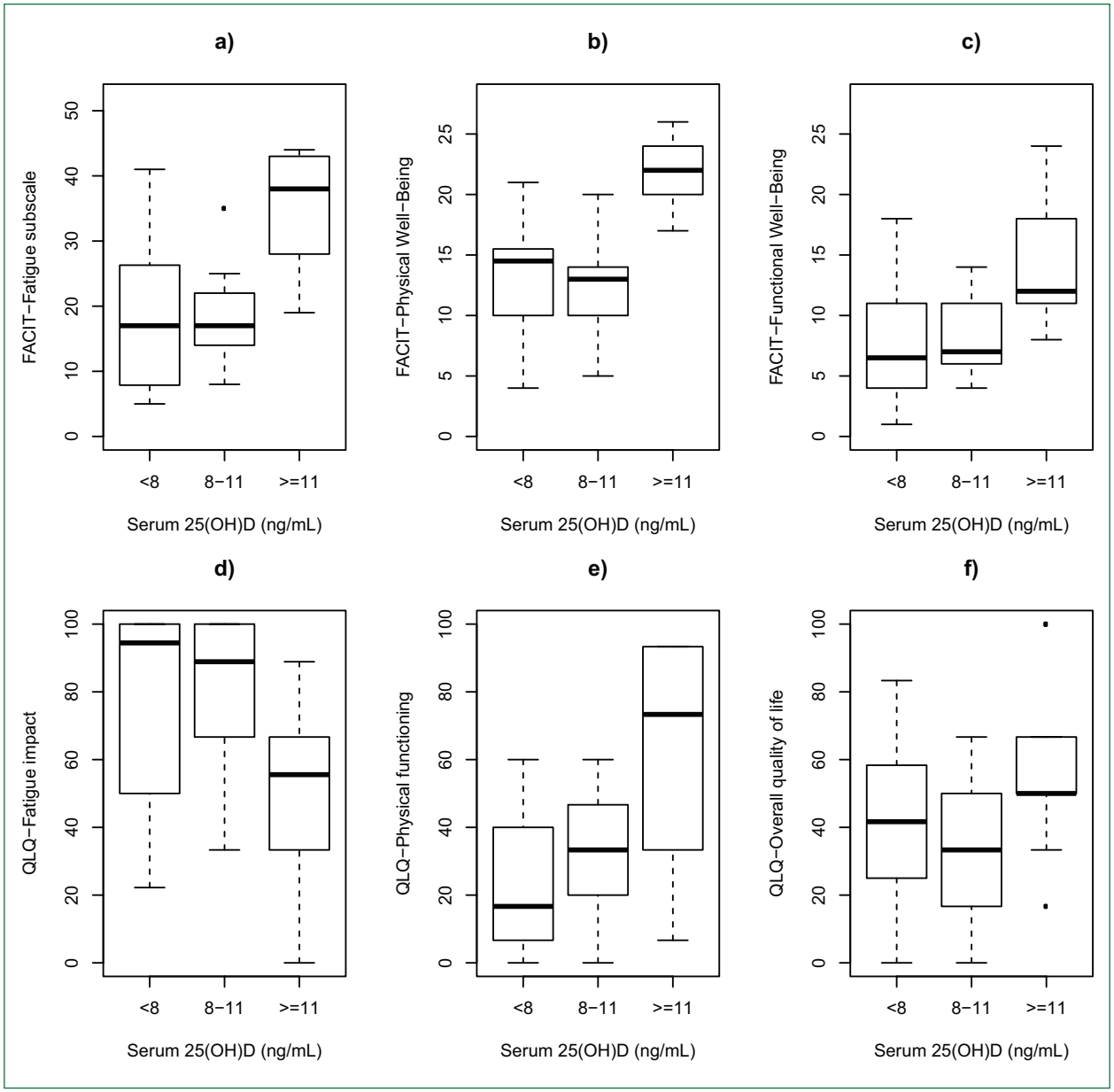

Figure 1. Association between the tertiles of serum 25(OH)D, in ng/mL, and quality-of-life-related parameters. Boxplot analysis of the association between tertiles of 25(OH)D in the X-axis and patient-reported: (a) FACIT fatigue subscale score, (b) FACIT-physical well-being, (c) FACIT-functional well-being, (d) QLQ-fatigue impact, (e) QLQ-physical functioning, and (f) QLQ-overall quality of life.

symptom with the highest impact in advanced cancer patients in palliative care and suggesting a new line of research with vitamin D to reduce fatigue and improve physical and functional status. Although a direct relationship between serum vitamin D levels and QL could not be demonstrated, it would be reasonable to expect that, by reducing fatigue, health-related QL, as perceived by these patients, could be improved. Given this hypothesis, a randomized clinical trial, with EudraCT number 2013-003478-29,[26] has been designed to test it.

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Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical standards

This study was approved by the Hospital Universitari Arnau de Vilanova ethics committee and has, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All participants gave their informed consent prior to their inclusion in the study. No details that might disclose the identity of the participants under study is provided.

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