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RESEARCH ARTICLE

Prognostic Value of Vitamin-D Level in Non-metastatic Breast Cancer Patients in Saudi Arabia

Shereef Elsamany[1,2], Omaima Elemam[1,2], Ahmed Zeeneldin[1,3], Soha Elmorsy[4,5] Ahmed Khatry[6], Faisal Alhuthali[6], Suha Alsayed[6]

[1]Oncology Center, King Abdullah Medical City, Makkah Saudi Arabia. [2]Oncology Center, Mansoura University, Mansoura, Egypt. [3]National Cancer Institute, Cairo University, Cairo, Egypt. [4]Research Center, King Abdullah Medical City, Makkah Saudi Arabia. [5]Pharmacology, Faculty of Medicine, Cairo University, Cairo, Egypt. [6]Research, Um Alqura University, Makkah, Saudia Arabia.

Abstract

Background: Deficiency of vitamin-D (Vit-D) was associated with poor survival outcome in several studies across different tumour types. The present study aims to assess the prevalence and prognostic value of Vit-D deficiency among breast cancer patients in a single institution in Saudi Arabia. **Methods:** In this retrospective study, we screened patients who presented with non-metastatic breast cancer to King Abdullah Medical City, Saudi Arabia from June 2011 to December 2015. We checked baseline Vit-D level before starting systemic therapy in addition to other clinicopathological factors. Low Vit-D was defined as Vit-D level less than 30 ng /ml. The relations of Vit-D level (taking the median as the cutoff) with clinicopathological factors were assessed using Chi-Square test. Differences in survival outcome were compared using log rank test. **Results:** We screened 340 patients with non-metastatic breast cancer. Baseline Vit-D levels were available for 189 patients. The median age was 50 years (range: 26- 86 years). Noteworthy, 169 (89.4%) of patients had Vit-D level <30 ng/ml with a median of 14.9 ng/ml (range: 4.0 - 45.0). Low Vit-D level (below the median) was significantly more common in premenopausal (p=0.011) and ER-negative patients (p=0.011). However, lymphovascular invasion (p=0.001), clinically (p=0.023) and pathologically positive axillary LNs (p=0.041) were linked with higher Vit- D level. After a median follow up period of 58.2 months, 14 patients died and 40 relapsed. The 5-year disease-free survival (DFS) rates was 74.8%. The 5-year DFS rate in patients with higher Vit-D level above the median was 78.8% compared to 71.1% in patients with lower Vit-D level with no statistically significance difference (p= 0.22). The 5-year overall survival (OS) rate was 90.2%. Meanwhile, no difference in 5-year OS rate in patients with higher and lower Vit-D levels (90.3% and 89.7% respectively, p=0.6). **Conclusion:** Low Vit-D level was prevalent among the studied breast cancer patients. Low Vit-D level was associated with ER-negative phenotype and premenopausal patients. Baseline Vit-D level was not significantly linked with survival outcome.

Keywords: Vitamin D- Breast Cancer- prognosis

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Introduction

Vitamin D (Vit-D) plays a vital role in calcium homeostasis, skeletal metabolism in addition to other vital physiological roles. Vit-D deficiency is a common health problem with numerous health consequences including osteomalacia, osteoporosis and fractures in adults [1].

Many reports showed an association between serum Vit-D deficiency and development of several types of cancer, including breast, colorectal, kidney and pancreatic cancers [2-3]. Several studies have confirmed that vitamin D receptors (VDR) are expressed in normal breast tissues and also in breast cancer biopsy specimens [4-5]. Noteworthy, Vit-D promotes apoptosis through the insulin-like growth factor receptor 1 (IGFR)- (PI3K)-Akt-dependent signaling pathway [3-6]. Therefore, deregulation of Vit-D signaling and related metabolic pathways was suggested to play an important role in tumour growth [7]. Meanwhile, large epidemiological studies suggested that Vit- D intake has a protective role

Corresponding Author:
Shereef Elsamany
Oncology Center, King Abdullah Medical City, Makkah Saudi Arabia.
Email: shereefmohamad@yahoo.com

against breast cancer development [8-9].

However, the prognostic value of VDR expression and circulating Vit-D level still remains controversial. Several studies reported that deficiency of Vit-D was associated with poor survival outcome across different tumour types while other studies reported different conclusions [10-13]. The present study aims to assess the prognostic value of Vit-D deficiency among non-metastatic breast cancer patients in a single institution in Saudi Arabia. This may give rise to an easy prognostic parameter that can be assessed in daily practice.

Materials and Methods

Study population

Patients with histologically confirmed non-metastatic breast cancer who presented to King Abdullah Medical City, Saudi Arabia from June 2011 to December 2015, were included. Enrolled patients must have available baseline serum Vit-D level before starting any systemic therapy.

Study design and procedures

In this retrospective study, eligible patients must have adequate medical records. We checked baseline Vit-D level before starting systemic therapy in addition to other clinicopathological factors. Different parameters were collected including age, gender, stage at diagnosis, body mass index (BMI), pathological type, grade, ER, PR and HER2 status in addition to treatment data including type and number of chemotherapy cycles, hormonal therapy and trastuzumab (if applicable). Dates of disease relapse and death if any, were recorded.

Statistical analysis

SPSS version 21 statistical program was used. Descriptive statistics were performed for all clinical, laboratory and pathological data. Low Vit-D was defined as Vit-D level less than 30 ng /ml. The relations of Vit-D level (taking 30 ng/ ml and the median as the cutoffs) with clinico-pathological factors were assessed using Chi-Square test. Different potential prognostic factors were assessed in relation with disease free survival (DFS) and overall survival (OS). Survival data was presented by Kaplan Meier method where cases with no recorded events (death or relapse) were censored at the date of last contact. Comparisons of survival outcome among different parameters were assessed using the log rank test. A two-sided alpha was set at 0.05. DFS was defined as the time from date of breast surgery to date of documented tumour relapse or death. OS was defined as the time from the date of diagnosis of breast cancer till the date of death.

Results

Patients' and tumor characteristics

We screened 340 patients with non-metastatic breast cancer. Baseline Vit-D levels were available for 189 patients with a median level of 14.9 ng/ml (range: 4.0 - 45.0). Noteworthy, 169 (89.4%) of patients had Vit-D level <30 ng/ml. Using 30 ng/ml as the cutoff, there was no significant association between different parameters and Vit-D level. We therefore, used the median Vit-D level as the cutoff to have enough patients for comparison. The median age was 50 years (range: 26- 86 years) and it was significantly lower in patients with lower compared to higher Vit-D levels (47 vs. 51 years respectively, p=0.04). Similarly, Low Vit-D level (below the median) was significantly more common in premenopausal compared to postmenopausal patients (59.4%, 40.9%, respectively, p=0.01) and ER-negative vs. positive patients (63.1% vs 43.5%, respectively, p=0.01). However, lymphovascular invasion (LVI) (72.2% vs. 27.8%, p=0.001), clinically (62.5% vs. 37.5% respectively, p=0.02) and pathologically positive axillary LNs (p=0.04) were linked with higher Vit- D level. However, other clinicopathological factors did not significantly differ according to Vit-D level (Table 1).

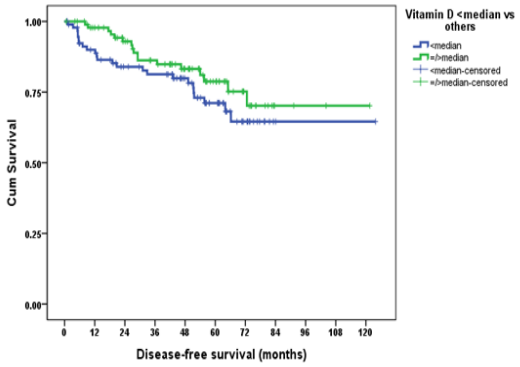

Figure 1. Disease-free Survival of Study Patients According to Vitamin D Level

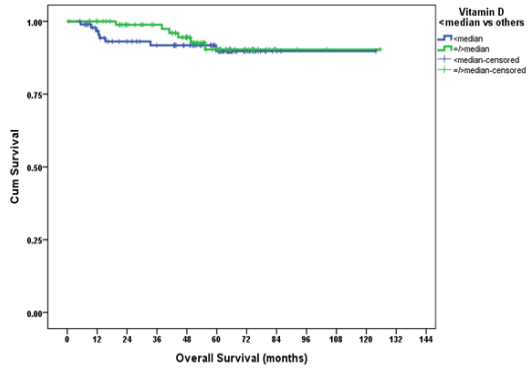

Figure 2. Overall Survival of Study Patients According to Vitamin D Level

Survival outcome

After a median follow up period of 58.2 months, 14 patients died and 40 relapsed. No difference in the rate of relapse between patients with lower vs. higher Vit-D level using different cutoffs, (Table 1). The 5-year DFS rate was 74.8%. Using 30 ng/ml as the cutoff, no difference in DFS between higher and lower Vit-D levels (73.5% vs. 75%, p=0.38) was found. Using the median as the cutoff,

Table 1. Baseline Patients' and Tumor Characteristics According to Vitamin D Level

	Total=189 No	Vitamin D < median No (%)	Vitamin D ≥ median No (%)	P
Parameters				
Median age (range)	50 (26-86)	47 (26-76)	51 (31-86)	0.04
Menopausal status				
Premenopausal	96	57 (59.4)	39 (40.6)	0.01
Postmenopausal	93	38 (40.9)	55 (59.1)	
Body mass index				
<25	19	13 (68.4)	6 (31.6)	
25-29.9	69	31 (44.9)	38 (55.1)	0.25
30-39.9	79	38 (48.1)	41 (51.9)	
≥40	22	13 (59.1)	9 (40.9)	
Pathology				
IDC	178	89 (50.0)	89 (50.0)	0.07
ILC	7	2 (28.6)	5 (71.4)	
Other	4	4 (100.0)	0 (0.0)	
Grade				
Grade 1	11	8 (72.7)	3 (27.3)	
Grade 2	104	51 (49.0)	53 (51.0)	0.07
Grade 3	63	34(54.0)	29 (46.0)	
Unknown	11	2 (18.2)	9 (81.8)	
Lymphovascular invasion				
Yes	54	15 (27.8)	39 (72.2)	<0.001
No	127	76 (59.8)	51 (40.2)	
ER status				
Negative	65	41 (63.1)	24 (36.9)	
Positive	124	54 (43.5)	70 (56.5)	0.01
PR Status				
Negative	82	46 (56.1)	36 (43.9)	0.16
Positive	107	49 (45.8)	58 (54.2)	
HER2 status				
Negative	124	62 (50.0)	62 (50.0)	
Positive	62	33 (53.2)	29 (46.8)	0.19
Unknown	3	0 (0.0)	3 (100.0)	
Clinical Stage				
Stage I	20	12 (60.0)	8 (40.0)	
Stage II	88	41 (46.6)	47 (53.4)	
Stage IIIA	52	30 (57.7)	22 (42.3)	0.42
Stage IIIB	17	6 (35.3)	11 (64.7)	
Unknown	12	6 (50.0)	6 (50.0)	
Clinical T stage				
Tx	13	8 (61.5)	5 (38.5)	
T0	9	4 (44.4)	5 (55.6)	
T1	32	18 (56.3)	14 (43.8)	0.18
T2	80	34 (42.5)	46 (57.5)	
T3	28	18 (64.3)	10 (35.7)	
T4	11	3 (27.3)	8 (72.7)	
Clinical LN status				
Negative	65	38 (58.5)	27 (41.5)	
Positive	72	27(37.5)	45 (62.5)	0.02
Nx	52	30 (57.7)	22 (42.3)	
Pathological N				
Nx	5	1 (20.0)	4 (80.0)	
N0	91	54 (59.3)	37 (40.7)	
N1	49	18 (36.7)	31 (63.3)	0.04
N2	28	16 (57.1)	12 (42.9)	
N3	16	6 (37.5)	10 (62.5)	
Relapse				
Yes	40	23 (57.5)	17 (42.5)	0.30
No	149	72 (48.3)	77 (51.7)	

the 5-year DFS rates were 78.8% vs. 71.1%, in patients with higher compared to lower Vit-D levels, respectively. However, it did not reach statistical significance (p= 0.22) (Figure 1). Lower clinical (p=0.001) and pathological stages (stage I, II) (0.001) and higher BMI (p=0.04) were the only factors associated with better DFS rates. Other clinico-pathological parameters were not linked with DFS outcome (Table 2).

The 5-year OS rate was 90.2%. Using 30 ng/ml as the cutoff, no difference in OS between higher and lower Vit-D levels (93.5% vs. 85%, p=0.09) was found. Similarly, using the median as the cutoff, no difference in 5-year OS rate in patients with higher and lower Vit-D levels (90.3% and 89.7% respectively, p=0.6) (Figure 2). OS was significantly higher in patients with lower pathologic stage (stage I, II), (p= 0.006). Meanwhile, no difference in OS outcome according to other clinico-pathological factors (Table 3).

Discussion

In this study, we assessed the prognostic value of baseline Vit-D level in a cohort of early breast cancer patients in a single institution in Saudi Arabia. Noteworthy, the great majority of patients (89%) had low Vit-D level below the reference value and even half of the patients had considerably low values (< 14 ng/ml).This highlights the prevalence of low Vit-D levels among Saudi patients with a median age of 50 years. This points to the magnitude of the problem of low Vit-D even among this cohort of generally young healthy patients in Saudi Arabia.

Noteworthy, lower Vit-D level was significantly linked with ER-negative phenotype and premenopausal status, features generally linked with more aggressive tumour behavior. Meanwhile, higher Vit-D values were linked with clinically and pathologically-positive lymph nodes and lymphovascular invasion. This conflicting data highlights the need to explore those findings in a larger cohort of patients.

Several studies reported an association between Vit-D deficiency and poor survival. In a prospective study including 512 patients with early breast cancer, low Vit-D was significantly linked with the risk of distant recurrence and overall survival [11]. Similarly, low Vit-D

Table 2. Disease-free Survival in Various Subgroups

Parameters	Total=189 No	5-year DFS (%)	P
Body mass index			
<25	19	81.7%	
25-29.9	69	63.2%	0.04
30-39.9	79	82.6%	
≥40	22	79.5%	
Menopausal status			
Premenopausal	96	70.4%	0.27
Postmenopausal	93	78.9%	
Clinical Stage			
Stag I-II	108	83.0%	0.001
Stage III	69	66.1%	
Clinical T			
T0-2	121	80.6%	<0.001
T3-4	39	58.9%	
Clinical LN status			
Negative	65	77.1%	
Positive	72	74.2%	0.70
Nx	52	74.0%	
Pathology			
IDC	178	74.6%	
ILC	7	60.0%	0.42
Other	4	100.0%	
Multicentricity			
Yes	26	61.7%	0.22
No	163	76.5%	
Lymphovascular invasion			
Yes	54	69.1%	
No	127	77.1%	0.11
Grade			
Grade 1	11	66.7%	
Grade 2	104	74.2%	0.51
Grade 3	63	80.8%	
Unknown	11	62.3%	
ER status			
Negative	65	70.8%	0.18
Positive	124	76.7%	
PR Status			
Negative	82	72.3%	0.40
Positive	107	76.5%	
HER2 status			
Negative	124	77.9%	
Positive	62	70.1%	0.28
Unknown	3	00.0%	
Pathologic T stage			
T0-2	159	76.2%	0.04
T3-4	24	65.2%	
Pathological N			
N0	91	86.8%	0.001
N+	93	62.3%	

Table 2. Continued

Parameters	Total=189 No	5-year DFS (%)	P
Pathological Stage			
Stage 0-II	130	79.6%	0.02
Stage III	57	65.2%	
Chemotherapy cycles Number			
≤6	74	70.6%	0.67
>6	91	74.3	
Chemotherapy Type			
Anthracycline & Taxane	135	70.9%	
Anthracycline only	23	78.3%	0.69
Taxane only	7	83.3%	
Vitamin D			
<median	95	71.1%	0.22
≥ median	94	78.8%	

Table 3. Overall Survival (OS) in Various Subgroups

Parameters	Total 189	5-year OS (%)	P
Body mass index			
<25	19	92.9%	
25-29.9	69	85.3%	0.17
30-39.9	79	91.2%	
≥40	22	100.0%	
Body mass index			
<30	88	86.7%	0.06
≥ 30	101	93.0%	
Clinical Stage			
Stag I-II	108	92.0%	0.16
Stage III	69	87.2%	
Pathology			
IDC	178	91.1%	
ILC	7	53.3%	0.05
Other	4	100.0%	
Menopausal status			
Premenopausal	96	86.6%	0.18
Postmenopausal	93	93.4%	
Clinical T			
T0-2	121	92.8%	0.17
T3-4	39	87.3%	
Lymphovascular invasion			
Yes	54	85.9%	0.13
No	127	92.2%	
Grade			
Grade 1	11	100.0%	
Grade 2	104	87.0%	0.52
Grade 3	63	94.9%	
Unknown	11	87.5%	
Clinical LN status			
Negative	65	91.3%	
Positive	72	89.0%	0.79
Nx	52	91.0%	

Table 3. Continued

Parameters	Total=189 No	5-year DFS (%)	P
ER status			
Negative	65	86.8 %	0.13
Positive	124	91.8 %	
PR Status			
Negative	82	87.6 %	0.21
Positive	107	91.8 %	
HER2 status			
Negative	124	93.3 %	
Positive	62	85.9 %	0.14
Unknown	3	0.00 %	
Pathological T			
T0-2	159	91.1 %	0.22
T3-4	24	85.7 %	
Pathological N			
N0	91	94.0 %	0.09
N+	93	87.5 %	
Pathologic Stage			
Stage 0-II	130	94.0 %	0.01
Stage III	57	82.9 %	
Chemotherapy			
Yes	165	90.4 %	0.95
No	24	86.3 %	
Chemotherapy cycles Number			
≤6	74	90.4 %	0.87
>6	91	90.5 %	
Chemotherapy Type			
Anthracycline & Taxane	135	89.0 %	
Anthracycline only	23	95.0 %	0.61
Taxane only	7	100.0 %	
Vitamin D			
<median	95	89.7 %	0.60
≥ median	94	90.3 %	

level was significantly associated with poor OS and DFS in a larger cohort of 1,295 postmenopausal breast cancer patients [13]. However, despite the fact that several epidemiologic and clinical studies suggested that Vit- D deficiency may be associated with breast cancer outcome, other studies did not display any association. This may be attributed to timing of measurement of the vitamin D, stage, menopausal status and hormonal receptor status [14]. Noteworthy, the association of Vit-D level and survival outcome were assesses in two meta-analyses, involving 8 and 5 studies. These meta-analyses showed an association of low Vit-D level with recurrence in addition to overall and breast cancer-specific mortality in breast cancer patients [15-16].

In our study, Vit-D level was not linked with survival outcome. Meanwhile, almost all patients with low Vit-D, received calcium and Vit-D supplementation later on in their disease course, which may mitigate or modulate any potential prognostic value. Furthermore, only 10% of patients had normal Vit-D levels above the reference value which limits the validity of comparing the survival outcome of low vs. normal Vit-D levels in our study. Meanwhile, there was a trend towards improved DFS in those with higher Vit-D level taking the median as the cutoff. However, that analysis was actually comparing low vs. higher (but still almost lower than normal value). Furthermore, only 14 patients died among the study population, which limits assessment of OS as data is still immature for OS comparison.

In conclusion, low Vit-D level was prevalent among the studied breast cancer patients. Low Vit-D level was associated with ER-negative phenotype and premenopausal patients. Baseline Vit-D level was not significantly linked with survival outcome.

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