International Journal of Research and Review
[Indexed, Peer-Reviewed Journal]
Volume 13; Issue: 7; July 2026
Website: www.ijrrjournal.com
Research Paper *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Low Vitamin D Receptor Expression and Low Vitamin D Levels as Risk Factors for Bone Metastasis in Stage III-IV Breast Cancer Patients

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DOI: https://doi.org/10.52403/ijrr.20260721

ABSTRACT

Bone metastasis is one of the most frequent complications in advanced breast cancer and contributes substantially to morbidity. Vitamin D and the Vitamin D Receptor (VDR) are thought to play a role in bone metastasis by regulating tumor cell proliferation, differentiation, apoptosis, and bone homeostasis. This study aimed to analyze the association of VDR expression and low vitamin D levels with bone metastasis in patients with stage III-IV breast cancer. A case-control study was conducted involving 38 breast cancer patients at Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar, consisting of 19 patients with bone metastasis and 19 without bone metastasis. VDR expression was assessed in tumor tissue by immunohistochemistry using the Immunoreactive Score, while ELISA measured serum vitamin D levels. Statistical analysis included bivariate tests and multivariable logistic regression. Low VDR expression was found in 10.5% of cases and 5.3% of controls, with no significant association with bone metastasis (OR 2.118; p=1.000). In contrast, vitamin D levels <20 ng/mL were more common in the case group than in the control group, 57.9% versus 21.1%, and were significantly associated with bone metastasis (OR 5.156; 95%CI 1.234-21.554; p=0.045). In multivariable analysis, vitamin D levels <20 ng/mL remained independently associated with bone metastasis (aOR 13.629; 95%CI 1.826-101.729; p=0.011). In conclusion, low vitamin D levels were associated with bone metastasis, whereas VDR expression was not significantly associated.

Keywords: breast cancer, bone metastasis, vitamin D, Vitamin D Receptor, VDR

INTRODUCTION

Bone is one of the most common sites of metastasis, alongside the lungs and liver. Metastatic Bone Disease (MBD) is a bone malignancy that is a common complication of breast, prostate, thyroid, colon, rectal, and kidney cancers, and its presence is a marker of poor prognosis with a low five-year survival in breast cancer. Breast cancer itself is the most common malignancy in women worldwide, and despite continued advancements in therapy, as many as 65–75% of patients will develop MBD, and 85% of patients who die have MBD, with an estimated 280,000 new cases of MBD each year in the United States [1]. Once patients are diagnosed with MBD, prognosis worsens, and quality of life decreases due to pathological fractures, spinal cord

compression, or hypercalcemia requiring surgery, radiotherapy, or medication, thus increasing the cost burden and utilization of healthcare resources [2]. To date, many serum biomarkers and pathological examinations have not been widely utilized to predict the risk of bone metastasis in breast cancer patients.

Vitamin D is a hormone that regulates cellular cascades in various body systems, regulates calcium levels, and can inhibit the growth of breast cancer cells. Vitamin D binds to the Vitamin D Receptor (VDR) to modulate proliferation and apoptosis in various cells, including cancer cells, and VDR ligands are known to influence tumor growth and metastatic potential. Loss of VDR promotes the transition of epithelial cells to mesenchymal cells, which increases invasiveness and bone metastasis, and low VDR expression has been shown to increase metastatic potential in melanoma, colorectal cancer, and urothelial cancer. However, few studies have investigated VDR expression and vitamin D levels in relation to bone metastasis in breast cancer [3,4].

Based on this, this study aims to analyze VDR expression and low vitamin D levels as risk factors for bone metastasis in stage III–IV breast cancer patients, so that it is hoped that it can be an alternative in detecting bone metastasis in breast cancer patients.

MATERIALS & METHODS

Research Design

This study is an analytical observational study with a case-control design, which groups subjects into a case group (breast cancer with bone metastasis) and a control group (breast cancer without bone metastasis) to then explore the differences in risk factors summarized in the odds ratio; the study was conducted at Ngoerah Hospital, Denpasar, in the period March 2025 to March 2026.

Study Population

The study population was all breast cancer patients at the Orthopedic Polyclinic and Oncology Polyclinic of Ngoerah General Hospital, with samples consisting of female patients aged 40–65 years who suffered from breast cancer, both with and without MBD; the sample size was calculated using an unpaired categorical comparative formula with a risk factor proportion of 75.2% in the case group and 21.87% in the control group [5], Zα 1.96 and Zβ 0.842, resulting in 38 subjects divided into 19 cases and 19 controls through consecutive sampling techniques.

Eligibility Criteria

Inclusion criteria included patients diagnosed with breast cancer who had undergone biopsy, women aged 40–65 years, with bone metastatic lesions that had been restaged for the case group, and were willing to be research subjects; exclusion criteria included metastases other than bone, bone metastases originating from other primary cancers, incomplete data, and refusal to participate, while subjects who withdrew were categorized as dropouts.

Research Variables

The independent variables were VDR expression and vitamin D levels, the dependent variable was bone metastasis (MBD), and the control variables included age, gender, obesity, parity, comorbidities, metastasis to other sites, and administration of chemotherapy and/or hormonal therapy; VDR expression was assessed in tumor tissue by immunohistochemistry and scored based on the Immunoreactive Score (IRS) which was categorized as low if IRS ≤6 and high if >6 [6], while serum vitamin D levels were measured by the ELISA method and expressed in ng/mL, with low levels defined as 25(OH)D <20 ng/mL according to The Endocrine Society guidelines [7].

Data Collection Procedure

Primary data in the form of vitamin D levels and VDR expression were obtained from the Clinical Pathology and Anatomical Pathology Laboratories, while patient characteristics data were collected through

medical records and confirmation by telephone; immunohistochemical staining was performed using the Automatic Immunostainer Bondmax Leica with tissue cut 5 µm from paraffin blocks, deparaffinized, rehydrated, blocked endogenous peroxidase, antigen retrieval was performed with 0.01 M citrate buffer at 98°C, incubated with VDR primary antibody (mouse monoclonal D-6, sc-13133, Santa Cruz Biotechnology) at a dilution of 1:200, followed by a horseradish peroxidase-based detection system (EnVision+), DAB chromogen, and Mayer's hematoxylin counterstain, then expression was evaluated semiquantitatively in the nucleus and cytoplasm of tumor cells using a light microscope.

Data Analysis

The analysis was conducted using SPSS version 28 software, including descriptive analysis for subject characteristics, bivariate analysis using 2×2 cross tabulation with Chi-square test (Yates correction) or Fisher test if the conditions were not met to obtain the Odds Ratio, as well as multivariate logistic regression analysis by entering all independent variables to obtain the adjusted Odds Ratio, with a p value <0.05 considered significant.

RESULT

Baseline Characteristics of the Subjects

In both groups, most subjects were aged >50 years, namely 14 of 19 patients (73.7%) in the bone-metastatic bone disease (MBD) group and 13 of 19 patients (68.4%) in the control group. Bivariate analysis showed that age >50 years was not significantly associated with the occurrence of MBD (OR 1.292; 95% CI 0.317–5.275; p=0.721). Based on clinical stage, stage IV was more frequent in the MBD group (12 of 19 patients; 63.2%), whereas stage III was more frequent in the control group (11 of 19 patients; 57.9%); however, this difference was not statistically significant (OR 2.357; 95% CI 0.640–8.677; p=0.194). The proportion of patients receiving chemotherapy was higher in the MBD group than in the control group, namely 11 patients (57.9%) versus 5 patients (26.3%), and this difference was statistically significant (OR 3.850; 95% CI 0.980–15.124; p=0.049). Meanwhile, the proportion of patients receiving hormonal therapy was relatively similar between the MBD and control groups, namely 12 patients (63.2%) and 11 patients (57.9%), respectively, with no significant association with MBD (OR 1.247; 95% CI 0.339–4.589; p=0.740).

Table 1. Baseline Characteristics of the Subjects

Characteristic	Case group (n=19)	Control group (n=19)	OR	95% CI	p-value
Age			1.292	0.317–5.275	0.721
>50 years	14 (73.7%)	13 (68.4%)			
≤50 years	5 (26.3%)	6 (31.6%)			
Clinical stage			2.357	0.640–8.677	0.194
Stage IV	12 (63.2%)	8 (42.1%)			
Stage III	7 (36.8%)	11 (57.9%)			
Chemotherapy			3.850	0.980–15.124	0.049*
Yes	11 (57.9%)	5 (26.3%)			
No	8 (42.1%)	14 (73.7%)			
Hormonal therapy			1.247	0.339–4.589	0.740
Yes	12 (63.2%)	11 (57.9%)			
No	7 (36.8%)	8 (42.1%)			

*Statistically significant at p<0.05.

Vitamin D Receptor (VDR) Expression

VDR expression was assessed by immunohistochemistry on breast tumor tissue and scored using the Immunoreactive Score (IRS), then categorized as ≤6 and >6. Most samples in both groups showed VDR

expression >6. In the case group, 17 of 19 patients (89.5%) had VDR expression >6, whereas 2 patients (10.5%) had VDR expression ≤6. In the control group, 18 of 19 patients (94.7%) had VDR expression >6, whereas 1 patient (5.3%) had VDR expression ≤6. Fisher's Exact test showed that the difference in the distribution of VDR expression between the case and control groups was not statistically significant (p=1.000).

Table 2. Association of VDR Expression with the Occurrence of Bone Metastasis

VDR expression	Case group (n=19)	Control group (n=19)	OR	95% CI	p value
≤6	2 (10.5%)	1 (5.3%)	2.118	0.176	1.000
>6	17 (89.5%)	8 (94.7%)			

Analysis using Fisher's Exact test. Results were considered significant at p<0.05.

Serum Vitamin D Levels

Serum vitamin D levels were measured using the enzyme-linked immunosorbent assay (ELISA) method and categorized as <20 ng/mL and ≥20 ng/mL. The MBD group had a higher proportion of vitamin D <20 ng/mL than the control group, namely 11 of 19 patients (57.9%) versus 4 of 19 patients (21.1%), whereas vitamin D ≥20 ng/mL was lower in the MBD group than in the control group, namely 8 of 19 patients (42.1%) versus 15 of 19 patients (78.9%). The Pearson Chi-Square test showed an association between vitamin D <20 ng/mL and the occurrence of MBD, with OR 5.156 (95% CI 1.234–21.554; p=0.045), indicating that vitamin D <20 ng/mL in this study was associated with a higher likelihood of MBD compared with levels ≥20 ng/mL.

Table 3. Association of Vitamin D Levels with the Occurrence of Bone Metastasis

Vitamin D level	Case group (n=19)	Control group (n=19)	OR	95% CI	p value
<20 ng/mL	11 (57.9%)	4 (21.1%)	5.156	1.234–21.554	0.045*
≥20 ng/mL	8 (42.1%)	15 (78.9%)			

Analysis using the Pearson Chi-Square test. Results were considered significant at p≤0.05.

Multivariate Analysis

After controlling for the confounding variables of age, clinical stage, chemotherapy, and hormonal therapy, only vitamin D <20 ng/mL was significantly associated with the occurrence of MBD in breast cancer patients. Patients with vitamin D <20 ng/mL had a 13.629-fold likelihood of developing MBD compared with patients with vitamin D ≥20 ng/mL (aOR 13.629; 95% CI 1.826–101.729; p=0.011). Meanwhile, VDR expression ≤6 showed no significant association with MBD after multivariate adjustment (aOR 1.198; 95% CI 0.054–26.373; p=0.909). Age >50 years was also not significantly associated with MBD (aOR 3.154; 95% CI 0.436–22.819; p=0.255), as were clinical stage IV (aOR 4.195; 95% CI 0.657–26.767; p=0.129), chemotherapy (aOR 7.222; 95% CI 0.615–84.818; p=0.116), and hormonal therapy (aOR 0.935; 95% CI 0.076–11.474; p=0.958).

Table 4. Multivariate Analysis of the Association of Vitamin D Levels and VDR Expression with the Occurrence of MBD After Controlling for Confounding Variables

Variable	B	S.E.	aOR	95% CI	p value
Vitamin D (<20 ng/mL)	2.612	1.026	13.629	1.826–101.729	0.011*
VDR (≤6)	0.181	1.578	1.198	0.054–26.373	0.909
Age (>50 years)	1.149	1.010	3.154	0.436–22.819	0.255
Clinical stage (IV)	1.434	0.946	4.195	0.657–26.767	0.129
Chemotherapy (Yes)	1.977	1.257	7.222	0.615–84.818	0.116
Hormonal therapy (Yes)	-0.067	1.279	0.935	0.076–11.474	0.958

Analysis using logistic regression. Results were considered significant at p≤0.05.

Based on this logistic model, the probability of MBD for a given patient can be calculated using the value of each variable in the equation. In a patient with a relatively favorable profile, namely, vitamin D ≥20 ng/mL, VDR expression >6, age ≤50 years, stage III, not receiving chemotherapy, and not receiving hormonal therapy, the model probability of bone metastasis was approximately 3.2%. Conversely, when the vitamin D level changed to <20 ng/mL with the other factors unchanged, the model probability of MBD increased to approximately 31.3%. In the combination of vitamin D <20 ng/mL, age >50 years, stage IV, and undergoing chemotherapy, the model probability of MBD increased to approximately 97.8% within the study sample.

DISCUSSION

This study found that low VDR expression was not significantly associated with bone metastasis (10.5% in cases vs. 5.3% in controls; OR 2.118; p=1.000), while vitamin D levels <20 ng/mL were significantly associated and remained independent after adjustment for confounding variables (OR 5.156; 95% CI 1.234–21.554; p=0.045; aOR 13.629; 95% CI 1.826–101.729; p=0.011). In baseline characteristics, the MBD group was more likely to have stage IV disease and more likely to have received chemotherapy, a pattern consistent with the predominance of advanced disease in patients with bone metastasis reported by Anwar et al., who also found an association between advanced stage and positive axillary nodes with bone metastasis [8]. Other clinicopathological factors, such as tumor size and postmenopausal status, also contribute to the risk of bone metastasis [9], so differences in stage between groups are potential confounders that are controlled for in multivariate analysis.

Low VDR expression was more common in the MBD group, but the difference was not statistically significant. This result does not negate the biological role of VDR, but rather reflects the limited power of the study due to the small sample size and the very small proportion of low VDR cases in both groups. This finding differs from Ding et al. who, in 119 breast cancer tissues, reported lower VDR expression in bone metastases with an AUC of 0.661 [10], and Horas et al. who showed a decrease in VDR expression in bone metastases compared to paired primary tumors with strong significance [11,12]. Other studies reported that VDR was still detected in many secondary bone lesions [13], while lower VDR expression was associated with aggressive tumor characteristics such as the triple negative subtype [14] and with poorer survival [15]. Differences in immunohistochemical assessment methods between studies may influence the reported proportions. In addition, the detection of VDR protein in immunohistochemistry does not guarantee that the receptor remains functional, because the activity of the vitamin D pathway depends on the ability of VDR to form heterodimers, translocate to the nucleus, and recruit transcriptional coregulators, so that normal expression in staining does not automatically reflect effective VDR signaling.

In contrast, vitamin D levels <20 ng/mL were significantly associated with MBD and were the only independent factor in multivariate analysis. This finding is consistent with Mohamed et al., who reported that baseline vitamin D deficiency increased the risk of bone metastases during follow-up [5]. Vitamin D deficiency is also common in newly diagnosed breast cancer patients [16,18] and tends to worsen during chemotherapy [17], while meta-analyses have shown that higher vitamin D status is associated with better breast cancer outcomes [20]. However, this association is not always consistent across populations, as some studies did not find strong evidence that prediagnosis vitamin D levels alter the association of VDR expression with mortality [19], thus the direction of the association of vitamin D with disease progression may vary. Differences in the threshold for defining deficiency and the

timing of sampling between studies may also explain the variation in reported risk magnitudes.

Biologically, the active form of $1,25(OH)_2D$ works through binding to VDR to regulate the transcription of genes involved in cell cycle control, apoptosis, and differentiation, as well as suppressing processes related to metastasis including epithelial to mesenchymal transition [21]. Experimental data show $1,25(OH)_2D$ reduces the metastatic ability of breast cancer cells in an in vitro model of breast spread to bone [22], while loss of VDR is associated with activation of the Wnt/β-catenin pathway and inflammatory mediators such as IL-6 and IL-8 that promote osteoclastogenesis [23], as well as with a phenotypic shift towards EMT and increased skeletal colonization [12]. At the bone level, vitamin D deficiency accelerates the resorption and release of growth factors from the bone matrix, and animal models show vitamin D deficiency increases intraskeletal tumor growth [24]. This mechanism explains how unfavorable endocrine conditions can amplify the cycle of bone resorption that favors tumor colonization while increasing the morbidity burden of bone metastases in the form of pain, pathological fractures, and medullary compression [25].

The strength of this study lies in the use of two biomarkers simultaneously: immunohistochemical tissue VDR expression and serum vitamin D levels, as well as adjustment for confounding variables through multivariate analysis. However, this study has several limitations. The small sample size reduces the power of the test, particularly for VDR, because the proportion of cases with low expression is very small, so non-significant results should be interpreted with caution. In the multivariate analysis, six variables were included for a limited number of events, as reflected in the very wide confidence interval for the vitamin D aOR (1.826–101.729), making this estimate susceptible to sparse data bias, and its magnitude cannot be interpreted as a precise effect size. The case-control design also cannot confirm temporal relationships, while vitamin D levels, which are influenced by the timing of sampling related to chemotherapy and sun exposure, may influence interpretation [26]. This study is from a single center, so its generalizability is limited.

CONCLUSION

Low vitamin D levels (<20 ng/mL) are an independent risk factor for bone metastasis in stage III–IV breast cancer patients, while low VDR expression does not show a significant association; vitamin D status has the potential to be used as a biomarker in stratifying the risk of bone metastasis, so further research is recommended with a larger sample size and specific according to breast cancer subtype, as well as studies on the effect of vitamin D supplementation on reducing the risk of metastasis.

Declaration by Authors

Ethical Approval: This study has been approved by the ethics committee with approval number 2463/UN14.2.2.VII.14/LT/2025

Acknowledgement: We express our deepest gratitude to all parties for their support of this study.

Source of Funding: All funding was provided by the authors without external sources.

Conflict of Interest: No conflicts of interest declared.

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How to cite this article: Hendra Aryudi Hamzah, I Gede Eka Wiratnaya, Lanang N. A. Artha Wiguna, I Wayan Juli Sumadi. Low vitamin D receptor expression and low vitamin D levels as risk factors for bone metastasis in stage III-IV breast cancer patients. *International Journal of Research and Review*. 2026; 13(7): 175-182. DOI: *https://doi.org/10.52403/ijrr.20260721*

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