Measurement of Vitamin D Levels in Breast Cancer Patients and Association with Mean Platelet Volume: A Single Center Observational Study

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Abstract

Background: Breast cancer is the most common female malignancy. The relationship between vitamin D deficiency and the development of breast cancer is supported in various studies. Likewise, the interactions between platelets and cancers are increasingly investigated these days. Mean platelet volume (MPV) is an inflammatory marker that increases due to inflammation. Studies have shown that Vitamin D plays a pivotal role in lowering inflammation while its deficiency instigates the rise of inflammatory burden.

Objective: The study aimed to assess any relationship between MPV and Vitamin D levels amongst the breast cancer population in our local setting.

Methods: A cross-sectional study was conducted at the Department of Clinical Pathology at AECH INMOL Lahore from May to October 2023. Female patients (n=64) were enrolled after informed consent. Platelet parameters and levels of 25-hydroxyvitamin D were performed using a Sysmex analyzer and Electro chemiluminescence method respectively. The relationship between the variables was analyzed statistically. P Value <0.05 was considered significant.

Results: The mean age of the patient population (n=64) was 45.77+11.62 years. Vitamin D was deficient in 46 (71.9%) patients. Data were stratified according to age which revealed that in the younger patients group (<40 Years, n= 26) only 4 (15.4%) had normal Vitamin D levels while 22 (84.6%) had low serum levels of vitamin D. In older patients (>40) years) normal serum vitamin D levels were seen in 12 (31.6%) while 24 (63.2%) were deficient. Most patients (n=50; 78.1%) had MPV within the normal range (Mean13.66+24.71fL). Only 2 (3.1%) had MPV <8.30 while 12 (18.8%) had values >12.10. An inverse weak but insignificant relationship was found between MPV and vitamin D levels (r = -0.101, p=0.427).

Conclusion: Vitamin D deficiency is highly prevalent in studied breast cancer patients. Non-significant association between elevated MPV and vitamin D deficiency was found. Further studies are required to study the MPV and vitamin D deficiency relationship in a large cohort of patients.

Keywords: *25-Hydroxyvitamin D deficiency, mean platelet volume, breast cancer epidemiology, association, platelets.*

INTRODUCTION

Vitamin D often termed as “sunshine hormone” is a fat-soluble vitamin mainly produced by the skin on exposure to sunlight. It has been related to bone mineralization as well as regulating calcium and phosphate homeostasis for a long time [1]. Current scientific literature has opened new vistas exploring the role of Vitamin D in non-bone tissues for instance brain and musculoskeletal system. Vitamin D receptor is also expressed in cancerous tissues and the role of Vitamin D in modulating various signaling pathways that are linked with cell proliferation, differentiation, and apoptosis has also been demonstrated in preclinical studies [2, 3].

Substantial research is being done showing the relationship between Vitamin D with cancer especially on maintaining normal serum levels for preventive purposes [4]. There is increasing evidence supporting the relationship between vitamin D deficiency and the development of breast cancer. The data is not limited to the development of breast cancer but more aggressive phenotypes have also been linked to vitamin D deficiency [5].

On the other hand, the interactions between platelets and cancers are a topic of interest nowadays. Cancer patients are more susceptible to thrombosis and 20-30% of all first venous thromboembolisms (VTEs) have been observed in these patients. Vitamin D deficiency is also associated with an increase in Mean Platelet volume (MPV) which mirrors the size of platelets and indicates platelet function [6]. Literature supports the inverse association between Vitamin D status and breast cancer risk. There is increasing evidence and epidemiological data available that favors the concept that increased levels of circulating Vitamin D are linked with decreased breast cancer risk and a decrease in MPV. All such observations have increased the interest in the use of Vitamin D for breast cancer prevention.

Vitamin D deficiency is highly prevalent worldwide and reportedly 73% of our population is experiencing vitamin D deficiency [7]. Facts about breast cancer in Pakistan

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are even more alarming. Scientific data published in 2023 has illustrated that Pakistan shares the highest breast cancer death rate in the world. It was also revealed that a rise in breast cancer incidence rate was more than 3 times during 1990-2019 while breast cancer-related deaths increased 2-3 times in this period [8].

Keeping in view all the above-mentioned facts, the present study was designed to assess the status of vitamin D levels and to further establish whether there is a relationship between MPV and Vitamin D amongst the breast cancer population in our local setting.

MATERIALS AND METHODS

It was a cross-sectional study conducted at the Department of Clinical Pathology AECH INMOL Lahore from May to October 2023 after obtaining permission from the institutional review board (INM/PA/15.4023). Nonprobability consecutive sampling was done. Female patients registered at our hospital and referred to the Department of Clinical Pathology for Hematological tests were enrolled after informed consent. Platelet parameters including platelet counts, MPV, PDW, P-LCR, and PCT were performed as a part of CBC using a Sysmex analyzer and data were recorded. Serum levels of vitamin D (25-hydroxyvitamin D) were measured by Electro chemiluminescence (ECLIA) method using a Cobas e 411 analyzer.

The normal range for Mean platelet volume (MPV) was considered between 8.3-12.1 (fL) while Vitamin D levels between 30-100ng/mL were normal. The values above and below these were considered as high and low respectively.

SPSS v.20.0 was used for data analysis. Frequencies and percentages were computed for categorical variables. Numerical variables were summarized as mean ± standard deviation. A chi-square test was applied to compare age groups and MPV levels with vitamin D levels (low, normal, high). The relationship between the variables was analyzed using Pearson's correlation. p-value <0.05 was considered statistically significant. Data were binned concerning age, Vitamin D levels, and MPV.

RESULTS

The mean age of the patients (n=64) was 45.77+11.62 (range: 25.0-72.0) Years (**Table 1**). Vitamin D levels of all enrolled patients were measured. Mean levels of Vitamin D were found to be 27.04 +26.87ng/mL (range: 6.25-107.59), (**Table 1**). Data were binned concerning Serum vitamin D levels as deficient, normal, and high. It was observed that a highly significant population (p<0.001) was Vitamin D deficient. The majority of the patients *i.e.* 46 (71.9%) had low vitamin D levels while normal levels were seen in 16 (25.0%) and only 2 (3.1%) had elevated vitamin D levels (**Table 2**).

Table 1: Patient characteristics and laboratory parameters (n=64).

Variable	Mean value	Standard Deviation	Range (min-max)
Age (Years)	25.77	11.614	25.0-72.0
Platelet Parameters:			
PLT (x103/µL)	313.83	104.687	26.0-686.0
PDW (fL)	12.79	3.24	7.70-20.40
MPV (fL)	13.66	24.71	7.90-208.00
PLCR (%)	32.27	28.80	0.61-240.0
PCT (%)	0.333	0.102	0.13-0.75
Serum Vitamin D Levels (ng/mL):			
Vitamin D	27.041	26.873	6.25-107.59

* PLT= Platelet count, PDW= Platelet distribution width, MPV= Mean platelet volume, PLCR=Platelet larger cell ratio, PCT= Plateletcrit

Table 2: Vitamin D and mean platelet volume (MPV) values in patient population and stratification with respect to age groups.

Variables	Frequencies (%)	p-value
Vitamin D Levels:		
Low	46(71.9)	<0.001
Normal	16(25.0	
High	2(3.1)	
MPV Values:		
Low (< 8.30)	2(3.1)	<0.001
Normal (8.30-12.09)	50(78.1)	
High (12.10+)	12(18.8)	
MPV Values w.r.t. age groups:		
<40 Year age group		0.215
Low (< 8.30)	2(7.7)	
Normal (8.30-12.09)	19(73.1)	
High (12.10+)	5(19.2)	
>40 Years age group		
Low (< 8.30)	0(0)	
Normal (8.30-12.09)	31(81.6)	
High (12.10+)	7(18.4)	

Table 3: Association of vitamin D levels with age groups and MPV levels.

Age(group)	Vitamin D Levels (groups)			p-value	Spearman's rho
	Low n(%)	Normal n(%)	High n(%)		
<40 Years (n=26)	22(84.6%)	4(15.4%)	0(0.0)	0.054	0.242
>40 Years (n=38)	24(63.2%)	12(31.6%)	2(5.3%)		
MPV values:					
Low (n=2)	2(100.0%)	0(0)	0(0%)	0.427	-0.101
Normal (n=50)	36(72.0%)	13(26.0%)	1(2.0%)		
High (n=12)	8(66.7%)	3(25.0%)	1(2.0%)		

Data were stratified concerning age to find out the relationship of vitamin D deficiency with the age of participants (**Table 3**). Out of a total of 64 patients, 26 (40.6%) were <40 years of age while 38 (59.4%) were >40 years. It was observed that younger patients were more deficient in serum vitamin D levels as compared to the older ones (**Table 2**). The difference was statistically insignificant (p=0.137). In the younger patients group (<40 Years, n= 26) only 4 (15.4%) had normal Vitamin D levels while 22 (84.6%) had low serum levels of vitamin D. No patient in this age group had elevated serum levels (**Table 3**). Older patients (>40 years, n=38) had

normal serum vitamin D levels in 12 (31.6%) while 24 (63.2%) were deficient and 2 (5.3%) in this group had elevated Vitamin D levels (**Table 3**).

Hematological tests were performed and platelet counts along with MPV were measured as a part of the complete blood count (CBC) in all patients. The mean platelet count was found to be 313.83 +104.687 (26.0- 686.0). The mean platelet volume (MPV) was 13.66+24. 71fL (7.90-208.0). Platelet parameters are tabulated (**Table 1**). A highly significant (p<0.001) patient population had MPV within the normal range. Out of a total of 64 subjects, 2 (3.1%) had MPV <8.30 while 12 (18.8%) had values >12.10. The majority, 50 (78.1%) had normal MPV values ranging from 8.30-12.09 (**Table 2**). Comparison of MPV with vitamin D levels is detailed in Table **3**. Low MPV was observed in 2 patients and both had low vitamin D levels (**Table 3**). A total of 50 patients had normal MPV with 36(72.0%), 13 (26.0%), and 1(2.0%) having low, normal, and high vitamin D levels respectively in this sub-group (**Table 3**). High MPV was observed in 12 patients with 8 (66.7%), 3 (25.0%), and 1 (2.0%) having low, normal, and high vitamin D levels respectively. MPV levels have been tabulated concerning the age groups of the patients (**Table 2**). Spearman correlation coefficient (rho) was applied and an inverse weak but insignificant relationship was found between MPV and vitamin D levels (r = -0.101, p=0.427), (**Table 3**).

DISCUSSION

Vitamin D is a fat-soluble steroid hormone mainly associated with calcium metabolism and bone health. It is now being linked with hypertension, cardiovascular diseases, and various cancers, especially breast cancer and type 2 diabetes mellitus [9, 10]. A lot of literature is being published identifying the probable link of vitamin deficiency with breast cancer and evaluating the role of normal circulating vitamin D levels (above 45 ng/mL) having a protective role against it [11, 12].

Recent studies and meta-analyses have supported the inverse relationship between vitamin D levels and breast cancer risk. Mohr *et al.* have reported that serum vitamin D levels of 47 ng/mL are associated with a 50% lowering of breast cancer risk [13]. Similar findings have been observed in a recent systematic review showing that elevated serum Vitamin D levels not only decrease the breast cancer risk but also have an association with decreased recurrence rate in breast cancer patients. Conversely, vitamin D deficiency is found to be predominant among breast cancer patients [14, 15].

Our results are in concordance with the literature depicting that a highly significant patient were vitamin D deficient *i.e.* 46 (71.9%) had low vitamin D levels, normal levels were observed in 16 (25.0%), and only 2 (3.1%) had elevated vitamin D levels (**Fig. 1**).

Elderly women aged more than forty years are more affected by vitamin D deficiency because patterns of post-

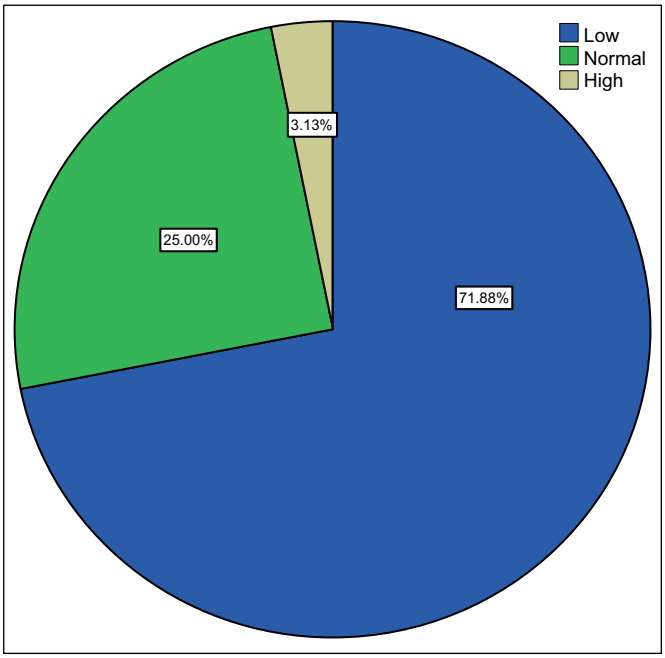

Fig. (1): Patient groups with respect to vitamin D levels.

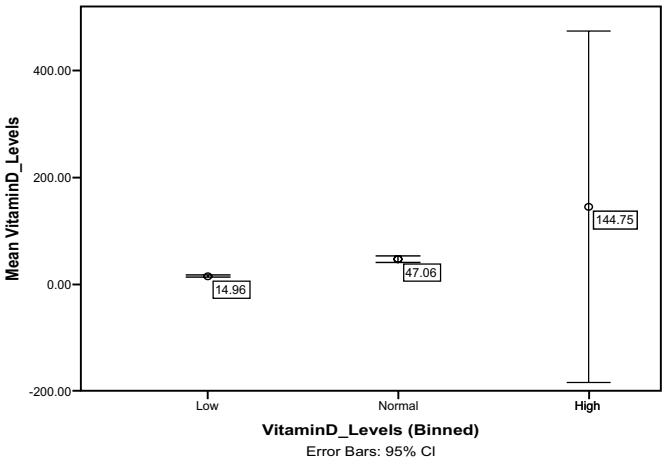

Fig. (2): Mean circulating vitamin D levels in patients groups.

menopausal bone loss and age-related osteoporosis are driven by vitamin D levels [16]. Studies in South Asia have reported vitamin D insufficiency as high as 70.6% -99.7% in adult women [16-18].

The results of our study have shown that vitamin D insufficiency is 63.2% among adult women. To our surprise, the rate was higher in younger women (<40 years) being 84.6%. Similar findings have been reported by Arshad and Zaidi while studying vitamin D levels among children, adolescents, adults, and elders in the Pakistani population [7]. The authors found that Vitamin D deficiency was most common in adolescents followed by children 6-12 and adults 19-50 years 71%, 65%, and 59% respectively. While elders >50 years old had only 45% vitamin D deficiency. Elderly people had 28% vitamin D sufficiency which was the highest among all age groups [7] (**Fig. 2**). Lesser exposure to the ultraviolet sun rays, increasing indoor lifestyle, and nutritional deficiencies may be the underlying reasons.

The researchers are now working on the relationship of vitamin D deficiency with elevated inflammatory markers including mean platelet volume. Mean platelet volume (MPV) corresponds to the platelet size which tends to become larger after some infections or inflammatory stimuli [19].

It has been observed that vitamin D deficiency even in healthy subjects may result in increased MPV [20]. Moreover, studies have shown that vitamin D deficiency triggers more immense inflammation in immuno-compromised patients while vitamin D has a positive impact on lowering inflammatory burden [21, 22]. High MPV values generally indicate low-grade inflammatory diseases. Elevated levels are also observed in ulcerative colitis, Fibromyalgia, coronary artery disease, venous thromboembolism, diabetes, hypertension, and stroke [1, 6].

We have observed MPV levels in our patient population. Most of our patients had MPV within the normal range *i.e.* 50 (78.1%) while 12 (18.8%) had an elevated level. MPV was further correlated with vitamin D levels by applying the Spearman correlation coefficient (rho). An inverse weak but insignificant relationship was found between MPV and vitamin D levels (r=-0.101, p=0.427). A similar weak inverse (r=0.17) relationship was also determined between these two by Yildirim *et al.* in patients with Fibromyalgia [1].

Similarly, alteration of MPV is reported in breast, ovarian, gastric, colon, and lung cancer [23]. Furthermore, the studies on the clinical significance of platelet volume indices including MPV and PDW have shown that these parameters were significantly higher in metastatic patients as compared to the locally advanced disease. While both (local and metastatic) groups had significantly high levels as compared to the controls [24]. In our case, the significance couldn't be achieved may be due to the small sample size. Population-level studies may be designed to find the association.

The results of our study warrant the measurement of vitamin D levels in breast cancer patients especially in those patients where MPV is found to be high. Measurement of Vitamin D levels not only has preventive role in breast cancer but it has a potential against disease recurrence.

Our study has certain limitations like it was a single-centered study and stages were not taken into account because of the small sample size. Moreover, we could not determine the effects of Vitamin D levels and MPV on disease prognosis due to time constraints. Further studies with large sample sizes and more follow-up time may be useful to enlighten the correlation.

CONCLUSION

Vitamin D deficiency is highly prevalent in breast cancer patients in our local setting. In a developing country like Pakistan which has an alarmingly high rate of both breast cancer and Vitamin D deficiency, awareness campaigns for improving serum levels of Vitamin D as a modifiable risk factor of breast cancer may help in breast cancer prevention and prognosis. In this study, elevated MPV was not significantly associated with vitamin D deficiency. However, an inverse weak relationship was observed. Further studies with a larger cohort may be planned to find a potential relationship.

ETHICS APPROVAL

Ethical approval was obtained from the Institutional Ethical Review Board (INM/PA/15.4023. All procedures performed in studies involving human participants followed the ethical standards of the institution and the Helsinki Declaration.

CONSENT FOR PUBLICATION

Written informed consent was taken from the participants.

AVAILABILITY OF DATA

Data is available from the corresponding author on a reasonable request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

Dr. Mariam Faiz and Dr. Amira Shami designed the study. Fatima Malik and Muhammad Numan collected data from medical records. Dr. Ismat Fatima analyzed the data. Dr. Mariam Faiz and Dr. Ismat Fatima drafted the manuscript. All authors have critically reviewed and approved the final draft and are responsible for the content.

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