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(RESEARCH ARTICLE)

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The vitamin- D quantity versus bone quality: A logistic based regression modeling in Jordanian cohort who at higher risk of osteoporotic fracture

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Abstract

Background: Several studies validated the positive impacts of Cholecalciferol derivatives; including dietary and non-dietary sources, on the bone architectural contents and the overall skeleton densities. We primarily aimed in this study to explore the optimal thresholds for the studied patients' 25-OH Cholecalciferol levels that are correlated with the higher probabilities for having lumbar bone mineral density (LBMD) exceeding 0.835 g per cm2 and femoral hip bone mineral density (fH_BMD) exceeding 0.755 g per cm2.

Methods: An observational retrospective study was conducted for patients, who are at risk of osteoporotic fracture, Firstly, a Binary Logistic Regression analysis was separately conducted for the investigated patients' vitamin D levels against the patients' fH_BMD ≥0.755 (Positive state) vs <0.755 (Negative state) and against the patients' LBMD≥ 0.835 (Positive state) vs <0.835 (Negative state). Both the Receiver Operating Characteristic and the Sensitivity analyses were thereafter be conducted and the performances indices were explored.

Results: Our constructed BLgR models, that logistically integrated the binary correlation between the investigated patients' Vit D levels and their femoral hip or lumbar bone mineral densities, respectively, were constructed as $[= e^{(-1.455+0.109\times \text{Vit D})} / 1+ e^{(-1.455+0.109\times \text{Vit D})}]$ or $[= e^{(-22.127+0.829\times \text{Vit D})} / 1+ e^{(-22.127+0.829\times \text{Vit D})}]$, respectively.

Conclusion: The optimal Vitamin D levels for our investigated Jordanian cohort to have a higher probability of lumber and femoral hip bone mineral; densities were identified at 27.05 ng/ml and 27.25 ng/ml, respectively.

Keywords: Vitamin D levels; 25-hydroxy Cholecalciferol; Binary Logistic Regression; Bone mineral density; Osteoporotic fracture; Jordanian cohort

1. Introduction

Cholecalciferol, the scienfic name of Vitamin D, is maninly synthesized the skin under the impact of ultraviolet light or more commonly obtained directly from dietary sources or phrmaceutical formulations. Animal livers and fish oils are commonly considered as a rich source of dietary vitamin D [1-2].

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Both the animal (Cholecalciferol) and the plant (Ergocalciferol) forms of Vitamin D are physiologically inactive and need in-vivo two sequential hydroxylation processes in the liver and kidney at 25 and 1 carbons via organ specific organ hydroxilase enzymes, respectievly. The final 1, 25 dihydroxy-Cholecalciferol form is the physiologically active form of Vitaminb D and is frequently signed as Calcitriol [3-5].

Endogenously, the Calcitriol enter most cells to bind various tissue specific Vitamin D receptors. Binding the Vitamin D receptors will subsequently activate the responsive gene to synthesize more calcium binding proteins. These calcium binding proteins will mediate most of the Vitamin D physiological functions, of particular the active absorption of calcium from the gut and suprress the synthesis rate of the parathyroid hormone (PTH). Mechanistically, the PTH enhance Vitamin D hydroxaltion in the kidney at position 1 and conversely will negatively affect the PTH secretion. (6-7)

The major long-term clinical consequences of the Vitamin D deficiency are primarily encountered on the lower bone-mineralization tendencies and consequently higher probability of low bone minerals quantity and overall poor bone quality. A dual low bone quantity and quality is traditionally known as a strong confounder in patients with higher risk of osteoporotic fracture [8-9].

We primarily aimed in this study to explore the optimal thresholds for the studied patients' 25-OH Cholecalciferol levels that are correlated with the higher probabilities for having lumbar bone mineral density (LBMD) exceeding 0.835 g per cm2 and femoral hip bone mineral density (fH_BMD) exceeding 0.755 g per cm2.

2. Material and methods

This observational study trial was retrospectively pursued for patients who attended to the rehabilitation clinic between Sep 2021 and Nov 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid/Jordan. Assessed patients with evidences for bone metastasis, renal/non—renal metabolic osteodystrophy, actively on anti-resorptive therapy were excluded from this study.

Dual-emission X-ray absorptiometry (DEXA) scans of the proximal femoral hip and anteroposterior spine participant's data were used to yield both the study's tested dependent outcomes; the femoral hip bone mineral density (fH_BMD) and the lumbar bone mineral density (LBMD). The corresponding bone mineral densities (BMDs) were automatically calculated from the DEXA related T and Z scores.

Firstly, the Binary Logistic Regression (BLgR) analysis was conducted for the tested patients' Vit D levels against the probability for patients having LBMD ≥0.835 g/cm^2 or fH_BMD≥0.755 g/cm^2 (the positive actual state which was assigned as 1) versus the probability for patients having LBMD <0.835 g/cm^2 or fH_BMD≥0.755 g/cm^2 (the negative actual state which was assigned as 0), to explore the degree of correlations, determine how much of total variations in the dependent variable can be explained by the independent variables, and assess the quality of the prediction of the dependent variable.

Secondly, the Receiver Operating Characteristic (ROC) test was conducted to explore the area under the ROC curves (AUROCs) for the tested prognosticator; the patients' Vit D level, against the patients' LBMD ≥0.835 g/cm^2 versus LBMD <0.835 g/cm^2 or fH_BMD≥0.755 g/cm^2 versus fH_BMD<0.755 g/cm^2. Thereafter, the sensitivity analysis was processed on a total of 206 processed cases for the aforementioned investigated prognosticator against the two dichotomized lumbar and femoral related BMDs.

The Sensitivity analysis was primarily conducted to explore the optimal cut-off points, sensitivities (TPRs), specificities (TNRs), positive and negative predictive values (PPVs and NPVs), positive and negative likelihoods ratios (PLRs and NLRs), and the Youden and accuracy indices (YIs and AIs). All the three previously conducted analysis tests were used to illustrate the binary logistic regression correlation for the patients' Vit D levels versus LBMD and fH_BMD. Statistical analysis was performed using Statistical Package for Social Science (SPSS) software version 23.0. Statistical significance was set at 5%.

3. Results

Our constructed BLgR models, that logistically integrated the binary correlation between the investigated patients' Vit D levels and their femoral hip or lumbar bone mineral densities, respectively, were constructed as [$= e^{(-1.455+0.109\times \text{Vit D})} / 1+ e^{(-1.455+0.109\times \text{Vit D})}$] or [$= e^{(-22.127+0.829\times \text{Vit D})} / 1+ e^{(-22.127+0.829\times \text{Vit D})}$], respectively.

The explained variations in the two separately investigated dependent variable; LBMD and fH_BMD, against the tested patients' Vit D levels and based on our explored BLgR models ranged from 12.2%-18.1% and 65.2%-86.9%, respectively, depending on whether you reference the Cox & Snell R2 or Nagelkerke R2 methods, respectively. Also, approximately 76.7% and 94.2%, respectively, of the cases can be correctly and significantly classified based on the two constructed BLgR models.

The ROC analysis was conducted on a total of 206 eligible tested patients. Actually, 155 cases and 103 cases versus 51 and 103 were considered as the positive states of outcomes of interest (OI) [LBMD≥0.835 g/cm^2 and fH_BMD≥0.755 g/cm^2] versus the negative states of OI [LBMD<0.835 g/cm^2 and fH_BMD<0.755 g/cm^2]. The AUROC±SEMs were determined at 0.739±0.034 (95% CI; 0.672-0.806) and 0.981±0.009 (95% CI; 0.964-0.998), respectively.

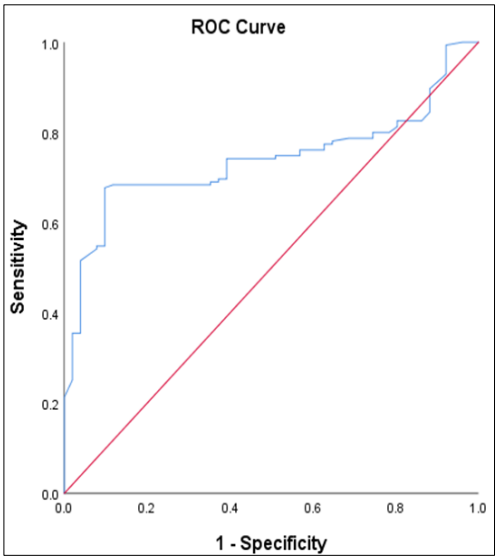
The optimal Vit D levels in this study for our investigated Jordanian cohort for the LBMD≥0.835 g/cm^2 rather than <0.835 g/cm^2 and the fH_BMD≥0.755 g/cm^2 rather than <0.755 g/cm^2, were identified at 27.05 ng/ml and 27.25 ng/ml, respectively. These 2 explored optimal patients' Vit D threshold had sensitivities, specificities, and accuracy indices of [67.7%, 90.20%, and 73.30%] and [99%, 94.17%, and 97.83%], respectively. Other Sensitivity indices were fully presented on the Table 2. All other tested patients' analysis results and illustrations were clearly and fully presented in Table 1 and Figure 1-2.

Table 1. The Binary Logistic Regression analysis for the Jordanian investigated patients Vit D levels, who attended to the rehabilitation clinic between Sep 2021 and Nov 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid/Jordan, against the probability of having LBMD≥0.835 g/cm^2 or fH_BMD≥0.755 g/cm^2

Tested predictors	B±SEM	Wald	Sig.	Exp(B)	95% C.I.for EXP(B)		χ2(df)	VR	%Cases
					Lower	Upper			
LBMD≥0.835 g/cm^2	= $e^{(--1.455+0.109\times \text{Vit D})}$ /1+ $e^{(--1.455+0.109\times \text{Vit D})}$								
Vit D (ng/ml)	0.109±0.023	21.945	0.000	1.115	1.065	1.167	(8) 33.287	12.2%-18.1%	76.7%
Constant	-1.455±0.537	7.338	0.007	0.234					
fH_BMD≥0.755 g/cm^2	= $e^{(--22.127+0.829\times \text{Vit D})}$ /1+ $e^{(--22.127+0.829\times \text{Vit D})}$								
Vit D (ng/ml)	0.829±0.159	27.111	0.000	2.291	1.677	3.130	(8) 4.149	65.2%-86.9%	94.2%
Constant	-22.127±4.39	25.308	0.000	0.000					

The Binary Logistic Regression (BLgR) analysis was conducted for the tested patients' Vit D levels against the probability for patients having LBMD ≥0.835 g/cm2 or fH_BMD≥0.755 g/cm2 (the positive actual state which was assigned as 1) versus the probability for patients having LBMD <0.835 g/cm2 or fH_BMD≥0.755 g/cm2 (the negative actual state which was assigned as 0), to explore the degree of correlations, determine how much of total variations in the dependent variable can be explained by the independent variables, and assess the quality of the prediction of the dependent variable.

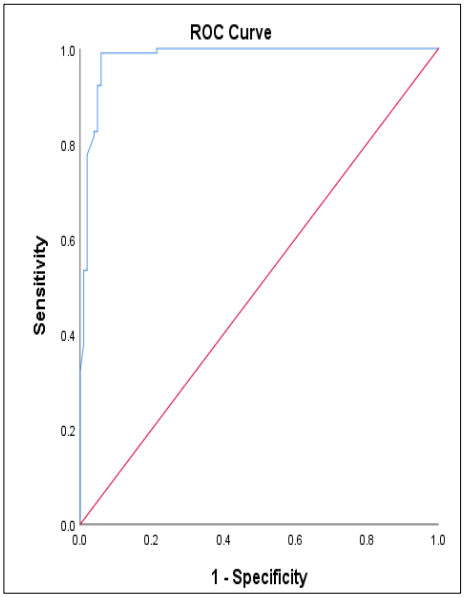
The patients' Vit D levels against the patients' LBMD≥0.835 g/cm² vs <0.835 g/cm²



Positive OI (LBMD≥0.835 g/cm²)	155
Negative OI (LBMD<0.835 g/cm²)	**51**
Missing	**3**

AUC±SEM	p-Value
0.739±0.034 (95% CI; 0.672-0.806)	**0.000**

The patients' Vit D levels against the patients' fH_BMD≥ 0.755 g/cm² vs <0.755 g/cm²



Positive OI (fH_BMD≥0.755 g/cm2)	103
Negative OI (fH_BMD<0.755 g/cm2)	103
Missing	3

AUC±SEM	p-Value
0.981±0.009 (95% CI; 0.964-0.998)	0.000

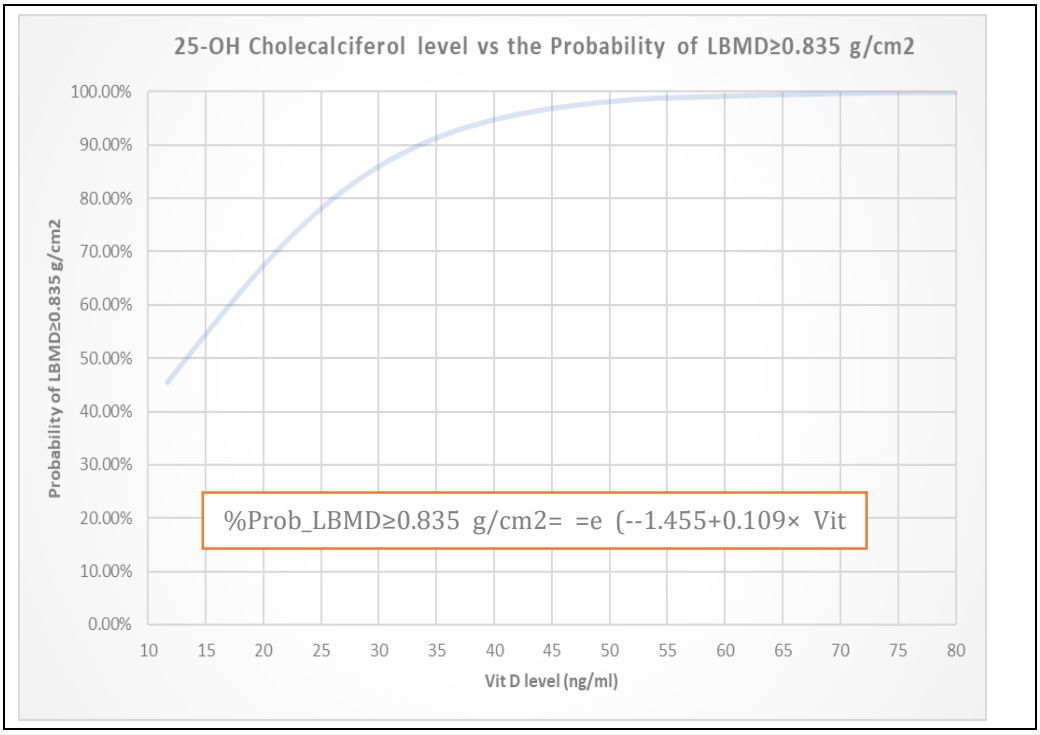
Figure 1 The Receiver Operating Characteristic (ROC) test was conducted to explore the area under the ROC curves (AUROCs) for the tested prognosticator; the patients' Vit D level, against the patients' LBMD ≥0.835 g/cm² or fH_BMD≥0.755 g/cm² (the positive actual state which was assigned as 1) versus the patients' LBMD <0.835 g/cm² or fH_BMD≥0.755 g/cm² (the negative actual state which was assigned as 0), respectively, for patients who attended to the rehabilitation clinic between Sep 2021 and Nov 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid/Jordan

Table 2 The optimal cut-off points, TPRs, TNRs, FPRs, YIs, TNRs, PPVs, NPVs, NLRs, PLRs, and AIs for the tested prognosticator; the patients Vit D levels, against the patients' LBMD ≥0.835 g/cm2 or fH_BMD≥0.755 g/cm2) versus the patients' LBMD <0.835 g/cm2 or fH_BMD≥0.755 g/cm2, respectively, for patients who attended to the rehabilitation clinic between Sep 2021 and Nov 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid/Jordan.

Prognostic Indicator	Cutoff	TPR	FPR	YI	TNR	PPV	NPV	NLR	PLR	AI
LBMD≥0.835 g/cm²										
Vit D level (ng/ml)	27.05	67.7%	9.8%	57.94%	90.20%	95.45%	47.92%	35.76%	690.97%	73.30%
fH_BMD≥0.755 g/cm²										
Vit D level (ng/ml)	27.25	99%	5.8%	93.20%	94.17%	98.10%	96.96%	1.03%	1700%	97.83%

The sensitivity analysis was processed on a total of 206 processed cases for the investigated prognosticator; the patients' Vit D levels, in the Jordanian investigated patients, against the patients' LBMD ≥0.835 g/cm2 or fH_BMD≥0.755 g/cm2 (the positive actual state which was assigned as 1) versus the patients' LBMD <0.835 g/cm2 or fH_BMD≥0.755 g/cm2 (the negative actual state which was assigned as 0), respectively, for patients who attended to the rehabilitation clinic between Sep 2021 and Nov 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid/Jordan.

The Sensitivity analysis was primarily conducted to explore the optimal cut-off points, sensitivities (TPRs), specificities (TNRs), positive and negative predictive values (PPVs and NPVs), positive and negative likelihoods ratios (PLRs and NLRs), and the Youden and accuracy indices (YIs and AIs)



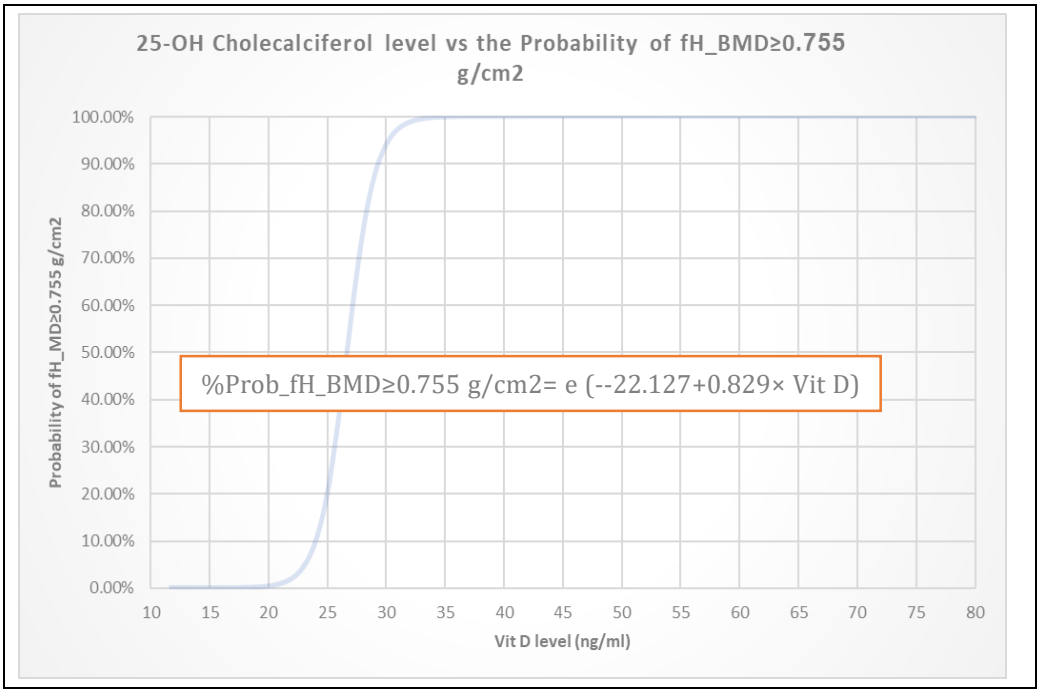


Figure 2 The Binary Logistic Regression correlation between the patients' Vit D levels, as measured 25-hydroxy Cholecalciferol, against the probability for patients having LBMD ≥0.835 g/cm2 or fH_BMD≥0.755 g/cm2 (the positive actual state which was assigned as 1) versus the probability for patients having LBMD <0.835 g/cm2 or fH_BMD≥0.755 g/cm2 (the negative actual state which was assigned as 0), for patients who attended to the rehabilitation clinic between Sep 2021 and Nov 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid/Jordan

4. Discussion

Our retrospective observational study was conducted on a wide investigational aged Jordanian cohort of both genders, to explore the optimal thresholds for the studied patients' 25-OH Cholecalciferol levels that were accompanied with higher BMDs on lumbar and femoral hip.

A positive and significant association between the patients' Vitamin D level against the patients' LBMD or fH_BMD, has been noted in our study. According to the constructed BLgR models, an odd ratio of 1.115 for having a probability of LBMD≥0,835 g/cm2 over LBMD <0.835 g/cm2 were substantially revealed, particularly when the 25-OH Cholecalciferol levels were not less than 27.05 ng/ml. Similarly, an odd ratio of 2.291 for having a probability of fH_BMD≥0,755 g/cm2 over fH_BMD<0.755 g/cm2 was significantly observed in this study, especially when the 25-OH Cholecalciferol levels were above 27.25 ng/ml.

5. Conclusion

Our results revealed significant positive logistic regression correlations between the patients' Vitamin D statuses and levels for having LBMD≥0.835 g/cm^2 and fH_BMD≥0.755 g/cm^2 and consequently higher probability of lower osteoporotic fracture risk. The optimal Vit D levels in this study for our investigated Jordanian cohort were identified at 27.05 ng/ml and 27.25 ng/ml, respectively. This study is limited by its retrospective design, single-center, and relatively small sample size.

Compliance with ethical standards

Acknowledgement

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Disclosure of conflict of interest

There is no conflict of interest in this manuscript

Statement of ethical approval

There is no animal/human subject involvement in this manuscript

Statement of informed consent

Owing to the retrospective design of this study, the informed consent form was waived.

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