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25-hydroxy vitamin D levels in patients with myelofibrosis and potential relationships with disease severity: A case-control study

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Ethics Committee Approval
The study was approved by the Clinical Research Ethics Committee of Dr. Lütfi Kırdar State Hospital (decision date: December 29, 2021, decision number: 2021/514/216/5).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Although vitamin D deficiency has been associated with cancer and its prognosis, data is unclear regarding associations with myelofibrosis. This study aimed to measure 25-hydroxy vitamin D levels in patients with myelofibrosis and to evaluate its relationship with prognoses.
Methods: This case-control study consisted of 72 patients with myelofibrosis and 75 controls. The Dynamic International Prognostic Scoring System was used to determine prognostic risk groups, and patients were divided into two subgroups: intermediate-1 (low risk) and intermediate-2 (high risk).
Results: The median 25-OHD levels were decreased in the myelofibrosis group more so than in the controls (13.05 vs. 23.0 ng/mL, $P<0.001$). A cut-off value of ≤ 16.5 ng/mL yielded a sensitivity of 84.72% and a specificity of 80% for the identification of patients with myelofibrosis. This impact was also evident when adjusted for age and sex, showing that patients with low 25-hydroxy vitamin D (≤16.5) had a 23.787-fold higher probability to have myelofibrosis (OR: 23.787, 95% CI: 9.676-58.479, $P<0.001$). When examined for the two prognostic subgroups, 25-hydroxy vitamin D was found to be significantly lower in the intermediate-2 and high subgroup ($P=0.017$). For a cut-off value of ≤13.7 ng/mL, 25-hydroxy vitamin D level was able to discriminate patients in the intermediate-2 and high subgroup from those with lower risk (sensitivity: 77.8%, specificity: 55.6%).
Conclusion: A serum 25-hydroxy vitamin D level may serve as a biomarker associated with myelofibrosis diagnosis and prognosis; however, the discriminatory value for prognostic groups was low, indicating the need for larger and longitudinally-designed studies.

Keywords: dynamic international prognostic scoring system, myeloproliferative neoplasm, myelofibrosis, prognosis, vitamin D

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Introduction

Myelofibrosis is an uncommon hematological neoplasm arising from clonal abnormalities in stem cells, displaying both clinical and biological heterogeneity [1]. It has an incidence between 0.47 and 1.98 per 100,000 individuals, and greatly shortens life expectancy (median survival 5.2–5.9 years) [2,3]. Clinical presentation varies greatly from patient to patient, but typically includes debilitating systemic effects such as weight loss, night sweats, fever, hepatosplenomegaly, and vascular complications. Additionally, myelofibrosis can lead to the development of acute leukemia [3]. Disruption of the JAK/STAT signaling pathway is a recognized mechanism leading to myelofibrosis, resulting in myeloproliferation, cytopenia, cytokine secretion, bone marrow hyper-cellularity, collagen and reticulin fibrosis, bone modification and extramedullary hematopoiesis [4]. Given the high variability in clinical presentation and short survival, it is critical to identify determinants that can be used to guide treatment decisions and act as prognostic indicators.

A pleiotropic, fat-soluble secosteroid hormone with a major regulatory function in calcium and phosphorus homeostasis, vitamin D is recognized as contributing to a wide range of disease conditions [5]. Vitamin D also plays a crucial role in the immune system as an anti-inflammatory, immunomodulatory, anti-fibrotic, and antioxidant molecule, and is also involved in the pathogenesis of various clinical conditions in non-skeletal tissues, including malignancies [6,7]. Vitamin D may inhibit tumorigenesis by modulating inflammatory responses, cellular survival, cell-cell interactions, and angiogenesis –all of which can impact cancer spread and progression [8]. Previous observational studies have found a link between vitamin D deficiency and a higher chance of developing cancer as well as a worse prognosis [9]. To date, there have been case reports examining vitamin D levels in patients with myelofibrosis, but the results are uncertain and information regarding its clinical or prognostic significance is lacking [10]. Therefore, our goal was to measure 25-hydroxy vitamin D levels in myelofibrosis patients and assess any potential associations with the prognosis of the condition.

Materials and methods

Study population

This case-control study was carried out between May 2022 and May 2023 in the Department of Hematology of Kartal Dr. Lutfi Kirdar City Hospital, Istanbul, Turkey. The study had 72 myelofibrosis patients who were 18 years of age or older and 75 healthy controls. Subjects in the healthy control group were consecutively included among those referred for routine evaluations from primary care physicians, given that they were not referred for any specific suspicion and did not have any comorbidities. The patient group was chosen based on inclusion/exclusion criteria.

Myelofibrosis was diagnosed using the updated World Health Organization 2022 categorization criteria, which were supported by biochemical analysis, cytogenetic testing, and bone marrow biopsies [11]. Participants with a history of chronic or inflammatory diseases, rheumatological disorders, severe liver or kidney disease, and malignancies other than myeloproliferative neoplasms were excluded from the study. Subjects referred for allogenic stem cell transplantation, or participants presenting with acute malignancies such as AML or ALL were also excluded. The control group was comprised of 75 healthy people aged 18 years and older, with no history of malignancies and no known disease. Sex, age, body mass index (BMI), smoking status, type of myelofibrosis, Eastern Cooperative Oncology Group (ECOG) performance status, and the presence of comorbid conditions like ischemic heart failure, hypertension, diabetes mellitus, peripheral arterial hypertension, hypothyroidism, or hepatomegaly were obtained from files and pertinent records. Additionally, spleen size, peripheral blood blasts, presence of constitutional symptoms such as weight loss, night sweats and fever were recorded based on the Dynamic International Prognostic Scoring System (DIPSS). In addition, cytogenetic profiles were examined, including mutations of Janus kinase (JAK) 2, JAK2 exon 12, calreticulin (CALR), and myeloproliferative leukemia virus oncogene (MPL), all of which were collected from the most recent data available for each subject.

The Kartal Dr. Lutfi Kirdar City Hospital's Clinical Study Ethics Committee accepted all study methods. All ethical principles specified in the Declaration of Helsinki (Decision date: 29.05.2023 and Decision number: 2023/514/250/7) were also accepted.

Prognostic stratification

DIPSS is prognostic risk stratification tool. It is calculated by utilizing five variables: 1 point for age >65 years, 2 points for hemoglobin value <10 g/dL, 1 point for peripheral blood blasts ≥1%, 1 point for presence of constitutional symptoms, and 1 point for white blood cell counts $>25 \times 10^9$/L [4]. Risk groups were as follows: low-risk (0 points), intermediate-1 risk (1 or 2 points), intermediate-2 risk (3 or 4 points), and high-risk (5 or 6 points). All myelofibrosis patients were evaluated using a DIPSS score at the time of the last follow-up. ECOG performance status was employed to evaluate functionality by determining an individual's level of functioning in relation to daily activities and physical capabilities, including work and walking. This assessment was quantified on a scale ranging from 0 to 5 points [12]. A lower ECOG score of 0 and 1 defines fewer activity restrictions, while a higher score indicates elevated disability or mortality. All measurements were carried out by the same clinician with strict measures to ensure reliability and reproducibility.

Biochemical analysis

Each participant was asked to provide blood samples, which were drawn from the antecubital vein following an overnight fast in preparation for the laboratory analyses. To collect serum, serum separator tubes were centrifuged at 2400 g for 7 minutes. Using a Mindray BC-6800 analyzer (Mindray, China), the full blood count, comprising hemoglobin and the hematocrit levels, mean corpuscular volume (MCV), white blood cell (WBC), and platelet values, were determined. On an Architect c8000 autoanalyzer (Abbott, USA), serum creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), total protein, albumin, and C-reactive protein (CRP) were measured. Using a UniCel DxI

800 (Beckman Coulter, USA), a chemiluminescent enzyme immunoassay was used to measure the levels of 25-hydroxyvitamin D and vitamin B12. Of note, mutation analyses including JAK2, JAK2 exon 12, CALR, and MPL were performed in duplicate at the hospital.

Statistical analysis

The data analysis was conducted using IBM SPSS Statistics for Windows, Version 28.0. The normality of distribution was assessed using the Shapiro-Wilk test. Continuous variables were presented as mean (standard deviation) or median (1st quartile-3rd quartile), depending on the normality of distribution. Categorical variables were expressed as frequency (percentage). For normally distributed variables, the Student's t-test was used for analysis, while the Mann-Whitney U test was employed for non-normally distributed variables. Categorical variables were analyzed using chi-square tests or Fisher's exact tests as appropriate. The discrimination performance of 25-hydroxy vitamin D was assessed through the receiver operating characteristic (ROC) curve analysis. The Youden index was used to calculate the best cut-off positions. For the chosen cut-off values, sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Odds ratios (OR) were also computed for the determined cut-off points using logistic regression analysis. The cutoff for statistical significance was *P*-value <0.05.

Results

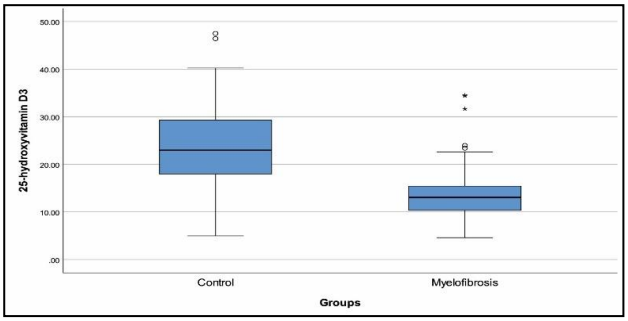
Seventy-two patients diagnosed with myelofibrosis and 75 healthy individuals were enrolled in the study. The mean age in the patient group was 63.71 (7.87) years, and 44 (61.11%) were males. The control group consisted of 40 (53.33%) males, and the mean age was 60.59 (10.21) years. The groups were similar for age and sex distribution. The mean 25-hydroxy vitamin D levels were 13.05 (10.35-15.45) ng/mL in the myelofibrosis group and 23.0 (17.7-29.5) ng/mL in the control group (*P*<0.001) (Table 1, Figure 1).

Table 1: Summary of age, sex and 25-hydroxy vitamin D levels with regard to groups

		Groups		
	Total (n=147)	**Control (n=75)**	**Myelofibrosis (n=72)**	***P*-value**
Age, years	62.12 (9.24)	60.59 (10.21)	63.71 (7.87)	0.039
Sex				
Male, (n/%)	84 (57.14%)	40 (53.33%)	44 (61.11%)	0.341
Female, (n/%)	63 (42.86%)	35 (46.67%)	28 (38.89%)	
25-hydroxy vitamin D, ng/mL	16.12 (12.40-24.30)	23.00 (17.70-29.50)	13.05 (10.35-15.45)	<0.001

Data are given as mean (standard deviation) or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.

Figure 1: Box-plot of the 25-hydroxy vitamin D with regard to groups



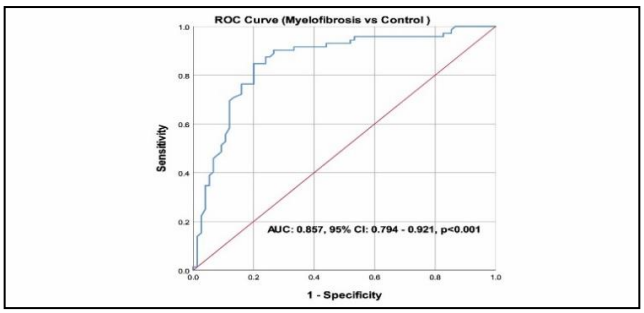
We determined the 25-hydroxy vitamin D level to distinguish between myelofibrosis patients and healthy controls by ROC analysis. The sensitivity and specificity values for the cut-off (≤16.5 ng/mL) were 84.72% and 80%, respectively. Patients with a low 25-hydroxy vitamin D level (≤16.5) had a 23.787-fold higher probability of having myelofibrosis than others after adjusting for sex and age (OR: 23.787, 95% CI: 9.676-58.479, *P*<0.001) (Table 2, Figure 2).

Table 2: Performance of 25-hydroxy vitamin D to discriminate patients with myelofibrosis and healthy controls

Cut-off	**≤16.5**
Sensitivity	84.72%
Specificity	80.00%
Accuracy	82.31%
PPV	80.26%
NPV	84.51%
AUC (95% CI)	0.857 (0.794-0.921)
***P*-value for AUC**	<0.001
OR (95% CI)	22.182 (9.426-52.197)
***P*-value for OR**	<0.001
Adjusted OR (95% CI) (1)	23.787 (9.676-58.479)
***P*-value for adjusted OR**	<0.001

PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under ROC curve, CI: Confidence intervals, OR: Odds ratio, (1) Adjusted for age and sex.

Figure 2: ROC curve of the 25-hydroxy vitamin D to discriminate patients with myelofibrosis and healthy controls



ROC: Receiver operating characteristic analysis, AUC: Area under the curve, CI: Confidence interval

The DIPSS risk groups of the patients were as follows: 19 low risk, 17 intermediate-1, 30 intermediate-2, and 6 high risk. The patient population was then further divided into two subgroups: (i) Low and intermediate-1 and (ii) Intermediate-2 and high, with respect to DIPSS risk groups. No significant differences were found between the groups regarding age, sex, BMI, ECOG performance status, smoking status, comorbidities, type of myelofibrosis, the presence of mutations, and hepatomegaly (all, *P*>0.05). Spleen size was greater in the intermediate-2 and high group compared to the low and intermediate-1 group (20.19 [2.94] cm vs. 18.24 [2.85] cm, *P*=0.006) (Table 3).

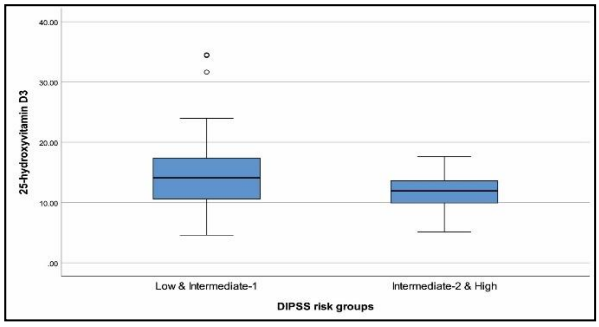
Table 3: Demographics and clinical characteristics with regard to DIPSS risk groups

		DIPSS risk groups		
	Total (n=72)	**Low & Intermediate-1 (n=36)**	**Intermediate-2 & High (n=36)**	***P*-value**
Age, years	63.71 (7.87)	64.18 (7.56)	63.25 (8.24)	0.621
Sex				
Male, (n/%)	44 (61.11%)	23 (63.89%)	21 (58.33%)	0.809
Female, (n/%)	28 (38.89%)	13 (36.11%)	15 (41.67%)	
Body mass index, kg/m^2	26.4 (23.4-29.1)	26.8 (24.0-29.3)	26.3 (22.8-28.7)	0.258
ECOG performance status				
0, (n/%)	67 (93.06%)	34 (94.44%)	33 (91.67%)	1.000
1, (n/%)	5 (6.94%)	2 (5.56%)	3 (8.33%)	
Smoker, (n/%)	19 (26.39%)	11 (30.56%)	8 (22.22%)	0.593
Comorbidities				
Ischemic heart disease, (n/%)	15 (20.83%)	4 (11.11%)	11 (30.56%)	0.082
Hypertension, (n/%)	22 (30.56%)	13 (36.11%)	9 (25%)	0.443
Diabetes mellitus, (n/%)	18 (25%)	9 (25%)	9 (25%)	1.000
Peripheral arterial disease, (n/%)	3 (4.17%)	2 (5.56%)	1 (2.78%)	1.000
Hypothyroidism, (n/%)	10 (13.89%)	5 (13.89%)	5 (13.89%)	1.000
Type of myelofibrosis				
Primary, (n/%)	24 (33.33%)	16 (44.44%)	8 (22.22%)	0.080
Secondary, (n/%)	48 (66.67%)	20 (55.56%)	28 (77.78%)	
Mutations				
JAK2, (n/%)	33 (45.83%)	15 (41.67%)	18 (50%)	0.636
JAK2 exon 12, (n=25) (n/%)	0 (0%)	0 (0%)	0 (0%)	N/A
CALR, (n=49) (n/%)	2 (4.08%)	1 (4.55%)	1 (3.70%)	1.000
MPL, (n=49) (n/%)	0 (0%)	0 (0%)	0 (0%)	N/A
Hepatomegaly, (n/%)	29 (40.28%)	18 (50%)	11 (30.56%)	0.149
Size of spleen, cm	19.22 (3.04)	18.24 (2.85)	20.19 (2.94)	0.006
DIPSS risk group				
Low, (n/%)	19 (26.39%)	19 (52.78%)	0 (0%)	<0.001
Intermediate-1, (n/%)	17 (23.61%)	17 (47.22%)	0 (0%)	
Intermediate-2, (n/%)	30 (41.67%)	0 (0%)	30 (83.33%)	
High, (n/%)	6 (8.33%)	0 (0%)	6 (16.67%)	

DIPSS: Dynamic International Prognostic Scoring System, ECOG: Eastern Cooperative Oncology Group, JAK: Januse kinase, CALR: Calreticulin, MPL: Myeloproliferative leukemia virus oncogene. Data are given as mean (standard deviation) or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.

25-hydroxy vitamin D levels were found to be 14.1 (10.6-17.35) ng/mL in the low and intermediate-1 subgroup and 11.95 (9.95-13.6) ng/mL in the intermediate-2 and high subgroup (P=0.017) (Figure 3). No significant differences were found for vitamin B12, creatinine, AST, ALT, LDH, total protein, albumin, CRP, and MCV and platelet values. WBC, hemoglobin and hematocrit values were significantly lower in the intermediate-2 and high subgroup (all, P<0.05) (Table 4).

Figure 3: Box-plot of the 25-hydroxy vitamin D with regard to DIPSS risk groups



DIPSS: Dynamic International Prognostic Scoring System

Table 4: Laboratory measurements with regard to DIPSS risk groups

		DIPSS risk groups		
	Total (n=72)	**Low & Intermediate-1 (n=36)**	**Intermediate-2 & High (n=36)**	***P*-value**
25-hydroxy vitamin D, ng/mL	13.05 (10.35-15.45)	14.10 (10.60-17.35)	11.95 (9.95-13.60)	0.017
Vitamin B12, pg/mL (n=49)	340.96 (109.47)	331.92 (126.93)	351.17 (87.38)	0.545
Creatinine, mg/dL	0.83 (0.65-1.01)	0.81 (0.65-0.96)	0.89 (0.66-1.06)	0.327
AST, U/L	20 (17-22)	20 (17-20.5)	19.5 (17-23.5)	0.359
ALT, U/L	17 (13-23.5)	16 (13.5-21)	20 (12-24.5)	0.376
LDH, U/L	237 (207-313)	245.5 (209-294)	226.5 (192.5-415)	0.723
Total protein, g/dL	7.00 (6.70-7.45)	7.00 (6.60-7.50)	7.05 (6.85-7.30)	0.236
Albumin, g/dL	4.63 (0.25)	4.59 (0.27)	4.67 (0.23)	0.207
CRP, g/dL	1.27 (0.66-2.28)	1.23 (0.79-2.28)	1.28 (0.59-2.34)	0.951
White Blood Cell, 10^9/L	8.21 (5.90-10.46)	9.29 (7.13-14.15)	7.19 (4.59-8.87)	0.002
Hemoglobin, g/dL	11.71 (10.06-12.55)	12.55 (12.00-13.05)	10.06 (8.71-10.90)	<0.001
Hematocrit, %	34.90 (5.59)	39.67 (2.37)	30.14 (3.33)	<0.001
MCV, Fl	90.1 (82.9-101.1)	86.15 (82.6-99.6)	91.2 (84.1-103.5)	0.162
Platelet (x10^3)	353 (257.5-502)	375.5 (286-510)	334.5 (254-502)	0.430

DIPSS: Dynamic International Prognostic Scoring System, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, MCV: Mean corpuscular volume. Data are given as mean (standard deviation) or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables

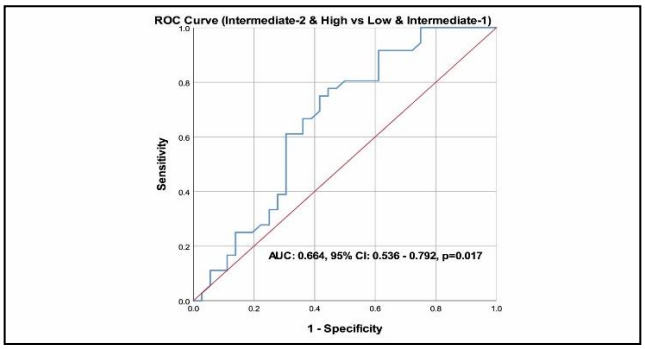
We determined the 25-hydroxy vitamin D level that would allow discrimination of the two subgroups. The cut-off value was <13.7 ng/mL, and resulted in a specificity of 55.6% and sensitivity of 77.8%. Patients with low 25-hydroxy vitamin D (≤13.7) had a 4.695-fold higher likelihood of being categorized in the intermediate-2 and high-risk subgroup, after adjusting for sex and age (OR: 4.695, 95% CI: 1.638-13.459, P=0.004) (Table 5, Figure 4).

Table 5: Performance of 25-hydroxy vitamin D to discriminate patients with intermediate-2 & high risk and low & intermediate-1 risk

Cut-off	**≤13.7**
Sensitivity	77.78%
Specificity	55.56%
Accuracy	66.67%
PPV	63.64%
NPV	71.43%
AUC (95% CI)	0.664 (0.536-0.792)
***P*-value for AUC**	0.017
OR (95% CI)	4.375 (1.571-12.187)
***P*-value for OR**	0.005
Adjusted OR (95% CI) (1)	4.695 (1.638-13.459)
***P*-value for adjusted OR**	0.004

PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under ROC curve, CI: Confidence intervals, OR: Odds ratio, (1) Adjusted for age and sex

Figure 4: ROC curve of the 25-hydroxy vitamin D to discriminate patients with intermediate-2 & high risk from those with low & intermediate-1 risk



DIPSS: Dynamic International Prognostic Scoring System, ROC: Receiver operating characteristic analysis, AUC: Area under the curve, CI: Confidence interval

Discussion

The goal of the study was to determine the levels of 25-hydroxy vitamin D in myelofibrosis patients and possibly determine how they relate to the disease's prognosis. With a cut-off value of 16.5 ng/mL that produced good sensitivity and specificity, we discovered that patients with myelofibrosis could be distinguished from controls by having lower 25-hydroxy vitamin D levels. We also showed that lower 25-hydroxy vitamin D levels were linked to a larger chance of having a worse prognostic score, but the ROC analysis reported that accuracy was poor. Notably, after adjusting for gender and age, these associations held true.

Humans require adequate amounts of vitamin D, which can be taken through food sources, including supplements, or produced in the skin by exposure to ultraviolet B rays from sunshine. The 1.25-dihydroxy vitamin D that is produced in the body as a result of hydroxylation occurs in the liver and proximal tubule. By attaching to the vitamin D receptor, this active version performs as a steroid hormone [13]. Hematopoietic stem cells, macrophages, thymocytes, activated lymphocytes, and monocytes all contain the vitamin D receptor. The modulation of many signaling pathways connected to cellular processes like proliferation, differentiation, autophagy, apoptosis, and epithelial-mesenchymal transition is thought to be a function of the vitamin D receptor. Additionally, this affects how cells interact with their surroundings, affecting processes including angiogenesis, oxidative stress, inflammatory response, and both innate and adaptive immunity [14-16]. Adequate levels of vitamin D are essential for normal hematopoiesis. Insufficient vitamin D levels can result in the suppression of bone marrow cell lines, leading to clinical manifestations, such as neutropenia, anemia, and thrombocytopenia [17]. The functional form of vitamin D is not suitable for direct measurement due to its short half-life of 4-6 hours and significantly lower circulating levels compared to the primary storage form, known as 25-hydroxy vitamin D [18]. As a result, the levels of 25-hydroxy vitamin D have been used as a marker of vitamin D shortage in various investigations, including the present study. According to current diagnostic guidelines, vitamin D insufficiency is frequently seen in the general population and is widely evaluated in clinical settings around the world.

It has been reported that a lack of vitamin D raises the risk of certain cancers, including hematological malignancies [19]. In a study of 332 newly diagnosed diffuse large B-cell

lymphoma patients, Chen et al. found that 92.8% of patients had vitamin D deficiency (30 ng/mL) [20]. Although not as common, Shanafelt et al. [21] also showed widespread vitamin D insufficiency in patients with chronic lymphocytic leukemia (30% of 309 patients), and suggested an impact on overall survival. In 97 adult patients with newly diagnosed acute myeloid leukemia who were receiving intensive care, Lee et al. [22] found that 35% of patients had insufficiency (20-30 ng/mL) and 30% had deficiency (20 ng/mL). Additionally, these patients' relapse-free survival was worse than that of patients with normal levels of 25-hydroxy vitamin D. There are limited reports of primary myelofibrosis despite the high prevalence of vitamin D insufficiency. Pardanani et al. [10] showed in 247 primary myelofibrosis patients that 48% and 9% of myelofibrosis patients, respectively, had vitamin D insufficiency and severe deficiency. We repeatedly discovered lower 25-hydroxy vitamin D levels in myelofibrosis patients compared to controls, and that the existence of myelofibrosis could be accurately predicted by a cut-off level of 16.5 ng/mL. To understand if this difference is related to the pathophysiology of myelofibrosis or whether it is an outcome of the condition, more research is necessary. To this end, it can be postulated that inadequate vitamin D levels could impair the immune system and facilitate tumor development and growth. Given the vitamin D deficiency observed in myelofibrosis patients, we believe that it is crucial to assess whether vitamin D supplementation can benefit myelofibrosis patients.

Myelofibrosis can arise either as an idiopathic condition or as a secondary manifestation associated with various conditions. These conditions include chronic kidney failure, hypoparathyroidism, lymphoma, acute lymphoblastic leukemia, neuroblastoma, osteopetrosis, tuberculosis, and systemic lupus erythematosus [23]. A limited number of case-report studies have also reported secondary myelofibrosis caused by vitamin D deficiency, suggesting that it is due to secondary elevation of parathormone or nutritional factors. Balkan et al. [23] presented a case report in a six-month-old infant who developed secondary myelofibrosis and found that myelofibrosis rapidly resolved after vitamin D treatment. Venkatnarayan et al. [24] revealed a ten-month-old rachitic male infant with hepatosplenomegaly and anemia secondary to bone marrow fibrosis, whose clinical characteristics improved following vitamin D treatment. In a study conducted by Yetgin and colleagues [25], they observed that in a group of 12 infants with rickets and anemia, early indications of myelofibrosis were evident through increased reticulin levels. Furthermore, they found that more advanced stages of rickets led to varying degrees of bone marrow myelofibrosis.

Interestingly, increased parathormone levels can also cause bone resorption and deposition through stimulation of osteoblasts and osteoclasts, as well as decrease erythropoietin receptors on erythroid progenitor cells, inducing defective new bone formation and medullary fibrosis [26]. For instance, Stephan et al. [27] demonstrated a relationship between increased PTH level and myelofibrosis in rachitic infants. Furthermore, myelofibrosis associated with vitamin D deficiency can contribute to reduced levels of active vitamin D metabolites. These metabolites play a role in the maturation of megakaryocyte and monocyte precursors. The deficiency of active vitamin D metabolites can lead to impaired collagen breakdown and increased deposition, which are characteristic features of myelofibrosis [28]. These pathways suggest that vitamin D may affect myelofibrosis, and they may also be responsible for the low vitamin D levels found in our patient sample.

In order to choose the best therapeutic approaches for patients, improve their prognosis, and gain a better understanding of the pathophysiology of the disease, it is essential to define the prognostic variables for myelofibrosis. Many prognostic models, such as the mutation-enhanced International Prognostic Scoring System (MIPSS) and DIPSS, have been created to forecast survival in primary and secondary myelofibrosis [29]. As a prognostic predictor, we used DIPSS. A limited number of studies have been published to date, evaluating the correlation between serum 25-hydroxy vitamin D levels and the prognosis of cancer patients, including those with breast and colorectal cancer [30]. However, there is a need to determine whether vitamin D is an effective and beneficial prognostic factor for myelofibrosis patients. We are aware of only one study that looked at 25-hydroxy vitamin D level as a predictive factor. In 247 patients with primary myelofibrosis, Pardanani et al. [10] found no correlation between vitamin D deficiency and overall and disease-free survival. In contrast, we demonstrated that myelofibrosis patients with low 25-hydroxy vitamin D levels tended toward poor prognoses. We discovered that patients with a high prognosis score could be distinguished from those with a poor prognostic score using the 25-hydroxy vitamin D cut-off value of 13.7 ng/mL. Measurement of 25-hydroxy vitamin D levels may not have a reliable role in prognostication, because overall accuracy is too low. However, more research is needed to determine the impact of vitamin D levels on the outlook for myelofibrosis as well as the direction of the association over time.

Limitations

The study did have some drawbacks, including a small sample size, a retrospective design originating from a single institution, the heterogeneity of myelofibrosis patients' illness status, and the fact that they received various medications. In addition, we were unable to use different prognostic indicators, as DIPSS was the only scoring system that was used consistently in all patients. Finally, the measurement of 25-hydroxy vitamin D levels are influenced by diet, geographic region, lifestyle, and environmental factors, so these may have contributed to our results [19]. Nonetheless, we adjusted for age and sex to assess whether the relationship between low vitamin D and myelofibrosis persisted, showing that these factors did not alter the demonstrated relationships.

Conclusions

We demonstrated that lower serum 25-hydroxy vitamin D level may serve as a reliable biomarker that is closely associated with the presence of myelofibrosis. Additionally, despite far lower accuracy, vitamin D levels also appear to be associated with the prognostic score. The potential role of vitamin D supplementation on prognosis of myelofibrosis and its impact on progression should be addressed with further studies with larger sample sizes and a longer follow-up.

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