Int J Cancer Manag. January-December 2024; 17(1): e144271. https://doi.org/10.5812/ijcm-144271.

Published online: 2024 September 24. **Research Article**

Association Between Serum Levels of Vitamin D and Biochemical Markers Among Hematopoietic Stem Cell Transplantation Candidates: A Cross-Sectional Study

Hoda Zahedi [1,2], Reza Amiri Khosroshahi [2], Omid Sadeghi [3], Mahshid Mehdizadeh [1], Sayeh Parkhideh [1], Mohammad Hadizadeh [4], Fatemeh Naeini [2], Abbas Hajifathali [1,*], Mahdi Shadnoush [2,**]

[1] Hematopoietic Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2] Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
[3] Department of Community Nutrition, Nutrition and Food Security Research Center, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran
[4] Cancer Research Centre (CRC), Shahid Beheshti University of Medical Sciences, Tehran, Iran

[*] Corresponding Author: Hematopoietic Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: hajifathali@yahoo.com
[**] Corresponding Author: Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran. Email: mshadnoush@gmail.com

Received 2023 December 23; **Revised** 2024 June 23; **Accepted** 2024 July 20.

Abstract

Background: Although vitamin D has been known as an effective substance in bone homeostasis, recent studies indicated a number of other biological properties attributed to vitamin D. Patients, who are candidates for hematopoietic stem cell transplantation (HSCT), were shown to be at high risk of vitamin D deficiency.

Objectives: This study aimed at exploring the association between serum levels of vitamin D and biochemical markers among HSCT candidates.

Methods: Totally, 214 patients, aged 18 to 65 years, were recruited in the current cross-sectional study. Within 24 hours of admission to the Bone Marrow Transplant ward, baseline clinical and demographic characteristics of study participants, serum levels of vitamin D, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), hemoglobin, albumin, total protein, CRP-albumin ratio (CAR), and body mass index (BMI) were assessed. Participants were divided into 4 groups based on their serum vitamin D levels: Subjects with deficient, insufficient, sufficient, and optimal levels of vitamin D.

Results: Across the 4 defined categories of serum vitamin D levels, there was no significant difference in terms of BMI, laboratory parameters, inflammatory factors, and biochemical markers. This lack of significant variation remained in both unadjusted and adjusted models.

Conclusions: These observations indicate a lack of significant association between serum vitamin D levels and BMI, inflammatory factors, and biochemical markers in individuals undergoing evaluation for HSTC.

Keywords: Vitamin D, Patients with Malignancy, HSCT, Biochemical Markers, Inflammation

1. Background

Hematopoietic stem cell transplantation (HSCT) has recently emerged as a significant therapeutic approach for various cancers, particularly multiple myeloma or leukemia (1). However, despite the reported achievements with this therapy, patients undergoing HSCT experience a number of side effects, including anorexia, mucositis, nausea, vomiting, and infection (2). These side effects, which may be, at least in part, attributed to chemotherapy, high-dose radiotherapy, and different medications (immunosuppressive drugs, antibiotics, and steroids) used with the patients, can lead to suppressed food intake and compromised digestion and/or absorption of different nutrients (3), ultimately resulting in moderate to severe malnutrition (4). There is evidence that malnourished patients have reduced tolerance to anti-cancer therapy and more

severe post-transplant outcomes, including extended hospital stays, reduced quality of life, and even increased mortality rates (5-9).

Of different nutrients, vitamin D is of particular interest due to its important role in a number of immunologic processes, such as reducing the number of pro-inflammatory lymphocytes, increasing anti-inflammatory substances, and promoting bone marrow recovery (10, 11). Vitamin D has also been shown to possess other important biological roles in the cardiovascular system (12), oncology (12), blood diseases (13), bone homeostasis (14), and autoimmunity (15, 16) among patients with different conditions. For example, there is evidence that vitamin D serum levels are associated with Body Mass Index (BMI), serum levels of albumin, and inflammatory factors in patients with colorectal and prostate cancer (17, 18). Importantly, patients, undergoing HSCT, are more exposed to vitamin D deficiency than the general population (19), with the pre-transplant deficiency rates reported to be as high as 70% (20). This susceptibility may be attributable to different factors, including prior chemotherapy, radiation, poor nutrition, and limited sun exposure (21, 22), all of which contribute to several post-transplant outcomes due to vitamin D among these patients (23).

Despite the increasing use of HSCT as a prominent cancer therapy, and the evident importance of vitamin D in immunity functions, no previous study, to the best of our knowledge, has explored the relationship between serum vitamin D levels and biochemical factors among potential HSCT candidates.

2. Objectives

Accordingly, this cross-sectional study aimed at investigating the relationship between serum levels of vitamin D and biochemical markers in patients who are candidates for HSCT.

3. Methods

3.1. Subjects

Between August 2020 and November 2021, 214 adult patients (aged 18 to 65 years), who were hospitalized in Taleghani Hospital's bone marrow transplant ward (Tehran, Iran) to undergo HSCT, and provided written consent forms, were recruited. Based on pathological results, the presence of hematological malignancies including multiple myeloma (MM), Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), Acute Myeloid Leukemia (AML), and acute lymphocytic leukemia (ALL) was confirmed. The current study was carried out under the ethical guidelines of the Declaration of Helsinki and its later revisions, as approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1402.280).

3.2. Inclusion and Exclusion Criteria

Adult patients aged 18 to 65 years, hospitalized in Taleghani Hospital's bone marrow transplant ward (Tehran, Iran), and candidates for HSCT were included in the study. Patients had to have a diagnosis of hematological malignancies, such as multiple myeloma, Hodgkin lymphoma, non-Hodgkin lymphoma, acute myeloid leukemia, or acute lymphocytic leukemia, and provide written consent to participate.

Exclusion criteria comprised patients with incomplete clinical or biochemical data, those who had undergone prior HSCT or other significant treatments affecting vitamin D levels or biochemical markers before the study period, patients with other chronic conditions that could confound the study results such as chronic kidney disease or severe liver disease, and those taking vitamin D supplements or other medications that could affect vitamin D metabolism during the study period.

3.3. Measurements

Within the first 24 hours of admission to the bone marrow transplant ward, all measures were collected. Patients' demographic characteristics, including age, sex, diagnosis, type of stem cell transplantation, and laboratory tests were all recorded. Anthropometric measurements of height and weight were also taken. Weight was accurately estimated to be within 0.1 kg while wearing no shoes and few other clothes. With an accuracy of 0.1 cm, the patients' standing height was measured without shoes (Balas Company, Iran). BMI was, then, calculated by dividing the weight (kg) by the square of the height (m^2).

Serum levels of albumin and total protein were measured by the photometric technique using a commercial kit (Pars Azmoon Co., Tehran, Iran). C-reactive protein (CRP) concentrations and Erythrocyte Sedimentation Rate (ESR) were also assessed by immunoturbidimetric assays using commercial kits from Pars Azmoon Co (Tehran, Iran) and the Westergren technique, respectively. The HPLC method was used to measure the blood 25-hydroxycholecalciferol (25-OH Vitamin D) levels. By dividing the serum CRP concentration by the albumin concentration, CAR was calculated (24). A spectrophotometric approach was also used to assess the serum hemoglobin levels. All assays

were carried out according to the manufacturer's instructions based on established methods.

3.4. Blood Sampling

Venous blood samples were collected within the first 24 hours of admission and processed for laboratory analysis. Blood samples were centrifuged at 3000 rpm for 10 min at 4°C to collect serum samples. Serum samples were stored at -80°C until the biochemical analysis, except for ESR, which was assessed immediately.

3.5. Statistical Analysis

Statistical analysis was performed, using the SPSS software (Version 20; IBM Corp., Armonk, NY, USA). Data were reported as mean ± SD for continuous variables and frequency (%) for categorical variables. Patients were categorized into 4 groups based on serum levels of vitamin D (subjects with deficient, insufficient, sufficient, and optimal serum levels of vitamin D). An independent sample *t*-test was performed to analyze differences in continuous variables between study patients across 4 categories. The distribution of categorical characteristics across these categories was also evaluated, using the chi-square test. We conducted a one-way analysis of covariance (ANCOVA) to evaluate the multivariable-adjusted means of inflammatory biomarkers, biochemical markers, and BMI. Different variables, including age, gender, BMI, type of malignancy, and serum levels of magnesium and calcium were adjusted as potential confounders. Statistics were considered significant at $P < 0.05$.

4. Results

In the current cross-sectional study, 214 bone marrow transplant candidates, including 121 men (56.5%), were evaluated. Vitamin D deficiency (25 [OH] D < 10 ng/mL) was observed in 14% of participants. The baseline demographic and clinical characteristics of participants across serum levels of vitamin D are summarized in Table 1. The mean age (± SD) of the participants was 41.33 ± 15.23 years. There was no significant difference between the weight and BMI of participants across 4 categories of serum levels of vitamin D. While the most prevalent malignancy was MM (32.7%), individuals with HL and AML were more likely to be vitamin D deficient, compared to those with other types of malignancies (30.0%).

Laboratory parameters of study participants are presented in Table 2. There were no significant differences in hematological parameters, electrolyte status, liver function indices, renal function-related factors, and coagulation tests across categories of serum levels of vitamin D. However, there was a trend in red blood cell (RBC), hematocrit, and sodium (Na) levels ($P < 0.06$).

The associations between serum levels of vitamin D and inflammatory factors, as well as biochemical parameters and BMI, are shown in Table 3. No significant differences were found in BMI, inflammatory biomarkers, and biochemical parameters, comparing the highest and lowest serum levels of vitamin D, in both crude and adjusted models. Although patients with vitamin D deficiency had lower BMI and hemoglobin levels, as well as higher CRP, CRP/Alb, and total protein values, both before and after adjustment for potential confounding variables, these differences were not statistically significant.

5. Discussion

There is a body of evidence suggesting that vitamin D plays a pivotal role in the prognosis of various cancers (25, 26), as well as inflammation (27, 28). To the best of our knowledge, this is the first study investigating the associations between serum levels of vitamin D and a number of biochemical markers and anthropometric measures in patients with hematological malignancies, considered for HSCT. Our findings reveal no significant differences in BMI, laboratory parameters, inflammatory factors, or biochemical markers among study participants across different categories of serum vitamin D levels, indicating no significant associations between these markers among HSCT candidates.

Previous studies showed a direct correlation between higher serum levels of 25 (OH) D and an improved survival rate among patients with different cancers, including colon, breast, prostate (29), non-small cell lung, cancer (30) and Hodgkin's lymphoma (29). Moreover, a substantial proportion of cancer patients experience muscle weakness, musculoskeletal problems, and cognitive disorders, all of which may be indicative of vitamin D deficiency (31, 32). Our study reveals that 14% of patients had deficient levels of vitamin D (25 [OH] D < 10 ng/mL), while 76% had insufficient levels (25 [OH] D: 10 - 30 ng/mL), and only 24% had sufficient levels (25 [OH] D ≥ 30 ng/mL). A case-control study, involving children considered for HSCT, reported significantly lower serum levels of vitamin D in patients, compared to healthy controls, with 27% of patients found to be vitamin D deficient (defined as serum levels lower than 15 ng/mL) (33). Similarly, in another study, conducted on 102 adults who were

Table 1. Demographic and Clinical Characteristics of Patients with Malignancy Across Four Categories of Serum Levels of Vitamin D [a]

Characteristics	Total (N = 214)	< 10 ng/mL (n = 30)	10 - 20 ng/mL (n = 90)	20 - 30 ng/mL (n = 42)	≥ 30 ng/mL (n = 52)	P-Value [b]
Age (y)	41.33 ± 15.23	33.10 ±1 2.70	40.45 ±1 3.09	45.89 ± 19.16	43.90 ± 14.74	0.002
Gender (male)	121 (56.5)	14 (46.7)	57 (63.3)	22 (52.4)	28 (53.8)	0.344
Weight (kg)	76.96 ± 14.54	70.62 ± 13.88	77.85 ± 14.59	78.78 ± 13.80	77.58 ± 14.56	0.078
BMI (kg/m2)	27.05 ± 4.62	25.37 ± 3.82	26.81 ± 4.40	28.05 ± 5.14	27.63 ± 4.81	0.072
Type of malignancy						0.122
MM	70 (32.7)	6 (20)	25 (27.8)	22 (54.2)	17 (32.7)	
HL	46 (21.5)	9 (30)	21 (23.3)	8 (19)	8 (15.4)	
NHL	25 (11.7)	2 (6.7)	10 (11.1)	6 (14.3)	7 (13.5)	
AML	47 (22)	9 (30)	23 (25.6)	4 (9.5)	11 (21.2)	
ALL	26 (12.1)	4 (13.3)	11 (12.2)	2 (4.8)	9 (17.3)	

Abbreviations: ng/mL, nanograms per milliliter; BMI, Body Mass Index; MM, multiple myeloma; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; AML, acute myeloid leukemia; ALL, acute lymphocytic leukemia; NRS, nutrition risk screening.

[a] Values are expressed as mean ± SD or No. (%).

[b] Obtained from the independent sample *t*-test or chi-square test, where appropriate.

considered for allogeneic HSCT, 89.2% of the patients were found to have insufficient vitamin D levels (25 [OH] D < 30 ng/mL) before transplantation, with 23.5% of the patients had vitamin D deficiency (19).

We found no significant association between vitamin D levels and BMI. Our findings are in alignment with a number of studies, showing no significant role for body weight in vitamin D status (33). However, limited studies indicate that vitamin D level was inversely associated with BMI colorectal cancer patients (17); so, those patients with higher BMI were found to have lower levels of vitamin D. Interestingly, fat mass was reported to account for the reduction in serum levels of vitamin D, as an independent factor (19). While more evidence is available on the inverse association between vitamin D levels and BMI among healthy populations (34, 35), further investigations are required to better define the role of body weight in the modulation of vitamin D levels in cancer patients.

While the activation of systemic inflammatory response was shown to be associated with cancer progression (36), the association between vitamin D levels and inflammation remains of debate, with a number of studies showing that inflammation can reduce the serum levels of vitamin D (37-39). In the present study, there was no significant difference between inflammatory biomarkers across different categories of serum vitamin D levels; although the mean CRP was non-significantly higher in patients with vitamin D deficiency, compared with other patients. This finding was in line with a case-control study, indicating a negative correlation between serum levels of vitamin D and CRP and IL-8 in prostate cancer patients (18). Similar findings were also observed in colorectal cancer patients (17). A number of studies also support the relationship between vitamin D levels and other inflammatory biomarkers in healthy lean and obese participants (40, 41). Indeed, the active metabolite of vitamin D, 1,25 (OH)2 D, was shown to have anti-inflammatory properties by changing the inflammatory profile, Th1/Th17, to the anti-inflammatory profile, Th2/Treg (42), which, in turn, lead to increased production of anti-inflammatory agents, and reduced levels of pro-inflammatory factors (43).

There is evidence showing that albumin levels are independently associated with vitamin D deficiency. Albumin and vitamin D binding protein (DBP) are the most important markers that regulate the circulating level of 25 (OH) D (26). Only 0.1% of vitamin D is free in circulation, while the remaining 90% of vitamin D is bound to DBP, and 9.9% of vitamin D is bound to albumin; therefore, vitamin D availability is dependent on albumin and DBP levels (44, 45). Accordingly, serum albumin levels were found to be an effective measurement among most malnutrition assessment tools (46). While albumin level has not been approved as a marker of malnutrition due to its susceptibility to acute inflammation, infection, and trauma (46), it can be still used along with the other common inflammatory biomarkers such as CRP and WBC in predicting the prognosis of cancer patients (36). In our study, the average albumin level was lower in patients with vitamin D deficiency, while this difference was not statistically significant. Despite our findings, a positive correlation was reported between vitamin D and albumin levels in the general population and cancer patients (17, 47). While the observed discrepancies may

Table 2. Laboratory Parameters of Patients with Malignancy Across Four Categories of Serum Levels of Vitamin D [a]

Characteristics	Total (N = 214)	<10 ng/mL (n = 30)	10-20 ng/mL (n = 90)	20-30 ng/mL (n = 42)	≥ 30 ng/mL (n = 52)	P-Value [b]
CBC						
RBC (Million/µL)	4.08 ± 0.78	3.85 ± 0.86	4.20 ± 0.78	4.17 ± 0.49	3.95 ± 0.75	0.057
WBC (× 10^3/µL)	5.17 ± 1.81	5.23 ± 2.28	5.25 ± 1.88	5.21 ± 1.81	4.97 ± 1.36	0.835
Platelet (× 10^3/µL)	189.66 ± 66.59	171.10 ± 64.16	191.65 ± 64.21	207.45 ± 75.25	182.57 ± 62.55	0.111
Hgb (g/dL)	11.90 ± 1.93	11.28 ± 2.12	12.06 ± 2.01	12.01 ± 1.35	11.86 ± 2.06	0.282
Hct (%)	34.75 ± 5.60	32.33 ± 7.95	35.48 ± 5.34	35.29 ± 3.62	34.45 ± 5.48	0.052
Electrolyte status						
Na (mEq/L)	141.91 ± 3.05	140.86 ± 2.82	142.28 ± 2.19	142.45 ± 2.49	141.44 ± 3.20	0.059
K (mEq/L)	4.16 ± 2.41	5.17 ± 6.39	3.98 ± 0.34	4.10 ± 0.32	3.94 ± 0.32	0.103
Ca (mg/dL)	9.61 ± 0.91	9.45 ± 0.58	9.50 ± 0.66	9.73 ± 0.52	9.79 ± 1.50	0.189
P (mg/dL)	3.95 ± 0.64	4.08 ± 0.66	3.92 ± 0.65	3.92 ± 0.72	3.98 ± 0.55	0.656
Mg (mEq/L)	1.93 ± 0.21	1.95 ± 0.26	1.92 ± 0.22	1.98 ± 0.21	1.89 ± 0.21	0.267
Liver function tests						
ALT (U/L)	33.53 ± 18.19	29.10 ± 17.63	35.06 ± 18.72	31.64 ± 17.82	34.96 ± 17.82	0.365
AST (U/L)	26.82 ± 10.27	26.20 ± 11.55	26.13 ± 9.33	26.07 ± 9.27	29.00 ± 11.70	0.382
ALP (U/L)	208.93 ± 67.57	217.90 ± 64.53	209.63 ± 70.97	196.07 ± 54.44	212.96 ± 72.98	0.526
Bilirubin-T (mg/dL)	0.92 ± 1.96	0.83 ± 0.46	1.05 ± 2.99	0.86 ± 0.52	0.81 ± 0.31	0.889
Bilirubin-D (mg/dL)	0.30 ± 0.14	0.30 ± 0.15	0.29 ± 0.12	0.32 ± 0.19	0.29 ± 0.12	0.700
Renal function tests						
BUN (mg/dL)	13.97 ± 3.88	13.17 ± 3.31	13.80 ± 3.69	14.50 ± 3.91	14.29 ± 4.44	0.472
Cr (mg/dL)	0.94 ± 0.16	0.90 ± 0.17	0.95 ± 0.16	0.94 ± 0.18	0.96 ± 0.15	0.379
Coagulation tests						
PT	12.22 ± 1.01	12.40 ± 0.89	12.11 ± 1.33	12.25 ± 0.52	12.30 ± 0.67	0.530
PTT	31.14 ± 5.73	32.20 ± 5.40	31.02 ± 6.27	31.54 ± 6.29	30.42 ± 4.33	0.558
INR	1.12 ± 0.99	1.03 ± 0.07	1.25 ± 1.52	1.02 ± 0.06	1.03 ± 0.07	0.463

Abbreviations: CBC, complete blood count; RBC, red blood cell; WBC, white blood cell; PLT, platelet; Hgb, hemoglobin; hematocrit; Na, sodium; K, potassium; Ca, calcium; P, phosphor; Mg, magnesium; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; Cr, creatinine; PT, prothrombin time; PTT, partial thromboplastin Time; INR, international normalized ratio.

[a] Values are expressed as mean ± SD.

[b] Obtained from the independent sample *t*-test

be due to differences in the pathophysiology of the disease, race, gender distribution, weather, and sunlight, further studies, with a larger sample size, are needed to clarify this issue.

Vitamin D deficiency is more prevalent among HSCT patients due to several risk factors such as reduced exposure to sunlight (22), glucocorticoids use (48), gastrointestinal GVHD (49), inadequate dietary intake (50), skin pigmentation (51), and absorption problems (52). Therefore, vitamin D deficiency is more common after transplantation, in comparison with the time of admission for HSCT (53, 54).

Vitamin D deficiency is common in HSCT patients and is linked to adverse outcomes like increased infection risk, higher GVHD incidence, bone demineralization, poorer survival rates, and reduced quality of life (19, 21). Factors contributing to deficiency include reduced sunlight, glucocorticoid use, GVHD, poor diet, and absorption issues (23). Managing vitamin D levels could enhance immune function, decrease GVHD severity, improve bone health, increase survival, and improve overall well-being (42, 51). Future studies should explore the benefits of vitamin D supplementation in HSCT care.

Our study had several strengths. The high homogeneity of the population, who were all HSCT candidates, and data collection before the initiation of the conditioning chemotherapy regimen were among the strengths of our study. Nevertheless, this study has a number of limitations, of which, the major one was its cross-sectional design. A longitudinal approach following patients after transplantation could provide a clearer picture of the relationship between vitamin D and biochemical markers. Despite several studies investigating the association between vitamin D deficiency and post-transplantation outcomes, it is

Table 3. Multivariable-Adjusted Means for Inflammatory Markers, BMI, and Biochemical Parameters of Study Patients Across Four Categories of Serum Levels of Vitamin D [a, b, c]

Variables	< 10 ng/mL (N = 30)	10 - 20 ng/mL (n = 90)	20 - 30 ng/mL (n = 42)	≥ 30 ng/mL (n = 52)	P-Value [d]
BMI (kg/m ^{2})					
Crude	25.37 ± 0.83	26.81 ± 0.48	28.05 ± 0.70	27.63 ± 0.63	0.072
Model 1	25.81 ± 0.83	26.96 ± 0.47	27.68 ± 0.69	27.42 ± 0.62	0.354
Model 2	25.80 ± 0.83	27.00 ± 0.47	27.53 ± 0.70	27.48 ± 0.62	0.385
CRP (mg/L)					
Crude	15.16 ± 2.92	9.42 ± 1.69	7.21 ± 2.47	11.12 ± 2.26	0.198
Model 1	13.46 ± 2.97	9.41 ± 1.69	8.01 ± 2.48	11.49 ± 2.56	0.474
Model 2	13.13 ± 2.98	9.21 ± 1.69	8.14 ± 2.50	11.93 ± 2.27	0.463
ESR (mm/hr.)					
Crude	24.62 ± 4.16	24.42 ± 2.55	23.30 ± 3.52	26.18 ± 3.20	0.945
Model 1	23.74 ± 4.13	25.19 ± 2.47	22.83 ± 3.50	25.89 ± 3.09	0.911
Model 2	23.41 ± 4.14	24.87 ± 2.48	23.30 ± 3.52	26.22 ± 3.12	0.918
Albumin (g/dL)					
Crude	4.47 ± 0.07	4.48 ± 0.04	4.49 ± 0.06	4.48 ± 0.05	0.995
Model 1	4.44 ± 0.78	4.47 ± 0.04	4.52 ± 0.06	4.42 ± 0.05	0.890
Model 2	4.45 ± 0.07	4.48 ± 0.04	4.50 ± 0.06	4.48 ± 0.05	0.974
Total protein (g/dL)					
Crude	7.16 ± 0.14	6.99 ± 0.08	6.99 ± 0.12	6.98 ± 0.11	0.750
Model 1	7.13 ± 0.14	6.98 ± 0.08	7.03 ± 0.12	7.00 ± 0.11	0.842
Model 2	7.14 ± 0.14	6.99 ± 0.85	7.01 ± 0.12	6.99 ± 0.11	0.824
Hemoglobin (g/dL)					
Crude	11.28 ± 0.35	12.06 ± 0.20	12.01 ± 0.29	11.88 ± 0.26	0..282
Model 1	11.41 ± 0.34	11.97 ± 0.19	12.05 ± 0.28	11.91 ± 0.25	0.494
Model 2	11.46 ± 0.33	12.01 ± 0.19	11.98 ± 0.28	11.88 ± 0.25	0.546
CRP/Alb					
Crude	3.41 ± 0.69	2.19 ± 0.40	1.59 ± 0.58	2.55 ± 0.54	0.240
Model 1	3.02 ± 0.71	2.20 ± 0.40	1.78 ± 0.59	2.63 ± 0.54	0.533
Model 2	2.99 ± 0.71	2.15 ± 0.40	1.83 ± 0.59	2.72 ± 0.54	0.539

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NRS, nutrition risk screening.

[a] Values are expressed as mean ± SE.

[b] Model 1: Adjusted for age, gender, and malignancy type.

[c] Model 2: Further adjustment for serum levels of magnesium and calcium.

[d] Obtained from one-way analysis of covariance.

necessary to evaluate this association in the Iranian population, recognizing significant differences in environmental conditions and race that could affect serum vitamin D levels.

5.1. Conclusions

In summary, there was no significant association between serum levels of vitamin D and BMI, inflammatory factors, and biochemical markers in HSCT candidate patients. While previous studies have explored the association between serum vitamin D levels and post-transplantation outcomes in different groups of participants, this study was the first to investigate the association between serum levels of vitamin D and various biochemical markers in HSCT candidate patients. Future studies with larger sample sizes and different designs (case-control or longitudinal designs) could provide further insights into the relationship between vitamin D and biochemical markers, particularly with a focus on investigating the effects of vitamin D supplementation on public health outcomes in HSCT candidate patients.

Acknowledgements

The authors are grateful to the BMT ward of Taleghani Hospital and express their sincere appreciation to all

patients who took part in the study, as well as the nursing staff who provided valuable assistance.

Footnotes

Authors' Contribution: The original research concept and design were a collaborative effort between M. Sh. and A. H.; H. Z. conducted data collection and drafting of the manuscript; R. A. Kh. and O. S. were responsible for paper revisions, generating figures and tables, and offering guidance on statistical analysis and data interpretation; technical and material support was provided by S. P. and M. M.; M. H. and F. N. managed participant interactions, data collection, and administration of relevant questionnaires. The final version of the paper was approved by all authors.

Conflict of Interests Statement: The authors declared that they have no conflict of interest.

Data Availability: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethical Approval: This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1402.280). All methods were performed in accordance with the relevant guidelines and regulations. This study was carried out under the ethical guidelines of the Declaration of Helsinki and its later revisions.

Funding/Support: Shahid Beheshti University of Medical Sciences provided funding for the current study under grant number 43006935.

Informed Consent: All participants provided informed consent prior to the investigation.

References

1. Huang XJ. Hematopoietic stem cell transplantation in China: Current status and prospects. *Am J Blood Res*. 2011;**1**(1):90-7. [PubMed ID: 22432069]. [PubMed Central ID: PMC3301412].
2. Bazinet A, Popradi G. A general practitioner's guide to hematopoietic stem-cell transplantation. *Curr Oncol*. 2019;**26**(3):187-91. [PubMed ID: 31285665]. [PubMed Central ID: PMC6588058]. https://doi.org/10.3747/co.26.5033.
3. Fuji S, Einsele H, Savani BN, Kapp M. Systematic nutritional support in allogeneic hematopoietic stem cell transplant recipients. *Biol Blood Marrow Transplant*. 2015;**21**(10):1707-13. [PubMed ID: 26172477]. https://doi.org/10.1016/j.bbmt.2015.07.003.
4. Martin-Salces M, de Paz R, Canales MA, Mesejo A, Hernandez-Navarro F. Nutritional recommendations in hematopoietic stem cell transplantation. *Nutrition*. 2008;**24**(7-8):769-75. [PubMed ID: 18468863]. https://doi.org/10.1016/j.nut.2008.02.021.
5. Le Blanc K, Ringdén O, Remberger M. A low body mass index is correlated with poor survival after allogeneic stem cell transplantation. *Haematologica*. 2003;**88**(9):1044-52. [PubMed ID: 12969813].
6. White M, Murphy AJ, Hastings Y, Shergold J, Young J, Montgomery C, et al. Nutritional status and energy expenditure in children pre-bone-marrow-transplant. *Bone Marrow Transplant*. 2005;**35**(8):775-9. [PubMed ID: 15765115]. https://doi.org/10.1038/sj.bmt.1704891.
7. Deeg HJ, Seidel K, Bruemmer B, Pepe MS, Appelbaum FR. Impact of patient weight on non-relapse mortality after marrow transplantation. *Bone Marrow Transplant*. 1995;**15**(3):461-8. [PubMed ID: 7599573].
8. McDiarmid S. Nutritional support of the patient receiving high-dose therapy with hematopoietic stem cell support. *Can Oncol Nurs J*. 2002;**12**(2):102-15. [PubMed ID: 12181941]. https://doi.org/10.5737/1181912x122102107.
9. Correia MI, Waitzberg DL. The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. *Clin Nutr*. 2003;**22**(3):235-9. [PubMed ID: 12765661]. https://doi.org/10.1016/s0261-5614(02)00215-7.
10. Cortes M, Chen MJ, Stachura DL, Liu SY, Kwan W, Wright F, et al. Developmental Vitamin D availability impacts hematopoietic stem cell production. *Cell Rep*. 2016;**17**(2):458-68. [PubMed ID: 27705794]. [PubMed Central ID: PMC5338633]. https://doi.org/10.1016/j.celrep.2016.09.012.
11. Grande A, Montanari M, Tagliafico E, Manfredini R, Marani TZ, Siena M, et al. Physiological levels of 1α, 25 dihydroxyvitamin D3 induce the monocytic commitment of CD34+ hematopoietic progenitors. *J Leukocyte Biol*. 2002;**71**(4):641-51. https://doi.org/10.1189/jlb.71.4.641.
12. Egan KM, Sosman JA, Blot WJ. Sunlight and reduced risk of cancer: Is the real story vitamin D? *J Natl Cancer Inst*. 2005;**97**(3):161-3. [PubMed ID: 15687354]. https://doi.org/10.1093/jnci/dji047.
13. Shanafelt TD, Drake MT, Maurer MJ, Allmer C, Rabe KG, Slager SL, et al. Vitamin D insufficiency and prognosis in chronic lymphocytic leukemia. *Blood*. 2011;**117**(5):1492-8. [PubMed ID: 21048153]. [PubMed Central ID: PMC3056589]. https://doi.org/10.1182/blood-2010-07-295683.
14. Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G. Vitamin D: Metabolism, molecular mechanism of action, and pleiotropic effects. *Physiol Rev*. 2016;**96**(1):365-408. [PubMed ID: 26681795]. [PubMed Central ID: PMC4839493]. https://doi.org/10.1152/physrev.00014.2015.
15. Benrashid M, Moyers K, Mohty M, Savani BN. Vitamin D deficiency, autoimmunity, and graft-versus-host-disease risk: Implication for preventive therapy. *Exp Hematol*. 2012;**40**(4):263-7. [PubMed ID: 22265707]. https://doi.org/10.1016/j.exphem.2012.01.006.
16. Rosen Y, Daich J, Soliman I, Brathwaite E, Shoenfeld Y. Vitamin D and autoimmunity. *Scand J Rheumatol*. 2016;**45**(6):439-47. [PubMed ID: 27191042]. https://doi.org/10.3109/03009742.2016.1151072.
17. Väyrynen JP, Mutt SJ, Herzig KH, Väyrynen SA, Kantola T, Karhu T, et al. Decreased preoperative serum 25-Hydroxyvitamin D levels in colorectal cancer are associated with systemic inflammation and serrated morphology. *Sci Rep*. 2016;**6**:36519. [PubMed ID: 27819306]. [PubMed Central ID: PMC5098144]. https://doi.org/10.1038/srep36519.
18. Xie DD, Chen YH, Xu S, Zhang C, Wang DM, Wang H, et al. Low vitamin D status is associated with inflammation in patients with prostate cancer. *Oncotarget*. 2017;**8**(13):22076-85. [PubMed ID: 28423553]. [PubMed Central ID: PMC5400647]. https://doi.org/10.18632/oncotarget.16195.
19. Urbain P, Ihorst G, Biesalski HK, Bertz H. Course of serum 25-hydroxyvitamin D(3) status and its influencing factors in adults undergoing allogeneic hematopoietic cell transplantation. *Ann*

Hematol. 2012;**91**(5):759-66. [PubMed ID: 22080146]. https://doi.org/10.1007/s00277-011-1365-2.

20. Dahir K, Perry B, Jagasia S. Post-transplantation bone disease: Prevalence, monitoring, prevention, and management guidelines. *Blood and Marrow Transplantation Long-Term Management: Prevention and Complications*. 2013:151-61. https://doi.org/10.1002/9781118473306.ch15.
21. Stein EM, Shane E. Vitamin D in organ transplantation. *Osteoporos Int*. 2011;**22**(7):2107-18. [PubMed ID: 21207011]. [PubMed Central ID: PMC4139072]. https://doi.org/10.1007/s00198-010-1523-8.
22. Kolb HJ, Socié G, Duell T, Van Lint MT, Tichelli A, Apperley JF, et al. Malignant neoplasms in long-term survivors of bone marrow transplantation. Late effects working party of the european cooperative group for blood and marrow transplantation and the european late effect project group. *Ann Intern Med*. 1999;**131**(10):738-44. [PubMed ID: 10577296]. https://doi.org/10.7326/0003-4819-131-10-199911160-00004.
23. Ros-Soto J, Anthias C, Madrigal A, Snowden JA. Vitamin D: Is it important in haematopoietic stem cell transplantation? A review. *Bone Marrow Transplant*. 2019;**54**(6):810-20. [PubMed ID: 30401967]. https://doi.org/10.1038/s41409-018-0377-0.
24. Fairclough E, Cairns E, Hamilton J, Kelly C. Evaluation of a modified early warning system for acute medical admissions and comparison with C-reactive protein/albumin ratio as a predictor of patient outcome. *Clin Med (Lond)*. 2009;**9**(1):30-3. [PubMed ID: 19271597]. [PubMed Central ID: PMC5922628]. https://doi.org/10.7861/clinmedicine.9-1-30.
25. Giovannucci E, Liu Y, Rimm EB, Hollis BW, Fuchs CS, Stampfer MJ, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *J Natl Cancer Inst*. 2006;**98**(7):451-9. [PubMed ID: 16595781]. https://doi.org/10.1093/jnci/djj101.
26. Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med*. 2019;**380**(1):33-44. [PubMed ID: 30415629]. [PubMed Central ID: PMC6425757]. https://doi.org/10.1056/NEJMoa1809944.
27. Cannell JJ, Vieth R, Umhau JC, Holick MF, Grant WB, Madronich S, et al. Epidemic influenza and vitamin D. *Epidemiol Infect*. 2006;**134**(6):1129-40. [PubMed ID: 16959053]. [PubMed Central ID: PMC2870528]. https://doi.org/10.1017/s0950268806007175.
28. El-Sharkawy A, Malki A. Vitamin D signaling in inflammation and cancer: Molecular mechanisms and therapeutic implications. *Molecules*. 2020;**25**(14). [PubMed ID: 32679655]. [PubMed Central ID: PMC7397283]. https://doi.org/10.3390/molecules25143219.
29. Porojnicu A, Robsahm TE, Berg JP, Moan J. Season of diagnosis is a predictor of cancer survival. Sun-induced vitamin D may be involved: A possible role of sun-induced Vitamin D. *J Steroid Biochem Mol Biol*. 2007;**103**(3-5):675-8. [PubMed ID: 17229569]. https://doi.org/10.1016/j.jsbmb.2006.12.031.
30. Vaughan-Shaw PG, O'Sullivan F, Farrington SM, Theodoratou E, Campbell H, Dunlop MG, et al. The impact of vitamin D pathway genetic variation and circulating 25-hydroxyvitamin D on cancer outcome: Systematic review and meta-analysis. *Br J Cancer*. 2017;**116**(8):1092-110. [PubMed ID: 28301870]. [PubMed Central ID: PMC5396104]. https://doi.org/10.1038/bjc.2017.44.
31. Mascarenhas R, Mobarhan S. Hypovitaminosis D-induced pain. *Nutr Rev*. 2004;**62**(9):354-9. [PubMed ID: 15497769]. https://doi.org/10.1111/j.1753-4887.2004.tb00061.x.
32. Venning G. Recent developments in vitamin D deficiency and muscle weakness among elderly people. *Bmj*. 2005;**330**(7490):524-6. [PubMed ID: 15746134]. [PubMed Central ID: PMC552815]. https://doi.org/10.1136/bmj.330.7490.524.
33. Simmons J, Sheedy C, Lee H, Koh S, Alvarez J, Koyama T, et al. Prevalence of 25-hydroxyvitamin D deficiency in child and adolescent patients undergoing hematopoietic cell transplantation compared to a healthy population. *Pediatr Blood Cancer*. 2013;**60**(12):2025-30. [PubMed ID: 23868793]. https://doi.org/10.1002/pbc.24684.
34. Vimaleswaran KS, Berry DJ, Lu C, Tikkanen E, Pilz S, Hiraki LT, et al. Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. *PLoS Med*. 2013;**10**(2). e1001383. [PubMed ID: 23393431]. [PubMed Central ID: PMC3564800]. https://doi.org/10.1371/journal.pmed.1001383.
35. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr*. 2000;**72**(3):690-3. [PubMed ID: 10966885]. https://doi.org/10.1093/ajcn/72.3.690.
36. McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: A decade of experience in patients with cancer. *Cancer Treat Rev*. 2013;**39**(5):534-40. [PubMed ID: 22995477]. https://doi.org/10.1016/j.ctrv.2012.08.003.
37. Autier P, Boniol M, Pizot C, Mullie P. Vitamin D status and ill health: A systematic review. *Lancet Diabetes Endocrinol*. 2014;**2**(1):76-89. [PubMed ID: 24622671]. https://doi.org/10.1016/s2213-8587(13)70165-7.
38. Henriksen VT, Rogers VE, Rasmussen GL, Trawick RH, Momberger NG, Aguirre D, et al. Pro-inflammatory cytokines mediate the decrease in serum 25(OH)D concentrations after total knee arthroplasty? *Med Hypotheses*. 2014;**82**(2):134-7. [PubMed ID: 24332533]. https://doi.org/10.1016/j.mehy.2013.11.020.
39. Marcotorchino J, Gouranton E, Romier B, Tourniaire F, Astier J, Malezet C, et al. Vitamin D reduces the inflammatory response and restores glucose uptake in adipocytes. *Mol Nutr Food Res*. 2012;**56**(12):1771-82. [PubMed ID: 23065818]. https://doi.org/10.1002/mnfr.201200383.
40. Amer M, Qayyum R. Relation between serum 25-hydroxyvitamin D and c-reactive protein in asymptomatic adults (from the continuous national health and nutrition examination Survey 2001 to 2006). *Am J Cardiol*. 2012;**109**(2):226-30. [PubMed ID: 21996139]. https://doi.org/10.1016/j.amjcard.2011.08.032.
41. Bellia A, Garcovich C, D'Adamo M, Lombardo M, Tesauro M, Donadel G, et al. Serum 25-hydroxyvitamin D levels are inversely associated with systemic inflammation in severe obese subjects. *Internal Emergency Medicine*. 2013;**8**:33-40. https://doi.org/10.1007/s11739-011-0559-x.
42. Guillot X, Semerano L, Saidenberg-Kermanac'h N, Falgarone G, Boissier MC. Vitamin D and inflammation. *Joint Bone Spine*. 2010;**77**(6):552-7. [PubMed ID: 21067953]. https://doi.org/10.1016/j.jbspin.2010.09.018.
43. Aranow C. Vitamin D and the immune system. *J Investig Med*. 2011;**59**(6):881-6. [PubMed ID: 21527855]. [PubMed Central ID: PMC3166406]. https://doi.org/10.2310/JIM.0b013e31821b8755.
44. Jemielita TO, Leonard MB, Baker J, Sayed S, Zemel BS, Shults J, et al. Association of 25-hydroxyvitamin D with areal and volumetric measures of bone mineral density and parathyroid hormone: Impact of vitamin D-binding protein and its assays. *Osteoporos Int*. 2016;**27**(2):617-26. [PubMed ID: 26359185]. [PubMed Central ID: PMC4924926]. https://doi.org/10.1007/s00198-015-3296-6.
45. Chun RF. New perspectives on the vitamin D binding protein. *Cell Biochem Funct*. 2012;**30**(6):445-56. [PubMed ID: 22528806]. https://doi.org/10.1002/cbf.2835.
46. Gilliland TM, Villafane-Ferriol N, Shah KP, Shah RM, Tran Cao HS, Massarweh NN, et al. Nutritional and metabolic derangements in pancreatic cancer and pancreatic resection. *Nutrients*. 2017;**9**(3). [PubMed ID: 28272344]. [PubMed Central ID: PMC5372906]. https://doi.org/10.3390/nu9030243.

47. Ghashut RA, Talwar D, Kinsella J, Duncan A, McMillan DC. The effect of the systemic inflammatory response on plasma vitamin 25 (OH) D concentrations adjusted for albumin. *PLoS One*. 2014;**9**(3). e92614. [PubMed ID: 24667823]. [PubMed Central ID: PMC3965436]. https://doi.org/10.1371/journal.pone.0092614.
48. Kano K, Suda T. Serum 25 (OH) D and 24,25 (OH)2 levels in childhood nephrosis under different therapeutic regimens of steroid administration. *Eur J Pediatr*. 1982;**138**(2):162-5. [PubMed ID: 7094938]. https://doi.org/10.1007/bf00441145.
49. Stern JM. Nutritional assesment and management of malabsorption in the hematopoietic stem cell transplant patient. *J Am Diet Assoc*. 2002;**102**(12):1812-5. discussion 1815-6. [PubMed ID: 12487547]. https://doi.org/10.1016/s0002-8223(02)90389-5.
50. Duncan CN, Vrooman L, Apfelbaum EM, Whitley K, Bechard L, Lehmann LE. 25-hydroxy vitamin D deficiency following pediatric hematopoietic stem cell transplant. *Biol Blood Marrow Transplant*. 2011;**17**(5):749-53. [PubMed ID: 20951818]. https://doi.org/10.1016/j.bbmt.2010.10.009.
51. Joseph RW, Alousi A, Konda B, Komanduri K, Neumann J, Trevino C, et al. High incidence of vitamin D deficiency in patients undergoing allogeneic stem cell transplantation. *Am J Hematol*. 2011;**86**(11):954-6. [PubMed ID: 21948087]. https://doi.org/10.1002/ajh.22143.
52. Thacher TD, Clarke BL. Vitamin D insufficiency. *Mayo Clin Proc*. 2011;**86**(1):50-60. [PubMed ID: 21193656]. [PubMed Central ID: PMC3012634]. https://doi.org/10.4065/mcp.2010.0567.
53. Beebe K, Magee K, McNulty A, Stahlecker J, Salzberg D, Miller H, et al. Vitamin D deficiency and outcomes in pediatric hematopoietic stem cell transplantation. *Pediatr Blood Cancer*. 2018;**65**(2). [PubMed ID: 28960811]. https://doi.org/10.1002/pbc.26817.
54. Sproat L, Bolwell B, Rybicki L, Dean R, Sobecks R, Pohlman B, et al. Vitamin D level after allogeneic hematopoietic stem cell transplant. *Biol Blood Marrow Transplant*. 2011;**17**(7):1079-83. [PubMed ID: 21193053]. https://doi.org/10.1016/j.bbmt.2010.12.704.