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Original Article

Is there a relationship between vitamin D levels and graft versus host disease?

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ABSTRACT

Objective: Vitamin D deficiency is common in adult patients undergoing allogenic hematopoietic stem cell transplantation (allo-HSCT). Since vitamin D is an important regulatory factor for the immune system, vitamin D deficiency may have effects on antitumor activity, relapse rates, graft versus host disease (GVHD) occurrence and infection rates in allo-HSCT. We aimed to investigate the effects of vitamin D levels on the outcome of allo-HSCT.
Material and methods: This study included 211 patients who underwent allo-HSCT at seven transplant centers in Türkiye. The impact of pretransplant vitamin D level on overall survival (OS), relapse rate, GVHD occurrence and engraftment times was analyzed retrospectively
Results: Pretransplant vitamin D levels were not related to the neutrophil engraftment day (p: 0.887), relapse rate (p: 0.433) and GVHD occurrence (p: 0.391). At a median follow-up of 14 months, OS was 84.8 % and median OS was not reached. Univariate Cox Regression analysis showed that higher levels of vitamin D (>12 ng/mL) affected the survival rates (p = 0.029) (HR: 0.392: 95 % CI: 10.170–0.907).
Conclusion: In our study, pretransplant vitamin D levels were not related to GVHD occurrence, relapse rate and engraftment times. However, we found that higher levels of pretransplant vitamin D levels (threshold is 12 ng/mL) were associated with increased survival. Further studies with a larger population are necessary to reveal the role of vitamin D in patients undergoing allo-HSCT.

1. Introduction

It is well known that vitamin D is very important for calcium homeostasis. Beyond this, its effect on the immune system functions has been shown. Vitamin D modulates the differentiation and activation of lymphocytes. It plays a role in the regulation of both innate and adaptive immune responses. Vitamin D deficiency has been reported to be related to various infections such as tuberculosis and cytomegalovirus infection, confirming its immune-modulatory effect [1–5]. People get vitamin D through exposure to sunlight and diet. In many hematological malignancies, intensive treatments are used and patients have to stay in hospital for a long time. Therefore, they cannot be exposed to sunlight. In addition, oral intake decreases during the treatment process and malabsorption may also occur. As a result of all these, vitamin D deficiency is quite common in these patients [6,7].

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a process that involves reconstructing the immune system. One of the most important goals in the transplantation process is to prevent the

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donor's immune cells from damaging the patient's tissues while exhibiting maximum antitumor effects in the patient. Therefore, each factor that regulates the immune system is of great importance in the transplantation process. While decreased antitumor activity and immune system dysfunction are associated with relapsed disease, uncontrolled damage to the patient's tissues by donor T lymphocytes causes graft versus host disease (GVHD). Opportunistic infectious agents can be seen during and after allo-HSCT. Therefore, rapid recovery of the immune system is very important in combating such infections.

Since vitamin D is an important regulatory factor for the immune system, vitamin D deficiency may have effects on antitumor activity, relapse rates, GVHD occurrence and infection rates in allo-HSCT process [8,9]. An association between chronic and acute GVHD and low level of vitamin D has been reported in recent studies in HSCT recipients [10–19]. While some studies have found that vitamin D deficiency is associated with decreased survival after transplantation [11,12], others have found no association between vitamin D and survival [20]. In addition, some centers reported that lower levels of vitamin D are associated with a higher relapse rate [21].

There are limited studies about the effects of vitamin D levels on the outcome of allo-HSCT recipients. This study aimed to investigate the effects of vitamin D levels on the allo-HSCT process.

2. Material and methods

This study included 211 patients who underwent allogeneic HCT at seven transplant centers in Turkey between 2018 and 2024. The data including age, gender, body mass index, Eastern Cooperative Oncology Group performance score, pre-transplant disease status, occurrence of relapsed disease after allo-HSCT, HCT comorbidity index score, age adjusted HCT comorbidity index score, European Society for Blood and Marrow Transplantation score, Disease Risk Index score, amount of infused $CD34^+$ cell, neutrophil and platelet engraftment day, occurrence of engraftment syndrome, blood group incompatibility, occurrence of sinusoidal obstruction syndrome (SOS), GVHD occurrence and type of organ involvement, acute GVHD Minesota risk score, GVHD Magic grade, acute GVHD occurrence day were retrospectively analyzed.

Laboratory results prior to HSCT (within 2 weeks) including vitamin D, hemoglobin, white blood cell, neutrophil, lymphocyte and thrombocyte counts, lactate dehydrogenase and ferritin levels were obtained from medical records. Measurement of serum 25-hydroxyvitamin D3 (25D3) levels was used to assess whole body vitamin D status and define vitamin D deficiency. Those with serum 25D3 level of < 12 ng/mL were considered to have vitamin D deficiency [22]. All measurements were carried out using accredited laboratory methods. At the time of serum analyzes and at the time of HSCT, none of the patients received vitamin D replacement therapy.

The engraftment definition for neutrophils was defined as the first day when the absolute neutrophil count was $> 500/mm^3$ or $1000/mm^3$ for 3 consecutive days without any support and thrombocyte engraftment was defined as the first day when the thrombocyte count was $> 20{,}000/mm^3$ for 3 consecutive days without any support [23].

2.1. Statistical analysis

IBM SPSS Statistics (version 26) was used for statistical analysis. One-Sample Kolmogorov-Smirnov test was used for data distribution. Descriptive statistics were used to present the data. Categorical data were presented as numbers and ratios and numerical data were presented as median, minimum and maximum. Mann Whitney U and Chi Square tests were used for quantitative and categorical comparisons of the pre-transplantation vitamin D levels with the engraftment days; relapse and GVHD development rates. Overall survival (OS) was described as duration from the date of allogeneic HCT to the date of death or to the latest follow-up date for the survivors. Kaplan–Meier survival analysis was applied for OS and the log-rank test was used to examine whether vitamin D levels affecting the survival. Univariate Cox Regression analysis was applied to evaluate factors affecting survival. Multivariate Cox Regression analysis was applied when there are multiple potentially interacting covariates in Univariate analysis. A two-sided p-value of ≤ 0.05 was considered statistically significant.

3. Results

3.1. Demographic characteristics and laboratory results prior to HSCT

Demographic characteristics and laboratory results of the patients prior to HSCT are given in Table 1. The disease distribution of the patients included in this study was as follows: Acute lymphoblastic leukemia (n = 65), acute myeloid leukemia (n = 115), multiple myeloma (n = 4), myelodysplastic neoplasm (n = 4), Hodgkin lymphoma (n = 4), non-Hodgkin lymphoma (n = 8), myelofibrosis (n = 3), chronic myeloid leukemia (n = 2) and aplastic anemia (n = 6). Ninety-three (44.1 %) patients were female and 118 (55.9 %) patients were male. The median age was 37 years (range, 14–64 years). The median follow-up duration was 14 months (range, 1–54 months). Median pretransplant 25D3 serum level was 10 ng/mL (range, 1–60.48 ng/mL). The number of patients with pretransplant serum 25D3 levels below 12 ng/mL was 125.

3.2. Baseline patient and transplant characteristics

Baseline patient and transplant characteristics are given in Table 2. Nine percent of the patients had prior HSCT (3.3 % allogeneic HCT, 5.7 % autologous HCT). The median amount of infused $CD34^+$ cell was 6.85×10^6/kg (range, 4.08–11.30 $\times 10^6$/kg). Eighty two percent of the patients received a myeloablative conditioning regimen (MAC) and

Table 1
Demographic characteristics and laboratory results prior to transplantation.

Parameters	n = 211
Age, years	37(14−64)
Gender (Female/Male)	93(44.1)/118(55.9)
BMI	25 (14.80–44.27)
ECOG PS	0(0−2)
Primary Disease	
• AML	115(54.5)
• cML	2(0.9)
• Ph+ B-ALL	8(3.8)
• Ph- B-ALL	43(20.4)
• HL	4(1.9)
• MDS	4(1.9)
• B-NHL	6(2.8)
• T-NHL	2(0.9)
• MF	3(1.4)
• AA	6(2.8)
• MM	4(1.9)
• t-all	14(6.6)
Number of Pre-Transplant Chemotherapy Line	2(1−7)
Pre-Transplant Disease Status (Complete Remission)	166(78.7)
Vitamin D (ng/mL)	10 (1.00–60.48)
Hemoglobin (g/dL)	9.8 (6.20–14.30)
WBC (x10^6/cell)	4600 (300–56,000)
Neutrophil (x10^6/cell)	2900 (10–32,000)
Lymphocyte (x10^6/cell)	965 (230–15,000)
Platelet (x10^6/cell)	139(12–562)
LDH (U/L)	234(65–816)
Ferritin (ng/mL)	1429(18–15,922)

Continuous variables expressed as median, minimum and maximum; categorical variables were expressed as numbers and percentages. AA: Aplastic Anemia, aGVHD: Acute Graft Versus Host Disease, AML: Acute Myeloid Leukemia, B-ALL: B Cell Acute Lymphoblastic Leukemia, BMI: Body Mass Index, CML: Chronic Myeloid Leukemia, ECOG PS: Eastern Cooperative Oncology Group Performance Score, HL: Hodgkin lymphoma, MDS: Myelodysplastic Neoplasm, MF: Myelofibrosis, MM: Multiple Myeloma, NHL: Non-Hodgkin lymphoma, Ph: Philadelphia Chromosome, T-ALL: T Cell Acute Lymphoblastic Leukemia, WBC: White blood cell, LDH: lactate dehydrogenase.

Table 2
Baseline patient and transplant characteristics.

Parameters	n = 211
Prior Transplant	
• Allogeneic HSCT	7 (3.3)
• Autologous HSCT	12 (5.7)
HCT-CI score	0(0–3)
A-HCT-CI score	1(0–4)
EBMT score	2(0–5)
DRI score	2(1–4)
The infused CD34^{+} cell (x10^{6}/kg/cell)	6.85(4.08–11.30)
Donor Age	37 years (14–64)
Donor Type	
• HLA Matched Related Donor	125(59.2)
• HLA Matched Unrelated Donor	22(10.4)
• HLA Missmatched Related Donor	5(2.4)
• HLA Missmatched Unrelated Donor	32(15.2)
• Haploidentical Donor	27(12.8)
Conditioning Regimen	
• MAC	173(82)
• RIC	38(18)
Post Transplant Cyclophosphamide Dose	
• 25 mg/kg	31(14.7)
• 50 mg/kg	141(66.8)
• Other doses	10(4.7)
• Not given	29(13.7)
Blood group Incompatibility	
• Major	32(15.2)
• Minor	34(16.1)
• Major + minor	2(0.9)
Received DLI	4 (1.9)

Continuous variables expressed as median, minimum and maximum; categorical variables were expressed as numbers and percentages. A-HCT-CI: Age Adjusted Hematopoietic Cell Transplantation Comorbidity Index, DLI: Donor Lymphocyte Infusion, DRI: Disease Risk Index, EBMT: European Society for Blood and Marrow Transplantation, HSCT: Hematopoietic Cell Transplantation, HCT-CI: Hematopoietic Cell Transplantation Comorbidity Index, HLA: Human Leukocyte Antigen, MAC: Myeloablative Conditioning, RIC: Reduced Intensity Conditioning.

18 % of the patients received a reduced intensity conditioning (RIC) regimen. Eighty six percent of the patients received post-HSCT cyclophosphamide for GVHD prophylaxis.

3.3. Engraftment durations, relapsed disease and sinusoidal obstruction syndrome

The median platelet engraftment time was 15 days (range, 7–61 days) and the median neutrophil engraftment time was 15 days (range, 11–61 days). Pretransplant vitamin D levels were not related to the neutrophil engraftment day ($p = 0.887$). Fifty-eight patients (33.5 %) had relapsed disease after HSCT. Pretransplant vitamin D levels were not related to the relapse rate ($p = 0.433$). Engraftment syndrome occurred in 3 patients (1.5 %) and 4 patients (1.9 %) had SOS (Table 3). Vitamin D levels were not related to the engraftment syndrome and SOS occurrence (both $p > 0.05$).

Table 3
Engraftment durations, relapse, engraftment syndrome and SOS occurrence.

Parameters	n = 211
Relapsed Disease After HSCT	58(33.5)
Neutrophil Engraftment (day) (median, min-max)	15(11−61)
Platelet Engraftment (day) (median, min-max)	15(7−61)
Engraftment syndrome occurrence	3(1.5)
SOS occurrence	4(1.9)

Data were expressed as numbers and percentages, HSCT: Hematopoietic cell transplantation, SOS: Sinusoidal obstruction syndrome

3.4. Pretransplant Vitamin D Status and GVHD

GVHD occurred in 44.1 % of the patients. Among those who had GVHD, 75.5 % had acute and 19.4 % had chronic GVHD. Pretransplant vitamin D levels were not related to GVHD occurrence ($p = 0.391$) and GVHD type ($p = 0.880$). The cumulative incidence of acute and chronic GVHD, organ involvement, Minesota Risk Score and Magic grade are given in Table 4.

3.5. Overall survival (OS)

At a median follow-up of 14 months, survival was 84.8 % and the median OS was not reached. Survival comparisons based on vitamin D levels (threshold is 12 ng/mL) revealed that higher levels were associated with increased survival (log rank: 0.022). Twenty five out of 125 patients having lower vitamin D levels were not alive; whereas 7 out of 86 patients having higher vitamin D levels were not alive at the end of the follow up time (Fig. 1). Univariate Cox Regression analysis showed that higher levels of vitamin D (>12 ng/mL), LDH and conditioning intensity affected the survival rates (all $p < 0.05$). Multivariate Cox regression analysis showed that lower vitamin D levels and a RIC regimen were related to the inferior survival rates (Table 5).

4. Discussion

Due to the decreased oral intake and exposure to sunlight during allo-HSCT, pretransplant vitamin D deficiency is common. It was reported that 70–90 % of HSCT recipients have vitamin D deficiency [16,24]. In the study conducted by Radujkovic et al., median pretransplant 25D3 serum level was 11.8 ng/mL [21] and, in the study conducted by Dikyar et al., median pretransplant 25D3 serum level was 12.8 ng/mL [25]. In our study, the median pretransplant 25D3 serum level was 10 ng/mL (range, 1–60.48 ng/mL) and the number of patients with pretransplant serum 25D3 levels below 12 ng/mL was 125 (59.2 %).

It has been clearly demonstrated that vitamin D has an important role in the proliferation and differentiation of hematopoietic cells. Therefore, it has been a matter of curiosity as to how vitamin D deficiency will affect engraftment times in allo-HSCT recipients. In one study, it was found that neutrophil engraftment times were longer [14 (10–26) days vs 12 (10–21) days; $p = 0.032$] in patients with vitamin D deficiency (25D3 serum level <20 μg/L) [24]. In our study, the median platelet engraftment time was 15 days (range, 7–61 days) and the median neutrophil engraftment time was 15 days (range, 11–61 days). Pretransplant vitamin D levels were not related to the neutrophil engraftment day ($p = 0.887$).

It was demonstrated that vitamin D reduces dendritic cell dependent stimulation of alloreactive lymphocytes and can reduce the effects of GVHD [26]. In the study conducted by Glotzbecker et al., the cumulative incidence of grades II–IV acute GVHD at 100 days was 53.1 % in patients with vitamin D level of < 25 ng/mL, versus 33.3 % in patients with

Table 4
GVHD data.

Parameters	n = 211
GVHD	93(44.1)
• Skin	71(80)
• Gastrointestinal system	20(9.4)
• Liver	32(15.1)
GVHD Type	
• Acute	74(75.5)
• Chronic	19(19.4)
• Overlap	5(5.1)
Post Transplant GVHD occurrence, days	82(12−373)
Acute GVHD Minesota Risk Score (high risk)	6(2.8)
GVHD Grade Magic (Gr 3–4)	25(36.2)

Data were expressed as numbers and percentages, GVHD: Acute Graft Versus Host Disease.

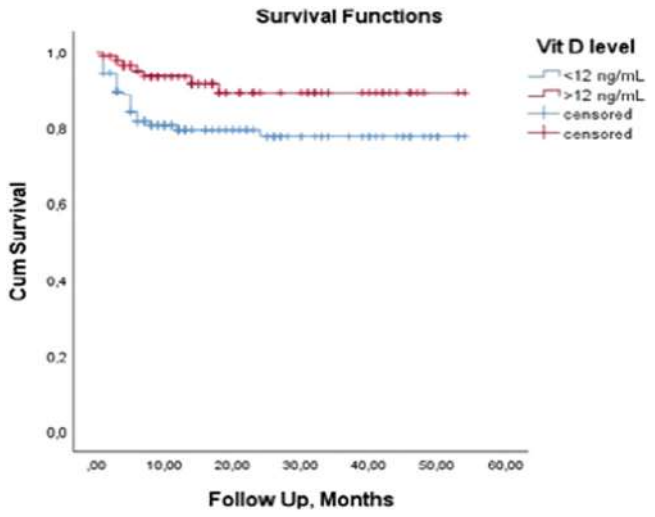

Fig. 1. Survival comparisons based on vitamin D levels (Log Rank: 0.022).

vitamin D level of ⩾25 ng/mL (p = 0.13). The cumulative incidence of chronic GVHD at 2 years in patients with a vitamin D level of < 25 ng/mL was 63.8 %, compared with 23.8 % in patients with a vitamin D level of ⩾25 ng/mL (p = 0.009). In the same study, the 2 year cumulative incidence of chronic GVHD was significantly higher in patients with a vitamin D level of < 25 ng/mL compared with those with a vitamin D level of ⩾25 ng/mL (54.5 % versus 14.3 %, p = 0.005) [20]. Similarly, some other reports have shown the association between vitamin D deficiency with a higher incidence of acute and chronic GVHD [16,19]. On the other hand, some studies have not found a relationship between vitamin D deficiency and GVHD rates. In the study conducted by Radujkovic et al., vitamin D deficiency (serum 25D3 level < 20 ng/mL) had no significant impact on the cumulative incidence of acute and chronic GVHD [21]. Wallace et al. also did not find an association between low vitamin D levels and rates of acute and chronic GVHD [13]. In the study conducted by Soydan et al., the incidence of grade 2–4 acute GVHD, chronic GVHD were not statistically different in patients with severe vitamin D deficiency (<10 ng/mL) compared with patients who had vitamin D levels of > 10 ng/mL [27]. Similarly, Dikyar et al., observed no statistical difference between low (<20 μg/L) and high (>20 μg/L) vitamin D groups in terms of acute and chronic GVHD [25]. In our study, GVHD occurred in 44.1 % of the patients. Among those who had GVHD, 75.5 % had acute and 19.4 % had chronic GVHD. Pretransplant vitamin D levels were not related to GVHD occurrence (p = 0.391) and GVHD type (p: 0.880).

The proapoptotic effects of vitamin D are well known, and low vitamin D levels have been shown to increase clonal proliferation of leukemic cells [28]. Therefore, whether vitamin D deficiency affects the incidence of relapse after allo-HSCT has been one of the questions of interest. Recent studies have shown that lower levels of serum 25(OH) D3 are associated with a higher relapse rate and poorer prognosis in patients with hematologic malignancies [11,21,29,30]. In the study conducted by Radujkovic et al., vitamin D deficiency (serum 25D3 level <20 ng/mL) was significantly associated with a higher relapse risk (HR, 1.96; p = 0.006) and inferior survival (HR, 1.78; p = 0.007) [21]. Similarly, in the study conducted by Wallace et al., severe vitamin D deficiency (<20 ng/mL) at 100 days after HSCT was associated with decreased OS (p = 0.044) [13]. At a median follow-up of 16 months, Dikyar et al., found the probability of progression free survival (PFS) to be higher in the high vitamin D (>20 μg/L) group compared to low vitamin D (<20 μg/L) group [63.5 % vs 72.5 %, p > 0.05] arms, without statistical significance [25]. Contrary to the results reported in these studies, there are also studies that did not find a relationship between vitamin D deficiency and relapse rates and survival. In the study conducted by Glotzbecker et al., no differences regarding relapse-free survival were observed between patients with low (<25 ng/mL) and high (≥25 ng/mL) vitamin D levels [20]. Similarly, Soydan et al., did not find a significant difference between two groups (<10 ng/mL level of vitamin D vs other) in terms of 1 and 2-year PFS (%69 vs %68 and %65 vs %60) and OS (%73 vs %73 and %67 vs %60) [27]. In our study, 58 patients (33.5 %) had relapsed disease after allo-HSCT. Pretransplant vitamin D levels were not related to the relaps rate (p = 0.433). At a median follow-up of 14 months, OS was 84.8 % and median OS was not reached. Survival comparisons based on vitamin D levels (threshold is 12 ng/mL) revealed that higher levels were associated with increased survival (log rank: 0.022). Twenty five out of 125 patients having lower vitamin D levels were not alive; whereas 7 out of 86 patients having higher vitamin D levels were not alive at the end of the follow up time. Univariate Cox Regression analysis showed that higher levels of vitamin D (>12 ng/mL) affected the survival rates (p = 0.029) (HR: 0.392: 95 % CI: 10.170–0.907).

In conclusion, vitamin D deficiency is common in adult patients undergoing allo-HSCT. Unlike other studies, in our study, pretransplant vitamin D levels were not related to GVHD occurrence, relaps rate and engraftment times. However, we found that higher levels of pretransplant vitamin 25(OH)D3 levels (threshold is 12 ng/mL) were associated with increased survival. Further studies with larger population are necessary to reveal the role of vitamin D in patients undergoing allo-HSCT.

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Table 5
Univariate and multivariate analyses of clinical parameters on OS.

	Univariate	Model		Multivariate	Model	
Parameter	HR	95 % CI	p	HR	95 % CI	p
Age, years			0.339			
Gender			0.409			
BMI			0.994			
ECOG PS			0.129			
Pretransplant Vit-D	0.392	0.170–0.907	**0.029**	0.328	0.140–0.771	**0.011**
Pretransplant Hemoglobin	0.594	0.290–1.215	0.153			
Pretransplant WBC			0.409			
Pretransplant Neutrophil			0.255			
Pretransplant Platelet	0.502	0.242–1.041	0.053			
Pretransplant LDH	1.003	1.00–1.005	**0.043**			
Pretransplant Ferritin			0.223			
Conditioning Intensity	0.404	0.185–0.879	**0.018**	0.318	0.143–0.708	**0.05**

BMI: Body Mass Index, ECOG PS: Eastern Cooperative Oncology Group Performance Score, LDH: lactate dehydrogenase, WBC: White blood cell.

Conflict of interest

No conflict of interest was declared by the authors.

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