The Relationship of Vitamin D Levels with Hematological Neoplasia

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ABSTRACT

Vitamin D consists of fat-soluble pro-hormones and plays role in Ca2 and P transport and bone mineralization. While it has been observed that various cancer formations decrease with higher levels of vitamin D, it has been found that individuals with hematological diseases have lower levels. Herein, we aimed to investigate the relationship between vitamin D levels and treatment response rates, survival and clinical characteristics in hematological malignancies with our study. A total of 250 patients who applied to the Hematology Clinic of Ankara Diskapi Yildirim Beyazit Education and Research Hospital between 2013 and 2022 were included in the study. Patients' data were retrospectively analyzed. 10 of the patients had acute lymphoblastic leukemia (ALL), 39 had Acute Myeloid Leukemia (AML), 49 had Diffuse Large B-Cell Lymphoma (DLBCL), 32 had Hodgkin Lymphoma (HL), 51 had Chronic Lymphocytic Leukemia (CLL), 63 had Multiple Myeloma (MM) and 6 had Mantle Cell Lymphoma (MCL). AML patients with low vitamin D levels were found to have higher hemoglobin levels (p= 0.012). DLBCL patients with low vitamin D levels, had higher beta 2 microglobulin levels (p= 0.036). In CLL patients, those with low vitamin D levels were found to have higher absolute lymphocyte count (p= 0.008) and lymphocyte ratios (p= 0.003). MM patients with low vitamin D levels were found to have more CRAB symptoms (p= 0.045). In regression analysis borderline significant correlation has been found between vitamin D levels and the rate of mortality in MM patients. Our study revealed that vitamin D levels may play an important role in the prognosis of hematological malignancies.

Keywords: Vitamin D, Hematology, Neoplasia

INTRODUCTION

Two main forms of vitamin D are; vitamin D3 or cholecalciferol, which is formed exposure to sunlight or ultraviolet light and vitamin D2 or ergocalciferol, obtained by irradiation of plant material of foods. The differrence in the formation of these two forms is due to the difference in their side chains. Limitations in obtaining vitamin D from sunlight are having a pigmented skin, clothing, age and the use of sunscreen. Vitamin D3 is hydroxylated to 25 hydroxy vitamin D3 in the liver and then hydroxylated to 1,25 dihydroxy vitamin D3 in the kidney. Risk factors for vitamin D deficiency are premature birth, less exposure to sunlight, malabsorption, pigmented skin, advanced age and obesity. Older people produce less vitamin D than the younger people. The prevalence of vitamin D deficiency is much higher in African Americans with pigmented skin.[1] African Americans with very dark skin have a Sun Protection Factor of 15, so their ability to make vitamin D is reduced by up to 99% compared to other people.[2] Adult patients with 25(OH)D levels of < 50 nmol/L had a 30-50% increased risk of evolving colorectal, breast, prostate, and many other cancers.[2]

Vitamin D deficiency caueses high parathormon secretion due to low serum 1,25 dihydroxy vitamin D and low calcium. This causes high bone turnover and bone resorption.[1] Vitamin D plays other physiological roles besides calcium metabolism.

These effects are defined as non-physiological effects of vitamin D and were described 30 years ago with the detection of 1,25 hydroxy vitamin D3 cell receptors in several cell lines. Vitamin D receptors have been seen in many cells, which explains the many effects of vitamin D. Among the non-classical effects of vitamin D, there are also effects on the immune system. Calcium and 1,25 dihydroxy vitamin D levels are high in people with granulomatous disease such as sarcoidosis. The active form of vitamin D, 1,25 dihydroxy vitamin D, promotes monocytic differentiation of the promyelocytic leukemia cell line, HL60. It is also known that this form induces normal mononuclear blood cells to differentiate into the monocyte macrophage pathway.[3]

Vitamin D is classically known as the main regulator of bone metabolism. In addition to this effect of vitamin D, it is thought that vitamin D may be a factor in the formation of some diseases, including kidney diseases, infectious diseases, cardiovascular diseases, autoimmune diseases and even cancers according to studies and data obtained.[4] The active form of vitamin D, 1,25 dihydroxy vitamin D, combines with the vitamin D receptor (VDR) and thus activates many genes. Vitamin D receptors affect the cardiovascular system through many systems such as inflammation, thrombosis and the renin angiotensin aldosterone system. According to recent studies, while it is known that vitamin D level has negative effect on metabolic conditions such as type 2 diabetes mellitus (DM), body mass index, islet beta cell function and insulin resistance, on the contrary, vitamin D deficiency has a positive correlation with insulin sensitivity. People with vitamin D deficiency are more likely to have insulin resistance and develop type 2 DM. In addition, considering the effect of vitamin D on the immune system and its antifibrotic effect, vitamin D may play a role in the physiopathology of chronic liver diseases.[5]

The International Agency for Research on Cancer (IARC) published a report on the relationship between vitamin D and cancer in November 2008. In a meta-analysis from observational studies, some of the authors of the IARC report examine the relationship between measured vitamin D levels and cancer risk. Estimates for colorectal, breast and prostate cancer risk.[6] The biological functions of vitamin D that contribute to its effects on cancer prevention have recently started to be noticed clearly. After activation, 1,25 hydroxy vitamin D acts as a strong inhibitor of cell proliferation and shows this effect on both normal and cancerous cells.[7] Vitamin D levels below 20 ng/ml leads to 30-50% increase in breast, colorectal and prostate cancers and low vitamin D levels also effect mortality.[5] In our study, we have aimed to investigate the relationship between hematological malignancies and vitamin D levels, and the effect of vitamin D levels on the prognosis of hematological malignancies.

PATIENTS AND METHODS

This study included a total of 250 patients who applied to Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital Hematology Clinic for diagnosis, follow-up and treatment between the years 2013-2022. Patients were 18 years or older. Our study was planned as retrospective study. The data were obtained from the patient files and the hospital registry system.1231 patients who applied to the clinic were screened and those who did not have vitamin D level at the time of diagnosis (n:981) were excluded from the study. An up-to-date database was created by examining the data of the remaining 250 patients. Age, gender, comorbidities, date of disease diagnosis, whether there is a refractory disease, immunophenotype of the disease, disease stage, treatments, treatment responses, minimal residual disease (MRD), laboratory result values at the time of diagnosis (hemoglobin, sedimentation, calcium, uric acid, phosphorus, blood urea nitrogen (BUN), creatinine, white blood cell count, absolute lymphocyte count, blast in the bone marrow ratio), total protein, albumin, beta-2 microglobulin, lactate dehydrogenase (LDH), liver size, spleen size, vitamin D level at the diagnosis, post-diagnosis vitamin D levels, cytogenetic test, cytogenetic risk, autologous bone marrow transplantation, transplantation date, preparation regimen, Eastern Cooperative Oncology Group score (ECOG), disease status before transplantation, mortality, the reason for treatment related mortality (TRM), patients' last follow-up or death date, the disease status at the last follow up, relapse and the relapse dates

were recorded retrospectively from the patient files and the hospital registry system. In addition to this immunophenotypes of ALL patients, extra medullary involvement, primary or secondary disease in AML patients, international prognostic index (IPI) and revised international prognostic index (R-IPI) scores, B symptoms, bulky disease, Deauville score after treatment in Hodgkin Lymphoma, international prognostic score (IPS)-3 and IPS-7 values, serum M protein level, M protein type, presence of osteolytic bone lesion at diagnosis, presence of CRAB factor and SLiM criteria at diagnosis, international scoring system (ISS) and revised international scoring system (R-ISS) at diagnosis stage in multiple myeloma (MM) patients were evaluated from hospital database and patients files.

The ethics committee approval decision date of our research is 03.02.2020 and the decision no: 81/04.

Statistical Analyses

After file reviews and data collection with the hospital registry system, all statistical analysis was performed with IBM© SPSS© Statistics Version 25.0 for Windows (Armonk, NY: IBM Corporation, 2017). First, descriptive statistics were performed for all patients. Categorical data were first analyzed with the chi-square or fisher exact test. For continuous data, distribution analysis was first performed. The distribution of continuous data was analyzed with the "Kolmogorov-Smirnov" test. Normally distributed continuous data were analyzed with the "T-test" or "Anova" test. Non-parametric data were analyzed with the "Mann-Whitney U" test or the "Kruskal Wallis" test. Survival analysis performed with Kaplan-Meier method. The effect of vitamin D levels on mortality was investigated using logistic regression analysis. The statistical significance limit was accepted as $p< 0.05$. The borderline statistical significance limit was accepted as $p< 0.1$.

RESULTS

250 patients included in our study were analyzed. Ten of our patients were diagnosed as ALL, 39 as AML, 49 as DLBCL, 32 as HL, 51 as CLL, 63 as MM and 6 as Mantle Cell Lymphoma. Vitamin D values for all malignancies were compared with all parameters as quadruple and double groups. The double groups consist two groups of patients which are the patients with vitamin D level 0-19 ng/ml and the patients with vitamin D level equal or upper than 20 ng/ml. The quadruple groups consist of 4 groups which were the patients with vitamin D levels 0-9 ng/ml, 10-19 ng/ml, 20-29 ng/ml and 30 ng/ml and above.

In ALL patients; six of ten patients were male. While there was no refractory disease in seven patients, it was present in three patients. Two of the ten patients followed have died while eight patients were alive. Central nervous system involvement was not observed in any of the patients. While the number of cures for three patients to achieve complete remission is four, it is two cures for three patients and one cure for one patient. MRD negativity was not observed in six patients, while negativity was observed in two patients. ECOG value was one in three patients, while in seven patients was the ECOG value was zero, at the time of diagnosis. The vitamin D level at the time of diagnosis was below 20 ng/ml in eight patients and it was above 20 ng/ml in two patients. Treatment-related mortality was observed in only two patients out of ten. Considering the descriptive data in ALL patients; it was seen the mean value of each data was as follows; hemoglobin 9.6 g/dl, white blood cell count 62132/ μL, platelet 72200 /μL, creatinine 0,8 mg/dl, BUN 15.6 mg/dl, ALT 47.8 U/L, AST 43.7 U/L and LDH was 1095.6 U/L. A significant relationship was found only between vitamin D and creatinine in ALL patients ($p= 0.021$). No significant results could be obtained in terms of disease-free survival and overall survival.

In AML patients; 23 of 39 patients were male. Only nine patients had recurrence. Twenty-eight patients have died during follow-up. Of 39 patients, one had myeloproliferative disease related AML, one had AML secondary to myelodysplastic syndrome (MDS) and 30 had primary AML. Twenty-six patients had refractory disease. While no recurrence was observed in thirty patients, recurrence was observed once in seven patients and twice in two patients. Refractory response was observed in 20 patients after induction therapy, complete response was observed in 14 patients and MRD was negative in three patients. While the ECOG score

Table 1. Comparison of continuous data of acute myeloid leukemia patients with Vitamin D dual group

Parameter	Vitamin D value (0-19.9 ng/ml)	Vitamin D Value (20 ng/ml or above)	p
White Blood Count (/µL)	18800 (840/109500)	7850 (1700/33900)	0.216
Hemoglobin (g/dl)	8.4 (4.6/13.7)	9.2 (7.7/15.3)	0.091
Platelet Count (/µL)	45000 (2400/156000)	74000 (16700/386000)	0.296
Creatinine (mg/dl)	0.95 (0.4/3.1)	1.05 (0.44/1.34)	0.711
BUN (mg/dl)	18.6 (9/64.48)	20.275 (12/26.16)	0.936
ALT (U/L)	19 (6/75)	19.5 (6/139)	0.606
AST (U/L)	24 (9/141)	31.5 (11/136)	0.350
LDH (U/L)	386 (116/1263)	408.5 (107/2128)	0.908

of 19 patients was zero at the time of diagnosis, the ECOG score of 15 patients was one and the ECOG score of 5 patients was 2. While the vitamin D level was below 20 ng/ml in 29 patients at the time of diagnosis, it was above 20 ng/ml in ten patients. The cytogenetic risk group of five patients was poor, the risk group of 13 patients was moderate and the risk group of 5 patients was favorable. While t (8;21) was positive in three patients, inv 16 was positive in 2 patients. Other translocations were present in 18 patients. Twenty- six patients had primary refractory disease at last sight, ten patients were in complete remission and two patients were MRD negative. Considering the descriptive data in AML patients; it was seen the mean value of each data was as follows; hemoglobin 8.7 g/dl, white blood cell count 14700/ μL, platelet count 48000/ μL, creatinine 1.02 mg/dl, BUN 18.6 mg/dl, ALT 19 U/L, AST 25 U/L and LDH was 386 U/L. Comparison of vitamin D dual group with hemoglobin (p= 0.091) and cytogenetic risk group (p=0,073) was found to be borderline significant (Table 1). The comparison of the vitamin D quadruple group and the presence of translocation (p= 0.065) was found to be borderline significantly related, while the hemoglobin value (p= 0.012) and ECOG score (p= 0.05) were found to be statistically significantly related with vitamin D levels. No significant results could be obtained in terms of disease-free survival and overall survival.

Among DLBCL patients; 32 of 49 patient screened were women. 12 of the patients have died during follow-up. Recurrence was seen in only seven patients. Recurrence was seen three times in three patients, two times in two patients and one time in two patients. 14 patients had B symptoms at the time of diagnosis; three of them had fever, four of them had night sweats and seven had weight loss. While the diagnostic ECOG score of eighteen patients was zero, it was one in seventeen patients, two in eight patients, three in four patients and four in one patient. Ten patients had central nervous system involvement. While 21 patients had extra nodal lesion involvement, only 11 patients had bulky disease at diagnosis. While double hit was observed in three patients, only two patients had triple hit. The histological subtype was germinal center in ten patients and the activated lymphocyte type in twenty-five patients. Considering the descriptive data in DLBCL patients; it was seen the mean value of each data was as follows; hemoglobin 8,8 g/dl, white blood cell count 7500/ μL, platelet count 10000/ μL, creatinine 0.44 mg/dl, BUN 16.35 mg/dl, ALT 13 U/L, AST 19 U/L, absolute lymphocyte counts 1310/ μL, lymphocyte ratio 17.2, CRP 22.9 mg/L, sedimentation 33 mm/H, total protein 6,61 g/dl, albumin 3.68 g/dl, uric acid 5.49 mg/dl, beta 2 microglobulin 3.035 mg/dl and LDH was 307 U/L. The presence of extra nodal lesion (p= 0.094), R-IPI score(p= 0.068), BUN (p= 0.082), uric acid (p= 0.074) values were statistically borderline significantly related with the vitamin D dual group, while AST (p= 0.043) and beta 2 microglobulin (p= 0.036) were significantly related (Table 2). When vitamin D was compared with the quadruple group the presence of bulky disease (p= 0.079) was borderline significantly related while beta 2 microglobulin level (p= 0.049) was significantly related with vitamin D levels. No significant results could be obtained in terms of disease-free survival and overall survival.

Table 2. Comparison of continuous data of diffuse large B-cell lymphoma patients with Vitamin D dual group

Parameter	Vitamin D Value (0-19.9 ng/ml)	Vitamin D Value (20 ng/ml or above)	p
White Blood Count (/µL)	8200 (1800/21900)	7150 (5300/11800)	0.691
Absolute Lymphocyte Count (/µL)	1310 (500/9000)	1450 (500/2100)	0.747
Lymphocyte Ratio (%)	17.3 (2.5/57)	16.5 (7.5/39.9)	0.970
Hemoglobin (g/dl)	8.8 (12/17)	10.4 (12.3/16)	0.479
Platelet Count (/µL)	10000 (245000/767000)	189000 (260000/428000)	0.620
Creatinine (mg/dl)	0.44 (0.82/8.3)	0.51 (0.785/9.3)	0.728
BUN (mg/dl)	18.12 (7/48.59)	13.78 (9.34/20.56)	0.082
ALT (U/L)	13 (4/159)	12.5 (6/31)	0.619
AST (U/L)	20 (9/246)	16.5 (10/20)	0.043
CRP (mg/L)	24.3 (1.35/294)	12.4 (4.23/49.1)	0.154
Sedimentation (mm/H)	30 (5/120)	47.5 (26/70)	0.218
Total Protein (g/dl)	6.61 (5.26/8.5)	6.715 (4.33/7.8)	0.826
Albumin (g/dl)	3.77 (2.18/4.54)	3.445 (2.25/5.08)	0.775
Uric Acid (mg/dl)	5.73 (3.38/10.49)	4.965 (1.35/7.43)	0.074
Beta-2 microglobulin (mg/dl)	3.54 (1.38/109)	2.85 (1.72/3.33)	0.036
LDH (U/L)	308 (120/4527)	237 (127/626)	0.229

In CLL patients; twenty-five of the fifty-one patients were women. Recurrence was observed in only one patient. Four of the patients have died. The cause of death in all of these patients was metabolic disorders. Eleven patients had B symptoms at diagnosis; five of them had weight loss, four had night sweats and two had fever. According to the Binet staging system, fifteen were stage A, twenty-seven were stage B and four were stage C. Bulky disease was seen in only one patient and no extra nodal lesion was found in any patient. CLL IPI score was low in 23 patients, moderate in nineteen patients and high in eight patients. While the ECOG score of 22 patients at the time of diagnosis was zero, it was one in 24 patients, two in three patients and three in one patient. Ten patients had only hepatomegaly, eleven patients had only splenomegaly and two patients had hepatosplenomegaly. There was no hepatosplenomegaly in twenty-five patients. Bone marrow biopsy appearance was diffuse in five patients and nodular in five patients. While the vitamin D level of thirty -three patients was below 20 ng /ml, it was above 20 ng/ml in 18 patients. Considering the descriptive data in CLL patients; it was seen the mean value of each data was as follows; hemoglobin 13.5 g/dl, white blood cell count 20700/ μL, platelet count 204000/ μL, creatinine 0.93 mg/dl, BUN 16.815 mg/dl, ALT 14 U/L, AST 17,5 U/L, absolute lymphocyte counts 14320/ μL, lymphocyte ratio 69.2, CRP 3.61 mg/L, sedimentation 8 mm/H, total protein 6.825 g/dl, albumin 4.36 g/dl, uric acid 5.935 mg/dl, beta 3.285 microglobulin 3.035 mg/dl and LDH was 193 U/L. It was seen that vitamin D dual group and white blood cell count (p= 0.026), absolute lymphocyte count (p= 0.008), lymphocyte ratio (p= 0.003) and BUN (p= 0.029) were found to be significant (Table 3). Comparison of the presence of B symptoms (p= 0.031) and lymphocyte ratio (p= 0.036) with the vitamin D quadruple group was found to be statistically significantly related, while the comparison of BUN (p= 0.064) and absolute lymphocyte count (p= 0.059) was found to be borderline significantly related with vitamin D levels. No significant results could be obtained in terms of disease-free survival and overall survival.

In HL patients; 15 of 32 patients were women. Recurrence was seen in only two patients. Two patients have died during their follow-up. One patient died due to relapse disease and the other patient died because of metabolic disorders. One patient underwent autologous bone marrow transplantation. Seventeen patients had a diagnosis ECOG score of zero, fifteen patients had a diagnostic ECOG score of 1. Half of the patients had B symptoms at the time of diagnosis; weight loss

Table 3. Comparison of continuous data of chronic Lymphocytic leukemia patients with Vitamin D in two groups

Parameters	Vitamin D value ng/ml (0-19.9)	Vitamin D value ng/ml (20 or above)	p
White Blood Count (/µL)	25680 (8250/173000)	17250 (10420/278000)	0.026
Absolute Lymphocyte Count (/µL)	20000 (4060/162100)	10350 (5300/197000)	0.008
Lymphocyte Ratio (%)	76.6 (39.1/93.3)	59.95 (46/85.3)	0.003
Hemoglobin (g/dl)	13.6 (7.5/16.6)	13.25 (8.9/18.6)	0.251
Platelet Count (/µL)	203000 (17000/443000)	205000 (21000/396000)	0.771
Creatinine (mg/dl)	0.94 (0.59/1.73)	0.915 (0.58/1.15)	0.406
BUN (mg/dl)	17.875 (9.38/38.3)	15.395 (9.53/20)	0.029
ALT (U/L)	13.5 (5/43)	16 (6/22)	0.673
AST (U/L)	18 (11/35)	17.25 (15/46)	0.696
CRP (mg/L)	4.61 (0.41/34.7)	3.07 (1.3/4.62)	0.133
Sedimentation (mm/H)	6 (2/49)	11 (3/29)	0.495
Total Protein (g/dl)	6.8 (5.79/14.59)	7.16 (5.91/7.84)	0.936
Albumin (g/dl)	4.3 (2.53/5.05)	4.49 (4.04/5.15)	0.168
Uric Acid (mg/dl)	6.24 (3.04/9)	5.54 (3.6/7.98)	0.267
Beta 2 Microglobulin (mg/dl)	3.86 (2.08/5.82)	3.09 (1.71/5.13)	0.165
LDH (U/L)	190 (140/294)	201 (152/819)	0.182

was observed in 7 patients, night sweats in 7 patients and fever in two patients. When the disease subtypes were examined, 13 patients were nodular sclerosis, 13 patients were mixed cellular, 5 patients were nodular lymphocyte predominant and 1 patient was lymphocyte rich. Extra nodal lesion was seen in seven patients. six patients had bulky disease. At the time of diagnosis, 26 patients had a vitamin D level below 20 ng/ml, while 6 patients had a level above 20 ng/ml. Considering the Deauville score after the first treatment, the score was 1 in 1 patient, 2 in 6 patients, 3 in 4 patients and 4 in 1 patient. The disease status of 18 patients at the time of last presentation was complete remission, one patient had refractory disease and 1 patient had relapsed disease. Considering the descriptive data in HL patients; it was seen the mean value of each data was as follows; hemoglobin 12.9 g/dl, white blood cell count 8000/ μL, platelet count 329000/ μL, creatinine 0.77 mg/dl, BUN 12.14 mg/dl, ALT 25 U/L, AST 21 U/L, absolute lymphocyte counts 1695/ μL, lymphocyte ratio 20.95, CRP 19.8 mg/L, sedimentation 18.5 mm/H, total protein 7.2 g/dl, albumin 4.14 g/dl, uric acid 4.7 mg/dl, beta 2 microglobulin 2.385 mg/dl and LDH was 213 U/L. When the data were compared with vitamin D dual group, the presence of B symptoms (p= 0.070) was borderline significantly related with vitamin D levels. When the data were compared with the vitamin D quadruple group, the IPS-3 score (p= 0.007) was statistically significantly related with vitamin D levels while the ECOG score was (p= 0.089) borderline significantly related (Table 4). No significant results could be obtained in terms of disease-free survival and overall survival.

In Mantle Cell Lymphoma patients; four of six patients were female. One patient has died. No recurrence was observed in any of the patients. The ECOG score at the time of diagnosis was zero in three patients and one in the other three patients. Autologous bone marrow transplantation was performed in one patient. None of the patients had B symptoms. Central nervous system involvement was not observed in any patient. Histological type was in five patients and blastoid type in one patient. Extra nodal lesion was seen in four patients. Bulky disease was absent in any of the patient. Vitamin D level at the time of diagnosis in two patients was below 20 ng/ml and in four patients it was above 20 ng/ml. The disease status after first treatment was complete remission in three patients and partial remission in the other three patients. Considering the descriptive data in MCL patients; it was seen the mean value of each data was as follows;

Table 4. Comparison of categorical data of Hodgkin lymphoma patients with Vitamin D quadruple group

Parameters	Vitamin D value ng/ml (0-9.9)	Vitamin D value ng/ml (10-19.9)	Vitamin D value ng/ml (20-29.9)	Vitamin D value (30 ng/ml or above)	p
Male/Female	4/8	10/4	2/1	1/3	0.216
No Relapse /Relapse in Absent	12/0	11/2	3/0	3/0	0.398
Ex Present /Ex Absent	12/0	12/2	3/0	3/0	0.433
Autologous Bone Marrow Transplantation Present/Absent	12/0	13/1	3/0	3/0	0.723
ECOG Score at Diagnosis 0/1	9/3	6/8	2/1	0/3	0.089
Presence of B Symptoms at Diagnosis Present/Absent	5/7	10/4	0/2	1/2	0.101
Disease Status at Diagnosis: Early Stage Good Risk /Early Stage Poor Risk /Advanced Stage (3-4)Disease	4/4/4	5/3/6	0/1/2	0/1/2	0.743
IPS-3 Score Low Risk/Medium Risk/High Risk	9/3/0	6/8/0	0/3/0	2/0/1	0.007
IPS-7 Score Low Risk/Medium Risk/High Risk	9/2/1	7/6/0	1/2/0	2/0/1	0.168
Treatment Related Mortality Present/Absent	12/0	10/1	3/0	3/0	0.638

hemoglobin 11.35 g/dl, white blood cell count 10100/ μL, platelet count 212000/ μL, creatinine 1.12 mg/dl, BUN 14,49 mg/dl , ALT 10,55 U/L , AST 19.5 U/L, absolute lymphocyte count 5890/ μL ,lymphocyte ratio 54.295, CRP 4.53 mg/L, sedimentation 29,5 mm/H, total protein 6,42 g/dl, albumin 4.185 g/dl, uric acid 6,42 mg/dl, beta 2 microglobulin 4.775 mg/dl and LDH was 251.5 U/L. Due to the small number of patients, only vitamin D could be compared with the dual group. Only the comparison with platelet (p= 0.064) was found to be borderline significantly related with vitamin D levels. No significant results could be obtained in terms of disease-free survival and overall survival.

In MM patients; 34 of 63 patients were male. There was recurrence in 12 patients. 10 of them relapsed once and 2 of them relapsed twice. 16 patients have died. The cause of death in 14 patients was metabolic disorder, infection in one patient and relapsed disease in one patient. The ECOG score at the time of diagnosis in 28 patients was zero, one in 25 patients and two in ten patients. The ISS score of 30 patients was three, two of fifteen patients, one of ten patients. A total of 19 patients underwent autologous bone marrow transplantation. While the vitamin D level of 44 patients was below 20 ng /ml at the time of diagnosis, it was above 20 ng /ml in 19 patients. The disease status before autologous bone marrow transplantation negative for MRD in one patient, VGPR in 5 patients, PR in 8 patients and SD in 2 patients. The disease status after autologous bone marrow transplantation was negative for MRD in one patient, VGPR in three patients, PR in 8 patients and SD in 2 patients. While the reason for starting treatment in 14 patients was SLIM findings, 38 patients were CRAB findings. 25 patients had one or more osteolytic bone lesions at diagnosis. Considering the descriptive data in MM patients; it was seen the mean value of each data was as follows; hemoglobin 10.1 g/dl, white blood cell count 6700/ μL, platelet count 200000/ μL, creatinine 1.3 fmg/dl, BUN 24.13 mg/dl, ALT 16 U/L, AST 19 U/L, CRP 8.55 mg/L, sedimentation 44 mm/H, total protein 7.94 g/dl, albumin 3.58 g/dl, uric acid 7.4 mg/dl, beta 2 microglobulin 5.72 mg/dl, phosphorus 3.92 mg/dl, calcium 9.56 mg/dl and LDH was 179 U/L. When the vitamin D dual group data were compared, it was found

Table 5. Comparison of continuous data of Multiple Myeloma patients with Vitamin D in dual group

Parameter	Vitamin D value (0-19.9 ng/ml)	Vitamin D value (20 ng/ml or above)	p
White Blood Count (/µL)	6350 (440/13720)	6700 (3100/15300)	0.564
Hemoglobin (g/dl)	9.8 (6.2/15.5)	11 (7.1/14.8)	0.247
Platelet Count (/µL)	203500 (48000/498000)	171000 (117000/483000)	0.605
Creatinine (mg/dl)	1.365 (0.58/9.8)	1.06 (0.56/3.03)	0.185
BUN (mg/dl)	24.2 (11.21/109.30)	21.96 (12.61/80.37)	0.302
ALT (U/L)	16 (5/113)	15 (5/88)	0.747
AST (U/L)	19 (5/79)	19.65 (12/71)	0.476
CRP (mg/L)	9.845 (0.04/219)	5.33 (0.67/161)	0.223
Sedimentation (mm/H)	55 (3/140)	35 (6/140)	0.172
Calcium (mg/dl)	9.36 (6.21/13.53)	9.87 (8.4/14.51)	0.033
Phosphorus (mg/dl)	4.16 (1.70/7.87)	3.6 (2.28/4.75)	0.151
Total Protein (g/dl)	7.935 (4.59/14.26)	8.41 (5.9/10.85)	0.808
Albumin (g/dl)	3.41 (1.56/4.85)	3.99 (2.67/4.8)	0.044
Uric Acid (mg/dl)	7.525 (2.5/15.6)	6.67 (3.28/10.9)	0.116
Beta 2 Macroglobulin (mg/dl)	6.15 (1.74/57.9)	4.505 (1.87/20.3)	0.066
LDH (U/L)	169 (94/1776)	182 (115/2570)	0.305
Bone Marrow Plasma Cell Ratio (%)	40 (10/90)	30 (10/60)	0.505

that which CRAB findings (p= 0.045), calcium (p= 0.033) and albumin (p= 0.044) were statistically significantly related, while beta 2 microglobulin value (p= 0.066), gender (p= 0.073), presence of death (p= 0.075), ISS score (p= 0.087) were found to be borderline significantly related with vitamin D levels (Table 5). When the vitamin D quadruple group was compared, death (p= 0.041), disease status after autologous bone marrow transplantation (p= 0.028), presence of one or more osteolytic lesions at diagnosis (p= 0.049), phosphorus (p= 0.007), albumin (p= 0.044), bone marrow plasma cell ratio (p= 0.044) and BUN (p= 0.05) were found to be statistically significantly related with vitamin D levels, while uric acid (p= 0.097), pre-autologous bone marrow transplantation disease status (p= 0.054) and comorbidities (p= 0.086) were found to be borderline significantly related with D vitamin levels. No significant results could be obtained in terms of disease-free survival and overall survival. The relationship between vitamin D groups and whether patients died or not was analyzed by logistic regression analysis. A borderline significant (p= 0.091) relationship was seen only in MM patients.

DISCUSSION

Vitamin D is classically known as the main source and regulator of bone metabolism and minerals.[4] Generally, serum vitamin D levels are classified as deficient, insufficient and adequate. According to the Endocrine Society, vitamin D level above 30 ng/ml was evaluated as sufficient, while its insufficient was defined as 21-29 ng/ml and deficiency was defined as below 20 ng /ml.[8] In addition to contribution of vitamin D to the musculoskeletal system; it has also been observed to be associated with various diseases such as some autoimmune diseases, cardiovascular system diseases, kidney diseases and cancer. In the study of Garland et al., it was shown that there is an inverse relationship between colon cancer and vitamin D. Based on this information they thought that vitamin D was protective against cancer. In a study conducted in the light of this information, it was observed that cancer mortality was significantly reduced in men with vitamin D levels below 50 nmol/L.[4] In general, it has been observed that low serum vitamin D value in hematological cancers is associated with higher malignant cell load and poorer disease course. In meta-analysis of seven published studies involv-

ing 2643 patients with hematologic cancer, low vitamin D levels were associated with shortened overall survival and disease-free survival.[8] In the present study, the effects of vitamin D levels on overall survival, disease-free survival, biochemical and complete blood count parameters, disease prognosis and treatment response in patients were investigated.

When the hematological malignancies we examined were evaluated individually; as a result of the quadruple comparison of only creatinine value and vitamin D in ALL patients, the p value was found to be 0.021 and we thought that vitamin D levels indirectly may effect the prognosis of ALL patients by effecting creatinine. We could not find any study supporting our finding in the literature.

In a study conducted by Morton A, et al.; it was aimed to investigate the prevalence and predictive factors of vitamin D deficiency in patients with malignancy. Vitamin D levels were measured in 100 patients without hematological cancer. The mean ECOG score of this patient group was 2 and vitamin D levels were 56 nmol/l. As a result of the study, it was thought that having a low performance status was a predictor of low vitamin D level.[9] In the present study, when the vitamin D dual group in AML patients was compared with the cytogenetic risk groups of the patients, the p value was found to be 0.073 and it was found to be borderline significant. It was observed that there was no patient in the good cytogenetic risk group in the group with high vitamin D. When the relationship between vitamin D and cytogenetic risk group was scanned, there was no data proving this in the literature. When the vitamin D four-group and translocation of the patients were compared, we found that the translocations with good prognosis were seen in the groups with low vitamin D (p= 0.065). This hypothesis should be supported by new studies in the literature. Both translocation and the cytogenetic risk group in AML patients since it is associated with the vitamin D levels, the question of how vitamin D effects genetic risk or whether it prevents mutation comes to mind. We could not find study showing this relationship in the literature. Hemoglobin levels were found to be significant when compared both dual group (p= 0.091) and quadruple group (p= 0.012) and hemoglobin levels were found to be relatively higher in the groups with high vitamin D levels. This relationship we found should be supported by other studies. Lee et al, AML newly diagnosed and starting treatment the prevalence of serum vitamin D deficiency was evaluated in 97 patients. As a result of this study, vitamin D levels were not sufficient in 65% of the patients; it was observed that 30% of them are incomplete and 35 % them are insufficient. Patients with below-normal levels of vitamin D had worse disease-free survival.[10] In the present study, however, no significant relationship was found between vitamin D levels and disease-free and overall survival.

In DLBCL patients when the vitamin D quadruple group was compared with the stage of the disease, the p value was found to be borderline significant (p= 0.081). It was observed that the diseases of the people in the group with low vitamin D were at an advanced stage at diagnosis. When we examine the literature in order to evaluate why patients with low vitamin D levels are more advanced stage at the time of diagnosis, shows symptoms later or whether the disease progresses more rapidly; ın a study consisting of 195 patients who applied to the radiation oncology clinic in the USA between 2008 and 2010; the vitamin D levels of the patients were requested and it was seen that 74% of the patients were insufficient or deficient in vitamin D. Vitamin D replacement was given to patients with low values. Regardless of patients' gender and age, low vitamin D levels are predicted for more advanced disease.11 In the present study, when the vitamin D dual group and uric acid levels were compared, it was found borderline significant (p= 0.074). It is seen that the uric acid levels are higher in the group with low vitamin D. In the study of Prochazka TK, et al., high uric acid levels were found to be a negative risk factor for overall survival and disease-free survival in DLBCL patients.[12] When we examined the relationship between vitamin D level and uric acid; ın a meta-analysis study consisting of 1045 studies; a level of 30 ng/ml and above was accepted as adequate level, 20-30 ng/ml as insufficiency and below 20 ng/ml as deficiency; it was observed that the uric acid levels of those with sufficient vitamin D levels were lower than the patients in the group with deficiency and insufficiency.[13] In a

study[14] AST levels in DLBCL patients were examined and an AST level of 33.3 U/L was used as the optimal threshold value in determining the prognosis. It was observed that patients in the group with an AST value higher than this threshold had worse clinical features and a lower 2-year overall survival than those with a lower level.[14] In the present study, the comparison of vitamin D with the dual group and AST, it was found significant (p= 0.043). In the comparison of vitamin D quadruple group and bulky disease was considered borderline significant (p= 0.079). In a study when we reviewed the literature, while investigating vitamin D deficiency in the elderly patient group with DLBCL, low vitamin D level was associated with a higher IPI score, multiple extra nodal involvement and bulky disease.[15] In a study that included 208 newly diagnosed DLBCL patients in total; was found to be an independent prognostic factor in terms of both overall survival (p= 0.006) and disease-free survival (p= 0.001).[16] In the present study, however it was not found to be significant in terms of both disease-free survival and overall survival.

In CLL patients in the present study, when we compared the vitamin D double group and the white blood cell count, it was found to be significant (p= 0.026). It was observed that the mean white blood cell count was higher in the group with low vitamin D levels. This finding should be supported by other studies in the literature. When vitamin D double group and absolute lymphocyte count were compared, it was significant (p= 0.008). The mean absolute lymphocyte count was higher in the group with low vitamin D value. In a study obtained by combining two cohorts, vitamin D levels were also measured along with various laboratory tests in a group of CLL patients. In this study, no significant relationship was found between the group with vitamin D deficiency and absolute lymphocyte count.[17] When vitamin D double (p= 0.003) and quadruple groups (p= 0.039) compared, both results were found to be significant. In a retrospective study to evaluate the relationship between vitamin D and inflammation in 4210 patients, patients were divided into 2 groups according to their vitamin D levels. The first group consisted of patients with vitamin D levels below 20 ng/ml and the second group consisted of patients with 20 ng /ml and above. Among these patients it was observed that the platelet-lymphocyte ratio and the neutrophil-lymphocyte ratio were much higher in patients with low vitamin D.[18] Significant relationship was found in the comparison of vitamin D groups with lymphocyte ratio and absolute lymphocyte count, therefore it may be speculated that vitamin D levels affect the lymphocyte doubling time. There is no data in the literature regarding this issue. In our study, no significant results were obtained in terms of overall survival and disease-free survival when vitamin D was compared with the quadruple and dual groups. In a study conducted at Duke University Hospital in 185 of patients diagnosed with CLL and not treated for 12 months, it was observed that basal vitamin D levels did not produce a significant result in terms of time to treatment and overall survival.[19]

In HL patients of our study, comparison of vitamin D dual group and B symptoms was found to be borderline significant (p= 0.070). It was observed that the rate of B symptoms was lower in the group with low vitamin D. When we searched the literature to answer questions such as whether B symptoms were observed less frequently in the group with low vitamin D levels and whether vitamin D was necessary for the patient to give B symptoms, we could not directly reach a comparison result. In a study by Borchman S, et al., on 351 HL patients; it was observed that approximately 50% of the patients had low levels of vitamin D at the time of diagnosis, regardless of the stage of the disease and other risk factors. As a result of this study, it was observed that patients with vitamin D deficiency had lower disease -free survival and overall survival.[20] In the present study, however, no significant results were obtained when vitamin D double and quadruple groups were compared with overall and disease- free survival.

In the present study, in MM patients; comparison of the presence of vitamin D dual group and CRAB findings result was found significant (p= 0.045). When we look at the details of findings, we see that one or more of CRAB findings are seen much more in the group with low vitamin D group than in the group with high vitamin D. Gedik H., et al., retrospectively studied 31 MM patients; it was seen that the mean vitamin D level of all pa-

tients was 11.9±7.6 ng/ml and the presence of one or more the CRAB findings was detected in almost all patients. It was thought that decreased vitamin D levels may affect the prognosis of MM patients by affecting tumor metabolism besides the skeletal system.[21] In our study, as a result of the comparison of the ISS score with the vitamin D binary group, it was found to be borderline significant (p= 0.087). We see a higher ISS score in the group with low vitamin D. We could not evaluate the existence of a direct study in the literature comparing vitamin D level and ISS score level in MM patients. When we examine the albumin level and beta 2 microglobulin level, which are the parameters affecting the ISS score, respectively; in the comparison of vitamin D levels in both double and quadruple groups and albumin levels, it was found significant (p= 0.044). In the comparison of vitamin D dual group and albumin, it was observed that the average albumin value was 3.41 g/dl in the group with vitamin D level of 19 ng/ml and below and the average value of albumin was 3.99/ dl in the group with 20ng/ml and above. In the comparison with the other groups the albumin level was found to be lower in the group with low vitamin D levels compared to the other groups. In another study conducted in a group of 148 newly diagnosed MM patients between 2004 and 2008, the vitamin D levels of the patients were measured within 14 days of the diagnosis and it was observed that the vitamin D level was below 20 ng/ml in 35 patients. When the vitamin D level was normal and the deficient group was compared no significant demographic difference was observed and it was observed that the albumin level was lower in the vitamin D deficient group in these patient groups.[22] When we examine the second parameter that affects the ISS score, beta 2 microglobulin; in our study comparison of beta 2 microglobulin levels and vitamin D dual group it was found significant (p= 0.066). Beta 2 microglobulin levels were found to be higher in the group with low vitamin D levels. The negative effects of high levels of beta 2 microglobulin, which is also the cornerstone of the ISS scoring system, on survival in MM patients have been shown in various studies.[23] When we searched the literature, we could not find a study evaluating the direct relationship between vitamin D and beta 2 microglobulin levels. As has been demonstrated in various studies, gender has been found to be among the epidemiological risk factors for MM, especially men are at higher risk of developing MM than women.[24] In the present study, the result of the comparison of the vitamin D dual group and gender was found to be borderline significant (p= 0.073). Of the 63 MM patients included in our study, 34 were male and 29 were female. In the group with low vitamin D, male gender is more common. In the present study, when the vitamin D quadruple group was compared with phosphorus, it was observed that the phosphorus levels in the group with low vitamin D levels at the time of diagnosis were higher than the other groups. This comparison was found to be significant (p= 0.007). However, this result should be supported by other studies in the literature. In our study, a borderline significantly relationship (p= 0.097) was found between the vitamin D quadruple group and the uric acid levels. It was observed that uric acid levels were relatively higher in groups with low vitamin D levels. In the study of Matzner Y, et al., it was observed that the overall survival time was shorter in patients with hyperuricemia at the time of diagnosis in MM patients.[25] When the vitamin D quadruple group was compared with the evaluation of the disease status before autologous bone marrow transplantation, it was observed that the disease status was better in the group with low vitamin D (p= 0.054). In the comparison of the vitamin D quadruple group and the disease status after autologous bone marrow transplantation, it was found to be significant (p= 0.028). In this comparison, the disease status of the group with low vitamin D was relatively better after autologous bone marrow transplantation compared to the other groups. Patients with hematological malignancies were screened. Vitamin D deficiency may be adverse in terms of various outcomes such as bone health, recurrence, graft versus host disease after bone marrow transplantation. Vitamin D level which is considered as a modifiable risk factor that can be used to optimize bone marrow transplant outcomes.[26] When we compared the bone marrow plasma cell ratio at the time of diagnosis and quadruple groups with vitamin D levels, we observed that the bone marrow plasma cell ratio was higher in the group with low vitamin D than in the other groups (p= 0.044). In a retrospective study conducted on 83 MM patients

diagnosed between 2007 and 2014 in the literature, vitamin D levels and other laboratory values of the patients were examined. It was observed that the plasma cell ratio was higher in the group with low vitamin D level below 10 ng /ml compared to the other groups.[27]

In the present study, in MCL patients when the platelet and vitamin D dual groups were compared, it was found to be borderline significant (0.064). It is seen that the platelet level higher in the patient group with low vitamin D levels. We could not find a direct relationship between platelets and vitamin D in MCL patients in the literature. However, as a result of study conducted by Park YC, including 3190 patients in total, who applied to a health institution for screening purposes, it was observed that the platelet levels were higher in the vitamin D deficient group compared to the inadequate group.[28] In a study conducted on 70 patients with newly diagnosed mantle cell lymphoma; 40 of this patient group were found to be vitamin D deficient. The definition of vitamin D deficiency in the study was determined according to the international vitamin D classification standard and was accepted as 50 nmol/L. As a result of this study, worse disease-free survival and overall survival rates were seen in the group with low vitamin D.[16] In the present study, however, no comparison could be made with disease-free survival, since none of the patients included in the study had recurrence. Comparison of overall survival with dual vitamin D group was found to be meaningless.

The retrospective design of our study is the most significant limitation. When disease subgroups are taken into account one by one, the small number of patients analyzed in each groups are considered another significant constraint. The absence of adequate genetic and prognostic evaluations in patient records is perceived as another constraining factor in our study.

Conclusion

In conclusion, we have observed that vitamin D deficiency caused adverse effects on hematological malignancies in the present study. An association between Vitamin D levels and creatinine has been observed in the ALL patient group. It was observed that the ECOG performance score was higher in the group with low vitamin D in the AML patient group. It was observed that hemoglobin levels were higher in the groups with high vitamin D in the AML group. Beta 2 microglobulin levels were found to be higher in the DLBCL patient group in the groups with low vitamin D. In the CLL patient group, low vitamin D levels were found to be have higher white blood cell counts and absolute lymphocyte count and lymphocyte ratios were found to be higher. It was observed that B symptoms were less in the group with low vitamin D in CLL patients. It was observed that the number of patients with low IPS-3 score was higher in the group with low vitamin D in the HL patient group. It was determined that CRAB findings were more common in the group with low vitamin D in the MM patient group. In the MM patient group, albumin and calcium levels were found to be lower in the patient group with low vitamin D. We observed a relationship between vitamin D and the presence of osteolytic lesions and disease status after autologous bone marrow transplantation in MM patients. It was observed that the rate of bone marrow plasma cell was higher in the group with low vitamin D in MM patients. Although borderline significance was found in the regression analysis, a correlation was found between vitamin D levels and the proportion of patients with multiple myeloma who died. It would not be correct to generalize this study we conducted to all patients with hematological malignancies due to patient limitations. The results we obtained in our study should be supported by new and more comprehensive studies, preferably prospective and randomized controlled.

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