

## Importance of vitamin d level in early-stage chronic lymphocytic leukemia and its comparison with healthy population

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### SUMMARY

*Chronic lymphocytic leukemia (CLL) is a chronic lymphoproliferative hematological malignancy accompanied by a monoclonal proliferation of mature B lymphocytes. Vitamin D is vital in calcium hemostasis in serum and skeletal system and is involved in several other cellular processes such as differentiation, proliferation, apoptosis, and angiogenesis. Vitamin D receptors were also demonstrated in normal or malignant hematopoietic cells. The correlation of low serum vitamin D levels with colorectal, breast, and other solid-organ neoplasms is well known. With regard to CLL, vitamin D inadequacy is related to bad prognosis, bad overall survival, and necessity to start treatment early. This study aimed to compare vitamin D levels of patients with early-stage CLL and controls and to examine its relationship with prognostic indicators.*

*The study included 33 patients with early-stage CLL treated at Atatürk Training and Research Hospital Hematology Clinic between 2015 and 2017 and 34 healthy controls. Age and gender distribution in both groups was similar. Patients with <20 ng/mL vitamin D level were considered as vitamin D deficient.*

*Vitamin D deficiency was detected in 26/33 patients with CLL and 16/34 controls. A statistically significant difference in vitamin D deficiency was found between these two groups ( $P = 0.003$ ). CLL cases were compared in terms of RAI stage, splenomegaly, hepatomegaly, and presence of B symptoms. However, no significant difference was observed.*

*This study demonstrated that vitamin D levels of patients with early-stage CLL were significantly low in comparison with those of healthy population, in line with the literature. More comprehensive studies are required for assessing the effects of low vitamin D levels on the prognosis of patients with early-stage CLL.*

*Key words: Early-stage CLL, prognosis, vitamin D deficiency*

### INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a chronic lymphoproliferative hematological malignancy accompanied by a monoclonal proliferation of mature B lymphocytes. CLL is the most common type of adult leukemia with 5/100,000 incidence rate every year in Western countries (1-3). CLL is a disease that mostly affects elder; 80% of the patients are aged more than 50 years (4,5). However, CLL has a heterogeneous course according to the clinical and molecular characteristics (6,7).

Vitamin D deficiency is quite common around the world. Besides regulating serum calcium and skeletal homeostasis, vitamin D is involved in several other cellular processes including differentiation, proliferation, apoptosis, metastatic potential, and regulation of angiogenesis (8). Vitamin D receptors were also demonstrated in normal or malignant hematopoietic cells. Low serum vitamin D levels are related to colorectal, breast, and other solid-organ neoplasms (9-11).

A double-blind, randomized, and placebo-controlled study demonstrated that the cancer risk of women taking vitamin D replacement daily reduced by 60%–77%. (12). Vitamin D deficiency in patients with CLL has emerged as a new, independent, poor prognostic factor in recent years. (13). Meanwhile, low serum vitamin D levels are related to short overall survival and necessity to start treatment early (14).

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**TABLE 1:** Age and gender characteristics of patients with CLL and healthy controls.

	CLL	Healthy controls
Age	60 (± SD 14)	58 (± SD 11.5)
Gender (F/M)	15 (45.5%)/ 18 (54.5%)	13 (38.9%)/ 21 (61.1%)
Vitamin D levels		
Normal >20 ng/mL	3 / 33 (22%)	18 / 34 (53%)
Low <20 ng/mL, n (%)	26 / 33 (78%)	16 / 34 (47%)

The present study compared serum vitamin D levels of patients with early-stage CLL and normal healthy controls. It also examined the correlation between vitamin D levels and other risk factors such as RAI stage of the disease, B symptoms, and organomegaly.

## MATERIALS AND METHODS

This study included 33 patients with early-stage CLL at Atatürk Training and Research Hospital Hematology Clinic between 2015 and 2017. It also involved 34 healthy controls whose vitamin D level was checked during their routine follow-up. Vitamin D deficiency was considered as 20 ng/mL or lower. The studied blood samples were venous blood drawn after 8 hours of fasting. Vitamin D levels were checked by the liquid chromatography method. Data collected from computer registers were statistically analyzed using SPSS version 16.0 (SPSS Inc., IL, USA). Categorical variables were compared using the chi-square test, whereas numerical variables were compared using the Mann–Whitney U test. P values less than 0.05 were considered significant.

## RESULTS

Age, gender, and vitamin D levels of patients with CLL and healthy controls are shown in table 1. No statistically significant differences were found between two groups with respect to age and gender distribution. The average follow-up duration of patients with CLL was reported as 44 months (12–102 months). Details on stages of the patients, B symptoms (fever, night sweating, and weight loss), and organomegaly are summarized in Table 2.

Further, 14 of 26 (53.8%) patients with CLL having low vitamin D level were males and 12 (46.2%) were females. Also, 13 (50%) of the patients with CLL having low vitamin D level were aged more than 65 years. With regard to RAI stages, 14 (53.9%) patients were at stage 2, 8 (30.8%) were at stage 1, and 4 (15.4%) were at stage 0. Moreover, 7 (26.9%) of the patients had hepatomegaly, 12 (46.2%) had splenomegaly, and 3 (11.5%) had B symptoms. Out of seven (21.2%) patients with CLL having normal vitamin D levels, four (47.1%) were at RAI stage 2 and three (42.9%) were at RAI stage 1. Five (71.4%) of the patients were aged 65 years or above; four (57.1%) were males and three (42.9%) were females. Three (42.9%) patients having normal vitamin D level had B symptoms.

Also, 10 of 16 (62.5%) controls having low vitamin D level were females and 6 (37%) were males. Six (37%) of these patients were aged 65 years or above.

Vitamin D deficiency was detected in 26 (78.8%) patients with CLL 16 (47%) controls. A statistically significant difference was observed between two groups in terms of vitamin D deficiency ( $P = 0.003$ ). Patients with CLL were compared in terms of RAI

**TABLE 2:** Characteristics of patients with CLL.

RAI stage (stage 0/1/2)	n: 4 (12.1%)/n: 19 (57.6%)/n: 10 (30.3%)
Presence of B symptoms	5 (15.2%)
Splenomegaly	14 (42.4%)
Hepatomegaly	5 (5.2%)
Hemoglobin	13.3 g/L(7.80–17.50 g/L)
Thrombocyte count	191,000 ´ 106/L (10,000–335,000 ´ 106/L)
Leukocyte count	14,900 ´ 106/L (1700–13,400 ´ 106/L)
Lactate dehydrogenase	227 (140–396)

stage, splenomegaly, hepatomegaly, and presence of B symptoms according to vitamin D levels, but no significant difference was observed.

## DISCUSSION

CLL is the most common type of adult-age leukemias. It is characterized by the increase in monoclonal B lymphocytosis (15). Usually, treatment and cure are not expected in patients with CLL. The treatment is focused on keeping the disease under control and establishing control over symptoms rather than on curing the disease. Therefore, it is significant to know the factors affecting prognosis in patient with noncurative CLL because the disease has a slow progression. Shanafelt et al. detected vitamin D deficiency in 30.5% of patients with CLL demonstrated a decline in the duration between vitamin D deficiency and the start of the treatment and total survival (14). They also reported that knowing vitamin D deficiency as a modifiable factor might be significant in patients recently diagnosed with B-CLL (14). Serum vitamin D deficiency is common around the world. It is encountered in the ratio of 25%–50% during routine clinical examination (16).

Studies on vitamin D deficiency in patients with CLL are rather limited. Parveen et al. detected vitamin D deficiency in 56.7% of patients with CLL (17). Vitamin D deficiency is detected in 82.2% of patients with early-stage CLL, which is a fairly high rate (18). It is argued that vitamin D levels might be a factor affecting the process of starting the treatment and maintaining normal vitamin D levels might retard disease progression in patients with CLL (18). Another study demonstrated that high vitamin D levels decreased CLL risk while vitamin D deficiency was accompanied by a progressive increase in the incidence of CLL (19).

Vitamin D deficiency was detected in 78% of patients with early-stage CLL, which is parallel to previous findings. The difference in data regarding vitamin D deficiency might be related to environmental factors, ethnic backgrounds, and dietary habits of societies.

In our study, vitamin D levels of 26/33 (78%) of patients with CLL were statistically significantly lower compared with those of healthy controls ( $P = 0.003$ ).

Vitamin D is a multifunctional hormone (20). Several studies indicate that it is effective against cell proliferation, differentiation,

and apoptosis (21). B-CLL cells express vitamin D receptor more than normal B and T lymphocytes. The use of a pharmacological dose of vitamin D induced the apoptosis of CLL cells in vitro via p53-independent mechanism (22). Vitamin D inhibited the proliferation of lymphocytes and induces differentiation in vitro (23,24). A study on 229 patients with CLL demonstrated no correlation between vitamin D deficiency, absolute number of lymphocytes, and advanced-stage disease (14).

The present study showed no correlation between RAI stage, presence of anemia, splenomegaly, hepatomegaly, presence of B symptoms, and vitamin D deficiency.

Although the correlation between vitamin D levels and solid tumor risk is well known, the relation between hematological malignancy and vitamin D levels needs further investigation. Previous studies aiming to explain the potential effect of vitamin replacement on cancer prevention did not always yield positive results (25). A study on 34 patients with low-grade NHL reported tumor regression in 24% of the patients treated with 1,25(OH)D' synthetic analog (four full remissions and four partial remissions) (26). The vitamin D levels of patients should be measured and monitored regularly to maintain an optimal level (27). A meta-analysis conducted in China reported that low serum vitamin D levels in hematological malignancy might be related to bad prognosis (21). Another study argued that vitamin D deficiency led to disease progression and negative response to treatment in patients with CLL (28). A 13-month remission was unexpectedly observed in a patient with CLL having vitamin D deficiency after administering cholecalciferol (29).

## CONCLUSIONS

A limitation of this study was that it was performed on a limited number of patients with early-stage CLL. However, this was the first study on vitamin D levels in patients with early-stage CLL in Turkey. The vitamin D deficiency rate was found to be very high in Turkish patients. The measurement of vitamin D levels in patients with early-stage CLL and adequate replacement might help in controlling disease progression and improving response to treatment. Therefore, vitamin D levels can be considered as a prognostic indicator of the disease independent of its clinical stage. Larger-scale, randomized, controlled studies should be conducted to validate the findings.

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