

Predictive value of serum vitamin B12 elevation in acute leukemia

Akut lösemilerde serum vitamin B12 yüksekliğinin prediktif değeri

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Abstract

Purpose: In this study; we sought to assess whether elevated vitamin B12 levels during the course of diagnosis might be a predictor of acute leukemias.

Materials and methods: The study was prepared by retrospectively evaluating the anamnesis and laboratory information of 95 patients diagnosed with acute leukemia (AML or ALL). Those who had any of the conditions clearly known to increase vitamin B12 levels by scanning their anamnesis and laboratory information were not included in the study.

Results: In total, it was observed that serum vitamin B12 level at the time of diagnosis was above the normal reference range (>771ng/L) in 36% of the patients. In the survival analysis performed to evaluate the effect of high serum vitamin B12 levels on prognosis, no statistically significant difference was found.

Conclusion: The data we obtained from this study shows that high serum vitamin B12 levels may have predictive value for acute leukemia.

Key words: Acute leukemia, cancer, cobalamin, vitamin B12.

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Öz

Amaç: Bu çalışmada; tanı anında bakılan yüksek vitamin B12 düzeylerinin akut lösemilerde prediktif bir faktör olup olmadığını belirlemeyi amaçladık.

Gereç ve yöntem: Çalışmamız akut lösemi (AML ve ya ALL) tanısı alan 95 hastanın anamnez ve laboratuvar bilgileri retrospektif olarak değerlendirilerek hazırlanmıştır. Anamnez ve laboratuvar bilgileri taranarak B12 vitamini düzeyini yükselttiği açıkça bilinen durumlardan herhangi birine sahip olanlar çalışmaya dahil edilmemiştir.

Bulgular: Toplamda hastaların %36'sında tanı anındaki serum vitamin B12 düzeyinin normal referans aralığının (>771ng/L) üzerinde olduğu görüldü. Yüksek serum vitamin B12 düzeyinin prognoza etkisini değerlendirmek için yapılan sağ kalım analizinde istatistiksel olarak anlamlı bir fark gözlenmedi.

Sonuç: Bu çalışmadan elde ettiğimiz veriler; yüksek serum vitamin B12 düzeylerinin akut lösemi için öngörü değeri olabileceğini göstermektedir.

Anahtar kelimeler: Akut lösemi, kanser, kobalamin, vitamin B12.

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Introduction

Acute leukemias are important due to their rapid progression and mortality, although they are relatively rare malignancies, considering their share in all malignancies 1% for acute myeloid leukemia (AML), 0.3% for acute lymphoblastic leukemia (ALL) [1, 2]. Despite all the improvements achieved, 5-year survival rates are 28.7% for AML and 68.8% for ALL [1, 2]. Therefore, advances in the management of these diseases are very important.

Vitamin B12 (cobalamin, Cbl) is an essential vitamin for humans [3]. A cobalamin level measured from peripheral blood above the reference values is called hypercobalaminemia [4]. Hypercobalaminemia has been reported to be iatrogenic as well as been associated to some diseases such as liver diseases, alcoholism, kidney diseases, autoimmune diseases and infections [3-5]. Although varying degrees of vitamin B12 levels have been reported in different studies in solid neoplasms and hematological malignancies, the frequency of hypercobalaminemia at the time of diagnosis and the underlying pathogenesis are not clearly clarified in neoplastic patients [6-8]. It has been reported that the increase in circulating cobalamin binding protein haptocorrin may be associated with high plasma cobalamin levels. Although the physiological function of this protein, which can originate from many tissues, is not fully known, it has been shown to increase in some cancer types [6, 7]. Therefore, it has been stated that haptocorrin may be a cause of serum vitamin B12 elevation detected in malignancies [4, 6, 7].

Among hematological malignancies, high serum cobalamin levels can be detected due to the haptocorrin-like protein transcobalamin-III (TC-III), which is caused by increased leukocytes in myeloproliferative diseases, especially in chronic myeloid leukemia (CML) [9, 10]. There is not enough data in the literature regarding hypercobalaminemia in acute leukemia. Therefore, the purpose of this study was to determine the frequency of high levels of vitamin B12 in acute leukemias at the diagnosis time, to evaluate whether increased vitamin

B12 levels could be a predictive factor for this disease and to reveal its relationship with prognosis in the patients. In this way, we aimed to contribute to the literature in terms of early diagnosis and management of acute leukemia.

Materials and methods

Participants, procedures and demographics

This study was prepared by retrospectively evaluating the anamnesis and laboratory information of 95 patients diagnosed with acute leukemia (AML or ALL) at Hospital between 24.10.2006-08.04.2019. Patients whose diagnosis was made at an external center and those whose blood vitamin B12 level was not measured at the time of diagnosis were not included in the study. In addition, by screening the anamnesis and laboratory information, those who had any of the conditions known to increase the levels of vitamin B12 at the diagnosis time were also excluded from the study. At this point, the following are determined as exclusion criteria: reduced glomerular filtration rate (tGFR CKD-EPI <45 ml/min/1.73 m²), ALT (Alanine Aminotransferase) and / or AST (Aspartate Aminotransferase) >100 IU/L, history of chronic hepatic failure, hepatitis (HAV, HBV, and HCV) infection, history of rheumatological disease, history of autoimmune disease, clinical or laboratory findings of infectious disease, intake of vitamin B12 supplements in oral or injection form, excessive alcohol consumption (for women more than seven drinks, for men more than fourteen drinks which contain about 14 grams of pure alcohol per week), excessive meat consumption (more than 3 servings per week) [11, 12]. All individuals who did not meet these criteria and were diagnosed with acute leukemia between the ages of 18-90 were included in the investigation. Patients were classified as male or female based on their gender. They were grouped as Aegean, Mediterranean and other according to the regions they live in. They were classified as low or normal (≤ 10 K/uL) and higher than normal (>10 K/uL) according to the absolute leukocyte count and they were grouped as low or normal (≤ 771 ng/L) and higher than normal (>771 ng/L) according to B12 level. Normal serum vitamin B12 reference values in

Pamukkale University Hospital Laboratory were 211-911 pg/mL. Our research was carried out in accordance with the Helsinki Declaration 2008 principles. This retrospective study was approved by the Pamukkale University Non-Invasive Clinical Research Ethical Committee.

Statistical analysis

The data was analyzed utilizing SPSS 22.0 [IBM SPSS Statistics 22 software (Armonk, NY: IBM Corp.)] package program. Continuous variables were represented as mean \pm standard deviation (S.D.), while categorical variables were represented as frequencies and percentages. In order to examine the relationships between categorical variables, the Pearson chi-square test was used. The log-rank test was used to compare survival curves calculated by the Kaplan-Meier method. Statistical significance was defined as $p < 0.05$.

Results

Eighty-one (85%) of the patients included in the study had AML and 14 (15%) had ALL. There was a relatively balanced distribution in terms of gender, with 41 (43%) female and 54 (57%) male patients. The average age of the patients at the diagnosis was 48 ± 18.1 . At the beginning of the work; while 21 (22%) of the examined patients passed away, 74 (78%) were alive.

In total, it was observed that 32 (34%) of the patients had absolute leukocyte count above normal (>10 K/uL) at the time of diagnosis, 63 (66%) were lower than normal or in the normal reference range (≤ 10 K/uL). There was no statistical significant difference between the groups with low or normal / high leukocyte count in terms of high vitamin B12 level [χ^2 (1, N=95) 0.06, ($p=0.8$)]. In other words, vitamin

B12 elevation in the patients studied was not associated with leukocytosis.

In total, it was observed that the vitamin B12 level at the time of diagnosis was above the normal reference range (>771 ng/L) in 34 (36%) of the patients. These data were crucial in terms of showing that high vitamin B12 levels can be an important finding for the early diagnosis of acute leukemias. This rate was determined as 37% (30/81) among patients with AML diagnosis and 29% (4/14) among patients with ALL diagnosis, and this difference was not statistically significant [χ^2 (1, N=95) 0.3, ($p=0.54$)]. No significant difference was observed between the groups in terms of high B12 level according to gender and living area. [respectively; χ^2 (1, N=95) 0.02, ($p=0.88$). χ^2 (2, N=95) 1.8, ($p=0.54$)].

Survival analyzes were also performed to evaluate the effect of elevated serum vitamin B12 levels on prognosis in patients with acute leukemia. However, there was no statistically significant difference in terms of survival between the groups with and without vitamin B12 levels above normal ((log-rank test, $p=0.641$). There was also no significant difference between the 1-year survival, 2-year survival, 3-year survival, and 5-year survival subgroups (Table 1). In terms of overall survival rates, no statistically significant difference was found between the groups (Figure 1). This data was important in that it showed that the high vitamin B12 level at the time of diagnosis did not affect the survival rate in patients with acute leukemia, and therefore it was not directly related to the prognosis.

Mean survival time for low/normal and high B12 levels was 116.9 (100.9-133.0) and 105.0 (78.5-131.5) mo, respectively.

Table 1. Vitamin B12 level elevation ratios and p values by groups

	B12≤771 ng/L		B12>771 ng/L		Chi-square value	p value
	N	%	N	%		
Diagnosis						
AML	51	63	30	37	0.372	0.542*
ALL	10	71.4	4	28.6		
Gender						
Woman	26	63.4	15	36.6	0.02	0.888*
Male	35	64.8	19	35.2		
Region of residence						
Aegean	58	64.4	32	35.6	1.874	0.546**
Mediterranean	3	75	1	25		
Other	0	0	1	100		
Absolute leukocyte count						
>10 K/uL	20	62.5	12	37.5	0.061	0.804*
≤10 K/uL	41	65.1	22	34.9		
1 year survival						
Yes	56	64.4	31	35.6	0.11	1.00**
No	5	62.5	3	37.5		
2 years survival						
Yes	40	63.5	23	36.5	0.154	0.695*
No	11	68.8	5	31.2		
3 years survival						
Yes	36	69.2	16	30.8	0.004	0.948*
No	13	68.4	6	31.6		
5 years survival						
Yes	18	64.3	10	35.7	0.003	0.959*
No	13	65	7	35		

*: Pearson Chi-square test, **: Fisher's Exact test

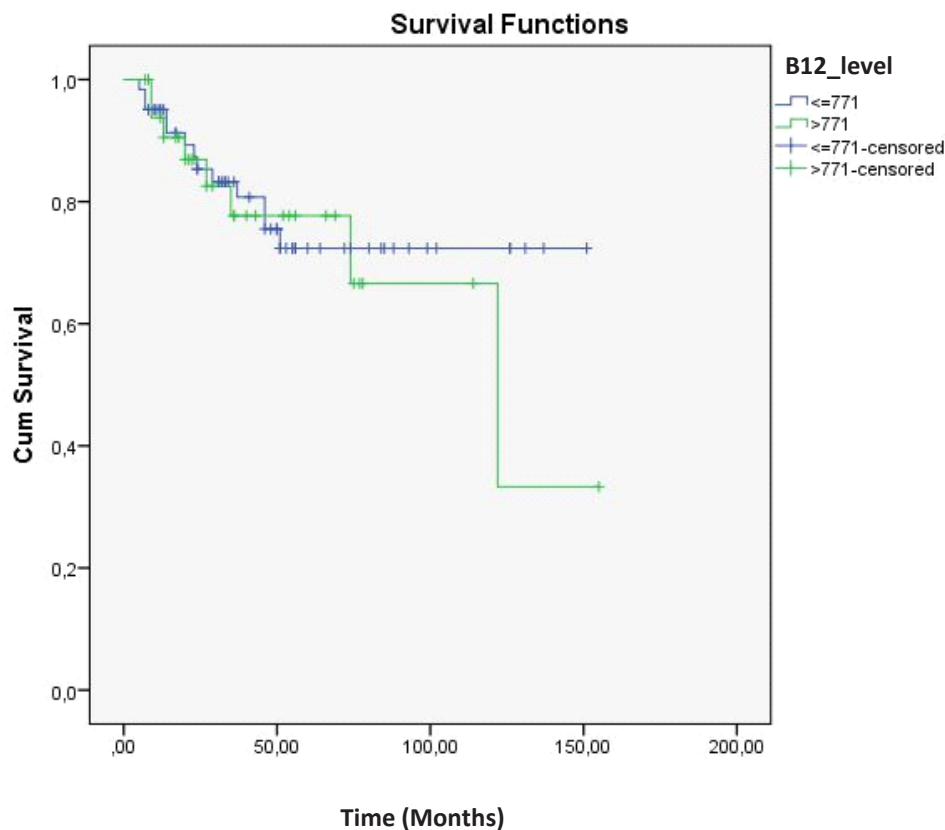


Figure 1. Survival curve according to serum B12 levels of patients with acute leukemia

Discussion

A high-level serum vitamin B12 is an important clinical finding as much as low-level serum vitamin B12 [3]. The relation of some clinical conditions (liver diseases, alcoholism, kidney diseases, autoimmune diseases and infections) with serum vitamin B12 level is well known [3, 4]. In the study; Those with high vitamin B12 levels had a significantly higher risk of malignancy during the 1-year follow-up. In addition, it has been observed that this risk is especially higher for hematological malignancies [13]. In a Latvian cohort study, the odds ratios for total and myeloid leukemia (acute, chronic, and unspecified) in patients with elevated B12 were 6.0 (95% CI 4.7-7.6; $p < 0.0001$) and 19.2 (95% CI 13.1-28.0; $p < 0.0001$), when compared to the control group. Thus, it was concluded that increased serum vitamin B12 levels may be a potential marker for oncohematological disorders [14]. Similarly, in a study conducted in Denmark; approximately 40,000 people who did not use vitamin B12 injections and had no known cancer history were examined for 2 years and malignancy was detected in 6.7% of those with high serum vitamin B12 levels in the first 6 months (mo) of the follow-up, whereas malignancy was detected in 2.6% of those with normal vitamin B12 levels [15]. However, there is not enough data regarding the predictive value of serum vitamin B12 level elevation in acute leukemia. Therefore, this issue was discussed in this study and as a result, serum vitamin B12 level of 36% of the patients with acute leukemia was found above normal reference values at the time of diagnosis. This indicates that high serum vitamin B12 levels may be predictive in terms of acute leukemia. At this point, performing complete blood count and peripheral blood smear tests in patients with high vitamin B12 levels in hospital admissions may be beneficial in terms of early diagnosis.

Although there are various studies in the literature regarding the relation of high vitamin B12 level with prognosis and mortality, there is not enough data on this issue in patients with acute leukemia. In a cohort study published in the journal *Cancer Epidemiology*, data on approximately 25,000 cancer patients were examined, and it was discovered that patients with high vitamin B12 levels had significantly lower 1-year survival rates than patients with

normal levels [(1-year survival,%) Cbl: 200-600 pmol/L: 69.3%; 601-800 pmol/L: 49.6%; >800 pmol/L: 35.8%; comparison cohort: 72.6%] [16]. In another study published in 2018, the data of 523 metastatic cancer patients were evaluated retrospectively. The median survival time in the high B12 group (>911 pg/mL) was 1.8 months and 5.1 months in the normal B12 group (211-911 pg/mL) ($p < 0.001$). According to multivariate analysis, serum vitamin B12 level was a distinct prognostic factor for overall survival ($p < 0.001$) [17]. In another study evaluating 90 patients with hepatocellular carcinoma, it was found that survival times were lower in patients with high B12 levels. HCC patients with the highest serum B12 levels (>1,500 ng/l) had significantly lower survival (mean survival of 13.5 mo) than those in the second and lowest levels group [18]. In another study published in 2017 with the participation of 190 patients over 65 years of age in the geriatric ward, it was observed that hematological disorders were 5.7 times higher in those with high vitamin B12 levels compared to normal ones (OR=5.7; $p = 0.001$) [19].

In our study, no significant difference was observed in terms of survival between acute leukemia patients with and without high vitamin B12 levels at the time of diagnosis, thus it was concluded that high vitamin B12 levels in these patients did not have prognostic value. The study's main limitation is the relatively small sample size. Furthermore, due to the study's retrospective design, selection bias may exist. The strengths of this study include the good quality of the data. Furthermore, we were able to exclude persons who had been given cobalamin supplement and most of those who had any of the conditions known to increase vitamin B12 levels.

In conclusion, although the data we obtained from this study indicate that high serum vitamin B12 levels may have predictive value for acute leukemia, but do not have a prognostic value, more studies are needed to reach a clear conclusion.

Conflict of interest: The authors declare no conflict of interests for this study.

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Informed consent: Patients alive at the time of data collection provided informed consent.

Ethics committee approval: This retrospective study was approved by the Pamukkale University Non-Invasive Clinical Research Ethical Committee. (date:08/07/2020 and number: 60116787-020/41159).

Authors' contributions to the article

A.U. and B.U.K. constructed the main idea and hypothesis of the study. A.U., B.U.K., S.H., G.A.C. and N.G.; they developed the theory and arranged/edited the material and method section. A.B., B.U.K., S.H., G.A.C. and N.G. have done the evaluation of the data in the Results section. Discussion section of the article written by A.U. and B.U.K. who also reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version. It should be written after the references.