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An Indipendent Predictor of Mortality in Hospitalized Patients:Vitamin B12

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ABSTRACT

Objectives: Increased vitamin B12 levels are associated with mortality. We aim to define the relationship between B12 levels and 6 months,12 months, and 48 months mortality.

Methods: We investigated 455 patients hospitalized in the internal medicine clinic from 01.01.2014 to 30.06.2014. Patients younger than 18 years old, with chronic heart failure, hematological malignancies, solid tumors, chronic liver disease, and end-stage kidney disease were excluded. Patients with a vitamin B12 below and below the reference range were excluded. Laboratory parameters and vitamin B12 levels were compared between survival and non-survival groups at 6 months,12 months, and 48 months. Mortality data for 6 months,12 months, and 48 months after the first hospitalization day were obtained.

Results: The mortality percentages of patients were evaluated on the 6th, 12th, and 48th months. Age, complete blood count parameters (hemoglobin, white blood cell, and platelet), acute phase reactants, and serum vitamin B12 levels were compared between patient groups. Increased vitamin B12 level was found to be correlated with acute phase reactants (C reactive protein, albumin, ferritin, sedimentation) and hemoglobin. Regression analysis revealed that increased vitamin B12 levels, ferritin, sedimentation, white blood cell, and low albumin levels were statistically significant in 6th-month mortality. High white blood cell count and low albumin levels were statistically significantly correlated with mortality in the 12th and 48th months.

Conclusion: Increased vitamin B12 levels were effective in predicting 6-month, 12-month, and 48-month mortality. Age-decreased albumin levels, acute phase reactants, and increased B12 levels were identified in hospitalized patients as risk factors for short, mid-term, and long-term mortality.

Keywords: Vitamin b12, Mortality, Hospitalized patients

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Vitamin B12, also called cobalamin, is a water-soluble vitamin. Humans cannot synthesize cobalamin, and its levels depend on dietary intake. Fish, meat, dairy products, and fortified cereals are sources of Vitamin B12. Vitamin B12 is released from food particles and proteins by gastric acid and pepsin. Then, cobalamin binds to R protein released from the salivary glands. Gastric mucosa stimulates the secretion of intrinsic factor (IF) from parietal cells, and cobalamin is released from the R protein, which binds to IF in the duodenum. Cobalamin is transported up to the ileum by binding to the IF. Cobalamin is separated from IF in the terminal ileum and is absorbed by enterocytes. In this absorption, the IF also takes part through the specific cubilin receptors in the ileum. Vitamin B12, which passes through the enterocyte apical membrane into the bloodstream, is bound in the blood by transcobalamin II and transported to the tissues where it will be stored.[1] The four primary metabolites of vitamin B12 are Cyanocobalamin, hydroxycobalamin, deoxyadenosyl, cobalamin, and methylcobalamin. Deoxyadenosyl cobalamin and methylcobalamin are active metabolites of vitamin B12 in tissues and act as cofactors in the body's two main enzyme system pathways. These pathways are methylation of homocysteine to methionine (methionine synthase reaction) and isomerization of methyl malonate to succinate (formation of succinyl coenzyme A). The methionine synthase reaction provides the necessary elements for DNA production. The formation of succinyl-coenzyme A is required for the entrance of lipids to the citric acid cycle and carbohydrate metabolism.[2] Vitamin B12 is involved in DNA synthesis and repair within the cell. It is an important vitamin for normal, hematologic, and nervous development. Decreased B12 levels, its causes, and treatment are well known by clinicians, as shown by extensive literature.[3,4] The causes of increased B12 vitamin levels have been better explained over the years.[5,6] Increased B12 levels are associated with the following conditions: renal failure, cancer, hematological malignancy, and hepatic diseases such as cirrhosis, hepatitis, hepatocellular carcinoma, and metastatic liver tumor. The upregulation of transcobalamin synthesis, increased cellular cobalamin release, or decreased cobalamin clearance are thought to increase vitamin B12 levels.[7] However, certain pathophysiological mechanisms of increased inflammation and mortality in patients with increased vitamin B12 levels are still unknown.[8-10] This study aims to define the relationship between vitamin B12 levels, other biochemical parameters, and mortality.". This study aims to define the relationship between vitamin B12 levels, other biochemical parameters, and mortality.

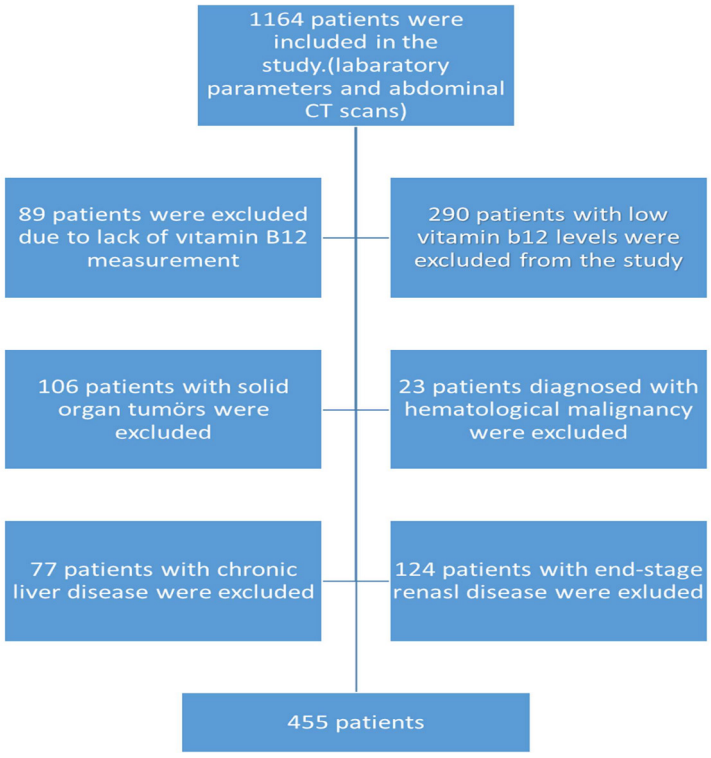

Figure 1. A tree diagram of patients was included and discarded in the study.

METHODS

Study Participants and Laboratory Analysis

This study was accepted by the local Ethics Committee of Haseki Training and Research Hospital, University of Health Sciences, Istanbul, Turkey. This retrospective cohort study was managed according to principles of good clinical practice and the declaration of Helsinki. Ethics committee approval was obtained from Haseki Training and Research Hospital. (No 192-2022- 19.10.2022). We investigated 455 patients (195 men and 260 women) hospitalized in the internal medicine clinic from 01.01.2014 to 30.06.2014 in Haseki Training and Research Hospital. Patients who are under 18 years old, with chronic heart failure, solid and/or hematological malignancies, solid tumors, chronic liver disease, and end-stage kidney disease were excluded (Figure 1). Patients with a vitamin B12 level below and above the hospital laboratory's reference range (100-914 pg/mL) were excluded. Laboratory parameters and vitamin B12 levels were compared between survival and non-survival groups at 6 months,12 months, and 48 months. Mortality data of 6 months (short term), 12 months (mid-term), and 48 months (long term) after the first hospitalization day were obtained. Patient demographic information, past medical history, mortality data, and laboratory examination for the study were taken from the electronic hospital management system dispensing records and Haseki Training and Research Hospital databases. Biochemical parameters were analyzed for all study participants. Blood samples were taken after 12 hours of fasting in the morning on the first day of hospitalization. Hemogram (CBC), serum vitamin B12 levels, and acute phase reactants, including albumin, ferritin, sedimentation, and c reactive protein levels, were analyzed.

Statistical Analysis

Data are stated as the mean ± standard deviation. A statistical analysis was accomplished using SPSS 24.0 (SPSS Inc. Chicago, IL, USA). Basic descriptive statistical parameters, including the means, standard deviations, ranges, and percentages, were performed. The normality of the distribution was examined using the Kolmogorov–Smirnov test. The Mann checked mean values between two independent groups– the Whitney U test for continuous variables and the chi-square ($\chi 2$) test for categorical parameters; comparisons between more than two subgroups were performed by ANOVA and Kruskal–Wallis tests. Bivariate correlations were studied by Pearson's (continuous variables). Differences were thought statistically significant if the two-tailed p-value was less than 0.05.

RESULTS

This study consisted of 455 patients hospitalized in our hospital's internal medicine clinic and followed up for four years. The mean age of study participants was 65.54±18.07 years. In this study, 103 of 455 patients had chronic kidney disease (excluding end-stage renal disease), 124 with heart failure, 122 with ischemic heart disease, 61 with Chronic Obstructive Pulmonary Disease (COPD), 14 with peripheral artery disease, 66 with cerebrovascular disease, 87 with type 2 diabetes, 32 with dementia and 21 with rheumatic disease. The mortality percentages of patients were evaluated on the 6th, 12th, and 48th months after the hospitalization. The mortality rates were 21.2% (55) in women and 23.6% (46) in men at the end of 6th month, 26.5% (69) in female and 27.7 (54) % in male at the end of 12th month and 50.4% (131) in female and 46.7% (91) in male at the end of 48th month, as shown in Table 1 ($p<0.533$, $p<0.78$, $p<0.49$ respectively). Age, CBC parameters (hemoglobin, white blood cell, and

Table 1. Survival and non-survival number of patients in 6th, 12th, and 48th months

	Survival n (%)	Non-survival n (%)	Total
6th Months	354 (77.8 %)	101 (22.2 %)	455
12th Months	332 (72.9 %)	123 (27.1 %)	455
48th Months	233 (51.2 %)	222 (48.8 %)	455

Table 2. Vitamin B12 and laboratory parameters analysis in survival and non-survival groups in the 6th, 12th, and 48th months.

	Survival	Non-survival	*p*
6th months			
Age (Year)	63.24± 18.27	75.81± 11.87	**0.000**
Albumin (g/dL)	3.4± 0.57	2.8± 0.59	**0.0001**
CRP (mg/L)	49.8± 73.1	73.1± 79.2	**0.0001**
Ferritin (ng/mL)	141± 211.8	279.6± 359.6	**0.0001**
Vitamin B12 (ng/L)	447.5± 341.6	626.3± 416.4	**0.0001**
Hemoglobin (g/dL)	11.1± 2.3	10.6± 2	**0.024**
White blood cell ($\times10^9$/L)	8.4± 3.6	10.2± 5.2	**0.002**
Platelet ($\times10^3$ /μL)	259± 107.2	247.1± 113.6	0.35
Sedimentation (mm/h)	37.8± 29.1	44.6± 34.3	**0.05**
12th months			
Age (Year)	62.33± 18.17	76.01± 12.24	**0.000**
Albumin (g/dL)	3.4± 0.5	2.9± 0.5	**0.0001**
CRP (mg/L)	47.8± 71.8	86.3± 80.5	**0.0001**
Ferritin (ng/mL)	142.8± 217.1	249.4± 333.7	**0.0001**
Vitamin B12 (ng/L)	434.1± 325.4	630.5± 429.7	**0.0001**
Hemoglobin (g/dL)	11.2± 2.3	10.6± 2	**0.02**
White blood cell ($\times10^9$/L)	8.4± 3.6	9.9± 4.9	**0.001**
Platelet ($\times10^3$ /μL)	258.2± 106.8	251.5± 113.9	0.5
Sedimentation (mm/h)	37.1± 29	45.3± 33.4	**0.01**
48th months			
Age (Year)	57.15± 17.76	75.36± 12.32	**0.000**
Albumin (g/dL)	3.5± 0.5	3± 0.5	**0.0001**
CRP (mg/L)	45.4± 72.9	71.6± 77.2	**0.0001**
Ferritin (ng/mL)	134.3± 201.3	210.6± 301.7	**0.002**
Vitamin B12 (ng/L)	407.3± 298.6	571± 410.9	**0.0001**
Hemoglobin (g/dL)	11.2± 2.5	10.8± 2	0.1
White blood cell ($\times10^9$/L)	8.1± 3.6	9.6± 4.4	**0.001**
Platelet ($\times10^3$ /μL)	256.4± 111.3	256.4± 106.1	0.9
Sedimentation (mm/h)	34.7± 28.9	44.1± 31.3	**0.01**

Statistical significance is shown in bold-faced type ($p < 0.05$). CRP= C-Reactive Protein

platelet), acute phase reactants, and serum vitamin B12 levels were compared between patient groups (Table 2). Age, decreased albumin and hemoglobin, increased CRP, ferritin, WBC, sedimentation, and vitamin B12 levels were associated with increased mortality. Increased vitamin B12 level was found to be correlated with acute phase reactants (CRP, albumin, ferritin, sedimentation) and decreased hemoglobin (Table 3).

Table 3. Correlation Analysis of Vitamin B12 and laboratory parameters

	r	*p*
CRP (mg/L)	0.11	**0.01**
Albumin (g/dL)	-0.18	**0.0001**
Ferritin (ng/mL)	0.09	**0.04**
Hemoglobin (g/dl)	-0.1	**0.02**
White blood cell ($\times10^9$/L)	0.08	**0.06**
Platelet ($\times10^3$ /µL)	0.002	0.9
Sedimentation (mm/h)	0.01	**0.02**

Statistical significance is shown in bold-faced type ($p < 0.05$).
CRP= C-Reactive Protein

Regression analysis revealed that increased vitamin B12 levels, ferritin, sedimentation, white blood cells, and decreased albumin levels were found to be statistically significant in 6th-month mortality. Increased white blood cell and decreased albumin levels were statistically significant in 12th and 48th month mortality (Table 4).

Table 4. Regression Analysis of Vitamin B12 and laboratory parameters in survival and non-survival groups in 6-12 and 48. mounts.

	OR	P
6th months		
Albumin (g/dL)	0.3	**0.001**
Ferritin (ng/mL)	1	**0.004**
Vitamin B12 (ng/L)	1	**0.02**
White blood cell ($\times10^9$/L)	1	**0.004**
Sedimentation (mm/h)	0.99	**0.06**
12th months		
Albumin (g/dL)	0.3	**0.02**
Vitamin B12 (ng/L)	1	**0.002**
White blood cell ($\times10^9$/L)	1	**0.001**
48th months		
Albumin (g/dL)	0.35	**0.0001**
Vitamin B12 (ng/L)	1	**0.0001**
Hemoglobin (g/dl)	1	**0.04**
White blood cell ($\times10^9$/L)	1	**0.002**

Statistical significance is shown in bold-faced type ($p < 0.05$).

DISCUSSION

Age, low albumin levels, acute phase reactants' levels (CRP, ferritin, sedimentation), and increased B12 levels were found to be predictive factors on short (6 months), medium (12 months), and long-term (48 months) mortality in hospitalized patients, in this study.

According to the regression analysis, the 6-month mortality of hospitalized patients was associated with increased vitamin B12, ferritin, white blood cell (WBC), sedimentation, and low albumin levels. On the 12th month, mortality was associated with increased vitamin B12 levels, white blood cells, and decreased albumin. At 48th months follow-up, mortality was associated with increased vitamin B12 levels, white blood cells, and decreased hemoglobin and albumin levels. In all 3 groups, increased white blood cell count and B12 levels and decreased albumin were related to mortality. Sedimentation and ferritin, effective in short-term mortality, are ineffective in the mid and long-term. Increased WBC count is one of the sepsis criteria. The association of sepsis with increased mortality is known.[11] Correspondingly, increased white blood cell count was also associated with mortality in our study.[12] In this study, the effect of low hemoglobin on long-term mortality may be due to deterioration of tissue perfusion. Similar to this result, it was found that low hemoglobin was associated with mortality in various studies.[13] It was observed that high vitamin B12 levels were associated with mortality in all 3 groups.

It has been known that an increased level of vitamin B12 was associated with myeloproliferative diseases, malignancies, kidney failure, liver diseases, and inflammatory diseases. Geissbühler et al.[8] showed a close correlation between CRP, vitamin B12 levels, and mortality in cancer patients followed in palliative care units. Another study conducted by Ju Feng Dou et al.[9] showed a correlation between high vitamin B12 levels, acute/chronic liver injury, and mortality. In a similar study, it was shown that there is a correlation between high vitamin B12 levels and prognosis in metastatic cancer patients.[10] In our study, unlike these studies, patients with hematological malignancy, solid tumors, patients with chronic liver disease, and end-stage kidney disease were excluded. In internal medicine clinic inpatients, vitamin B12 significantly correlated with acute phase reactants.

The effect and pathogenesis of mortality and inflammation of increased vitamin B12 levels are

still not apparent. but there are some theories. When the association between increased levels of transcobalamin and inflammatory diseases is evaluated, it is suggested that transcobalamin can behave like acute phase reactants.[8,14] Another reason is that it has increased serum B12 levels due to decreased cellular intake of vitamin B12 in the blood. 70-90% of the cobalamin in plasma is transported bound to haptocorrin. The binding of vitamin B12 to haptocorrin can be enhanced by decreased protein clearance by the liver, increased haptocorrin production, and increased leukocyte count in certain hematological disorders. This inhibits the binding of vitamin B12 to transcobalamin II, the physiological transport protein required for intracellular uptake, resulting in elevated plasma concentrations of vitamin B12.[15] In this case, vitamin B12 cannot be used by cells, which can lead to a condition similar to vitamin B12 deficiency. That's why high levels of vitamin B12 can theoretically be associated with a functional deficiency due to decreased intracellular concentration due to cell damage.[16]

Manzanares et al.[14] showed that vitamin B12 also has antioxidant and immune modulation duty. The mechanism has suggested the reduction of excess nitric oxide radicals and increased activity in the neuroimmune cholinergic anti-inflammatory pathway. Corcoran et al.[17] also showed an association between serum vitamin B12 levels and other inflammatory markers, such as C-reactive protein levels and the Sequential Organ Failure Assessment (SOFA) score. These findings show vitamin B12 levels increase as an inflammatory response. To summarize, our study revealed that high levels of vitamin B12 can be considered an indicator of inflammation. If we explain this role in predicting mortality, we can relate it to correlation with other acute phase reactants in short-, mid-, and long-term survival.

Limitatations

Our study has some limitations. It is a retrospective study based on biochemical studies and medical records. This was a single-center study, and our results must be confirmed in multicenter and prospective studies.

CONCLUSION

Increased vitamin B12 levels are strongly associated with short and long-term mortality development in internal medicine clinic inpatients. It can be evaluated as a biomarker in predicting mortality with inflammation markers.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

This study was accepted by the local Ethics Committee of Haseki Training and Research Hospital, University of Health Sciences, Istanbul, Turkey. This retrospective cohort study was managed according to principles of good clinical practice and the declaration of Helsinki. Ethics committee approval was obtained from Haseki Training and Research Hospital. (No 192-2022- 19.10.2022).

Authors' Contribution

Study Conception: BÇT, KS, FT, HEA; Study Design: BÇT, KS, FT, HEA; Supervision; BÇT, KS, FT, HEA; Funding: BÇT, KS, FT, HEA; Materials: HNŞ; Data Collection and/or Processing: BÇT, KS, FT, HEA; Analysis and/or Data Interpretation: BÇT, KS, FT, HEA; Literature Review: HEA; Critical Review: FT, HEA; Manuscript preparing: BÇT, KS, FT, HEA.

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