ORIGINAL RESEARCH

Elevated B12 levels and mortality among inpatients at a university hospital in Colombia

Hipervitaminemia B12 y mortalidad en pacientes hospitalizados en un hospital universitario en Colombia

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Abstract

Introduction: An association between high vitamin B12 levels and the occurrence of multiple diseases has been reported.

Objective: To describe the clinical characteristics of inpatients with high levels of vitamin B12, as well as their 1-year mortality rate.

Materials and methods: Retrospective observational study conducted in 93 patients with elevated B12 levels treated at the Hospital Universitario San Ignacio in Bogotá (Colombia) between 2013 and 2020. Data are described using measures of central tendency and dispersion. Bivariate analyses were performed (unpaired two-samples t-test, chi-square test or Mann-Whitney U test depending on the type of variable) to determine differences between patients with high B12 levels and those with very high levels.

Results: Participant's median age was 68 years, 62.36% were male, and 61.29% had two or more comorbidities related to high B12 levels. In addition, in 86.02% of the patients, vitamin B12 level was not interpreted as abnormal by the treating physician. Significant differences were found between patients with high B12 levels and those with very high levels in terms of history of smoking (*p*=0.043) and the presence of systemic lupus erythematosus (*p*=0.012). Finally, the 1-year mortality rate was 59.13%.

Conclusion: The 1-year mortality rate was high, and a high percentage of patients had at least two comorbidities that were associated with high B12 levels. Moreover, in most of the participants, the treating physician did not correctly interpret the elevated level of this vitamin.

Resumen

Introducción. Se ha reportado una asociación entre los niveles altos de vitamina B12 y la ocurrencia de múltiples enfermedades.

Objetivo. Describir las características clínicas de pacientes hospitalizados con hipervitaminemia B12, así como la tasa de mortalidad a 1 año.

Materiales y métodos. Estudio observacional retrospectivo realizado en 93 pacientes con hipervitaminemia B12 atendidos en el Hospital Universitario San Ignacio de Bogotá (Colombia) entre 2013 y 2020. Los datos se describen utilizando medidas de tendencia central y de dispersión. Se realizaron análisis bivariados (prueba t de dos colas no pareada, prueba chi-cuadrado o prueba U de Mann-Whitney según el tipo de variable) para determinar diferencias entre los pacientes con niveles altos de B12 y aquellos con niveles muy altos.

Resultados. La mediana de edad fue 68 años y el 62.36% de los pacientes eran hombres. El 61.29% de los participantes tenía dos o más comorbilidades asociadas con la hipervitaminemia B12. Además, en 86.02% el nivel de vitamina B12 no fue interpretado como anormal por el médico tratante. Se encontraron diferencias significativas en el antecedente de tabaquismo (*p*=0.043) y la presencia de lupus eritematoso sistémico (*p*=0.012) entre los pacientes con niveles altos de B12 y aquellos con niveles muy altos. Finalmente, la tasa de mortalidad a 1 año fue de 59.13%.

Conclusión. La tasa de mortalidad a 1 año fue alta y un elevado porcentaje de pacientes tenía al menos dos comorbilidades asociadas a la hipervitaminemia B12. Además, en la mayoría de participantes, el médico tratante no interpretó correctamente el nivel elevado de esta vitamina.

Introduction

Vitamin B12 (B12), also known as cobalamin, acts as a coenzyme in the synthesis of nucleic acids and in mitochondrial metabolism.[1,2] A deficiency of this vitamin may be associated with the presence of megaloblastic anemia, glossitis, dementia, peripheral neuropathy, among other diseases, so the measurement of its levels is frequent in clinical practice, especially when there is clinical suspicion of a deficiency.[3,4] Moreover, elevated B12 levels have been reported to be documented as an incidental finding in up to 18.5% of cases.[5,6]

High B12 levels have been associated with the presence of malignancy,[7] especially hematological malignancies such as chronic myeloid leukemia.[8] Some studies have also found associations between elevated B12 levels and the development of sepsis, acute and chronic liver disease, chronic kidney disease, and functional B12 deficiency.[9-12]

There are four major pathophysiological mechanisms that explain the presence of elevated B12 levels in blood: 1) a direct increase in plasma B12 by excess intake or administration, 2) a direct increase in plasma B12 by liberation from an internal reservoir, 3) an increase in transcobalamin (TCB) via excess production or lack of clearance, and 4) a quantitative deficiency or lack of affinity of TCB for B12.[6]

On the other hand, although several studies in inpatients have described a positive correlation between elevated B12 levels and mortality,[13-18] there is currently no consensus on the cut-off point, so it is generally defined as the upper limit of the normal range at each laboratory.[14,19] In addition, it should be noted that in some patients in these studies, the diagnosis or cause of death had not been clearly established at the time of measurement of B12 levels, nor is there a widely accepted diagnostic algorithm for the study of patients with high B12 levels in the hospital setting.

Considering the above, the objective of the present study was to describe the clinical characteristics of inpatients with high B12 levels, as well as the 1-year mortality rate found in patients with this condition.

Materials and methods

Study type and population

Retrospective observational study. The study population consisted of patients over 18 years of age treated at the Internal Medicine service of the Hospital Universitario San Ignacio in Bogotá (Colombia) between 2013 and 2020, and whose data on B12 levels measured in blood were accessible (N=12 703). Outpatients (n=8 903) and patients with B12 levels within the normal range (189-883pg/mL) or below this range (n=3 702) were excluded. Subsequently, patients with duplicate data (n=2) and those who reported the use of B12 supplements and multivitamins prior to measurement (n=3) were also excluded, so the final sample included 93 patients with elevated B12 levels. It should be noted that a checklist of inclusion criteria created using the Statement of Reports of Observational Studies in Epidemiology (STROBE) was used to select participants (Figure 1).
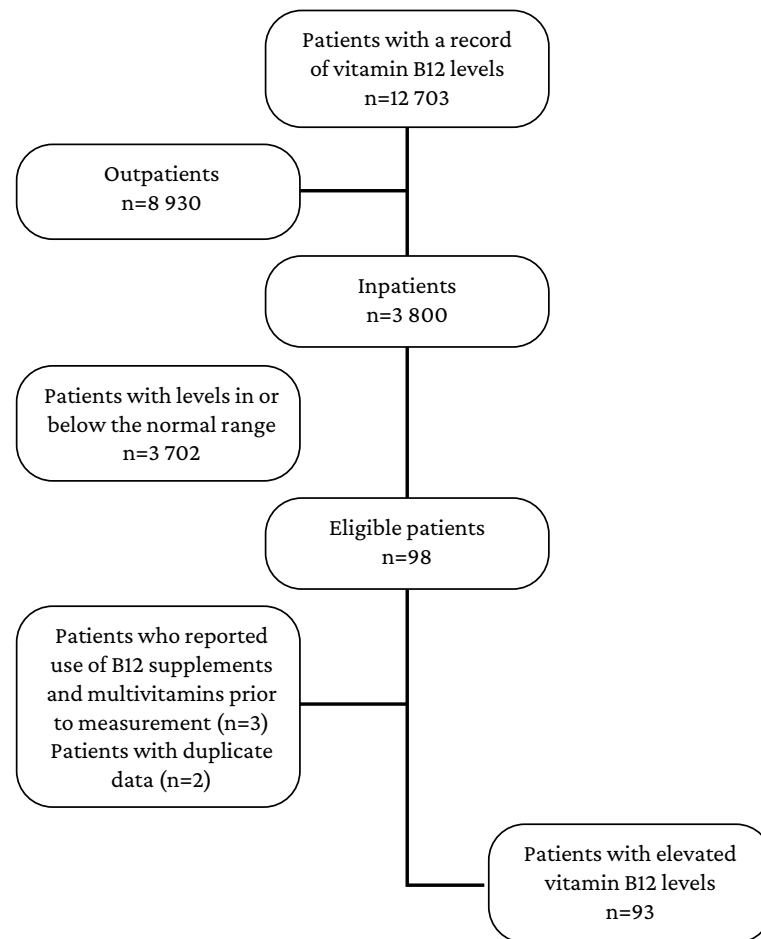
Figure 1. Flowchart of the selection of the study sample.
Source: Own elaboration.

Procedures

B12 levels were measured in the hospital laboratory using the chemiluminescent micropar-ticle immunoassay method (reference values: 189-883pg/mL). Participants were classified according to their B12 levels into patients with high levels (884-1 499pg/mL) and patients with very high levels (≥1 500pg/mL). The cutoff point used for the comparison between the two groups was taken from the cohort studies of Ryg *et al.*[20] and García-Rodríguez *et al.*[21]

Furthermore, based on the review of the participants' medical records, available in the electronic medical record software of the Hospital Universitario San Ignacio (Sistema de Atención Hospitalaria Integral), the following information was collected for each partici-pant: age, sex, body mass index (BMI), presence of comorbidities, laboratory test results, diagnostic imaging and biopsies, presence of folic acid deficiency, reason for requesting the measurement of B12 levels, and length of hospital stay. Importantly, the clinical data collected were those reported at the time of measurement of B12 levels.

Regarding comorbidities, the information collected was classified as follows:

- Smoking: all patients who had smoked for at least the last 6 months were classified as active smokers[22] and those who had a history of smoking but had not smoked in the last 6 months were classified as former smokers.
- Habitual alcohol consumption: defined as the consumption of alcohol at least once a week.

- Cardiovascular disease: defined as the presence of stroke, peripheral arterial disease, or coronary artery disease.
- Chronic kidney disease: the presence of this condition was determined based on the current KDIGO (Kidney Disease: Improving Global Outcomes) definition and classification: G3b, G4, G5.[23]
- Sepsis and septic shock: the presence of these conditions was established taking into account the current definitions of the Surviving Sepsis Campaign.[24]
- Human immunodeficiency virus (HIV): the presence of this condition was defined on the basis of the diagnosis confirmed by a second test using the Western blot laboratory technique.
- Autoimmune disease: a patient was considered to have one of these diseases if there was a diagnosis of autoimmune disease prior to admission or if it was diagnosed during the hospital stay by the rheumatology service using the diagnostic criteria established for these diseases.
- Liver disease: defined as having a transaminase level 3 times higher than the upper limit and/or a bilirubin level 1.5 times higher than the upper limit,[25] and was classified as chronic liver disease or acute liver failure.
- Cancer: defined as having a diagnosis of some type of cancer confirmed by histopathological report and extension studies performed or reported in the oncological assessment.

Regarding laboratory tests, data on the results of the following tests were collected: complete blood count, C-reactive protein (CRP) test, blood ferritin test, erythrocyte sedimentation rate (ESR), lactate dehydrogenase test, blood bilirubin test, alanine transaminase blood test, alkaline phosphatase blood test, creatinine blood test, folic acid test, and peripheral blood smear. These results were interpreted as per the normality values established for each by the laboratory.

Finally, to evaluate 1-year mortality, data on the date and cause of death of the participants who died were collected.

Statistical analysis

The information collected was recorded in the REDcap system (Vanderbilt University, Nashville, USA) for analysis. Data are described using absolute frequencies and percentages for categorical variables, and medians and interquartile ranges (IQR) for continuous variables due to a non-normal distribution of the data. In addition, bivariate analyses were performed to establish differences in the variables considered between patients with high B12 levels and those with very high levels, for which the unpaired two-samples t-test, the chi-squared test or the Mann-Whitney U test were used depending on the type of variable and the distribution of the data. The correlation between B12 levels and the levels of the inflammation markers CRP, ESR and ferritin was also evaluated using Spearman's correlation coefficient. All statistical analyses were performed in the statistical package STATA version 14, and a significance level of $p<0.05$ was considered.

Ethical considerations

The study followed the ethical principles for biomedical research involving human subjects established in the Declaration of Helsinki[26] and the scientific, technical and administrative standards for health research of Resolution 8430 of 1993 issued by the Colombian Ministry of Health.[27] Furthermore, it was approved by the ethics committee of the Hospital Universitario San Ignacio and the Pontificia Universidad Javeriana according to Minutes No. 21/2020 of September 24, 2020.

Results

Of the participants, 62.36% were men. The median age, BMI and length of hospital stay of the participants were 68 years (IQR=57-77), 19.8kg/m² (IQR=15.2-24.1), and 20 days (IQR=11-28), respectively. Most patients (90.32%) presented with at least one condition related to elevated B12 levels and 61.29% (n=57) presented with two or more. The most frequently associated comorbidities were sepsis (40.86%), diabetes mellitus (29.03%), and solid tumors (27.95%). Also, the presence of hematologic malignancies, chronic liver disease and chronic kidney disease was identified in 16.12%, 10.75% and 20.43% of the patients, respectively. The clinical characteristics of the patients included in the study are shown in Table 1.

Table 1. Clinical and demographic characteristics of patients with high vitamin B12 levels.

Variables		High vitamin B12 levels (n=93)
Sex, n (%)	Male	58 (62.36)
	Female	35 (37.64)
Age, years, median (IQR)		68 (57-77)
Body mass index, kg/m², median (IQR)		19.8 (15.2-24.1)
Regular alcohol consumption, n (%)		20 (21.50)
Smoking, n (%)	Former smoker	31 (33.33)
	Active smoker	3 (3.22)
Diabetes mellitus, n (%)		27 (29.03)
Cardiovascular disease, n (%)		24 (25.80)
Human immunodeficiency virus, n (%)		12 (12.90)
Sepsis, n (%)		38 (40.86)
Septic shock, n (%)		18 (19.35)
Acute liver failure, n (%)		16 (17.20)
Chronic liver disease, n (%)		10 (10.75)
Autoimmune disease, n (%)		14 (15.05)
Systemic lupus erythematosus, n (%)		6 (6.45)
Rheumatoid arthritis, n (%)		5 (5.37)
Other autoimmune diseases, n (%) *		3 (3.22)
Chronic kidney disease, n (%)		19 (20.43)
KDIGO Classification, n (%)	G3b	7 (7.52)
	G4	5 (5.37)
	G5	7 (7.52)
Hematologic neoplasm, n (%)		15 (16.12)
Lymphoma, n (%)		8 (8.60)
Multiple myeloma, n (%)		3 (3.22)
Other neoplasms, n (%)		4 (4.30)
Solid tumors, n (%)		26 (27.95)
Breast cancer, n (%)		3 (3.22)
Gastric cancer, n (%)		3 (3.22)
Prostate cancer, n (%)		3 (3.22)
Other types of cancer, n (%) †		17 (18.27)
Liver metastasis, n (%)		9 (9.67)
Length of hospital stay, days, median (IQR)		20 (11-28)
1-year mortality, n (%)		55 (59.13)

IQR: interquartile range; KDIGO: Kidney Disease: Improving Global Outcomes.
* Other autoimmune diseases: vasculitis, Sjögren's syndrome, autoimmune hepatitis, and Evans syndrome..
† Other types of cancer: lung, colorectal, pancreatic, cervical, and laryngeal cancer.
Source: Own elaboration.

The main reason for requesting the measurement of B12 levels was anemia (64.51%), followed by pancytopenia or other cytopenias (18.27%), and organic brain syndrome or peripheral neuropathy (15.07%); another cause was chronic diarrhea (2.15%). On the other hand, folic acid deficiency was found in 15.05% of the cases. Furthermore, in most patients (86.02%) the treating physician did not interpret elevated B12 levels as an abnormal finding.

In 19 patients (20.43%) a diagnosis of malignant solid tumor or hematologic neoplasm was made during hospitalization or in the following year. Of the 9 patients in whom a solid organ biopsy was performed during hospitalization, only 4 were diagnosed with cancer. Likewise, 9 patients required bone marrow biopsy, of which 7 were diagnosed with a hematologic neoplasm. Other studies frequently performed on the participants were computed tomography and magnetic resonance imaging, which were key to the diagnosis of cancer during the hospital stay in 47.37% of the cases.

The median plasma B12 concentration was 1 491pg/mL (IQR=1 064-2 623) and almost half of the participants (49.46%) had very high B12 levels at the time of hospitalization. When comparing patients with high and very high levels (Table 2), significant differences were observed in patients with presence or history of smoking (*p*=0.043) and presence of systemic lupus erythematosus (*p*=0.012). Furthermore, 27 patients died during hospitalization and 28 deaths were documented at 1-year follow-up, for a 1-year mortality rate of 59.13%. No statistically significant differences in 1-year mortality were found between the two groups (*p*=0.30).

Table 2. Comparison between subgroups according to vitamin B12 levels.

Variables		High vitamin B12 levels (884-1 499pg/mL) (n=47)	Very high vitamin B12 levels (≥1 500pg/mL) (n=46)	*p*-value
Sex	Male, n (%)	30 (63.82)	28 (60.86)	0.813
	Female, n (%)	17(36.17)	18(39.13)	0.859
Age, years, median (IQR)		68 (57-77)	67 (57-79)	0.966
Body mass index, kg/m², median (IQR)		19.6 (16-24.3)	19.9 (15.2-23.3)	0.984
Regular alcohol consumption, n (%)		9 (19.14)	11 (23.91)	0.610
Smoking, n (%)	Non-smoker	24 (51.06)	30 (65.21)	0.043
	Former smoker	20 (42.55)	11 (23.91)	
	Active smoker	0	3 (6.52)	
Diabetes mellitus, n (%)		16 (34.04)	11 (23.91)	0.282
Cardiovascular disease, n (%)		15 (31.91)	9 (19.56)	0.174
Human immunodeficiency virus, n (%)		5 (10.63)	7 (15.21)	0.515
Sepsis, n (%)		20 (42.55)	18 (39.13)	0.737
Septic shock, n (%)		8 (17.02)	10 (21.73)	0.628
Acute liver failure, n (%)		5 (10.63)	11 (23.91)	0.158
Chronic liver disease, n (%)		6 (12.76)	4 (8.69)	0.526
Autoimmune disease, n (%)		11 (23.40)	3 (6.52)	0.023
Systemic lupus erythematosus, n (%)		6 (12.76)	0	0.012
Rheumatoid arthritis, n (%)		5 (10.63)	0	0.056
Other autoimmune diseases, n (%) *		0	3(6.52)	0.479
Chronic kidney disease, n (%)		10 (21.27)	9 (19.56)	0.652
KDIGO Classification	G3b, n (%)	5 (10.63)	2 (4.34)	0.203
	G4, n (%	1 (2.12)	4 (8.69)	
	G5, n (%)	4 (8.51)	3 (6.52)	
Hematologic neoplasm, n (%)		7 (14.89)	8 (17.39)	0.743

Table 2. Comparison between subgroups according to vitamin B12 levels. (Continued)

Variables		High vitamin B12 levels (884-1 499pg/mL) (n=47)	Very high vitamin B12 levels (≥1 500pg/mL) (n=46)	p-value
Lymphoma, n (%)		5 (10.63)	3 (6.52)	0.714
Multiple myeloma, n (%)		0	3 (6.52)	0.117
Other neoplasms, n (%)		2 (4.25)	2 (4.34)	1.000
Solid tumors, n (%)		12 (25.53)	14 (30.43)	0.566
Breast cancer, n (%)		2 (4.25)	1 (2.17)	1.000
Gastric cancer (%)		0	3 (6.52)	
Prostate cancer, n (%)		2 (4.25)	1 (2.17)	1.000
Other types of cancer, n (%) †		8 (17.02)	9 (19.56)	0.751
Liver metastasis, n (%)		4 (8.51)	5 (10.86)	0.916
Length of hospital stay, días, median (IQR)		16 (10-28)	21 (11-28)	0.503
Folic acid levels, n (%)	Low	6(12.76)	8(17.39)	0.404
	Normal	37(78.72)	36(78.26)	
1-year mortality, n (%)		26 (55.31)	29(63.04)	0.302

IQR: interquartile range; KDIGO: Kidney Disease: Improving Global Outcomes.
* Other autoimmune diseases: vasculitis, Sjögren's syndrome, autoimmune hepatitis, and Evans syndrome.
† Other types of cancer: lung, colorectal, pancreatic, cervical, and laryngeal cancer.
Source: Own elaboration.

In the group of patients with sepsis (n=38) it was found that 47.37%, 52.63% and 47.30% presented septic shock, cancer, and very high B12 levels, respectively (Table 3).

Table 3. Clinical characteristics of patients with sepsis.

Variables		Patients with sepsis (n=38)
Sex, n (%)	Male	22 (57.89)
	Female	16 (42.11)
Age, years, mean (SD)		62.5 (13.35)
Body mass index, kg/m², median (IQR)		20.05 (16.53-23.88)
Septic shock, n (%)		18 (47.36)
Ferritin percentage >1 000, n (%), ng/mL		8 (21.05)
C-reactive protein >10, n (%)		3 (7.89)
Total bilirubin, median (IQR)		0.93 (0.57-3.13)
Vitamin B12 levels >1 500		18 (47.37)
Comorbidities, n (%)	Diabetes mellitus	6 (15.78)
	Human immunodeficiency virus	8 (21.05)
	Cancer of any type	20 (52.63)
Length of hospital stay, días, median (IQR)		27 (21-45)
1-year mortality, n (%)		27 (71.05)

IQR: interquartile range, SD: standard deviation.
Source: Own elaboration.

Finally, no significant correlation was found between B12 and CRP (rho=0.434; p=0.7624), ESR (rho=-0.0302; p=0.7736), or ferritin levels (rho=-0.2071; p=0.2122).

Discussion

In the present study, the prevalence of high B12 levels in the hospital setting was 2.60%, a figure lower than that reported in studies conducted in France, where the prevalence of high B12 levels ranged from 7.4% to 18%.[28-30] However, in those studies,[28-30] and the present research, the majority of participants had one or more conditions associated with elevated B12 levels, reinforcing that the interpretation of B12 hypervitaminosis is a clinical challenge.

There is currently no consensus on what the diagnostic approach should be when elevated B12 levels are detected, nor is there consensus on what the reference value is for determining B12 hypervitaminosis. In this regard, the upper limit of the normal laboratory range, around 1 000±100pg/mL (738±73.8pmol/L),[6,13,19] is usually considered, this being the interpretation used in the present study. This lack of clarity on the definition of a cutoff point also limits the interpretation of the available medical literature, so reaching a consensus on this value is a goal for future studies.

Although there is no classification of high B12 levels, in this study it was decided to evaluate the differences between patients with a high level (884-1 499pg/mL) and with a very high level (≥1 500pg/mL) of this vitamin. This is because previous studies, such as that of Flores-Guerreo *et al.*,[17] carried out in 5 571 patients in the United Kingdom with the aim of investigating the association of plasma B12 concentrations with all-cause mortality, have established that the risk of death is greater the higher the B12 level.

In the present study, significant differences were only found between both groups of patients in the presence of systemic lupus erythematosus (p=0.012) and in the presence or history of smoking (p=0.043). This could be related to the inflammation associated with these situations; however, it is not possible to establish a single explanation for this finding from the results found. The lack of significant differences in the presence of other comorbidities may be due to the small sample size of this study.

Similarly, no significant differences were found in mortality at 1-year follow-up. However, it should be considered that 59.13% of the patients had died by that time. At this point it is important to keep in mind that it is likely that the size of the sample and the time of observation could have significantly affected the possibility of finding differences between the two groups.

In the present study, physicians did not interpret high B12 levels as an abnormal finding in the majority of cases (86.02%), possibly because of the lack of knowledge about this condition and because there are still no clearly established protocols for its diagnosis.[30] This highlights the need to raise awareness of the importance of recognizing B12 hypervitaminosis and its clinical associations.

Some studies recommend that patients with high B12 levels should undergo an extensive history and physical examination, as this can help direct complementary laboratory and imaging tests to rule out possible causes of the elevation, such as the presence of liver disease, chronic kidney disease or hematologic neoplasms, or deficiencies of this vitamin.[10,31] Moreover, it is suggested to repeat the measurement of B12 levels when the patient has been discharged from hospitalization and within a reasonable period of time (at least 1 month) to rule out transient elevations.[19] The remainder of the diagnostic process should be guided by the patient's clinical manifestations; furthermore, in cases where unexplained elevation of B12 levels is found, the presence or future occurrence of cancer should not be ruled out.[6,28,29,32]

High plasma B12 concentrations have been associated with increased mortality in the hospitalized population, mainly in older adults.[17,33] This is in consistent with the findings of the present study, where 59.13% of the participants died within a follow-up period of 1 year.

Some studies have shown that high B12 levels are associated with high CRP levels,[21,34,35] which differs from the present study, where no significant correlation was found between high B12 levels and CRP, ESR, or ferritin levels. However, it is important to keep in mind that such studies[21,34,35] report such correlation by means of the B12 and CRP index, known as the BCI index, which was not considered in the present study.

Regarding the limitations of the present study, first of all, it can be said that there is a possible selection bias due to the retrospective nature of the study. Second, the sample size was small, although it should be considered that it is representative of the patients treated at the tertiary care hospital where the study was conducted. Third, the outpatient population was not considered and a second measurement of B12 levels was not performed to assess the persistence of B12 hypervitaminosis. Fourth, the follow-up time was short and there is no information on the cause of death.

In view of the above, prospective analytical studies involving outpatients and considering data from several measurements of B12 levels are needed to confirm the finding of B12 hypervitaminosis, which will better establish the usefulness of measuring elevated B12 levels in clinical practice.

Conclusion

Patients with B12 hypervitaminosis had high mortality after 1 year of follow-up. In addition, more than half of the participants had two or more comorbidities associated with elevated B12 levels. On the other hand, significant differences were found between patients with high B12 levels and those with very high levels in the presence of systemic lupus erythematosus and with a history of smoking. Finally, in most participants, physicians did not interpret elevated B12 levels as an abnormal finding. However, it should be noted that the results of the present study do not allow us to establish causality between B12 hypervitaminosis and comorbidities, and vice versa.

B12 hypervitaminosis is a clinical finding that must be evaluated in a rigorous and individualized manner, so it is always necessary to search for and confirm the cause or causes of these elevated levels. Likewise, it is necessary to conduct an in-depth and multidisciplinary research on the possible causes of the presence of elevated B12 levels in patients, taking into account the correlation between this factor and an increased risk of mortality and cancer. This can contribute to early diagnosis and timely management of these patients and, consequently, to better outcomes.

Conflicts of interest

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