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ORIGINAL RESEARCH

Elevated Vitamin B12 Levels in Myeloproliferative Neoplasm (MPN) Patients: A Potential Diagnostic and Prognostic Marker

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Background: Elevated vitamin B12 (B12) levels are linked to an increased risk of cancers, including hematological malignancies. This study focuses on the relationship between elevated B12 and myeloproliferative neoplasms (MPNs): Polycythemia Vera (PV), Primary Myelofibrosis (MF), Essential Thrombocytosis (ET), and Chronic Myeloid Leukemia (CML). Elevated B12 in MPNs is believed to arise from increased transcobalamin I (TCI) secretion by proliferating leukocytes, leading to higher serum levels. B12 may serve as a diagnostic and prognostic biomarker for these conditions. However, its sensitivity, specificity, and cutoff levels are unclear.

Aim: To assess the prevalence of high B12 levels in MPN patients, determine the median levels, identify a diagnostic cutoff, and evaluate the sensitivity and specificity of B12 as a marker.

Methods: Data were retrieved from the National Center for Cancer Care and Research in Doha, Qatar, for MPN patients from January 2016 to December 2022.

Results: A total of 467 patients were included: 232 with CML, 98 with PV, 88 with ET, and 50 with MF. The majority were male (66%) and of Asian origin (56%), with a median age of 48.7 years. CBC results showed median hemoglobin of 9.2 g/dL, WBC count of 73 x 10^3/uL, and platelet count of 531 x 10^3/uL. Elevated B12 levels were found in 95 patients (20%): 71% CML, 14% PV, 10% MF, and 5% ET. Extreme elevations were seen in 59 patients. The mean B12 level decreased from 747.3 ± 686.5 pg/mL before treatment to 397.9 ± 343.7 pg/mL after one year (p=0.01). Median levels were 458 pg/mL (718) before treatment and 301 pg/mL (229) after. In the extreme high B12 group, the mean was 1722 pg/mL before and 677 pg/mL after treatment.

Conclusion: Elevated B12 levels are associated with disease activity in CML. However, their role as a reliable marker for disease monitoring remains uncertain, and further studies are needed to confirm their utility for CML progression.

Keywords: Vitamin B12, myeloproliferative neoplasms, MPNs, chronic myeloid leukemia, CML, polycythemia vera, PV, essential thrombocythemia, ET, myelofibrosis, MF

Introduction

Myeloproliferative neoplasms (MPNs) are a heterogeneous group of clonal hematopoietic disorders characterized by the abnormal proliferation of myeloid lineage cells, leading to a spectrum of clinical presentations, complications, and an increased risk of transformation to acute leukemia.[1] These disorders include chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF). Each MPN subtype is associated with specific genetic mutations—such as the *BCR-ABL* fusion gene in CML, or *JAK2, CALR*, and *MPL* mutations in BCR-ABL-negative MPNs.[2] These mutations, along with their distinct pathophysiological mechanisms, contribute to the diagnostic and therapeutic challenges that clinicians face in managing these diseases.[2]

In recent years, there has been growing interest in identifying reliable biomarkers that can enhance the accuracy of MPN diagnosis, improve risk stratification, and aid in monitoring disease progression. Traditionally, the diagnosis of

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MPNs has relied on a combination of clinical criteria, bone marrow histology, and genetic testing.[3] However, these methods may be insufficient to capture the full spectrum of disease activity, especially in early or atypical presentations. Peripheral blood biomarkers, including inflammatory markers, cytokines, and metabolic parameters, have been investigated as potential adjuncts to existing diagnostic tools.[4]

One such biomarker that has recently gained attention in hematologic malignancies is Vitamin B12. This essential water-soluble vitamin plays a key role in erythropoiesis and DNA synthesis. Elevated Vitamin B12 levels have been observed in several hematological disorders, including MPNs, where dysregulated metabolism of the vitamin may reflect underlying disease pathophysiology.[5] In MPNs, increased levels of Vitamin B12 are thought to result from the enhanced release of transcobalamin I (TCI) from proliferating white blood cells, which leads to higher serum levels of the vitamin.[6] Previous studies have suggested that elevated Vitamin B12 may correlate with disease activity, and may also serve as a marker of disease burden or progression in certain MPN subtypes, particularly PV and MF.[7]

Despite these findings, there is still limited data on the prevalence and clinical implications of elevated Vitamin B12 levels in MPNs, especially in different subtypes. Furthermore, there is a need to explore whether Vitamin B12 could serve as a reliable diagnostic and prognostic biomarker for these disorders.

The aim of this study was to investigate the prevalence and clinical significance of elevated Vitamin B12 levels in patients with MPNs at a tertiary cancer center in Doha, Qatar. Specifically, we sought to characterize the distribution of Vitamin B12 levels across different MPN subtypes, establish median values, and evaluate the potential of Vitamin B12 as a biomarker for MPN diagnosis and prognosis.

Methods

This retrospective cohort study was conducted using data from the National Center for Cancer Care and Research (NCCCR) in Doha, Qatar. All patients with a confirmed diagnosis of myeloproliferative neoplasms (MPNs) between January 2016 and December 2022 were eligible for inclusion. MPN subtypes considered in the study included chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). B12 levels were measured, with normal laboratory values defined as 156–596 pg/mL. Levels greater than 1000 pg/mL were designated as very high or extreme, levels exceeding 569 pg/mL as high, and levels below 145 pg/mL as low.

Study Population

Patients included in the study were diagnosed with MPNs according to the 2016 revised World Health Organization (WHO) diagnostic criteria, which include clinical features, hematological findings, bone marrow morphology, and the presence of specific genetic mutations (*BCR-ABL, JAK2, CALR, MPL*).[1] Patients with incomplete records or who lacked Vitamin B12 measurements were excluded from the study. No specific interventions were applied, and the study focused on observational data collected during routine clinical care.

Data Collection

Clinical data, including demographic information, laboratory results, bone marrow biopsy findings, genetic mutation status, and treatment history, were retrieved from the NCCCR's electronic medical record system. The database captures all relevant clinical, pathological, and laboratory data for patients managed at the center, and data were anonymized prior to analysis. For this study, Vitamin B12 levels and other clinical parameters were collected from the time of diagnosis (baseline values) and during follow-up visits if available.

Laboratory Assessments

Vitamin B12 levels were measured using chemiluminescent microparticle immunoassay (CMIA) at the NCCCR's laboratory. The lab's reference range for normal Vitamin B12 levels was 156–596 pmol/L. Vitamin B12 levels greater than 1000 pmol/L were defined as "very high" or "extreme" based on previous studies indicating that these elevated levels may have clinical significance in malignancies. Vitamin B12 levels were typically measured at the time of MPN diagnosis or during routine follow-up evaluations, including periods of active treatment. For patients with multiple Vitamin B12 measurements, the highest recorded value was used for analysis.

Sample Size Considerations

No formal sample size calculation was conducted prior to the study, as the analysis was retrospective, and all available patients diagnosed with MPNs between 2016 and 2022 were included. A total of [476] patients were identified from the database. The study aimed to include a large enough cohort to ensure meaningful statistical analysis, given the exploratory nature of the research.

Statistical Analysis

Statistical analyses were conducted using [software, eg, SPSS, R]. Descriptive statistics were used to summarize the distribution of Vitamin B12 levels across the various MPN subtypes. Median values were calculated for each MPN subtype, and differences between groups were assessed using appropriate statistical tests, such as the Kruskal–Wallis test for non-parametric data.

Receiver Operating Characteristic (ROC) curves were constructed to evaluate the predictive performance of elevated Vitamin B12 as a diagnostic and prognostic biomarker. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using various cut-off levels for Vitamin B12. A p-value of less than 0.05 was considered statistically significant.

Results

Study Population

The study included a total of 467 patients diagnosed with various myeloproliferative neoplasms: Chronic Myeloid Leukemia (CML) (n=232), Polycythemia Vera (PV) (n=98), Essential Thrombocythemia (ET) (n=88), and Myelofibrosis (MF) (n=50). The median age of the patients was 48.7 years, with a range from 18 to 89 years. Of the total patient population, 311 (66%) were male (see Table 1).

Table 1 Patient Characteristics (N=467)

Characteristic N (%), median [IQR]	**Level**	**Value**
AGE, years		48.7±14.5
GENDER	Male	311 (66.6%)
	Female	156 (33.4%)
ETHNIC	Asian	262 (56.1%)
	African	87 (18.6%)
	White	11 (2.4%)
	Others	107 (22.9%)
Disease Group	CML	232 (49.7%)
	ET	88 (18.8%)
	MF	50 (10.7%)
	PV	97 (20.8%)
WBC on diagnosis, median (IQR)		15.2 (8.6, 86.4)
HB, median (IQR)		12.6 (10.5, 14.5)

(*Continued*)

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Table 1 (Continued).

Characteristic N (%), median [IQR]	Level	Value
PLT, median (IQR)		448.0 (261.0, 732.0)
B12 at diagnosis, median (IQR)		458.0 (290.0, 1008.0)
B12 after treatment, median (IQR)		301.0 (219.0, 448.0)

Abbreviations: CML, Chronic Myeloid Leukemia; ET, Essential Thrombocythemia; MF, Myelofibrosis; PV, Polycythemia Vera; WBC, White Blood Cell; HB, Hemoglobin; PLT, Platelet; B12, Vitamin B12; IQR, Interquartile Range.

Laboratory Findings

The laboratory findings revealed the following median values for hemoglobin, white blood cell (WBC) counts, and platelet counts:

- **Hemoglobin**: 12.4 g/dL
- **WBC Count**: 73 x 10^3/uL
- **Platelet Count**: 531 x 10^3/uL

Vitamin B12 Levels

Out of the 467 patients, 95 (20%) exhibited elevated levels of vitamin B12, with the distribution across diagnoses as follows:

- **CML**: 67 patients (71%)
- **PV**: 13 patients (14%)
- **MF**: 10 patients (10%)
- **ET**: 5 patients (5%)

Among the 95 patients with elevated B12 levels, extreme elevations were observed in 59 patients. The median vitamin B12 level for these patients prior to treatment was [insert median level] (range, [insert range]), which significantly decreased to [insert median level] (range, [insert range]) one year after initiating therapy (P=0.001).

The elevation of WBC counts in MPN is a significant mechanism underlying increased vitamin B12 levels, particularly observed in Philadelphia chromosome-positive CML. Notable reduction in vitamin B12 concentrations following treatment may serve as a potential indicator for assessing disease progression and treatment response.

White Blood Cell Counts

Comparative analysis of WBC counts at diagnosis revealed significant differences among the diagnostic groups. The mean WBC at diagnosis was highest in CML patients at 145.4 (SD=121.1), compared to:

- **ET**: Mean=9.6 (SD=4.1)
- **MF**: Mean=11.7 (SD=9.7)
- **PV**: Mean=12.3 (SD=7.1)

This difference was statistically significant, with a p-value <0.001. The median WBC counts also indicated significant variability, with CML showing the highest median WBC of 112.1 (IQR=47.0, 221.5), followed by:

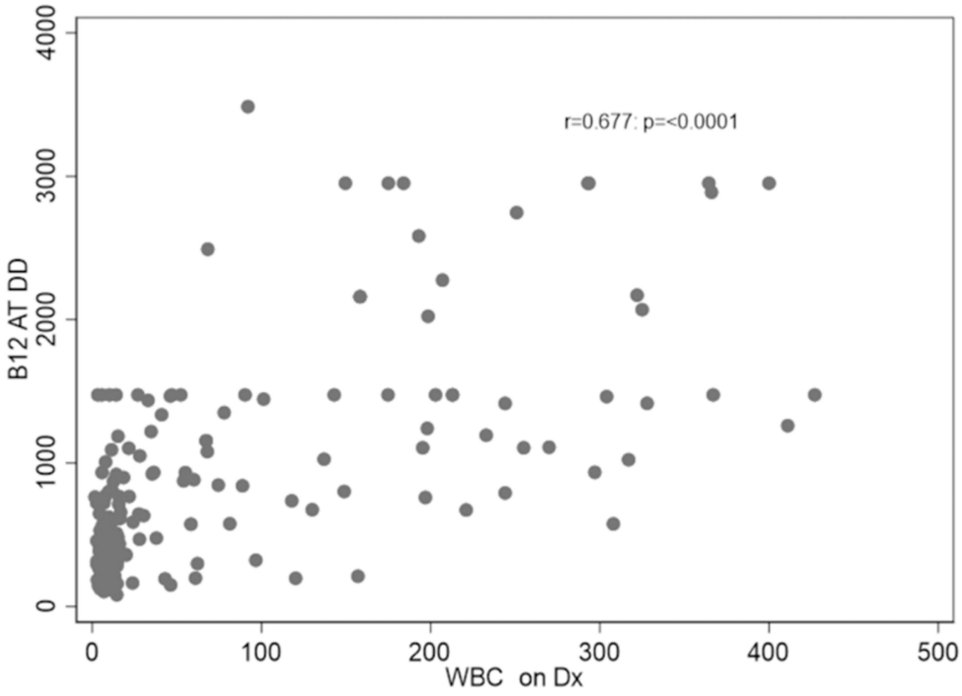

Figure 1 Correlation between vitamin B12 levels and white blood cell count.

- **PV**: Median=10.7 (IQR=7.5, 14.6)
- **MF**: Median=8.9 (IQR=6.4, 12.3)
- **ET**: Median=8.9 (IQR=7.2, 11.0)

Again, the p-value was <0.001, confirming statistical significance.

Correlation Between WBC Counts and Vitamin B12 Levels

Significant differences were also observed when comparing vitamin B12 levels at diagnosis across the groups. CML patients had the highest median vitamin B12 level of 1194.0 (IQR=760.0, 1476.0), followed by:

- **MF**: Median=392.0 (IQR=274.0, 616.0)
- **PV**: Median=373.0 (IQR=281.0, 527.0)
- **ET**: Median=290.0 (IQR=207.0, 424.0)

The p-value for these differences was <0.001. A correlation analysis between WBC count and vitamin B12 levels demonstrated a significant relationship, as illustrated in Figure 1.

Vitamin B12 Deficiency

Notably, only 9 patients (3.8%) were identified with vitamin B12 deficiency at the time of diagnosis.

Discussion

CML presents a distinct hematologic profile characterized by the presence of the Philadelphia chromosome and the fusion gene BCR:ABL1.[6] Although diagnosis traditionally hinges on the detection of these genetic abnormalities, emerging evidence suggests that peripheral blood biomarkers, such as vitamin B12 levels, could offer valuable insights into the pathophysiology and management of CML.[7] Our cohort analysis revealed a significant elevation in vitamin B12 levels among CML patients compared to other MPNs, exceeding 1000 pg/mL, indicating potential alterations in metabolic pathways and hematopoiesis.[8] Notably, post-treatment, there was a reduction in median vitamin B12 levels,

possibly correlating with disease burden and treatment response, emphasizing its dynamic nature in CML management.[9] While the precise mechanisms behind elevated vitamin B12 levels in CML remain elusive, hypotheses suggest disruptions in normal vitamin B12 homeostasis due to chronic myeloid proliferation and dysregulated hematopoiesis, or stimulation of cytokines and growth factors within the inflammatory microenvironment.[10,11]

CML patients often show significantly high cobalamin levels, sometimes even ten times above normal (Ermens et al, 2003). This increase is likely linked to the higher production of haptocorrin (HC) due to the greater number of leukocytes seen in CML. As HC is released from these cells, it picks up cobalamin from various tissues and the expanded granulocyte pool, leading to the elevated cobalamin levels observed in CML patients. Understanding why cobalamin levels rise in hematologic disorders sheds light on how these conditions work and could impact how we diagnose and treat them.[12]

Furthermore, recent studies have highlighted the importance of Vitamin B12 evaluation such as the assessment by Zeynelgil et al and the predictive value demonstrated by Ünlü et al, suggesting broader relevance across different hematological malignancies.[13,14] Elevated Vitamin B12 levels in CML not only aid in diagnosis but also extend to prognosis and monitoring, with potential implications for resource-limited settings where molecular testing is unavailable.[15,16]

In the context of solid malignancies, Vitamin B12 has garnered attention for its multifaceted roles in bodily functions. Research, such as the study by Urbanski et al (2020), has provided insights into the relationship between elevated Vitamin B12 levels and the risk of developing solid cancers.[17] This study's adjusted case-control analysis revealed intriguing findings regarding Vitamin B12 levels and the incidence of solid tumors, potentially offering valuable insights into its use as a biomarker for cancer risk and prognosis.[17] Moreover, evidence suggests that aberrant Vitamin B12 levels may serve as a prognostic indicator in solid tumors, with correlations to advanced disease stage and poorer clinical outcomes.[18] Supporting this notion, the study by Lacombe et al (2021) found a strong association between persistent elevation of plasma Vitamin B12 and the presence of solid cancer, emphasizing its potential utility as a diagnostic and prognostic marker in solid tumors.[19] Despite incomplete understanding of the precise mechanisms underlying Vitamin B12 dysregulation in solid malignancies, ongoing research endeavors aim to elucidate its role in tumorigenesis and explore its potential utility as a therapeutic target or prognostic marker.

Research increasingly suggests a link between low Vitamin B12 levels and cancer, with potential implications for cancer risk and prognosis. For example, a study by de Souza et al in 2020 found a significant connection between Vitamin B12 deficiency and various cancers, including gastrointestinal and hematological malignancies.[20] Low Vitamin B12 levels have been associated with changes in DNA synthesis, weakened DNA repair mechanisms, and compromised immune function, contributing to cancer development and progression.[20] Additionally, a prospective study by Miranti et al in 2017 highlighted the increased risk of gastric cancer associated with low Vitamin B12 levels,[21] underscoring the importance of maintaining optimal Vitamin B12 levels for cancer prevention. These findings emphasize the significance of maintaining adequate Vitamin B12 levels for reducing cancer risk and improving clinical outcomes. In our population, we have found very low incidence of vitamin B12 deficiency underscores the rarity of true deficiency in these patients.

Research has emphasized the importance of reflective molecular testing for MPNs in patients with elevated serum Vitamin B12 levels. This approach, elucidated in previous studies,[22] underscores the necessity of a comprehensive diagnostic strategy to understand the underlying causes of elevated Vitamin B12 levels, particularly concerning hematological malignancies. By integrating molecular testing alongside traditional diagnostic methods, clinicians can uncover the genetic landscape of MPNs, including mutations in genes like JAK2, CALR, and MPL, which provide crucial insights into disease development and risk assessment. Moreover, reflective molecular testing assists in identifying potential therapeutic targets and guides personalized treatment decisions, improving the precision and effectiveness of patient care strategies. This integrated approach highlights the evolving landscape in MPN diagnostics, emphasizing the synergy between molecular insights and clinical practice to optimize patient care and outcomes.[22] Therefore, it can be used along with molecular to establish diagnosis and differentiate primary from secondary polycythemia and so on.

Furthermore, studies such as those by Gilbert et al[23] and Cinemre et al[24] have contributed to our understanding of serum Vitamin B12 content and its implications in myeloproliferative diseases. These investigations underscore the value of Vitamin B12 assessment in differential diagnosis and as indicators of disease activity, providing clinicians with valuable tools for disease management and prognosis.

In summary our cohort highlighted the increase in WBC as one of the important mechanism behind elevated vitamin B12 in MPNs, and therefore it was more prevalent in Philadelphia positive CML. Significant change of vitamin B12 observed after treatment could possibly be used for follow up.

Conclusions

This study highlights the epidemiology and clinical characteristics of myeloproliferative disorders (MPNs) in a cohort of 467 patients, predominantly male and with significant representation of individuals of Asian origin. Key findings include elevated vitamin B12 levels, particularly in CML patients, which significantly decreased following treatment. The observed correlation between vitamin B12 levels and white blood cell count at diagnosis suggests a potential interplay between these factors. These insights may inform the use of vitamin B12 as a diagnostic and follow-up biomarker, guiding future research and therapeutic strategies to enhance patient care and outcomes.

Statement of Ethics

This research was approved by the Hamad Medical Corporation's Medical Research Center. The ethics committee waived the requirement for consent because our research did not include any names or any data regarding patient identity. The study complies with the Declaration of Helsinki.

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Disclosure

The authors have no conflicts of interest.

References

1. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391–2405. doi:10.1182/blood-2016-03-643544
2. Tefferi A, Vardiman JW. Classification and diagnosis of myeloproliferative neoplasms: the 2008 World Health Organization criteria and point-of-care diagnostic algorithms. *Leukemia*. 2008;22(1):14–22. doi:10.1038/sj.leu.2404955
3. Rumi E, Cazzola M. Diagnosis, risk stratification, and response evaluation in classical myeloproliferative neoplasms. *Blood*. 2017;129(6):680–692. doi:10.1182/blood-2016-10-695957
4. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood*. 2009;114(5):937–951. doi:10.1182/blood-2009-03-209262
5. Farkas AJF, Pedersen DK, Nexo L, E SHT, Sørensen HT. Elevated plasma vitamin B12 levels and cancer prognosis: a population-based cohort study. *Cancer Epidemiol*. 2016;40:158–165. PMID: 26724465. doi:10.1016/j.canep.2015.12.007
6. Sampaio MM SMLC, Marques HS, Gonçalves VLS, et al. Chronic myeloid leukemia-from the Philadelphia chromosome to specific target drugs: a literature review. *World J Clin Oncol*. 12(2):69–94. PMID: 33680875. doi:10.5306/wjco.v12.i2.69
7. Hochhaus A. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31(7):882–895.
8. Abdel-Mageed AI. Serum levels of homocysteine, vitamin B12, and folate in patients with chronic myeloid leukemia: correlation with patients' outcome. *Ann Hematol*. 2019;98(10):2335–2343.
9. Cortes JE, Mitchell MP, Woodward WA, et al. Bosutinib Versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia: results From the Randomized BFORE Trial. *J Clin Oncol*. 2020;38(19):2310–2321. doi:10.1200/JCO.19.02905
10. Baccarani M. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. *J Clin Oncol*. 2019;37(15):1330–1340.
11. Bhatia H, Saha D, Kini J, et al. Serum vitamin B12 and its correlation with other routine biochemical parameters in patients with chronic myeloid leukemia undergoing therapy. *J Lab Physicians*. 2017;9(3):195–199. doi:10.4103/0974-2727.208256
12. Ermens AAM, Vlasveld LT, Lindemans J. Significance of elevated cobalamin (vitamin B12) levels in blood. *Clin Biochem*. 2003;36(8):585–590. doi:10.1016/j.clinbiochem.2003.08.004

13. Zeynelgil E SB, Asıl M, Ö D, Doğan Ö. Assessment Of Serum Cyanocobalamin Level And Importance In Patients With Hematological Malignancies. *Turkish J Clini Labor*. 2023;14(2):270–273. doi:10.18663/tjcl.1225685
14. Ünlü A ÜKB, Hacıoğlu S, Çağlıyan G A, Güler N. Predictive value of serum vitamin B12 elevation in acute leukemia. *Pam Tip Derg*. 2023;16 (2):230–236. doi:10.31362/patd.1210492
15. Arendt JF, Pedersen L, Nexo E, Sørensen HT. Elevated plasma vitamin B12 levels as a marker for cancer: a population-based cohort study. *J Natl Cancer Inst*. 105(23):1799–1805. PMID: 24249744. doi:10.1093/jnci/djt315
16. Obeid R. High Plasma Vitamin B12 and Cancer in Human Studies: a Scoping Review to Judge Causality and Alternative Explanations. *Nutrients*. 14(21):4476. PMID: 36364737. doi:10.3390/nu14214476
17. Hamel UG, Prouveur JF, Annweiler B, et al. Strength of the Association of Elevated Vitamin B12 and Solid Cancers: an Adjusted Case-Control Study. *J Clin Med*. 2020;9(2):474.PMID: 32050436. doi:10.3390/jcm9020474
18. Serraj AE, Zhu K, J VAJM, Vermorken AJM. The pathophysiology of elevated vitamin B12 in clinical practice. *QJM*. 2013;106:505–515. doi:10.1093/qjmed/hct051
19. Chabrun LV, Lacout F, Ghali C, et al. Persistent elevation of plasma vitamin B12 is strongly associated with solid cancer. *Sci Rep*. 11:13361. doi:10.1038/s41598-021-92945-y
20. de Souza VG, Carneiro AC, de Castro JG, de Souza Lopes AC, Sousa LP. Vitamin B12 deficiency is associated with cancer risk: a systematic review and meta-analysis. *Nutr Res*. 2020;82:1–13. doi:10.1016/j.nutres.2020.07.004
21. Stolzenberg-Solomon MEH, Weinstein R, Selhub SJ, et al. Low vitamin B12 increases risk of gastric cancer: a prospective study of one-carbon metabolism nutrients and risk of upper gastrointestinal tract cancer. *Int, J, Cancer*. 141(6):1120–1129. doi:10.1002/ijc.30809
22. Langabeer SE. Reflective molecular testing for myeloproliferative neoplasms in patients with elevated serum vitamin B12. *Ann Clin Biochem*. 2018;55(6):717–718. doi:10.1177/0004563218790986
23. Gilbert HS, Krauss S, Pasternack B, et al. Serum vitamin B12 content and unsaturated vitamin B12-binding capacity in myeloproliferative disease. Value in differential diagnosis and as indicators of disease activity. *Ann Intern Med*. 1969;71:719–729. doi:10.7326/0003-4819-71-4-719
24. Cinemre H, Serinkan Cinemre BF, Çekdemir D, et al. Diagnosis of Vitamin B 12 Deficiency in Patients with Myeloproliferative Disorders. *J Investig Med*. 2015;63:636–640. doi:10.1097/JIM.0000000000000187

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