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ASSOCIATION OF ELEVATED VITAMIN B_{12} WITH ONCOHEMATOLOGICAL DISEASES IN A COHORT OF 79,524 PATIENTS FROM LATVIA

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Aim: **Currently there are some large-scale studies of elevated total vitamin B_{12} in relation to diseases and their prognosis. Aim of this retrospective study was to determine association of increased B_{12} as an additional diagnostic marker of oncohematological diseases by a statistical analysis of clinical data of 79,524 patients.** ***Materials and Methods:*** **Overall Latvian population representative data on B_{12} testing in 79,524 patients were obtained from laboratory database. The following exclusion criteria were applied: fluctuating B_{12} results within a three-month period, elevated (> 100 U/L) alanine transaminase or aspartate transaminase, hepatitis (HAV, HBV, and HCV) infection, reduced glomerular filtration rate (< 45 mL/min/1.73 m^2). As a control group, individuals with normal B_{12} level and any oncologic diagnosis (solid cancer or hematological malignancies) were selected.** ***Results:*** **After application of step-by-step exclusion filters, 1,373 patients were left with significantly increased level of plasma B_{12} (> 1,700 pg/mL). Odds ratios for oncohematological diseases in total and myeloid leukemia (including acute, chronic and unspecified) in patient group with elevated B_{12} were found to be 6.0 (95% CI 4.7–7.6; $p < 0.0001$) and 19.2 (95% CI 13.1–28.0; $p < 0.0001$), respectively, as compared to the control group.** ***Conclusion:*** **Elevated total B_{12} could be considered as a potential marker for oncohematological disorders.**
Key Words: **elevated total B_{12}, myeloid leukemia, oncohematological diseases.**

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Clinical laboratory practice often encounters patients with significantly increased plasma levels of total vitamin B_{12}. The etiology of this phenomenon has been understudied. Generally, elevated B_{12} is associated with liver and kidney damage, as well as with oncohematological processes.

It is not currently clear whether total B_{12} level can serve as a diagnostic and/or prognostic marker in oncohematology. It is necessary to clarify which onchematological diseases are associated with an increased level of B_{12}, applying exclusion criteria (e.g. liver and kidney damage) in selected patient group for the further research.

Vitamin B_{12}, also referred as cobalamin, is an organometallic water-soluble compound in which a cobalt atom is situated within a corrin ring. Vitamin B_{12} cannot be synthesized by the human body cells, though it is synthesized by a microbiota of the small intestine. The main external sources of the vitamin B_{12} are meat, fish, eggs and dairy products, seldom it is found in the products of plant origin. Vitamin B_{12} is the cofactor for two enzymes, methionine synthase and methylmalonyl-CoA-mutase.

Methionine synthase locates in the cytoplasm and requires vitamin B_{12} in the form of methylcobalamin to catalyze the conversion of homocysteine to an essential amino acid methionine. Thus, vitamin B_{12} is important for DNA synthesis, regenerating methionine for protein synthesis and methylation, as well as for the development and initial myelination of the central nervous system and for the maintenance of normal central nervous system function [1].

In the blood, B_{12} circulates in two forms — metabolically active and inactive. Transcobalamins (TCBs) are required for B_{12} transportation in the organism and for the liver uptake. TCB type I (TCBI) and III (TCBIII) ensure binding of 80% of the circulating vitamin B_{12}. These proteins belong to haptocorrin (HC) superfamily [2].

TCB type II (TCBII) plays essential role in the key processes of tissue and hepatic uptake of vitamin B_{12}. Metabolically active form consists of B_{12} bound to TCBII — holotranscobalamin II. Metabolically inactive B_{12} is bound to the HC, in this form B_{12} is accumulated in the liver. In cases of liver damage, inactive form increases and the level of total B_{12} also increases proportionally. HCs are produced by the granulocyte cell line, and along with myeloproliferative processes B_{12} plasma levels are also increased. Metabolically active form holotranscobalamin delivers B_{12} to the cells thus engaging it into biochemical pathways [3].

Currently there are multiple large-scale studies of elevated B_{12} in relation to the diseases and their prognosis in different patient populations [4, 5]. Arendt *et al.* [6] analyzed large cohort of Danish population for incidence of cancer in patients with elevated B_{12}. They found that elevated B_{12} was associated with the risk of subsequently diagnosed cancer. Ryg *et al.* [5] in their study used threshold of elevated B_{12} as 1,626 pg/mL (converted originally in article — 1,200 pmol/L). Standard incidence ratio of developing hematologic malignancies within one-year interval was found to be 24.14 (95% CI 19.51–29.54) [6]. Andres *et al.* [7]

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Abbreviations used: ALT – alanine transaminase; AST – aspartate transaminase; CBC – complete blood count; GFR – glomerular filtration rate; HC – haptocorrin; OR – odds ratio; SE – standard error; SIR – standardized incidence ratio; TCB – transcobalamin.

in their review article discusses the association of significantly high levels of B_{12} (> 9,000 pg/mL) with oncohematologic pathologies, including myeloproliferative disorders. It is hypothesized that B_{12} increase in myeloproliferative disorders is due to HCs release by granules of myeoloid cell lineage [7]. Chicke *et al.* [8] in their study including 2,064 patients report association of the elevated B_{12} (> 1,275 pg/mL) with blood malignancies ($p < 0.05$).

Unrelated to health condition B_{12} elevation in many cases could be explained as an excess intake of vitamin B_{12} supplements. Liberation from the internal reservoirs, overproduction of TCBs or disturbances in the process of the clearance also has influence on B_{12} elevation in blood [7, 9].

To estimate whether elevated B_{12} level could be considered as a diagnostic and prognostic marker for oncohematological disorders, a large-scale patient data statistical analysis is required. It is also important to identify and exclude unrelated to cancer cases of elevated B_{12}. For example, excessive B_{12} intake is relatively easy to identify in the anamnesis due to a fluctuation of the plasma B_{12} levels [8]. Liver diseases increase plasma B_{12} level during damage of hepatocyte therefore releasing B_{12} bounded to haptocorins [8, 10, 11]. Significant increase of plasma B_{12} might be related even to the kidney diseases. Carmel *et al*. [12] hypothesized that cellular uptake of cobalamin by the abundant TCBII receptors in the kidney may be involved in the pathophysiology of elevated B_{12} as well.

Vast majority of the studies on elevated B_{12} content are done with an application of simplified statistical methods usually by associating one parameter with the disease. The problem needs to be assessed from different aspects, using different algorithms and incorporating as many patients' data sets as possible in to the statistical analysis.

In this study, we applied multi-criteria statistical algorithm with critically considered exclusion criteria to a 79,524 unique total B_{12} patient data (79,524 unique patients with at least one total B_{12} measurement). Our goal was to analyze correlation of elevated B_{12} with oncohematological diseases in large Latvian population representative data.

MATERIALS AND METHODS

Patients. Data from all adult (⩾ 18 years old) patients requesting B_{12} analysis in the E. Gulbis Laboratory (Riga, Latvia) from January 2004 to January 2018 were included in the study (n = 79,524). All patients' data was pseudo-depersonalized. During that time laboratory performed more than 1,800,000 unique patient analysis that practically represents overall Latvian population (1,934,379 in 2017, Latvian statistical agency). Overall, each year the laboratory tests 1,200,000–1,300,000 patients.

The following exclusion criteria were defined:

1) fluctuating B_{12} value within 3 months from the first measurement;

2) elevated (> 100 U/L) alanine transaminase (ALT) or aspartate transaminase (AST);

3) decreased (< 45 mL/min/1.73 m^2) glomerular filtration rate (GFR);

4) positive viral hepatitis (HAV, HBV, HCV).

Three months interval was chosen as clinically relevant period to exclude B_{12} elevation unrelated to cancer (hepatotoxicity, nephrotoxicity) — for biochemical marker normalization.

Threshold of > 771 pg/mL (from Roche Diagnostics B_{12} test manual) was defined for the elevated B_{12}, and we defined > 1,700 pg/mL for the significantly elevated B_{12}. This high value was chosen to exclude elevated B_{12} unrelated to health conditions cases since B_{12} prescription as supplement and medication effects drastically blood B_{12} level.

For the control group (statistical threshold) we selected patients with normal B_{12} and any cancer diagnosis (C00–C97). Information about cancer diagnosis was derived from State registry for oncologic patients.

Laboratory methods. All analysis was performed in E. Gulbis Laboratory — a certified (ISO/IEC 17025, ISO 15189:2013) clinical laboratory (Riga, Latvia), which provides laboratory services in all regions of Latvia. All the testing was performed according to the reagent manufacturers' user manuals.

Total B_{12} was measured using electrochemiluminescence immunoassay method ECLIA on Cobas e411 analyzer (Roche Diagnostics, Switzerland). Holotranscobalamine II was measured using chemiluminescent immunoassay method on ADVIA Centaur XP system (Siemens Healthcare, Germany). Alanine transaminase and aspartate transaminase were measured on ADVIA 1200 analyzer (Siemens Healthcare, Germany). Folic acid was measured using electrochemiluminescence binding assay on Cobas e801 immunoassay analyzer (Roche Diagnostics, Switzerland). Homocysteine was measured using competitive immunoassay on ADVIA Centaur System (Siemens Healthcare, Germany).

Complete blood cells count (CBC) was detected by multiple commercially available assays with 5-part differentiation. Creatinine was measured using enzymatic reaction on ADVIA 1200 (Siemens Healthcare, Germany). GFR was determined using different formulas depending on patient's age, body weight and/or height data (protocols are available upon request).

HAV IgM was performed using IgM capture immunoassay on ADVIA Centaur XP system (Siemens Healthcare, Germany). HAV IgG was performed using competitive immunoassay on ADVIA Centaur XP System (Siemens Healthcare, Germany). Anti-HBs and HBsAg was performed using sandwich immunoassay on ADVIA Centaur XP System (Siemens Healthcare, Germany). Anti-HCV was performed using indirect sandwich immunoassay on ADVIA Centaur XP System (Siemens Healthcare, Germany).

Statistical analysis. For B_{12} association with oncologic diseases odds ratio (OR) was calculated

by formula given in Fig. 1. OR, standard error (SE) and confidence interval (95% CI) were calculated according to a practical medical statistics [13]. Test of significance (*p*-value) was calculated as the area of the normal distribution that falls outside ± z [14]. OR analysis was performed for all oncologic diseases listed in the laboratory database. In this article, we show only statistically significant results.

Initial group included data on 79,524 patients with at least one B_{12} measurement. These data were analyzed applying step-by-step exclusion algorithm. Patient group selection and analysis is shown in the flow chart (see Fig. 1). At first, the patients with fluctuating B_{12} analysis were excluded, n = 8,082. The number of patients with stable elevated B_{12} level is comparable to the number of patients with rapidly fluctuating B_{12} levels. Hypothetically, reason for such cases could be supplementary intake and B_{12} medication. For this reason, only the patients with stable elevated B_{12} values for more than 3-month period were included in the further analysis.

Further filters excluded patients with elevated ALT or AST within 3 months from B_{12} measurement, n = 2,263; decreased GFR within 3 months from B_{12} measurement, n = 1,106; ever positive for any viral hepatitis (HAV, HBV, HCV). Groups of interests for OR calculation were as follows: a) patients with significantly elevated B_{12} (significantly elevated B_{12} > 1700 pg/mL) and a cancer diagnosis (n = 162), b) patients with significantly elevated B_{12} without a cancer diagnosis (n = 698), c) patients with normal (197–771 pg/mL) B_{12} and a cancer diagnosis (n = 4,655), d) patients with normal B_{12} without a cancer diagnosis (n = 56,972). Flow chart shows OR calculation for all types of malignant tumors (solid and blood cancer). Patients' data with other cancer diagnosis are summarized in the Table.

RESULTS

Data of 79,524 patients were obtained with at least one B_{12} measurements during the study period. It was observed that the number of patients performing B_{12} test was increasing constantly over the study time, reflecting the increasing interest of B_{12} in the clinical diagnostics (Fig. 2). This increase is representative for the whole country, as the market share of E. Gulbis Laboratory in Latvia largely remained unchanged.

The number of 82,184 differs from 79,524, because it is not «processed», it includes all the results (inconclusive, repeated). Data analysis revealed the big number of patients with rapidly fluctuating B_{12} values within

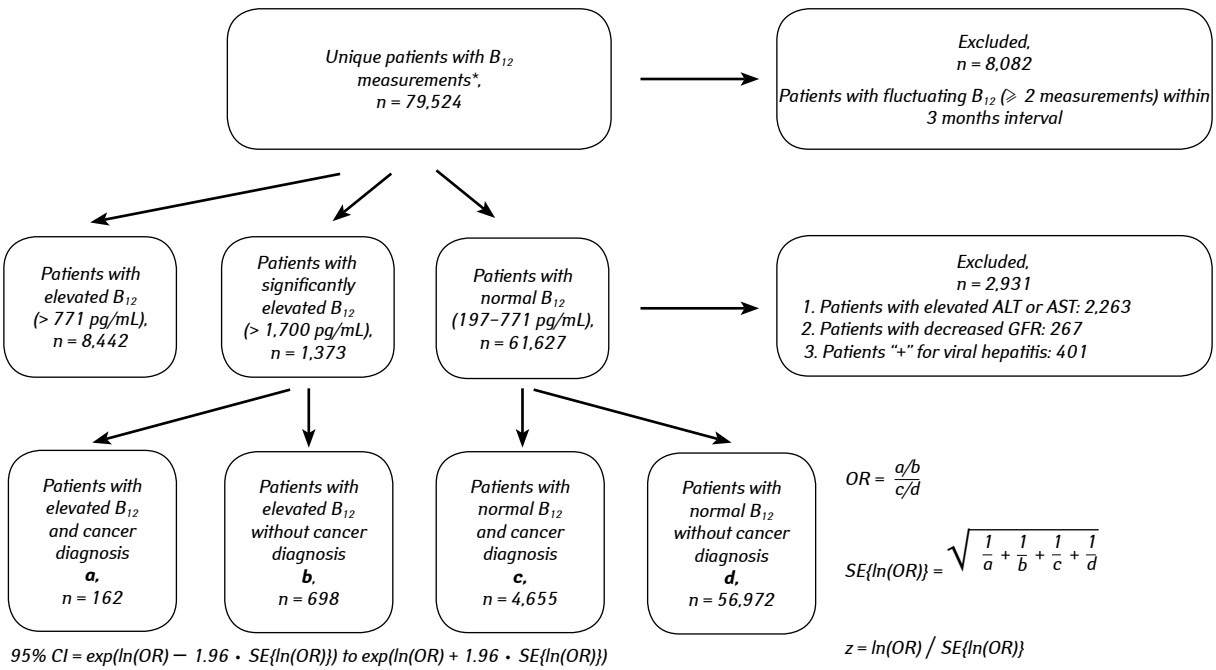

Fig. 1. Flow chart depicting selection of the patients of interest and OR calculation

Table. Multifactorial statistical analysis of B_{12} association with oncohematological disorders

Parameter	Diagnosis			
	C92	C81–C96	C00–C97	All patients
All patients with B_{12} measurements	308	1,658	7,090	79,524
Group 1 – patients with significantly elevated B_{12} > 1,700 pg/mL	63	140	320	1,373
Group 2 – patients with elevated B_{12} (771–1,700 pg/mL)	65	279	828	8,442
Patients with significantly elevated B_{12} (> 1,700 pg/mL) with normal AST, ALT, GFR, negative for viral hepatitis	35	75	162	860
Patients with normal B_{12} (197–771 pg/mL)	136	970	4,655	61,627
OR	**19.2**	**6.0**	**2.8**	
95% CI	**13.1–28.0**	**4.7–7.6**	**2.4–3.4**	
p	***p* < 0.0001**	***p* < 0.0001**	***p* < 0.0001**	

Note: C00–C97 – malignant tumors (solid and blood cancer); C92 – myeloid leukemia; C81–C96 – malignant tumors of the hematopoietic and lymphoid tissues. Diagnosis abbreviations are used according to WHO international classification of diseases (ICD-10). The Table represents total patients' database divided in three major groups: with significantly elevated B_{12} > 1,700 pg/mL, with elevated B_{12} (717–1,700 pg/mL) and with fluctuating B_{12} results.

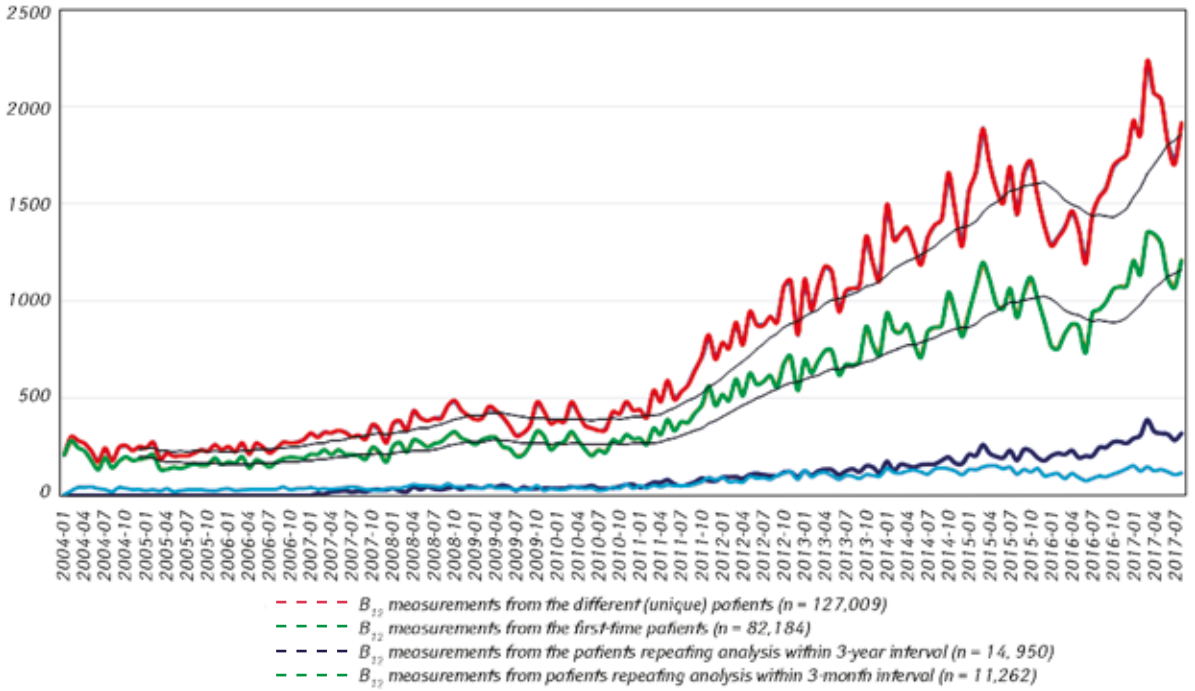

Fig. 2. Montlhy distribution of B_{12} tests during study

short period (n = 8,082); the fluctuation period between significantly elevated (> 1,700 pg/mL), normal (197–771 pg/mL) and reduced (< 197 pg/mL) B_{12} values was less than 3 month. A possible explanation of the rapid fluctuations of B_{12} level can be related to an irregular intake or therapeutic medication of supplementary B_{12}.

To check the importance of the excluded and other parameter changes, which are related to B_{12} metabolic pathway and kinetics, we performed different test results being out of normal reference range comparison to the B_{12} (Fig. 3).

Increased frequency of analysis being out of normal reference values (abnormal results) in the clinical testing are observed in hematologic, liver and kidney parameters when B_{12} is out for reference range (see Fig. 3). This observation shows importance of B_{12} parameter influencing/or resulting from other essential clinical parameters. Statistical fluctuations are seen due to a small part of patients performed multiple tests.

Abnormalities in hematologic parameters (CBC) show increased frequency when B_{12} is elevated or reduced in 30–65% of the cases (CBC, see Fig. 3). Folic acid has shown high abnormality frequency in more than 40% of the cases when B_{12} level is more than 3,000 pg/mL (FOLAT, see Fig. 3). Folic acid and B_{12} share the same metabolic pathway and abnormality of one of them influences the other.

OR was calculated to analyze whether B_{12} level could be considered as a potential diagnostic marker for oncologic diseases (see the Table). In cases when B_{12} is significantly elevated, the diagnosis of myeloid leukemia occurs 19 times more often. Oncohematological disorders occur 6 times more often, oncologic diagnosis — 2.8 times more often when B_{12} is significantly elevated. Assuming that cancer diagnosis for some reason correlates with B_{12} > 1,700 pg/ml, oncohematological diagnosis correlation is significantly stronger, i.e., at elevated levels of B_{12} in blood plasma (> 1,700 pg/ml) oncohematological diagnosis is more frequent.

DISCUSSION

In our study, we report strong association of significantly elevated B_{12} with oncohematological disorders of myeloid cell lineage origin. Our retrospective data are enough to suggest B_{12} as a potential diagnostic marker for myeloid leukemia when liver and kidney diseases are excluded.

Patients with elevated B_{12} level in the blood (> 3,000 pg/mL, reference value 119–663 pg/mL) not receiving B_{12} as a supplement to medication or food, are found quite often in our and other studies. In different studies elevated blood levels of B_{12} (> 820 pg/mL) were reported in 12–18% of hospitalized patients [8, 10, 12, 15]. In the available literature, explanations for such cases are incomplete burdening decision-making and patients' management. Increased levels of B_{12} related to a renal impairment, liver damage, and oncological processes have been reported in various sources [3, 7, 11, 16]. To understand B_{12} metabolism in general Nexo and Hoffmann-Lücke discusses the need for testing of holotranscobalamin, which is metabolically active form of B_{12} [17].

There are some studies on B_{12} usage as a prognostic marker for chronic liver disease [11] and hepatocellular carcinoma [16]. Different sources of literature associate elevation of HCs (partial fraction of B_{12}) with autoimmune lymphoproliferative disease [18] and hepatocellular carcinoma [19].

Chiche *et al.* [8] in their research including 2,064 patients report association of elevated elevated B_{12} (> 1,275 pg/mL) with blood malignancies ($p < 0.05$). Arendt *et al.* [6] analyzed large cohort of Danish population for incidence of different cancer types for cases

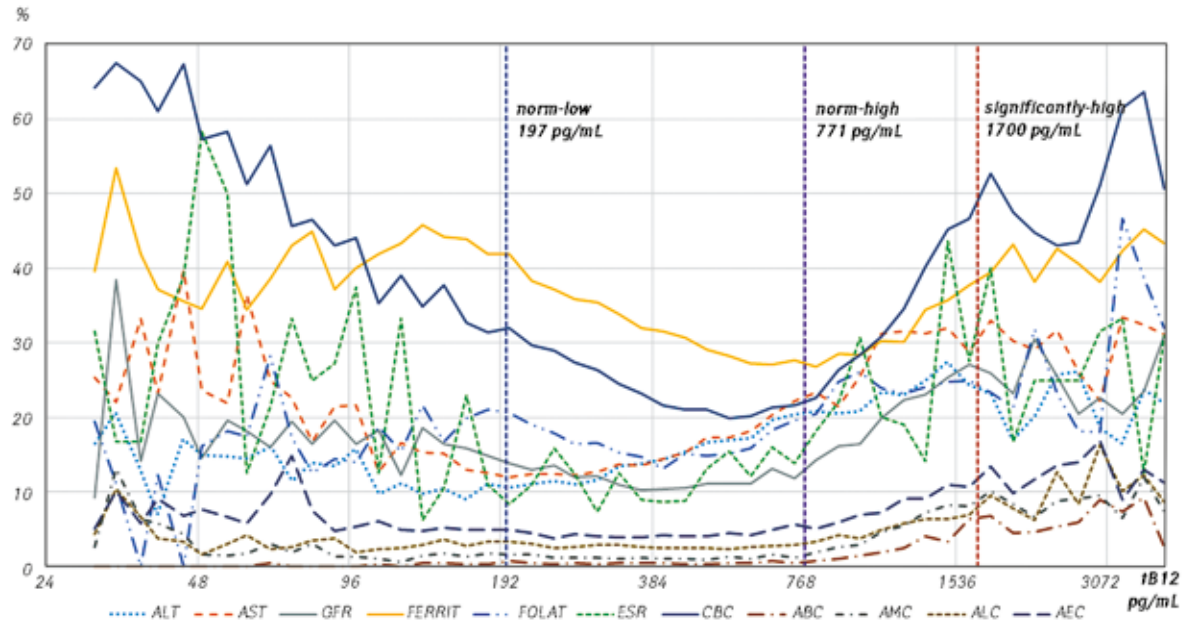

Fig. 3. Frequency of variety clinical tests being out of normal reference range in relation to the B_{12} values. Y-axis depicts frequency of different clinical analysis results being out of (lower and higher) normal reference values (%), X-axis shows B_{12} measurement units (pg/mL). Vertical lines indicate reference ranges — lowest normal (norm-low), highest normal (norm-high) and significantly high defined in this study. All clinical tests for each patient were performed in the 3-month interval of B_{12} measurement. GFR — glomerular filtration rate, FERRIT — ferritin, FOLAT — folic acid, ESR — erythrocyte sedimentation rate, CBC — complete blood count, ABC — absolute count of basophils, AMC — absolute count of monocytes, ALC — absolute count of lymphocytes, AEC — absolute count of eosinophils

with elevated B_{12} and found strong association of developing cancers of hematological origin within one year interval from elevation of B_{12} > 1,084 pg/mL (converted, originally in article 800 pmol/L) — standardized incidence ratio (SIR) 24.14 (95% CI 19.51–29.54), with overall oncohematological disease SIR of 4.52 (95% CI 4.23–4.82).

If we manipulate with these data, as SIR of elevated B_{12} division with SIR of disease incidence in overall population — 24.14/4.52 we get 5.3, what is comparable to our OR of 6.0. We accent that we analyzed overall population representative data, and excluded a lot of unrelated to cancer cases. We also could lose part of data, due to toxic effect of chemotherapy performed in oncohematological patients (exclusion criteria — elevation of ALT or AST, and decrease of GFR).

Our results including 79,524 patients confirm potential of B_{12} level as a diagnostic or prognostic marker for oncohematological disorders. Significantly elevated B_{12} level association with oncohematological diagnosis are shown, especially with myeloid leukemia. Further studies are necessary to understand B_{12} elevation mechanisms in oncohematological patients. Theoretically, elevation of B_{12} could be linked to HCs release by the granules of myeloid lineage cells in cases of myeloid leukemia, as it was discussed in multiple studies.

Investigations on elevated B_{12} in association with myeloid leukemia firstly appeared in literature in the middle of last century [20, 21]. Importance of B_{12} use as diagnostic tool for cancer has been actualized during the past ten years, but there are still some questions.

The number of patients with stable elevated B_{12} level (n = 8,082) is comparable to the number of patients with rapidly fluctuating B_{12} levels (n = 8,442). We hypothesized reason for such cases could be supplementary intake and B_{12} medication. Traditionally vitamin supplements contain B_{12} at much more than 100% of recommended day intake. Studies for B_{12} elevation in blood due to supplementary intake are required.

It is unclear, when B_{12} level increases in oncohematological patients — before or after CBC changes. In order to understand possible correlations between vitamin B_{12} level and oncohematological patients, in-depth analysis of patient's medical history and other results has to be performed in the next study phase.

We have identified an important group of primary diagnosed chronic myeloid leukemia patients for whom further investigations have to be continued in order to determine what kind of B_{12} form is elevated. For diagnostic purposes it is important to clarify whether B_{12} itself or any of its forms could serve as diagnostic marker of myeloid leukemias. It would be beneficial to address a correlation between fluctuations of B_{12} in response to the therapies of myeloid leukemia and their role in hepatotoxic effect.

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