



Research Article

Investigation of atherogenic indices associated with cardiometabolic risk in patients with low vitamin B12 levels

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Abstract

Objectives: This study aimed to investigate novel composite lipid indices, including the non-High Density Cholesterol/High Density Cholesterol ratio, Lipoprotein Combined Index, and Triglyceride-Glucose Index in adults with low vitamin B12 levels, alongside established markers such as Castelli Risk Index I, Castelli Risk Index II, and the Atherogenic Index of Plasma. By examining the relationship between vitamin B12 status and these indices, it aimed to clarify the role of low vitamin B12 levels in cardiometabolic risk.

Methods: This retrospective study included 400 participants. Glucose and lipid levels were measured using fasting serum samples. Composite lipid parameter values were calculated according to methodologies described in the literature. Results were compared between low vitamin B12 levels and control groups.

Results: In this study, low vitamin B12 levels were found to be associated with low high-density lipoprotein cholesterol ($p=0.035$), high atherogenic plasma index ($p=0.048$), and high triglyceride-glucose index ($p=0.043$). In contrast, no significant differences were observed between the groups in terms of Castelli Risk Index I, Castelli Risk Index II, non-High Density Cholesterol/High Density Cholesterol ratio, or Lipoprotein Combined Index. The area under the ROC curve was found to be \pm standard error of 0.557 ± 0.029 [95% CI: 0.501–0.613] ($p=0.048$) for the Atherogenic Plasma Index and \pm standard error of 0.557 ± 0.029 [95% CI: 0.500–0.613] ($p=0.049$) for the Triglyceride-Glucose Index.

Conclusion: In this study, B12 deficiency was associated with negative lipid indices. It is hypothesized that regular assessment of B12 levels and appropriate correction of deficiencies may help reduce cardiometabolic risk. Further prospective studies with comprehensive biomarkers are needed to clarify causality and clinical benefit.

Keywords: Atherogenic index of plasma, cardiometabolic risk, castelli risk index I, castelli risk index II, lipoprotein combined index, non-high density cholesterol/high density cholesterol ratio, triglyceride-glucose index, vitamin B12

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Vitamin B12 (cobalamin) is a water-soluble vitamin essential for hematopoietic and neurological function. Vitamin B12 (B12) deficiency primarily arises from insufficient dietary intake in vegetarians or vegans, older adults, pregnant women, and people with chronic alcohol consumption, as well as from decreased intestinal absorption due to conditions such as atrophic gastritis, malabsorption syndromes, or gastrointestinal surgeries. Certain medications, such as antacids and metformin, can also contribute to this deficiency [1]. The severity and clinical manifestations of low B12

levels depend on both its extent and duration. The hematologic, bone marrow, and nervous systems are the most affected systems. Megaloblastic anemia develops due to defective thymidine and consequently DNA synthesis in rapidly proliferating cells. Impaired myelin formation and repair can cause neurological complications, potentially leading to diverse symptoms such as cognitive decline and psychosis. Diagnosis is established through clinical evaluation supported by laboratory analyses that provide reliable predictive markers [2]. Epidemiological studies have reported associations

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between low B12 levels and obesity, hypertension, type 2 diabetes, and metabolic syndrome [3]. Beyond hematologic and neurological consequences, emerging evidence links B12 deficiency to cardiometabolic disorders through its impact on lipid metabolism [4]. The cellular role of vitamin B12 in lipogenesis is as follows: B12 deficiency reduces the production of methionine and *s*-adenosylmethionine (SAM) in the cell. This leads to an increase in homocysteine (hyperhomocysteinemia) and the accumulation of SAH. Increased *s*-adenosyl homocysteine (SAH) and decreased SAM reduce DNA methylation. This alters gene expression. Furthermore, low B12 levels impair methylmalonyl-CoA mutase (MCM) activity, leading to the accumulation of methylmalonic acid (MMA). Ultimately, this inhibits the beta-oxidation of fatty acids [3]. Dyslipidemia is a major contributor to atherosclerosis and cardiovascular disease [3]. Traditionally, an atherogenic lipid profile is defined by elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) levels, accompanied by decreased high-density lipoprotein cholesterol (HDL-C) [5]. Recently, new composite atherogenic indices that integrate multiple lipid parameters to better predict cardiovascular and metabolic risk have emerged [6, 7]. The Castelli Risk Index-I (CRI-I: Total Cholesterol/HDL-C ratio), Castelli Risk Index-II (CRI-II: LDL-C/HDL-C ratio), Atherogenic Index of Plasma (AIP: $\log_{10}[\text{TG}/\text{HDL-C}]$), and Lipoprotein Combined Index (LCI: Total Cholesterol \times TG \times LDL-C/HDL-C) have demonstrated strong associations with various cardiometabolic states [8]. Compared with traditional single lipid measurements, these indices provide a more comprehensive reflection of the balance between atherogenic and antiatherogenic lipoproteins [9]. NHHR (the ratio of non-high-density lipoprotein cholesterol (non-HDL-C) to HDL-C) is a novel lipid ratio introduced in 2022 following a large-scale longitudinal study involving 15,000 individuals conducted by Chinese researchers [10]. This ratio has demonstrated considerable potential in predicting the risk of various diseases, such as coronary artery disease, diabetes mellitus, abdominal aortic aneurysm, and carotid atherosclerosis. Compared with non-HDL-C alone, NHHR provides a more comprehensive and superior measure of atherosclerosis by incorporating both atherogenic (non-HDL-C) and protective (HDL-C) lipid components. Thus, it represents a novel composite lipid marker for atherosclerosis [11]. CRI-I, CRI-II, and AIP are ratios that can be easily calculated from a standard lipid profile. These ratios are independent risk markers for cardiovascular disease and are known to be elevated in patients with angiographically verified coronary artery disease [12]. Furthermore, novel markers such as lipoprotein combined index (LCI) have shown potential utility in detecting early atherosclerotic changes and predicting metabolic disturbances [9]. The Triglyceride-Glucose index (TyG) has also been identified as a strong predictor of cardiometabolic risk factors, vascular abnormalities, and mortality [13].

This study aimed to investigate novel composite lipid indices, including NHHR, LCI, and TyG, in adults with low B12

levels, alongside established markers such as CRI-I, CRI-II, and AIP. By examining the relationship between B12 status and these indices, it aimed to clarify the role of low B12 levels in cardiometabolic risk.

Materials and Methods

The current study was designed as a retrospective study. The study was approved by the Bursa City Hospital Scientific Research Ethics Committee with decision number 2025-19/3 dated 01.10.2025. We also declared that this study was conducted in accordance with the regulations set forth in the World Medical Association Scientific Research and Ethics Committee and the Helsinki Declaration. Between April 30, 2025, and October 31, 2025, the biochemical data of patients with low B12 levels were screened. Four hundred participants were included in the study. The patient group consisted of 200 people: 134 (67%) women and 66 (33%) men with low B12 levels. The control group consisted of 200 people: 142 (71%) women and 58 (29%) men with B12 levels within the reference range. Patients diagnosed with liver failure, hepatitis, elevated liver enzymes, fatty liver, renal failure, thyroid dysfunction, use of B12 supplements, diabetes mellitus, those using gastroprotective agents, pregnancy, hospitalized patients, atherosclerotic heart disease, malignancy, and use of medications causing low B12 levels (phenytoin, metformin, methotrexate) were excluded. Patients with folic acid levels within the reference ranges were included in the study. All data, including age, gender, ICD-10 diagnostic codes (International Statistical Classification of Diseases and Health Problems), and treatment protocols, were obtained from records in the hospital information management system. Glucose and lipid levels were analyzed in fasting serum samples using the Cobas 8000 Modular Analysis System (Cobas, Mannheim, Germany), an automated biochemical analyzer, while serum B12 levels were analyzed using the electrochemical luminescence immunoassay method on Cobas 8000 immunoassays (Roche Diagnostics, Mannheim, Germany). The original kits (Roche Diagnostics, Mannheim, Germany) were used for this study. The quality assurance procedures included periodic instrument calibration, adherence to standard operating protocols, and participation in external quality assessment schemes. Serum B12 levels were used to assess B12 status. Methylmalonic acid or total homocysteine levels, which are markers of tissue-level low B12 levels, were not included. Serum B12 levels had previously been shown to be valid indicators of B12 status in both individual and epidemiological settings [14]. In this study, values below 197 ng/L were defined as low B12 levels.

The calculated indices were as follows: CRI-I, CRI-II, AIP, NHHR, LCI, and TyG. The formulas used for these calculations followed previously published methodologies [9].

$\text{CRI-I} = \text{TC (mg/dL)} / \text{HDL-C (mg/dL)}$

$\text{CRI-II} = \text{LDL-C (mg/dL)} / \text{HDL-C (mg/dL)}$

$\text{AIP} = \log_{10}[\text{TG (mg/dL)} / \text{HDL-C (mg/dL)}]$

$$\text{NHHR} = \frac{(\text{TC (mg/dL)} - \text{HDL-C (mg/dL)})}{\text{HDL-C (mg/dL)}}$$

$$\text{LCI} = \frac{\text{TC (mg/dL)} \times \text{TG (mg/dL)} \times \text{LDL-C (mg/dL)}}{\text{HDL-C (mg/dL)}}$$

$$\text{TyG} = \ln \left[\frac{\text{TG (mg/dL)} \times \text{fasting glucose (mg/dL)}}{2} \right] \text{ [15].}$$

The outcomes were analyzed through a comparative assessment between the B12 deficient group and the control group.

Statistical analysis

Sample size calculation: Based on a small effect size (effect size $d=0.25$), assuming an alpha level (Type I error) of 0.05 and a power of 0.80 ($1 - \beta$), it was determined that a total of 398 individuals (199 per group) would be sufficient for the control and patient groups in the study planned to test the null hypothesis. The G*Power Statistical Program, version 3.1.9.4 (Universität Düsseldorf, Germany), was used for analyses. Continuous variables were expressed as mean \pm standard deviation, and categorical data were expressed as numbers and percentages. Normality analyses were performed using the Kolmogorov-Smirnov Goodness of Fit Test in between-group analyses of continuous variables. Student's T Test was used in between-group analyses of data conforming to a normal distribution, and the Mann-Whitney U Test was used in analyses of those not conforming to a normal distribution. Comparisons of categorical data were made using the Chi-square Test. ROC curve analysis was used to determine cut-off values for AIP and TyG indices in low B12 levels patients. In the presence of significant cut-off values, sensitivity, specificity, and positive and negative predictive values were calculated. When determining the cut-off values, the highest point of the Youden Index ($J = \text{Sensitivity} + \text{Specificity} - 1$), which maximizes the balance between

sensitivity and specificity, was used as the basis. A Type 1 error level of less than 5% was interpreted as indicating statistical significance of the test's diagnostic value. Since the indices tested in the study (AIP and TyG) are related biochemical parameters representing similar metabolic pathways, and each was tested as a pre-defined independent hypothesis, the standard alpha level (0.05) was maintained. Analyses were performed using IBM SPSS version 27.0 (IBM Corporation, Armonk, NY, USA), and $p < 0.05$ was considered statistically significant.

Results

No statistically significant difference was found between the groups in terms of age and sex ($p=0.277$ and $p=0.387$, respectively) (Table 1).

Serum HDL-C and B12 levels were significantly lower in the patient group compared with controls ($p=0.035$ and $p < 0.001$, respectively). No significant differences were observed for TC, TG, or LDL-C (Table 2). The AIP and TyG were significantly higher in patients with low B12 levels than in the control group ($p=0.048$ and $p=0.043$, respectively). In contrast, no significant differences were observed between the groups for the CRI-I, CRI-II, NHHR, or LCI (Table 3).

ROC analysis: For the AIP, the cut-off value was ≥ 0.25 , sensitivity was 65.0% [95% CI: 58.16–71.27], specificity was 45.5% [95% CI: 38.75–52.42], PPV was 54.4% [95% CI: 48.06–60.59], NPV was 56.5% [95% CI: 48.80–63.94], and area under the ROC curve \pm standard error was 0.557 ± 0.029 [95% CI: 0.501–0.613] ($p=0.048$).

Table 1. Comparison of groups in terms of age and sex characteristics

	Control group (n=200)	Patient group (n=200)	p
Age (years) (median (min-max))	37 (18–72)	39 (18–76)	0.277
Sex (n, %)			
Female	142 (71.0)	134 (67.0)	0.387
Male	58 (29.0)	66 (33.0)	

Min: Minimum; Max: Maximum.

Table 2. Comparison of groups in terms of some blood parameters (median, min-max)

	Control group (n=200)	Patient group (n=200)	p
TC (mg/dL)	183 (100–312)	182 (96–285)	0.914
TG (mg/dL)	96 (26–448)	106 (31–595)	0.121
HDL-C (mg/dL)	49 (23–90)	46 (25–131)	0.035
LDL-C (mg/dL)	112 (40–231)	111 (46–209)	0.855
Vitamin B12 (ng/L)	392 (197–764)	171.5 (103–196)	<0.001

Bold characters indicate statistical significance ($p < 0.05$). TC: Total cholesterol; TG: Triglyceride; HDL-C: High-density lipoprotein; LDL-C: Low-density lipoprotein.

Table 3. Comparison of groups in terms of atherogenic index profile parameters (median, min-max)

	Control group (n=200)	Patient group (n=200)	p
CRI-I	3.75 (1.87–9.14)	3.87 (1.69–8.46)	0.167
CRI-II	2.27 (0.7–6.6)	2.38 (0.92–5.45)	0.261
AIP	0.28 (-0.36–1.19)	0.34 (-0.36–1.32)	0.048
NHHR	2.75 (0.87–8.14)	2.87 (0.69–7.46)	0.167
LCI	40098 (2281–646819)	45684 (4180–641875)	0.192
TyG (Mean \pm SD)	8.34 \pm 0.49	8.45 \pm 0.53	0.043

Bold characters indicate statistical significance ($p < 0.05$). CRI-I: Castelli risk index I; CRI-II: Castelli risk index II; AIP: Atherogenic index of plasma; LCI: Lipoprotein combined index; NHHR: nonHDL/HDL ratio; TyG: Triglyceride glucose index; SD: Standard deviation.

Table 4. ROC analysis results and some cut-off values for AIP and TyG values in patients with low B12 levels

	Diagnostic test				ROC curve			
	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC	CI 95%	p
AIP	≥0.25	65.0 <i>[58.16–71.27]</i>	45.5 <i>[38.75–52.42]</i>	54.4 <i>[48.06–60.59]</i>	56.5 <i>[48.80–63.94]</i>	0.557±0.029	0.501–0.613	0.048
TyG	≥8.44	53.0 <i>[46.09–59.80]</i>	61.1 <i>[54.09–67.49]</i>	57.9 <i>[50.38–64.52]</i>	56.3 <i>[49.81–62.92]</i>	0.557±0.029	0.500–0.613	0.049

Bold characters indicate statistical significance ($p < 0.05$). Italic characters indicate the confidence interval for the group. AUC: Area under the curve; CI: Confidence interval; NPV: Negative predictive value; PPV: Positive predictive value; IP: Atherogenic Index of Plasma; TyG: Triglyceride-Glucose index.

For the TyG, the cut-off value was ≥ 8.44 , sensitivity was 53.0% [95% CI: 46.09–59.80], specificity was 61.1% [95% CI: 54.09–67.49], PPV was 57.9% [95% CI: 50.38–64.52], NPV was 56.3% [95% CI: 49.81–62.92], and area under the ROC curve \pm standard error was 0.557 ± 0.029 [95% CI: 0.500–0.613] ($p=0.049$) (Table 4 and Fig. 1).

Discussion

Cardiovascular diseases remain the leading cause of morbidity and mortality worldwide. Atherogenic dyslipidemia, typically characterized by elevated TG and LDL-C levels, together with reduced HDL-C, plays a central role in the pathogenesis of atherosclerosis, the key underlying mechanism of cardiovascular disease [16, 17]. Dyslipidemia is recognized as an independent risk factor for atherosclerotic cardiovascular conditions. Conventional lipid monitoring indicators employed in clinical practice, including LDL-C, demonstrate significant limitations [18].

Previous studies examining the association between B12 status and lipid metabolism have yielded inconsistent results [19]. In this context, composite lipid-derived indices are emerging as valuable alternatives, as they integrate multiple metabolic risk factors and better reflect the multifactorial nature of atherosclerosis. These indices, by encompassing broader lipid interactions and physiological processes, can offer greater predictive and diagnostic insight than isolated lipid parameters. Building upon both national and international data, four lipid-based indices have shown promising clinical potential: AIP, NHHR, the Apolipoprotein B/A1 ratio, and LCI [18]. In conclusion, the current study included not only traditional lipid measures but also these composite indices (specifically CRI-I, CRI-II, LCI, NHHR, and TyG) that have not previously been evaluated in adults with low B12 levels. AIP was also analyzed to provide a comprehensive assessment of atherogenicity in this population.

Previous research on the relationship between B12 levels and lipid metabolism has yielded diverse and sometimes conflicting results. Al-Musharaf et al. [14] conducted a study among young women aged 19–30 years. Participants with higher serum B12 concentrations exhibited lower TC, LDL-C, and TG levels, and reduced ratios of CRI-I, CRI-II, and AIP compared with those who had lower B12 levels. No significant difference was observed in HDL-C between groups. Although multiple

logistic regression showed an inverse association between serum B12 and dyslipidemia, it lost significance after adjustment for confounders. In contrast, this study was conducted on a larger adult population aged 18–76 years (Table 1). However, it found no significant difference in TC, LDL-C, CRI-I, CRI-II, or TG levels between the B12-deficient and control groups (Table 2). But HDL-C levels were significantly lower in the B12-deficient group ($p=0.035$), while AIP was significantly higher ($p=0.048$) (Table 3), indicating a potentially unfavorable lipid pattern associated with low B12 levels. Similarly, Kim et al. [20] reported no correlation between serum B12 concentrations and dyslipidemia or atherosclerotic events in a prospective 12-year follow-up of 421 healthy Korean adults. Their findings align with ours in that TC, LDL-C, CRI-I, CRI-II, and TG did not differ significantly between groups, but HDL-C was lower in individuals with low B12 levels ($p=0.035$).

Al-Qusous et al. [21] studied patients with hyperlipidemia and found an inverse relationship between B12 levels and

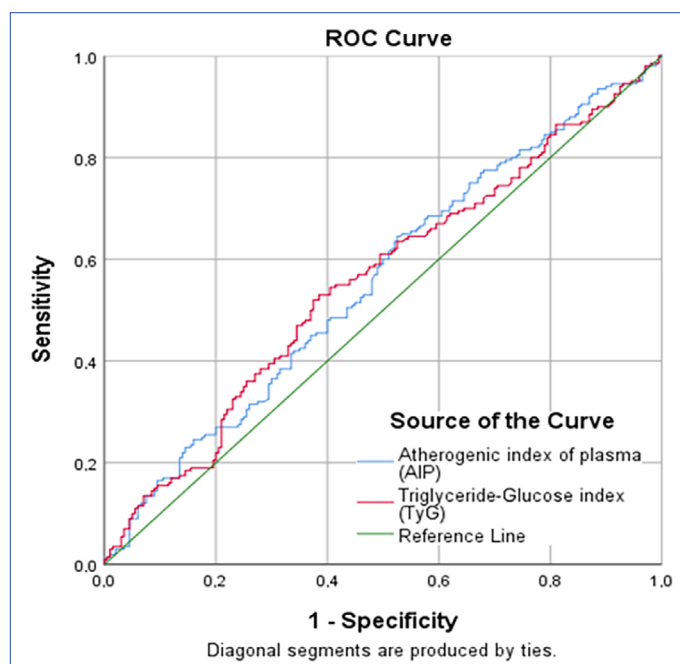


Figure 1. ROC curve graph for Atherogenic Index of Plasma (AIP) and Triglyceride Glucose Index (TyG) values in patients with low vitamin B12 levels.

ROC: Receiver operating characteristic.

TC in the control group. As B12 decreased, TC, LDL-C, and the TC/HDL-C ratio increased; however, only 3.3% of hyperlipidemic patients were actually B12 deficient. In this study, as B12 decreased, TC, LDL-C, and TC/HDL-C ratios did not change compared to the control group. Aureli et al. [22], in a cohort of children, adolescents, and young adults, found that serum lipid profiles (TC, HDL-C, LDL-C, and TG) were not influenced by cobalamin status. Our results showed no significant differences in TC, LDL-C, or TG between patients with low B12 levels and controls; yet HDL-C was notably lower in those with low B12 levels ($p=0.035$).

Devi [19] examined the link between B12 and AIP in the general population, and reported that low B12 levels were correlated with a poorer lipid profile, higher AIP, and increased blood pressure. Emphasized the potential role of B12 in cardiovascular protection, showing that as B12 levels declined, TC, TG, LDL-C, and AIP increased, while HDL-C decreased [19]. This study observed higher AIP values ($p=0.045$) and lower HDL-C levels ($p=0.035$) in the group with B12 deficiency, while no changes were observed in TC, TG, and LDL-C levels (Table 3). Another population-based study demonstrated negative correlations between B12 and TG ($r=-0.161$, $p<0.05$), TC ($r=-0.169$, $p<0.05$), and AIP ($r=-0.15$, $p<0.05$), suggesting that low B12 levels contribute to increased cardiovascular risk and unfavorable lipid parameters [23]. Consistently, this study also demonstrated a significant increase in AIP in individuals with B12 deficiency ($p=0.048$). However, there were no changes in TG and TC.

Aktaş and Pençe [15] found a negative correlation between B12 levels and both the TG/HDL-C ratio (AIP) and the TyG among obese patients with insulin resistance. Similarly, our results revealed that AIP and TyG were significantly higher in the low B12 levels group ($p=0.048$ and $p=0.043$, respectively). Sirivarasai et al. [24] observed significant associations between plasma B12, folate, and homocysteine levels in individuals over 65 years with hyperhomocysteinemia. They reported that elevated homocysteine correlated with arterial stiffness and higher Lipid Accumulation Product (LAP), TyG, and Visceral Adiposity Index (VAI).

Extensive literature has highlighted the significant predictive value of NHHR for established cardiovascular risk factors such as diabetes, hypertension, non-alcoholic fatty liver disease (NAFLD), and obstructive sleep apnea hypopnea syndrome [25]. In this study, NHHR, which has not been previously studied in the literature at low B12 levels, was found not to show a significant difference compared to the control group. Similarly, there are previous studies evaluating LCI as a cardiovascular risk predictor and prediabetes risk predictor in patients with acute coronary syndrome [9]. However, LCI, which has not been previously studied at low B12 levels, did not show a significant difference compared to the control group in this study.

In this study, low B12 levels were associated with low HDL-C ($p=0.035$), high AIP ($p=0.048$), and TyG ($p=0.043$). The ROC analysis for AIP demonstrated a statistically significant as-

sociation with the studied outcome ($p=0.048$). However, its overall discriminative performance was limited. The area under the curve (AUC) was 0.557, indicating a weak ability to distinguish between affected and non-affected individuals, only marginally better than chance. Although the sensitivity was relatively moderate (65.0%), suggesting that AIP could identify a proportion of true positive cases, the specificity was notably low (45.5%), reflecting a high rate of false-positive results. Furthermore, both the positive predictive value (54.4%) and negative predictive value (56.5%) were close to 50%, indicating limited clinical utility in predicting the presence or absence of the condition. Moreover, the 95% confidence interval (0.501–0.613) included the threshold for no discrimination. Taken together, these findings suggest that, despite achieving statistical significance, AIP has poor diagnostic accuracy and is insufficient as a standalone biomarker.

In the ROC analysis conducted to evaluate the diagnostic performance of the TyG, statistically significant outcome ($p=0.049$). The area under the curve (AUC=0.557) indicates that this parameter has limited power to discriminate the condition under investigation (Table 4 and Fig. 1). The low sensitivity (53.0%) and specificity (61.1%) values reveal that the TyG does not perform adequately in either identifying sick individuals or excluding healthy individuals. Similarly, the positive predictive value (57.9%) and negative predictive value (56.3%) results support the limited use of the test as a reliable predictive tool in clinical practice. Furthermore, the 95% confidence interval (0.500–0.613) includes the threshold of no discrimination, suggesting that the predictive capability of the parameter may be unreliable. Although the obtained p value is statistically significant, the evaluation together with the borderline significance and low AUC value indicates that the TyG is not a strong clinically distinctive biomarker. These findings suggest that the parameter should be interpreted with caution and preferably used in combination with other clinical or biochemical indicators.

In this study, low B12 levels were associated with lower HDL-C and higher AIP and TyG indices, suggesting an unfavorable lipid profile. However, ROC analyses demonstrated limited discriminatory power, and other indices (CRI-I, CRI-II, NHHR, LCI) did not differ significantly. These findings highlight a possible link between low B12 levels and cardiometabolic risk, but further prospective studies with comprehensive biomarkers are needed to clarify causality and clinical utility.

Limitations

It must be acknowledged that the study has some limitations. Firstly, the sample size is relatively small. Secondly, the study did not include methylmalonic acid or total homocysteine levels, which are markers of low B12 levels at the tissue level; only serum B12 levels were used as an indicator of deficiency. Since it is a retrospective study, the patients' body mass index (BMI) values were not recorded in the system and therefore could not be used in the study. Consequently, the effects of obesity on blood profiles were disregarded. Fur-

thermore, direct cardiovascular clinical outcomes were not evaluated in the current study. Future research, taking this into account, will be beneficial in determining the net effects of low B12 levels on the cardiovascular system.

Conclusion

In this study, B12 deficiency was associated with negative lipid indices. It is hypothesized that regular assessment of B12 levels and appropriate correction of deficiencies may help reduce cardiometabolic risk.

Disclosures

Ethics Committee Approval: The study was approved by the Bursa City Hospital Scientific Research Ethics Committee (no: 2025-19/3, date: 01/10/2025).

Informed Consent: Written informed consent was obtained.

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