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ORIGINAL RESEARCH

Associations Between Anorexia Nervosa Severity, Liver Dysfunction, and Cobalamin Serum Concentration

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Background: Anorexia nervosa (AN) is a severe psychiatric disorder characterized by extreme malnutrition, leading to multiple organ dysfunctions, including liver impairment. While AST and ALT are standard markers for liver dysfunction, recent reports suggest that elevated cobalamin (vitamin B12) levels are frequently observed in AN patients. However, the association between cobalamin levels and liver dysfunction remains unclear. This study aims to investigate the relationship between cobalamin levels, liver enzyme abnormalities, and body mass index (BMI) in AN patients.

Methods: This retrospective observational study included patients diagnosed with AN who visited the outpatient department or were hospitalized at Yokohama City University Medical Center between April 2012 and March 2021. Patients with alcohol use disorder, cancer, or vitamin supplementation were excluded. AST, ALT, and cobalamin levels were measured during routine blood tests, and BMI was calculated based on clinical records.

Results: BMI was significantly negatively correlated with AST ($r = -0.4703$, $p < 0.0001$) and ALT ($r = -0.3743$, $p < 0.0001$). Patients with cobalamin levels >4000 pg/mL exhibited significantly lower BMI compared to those with lower cobalamin levels. Additionally, higher cobalamin levels were associated with increased AST and ALT levels.

Conclusion: Elevated cobalamin levels, alongside AST and ALT, may serve as a possible supportive indicator of liver dysfunction and the severity of malnutrition in AN patients. Further research is needed to clarify the underlying mechanisms and clinical implications for nutritional assessment and liver dysfunction evaluation.

Plain Language Summary: Anorexia nervosa (AN) is a serious eating disorder that leads to severe weight loss and various health problems, including liver dysfunction. Doctors usually assess liver health by measuring liver enzymes. However, recent studies have shown that levels of cobalamin (vitamin B12) are often unusually high in people with AN. We analyzed medical records of patients with AN treated at our hospital, focusing on their body mass index (BMI), liver enzymes, and cobalamin levels. In this study, we examined the relationship between AN severity, liver dysfunction, and cobalamin levels. Elevated cobalamin levels were also linked to higher liver enzyme levels, suggesting a possible connection between liver function and cobalamin metabolism in AN. These findings suggest that measuring cobalamin, in addition to standard liver enzymes, may provide useful information about both liver function and nutritional status in people with AN. The reasons behind high cobalamin levels are not yet fully understood, but future research may help explain this phenomenon and clarify its clinical significance.

Keywords: anorexia nervosa, cobalamin, aspartate aminotransferase, alanine aminotransferase, body mass index

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Background

Anorexia nervosa (AN) is a serious psychiatric disorder that predominantly affects young females. It is characterized by self-imposed starvation, a distorted body image, and severe underweight. This disorder often leads to profound malnutrition, which contributes to various complications, including liver dysfunction. The causes of liver dysfunction in AN are not fully understood. However, mechanisms such as autophagy and hypoperfusion have been suggested as potential contributing factors.[1–3] Starvation-induced hepatic autophagy and mitochondrial dysfunction have been described, potentially increasing oxidative stress and hepatocyte injury.[4,5] Severe liver dysfunction can worsen malnutrition and further complicate treatment outcomes, necessitating careful management.[6–9] Recent case–control studies have also demonstrated oxidative stress and impaired hepatic energy metabolism in patients with severe AN.[10] Liver function in AN patients is typically evaluated using liver enzymes such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT).[11] Interestingly, one paradoxical finding in AN is the occurrence of elevated cobalamin (vitamin B12) levels, particularly in patients with extreme malnutrition. Recent studies have indicated that excessive cobalamin levels are more prevalent than deficiency in AN patients.[12,13] Furthermore, recent clinical data suggest that elevated cobalamin may be associated with increased AST and ALT as well as lower BMI in AN, raising the possibility that it reflects hepatic dysfunction in this context.[14,15] However, the direct association between elevated cobalamin and liver dysfunction has not been fully elucidated. This phenomenon raises important questions about the pathophysiology of liver dysfunction in such cases. Existing literature has primarily focused on changes in liver enzyme and cobalamin levels during the weight restoration phase of AN.[11] Case reports and experimental studies have described starvation-induced hepatic autophagy and mitochondrial structural changes, which may contribute to oxidative stress and hepatocyte injury.[4,5,16] However, little is known about how these markers behave across a broader spectrum of malnutrition severity, especially in patients with persistently low body mass index (BMI). To our knowledge, few studies have simultaneously examined BMI, liver enzyme levels, and cobalamin in AN patients. This integrative approach offers a complementary perspective, aiming to provide a broader understanding of metabolic disturbances in severe malnutrition. Our study is exploratory in nature and seeks to provide preliminary insights into the associations between BMI, liver enzyme levels, and cobalamin levels across different stages of malnutrition. Specifically, we aim to determine whether elevated cobalamin levels can serve as a potential marker for liver dysfunction in severely malnourished patients. Insights from this study could refine clinical assessments and facilitate the early detection of liver dysfunction, ultimately improving treatment strategies for this vulnerable population.

Methods

Patients

This study is a retrospective observational study including patients who visited the outpatient department or were hospitalized in the Department of Psychiatry at Yokohama City University Medical Center between April 2012 and March 2021. The center is a general hospital with multiple departments, including specialized psychiatric services. Patients diagnosed with anorexia nervosa (AN) based on DSM-IV or DSM-V criteria, as confirmed by a psychiatrist, were included. Since all included patients had a BMI below 17.5, their diagnosis also aligned with the ICD-10 criteria. Eligible patients underwent routine blood tests during regular care, which included measurements of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and cobalamin levels. Patients with a history of alcohol use disorder or cancer, as well as those currently taking vitamin supplements, were excluded. Height and weight were usually measured on the same day as the blood tests; if not available, the closest recorded measurement was used.

Measurements

Laboratory tests for AST, ALT, and cobalamin levels were conducted using standard clinical procedures. AST and ALT levels were measured using the LABOSPECT T008α(Hitachi). Cobalamin levels were measured using the cobas®8000 (Roche), which provides precise quantification up to 1500 pg/mL. Due to assay limitations, values above this threshold were categorized as either "1500–4000 pg/mL" or ">4000 pg/mL" without exact numerical values. These predefined categories were used in statistical analyses. BMI was classified into three categories to reflect the severity of malnutrition: BMI below 13 was considered severely underweight, BMI between 13 and 15 moderately underweight, and BMI

between 15 and 17.5 mildly underweight. Liver enzyme levels were categorized as follows: normal (AST ≤ 40 U/L, ALT ≤ 45 U/L), moderately elevated (AST > 40–120 U/L, ALT > 45–135 U/L), and severely elevated (AST > 120 U/L, ALT > 135 U/L). These thresholds were adapted from previous studies on liver dysfunction in patients with anorexia nervosa.[6] While reference ranges for AST and ALT may vary depending on assay methods, many clinical laboratories define normal AST as approximately 40 U/L and ALT as 45 U/L.[9,17]

Statistical Analysis

The relationships between BMI, AST, ALT, and cobalamin levels were analyzed using several statistical methods. Spearman's rank correlation coefficient was employed to assess the relationship between BMI and liver enzyme levels (AST and ALT). Differences in BMI across cobalamin level groups were evaluated using the Wilcoxon rank-sum test. Spearman's rank correlation coefficient was used to explore potential correlations between liver enzyme (AST and ALT) elevations and varying cobalamin levels. BMI, AST, and ALT were further classified into three groups based on the categorized cobalamin levels for stratified analysis. Analysis of covariance (ANCOVA) was conducted with BMI as the dependent variable and age, cobalamin levels, AST, and ALT as covariates to control for potential confounding effects. A p-value of <0.05 was considered statistically significant. All analyses were performed using JMP Pro 17 software to ensure accuracy and reliability.

Ethical Considerations

This study was approved by the Institutional Review Board of Yokohama City University Medical Center (Approval No. B210200004) and was conducted in accordance with the principles outlined in the Declaration of Helsinki. Given the retrospective nature of the study and the use of anonymized data, the Ethics Committee approved the use of an opt-out approach in place of written informed consent. Study details were publicly disclosed on the institution's website, allowing participants the opportunity to decline inclusion. All data were anonymized and analyzed using only clinical parameters without personal identifiers.

Results

Clinical Characteristics

The characteristics and clinical data of the patients are summarized in Table 1. The study population predominantly consisted of female patients with anorexia nervosa (AN), reflecting the typical gender distribution of this condition. Out of a total of 112 patients, 51 (45.5%) had a body mass index (BMI) below 13, 45 (40.2%) had a BMI between 13 and 15, and 16 (14.3%) had a BMI between 15 or above.

Table 1 Clinical, Demographic, and Biochemical Characteristics of Patients

N = 112	
Characteristic	**Median (IQR) / Number**
Age	17 (15–27.5)
Gender (Male/Female)	2/110
Weight (kg)	31.40 (28.5–34.8)
Height (m)	154.51 (152.2–159.2)
BMI (kg/m²)	13.14 (11.8–14.2)
AST (U/L)	29.5 (23.0–54.5)
ALT (U/L)	30.5 (18.0–72.3)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; IQR, interquartile range.

BMI and Liver Enzymes

The relationship between BMI and liver enzyme levels, specifically aspartate aminotransferase (AST) and alanine aminotransferase (ALT), was examined. There was a significant negative correlation between BMI and liver enzyme levels: the Spearman rank correlation coefficient for BMI and AST was −0.4703 ($p < 0.0001$), and for BMI and ALT, it was −0.3743 ($p < 0.0001$).

BMI and Cobalamin

The relationship between BMI and cobalamin levels was analyzed, as shown in Figure 1. Patients in the severely elevated cobalamin group had significantly lower BMI (12.39 ± 0.26) compared to those in the moderately elevated group (13.41 ± 0.34, $p = 0.0121$) and the normal cobalamin group (13.63 ± 0.24, $p = 0.0009$). This finding indicates a significant between-group difference in BMI based on cobalamin levels, suggesting an association between the severity of malnutrition and elevated cobalamin concentrations.

Liver Enzymes and Cobalamin Significant between-group differences in liver enzyme levels (AST and ALT) were observed across different cobalamin level categories, as illustrated in Figures 2 and 3. Elevated cobalamin levels were correlated with higher AST levels. In the severely elevated cobalamin group, AST levels were 318.20 ± 148.68 U/L, significantly higher than the normal group (32.73 ± 0.088 U/L, $p < 0.0001$) and moderately elevated group (42.33 ± 8.192 U/L, $p = 0.0829$). ALT levels showed a similar pattern; the severely elevated cobalamin group had ALT levels of 331.51 ± 141.40 U/L, while the normal group had 36.64 ± 5.71 U/L ($p < 0.01$). The moderately elevated group showed ALT levels of 49.79 ± 7.22 U/L, which were higher than those in the normal group ($p = 0.0359$). The difference in ALT levels between the severely and moderately elevated groups did not reach statistical significance ($p > 0.05$).

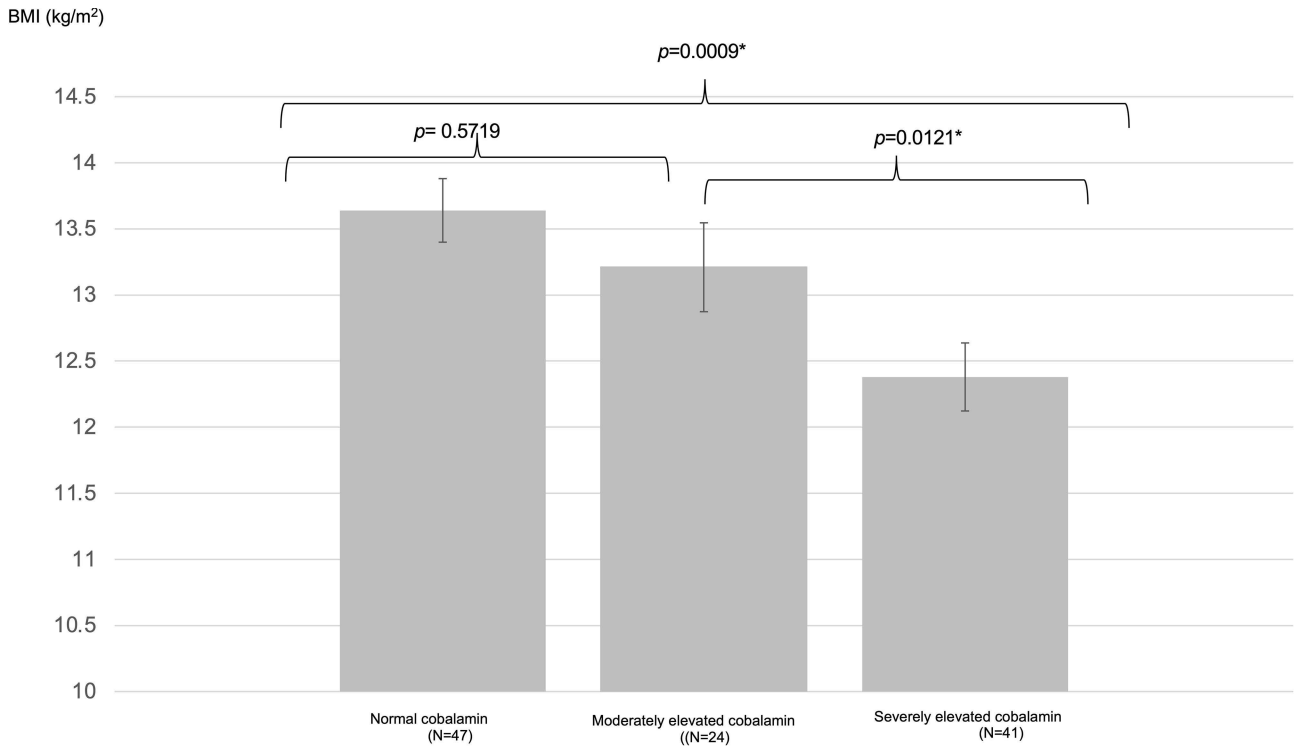

Figure 1 Relationship between BMI and cobalamin levels. Patients with severely elevated cobalamin levels (>4000 pg/mL) had significantly lower BMI compared to those with normal (799–1500 pg/mL) or moderately elevated (1500–4000 pg/mL) levels.
Note: *$p < 0.05$.

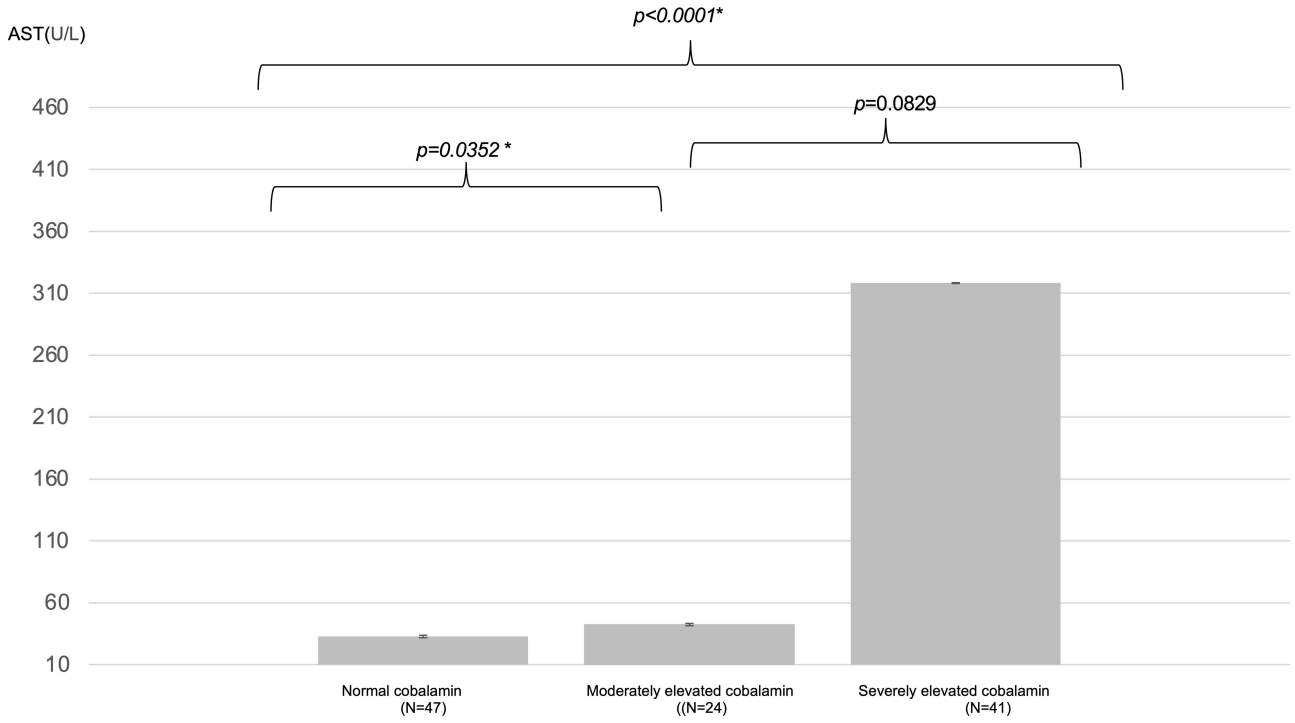

Figure 2 Relationship between cobalamin levels and AST. Severely elevated cobalamin levels were associated with higher AST values compared to normal levels. Normal cobalamin levels; 799–1500 pg/mL, Moderately elevated; 1500–4000 pg/mL, Severely elevated; >4000 pg/mL.
Note: *$p < 0.05$.

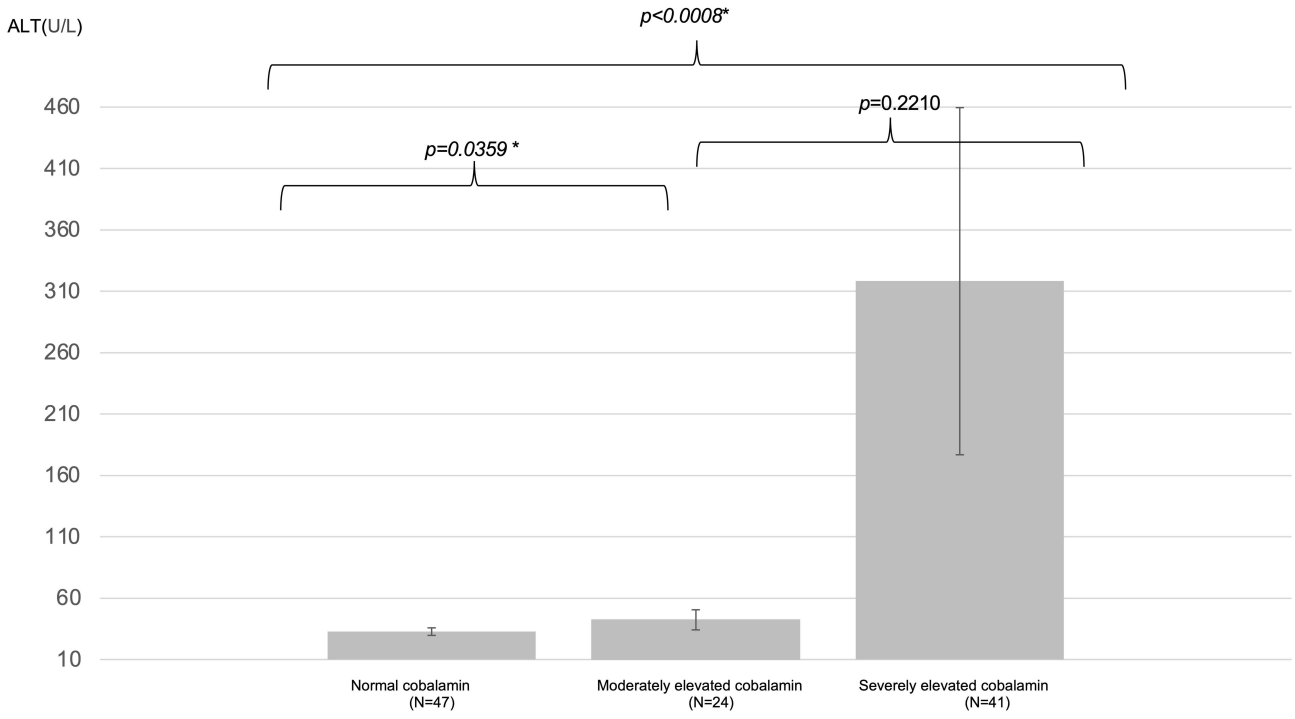

Figure 3 Relationship between cobalamin levels and ALT. Severely elevated cobalamin levels were associated with higher ALT values compared to normal levels. Normal cobalamin levels; 799–1500 pg/mL, Moderately elevated; 1500–4000 pg/mL, Severely elevated; >4000 pg/mL.
Note: *$p < 0.05$.

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Table 2 Comparison of AST, ALT and Cobalamin Levels Among Three BMI Groups

		Total	BMI < 13 (N=51)	13 ≤ BMI < 15 (N=45)	15 ≤ BMI (N=16)
AST (U/L)	Normal	75	23(45.1)	40(88.9)	12(75.0)
	Moderately elevated	26	17(33.3)	5(11.1)	4(25.0)
	Severely elevated	11	11(21.6)	0	0
ALT (U/L)	Normal	70	22(43.1)	35(77.8)	13(81.3)
	Moderately elevated	26	14(27.5)	9(20.0)	3(18.7)
	Severely elevated	16	15(29.4)	1(2.2)	0
Cobalamin (pg/mL)	Low	0	0	0	0
	Normal	47	15(29.4)	22(48.9)	10(62.5)
	Moderately elevated	24	9(17.6)	12(26.7)	3(18.8)
	Severely elevated	41	27(52.9)	11(24.4)	3(18.8)

Notes: Normal AST (≤ 40 U/L), Moderately elevated AST (> 40–120 U/L), Severely elevated AST (> 120 U/L), Normal ALT (≤ 45 U/L), Moderately elevated ALT (> 45–135), Severely elevated ALT (> 135U/L). Cobalamin categories: Normal (≤ 1500 pg/mL), Moderately elevated (1500–4000 pg/mL), Severely elevated (> 4000 pg/mL).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index.

Relationship Between Liver Dysfunction, Cobalamin and BMI

Table 2 shows a cross-tabulation of BMI subgroup with levels of AST, ALT, and cobalamin. Among patients with BMI < 13, 45.1% had normal AST levels and 43.1% had normal ALT levels, while only 29.4% had normal cobalamin levels. In the 13 ≤ BMI < 15 group, 77.8% had normal AST levels and 77.8% had normal ALT levels, with 48.9% showing normal cobalamin levels. Similarly, in the 15 ≤ BMI < 18 group, 75.0% had normal AST levels and 81.3% had normal ALT levels, whereas 62.5% had normal cobalamin levels. In addition, within the 13 ≤ BMI < 15 group, 24.4% of patients had severely elevated cobalamin levels, yet none had very high AST or ALT levels. This indicates that, in severely underweight patients, cobalamin abnormalities appeared more frequent than liver enzyme elevations.

Analysis of covariance (ANCOVA) was used to evaluate the impact of age, cobalamin levels, AST, and ALT on BMI. The analysis revealed a significant association between BMI and cobalamin levels ($p = 0.0129$), indicating that lower BMI is strongly linked with elevated cobalamin levels.

Discussion

Previous studies have explored the relationship between BMI and liver enzymes or between BMI and cobalamin in patients with anorexia nervosa (AN). A recent study reported that excessive cobalamin levels are frequently observed in AN patients.[12] However, their analysis primarily focused on the prevalence of elevated cobalamin rather than its potential association with liver dysfunction. Our study extends these observations by evaluating BMI, liver enzymes, and cobalamin together in AN patients, thereby providing complementary rather than entirely novel insights. Research has also shown that cobalamin levels can be elevated in patients with eating disorders. This finding is consistent with our results. While existing studies have primarily focused on the dynamics of liver enzymes and cobalamin during the weight restoration phase,[13,17] the association between liver dysfunction and elevated cobalamin levels in persistently low-BMI states remains less understood. In this study, we comprehensively evaluated the relationship between liver enzymes, cobalamin levels, and BMI in patients with anorexia nervosa (AN). Our analysis revealed that as BMI decreases, not only AST and ALT but also cobalamin levels tend to increase. This suggests that cobalamin, similar to AST and ALT, may serve as a supplementary indicator of liver dysfunction in AN patients, although causality cannot be inferred from our cross-sectional data. By evaluating AN patients across a broader BMI range, our study highlights the link between severe malnutrition, liver dysfunction, and cobalamin elevation, providing a complementary perspective to the existing body of research on metabolic disturbances in eating disorder patients.[8,11]

Moreover, after adjusting for covariates, we found a negative correlation between cobalamin levels and BMI, whereas no such association was observed with AST and ALT (Table 3).

Table 3 Results of ANCOVA Examining the Relationship Between BMI and AST, ALT and Cobalamin Levels

Covariates	BMI	
	F	p value
Age	0.6987	0.4051
Cobalamin	4.5380	0.0129*
AST	0.0034	0.9637
ALT	0.1032	0.7487

Note: *p < 0.05.
Abbreviations: ALT, alanine aminotransferase; ANCOVA, analysis of covariance; AST, aspartate aminotransferase; BMI, body mass index.

This result implies that cobalamin may be a useful supportive marker for detecting liver dysfunction associated with severe underweight in AN, but further longitudinal validation is needed.[9,17] The mechanisms underlying elevated cobalamin in the context of severe malnutrition in AN remain unclear, but several hypotheses exist. Recent studies have demonstrated that starvation-induced hepatic autophagy and mitochondrial dysfunction may contribute to oxidative stress and hepatocyte injury,[4,5] supporting the possibility that hepatocellular damage leads to cobalamin release. One possibility is that malnutrition and associated stress factors, such as autophagy, oxidative stress, and hypoxia, lead to an increased release of stored cobalamin from damaged hepatocytes into the bloodstream.[3,18–20] The liver, as the primary storage site for cobalamin, contains sufficient amounts to meet daily requirements for several years.[18,21] When hepatocyte integrity is compromised by inflammation, fat infiltration, or necrosis, cobalamin may leak into the blood, resulting in elevated serum levels.[13,19] Additionally, cellular breakdown due to hepatitis may further contribute to the release of stored cobalamin into the bloodstream.[13,20] However, the observation that some patients with extremely low BMI exhibited markedly elevated cobalamin despite normal AST/ALT suggests that mechanisms beyond overt hepatocyte necrosis or autophagy may also contribute. Starvation-related hepatic stress, including autophagy and mitochondrial dysfunction, may occur without parallel transaminase elevations.[4,5,20] In addition, impaired hepatic clearance or altered cobalamin metabolism, as suggested by recent functional assay studies in eating disorders,[14,15] as well as factors such as carrier protein shifts or macro-B12 complexes,[18,21] could play a role. Elevated serum cobalamin levels have been linked to liver dysfunction in other conditions, reflecting hepatic damage and impaired clearance.[20–22] This connection between cobalamin levels and liver dysfunction underscores the importance of monitoring cobalamin alongside liver enzymes in AN patients.

Our study examined BMI, liver enzyme activity, and cobalamin levels together in AN patients, which may provide a complementary perspective to existing literature. In conclusion, our findings indicate that elevated cobalamin levels can occur even when AST and ALT remain within normal ranges, particularly in cases of severe underweight. Measuring cobalamin levels alongside liver enzymes could complement the assessment of nutritional status and liver dysfunction in AN patients. Further research is warranted to clarify the mechanisms underlying cobalamin elevation in AN and to explore its role as a potential marker for liver dysfunction.

Limitations

Several limitations should be considered when interpreting the results of this study. First, the anorexia nervosa (AN) patients treated at our hospital may not represent the entire population of AN patients. Since the study was conducted at a single institution with a high proportion of patients with severely low body mass indices (BMIs), there may be a selection bias toward more severe cases of AN. This bias could limit the generalizability of our findings. Additionally, this also led to variability in sample sizes within each BMI subgroup, resulting in uneven group distributions. Second, the timing of blood tests was not consistent across all patients, which may have influenced the interpretation of serum levels. Although body weight and height were usually measured on the same day as blood sampling, in some cases the closest available

record was used; thus, a minor time lag between anthropometric and biochemical data cannot be excluded. Furthermore, this study did not distinguish between inpatients and outpatients, nor did it account for where patients were in their treatment course, such as whether they were in the early stages of treatment or in a longer-term follow-up phase. These factors could have influenced the biochemical data collected. Moreover, because this was a cross-sectional study in which each patient contributed only one biochemical snapshot over the nine-year period, dynamic changes in liver enzymes or cobalamin during acute deterioration or refeeding could not be evaluated. In addition, the small number of patients in some subgroups (eg, severely elevated AST, highest cobalamin tier) resulted in sample-size imbalance, which limited the statistical power to detect interaction effects or non-linear relationships. Furthermore, the single-center design enriched with severely underweight patients restricts generalizability to the broader AN population, and external validation is required. In addition, the absence of mechanistic measures such as mitochondrial function or functional cobalamin assays, which have been increasingly reported in recent literature,[4,5,14,15] further limits our ability to clarify the precise pathways underlying cobalamin elevation. Potential confounding factors such as dietary intake, subclinical infections, hemolysis, or genetic variations in cobalamin metabolism were also not systematically assessed; therefore, residual confounding cannot be excluded. Finally, the study did not measure diluted cobalamin values, limiting our ability to quantify extremely high cobalamin levels accurately. This restriction may have affected the precision of these specific measurements. Particularly for the >4000 pg/mL category, this classification does not represent a physiological cutoff but rather reflects the technical limitations of the assay. Nevertheless, this approach is consistent with previous studies using similar assays, although it may not fully capture the entire clinical spectrum of extreme hypercobalaminemia. Although this bias may limit generalizability, the inclusion of a high proportion of extremely low-BMI patients also allowed us to explore metabolic disturbances at the most severe end of malnutrition, which are underrepresented in prior studies. Future research should aim to address these limitations by exploring how varying levels of cobalamin might influence treatment approaches, with the goal of developing tailored nutritional therapies for anorexia nervosa. While our findings suggest that lower BMI may be more strongly associated with cobalamin abnormalities than with liver enzyme elevations, it should be noted that these observations were based solely on descriptive data and have not been statistically validated.

Conclusion

This study demonstrated that in patients with anorexia nervosa, lower BMI was associated not only with elevated levels of liver enzymes such as AST and ALT but also with increased serum cobalamin concentrations. Notably, elevated cobalamin levels were observed even in cases where liver enzyme levels remained within the normal range, suggesting that cobalamin may serve as a possible supportive biochemical indicator reflecting malnutrition severity and potential liver involvement, although this requires confirmation in longitudinal studies. These findings highlight the potential clinical utility of measuring cobalamin alongside conventional liver enzymes in the evaluation of undernourished patients with anorexia nervosa. However, given the cross-sectional design of this study, causality cannot be inferred, and further prospective investigations are needed to elucidate the underlying pathophysiological mechanisms of cobalamin elevation and its role in the clinical assessment of liver function in this population.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board of Yokohama City University Medical Center (Approval No. B210200004) and was conducted in accordance with the Declaration of Helsinki. Given the retrospective nature of the study and the use of anonymized data, the Ethics Committee approved the use of an opt-out approach in place of written informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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