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Admission Vitamin B12 and in Hospital Outcomes in Adults with Acute Hepatitis and Acute Liver Injury

Halil Şahin [1], Sami Çiftçi [2] and Berk Baş [3,*]

[1] Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, Istanbul Aydin University, 34295 Istanbul, Türkiye; halilshn33@gmail.com
[2] Department of Gastroenterology, Daviva Avcilar Hospital, 34320 Istanbul, Türkiye
[3] Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, Aydin Adnan Menderes University, 09100 Aydin, Türkiye
* Correspondence: berkcorn@gmail.com; Tel.: +90-5347070635

Abstract

Background/Objectives: Elevated serum vitamin B12 accompanies liver injury, but its relationship with outcomes in acute hepatitis remains uncertain. We evaluated admission vitamin B12 and an exploratory B12–ferritin index (BFI). **Methods:** This retrospective study included 186 adults hospitalized with acute hepatitis or acute liver injury (2018–2025). Outcomes included ward length of stay, transplantation, and in-hospital mortality; exploratory endpoints were ICU admission, encephalopathy, and an ICU-inclusive composite. Discrimination was assessed using ROC AUC, including comparison with MELD 3.0. Eight B12 values exceeded the assay limit of 4000 pg/mL and were top-coded in numerical analyses. **Results:** Nine (4.8%) patients died, one (0.5%) underwent transplantation, and 20 (10.8%) met the ICU-inclusive composite; all 20 were admitted to the ICU. Encephalopathy occurred in 11 (5.9%). Vitamin B12 AUCs were 0.935 (95% CI 0.891–0.979) for mortality, 0.944 (0.904–0.984) for death or transplantation, and 0.938 (0.897–0.980) for the composite. B12 was unrelated to ward length of stay (Spearman ρ = 0.017; p = 0.818). BFI did not improve discrimination over B12. In an exploratory model adjusted for age and MELD 3.0, the B12 association persisted (adjusted OR per 1000 pg/mL, 7.67; 95% CI 3.38–17.44). **Conclusions:** Admission B12 was associated with adverse in-hospital outcomes, but limited event counts, uncertain sampling–event timing, and assay censoring prevent clinical prediction claims. Prospective validation is needed.

Keywords: vitamin B12; cobalamin; acute hepatitis; acute liver injury; ferritin; prognosis

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1. Introduction

Hospitalized adults with acute hepatitis have heterogeneous trajectories, from recovery to intensive care, encephalopathy, and liver failure. Acute liver failure (ALF) requires coagulopathy and hepatic encephalopathy in an appropriate acute clinical context and must be distinguished from acute liver injury without loss of synthetic function [1,2]. Risk assessment is important, but association of a biomarker with outcomes does not establish its suitability for transplant decisions.

MELD 3.0 is the updated version of the MELD scoring system and incorporates routine biochemical variables. Like earlier MELD versions, it was designed primarily for advanced liver disease and liver transplantation settings, so its performance in

heterogeneous acute hepatitis requires separate evaluation. For perspective, the DILI-Inpt study modeled 21-day death or transplantation in 305 hospitalized patients with severe idiosyncratic drug-induced liver injury using bilirubin, INR, encephalopathy, and supplement exposure [3]. Its disease-specific population differs from ours.

Vitamin B12 is a plausible marker because the liver participates in cobalamin storage and handling. Increased total serum B12 may reflect hepatocyte injury or altered clearance of binding proteins. Sugihara et al. associated haptocorrin-bound B12 with severity and prognosis in chronic viral liver disease [4], whereas Dou et al. reported associations with disease severity and mortality in acute-on-chronic liver failure [5]. These populations differ from acute hepatitis without known chronic liver disease. A 2026 sepsis cohort also linked elevated B12 with short-term mortality, underscoring its lack of liver specificity [6].

Ferritin is another candidate marker. Extreme elevations occur in acute hepatitis, including patients who recover [7,8]; multicenter ALF data also implicate altered iron metabolism, particularly hepcidin, in prognosis [9]. Whether ferritin adds information beyond B12 requires direct comparison.

We examined admission B12 in relation to adverse in-hospital outcomes, compared its discrimination with ferritin, INR, and MELD 3.0, and explored a B12–Ferritin Index (BFI). The index and adjusted model were considered exploratory.

2. Materials and Methods

2.1. Study Design and Participants

This retrospective cohort study was conducted in the Department of Gastroenterology at Istanbul Aydin University Medical Park Florya Hospital, Istanbul, Türkiye. Adults hospitalized between January 2018 and December 2025 with acute hepatitis or acute liver injury were identified from institutional electronic records. Vitamin B12 testing was performed as part of the routine laboratory assessment within the first 24 h of presentation, rather than specifically in response to an adverse clinical event. Patients with unavailable vitamin B12 results or insufficient clinical data were excluded, as were those with known chronic liver disease or cirrhosis, hepatocellular carcinoma, previous liver transplantation, hematological disease, or active vitamin B12 supplementation. The final analytical cohort comprised 186 patients. The total number screened and exclusion counts were not available. Eligibility required ALT or AST ≥ 5 times the laboratory upper limit of normal (ULN). Patients with both aminotransferases below this threshold were not eligible.

The Istanbul Aydin University Non-Interventional Clinical Research Ethics Committee approved the study on 16 July 2026 (291/2026). The study followed the Declaration of Helsinki and STROBE guidelines [10]. ChatGPT (GPT-5, OpenAI, San Francisco, CA, USA) assisted with statistical code and language drafting; authors verified all analyses and interpretations.

2.2. Clinical Definitions and Outcome Ascertainment

Acute hepatitis or acute liver injury was defined as an acute clinical syndrome supported by elevated serum aminotransferases (ALT or AST ≥ 5 × ULN) and etiological assessment. The cohort was not restricted to a single biochemical injury pattern. Acute liver injury with coagulopathy was defined by INR ≥ 1.5 in the absence of encephalopathy. Acute liver failure (ALF) requires coagulopathy and encephalopathy during an acute illness, generally within 26 weeks, without pre-existing cirrhosis [1,2]. Because serial INR measurements and the timing of encephalopathy were unavailable in the analytical dataset, incident progression to ALF could not be established and was not analyzed.

Etiologies were assigned from the recorded clinical diagnoses after review of the available history, serology, imaging, and medication exposure. The investigators confirmed that evaluation of acute viral hepatitis included acute-phase serological markers and HBV DNA or HCV RNA testing, as appropriate; patients with known chronic liver disease were excluded. Patient-level serological patterns and prior viral test results were not available in the analytical dataset for independent adjudication of acute versus chronic infection. Autoimmune hepatitis (AIH) was diagnosed using clinical, laboratory, serological, and biopsy findings, with reference to the simplified International Autoimmune Hepatitis Group criteria [11]. All 37 AIH cases were newly diagnosed during the index hospitalization; none had a prior AIH diagnosis or previous AIH-directed treatment. Drug-induced or toxic liver injury was assigned based on recorded medication, herbal-product, or other toxic exposures and assessment of competing causes. The 56 drug-induced/toxic cases included hepatocellular, cholestatic, and mixed patterns of biochemical injury. Cases without an identified cause were classified as indeterminate. The pre-eclampsia-associated case was classified as pregnancy-associated liver injury. In all 56 drug-induced/toxic liver injury cases, admission ALT and ALP were available to estimate the R ratio, defined as (ALT/ALT ULN)/(ALP/ALP ULN). An illustrative analysis using ALT ULN 40 U/L and ALP ULN 120 U/L classified 53 cases as hepatocellular, two as mixed, and one as cholestatic; final counts require verification of the institution-specific ULNs.

The clinical outcomes of interest were gastroenterology ward length of stay, liver transplantation, and in-hospital mortality. Gastroenterology ward length of stay was defined as the number of days spent in that ward during the index hospitalization and excluded subsequent ICU time. It was included as a secondary descriptive indicator of the duration of ward-based clinical management, not as total hospital stay or a direct marker of hepatic injury severity. Additional exploratory outcomes included ICU admission, recorded hepatic encephalopathy, death or transplantation, and a composite of ICU admission, transplantation, or death. Each patient was counted once per binary outcome. The ICU-inclusive composite was identical in case membership to ICU admission because every patient meeting the composite endpoint was admitted to the ICU. A transplantation-only model was not fitted because only one patient underwent transplantation. Encephalopathy onset, West Haven grade, and contemporaneous INR were unavailable in the analytical dataset. All outcomes were limited to the index hospitalization.

2.3. Laboratory Measurements and Severity Scores

Vitamin B12, ferritin, aminotransferases, total bilirubin, INR, creatinine, and sodium were measured as part of the initial clinical laboratory assessment within the first 24 h of presentation. Vitamin B12 measurements were not specifically ordered because a patient had experienced an adverse clinical event. Nevertheless, precise patient-level dates and times of blood sampling relative to ICU admission or the onset of hepatic encephalopathy were not available in the analytical dataset. Consequently, it could not be confirmed that vitamin B12 sampling preceded these events in every patient. Measurements were performed in the central laboratory using automated methods. Vitamin B12 was reported in pg/mL and ferritin in ng/mL. Eight vitamin B12 results were reported as >4000 pg/mL because of the assay upper reporting limit. These observations were censored above the reporting limit rather than precisely measured at 4000 pg/mL. Analyzer and reagent details, reference intervals, and the dilution protocol were not available for reporting.

MELD 3.0 was calculated using the published Kim et al. formula from bilirubin, INR, creatinine, sodium, albumin (converted from g/L to g/dL), and sex, with score-specific laboratory bounds [12]. Unrounded values were analyzed as a continuous biochemical

comparator, not as clinical allocation scores. MELD 3.0 was the sole MELD-based score used to avoid redundant comparisons among its previous versions. None of the patients was receiving dialysis at admission.

2.4. Statistical Analysis

Continuous variables are presented as medians with the 25th and 75th percentiles, and categorical variables as counts and percentages. Group comparisons used two-sided Mann–Whitney U tests for continuous variables and Fisher's exact test for binary variables. Spearman coefficients summarized monotonic associations. The variables used in the reported analyses were complete for all 186 patients; no imputation was performed. Ward length of stay was examined separately using Spearman correlation and group comparisons. For numerical summaries and rank-based analyses, the eight above-limit vitamin B12 observations were represented by the same highest value (4000); this denotes top-coding, not exact concentration. No values above the reporting limit were imputed.

ROC analyses evaluated B12, ferritin, INR, MELD 3.0, and BFI for four endpoints. AUC 95% confidence intervals and paired comparisons with B12 used the nonparametric DeLong method [13]. Two-sided rank-sum tests assessed each marker against AUC = 0.5. Analyses were exploratory without multiplicity adjustment; normal-approximation intervals were restricted to 0–1.

Exploratory logistic regression assessed the ICU-inclusive endpoint using age, B12 (per 1000 pg/mL), and MELD 3.0 (per point). The prespecified three-variable model was recalculated using MELD 3.0, with coefficients and validation measures derived from all 186 records. B12 values above the reporting limit were assigned 4000 pg/mL, meaning regression estimates depend on top-coding. Odds ratios and Wald 95% confidence intervals were calculated by maximum likelihood. Only 20 events were available, limiting model stability.

Apparent AUC and Brier score were calculated. Internal assessment used 500 patient-level bootstrap samples (fixed seed), refitting the same three-variable model and estimating optimism in discrimination, Brier score, and calibration slope. This does not reproduce prior model selection or constitute external validation [14].

2.5. Exploratory Index and Sensitivity Analyses

The exploratory B12–Ferritin Index (BFI) was evaluated to examine whether combining the two admission biomarkers might improve discrimination of adverse in-hospital outcomes. The score assigned one point for vitamin B12 > 1774 pg/mL and one point for ferritin > 7178 ng/mL. Thus, a score of 0 indicated that neither biomarker exceeded its threshold, a score of 1 that one biomarker exceeded its threshold, and a score of 2 that both did. The thresholds were derived in this same cohort from different endpoints: the ICU-inclusive composite for vitamin B12 and in-hospital mortality for ferritin. Accordingly, the index was developed and assessed using the same patients; its performance is exploratory rather than externally validated. Strict greater-than thresholds were retained from the original index definition. A separate evaluation of vitamin B12 ≥ 1774 pg/mL assessed how classification of a value exactly equal to the threshold affected sensitivity. No threshold was interpreted as a clinical rule-out criterion.

Sensitivity analysis excluded one alcohol-associated hepatitis case and one pre-eclampsia-associated liver injury case because these uncommon etiologies might increase population heterogeneity. One additional patient who had declined treatment was excluded only in the sensitivity analysis because absence of treatment might influence clinical outcomes independently of the severity of hepatic injury. Treatment refusal was not treated as a separate etiological category; all three patients remained in the main analysis. Detailed treatment information for the other patients was not systematically

available and treatment-related variables were not included in BFI development or the multivariable models. Analyses were performed in Python 3.12.14 using NumPy, pandas, SciPy 1.17.0, and scikit-learn 1.8.0. Two-sided p values are reported, with $p < 0.05$ used as a descriptive significance threshold.

3. Results

3.1. Cohort Characteristics and Clinical Outcomes

The cohort included 186 adults, with a median age of 42.0 years (IQR 34.0–52.0); 90 (48.4%) were male. Median vitamin B12 was 1086.0 pg/mL (682.2–1627.8), ferritin 915.0 ng/mL (270.0–2475.2), and INR 1.40 (1.20–1.70). An admission INR ≥ 1.5 was recorded in 76 (40.9%) patients. Baseline characteristics and comparisons by the exploratory composite endpoint are shown in Table 1.

Table 1. Characteristics by the exploratory composite endpoint.

Variable	Total *n* = 186	No Event *n* = 166	Event *n* = 20	*p*
Age, years	42.0 (34.0–52.0)	41.0 (33.0–51.0)	52.5 (40.0–57.0)	0.013
Male sex, n (%)	90 (48.4)	83 (50.0)	7 (35.0)	0.242
Body mass index, kg/m²	25.0 (22.4–28.1)	24.8 (22.3–28.1)	26.1 (23.8–29.3)	0.395
Vitamin B12, pg/mL	1086.0 (682.2–1627.8)	1003.5 (659.0–1340.2)	2850.0 (1897.2–4000.0)	<0.001
Ferritin, ng/mL	915.0 (270.0–2475.2)	828.0 (270.0–2000.0)	2677.5 (780.5–12,782.5)	0.031
AST, U/L	982.5 (589.8–1964.8)	963.0 (582.2–1821.8)	1635.5 (875.2–3438.2)	0.017
ALT, U/L	1415.5 (743.2–2331.5)	1373.0 (743.2–2223.5)	2189.0 (997.0–3486.0)	0.091
Total bilirubin, mg/dL	9.4 (4.0–14.8)	9.0 (3.7–14.7)	12.4 (5.3–15.3)	0.211
INR	1.40 (1.20–1.70)	1.35 (1.20–1.60)	1.90 (1.47–2.30)	<0.001
Creatinine, mg/dL	0.71 (0.59–0.86)	0.71 (0.59–0.83)	0.78 (0.58–1.02)	0.304
Sodium, mmol/L	137.5 (136.0–139.0)	138.0 (136.0–139.0)	136.5 (134.8–140.2)	0.452
Gastroenterology ward stay, days	16.0 (10.2–20.8)	16.0 (11.0–20.0)	17.0 (7.8–25.0)	0.600
MELD 3.0	20.7 (16.6–24.7)	20.1 (16.2–23.9)	25.1 (22.1–27.0)	<0.001

Values are median (25th–75th percentile) unless otherwise stated. The exploratory composite endpoint comprised ICU admission, transplantation, or in-hospital death. All 20 patients meeting this endpoint were admitted to the ICU, including those who subsequently underwent transplantation or died; thus, the composite identified the same 20 patients as ICU admission alone. p values were calculated using two-sided Mann–Whitney U or Fisher's exact tests. AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease. Vitamin B12 summaries use top-coded values; 4000.0 at the upper quartile represents the assay limit rather than an exact measured concentration. Ward stay excludes subsequent ICU time.

The main recorded etiologies were acute hepatitis B in 79 (42.5%) patients, drug-induced or toxic hepatitis in 56 (30.1%) patients, and autoimmune hepatitis in 37 (19.9%) patients. The remaining categories were indeterminate injury, hepatitis A, hepatitis C, pregnancy-associated injury, and alcohol-associated hepatitis (Table 2).

Table 2. Recorded etiologies.

Etiology	Patients, *n* (%)	Composite Events, *n*
Acute hepatitis B	79 (42.5)	10
Drug-induced or toxic hepatitis	56 (30.1)	7
Autoimmune hepatitis	37 (19.9)	3
Indeterminate injury	5 (2.7)	0
Acute hepatitis A	4 (2.2)	0
Acute hepatitis C	3 (1.6)	0
Pregnancy-associated injury	1 (0.5)	0
Alcohol-associated hepatitis	1 (0.5)	0

Etiological categories reflect the recorded clinical diagnoses. The pregnancy-associated record was labeled pre-eclampsia. Small event counts precluded reliable adjusted etiological subgroup analyses.

The exploratory composite endpoint occurred in 20 (10.8%) patients. All 20 (100%) were admitted to the ICU, including 9 (4.8%) patients who died and 1 (0.5%) patient who underwent transplantation; the transplant recipient was not among the deaths. Thus, the composite endpoint identified the same 20 (10.8%) patients as ICU admission alone. Hepatic encephalopathy was recorded in 11 (5.9%) patients, all in the ICU group. Two of these 11 patients had an admission INR below 1.5, preventing reliable classification of subsequent ALF status. Death or transplantation occurred in 10 (5.4%) patients. Median gastroenterology ward stay was 16.0 days (IQR 10.2–20.8).

3.2. Vitamin B12 and Adverse Outcomes

Vitamin B12 was higher in patients with the exploratory composite endpoint than in those without it: 2850.0 pg/mL (1897.2–4000.0) versus 1003.5 pg/mL (659.0–1340.2), respectively ($p < 0.001$). Event patients were older and had higher AST, INR, MELD 3.0, and ferritin, whereas ALT, bilirubin, creatinine, and ward stay did not differ significantly (Table 1).

Non-survivors had a median vitamin B12 concentration of 2900.0 pg/mL (2700.0–4000.0), compared with 1008.0 pg/mL (674.0–1477.0) among survivors ($p < 0.001$). Corresponding values in patients with and without recorded encephalopathy were 2900.0 pg/mL (1923.0–3897.5) and 1008.0 pg/mL (672.0–1469.0), respectively ($p < 0.001$). Outcome-specific comparisons are summarized in Supplementary Table S1.

No statistically significant correlations were observed between vitamin B12 concentrations and the evaluated laboratory parameters or calculated liver disease severity scores (Supplementary Table S2). Vitamin B12 was also not significantly correlated with gastroenterology ward length of stay (Spearman $\rho = 0.017$; $p = 0.818$).

3.3. Discrimination and Adjusted Association

Vitamin B12 discriminated the ICU-inclusive composite with AUC 0.938 (95% CI 0.897–0.980; $p < 0.001$ versus chance), compared with MELD 3.0 at 0.770, INR at 0.775, and ferritin at 0.648 (Table 3). Paired DeLong tests favored B12 over MELD 3.0 ($p = 0.003$), INR ($p = 0.005$), and ferritin ($p < 0.001$). The composite contained exactly the same patients as ICU admission.

Table 3. Outcome-specific discrimination.

Marker	Composite or ICU 20 Events	Mortality 9 Events	Recorded HE 11 Events	Death or LT 10 Events
Vitamin B12, pg/mL	0.938 (0.897–0.980)	0.935 (0.891–0.979)	0.906 (0.837–0.975)	0.944 (0.904–0.984)
Ferritin, ng/mL	0.648 (0.483–0.814)	0.864 (0.744–0.983)	0.772 (0.622–0.923)	0.882 (0.772–0.992)
INR	0.775 (0.678–0.873)	0.883 (0.804–0.963)	0.796 (0.698–0.895)	0.881 (0.808–0.954)
MELD 3.0 (exploratory)	0.770 (0.667–0.873)	0.878 (0.772–0.983)	0.846 (0.753–0.938)	0.879 (0.784–0.973)
BFI	0.892 (0.816–0.969)	0.889 (0.762–1.000)	0.832 (0.699–0.966)	0.903 (0.787–1.000)

Table 3 shows AUCs (95% CI) using DeLong intervals; paired tests compare each marker with B12. ICU, intensive care unit; HE, hepatic encephalopathy; LT, liver transplantation; BFI, B12–Ferritin Index. The BFI uses B12 > 1774 pg/mL and ferritin > 7178 ng/mL. Estimates are in-sample, exploratory, and unadjusted for multiplicity.

For mortality, B12 AUC was 0.935 (95% CI 0.891–0.979) versus ferritin 0.864 (0.744–0.983) and MELD 3.0 0.878 (0.772–0.983); the paired B12–MELD 3.0 difference was not significant (p = 0.345). B12 AUC was 0.906 for encephalopathy and 0.944 for death/transplantation. Nine deaths and one transplantation limit precision.

At vitamin B12 > 1774 pg/mL, 18 of 20 (90.0%) patients who experienced the exploratory composite endpoint tested positive (sensitivity 90.0%; specificity 88.6%). Positive and negative predictive values were 48.6% and 98.7%, respectively. Defining a positive test as vitamin B12 ≥ 1774 pg/mL also classified one patient with a value exactly equal to 1774 pg/mL as positive. Because that patient experienced the composite endpoint, sensitivity increased to 95.0%, while specificity remained unchanged at 88.6%.

In the recalculated exploratory logistic model, B12 remained associated with the ICU-inclusive endpoint (adjusted OR [aOR] per 1000 pg/mL, 7.67; 95% CI 3.38–17.44; $p < 0.001$). MELD 3.0 was independently associated (aOR per point, 1.34; 95% CI 1.12–1.60; $p = 0.001$), whereas age was not (Table 4). Apparent model AUC was 0.948 and Brier score 0.047. In 500 fixed-model bootstrap samples, optimism-corrected AUC, Brier score, and calibration slope were 0.944, 0.053, and 0.902, respectively. The B12 coefficient is based on top-coded values and does not describe concentrations above 4000 pg/mL.

Table 4. Logistic regression for the exploratory composite endpoint.

Variable	Unadjusted OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Age, per year	1.04 (1.01–1.08)	0.023	1.00 (0.95–1.06)	0.944
Vitamin B12, per 1000 pg/mL	5.38 (3.06–9.46)	<0.001	7.67 (3.38–17.44)	<0.001
MELD 3.0, per point	1.23 (1.10–1.37)	<0.001	1.34 (1.12–1.60)	0.001

The model included 186 patients and 20 events, with age, top-coded B12, and MELD 3.0. ORs use Wald 95% CIs. Apparent AUC/Brier score were 0.948/0.047; bootstrap-corrected values were 0.944/0.053, with calibration slope 0.902 (500 resamples). Internal validation does not address earlier model selection or upper-limit censoring.

3.4. Exploratory BFI and Sensitivity Analysis

BFI scores were 0 in 140 (75.3%) patients, 1 in 38 (20.4%) patients, and 2 in 8 (4.3%) patients. The composite endpoint occurred in 2/140 (1.4%), 11/38 (28.9%), and 7/8 (87.5%),

respectively; corresponding mortality was 1/140 (0.7%), 3/38 (7.9%), and 5/8 (62.5%) (Table 5). The BFI AUC was 0.892 for the composite endpoint, 0.889 for mortality, and 0.832 for encephalopathy. For the composite endpoint, the BFI had a lower AUC than vitamin B12 alone when B12 was analyzed as a continuous laboratory measurement (0.892 vs. 0.938). This difference was not statistically significant (paired comparison $p = 0.102$), and the index did not demonstrate improved discrimination over vitamin B12 alone.

Table 5. Exploratory BFI and observed outcomes.

BFI Score	Patients, *n*	Composite or ICU *n* (%)	Recorded HE *n* (%)	Mortality *n* (%)
0	140	2 (1.4)	2 (1.4)	1 (0.7)
1	38	11 (28.9)	5 (13.2)	3 (7.9)
2	8	7 (87.5)	4 (50.0)	5 (62.5)

BFI: one point for vitamin B12 > 1774 pg/mL and one point for ferritin > 7178 ng/mL. The thresholds were developed using different outcomes in the same cohort. Counts and percentages are descriptive. The single transplantation occurred in the BFI 2 group. The index is not externally validated.

After exclusion of the two uncommon etiologies and the patient recorded as refusing treatment, 183 patients remained, including all 20 composite events. The vitamin B12 AUC was 0.941, compared with 0.938 in the full cohort. This sensitivity analysis does not resolve diagnostic uncertainty within the larger etiological groups.

4. Discussion

Higher admission vitamin B12 concentrations were associated with adverse in-hospital outcomes, including mortality, death or transplantation, and the exploratory ICU-inclusive composite. Vitamin B12 was not significantly associated with gastroenterology ward length of stay, which was included as a secondary descriptive measure of ward-based clinical management rather than as an indicator of overall hospitalization duration or liver injury severity. Ward time can be influenced by discharge practice and shortened by transfer to the ICU, transplantation, or death. Although the ICU-inclusive composite identified the same 20 patients as ICU admission, elevated B12 was also associated with mortality and recorded encephalopathy. All deaths and encephalopathy events occurred among ICU-admitted patients, however, and the small numbers (nine deaths and 11 encephalopathy cases) limit interpretation.

These findings extend evidence largely obtained in chronic liver disease. Sugihara et al. linked high B12 to haptocorrin in chronic viral liver disease [4], and Dou et al. reported mortality associations in acute-on-chronic liver failure [5]. Neither validates our acute hepatitis estimates. The 2026 sepsis cohort reported high B12 and subsequent mortality [6], further suggesting that hypercobalaminemia may reflect systemic illness rather than hepatic injury alone.

High total B12 may result from hepatocyte release or impaired binding-protein clearance [4]. We lacked haptocorrin, holotranscobalamin, methylmalonic acid, and serial B12 measurements to distinguish mechanisms. Absent correlations with aminotransferases or MELD 3.0 do not establish independence from inflammation or a direct measure of functional reserve. B12 remains a candidate risk-associated marker rather than a causal mediator.

Ferritin showed a different outcome pattern: its AUC was modest for the ICU-dominated composite but higher for mortality. This is compatible with prior reports of ferritin elevation in both severe and recovering acute hepatitis [7]. Anastasiou et al. studied 102 patients with ALF and associated high ferritin and low transferrin with worse outcomes [8]. That study, rather than a chronic liver disease cohort, is the more appropriate direct comparator for acute injury. Spivak et al. subsequently evaluated iron metabolism in a multicenter ALF cohort and linked lower hepcidin to reduced short-term survival [9]. Together, these data support continued investigation of iron-related markers without implying that ferritin and vitamin B12 must improve prediction when combined.

BFI did not improve discrimination over continuous B12. The highest BFI category contained only eight patients, and dichotomization discards information. Moreover, its cutoffs were derived from different endpoints in the same sample. Its high negative predictive value partly reflects low event prevalence and cannot justify discharge decisions or reduced monitoring.

Comparison with MELD 3.0 requires distinguishing statistical discrimination from clinical usefulness. B12 showed greater in-sample discrimination for the ICU-dominated composite, but its AUC advantage over MELD 3.0 was not significant for mortality (p = 0.345). The adjusted model suggested an association beyond age and MELD 3.0, yet the 20-event sample risks overfitting; bootstrap correction does not capture model-development uncertainty. Reporting standards emphasize calibration, validation, and transparent specification [14]. Neither a favorable AUC nor the fixed-model bootstrap establishes improvement in patient outcomes, transplant referral, or clinical decisions.

The cohort was dominated by acute hepatitis B, toxic/drug-induced injury, and newly diagnosed AIH. Event numbers were insufficient for reliable etiological subgroup adjustment. Although virological assessments and biopsy-supported AIH diagnoses were documented, individual diagnostic evidence and toxic-exposure subtypes could not be independently reviewed. The DILI-Inpt model [3] illustrates the importance of matching predictors and endpoints to a defined population; its 21-day results are not directly comparable with our in-hospital estimates. MELD 3.0, like its predecessors, was principally developed for chronic advanced liver disease and transplant candidates, not validated for this heterogeneous acute-hepatitis cohort.

Limitations include retrospective single-center selection, unavailable screening denominators, and uncertain temporal ordering of B12 sampling and deterioration. Although tests were routinely obtained within 24 h, exact blood-draw and ICU/encephalopathy timestamps were not retained; some B12 elevations may therefore reflect established rather than future critical illness. ICU admission also depends on local practice and capacity. Serial INR and encephalopathy timing were missing, preventing valid ascertainment of incident ALF. Treatment data were incomplete, leaving possible confounding; biochemical injury patterns in the DILI subgroup could not be assessed separately. Eight B12 values exceeded 4000 pg/mL: tied ranks and numerical top-coding cannot recover their actual concentrations, potentially affecting regression and calibration. Few events, multiple exploratory comparisons, and lack of external validation further constrain clinical applicability.

Despite these limitations, the observed associations between early vitamin B12 concentrations and adverse in-hospital outcomes provide preliminary evidence warranting investigation in independent prospective cohorts. Future studies should enroll consecutive patients, obtain precisely timed samples before the clinical endpoints, document assay limits and relevant treatment exposures, and independently adjudicate liver injury etiologies and encephalopathy. They should establish whether vitamin B12 adds calibrated, clinically useful information beyond existing assessment, rather than merely identify a new cutoff in the same cohort.

5. Conclusions

Higher B12 concentrations within 24 h of presentation were associated with adverse in-hospital outcomes in acute hepatitis or acute liver injury, but not ward length of stay. Exploratory BFI did not improve discrimination over B12 alone. The small event count, ICU-defined composite, uncertain sample–event timing, and censored B12 measurements preclude clinical adoption. Independent prospective validation is required.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/diagnostics16233975/s1, Table S1: Mortality comparisons; Table S2: Vitamin B12 correlations.

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Institutional Review Board Statement: Approved by the Istanbul Aydin University Non-Interventional Clinical Research Ethics Committee on 16 July 2026 (decision number 291/2026). The study followed the Declaration of Helsinki.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: De-identified data supporting the findings of this study may be made available from the corresponding author upon reasonable request, subject to institutional approval and applicable data protection requirements. The data are not publicly available due to patient confidentiality restrictions. ChatGPT (GPT-5, OpenAI, San Francisco, CA, USA) was used to assist with drafting the statistical analysis section and improving the language of the manuscript; all content was reviewed and verified by the authors, who take full responsibility for the final manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

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