Journal of General Medicine

Research Article

Ferritin as a Prognostic Marker for Mortality and Critical Inpatient Outcomes in the Alcohol Related Hepatitis Population

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Abstract

Background: Alcoholic hepatitis (AH) is a severe inflammatory liver disorder with mortality rates of 20–50% at 90 days. Ferritin is an acute-phase reactant elevated in AH due to hepatocellular injury, systemic inflammation, and altered iron homeostasis. Its prognostic significance in AH has not been fully elucidated. To evaluate the association between serum ferritin levels and short-term clinical outcomes in patients with alcoholic hepatitis.

Methods: This retrospective cohort study utilized the TriNetX US Collaborative Network. Patients with AH (ICD-10: K70.1, K70.10, K70.11) and documented serum ferritin were included. Patients with autoimmune hepatitis, viral hepatitis, hemochromatosis, Wilson disease, and primary biliary or sclerosing cholangitis were excluded. Patients were stratified into low-ferritin (1,000 ng/mL) and high-ferritin (≥1,000 ng/mL) cohorts. The primary outcome was all-cause mortality within 90 days. Secondary outcomes included hepatic failure, sepsis, shock, ascites, spontaneous bacterial peritonitis (SBP), esophageal variceal bleeding, and hepatic encephalopathy.

Results: Of 73,476 patients, 58,815 had ferritin 1,000 ng/mL, and 14,661 had ferritin ≥1,000 ng/mL. Patients with elevated ferritin had significantly higher 90-day mortality (20.0% vs. 8.7%; HR 2.66, p 0.001). Elevated ferritin was also associated with increased risks of hepatic failure (HR 1.55), sepsis (HR 1.85), shock (HR 1.94), ascites (HR 1.17), SBP (HR 1.52), and hepatic encephalopathy (HR 1.32) (all p 0.001). Esophageal variceal bleeding was less frequent in the high-ferritin cohort (HR 0.73, p 0.001).

Conclusion: Serum ferritin ≥1,000 ng/mL is associated with significantly worse 90-day outcomes in AH. Ferritin represents a simple, inexpensive biomarker that may aid in prognostic assessment and risk stratification. Prospective studies with multivariable adjustment are warranted.

Keywords: Ferritin 1; Sepsis 2; Alcohol 3.

INTRODUCTION

Alcoholic hepatitis (AH) is a clinical syndrome characterized by the rapid onset of jaundice in the setting of heavy and prolonged alcohol consumption, representing one of the most severe manifestations of alcohol-associated liver disease (ALD) [1,2]. The condition affects 10–35% of heavy drinkers, with hospitalization most common between ages 45 and 65 years and a male predominance [3]. The NIAAA Alcoholic Hepatitis Consortia defines AH as the onset of jaundice within 60 days of heavy alcohol consumption (>50 g/day) for a minimum of 6 months, with bilirubin >3 mg/dL, AST 50–400 U/L, and AST: ALT ratio >1.5, after exclusion of other causes of acute hepatitis [4].

The pathogenesis involves alcohol-mediated oxidative stress, reduction of nicotinamide adenine dinucleotide, inhibition of triglyceride oxidation, promotion of lipogenesis, and release of proinflammatory cytokines, causing hepatocellular injury [2]. Patients present with jaundice, fever, right upper quadrant pain, tender hepatomegaly, and signs of portal hypertension. Severe presentations include ascites, hepatic encephalopathy, and coagulopathy [1,2]. Histologically, AH is characterized by steatosis, hepatocyte ballooning, cholestasis, neutrophilic infiltration, and Mallory-Denk bodies [3].

Computed tomography or ultrasound is used to assess the liver and exclude biliary disorders. Laboratory evaluation includes liver function tests, prothrombin time/INR, creatinine, and serum sodium [3]. Treatment includes alcohol abstinence, nutritional support, and for severe AH (Maddrey discriminant function [MDF] ≥32 or MELD >20), a short course of prednisolone (40 mg/day for 28 days) after exclusion of infection [1]. Pentoxifylline is no longer recommended based on the STOPAH trial, which demonstrated no survival benefit [3-5]. The Lille score at day 7 guides continuation or cessation of corticosteroids [1-3]. Liver transplantation may be considered in select patients who are nonresponsive to steroids [1].

Mortality rates exceed 50% if not managed promptly, and several

Submitted: 15 June 2026 | **Accepted:** 07 July 2026 | **Published:** 08 July 2026

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Citation: Grover P, Kaur G, Jain R, Singh K, Singh B, (2026) Ferritin as a Prognostic Marker for Mortality and Critical Inpatient Outcomes in the Alcohol Related Hepatitis Population . J Gen Med 6(1): 1024.

prognostic scoring systems exist. The MELD score is the best static scoring system for predicting short-term mortality, with an AUC of 0.77 for 28-day mortality in a global study of 2,581 patients, outperforming the MDF (AUC 0.70) [6,7]. The combination of baseline MELD and Lille score at day 7 provides the best discrimination for medium-term mortality [3-7]. Other predictors include acute kidney injury, gastrointestinal bleeding, and protein-energy malnutrition [2].

Ferritin is an intracellular iron storage protein and an acute-phase reactant [8,9]. It is the principal storage protein for iron, with the liver serving as the principal storage site [8]. Serum (extracellular) ferritin is largely iron-poor and functions primarily as a biomarker; it should not be confused with transferrin, which is the plasma transport protein for iron [8,9]. Low serum ferritin is highly specific for iron deficiency anemia, while elevated values occur in transfusion-related iron overload, hemochromatosis, and inflammatory states [9,10]. In ALD, ethanol increases iron absorption, stimulates ferritin synthesis, and activates hepatic stellate cells, promoting fibrosis and inflammation [11]. Hepatocellular damage releases stored intracellular ferritin into the circulation, and proinflammatory cytokines further upregulate ferritin production [8,9].

Ferritin has been shown to correlate with disease severity in chronic liver disease. A meta-analysis of eight studies (n = 1,829) demonstrated that elevated serum ferritin was associated with increased mortality in decompensated cirrhosis (pooled unadjusted HR 2.38; 95% CI: 1.78–3.18) [12]. In severe AH specifically, Gkamprela et al., reported that the ferritin-to-hemoglobin ratio outperformed MELD, Maddrey, and Glasgow AH scores in predicting 28-day mortality in a cohort of 46 patients [13]. However, a study of 238 severe alcoholics found that ferritin was related to inflammatory cytokines (IL-6, IL-8) but not independently associated with mortality. After multivariable adjustment albumin, IL-6, alcohol cessation, and transferrin saturation index were the independent predictors [11]. Notably, Atkinson et al. evaluated iron parameters in 828 patients from the STOPAH trial and found that serum transferrin (not ferritin) was the best iron-related predictor of 28-day (AUC 0.72) and 90-day survival (AUC 0.65), with performance comparable to composite scoring systems [14].

Given these conflicting findings and the widespread availability and low cost of ferritin testing, we evaluated the association between serum ferritin levels and short-term clinical outcomes in a large, multicenter cohort of patients with AH.

MATERIALS AND METHODS

The Materials and Methods Data Source

This retrospective cohort study utilized the TriNetX US Collaborative Network, a federated database containing de-identified electronic health records from 70 healthcare organizations across the United States. This study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [15].

Study Population

Patients with a diagnosis of alcoholic hepatitis were identified using ICD-10 codes K70.1 (alcoholic hepatitis), K70.10 (alcoholic hepatitis without ascites), and K70.11 (alcoholic hepatitis with ascites). Eligible patients were required to have a documented first ferritin during admission.

Exclusion Criteria

Patients with the following conditions were excluded: autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, chronic hepatitis B, chronic hepatitis C, acute hepatitis B, acute hepatitis C, acute hepatitis A, acute hepatitis E, HFE gene analysis indicating hereditary hemochromatosis, and Wilson disease.

Cohort Definition

Patients were stratified according to their ferritin into a low-ferritin cohort (ferritin 1,000 ng/mL) and a high-ferritin cohort (ferritin ≥1,000 ng/mL).

Outcomes

The primary outcome was all-cause mortality within 90 days. Secondary outcomes included hepatic failure, sepsis, shock (circulatory failure causing tissue hypoperfusion), ascites, spontaneous bacterial peritonitis, esophageal variceal bleeding, and hepatic encephalopathy.

Statistical Analysis

Risk analyses were performed within a 90-day follow-up period beginning one day after cohort entry. Hazard ratios (HRs), risk ratios (RRs), and 95% confidence intervals (CIs) were calculated. Statistical significance was defined as p 0.05.

RESULTS

Patient Characteristics

A total of 73,476 patients met the inclusion criteria. The low-ferritin cohort included 58,815 patients, while the high-ferritin cohort included 14,661 patients.

Primary Outcome

Mortality: Patients with ferritin >1,000 ng/mL experienced significantly higher 90-day mortality compared with patients with ferritin <1,000 ng/mL (20.0% vs. 8.7%; HR 2.66, p 0.001). The probability of survival at 90 days was 90.58% in the low-ferritin cohort and 77.33% in the high-ferritin cohort (p 0.001).

Secondary Outcomes

Outcome	Ferritin 1,000	Ferritin ≥1,000	HR (p value)
Hepatic failure	20.8%	27.7%	1.55 (p 0.001)
Sepsis	9.1%	14.8%	1.85 (p 0.001)
Shock	4.7%	8.2%	1.94 (p 0.001)
Ascites	20.2%	21.2%	1.17 (p 0.001)
SBP	3.7%	5.0%	1.52 (p 0.001)
Variceal bleeding	1.9%	1.2%	0.73 (p 0.001)
Hepatic encephalopathy	9.5%	11.0%	1.32 (p 0.001)

Hepatic Failure

The incidence of hepatic failure was significantly greater among patients with elevated ferritin (27.7% vs. 20.8%; HR 1.55, p 0.001).

Sepsis

Patients with elevated ferritin demonstrated a substantially higher risk of sepsis (14.8% vs. 9.1%; HR 1.85, p 0.001).

Shock

Shock occurred significantly more frequently among patients with ferritin ≥1,000 ng/mL (8.2% vs. 4.7%; HR 1.94, p 0.001).

Ascites

Ascites was modestly more common in the high-ferritin group (21.2% vs. 20.2%; HR 1.17, p 0.001)..

Spontaneous Bacterial Peritonitis

SBP occurred more frequently in the high-ferritin cohort (5.0% vs.

3.7%; HR 1.52, p 0.001).

Esophageal Variceal Bleeding

Unexpectedly, esophageal variceal bleeding occurred less frequently in the high-ferritin cohort (1.2% vs. 1.9%; HR 0.73, p 0.001).

Hepatic Encephalopathy

Hepatic encephalopathy was more common in the high-ferritin group (11.0% vs. 9.5%; HR 1.32, p 0.001).

DISCUSSION

Ferritin serves not only as a marker of iron stores but also as an indicator of systemic inflammation and hepatocellular damage [8,9]. Ferritin > 1,000 ng/mL in alcoholic hepatitis reflects a combination of massive hepatocellular necrosis (releasing stored intracellular ferritin) and an acute-phase inflammatory response driven [16]. Alcohol downregulates hepcidin, leading to inappropriately increased duodenal iron absorption and hepatic iron deposition in up to 52% of patients with alcohol-associated liver disease [16]. The resulting labile ferrous iron generates reactive oxygen species (ROS), causing lipid peroxidation and mitochondrial damage. A meta-analysis of 1,829 patients with decompensated cirrhosis confirmed that elevated ferritin was associated with a pooled HR of 2.38 (95% CI 1.78–3.18) for mortality, with the prevalence of hyperferritinemia being highest in alcohol-associated liver disease [17].

In this large multicenter cohort of 73,476 patients with alcoholic hepatitis, serum ferritin levels >1,000 ng/mL were associated with substantially worse short-term outcomes, including a more than twofold increase in 90-day mortality (HR 2.66). This finding is consistent with a meta-analysis by Liu et al. demonstrating that elevated serum ferritin was associated with increased mortality in decompensated cirrhosis (pooled HR 2.38; 95% CI: 1.78–3.18) [12]. This is one of the largest retrospective analyses compared to previous studies.

The mortality association observed in this study (HR 2.66 for ferritin > 1000 ng/mL) is broadly consistent with prior smaller studies. Gkamprela et al., reported that the ferritin-to-hemoglobin ratio outperformed MELD, Maddrey, and Glasgow AH scores in predicting 28-day mortality in 46 patients with AH [13]. Vijayalekshmi et al., found that 82% of patients with severe AH had ferritin >500 ng/mL, and reticuloendothelial activation markers (including ferritin) correlated with MELD and SOFA scores [18].

However, the relationship between ferritin and mortality in ALD is not standard. Ribot-Hernández et al., studied 238 severe alcoholics and found that while ferritin was elevated and correlated with inflammatory cytokines, it was not in-dependently associated with mortality after multivariable adjustment; albumin, IL-6, alcohol cessation, and transferrin saturation index were the independent predictors [11]. Similarly, Atkinson et al., evaluated comprehensive iron parameters in 828 patients from the STOPAH trial. They found that serum transferrin, not ferritin, was the best iron-related predictor of survival (AUC 0.72 for 28-day mortality), with performance comparable to composite scoring systems [14]. These findings suggest that the prognostic value of ferritin may be confounded by disease severity.

The strong association with sepsis is plausible through two mechanisms: iron-enhanced microbial virulence and iron-mediated immune dysfunction. Excess circulating iron provides a critical growth substrate for bacterial pathogens, including Klebsiella, E. coli, and Pseudomonas, all of which have increased virulence in iron-replete environments [19]. Simultaneously, iron overload impairs host defenses through decreased phagocytosis by monocytes and polymorphonuclear leukocytes, alterations in T-lymphocyte subsets (increased CD8, decreased CD4), impaired immunoglobulin secretion, and suppression of complement function [19]. Tornai et al., demonstrated that ferritin >310μg/L was independently associated with bacterial infections in decompensated patients (sHR 2.335; 95% CI 1.193–4.568) [20]. The combination of alcohol-induced gut barrier disruption, bacterial translocation, and iron-mediated immune paralysis creates a particularly high-risk milieu for sepsis in this population [20].

Ferritin in cirrhosis correlates with markers of circulatory dysfunction. Ripoll et al. demonstrated significant negative correlations between ferritin and mean arterial pressure ($r = -0.360$, $p = 0.014$) and serum sodium ($r = -0.419$, $p = 0.002$), both hallmarks of the hyperdynamic circulatory state that predisposes to hemodynamic collapse [21]. The modest but statistically significant association with ascites is consistent with ferritin's correlation with liver insufficiency rather than portal hypertension per se. Ripoll et al. found that ferritin correlated with markers of hepatic synthetic failure (INR: $r = 0.333$; bilirubin: $r = 0.378$; MELD: $r = 0.293$) but not with hepatic venous pressure gradient (HVPG) [21]. The SBP association is supported by Maiwall et al., who demonstrated a significant correlation between ferritin and SBP ($p = 0.02$) in 318 patients with decompensated cirrhosis [22]. The mechanism is immune-mediated as discussed previously explained.

Tornai et al., found that patients who had previously survived variceal bleeding had significantly lower ferritin levels (median 43.1 vs. 146.6 μg/L, $p < 0.001$), like our study. The association between ferritin and hepatic encephalopathy is supported by Maiwall et al., who found a highly significant correlation ($p < 0.001$) between ferritin and HE in decompensated cirrhosis, with HE being the strongest independent predictor of early mortality (HR 3.47) [22]. Mechanistically, iron disrupts cerebral ammonia metabolism: Görg et al., demonstrated that ammonia-induced upregulation of heme oxygenase-1 (HO1) in astrocytes leads to elevated free ferrous iron levels in the brain, which triggers oxidative stress, endoplasmic reticulum stress, and astrocyte senescence, contributing to the neuropsychiatric manifestations of HE [24].

This study has several important limitations. First, its retrospective observational design precludes the establishment of causality. Second, the high-ferritin cohort likely differs substantially in baseline disease severity (higher bilirubin, higher MELD, more advanced liver disease), and the observed associations may partly reflect disease severity rather than an independent prognostic effect of ferritin. Third, a baseline characteristics table comparing demographics, laboratory values (bilirubin, AST, ALT, INR, creatinine, albumin, platelet count), and comorbidities between cohorts was not included, limiting assessment of between-group differences. Fourth, the ferritin threshold of 1,000 ng/mL was not empirically derived. Fifth, the timing of ferritin measurement relative to admission is defined as "same admission," and it is slightly nonspecific. Sixth, information regarding alcohol consumption patterns, corticosteroid therapy, MELD score, Maddrey discriminant function, and Lille score was unavailable, precluding assessment of whether ferritin adds incremental value beyond existing prognostic models. This also creates bias, given the prognostic value of concomitant infections and the MELD score itself. Seventh, ferritin is an acute-phase reactant and may reflect inflammation rather than iron overload alone [9]. Eighth, the accuracy of ICD-10 codes for identifying true AH in administrative databases is imperfect and may include patients with broader alcohol-related liver disease. Finally, subgroup analyses by ascites status (K70.10 vs. K70.11), sex, and age were not performed.

CONCLUSIONS

Serum ferritin >1,000 ng/mL is associated with significantly worse 90-day outcomes in patients with alcoholic hepatitis, including increased risks of hepatic failure, sepsis, shock, hepatic encephalopathy, spontaneous bacterial peritonitis, and mortality. Prospective studies with multivariable adjustment, formal comparison with existing prognostic scores (MELD, Lille), and evaluation of optimal ferritin thresholds are warranted to determine whether ferritin can be incorporated into clinical

prognostic models for AH.

AUTHOR CONTRIBUTIONS

"Conceptualization, B.S. and P.G.; methodology, B.S.; formal analysis, B.S.; investigation, B.S.; resources, B.S.; data curation, B.S.; writing—original draft preparation, G.K.; writing—review and editing, R.J.; visualization, K.S.; supervision, B.S. All authors have read and agreed to the published version of the manuscript.

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