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Research Article

Association of Serum Ferritin Levels with Liver Fibrosis Severity in Patients with Non-Alcoholic Fatty Liver Disease

Dr. Jairaj V Bomman [1], Dr. Aishhwarrya Umeshchandara G[2], Dr. Karthik Ravindra Dhaded[3]

[1]Assistant Professor, Department of Medical Gastroenterology, Gulbarga Institute of Medical Sciences - SSH – Kalaburagi, India.
[2]Consultant Endocrinologist at Laparoscopy Hospital Kalaburagi, India.
[3]Assistant Professor, Department of Peadiatric Surgery, Gulbarga Institute of Medical Sciences -SSH – Kalaburagi, India.

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Corresponding Author: Dr. Jairaj V Bomman, Department of Medical Gastroenterology, Gulbarga Institute of Medical Sciences -SSH – Kalaburagi, India.
Email: jrajbomman@gmail.com

ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease worldwide and encompasses a spectrum ranging from simple hepatic steatosis to non-alcoholic steatohepatitis, progressive fibrosis, cirrhosis, and hepatocellular carcinoma. Liver fibrosis is the strongest predictor of adverse clinical outcomes in NAFLD. Although liver biopsy remains the gold standard for fibrosis assessment, its invasive nature limits routine application. Serum ferritin, an acute-phase reactant and marker of iron metabolism, has been proposed as a potential non-invasive biomarker for identifying patients with advanced liver fibrosis. **Aim:** To evaluate the association between serum ferritin levels and liver fibrosis severity in patients with non-alcoholic fatty liver disease. **Materials and Methods:** A hospital-based cross-sectional observational study was conducted among 70 adult patients with ultrasonographically diagnosed NAFLD. Serum ferritin levels were estimated using standard laboratory methods. Liver fibrosis severity was assessed using transient elastography (FibroScan), Fibrosis-4 (FIB-4) Index, and NAFLD Fibrosis Score (NFS). Patients were categorized according to fibrosis stage, and serum ferritin concentrations were compared across different fibrosis groups. Statistical analysis was performed using SPSS software version 26. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. One-way ANOVA, Chi-square test, and correlation analysis were used where appropriate. A p-value <0.05 was considered statistically significant. **Results:** Among the 70 patients, 41.4% had mild fibrosis (F0–F1), 27.1% had moderate fibrosis (F2), 18.6% had advanced fibrosis (F3), and 12.9% had cirrhosis (F4) based on FibroScan findings. Mean serum ferritin levels increased progressively with fibrosis severity, from 182.6 ± 48.3 ng/mL in

F0–F1 patients to 438.2 ± 82.5 ng/mL in F4 patients ($p < 0.001$). Patients classified as high-risk according to FIB-4 and NAFLD Fibrosis Score also demonstrated significantly higher serum ferritin concentrations than low-risk groups ($p < 0.001$). A significant positive correlation was observed between serum ferritin levels and liver stiffness measurements, indicating that elevated ferritin was associated with worsening hepatic fibrosis. **Conclusion:** Serum ferritin levels are significantly associated with liver fibrosis severity in patients with non-alcoholic fatty liver disease. Although serum ferritin cannot replace established non-invasive fibrosis assessment tools, it represents a simple, inexpensive, and widely available adjunctive biomarker that may assist in identifying patients at increased risk of advanced fibrosis. Combining serum ferritin estimation with validated fibrosis scoring systems and transient elastography may improve early risk stratification and reduce the need for invasive liver biopsy.

Keywords: Non-alcoholic fatty liver disease, Serum ferritin, Liver fibrosis, FibroScan, FIB-4, NAFLD Fibrosis Score, Non-invasive biomarkers.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has become the most prevalent chronic liver disorder worldwide and is closely associated with obesity, insulin resistance, metabolic syndrome, and type 2 diabetes mellitus. It affects nearly one-quarter of the global population and is increasingly recognized as a leading indication for liver transplantation owing to progressive liver fibrosis and cirrhosis. Despite its high prevalence, only a subset of patients develops advanced fibrosis, making early identification of high-risk individuals an important clinical objective.[1]

NAFLD encompasses a spectrum ranging from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH), progressive fibrosis, cirrhosis, portal hypertension, and hepatocellular carcinoma. Among these pathological stages, liver fibrosis has emerged as the strongest independent predictor of liver-related complications and overall mortality. Therefore, accurate assessment of fibrosis severity is fundamental in guiding treatment decisions and predicting long-term prognosis.[2]

Liver biopsy remains the reference standard for diagnosing and staging fibrosis. However, because of its invasive nature, sampling variability, risk of complications, and limited patient acceptance, it is unsuitable for routine screening or serial follow-up. Consequently, several non-invasive methods have been developed, including transient elastography (FibroScan), Fibrosis-4 (FIB-4) Index, and the NAFLD Fibrosis Score (NFS), all of which have demonstrated acceptable diagnostic performance in identifying advanced fibrosis.[3,4]

Recent evidence suggests that iron metabolism plays an important role in the pathogenesis and progression of NAFLD. Ferritin is the principal intracellular iron storage protein and also functions as an acute-phase reactant. Elevated serum ferritin levels may reflect increased hepatic iron deposition, oxidative stress, hepatocyte injury, and chronic systemic inflammation. Iron-induced oxidative stress promotes activation of hepatic stellate cells, extracellular matrix deposition, and progressive hepatic fibrogenesis, thereby contributing to worsening liver fibrosis.[5]

Several clinical studies have demonstrated an association between elevated serum ferritin levels and advanced hepatic fibrosis in patients with NAFLD. Increased ferritin concentrations have been correlated with higher liver stiffness measurements, greater histological fibrosis, elevated aminotransferase levels, and increased

inflammatory activity. Nevertheless, published findings remain inconsistent, with some studies reporting only modest predictive value of ferritin when used as an isolated biomarker. These conflicting observations highlight the need for further evaluation of serum ferritin as an adjunctive non-invasive marker of fibrosis severity.[6,7]

Because serum ferritin estimation is inexpensive, widely available, and routinely performed in clinical practice, establishing its relationship with liver fibrosis could provide clinicians with an accessible tool for identifying patients requiring further evaluation by FibroScan or specialist referral. Combining serum ferritin with established fibrosis scoring systems may improve risk stratification and reduce unnecessary liver biopsies. [8]

Therefore, the present study aims to evaluate the association between serum ferritin levels and liver fibrosis severity in patients with non-alcoholic fatty liver disease using validated non-invasive fibrosis assessment methods including transient elastography, Fibrosis-4 Index, and NAFLD Fibrosis Score.

MATERIALS AND METHODS

Study Design

Hospital-based cross-sectional observational study.

Study Setting

Department of Gastroenterology/General Medicine of a tertiary care teaching hospital.

Study Duration

12 months after Institutional Ethics Committee approval.

Study Population

Adult patients diagnosed with non-alcoholic fatty liver disease attending outpatient or inpatient services.

Sample Size

70 patients with NAFLD.

Sampling Technique

Consecutive sampling.

Inclusion Criteria

- Age ≥18 years.
- Ultrasound evidence of fatty liver.
- Patients diagnosed with NAFLD.
- Willing to provide written informed consent.

Exclusion Criteria

- Significant alcohol consumption (>30 g/day in males and >20 g/day in females).
- Viral hepatitis.
- Autoimmune liver disease.
- Wilson disease.
- Hemochromatosis.
- Drug-induced liver disease.
- Hepatocellular carcinoma.
- Pregnancy.
- Known chronic inflammatory diseases affecting serum ferritin.

Study Procedure

After informed consent, demographic and clinical details will be recorded. Blood samples will be collected for estimation of serum ferritin and routine biochemical investigations. Liver fibrosis severity will be assessed using transient elastography (FibroScan). Fibrosis staging will also be evaluated using Fibrosis-4 (FIB-4) Index and NAFLD Fibrosis Score (NFS).

Assessment of Liver Fibrosis

FibroScan (Transient Elastography)

Liver stiffness measurement will be performed after overnight fasting using FibroScan.

Fibrosis stages:

- **F0–F1:**<7.0 kPa
- **F2:** 7.0–9.4 kPa
- **F3:** 9.5–12.4 kPa
- **F4:** ≥12.5 kPa

Fibrosis-4 (FIB-4) Index

[\text{FIB-4}=\frac{\text{Age}\times AST}{Platelet\times \sqrt{ALT}}]

Interpretation:

- <1.45 = Low fibrosis
- 1.45–3.25 = Intermediate fibrosis
- 3.25 = Advanced fibrosis

NAFLD Fibrosis Score (NFS)
Calculated using age, BMI, diabetes status, AST/ALT ratio, platelet count, and serum albumin.
Interpretation:

- <-1.455 = Low fibrosis
- -1.455 to 0.675 = Indeterminate
- 0.675 = Advanced fibrosis

Primary Outcome Measure
Association between serum ferritin levels and liver fibrosis severity.
Secondary Outcome Measures

- Correlation of serum ferritin with FibroScan liver stiffness.
- Correlation between serum ferritin and FIB-4 score.
- Correlation between serum ferritin and NAFLD Fibrosis Score.
- Diagnostic utility of serum ferritin for predicting advanced fibrosis.

Statistical Analysis
Data will be analyzed using SPSS version 26. Continuous variables will be expressed as mean ± SD, while categorical variables will be presented as frequencies and percentages. Student's t-test or one-way ANOVA will compare mean serum ferritin across fibrosis stages. Pearson or Spearman correlation coefficients will assess relationships between serum ferritin and fibrosis scores. Multivariate logistic regression will identify independent predictors of advanced fibrosis. Receiver operating characteristic (ROC) curve analysis will determine the diagnostic performance and optimal serum ferritin cutoff for advanced fibrosis. A p-value <0.05 will be considered statistically significant.

RESULTS
A total of **70 patients** with ultrasonographically confirmed non-alcoholic fatty liver disease (NAFLD) were included in the present study. Liver fibrosis severity was evaluated using transient elastography (FibroScan), Fibrosis-4 (FIB-4) Index, and NAFLD Fibrosis Score (NFS). Serum ferritin concentrations were compared across different fibrosis stages to determine their association with disease severity.

Table 1: Distribution of Patients According to Liver Fibrosis Stage by FibroScan

FibroScan Fibrosis Stage	Liver Stiffness (kPa)	Number (n=70)	Percentage (%)
F0–F1 (Mild)	<7.0	29	41.4
F2 (Moderate)	7.0–9.4	19	27.1
F3 (Advanced)	9.5–12.4	13	18.6
F4 (Cirrhosis)	≥12.5	9	12.9
Total	—	**70**	**100**

Among the 70 NAFLD patients, **41.4%** had mild fibrosis (F0–F1), whereas **58.6%** demonstrated clinically significant fibrosis (F2–F4). Advanced fibrosis (F3–F4) was identified in **31.5%** of patients, indicating that nearly one-third of the study population had severe liver disease requiring closer clinical monitoring.

Table 2: Comparison of Serum Ferritin Levels According to FibroScan Fibrosis Stage

Fibrosis Stage	Serum Ferritin (ng/mL) Mean ± SD	p value
F0–F1	182.6 ± 48.3	
F2	246.9 ± 55.7	
F3	332.8 ± 71.4	
F4	438.2 ± 82.5	**<0.001**

Mean serum ferritin levels increased progressively with advancing fibrosis. Patients with cirrhosis (F4) exhibited the highest ferritin concentration (**438.2 ± 82.5 ng/mL**), whereas those with mild fibrosis showed the lowest values (**182.6 ± 48.3 ng/mL**). The difference among fibrosis stages was

highly statistically significant (p<0.001), suggesting a strong association between elevated serum ferritin and liver fibrosis severity.

Table 3: Association of Serum Ferritin with Non-invasive Fibrosis Scores

Fibrosis Assessment	Category	Number (%)	Mean Serum Ferritin (ng/mL)	p value
FIB-4 Score	Low Risk (<1.45)	34 (48.6%)	191.5 ± 49.8	
	Intermediate (1.45–3.25)	24 (34.3%)	291.8 ± 67.2	
	High Risk (>3.25)	12 (17.1%)	401.6 ± 76.8	**<0.001**
NAFLD Fibrosis Score	Low Fibrosis	28 (40.0%)	185.9 ± 51.6	
	Indeterminate	24 (34.3%)	274.6 ± 63.4	
	Advanced Fibrosis	18 (25.7%)	396.8 ± 79.5	**<0.001**

Serum ferritin demonstrated a significant positive relationship with both validated non-invasive fibrosis scores. Patients classified as having high-risk fibrosis by FIB-4 exhibited a mean ferritin level of **401.6 ± 76.8 ng/mL**, which was more than double that observed in the low-risk group. Similarly, patients with advanced fibrosis according to the NAFLD Fibrosis Score had significantly higher ferritin concentrations (**396.8 ± 79.5 ng/mL**) than those with low fibrosis (**185.9 ± 51.6 ng/mL**). These differences were statistically highly significant (**p<0.001**).

Overall, findings suggest that elevated serum ferritin is strongly associated with advanced liver fibrosis and may serve as a useful adjunctive non-invasive biomarker when interpreted alongside established fibrosis assessment tools such as FibroScan, FIB-4, and NAFLD Fibrosis Score. Combining serum ferritin estimation with existing non-invasive scoring systems may improve early identification of patients at risk for progressive liver disease and reduce the need for invasive liver biopsy in selected clinical settings.

DISCUSSION

The present study evaluated the association between serum ferritin levels and liver fibrosis severity in patients with non-alcoholic fatty liver disease (NAFLD) using non-invasive fibrosis assessment tools, namely FibroScan, Fibrosis-4 (FIB-4) Index, and NAFLD Fibrosis Score (NFS). The results demonstrated that serum ferritin levels increased progressively with advancing fibrosis, with significantly higher concentrations observed among patients with advanced fibrosis (F3–F4). These findings indicate that serum ferritin may serve as an inexpensive and readily available biomarker reflecting the severity of hepatic fibrogenesis in NAFLD.

Liver fibrosis is the principal determinant of long-term prognosis in NAFLD, outweighing hepatic steatosis and necroinflammatory activity in predicting liver-related complications and mortality. Consequently, identifying reliable non-invasive biomarkers capable of recognizing advanced fibrosis remains an important clinical objective. Although transient elastography and validated fibrosis scoring systems are increasingly recommended in routine practice, additional laboratory markers may further improve early risk stratification.[9]

In the present study, approximately one-third of the study population had advanced fibrosis according to FibroScan, while serum ferritin concentrations increased significantly across successive fibrosis stages. This observation is

biologically plausible because ferritin reflects both iron storage and chronic inflammatory activity. Excess hepatic iron contributes to oxidative stress through generation of reactive oxygen species, resulting in hepatocyte injury, activation of hepatic stellate cells, collagen deposition, and progressive fibrosis. Therefore, elevated ferritin levels may indicate ongoing fibrogenesis rather than merely increased iron stores.[10]

Our findings are in agreement with the recent study by **Memar et al.**, who demonstrated a significant association between serum ferritin concentration and histological fibrosis severity in patients with NAFLD. Their study reported that patients with advanced fibrosis exhibited markedly higher serum ferritin values compared with those having mild disease, suggesting that ferritin may be useful as a supplementary non-invasive biomarker for fibrosis assessment. The authors also emphasized that serum ferritin should be interpreted in conjunction with established fibrosis scoring systems rather than as an isolated diagnostic marker.[10]

Similarly, the systematic review conducted by **Wang et al.** evaluated multiple observational studies investigating ferritin across different stages of NAFLD and concluded that elevated serum ferritin levels were consistently associated with greater disease severity, particularly among patients with advanced fibrosis and non-alcoholic steatohepatitis. However, the review also highlighted substantial heterogeneity among studies because serum ferritin is influenced by obesity, metabolic syndrome, systemic inflammation, and insulin resistance in addition to hepatic iron deposition.[11]

The evolving concept of metabolic dysfunction-associated fatty liver disease (MAFLD) further supports the close relationship between metabolic inflammation and progressive liver fibrosis. **Eslam et al.** proposed replacing the traditional NAFLD terminology with MAFLD to better reflect the underlying metabolic pathophysiology driving hepatic injury. Since ferritin is closely associated with chronic low-grade inflammation and metabolic dysfunction, elevated ferritin concentrations may also reflect the systemic metabolic abnormalities responsible for fibrosis progression.[12]

Our results also align with the changing epidemiological trends described by **Paik et al.**, who reported a continuously increasing global prevalence of NAFLD and non-alcoholic steatohepatitis, making early identification of advanced fibrosis increasingly important for reducing liver-related morbidity and mortality. The authors emphasized that readily available non-invasive biomarkers capable of identifying high-risk individuals will play an essential role in future screening strategies, particularly in resource-limited healthcare settings where access to liver biopsy or advanced imaging remains limited.[13]

Although the present study demonstrated a strong association between serum ferritin and liver fibrosis severity, serum ferritin should not be considered a standalone diagnostic test. Ferritin is an acute-phase reactant and may be elevated in chronic inflammatory disorders, infections, malignancy, metabolic syndrome, and obesity independent of liver fibrosis. Consequently, isolated ferritin measurement has limited specificity. The greatest clinical utility appears to be achieved when ferritin estimation is combined with validated non-invasive fibrosis assessment tools such as FibroScan, FIB-4, and NAFLD Fibrosis Score, thereby improving overall diagnostic confidence.[10–13]

The strengths of the present study include assessment of fibrosis using three validated non-invasive modalities and evaluation of serum ferritin as a simple laboratory parameter that is routinely available in clinical practice. However, certain limitations should be acknowledged. Liver

biopsy was not performed because of its invasive nature and associated risks. The relatively small sample size and single-center design may also restrict generalizability. Future multicenter prospective studies with larger populations and histological confirmation are warranted to establish optimal ferritin cut-off values for predicting advanced fibrosis and to evaluate its prognostic value during long-term follow-up.

CONCLUSION

The present study demonstrates that serum ferritin levels are significantly associated with increasing liver fibrosis severity among patients with non-alcoholic fatty liver disease. Elevated ferritin concentrations correlated with higher FibroScan liver stiffness measurements and increased non-invasive fibrosis scores, suggesting that serum ferritin reflects progressive hepatic fibrogenesis. Although ferritin alone cannot replace established fibrosis assessment methods, it represents a simple, inexpensive, and widely available adjunctive biomarker that may improve identification of patients at risk for advanced fibrosis. Integration of serum ferritin with validated non-invasive fibrosis assessment tools may facilitate earlier diagnosis, better risk stratification, timely referral for specialist care, and reduction in unnecessary invasive liver biopsies.

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