SERUM FERRITIN AS A PREDICTOR OF EARLY MORTALITY IN CHRONIC LIVER DISEASE AND ITS RELATION TO MELD SCORE

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ABSTRACT

BACKGROUND

Orthotopic liver transplantation is the only definitive treatment for end-stage liver disease. Liver transplant waiting list mortality remains a major concern. Hence, it is important to have early predictors of mortality in end-stage liver disease.

Aims and Objectives-

1. To assess the level of serum ferritin in chronic liver disease and its role as a predictor of early mortality.
2. To compare serum ferritin level in patients with chronic liver disease to Modified End-Stage Liver Disease (MELD) score and to measure serum ferritin in various complications of liver disease.

MATERIALS AND METHODS

This is a prospective observational study. After obtaining Institutional Ethical Committee approval, 250 consenting patients satisfying inclusion criteria were enrolled. Demographic, clinical, biochemical, ultrasonographic and endoscopic parameters were recorded by structured questionnaire. Serum ferritin level was measured (by chemiluminescent method) in each patient. Data analysis was done using SPSS software (Version 15). Tests of significance were done to find the objectives of the study.

RESULTS

Mean age of the study group was 52.2 years. Male:female ratio was 4.1:1. Serum ferritin was elevated in 41.2% of patients, decreased in 2% and normal in 56.8% of the patients. Increased ferritin level was found to predict early mortality in patients with chronic liver disease, area under curve was 0.682 with 95% CI (0.592 - 0.772). Ferritin level > 500 has a sensitivity of 53.8% and specificity of 74.4% to predict the mortality. Serum ferritin correlates positively with MELD score. Mean ferritin in ascites was 490.16, SBP- 479.52, variceal bleed- 700.88, hepatorenal syndrome- 627.01 and in hepatic encephalopathy- 572.59.

CONCLUSION

Elevated serum ferritin is an early predictor of mortality in CLD and it is elevated in various complications of chronic liver disease and correlates well with MELD score.

KEY WORDS

Serum Ferritin, Chronic Liver Disease (CLD), Modified End-Stage Liver Disease (MELD), Non-Alcoholic Steatohepatitis (NASH), Hepatitis B Virus (HBV).

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BACKGROUND

Liver is the largest vital organ of the body, weighing 1- 1.5 kg, which is 1.5 - 2.5% of the lean body mass and is about 1/50 of total body weight.¹ It plays a major role in synthesis of proteins, regulation of nutrients, metabolism and conjugation of bilirubin and drugs, detoxification, production of bile and maintenance of immunity (Kupffer cells).

Chronic Liver Disease (CLD) refers to disease of the liver, which had lasted more than six months. Disease process involves progressive destruction and regeneration of liver

parenchyma leading to fibrosis and cirrhosis. For predicting prognosis of end-stage liver disease, various prognostic models are in use.

An article published by Elizabeth et al² in Annals of Internal Medicine in 2003 showed correlation between ferritin levels and the degree of hepatic fibrosis. Cirrhosis had a probability of 7.4% when serum ferritin level was less than 1000 ng/ mL; when compared to 72% among those with ferritin levels more than 1000 ng/mL; when age and elevated liver enzymes were adjusted.

A Jacobs and M Norwood³ (in NEJM 1975) showed high ferritin concentrations associated with severe or active hepatocellular disease. Serum ferritin is an independent predictor of histologic severity and advanced fibrosis in patients with Non-Alcoholic Fatty Liver Disease (NAFLD) as studied by Kowdley KV et al.⁴

In recent times, Model for End-Stage Liver Disease (MELD) score has been developed to replace Child-Pugh score.⁵ The MELD score is significant in predicting the severity of liver disease and also in predicting mortality in cirrhosis. Number of studies have shown that MELD score

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predicts short-term mortality at 3 months. Hence, it is used to prioritise cadaveric liver transplants.

Some recent studies show that serum ferritin predicts mortality and complications of cirrhosis in patients with decompensated cirrhosis awaiting liver transplantation.⁶ Ferritin levels are significantly raised in acute liver failure.^{6,7} Ferritin is elevated in hepatic necroinflammation and can be used as a marker of liver disease. Among chronic liver diseases, apart from haemochromatosis, hyperferritinemia is also described in patients with metabolic syndrome, non-alcoholic fatty liver disease and viral related chronic liver diseases. In patients with NAFLD,⁸ studies have shown that in patients without iron accumulation in the liver, elevated ferritin concentration is more reflective of histological damage rather than iron overload.⁹

Ferritin is a 24-subunit evolutionarily conserved protein. Within the cytosol, ferritin stores iron in a non-toxic form which is soluble, thereby it protects cells from iron-mediated cytotoxic oxidation-reduction reactions. Damaged hepatocytes release ferritin into serum. It correlates with the rise in alkaline phosphatase. This signifies the presence of ferritin in cytosol of hepatocytes. Thus, serum ferritin can be used as an indirect marker of hepatic necroinflammation.

Currently, there are not much prognostic markers indicating very early mortality in chronic liver disease. Hence, in this study we attempt to study the role of serum ferritin in predicting the 15-day mortality of patients admitted with cirrhosis and also relation of serum ferritin to MELD score.

Aims and Objectives

Primary objective is to assess the level of serum ferritin in patients presenting with chronic liver disease and its role as a predictor of early mortality. Secondary objectives are comparing the level of serum ferritin with MELD score and measurement of serum ferritin in various complications of chronic liver disease.

MATERIALS AND METHODS

This is a prospective observational study, conducted among patients admitted to medical wards of Internal Medicine Department of Medical College Hospital, Trivandrum, done over a period of 1 year from January 2015. Total sample size was 250 and sample size was taken conveniently.

This is based on a study by Rakhi Maiwall et al¹⁰ according to which the serum ferritin predicts early mortality in patients with decompensated cirrhosis, proportion of death in high ferritin group was 41.5% and that in low ferritin group was 25%.

All patients with liver disease whose symptoms and signs persists for more than 6 months were classified as CLD, are included in the study. Diagnosis was supported by Ultrasonography (USG) of abdomen.

Patients with primary hemophagocytic and lymphohistiocytic syndromes, patients with iron overload, those with hepatocellular carcinoma, those with comorbidities with poor outcome- extrahepatic neoplasia, severe cardiopulmonary disease with NYHA > 3, oxygen dependent or steroid dependent COPD patients and patients who do not give an informed written consent were excluded.

Study was conducted using a structured data collection proforma. After ethical clearance, permissions were obtained from Head of the Department of Internal medicine. History, physical examination, blood investigations, radiographic assessment, ascitic fluid study and upper GI endoscopy were done to establish a diagnosis of CLD and its complications. Those found to have CLD were informed about the study in native language. After satisfying the exclusion criteria and getting informed consent, the structured proforma was filled with respective data with clinical details of patients including history and complications of chronic liver disease like ascites, hepatic encephalopathy, SBP, gastrointestinal bleed and hepatorenal syndrome.

Serum ferritin was measured in all patients using chemiluminescent method. A ferritin value of 23.9 - 336.2 ng/mL in males and 11 - 306.8 ng/mL in females was the normal levels set. For comparison with previous studies patients were divided as having ferritin levels < 200, 200-400 and > 400 ng/mL. MELD was calculated as $0.957 \times \log(\text{creatinine}) + 0.378 \times \log(\text{total bilirubin}) + 1.120 \times \log(\text{INR}) + 0.6431$.

Creatinine was measured by Jaffe's method and bilirubin by modified method of Pearlman and Lee.¹¹ Normal Prothrombin time was defined as 12.4 seconds and INR, 1. After obtaining the written informed consent, patients underwent upper gastrointestinal endoscopy on overnight fasting. Endoscopy was correlated with other findings to establish the diagnosis.

Data analysis was done using SPSS 15 version. The qualitative data were expressed as numbers and percentage. Descriptive statistics were mentioned as mean and standard deviation. Comparison of categorical variables was done by Chi-square test. Ferritin levels in CLD patients were estimated and its role in predicting mortality was analysed and ferritin levels were compared with MELD score using One-Way ANOVA and independent sample 't' test. ROC curve is used to find optimum cut-off value of ferritin for predicting mortality. Association of S. ferritin to mortality was assessed by univariate analysis. All statistical tests were 2 tailed and a significance level (p) of 0.05 was used.

RESULTS

In this prospective observational study, 250 patients with chronic liver disease who met the inclusion and exclusion criteria were studied. Serum ferritin was measured in all patients.

In this study, 201 patients were males (80.4%) and 49 (19.6%) were females. Majority of patients were between ages 40 - 60 years. Mean age of the study group was 52.2 years. Mean age in ferritin < 200 group was 53.3, 200-400 was 49.8 and > 400 was 52.1.

Most common aetiology of Chronic Liver Disease (CLD) was alcoholism in cirrhotic dose. It was present in 51.6% patients- 51.7% of < 200 ng/mL ferritin group, 57.2% of 200-400 and 47.1% of > 400 ng/mL group had alcoholism. 26% of patients had NASH- 28.4% in < 200 ng/mL, 16.3% of 200-400 and 28.2% of > 400 had NASH. 18% of our patients had hepatitis B. 10.3% of patients in < 200 ng/mL, 18.4% of 200-400 and 14.4% of > 400 ng/mL had hepatitis B. Hepatitis C was reported in 2.7%.

Frequency distribution of various etiologies in the sample		
Etiology	Frequency	Percent
Alcohol	129	51.6
HBV	36	14.4
HCV	7	2.8
NASH	65	26
OccultHBV	9	3.6
Autoimmune	5	2
Cryptogenic	13	5.2
Wilson's	2	0.8

Infections were present in 63.6% of patients. Pneumonia (21.2%), urinary tract infection (20.8%), cellulitis (14.8%) and SBP (19.6%) were the common infections reported in our study group. Pneumonia occurred in 19.8% of < 200, 26.5% of 200 - 400 and 21.2% of > 400 groups. Cellulitis occurred in 6%, 12.2% and 28.2% of < 200, 200 - 400 and > 400 groups respectively. SBP occurred in 19%, 14.3% and 23.5% of <200, 200-400 and > 400 ng/mL ferritin groups respectively.

Co-morbidities were present in 51.6% of population. Diabetes (22%), hypertension (22%), dyslipidaemia (8.4%) and CAD (6.4%) were the common co-morbidities in this study population.

Frequency distribution of various comorbidities in the sample		
Co morbidities	Frequency	Percent
Co morbidities	129	51.6
DM	55	22
HTN	55	22
CAD	16	6.4
COPD	2	0.8
CVA	2	0.8
TB	3	1.2
Seizure	5	2
Dyslipidemia	21	8.4
Thyroid	6	2.4
Psychiatric	2	0.8
CKD	2	0.8

Mean ferritin in the study group was 488.7 ng/mL. Serum ferritin was low in 2%, elevated in 56.8% and normal in rest of the patients. 46.4% had ferritin < 200, 19.6% had ferritin 200 - 400 and 34% had ferritin > 400 ng/mL.

Mean MELD score in < 200 group was 17.75, in 200 - 400 was 25.32 and > 400 group was 31.07. So as ferritin increases, MELD score also increases ($p < 0.001$) and there was significant correlation between MELD score and serum ferritin.

These findings correlate to the study by Walker et al.

Ferritin (ng/ml)	N	MELD score	
		Mean	sd
<200	116	17.758	6.0110
200-400	49	25.328	8.3413
>400	85	31.072	10.1527
Total	250	23.769	10.0193

Mean MELD Score in various Ferritin Groups

90% of patients belonged to Child C and 10% belonged to Child B- 16.4% of < 200, 6.1% of 200 - 400 and 3.5% of > 400ng/mL ferritin group belonged to Child B. 83.6% of < 200, 93.9% of 200 - 400 and 96.5% of > 400 belonged to Child C. As the Child score increases, serum ferritin increases and it was found to be significant ($p = 0.000$).

15.6% of patients expired among the study population. 6.9% of < 200, 20.4% of 200 - 400 and 24.7% of > 400 group died. As ferritin level increases, mortality increases and change was found to be significant. Mean ferritin in mortality group was 791.5 and that in alive group was 432.5 and the difference was significant. A ferritin value of 500 had a sensitivity of 53.8% and specificity of 74.4% with the area under curve of 0.682 with 95% CI (0.592 - 0.772).

Mortality	Ferritin						TOTAL		P
	<200		200-400		>400				
	N	%	N	%	N	%	N	%	
Dead	8	6.9	10	20.4	21	24.7	39	15.6	0.002
Alive	108	93.1	39	79.6	64	75.3	211	84.4	
Total	116	100	49	100	85	100	250	100	

Distribution of Mortality in various Ferritin Groups

144 (85.6%) patients had ascites. 81.9% of < 200, 87.8% of 200 - 400 and 89.4% of > 400 ng/mL ferritin group had ascites. This difference was not statistically significant. Mean ferritin in ascites group was 490.2 and that in non-ascitic group was 479.9. This is similar to Rakhi Maiwall et al study group, but ascites was not related to ferritin levels. In their study, Walker et al¹² also could not find significant association of ascites to ferritin.

50 (20%) of patients had Spontaneous Bacterial Peritonitis (SBP). Mean ferritin in those with SBP was 489.9 and those without was 489.1. The difference was not statistically significant. 19.8% of those in ferritin < 200, 14.3% of 200 - 400 and 23.5% of > 500 groups had SBP. The difference was not statistically significant.

Variceal bleed from Upper Gastrointestinal Tract (UGIB) was seen in 101 (40.4%) of patients. Mean ferritin in those with UGIB was 703.5 and those without was 344 ng/mL. It was statistically significant ($p < 0.001$). So as ferritin increases, occurrence of UGIB increases.

Hepatorenal syndrome occurred in 104 (41.6%) of patients. Mean ferritin in those with HRS was 588.7 and those without was 407.2 ng/mL. This difference was significant (p -

0.015). 23.3% of those in ferritin < 200, 57.1% of 200 - 400 and 57.7% of > 400 groups had HRS (p - 0.00).

	Ferritin						TOTAL		p
	<200		200-400		>400				
	N	%	N	%	N	%	N	%	
Ascites	95	81.9	43	87.8	76	89.4	214	85.6	0.290
UGIB	32	27.6	17	34.7	52	61.2	101	40.4	0.000
HE	54	46.6	29	59.2	61	71.8	144	57.6	0.002
SBP	23	19.8	7	14.3	20	23.5	50	20	0.435
HRS	27	23.3	28	57.1	49	57.6	104	41.6	0.000

Complications of Liver Disease in various Ferritin Groups

Hepatic Encephalopathy (HE) was seen in 144 (57.6%) of patients. Mean ferritin in those with HE was 572.7 and those without HE was 375.8 ng/mL. This difference was significant (p - 0.009). Mean ferritin in HE Grade 1 was 358.8, Grade 2 was 528.4, Grade 3 was 485.5 and Grade 4 was 599.9 ng/mL. So as ferritin increases, grade of hepatic encephalopathy also increases.

Mean haemoglobin in ferritin < 200 was 9.4, 200 - 400 was 9.5 and > 400 was 7.5 (p - 0.000). Total leucocyte count in < 200 group was 8962, 200 - 400 was 11045 and > 400 was 13049 (p - 0.000). Mean creatinine in < 200 was 1.3, 200 - 400 was 1.8 and > 400 was 2.1 (p - 0.001). Mean INR in < 200 was 1.7, 200 - 400 was 2.2 and > 400 was 3.3.

After analysis, CTP score, haemoglobin, total leucocyte count, MCV, blood urea, serum creatinine and PT/ INR independently had significant association to serum ferritin.

DISCUSSION

To allocate and prioritise the cadaveric liver to patients with decompensated chronic liver disease, the MELD score has been an excellent model. The MELD score includes many objective variables, while the CTP score consists of two subjective parameters, i.e. ascites and encephalopathy. The performance of these two scores was compared in several studies found conflicting results, but neither of these scores was validated for prediction of early mortality in patients with chronic liver disease like cirrhosis.¹³

Serum ferritin, which is primarily an intracellular protein constituting the major body iron stores is also present in serum in traces. Patients with liver disease have high serum ferritin levels due to hepatic necroinflammation and release of ferritin from damaged hepatocytes or secondary to macrophage activation.¹⁴⁻¹⁶ Walker et al demonstrated the predictability of serum ferritin more than 500 ng/mL for 6 month and 1 year mortality with accuracy.¹²

In this study, we noted that the patients with higher ferritin values tend to have increased frequency of liver related clinical events. A ferritin value of 500 ng/mL had a sensitivity of 53.8% and specificity of 74.4% with the area under curve of 0.682 with 95% CI (0.592 - 0.772) in our study.

In the present study, we looked into the role of serum ferritin in predicting the 15-day mortality of patients admitted with cirrhosis liver and also the relation of serum ferritin to MELD score in chronic liver disease. We categorised the patients in 3 groups based on ferritin concentration, i.e. less than 200 ng/mL, 200 to 400 ng/mL and more than 400 ng/mL.

Many previous studies noticed no difference in age and gender among the three groups and this is important in Indian context, where the females are supposed to have comparatively lower body iron stores as compared to males of same age. But in our study, there was significant gender wise difference of ferritin distribution among the three ferritin groups.

Also we noted the inverse correlation of serum ferritin to serum haemoglobin. This may be due to its release secondary to internalisation of haemoglobin - haptoglobin complexes as a response to combat the oxidative stress by activated macrophages in these patients.

We noted a significant association of ferritin with serum creatinine including type 1 HRS. The significance of iron in acute kidney injury has also been validated recently following the introduction of N-GAL, which is an important iron transporting and iron-translocating compound.¹⁷

Our study based on the serum ferritin values in decompensated cirrhotic patients highlights the significance of ferritin as a prognostic biomarker. Also it provides more information on predictors of early mortality.

Patients with infection/ sepsis were not included in most of the previous studies, which looked into ferritin for the effect of sepsis on raised ferritin as acute phase reactant. But we included patients with infection/ sepsis also in our group, as bacterial infection or sepsis is an important early cause of death in these patients.

The emphasis on ferritin as a biomarker, which can be non-specifically elevated in multitude of conditions remains one of the major limitations of our study. Also the exclusion of patients with iron overload might have led to a potential selection bias in this study.

In summary, our results also clearly reflect the prognostic significance of increased serum ferritin values in patients with decompensated liver disease and cirrhosis at short-term. However, further larger prospective studies with assessment of serum ferritin in all patients with cirrhosis irrespective of iron overload states are needed to validate these findings.

CONCLUSION

- Serum ferritin is a predictor of early mortality in patients with chronic liver disease.
- 41.2% of chronic liver disease patients had elevated serum ferritin, 2% had decreased serum ferritin and 56.8% had normal serum ferritin.
- Serum ferritin level has significant correlation to MELD score. As serum ferritin increases in chronic liver disease, MELD score also increases.
- Serum ferritin is elevated in various complications of chronic liver disease.

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