Section: Gastroenterology

Original Research Article

A HOSPITAL BASED RETROSPECTIVE STUDY TO EVALUATE THE SERUM FERRITIN AS A PROGNOSTIC FACTOR OF MORTALITY IN PATIENT'S WITH END STAGE OF LIVER DISEASE

Vijyant Tak[1], Rachit Gupta[2], Rashmi Tak[3], R. Pokherna[4]

[1]Junior Specialist, Department of Gastroenterology, SMS Hospital & Medical College, Jaipur, Rajasthan, India.
[2]Assistant Professor, Department of General Medicine, NIMS Medical College, Jaipur, Rajasthan, India.
[3]Senior Demonstrator, Department of Pathology, SMS Hospital & Medical College, Jaipur, Rajasthan, India.
[4]Senior Professor, Department of Gastroenterology, SMS Hospital & Medical College, Jaipur, Rajasthan, India.

Received *: 27/09/2024*
Received in revised form *: 18/10/2024*
Accepted *: 10/11/2024*

Corresponding Author:
Dr. Vijyant Tak,
Junior Specialist, Department of Gastroenterology, SMS Hospital & Medical College, Jaipur, Rajasthan, India.
Email: drvijyant@gmail.com

DOI: 10.70034/ijmedph.2024.4.155

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2024; 14 (4); 836-839

ABSTRACT

Background: Patients with end-stage liver disease (ESLD) show increased morbidity and mortality. The Model for End-stage Liver Disease (MELD) score is the preferred tool to predict 3-month survival in patients with ESLD. The aim of this study to investigate the serum ferritin level as a prognostic factor of mortality in patient's with end stage of liver disease.

Materials & Methods: A hospital based retrospective study of patients with end stage liver disease who were admitted to department of gastroenterology in SMS hospital and medical college during one year period. Demographic, clinical and biochemical markers were recorded. All other biochemical data were recorded within 24 h of the highest serum level of ferritin found in the patient's EMR to ensure valid correlation with other biochemical and clinical parameters. Spearman rank correlation coefficient was used to assess the association of various parameters with serum ferritin, and a comparison of correlation coefficient was performed between the three groups.

Results: The MELD score was significantly different between the three groups and with the rise in ferritin concentration there was an increase seen in the MELD score the median MELD score being 15, 20, and 24 in patients with serum ferritin <200 ng/mL, 200–400 ng/mL and more than 400 ng/mL respectively. The predictors which were significantly on univariate analysis were ferritin (p <0.0001), MELD score (<0.001**). Age and gender, were not significant on univariate analysis as predictors of 15 and 30 day mortality.

Conclusion: We concluded that clearly reflect the prognostic significance of raised ferritin in patients with decompensated cirrhosis, however larger prospective trials are needed to validate these findings.

Keywords: Decompensated Liver Cirrhosis, Mortality, MELD Score, Serum Ferritin.

INTRODUCTION

Patients with end-stage liver disease (ESLD) show increased morbidity and mortality, and up to 50% of subjects with decompensated cirrhosis die within 2 years.[1] Subsequently, biological markers and scoring systems have been developed to assess the prognosis of such patients.

Ferritin is an acute-phase protein and elevated serum levels are associated with a wide range of clinical conditions including diabetes mellitus,[2,3] chronic kidney disease,[4] inflammation,[5,6] and malignancy.[7] Patients suffering from liver diseases often present multiple of these factors.

Significantly raised levels are well-described in patients with acute liver failure where it is considered as a marker of macrophage activation syndrome.[8,9] It is released after damage to hepatocytes and correlates with raised ALT implicating its presence in the cytosol of

hepatocytes. It can hence be considered as a surrogate marker of hepatic necro-inflammation or ‘‘iron storage’’ in the liver. The serum concentration of ferritin varies by at least 25 percent during inflammatory processes.[10] Hyperferritinemia in chronic liver disease has been seen primarily in hereditary hemochromatosis and also secondary to iron overload in patients with metabolic syndrome and in patients with non-alcoholic fatty liver disease, alcohol related and viral related chronic liver diseases. In patients with NAFLD,[11] 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.[12] Iron causes oxidative stress by lipid peroxidation and hepatocyte damage, activation of hepatic stellate cells and has also been reported to cause malignant transformation of hepatocytes by causing DNA damage.[13]

Recently, raised serum ferritin concentration was shown to predict mortality and liver related clinical events in patients awaiting liver transplantation in decompensated cirrhosis.[14]

The Model for End-stage Liver Disease (MELD) score is the preferred tool to predict 3-month survival in patients with ESLD.[15] Several studies have evaluated the possibility for additions to enhance the predictive capability of the MELD score,16 including levels of sodium17and albumin.18 However, no studies have evaluated whether serum levels of ferritin can improve the predictability of the MELD score.[14] Furthermore, the MELD score is based on several parameters and must be calculated, which might limit its frequent use as a screening tool in clinical practice. The aim of this study to investigate the serum ferritin level as a prognostic factor of mortality in patient’s with end stage of liver disease.

MATERIALS AND METHODS

A hospital based retrospective study of patients with end stage liver disease who were admitted to the department of gastroenterology in SMS hospital and medical college during one year period.

Inclusion criteria: Patients with cirrhosis diagnosed on the basis of suggestive clinical, biochemical, and imaging or histological features.

Exclusion criteria: Patients with acute on chronic liver failure [APASL definition], hepatocellular carcinoma [HCC], pregnancy, comorbidities associated with poor outcome [extra-hepatic neoplasia, severe cardiopulmonary disease defined by a New York Heart Association score >3, or oxygen-dependent or steroid dependent chronic obstructive pulmonary disease], patients fitting criteria for primary hemophagocytic lymphohistiocytic syndrome, patients with evidence of iron overload with serum iron >150 gm/dl [confirmed with histology wherever possible], conditions associated with secondary iron overload like thalassemia, congenital dyserythropoetic or sideroblastic anemias.

Methods

Only patients in whom the serum ferritin level was determined at least once during hospitalization were included. Overall survival was documented by the treating physician during hospitalization and/or by routine follow-ups undertaken by our aftercare service, which noted a patient’s death in the EMR. ‘Overall survival’ was defined as the time between the highest level of serum ferritin recorded up to the patient’s death. Demographic, clinical and biochemical markers were recorded. For collection of biochemical data, the highest level of serum ferritin recorded during hospitalization was documented. All other biochemical data were recorded within 24 h of the highest serum level of ferritin found in the patient’s EMR to ensure valid correlation with other biochemical and clinical parameters.

Statistical Analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± standard deviation and median. Qualitative variables were correlated using Chi-square test. Spearman rank correlation coefficient was used to assess the association of various parameters with serum ferritin, and a comparison of correlation coefficient was performed between the three groups.

RESULTS

For the study 55 patients were included who met the inclusion and exclusion criteria. Considering ferritin <200 ng/mL, 200–400 ng/mL and more than 400 ng/mL there was no significant difference noted with respect to gender and age. The MELD score was significantly different between the three groups and with the rise in ferritin concentration there was an increase seen in the MELD score the median MELD score being 15, 20, and 24 in patients with serum ferritin <200 ng/mL, 200–400 ng/mL and more than 400 ng/mL respectively (table 1).

The univariate hazard ratios of various predictors with corresponding estimated survival at 15 days and 30 days and C-index is given in Table 2. The predictors which were significantly on univariate analysis were ferritin (p <0.0001), MELD score (<0.001**). Age and gender, were not significant on univariate analysis as predictors of 15 and 30 day mortality.

Table 1: Baseline characteristics of the study cohort based on their serum ferritin concentration

	Serum ferritin <200 ng/mL (n = 27)	Serum ferritin 200-400 ng/mL (n = 10)	Serum ferritin >400 ng/mL (n = 18)	p value
Age (years), Mean± SD	50±11.8	51±12.7	52.7± 13.5	>0.05
Sex (M:F)	24:3	8:2	12:6	>0.05
OUTCOME				
Dead	2 (7.40%)	3 (30%)	5 (27.77%)	<0.05*
Alive	25 (92.60%)	7 (70%)	13 (72.22%)	
Baseline MELD, Median (IQR)	15 (11-12)	20 (15-24)	24 (16-30)	<0.001
Final MELD score, Median (IQR)	22 (16-28)	27 (22-36)	28 (22-37)	<0.001

Table 2: Baseline characteristics of survivors vs. non-survivors with univariate hazard ratios for prediction of 15 days and 30 days mortality

Variable	Total patients (n = 55)	Survivors (n = 45)	Non-survivors (n = 10)	Univariate hazard ratio (HR), p value
Age (years), Mean± SD	52.3 ± 12.78	51.4 ± 13.0	55.6 ± 12.7	1.012, >0.05
Sex (M:F)	44:11	36:9	8:2	0.76, >0.05
Serum ferritin (ng/ml) Median (IQR)	213 (70-543)	174 (66-460)	403 (240-1100)	1.003, <0.05*
Baseline MELD, Median (IQR)	18 (13-24)	17 (13-23)	24 (16-29)	1.07, <0.001**
Final MELD score, Median (IQR)	25 (19-35)	25 (18-32)	37 (26-42)	1.08, <0.001**

DISCUSSION

Ferritin represents the principal protein for iron storage, and the liver is the main storage site of ferritin.[19] The iron is stored and occasionally exported back to the circulation via ferroportin in response to iron deficiency after being detoxified in the ferritin.[20] Moreover, it has been suggested that ferritin contributes to iron transport by sequestering iron when not required and releasing it when in demand.[21] Mounting evidence indicates that patients with liver diseases present higher levels of serum ferritin because necro-inflammation of liver tissues and release of ferritin from injured hepatocytes or a response to macrophage activation.[22,23] Serum ferritin concentration of more than 500 ng/mL has also been previously shown in a study by Walker et al. to predict 6 month and 1 year mortality with accuracy.[14] The effect of ferritin on mortality in this study was noted to be independent of MELD and patients with higher ferritin were reported to have an increased frequency of liver-related clinical events. Weismuller et al,[24] in his study showed that a cut-off serum ferritin of 365 ng/mL pre-transplantation best predicted recipient survival post-transplant. However, there are no studies available in the literature which have addressed the role of serum ferritin as a predictor of early mortality in patients with decompensated cirrhosis.

In the present study, we hence looked at serum ferritin as a predictor of early mortality at 15 days and 1 month in a cohort of decompensated inpatients of cirrhosis.

We categorized our patients into three groups based on ferritin concentration, i.e., less than 200 ng/mL, 200–400 ng/mL, and more than 400 ng/mL. There was no difference in age and gender between the three groups. This finding is more important in context to Indian patients where the females are supposed to have comparatively lower body iron stores as compared to the males of same age. We also found a significant difference in MELD scores which are already established prognostic scores in patients with decompensated cirrhosis between the three groups. Repeatedly explored in the field of hepatology is probably due to the simplicity and cost-effectiveness in routine practice. Moreover, it is tempting to consider that survival may be increased by effectively managing and optimizing iron dysregulation, which is common in cirrhosis, because serum ferritin is a sensitive biomarker of iron homeostasis.[25,26] Likewise, ferritin acts as an acute phase reactant in response to inflammatory action and thus facilitates the progression of advanced-stage liver diseases such as fibrosis, cirrhosis, and HCC.[27] On the other hand, it has been demonstrated that ferritin can suppress intensive iron overload and bears anti-inflammatory, immunomodulatory, and hepatoprotective effects.[28] Collectively, the pleiotropic functions of ferritin make the interpretation of its clinical utility even more complicated. Another concern that should be addressed is whether ferritin can be independently associated with other traditional scoring systems (eg, CTP class or MELD) by adding more pathophysiological information or whether it is just an indicator of underlying liver disease severity.

Our study done in hospitalized patients with decompensated cirrhotics not only provides more information on predictors of early mortality in these patients but also highlights the significance of ferritin as a prognostic biomarker. In previous studies which have looked into ferritin, patients with

sepsis were not included to exclude the effect of sepsis on raised ferritin considering it as an acute phase reactant. We however did not exclude these patients as bacterial infection or sepsis is an important cause of early death in these patients. Sepsis in itself was not recognized as a major predictor of death in our patients, possibly because we defined sepsis only in the presence of positive cultures and also patients with secondary iron overload were excluded from our study, leading to a potential of selection bias in the study cohort.

CONCLUSION

We concluded that clearly reflect the prognostic significance of raised ferritin in patients with decompensated cirrhosis, however larger prospective trials are needed to validate these findings.

REFERENCES

1. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. J Hepatol 2006; 44: 217–231.
2. Jehn M, Clark JM, Guallar E. Serum ferritin and risk of the metabolic syndrome in U.S. adults. Diabetes Care 2004; 27: 2422–2428.
3. Ford ES, Cogswell ME. Diabetes and serum ferritin concentration among U.S. adults. Diabetes Care 1999; 22: 1978–1983.
4. Kalantar-Zadeh K, Kalantar-Zadeh K, Lee GH. The fascinating but deceptive ferritin: To measure it or not to measure it in chronic kidney disease? Clin J Am Soc Nephrol 2006; 1(Suppl 1): S9–S18.
5. Kell DB, Pretorius E. Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. Metallomics 2014; 6: 748–773.
6. Depalma RG, Hayes VW, Chow BK, et al. Ferritin levels, inflammatory biomarkers, and mortality in peripheral arterial disease: A substudy of the Iron (Fe) and Atherosclerosis Study (FeAST) Trial. J Vasc Surg 2010; 51: 1498–1503.
7. Kalousova M, Krechler T, Jachymova M, et al. Ferritin as an independent mortality predictor in patients with pancreas cancer. Results of a pilot study. Tumour Biol 2012; 33: 1695–1700.
8. Hiraoka A, Horiike N, Akbar SM, Michitaka K, Matsuyama T, Onji M, et al. Soluble CD163 in patients with liver diseases: very high levels of soluble CD163 in patients with fulminant hepatic failure. J Gastroenterol 2005;40:52–56.
9. Møller HJ, Gronbaek H, Schiodt FV, Holland Fischer P, Schilsky M, Munoz S, et al. Soluble CD163 from activated macrophages predicts mortality in acute liver failure. J Hepatol 2007;47:671–676.
10. Beaton Melanie D, Adams Paul C, et al. Treatment of hyperferritinemia. Ann Hepatol 2012;11:294–300.
11. Zelber-Sagi Shira, Nitzan-Kaluski Dorit, Halpern Zamir, Oren Ran, et al. NAFLD and hyperinsulinemia are major determinants of serum ferritin levels. J Hepatol 2007;46:700–707.
12. Bugianesi E, Manzini P, D'Antico S, Vanni E, Longo F, Leone N, et al. Relative contribution of iron burden, HFE mutations, and insulin resistance to fibrosis in nonalcoholic fatty liver. Hepatology 2004;39:179–187.
13. Dongiovanni Paola, Fracanzani Anna Ludovica, Fargion Silvia, Valenti Luca, et al. Iron in fatty liver and in the metabolic syndrome: a promising therapeutic target. J Hepatol 2011;55:920–932.
14. Walker NM, Stuart KA, Ryan RJ, Desai S, Saab S, Nicol JA, et al. Serum ferritin concentration predicts mortality in patients awaiting liver transplantation. Hepatology 2010;51(5):1683–1691.
15. Singal AK, Kamath PS. Model for end-stage liver disease. J Clin Exp Hepatol 2013; 3: 50–60.
16. Cholongitas E, Marelli L, Shusang V, et al. A systematic review of the performance of the model for end-stage liver disease (MELD) in the setting of liver transplantation. Liver Transpl 2006; 12: 1049–1061.
17. Luca A, Angermayr B, Bertolini G, et al. An integrated MELD model including serum sodium and age improves the prediction of early mortality in patients with cirrhosis. Liver Transpl 2007; 13: 1174–1180.
18. Myers RP, Shaheen AA, Faris P, et al. Revision of MELD to include serum albumin improves prediction of mortality on the liver transplant waiting list. PLoS One 2013; 8: e51926–e51926.
19. Harrison PM, Arosio P. The ferritins: molecular properties, iron storage function and cellular regulation. Biochim Biophys Acta. 1996;1275(3):161–203.
20. Sakamoto S, Kawabata H, Masuda T, et al. H-Ferritin is preferentially incorporated by human erythroid cells through transferrin receptor 1 in a threshold-dependent manner. PLoS One. 2015;10(10):e0139915.
21. Anderson GJ, Frazer DM. Current understanding of iron homeostasis. Am J Clin Nutr. 2017;106(suppl 6):1559S–1566S.
22. Adams P. Management of elevated serum ferritin levels. Gastroenterol Hepatol (N Y). 2008;4(5):333–334.
23. Dev S, Babitt JL. Overview of iron metabolism in health and disease. Hemodial Int. 2017;21(suppl 1):S6–S20.
24. Weismüller TJ, Kirchner GI, Scherer MN, Negm AA, Schnitzbauer AA, Lehner F, et al. Serum ferritin concentration and transferrin saturation before liver transplantation predict decreased long-term recipient survival. Hepatology 2011;54(6):2114–2124.
25. Tornai D, Antal-Szalmas P, Tornai T, et al. Abnormal ferritin levels predict development of poor outcomes in cirrhotic outpatients: a cohort study. BMC Gastroenterol. 2021;21(1):94.
26. Gkamprela E, Deutsch M, Pectasides D. Iron deficiency anemia in chronic liver disease: etiopathogenesis, diagnosis and treatment. Ann Gastroenterol. 2017;30(4):405–413.
27. Hagstrom H, Nasr P, Bottai M, et al. Elevated serum ferritin is associated with increased mortality in non-alcoholic fatty liver disease after 16 years of follow-up. Liver Int. 2016;36(11):1688–1695.
28. Kernan KF, Carcillo JA. Hyperferritinemia and inflammation. Int Immunol. 2017;29(9):401–409.