Research Article

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Serum ferritin predicts early mortality in patients with decompensated cirrhosis

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Background & Aims: Serum ferritin is a known marker of hepatic necro-inflammation and has been studied to predict 1 year mortality and post-transplant survival in decompensated cirrhotics. However, there are no studies evaluating ferritin as a predictor of early mortality. We investigated whether serum ferritin levels could predict 15 day and 30 day mortality in patients with decompensated cirrhosis.

Methods: 318 patients with decompensated cirrhosis were included.

Results: Patients of decompensated cirrhosis [257 males, mean age of 51 [±13] years, were followed for a median of 31 days. Serum ferritin levels were significantly different between survivors and non-survivors [p <0.001] and showed significant correlation with MELD score [p <0.001], CTP score [p <0.001], leucocyte counts [TLC] [p <0.001], serum sodium [p <0.001], ACLF grades [p = 0.005], spontaneous bacterial peritonitis [SBP] [p = 0.02], hepatic encephalopathy [HE] [p <0.001] and hepatorenal syndrome [HRS] [p = 0.012]. Serum ferritin, etiology, MELD, HE, CTP score, sodium, TLC, and ACLF grades were significant predictors of mortality on univariate analysis. Ferritin [p = 0.04, HR 1.66 95% CI (1.02–2.73)] was a significant predictor of early mortality on multivariate analysis along with HE [p = 0.006, HR 3.47 95% CI (2.13–8.41)] (Model 1), TLC [p = 0.02, HR 1.81 95% CI (1.06–3.07)] (Model 2), ACLF grades [p = 0.018, HR 2.013,95% CI (1.126–3.60)], and CTP score [p <0.0001, HR 1.36 95% CI (1.17–1.59)] (Model 3).

Conclusion: Serum ferritin levels correlate with severity of hepatic decompensation and are associated with early liver related death independent of the MELD score in hospitalized patients with decompensated cirrhosis. This could also have a potential therapeutic implication.

Keywords: Decompensated cirrhosis; Portal hypertension; Ferritin; Mortality; Hyperferritinemia.

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Abbreviations: ALT, Alanine aminotransferase; NAFLD, Non-alcoholic fatty liver disease; DNA, Deoxyribonucleic acid; MELD, Model for End Stage Liver Disease; CTP, Child Turcott Pugh; HCC, Hepatocellular carcinoma; HVPG, Hepatic Venous Pressure Gradient; NASH, Non-Alcoholic steatohepatitis; HRS, Hepato Renal Syndrome; SBP, Spontaneous Bacterial Peritonitis; TS, Transferrin saturation; INR, International normalized ratio; OLT, Orthotopic liver transplantation.

Introduction

Serum ferritin is increased in iron overload, liver diseases, infections, inflammatory conditions, and malignancy [1]. Significantly raised levels are well-described in patients with acute liver failure where it is considered as a marker of macrophage activation syndrome [2,3]. 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 [4]. 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 [5] 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 [6]. 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 [7]. Recently, raised serum ferritin concentration was shown to predict mortality and liver related clinical events in patients awaiting liver transplantation in decompensated cirrhosis [8].

The MELD score has been shown by a number of studies to correlate with short-term mortality risk at 3 months and also to determine priorities in allocating cadaveric livers to transplant candidates. The Child-Turcotte [CTP] scoring system was the first of its kind in stratifying the seriousness of end-stage liver disease. There are some differences in the terminology of ACLF as proposed by the APASL in the East and the by the CLIFF consortium from the West [9,10]. In a recent study by Moreau *et al.* the significance of organ failure in patients with decompensated cirrhotics was

highlighted. Patients of ACLF which were defined based on the number and type of organ failures in their cohort of 1343 hospitalized patients were reported to have a 28 day mortality varying from 29.7% to 33.9% as compared to only 1.9% amongst patients who did not develop ACLF [10]. Despite this, currently there are no markers which identify very early mortality at 15 and 30 days in patients with decompensated cirrhosis.

We hence undertook this study to investigate serum ferritin as a prognostic marker to predict early mortality at 15 and 30 days in hospitalized patients with decompensated cirrhosis and to study its association with liver-related clinical events and ACLF grades in these patients.

Patients and methods

The study was conducted as a retrospective follow-up of a cohort of 318 consecutive in-patients of decompensated cirrhosis from January 2011 to January 2012 who fulfilled the inclusion and exclusion criteria.

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.

Patients with ACLF, which are diagnosed using the APASL criteria at our center [9] were excluded from this study. For analyzing the predictors of mortality in patients with decompensated cirrhotics with acute deterioration, we applied the CLIFF-SOFA score/ACLF grades. Clinical details of the patients including history and complications related to liver disease like ascites, HE, SBP, gastrointestinal bleed, HRS, and clinical course in the hospital were obtained from the medical records and were recorded in a specified liver disease proforma. Biochemical parameters including ferritin, iron, sodium, potassium, creatinine, liver function tests, hemoglobin, total and differential leucocyte and platelet counts were recorded. HCC was diagnosed using the radiological criteria proposed by the American Association for the Study of Liver Disease Practice Guidelines Committee [11]. HRS, ascites and SBP were diagnosed using the criteria proposed by the International Ascites Club and American Association for the Study of Liver Disease respectively [12,13]. Serum ferritin was used as a continuous and a categorical covariate. The delta MELD score was calculated for all patients using the baseline MELD and MELD at last follow up and patients were subsequently divided into increase in MELD of 5 points/month *vs.* less than 5 points/month.

Statistical analysis

Descriptive statistics were expressed as median [range] or number [%]. Comparison of continuous variables was done by the Mann–Whitney U and Kruskal-Wallis test and categorical variables by Fischer exact test or Pearson's χ^2 test. The ability of various variables to discriminate between survivors and non-survivors was assessed by Harrell's C-index. Ferritin was analyzed both as a categorical and continuous variable. Log transformation of ferritin and WBC was used to assess association with survival. Variables found significantly associated with mortality on univariate analysis and based on theoretical background were entered into multivariate analysis by Cox regression analysis Three different multivariate survival models were developed each incorporating serum ferritin. Kaplan Meier survival curves were developed. All statistical tests were 2-tailed, and a significance level [p] of 0.05 was used. All statistical tests were performed using SPSS for Windows version 19 and R 3.0.1.

Results

For the study 318 patients were included who met the inclusion and exclusion criteria. The baseline characteristics of the study cohort are shown in Tables 1 and 2. There were 257 (80.8%) males and mean age of the cohort was 51 (SD-13) years. These patients were followed for a median 31 days (IQR: 12–129). Fifty-two patients (16.4%) died on follow up. Ascites was seen in 258 (81%) patients and 154 (48.4%) patients had HE. SBP was present in 93 (29%) patients and 89 (28%) patients had HRS. The etiology of underlying chronic liver disease was related to alcohol in 105 (33%), hepatitis B in 15 (4.7%), hepatitis C in 39 (12.3%), cryptogenic in 79 (24.8%), NASH in 57 (17.9%), autoimmune in 5 (1.6%), and others in 7 (2.2%) patients. Hepatitis B and C co-infection was seen in 3 (0.9%) patients, Hepatitis B and alcohol in 5 (1.6%) and Hepatitis C and alcohol in 3 (0.9%) patients. The median ferritin concentration was 438 (72–537) ng/mL and MELD score was 17 (13–25). A total of 124 (39%) of patients had an increase in MELD of more than 5 points/month. Thirty-one patients (10%) were Child A, 119 (37%) Child B, and 168 (53%) were Child C.

The distribution of various variables based on outcome is depicted in Table 2. Ferritin was significantly different when considered both as continuous and categorical co-variate (<200 units, 200–400, ⩾400) between the survivors and non-survivors.

Baseline characteristics of the study subjects based on their ferritin concentration (Table 1)

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, 19, and 23 in patients with serum ferritin <200 ng/mL, 200–400 ng/mL and more than 400 ng/mL respectively. Similarly, the CTP score and sodium was significantly different between the three groups and patients with serum ferritin more than 400 had the highest median CTP score of 11 and marked hyponatremia as compared to the other groups. Furthermore patients with high ferritin (>400 ng/mL) had significantly more leucocytosis (p <0.001), hyperbilirubinemia (p <0.001), hypoalbuminemia (p = 0.002), and coagulopathy (p <0.001). The serum hemoglobin was also significantly different in the three groups, however showed an inverse rather than a direct correlation to ferritin (p = 0.007). Ferritin was also significantly different between various etiologies of liver (p = 0.013). It was significantly different between alcohol *vs.* other etiologies (p = 0.04) but not between viral or NASH *vs.* other etiologies (results not shown).

Association of ferritin with the liver related clinical events and ACLF grades

Ferritin concentration differed significantly in patients with and without HE (p <0.001), HRS (p = 0.012), SBP (p = 0.02) however not in patients with and without ascites (p = 0.49).

We also considered classifying our patients into ACLF grades according to the recent study by Moreau *et al.* (13). ACLF Grade 0 (No ACLF) was seen in 220 (69.5%) patients, ACLF Grade 1 in 39 (12.3%) patients, ACLF Grade 2 in 29 (9.4%) patients and ACLF Grade 3 in 28 (8.8%) patients. A significant association was also noted with increasing ACLF grades and ferritin concentration (p = 0.02). Presence of ACLF was seen in 33% of patients with ferritin >400 ng/mL as compared to only 20% with ferritin <200 ng/mL (Fig. 1).