ORIGINAL ARTICLE

SERUM FERRITIN AS A PREDICTOR OF 30 DAYS MORTALITY IN PATIENTS OF DECOMPENSATED CHRONIC LIVER DISEASE

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Background: Serum ferritin is marker for hepatic neco-inflammation and known 1 year mortality predictor in post-transplant patients. However, data on utility as early mortality predictor in patient of cirrhosis is scarce. We investigated whether ferritin can be used as one month mortality predictor in patients of decompensated cirrhosis. **Methods:** The study cohort included 132 patients in whom predictors of mortality were studied. **Results:** One hundred and thirty-two patients with 77 (58.33%) male with a mean age of 54 (±8.3) years with decompensated cirrhosis were followed for 30 days. enrolled for study. Majority of the patients had hepatitis C (71.4%) with 19 (14.3%) cases of hepatitis B related cirrhosis and 5.3%, 4.5% and 2.3% comprising alcoholic, autoimmune and Wilsons related decompensated cirrhosis respectively. Ninety-one (69.42%) patients were alive at end of study period, with serum ferritin levels were significantly different between the survivors and the non-survivors ($p< .001$) and showed significant correlation with CTP Score ($p <.001$) and MELD Score ($p <.001$). Regarding ferritin level and outcome, 76 (all alive) had ferritin level <200 ng/ml, 26 (13 alive, 13 died) had ferritin level between 200–400 ng/ml and 30 (2 alive, 28 died) had ferritin level >400 ng/ml ($p= .001$). With increasing ferritin level, CTP class as well as MELD score increased. Patients with raised ferritin levels were more likely to die compared to those with lower ferritin levels ($p <.001$). **Conclusion:** Serum ferritin levels correlate with severity of liver disease and are associated with early mortality in patients of decompensated cirrhosis independent of MELD score.

Keywords: Ferritin; Predictor; Chronic liver disease

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INTRODUCTION

Cirrhosis represents a late stage of progressive hepatic fibrosis characterized by distortion of the hepatic architecture and the formation of regenerative nodules. It is generally considered to be irreversible in its advanced stages at which point the only option may be liver transplantation. Various aetiological factors have been associated with chronic liver disease e.g alcohol, hepatitis B, C, alpha-1 antitrypsin deficiency cystic fibrosis etc. Among these causes hepatitis C is one of the leading cause of cirrhosis. Pathogenesis behind liver fibrosis is liver fibrogeneis. Early detection of liver fibrogenesis is important for timely treatment of patients.[1] Various markers and scoring systems have been used for assessing the severity of chronic liver disease. Child Turcotte-Pugh (CTP) and Model of End Stage Liver Disease (MELD) scoring system are widely used for classification of severity of chronic liver disease and to prioritize the patients for liver transplant. CTP class A patients have good prognosis with medium term survival[2], class B patients have variable prognosis. They may survive for a year or more or may deteriorate rapidly[3] whereas class C patients need liver transplantation urgently. Similarly, studies have shown MELD score predicting 3 months mortality in patients with chronic liver disease.[4] As cirrhosis, secondary to any cause, is one of the leading cause of death so it is really important that there should be some marker which can predict prognosis in decompensated chronic liver disease as earlier as one month.

Serum ferritin is an acute phase reactant. It plays defensive role against inflammatory stress on the body.[5] Ferritin levels can be measured in serum easily. It is increased in inflammatory process and malignancy. Raised ferritin levels in context of chronic liver disease are seen in hereditary haemochromatosis, NAFLD and virus related chronic liver diseases. In a patient of chronic liver disease without iron overload, serum ferritin levels are related to the histological liver parenchymal damage rather than iron accumulation.[6]

Purpose of this study is to find a biochemical marker such as serum ferritin level as a predictor of early mortality at 30 days in hospitalized patients with de-compensated chronic liver disease. So, in future, serum ferritin may be used as a surrogate marker or may be used in conjunction with other scoring system such as CTP in predicting early mortality in patients with chronic liver disease.

MATERIAL AND METHODS

This was a cross-sectional observational study carried out in department of Gastroenterology, medical unit-III, Services Hospital, Lahore. The

cohort comprised on 132 patients with decompensated cirrhosis diagnosed on the basis of history, clinical examination, biochemical markers and radiological evidences. The study excluded patients having serious comorbid conditions like heart failure with NYHA class III-IV, Chronic obstructive pulmonary disease, oxygen dependent, steroid dependents, hepatocellular carcinoma, acute liver failure, evidence of iron overload and secondary iron accumulation like thalassemia.

After approval of study design from institutional review board (IRB), patients of chronic liver disease who fulfilled inclusions and exclusion criteria were explained about the study and its outcome. The patients willing for participation study were requested to give informed consent. Detailed history and clinical examination was performed. Complications of cirrhosis like ascites, hepatic encephalopathy were also assessed from their previous clinical records, history, examination, and laboratory reports.

Laboratory investigations were sent for all patients along with their serum ferritin levels. MELD score was calculated for all patients. All data was entered in *pro forma*. Patients were followed after a period of 30 days through follow up and telephone to enquire about outcome. Only those patients who gave follow up after 1 month were included in our study. Serum ferritin levels of survivors and non-survivors was compared. Data was analyzed by computer program SPSS 21.

RESULTS

The study included 132 patients, of which seventy-seven (58.33) were male and fifty-five (41.66 %) were females with age ranging from 38 to 75 and mean age was 54 years. Baseline characteristics of study participants based on serum ferritin concentration, i.e., <200, 200–400 and >400 ng/ml has been shown in table-1. The table shows that age, CP lass, MELD score, presence of ascites and hepatic encephalopathy, and biochemical markers were significantly different between the subgroups with p value <0.05.

Table-2 shows the factors associated with 30 days mortality in patients with decompensated cirrhosis using multivariate logistic regression model. It was found that gender, cause of cirrhosis, ascites, hepatic encephalopathy, CP class and serum ferritin level were significantly associated with mortality in the study group. Rest of the factors did not significantly alter the survival in this study cohort.

Table-1: Baseline characteristics of study participants based on serum ferritin concentration

		Serum Ferritin <200	Serum Ferritin 200–400	Serum ferritin >400	*p*- value
Age(years)	mean(±SD)	52 (±7)	56 (±8)	57 (±10)	0.003
Gender	Male	47	14	16	0.635
	Female	29	12	14	
Etiology	Hepatitis B	10	5	4	0.485
	Hepatitis C	56	19	20	
	Alcohol	2	1	4	
	Autoimmune	4	0	2	
	Wilson	2	1	0	
	Cryptogenic	2	0	0	
Child Pugh Class	A	22	0	0	0.001
	B	42	10	4	
	C	12	16	26	
MELD	Mean (±SD)	9 (±3)	16 (±7)	18 (±3)	
Ascites	Absent	21	6	1	0.001
	Slight	30	7	1	
	Moderate	17	5	11	
	Severe	8	8	17	
Hepatic Encephalopathy	Absent	17	0	0	0.001
	Grade 1	44	2	0	
	Grade 2	13	15	6	
	Grade 3	2	5	11	
	Grade 4	0	4	13	
Prothrombin Time		15 (±2.7)	18.6 (±3.8)	17.6 (±4.6)	0.001
INR		1.14 (±0.13)	1.41 (±0.30)	1.36 (±0.38)	0.001
Total Bilirubin		1.3 (±1.2)	2.2 (2.7)	1.5(0.8)	0.030
Serum Albumin		2.4 (±0.6)	2.1 (±0.3)	2.1 (±0.5)	0.008
Creatinine		0.9 (±0.3)	1.7 (±0.7)	2.1 (±0.6)	0.001
Outcome	Alive	76	13	2	0.001
	Dead	0	13	28	

Table-2: Multivariate logistic regression model for factors associated with 30 days mortality in patients with decompensated cirrhosis

Variable		Outcome			
		Alive	Dead	Total	*p*-value
Gender					
	Male	58	19	77	0.001
	Female	33	22	55	
Cause of Cirrhosis					
	Hepatitis B	12	7	19	0.001
	Hepatitis C	67	28	95	
	Alcohol	3	4	7	
	Autoimmune	4	2	6	
	Wilson	3	0	3	
	Cryptogenic	2	0	2	
Ascites	Absent	27	1	28	0.001
	Slight	34	4	38	
	Moderate	20	13	33	
	Severe	10	23	33	
Hepatic Encephalopathy	Absent	17	0	17	0.001
	Grade 1	46	0	46	
	Grade 2	23	11	34	
	Grade 3	5	13	18	
	Grade 4	0	17	17	
Child Pugh Class	Class A	22	0	22	0.001
	Class B	50	6	56	
	Class C	19	35	54	
Serum Ferritin Level	<200ng/ml	76	0	76	0.001
	200-400ng/ml	13	13	26	
	>400ng/ml	2	28	30	

DISCUSSION

Chronic liver disease is important medical condition because of its high morbidity and mortality. Early diagnosis of cirrhosis is important for timely management of disease, to avoid its complications and to prioritize patients for liver transplantation. Various classification systems having been established to access the severity and outcome of disease like CP and MELD scoring system. These scoring systems access 3, 6 months mortality. So, it's really important to have a marker which can access mortality as early as 30 days. Serum ferritin is an acute phase reactant and it has been shown in various studies that its levels increase as liver disease advances. Keeping this in mind, we proposed that serum ferritin can predict mortality as early as 30 days. In our study, one hundred and thirty-two (132) patients participated and all patients had follow up after 1 month. Among these 132 patients, seventy-seven (58.33) were male and fifty-five (41.66 %) were females with age ranging from 38 to 75 and mean age was 54 years. Baseline characteristics of study participants based on serum ferritin concentration, i.e., <200, 200–400 and >400 ng/ml has been shown in table-1. It is evident that most of patients who had serum ferritin level >400 ng/ml were also having severe ascites, grade 3–4 hepatic encephalopathy and CP class C and MELD score of 18±3. Patients, who had serum ferritin level between 200–400 ng/ml, were mostly having moderate amount of ascites and hepatic encephalopathy between grades 2-3. Most of these patients were having CP class B and their MELD score was 16±7. Regarding cause of cirrhosis, 95 (71.4%) were hepatitis C, 19 (14.3%) were hepatitis B related cirrhosis while alcoholic, autoimmune and Wilson were 5.3%, 4.5% and 2.3% respectively. Patients were followed for the medium period of 30days. Serum ferritin levels were significantly different between the survivors and the non-survivors (p<.001) (Table-2). Ninety-one patients (69.42%) were among survivors and 41 (30.82%) patients were among non-survivors. Regarding hepatic encephalopathy grades, it was absented in 17(all survived), 46 (all 46 survived) were in grade I, 34 (23 alive, 11 died) were in grade II, 18 (5 alive 13 died) were in grade III and 17 (17 died) were in grade IV (p .001). Regarding child class and outcome, 22 (22 alive) patients were in class A, 56 (50 alive, 6 died) were in class B and 54 (19 alive, 35 died) were in class C (p .001). Regarding ferritin level and outcome 76 (76 alive) were having ferritin level <200 ng/ml, 26 (13 alive, 13 died) were having ferritin level between 200-400 ng/ml and 30 (2 alive, 28 died) were having ferritin level >400 ng/ml (p .001).

Patients having ferritin <200ng/ml had 100% survival while patients having serum ferritin 200-400ng/ml had 50% mortality and 50% survival. It was important to note that patients having serum ferritin >400 ng/ml had 93% mortality. It was also noted that with increasing ferritin level, CTP class increased as well as MELD Score. Patients who were higher ferritin were among non-survivors (p<.001). Of these three factors, strongest correlation of mortality with outcome was seen with ferritin e.g 28 out of 30 (93.3%) patients having ferritin level greater than 400 died (p <.001) but for high CTP class and high MELD score, the case is

not exactly like that e.g 35 patients in class C died out of 54 (64.8%).

Our study results were comparable with other similar studies. In one study, serum ferritin had been taken as 6 months and 1 year mortality predictor and was found that serum ferritin greater than 200 microg/L was an independent factor predicting increased 180-day and 1-year waiting list mortality.[7] Results of our study were also similar to another study in which serum ferritin was taken as predictor of mortality as early as 15 days and 30 days. In this study ferritin levels > 500 ng/ml were strongly associated with 15 days and 30 days mortality (p=0.006, HR 1.42).[8]

In one study done on best predictors in post-transplant patient and it was found that serum ferritin levels > 365 ng/ml and transfusion saturation <55% were associated with higher mortality in post-liver transplant patients.[9] It was seen in one study that serum ferritin is a marker of advanced fibrosis in patients of Non-alcoholic steatohepatitis.[10] Results of our study and various other studies showed that serum ferritin can be taken mortality predictor in patients with early cirrhosis as early as 30 days with high accuracy of results and such patients can be prioritize for liver transplant list.

Serum transferrin level has been shown to correlate with short term mortality in acute-on-chronic organ failure in patients with decompensated cirrhosis.[11] The investigators found that among the various markers for iron metabolism, serum transferrin level was the best predictor of 30-day mortality. In this study serum ferritin was significantly different between survivors and non-survivors but did not predict mortality. More studies are needed to elucidate the relationship of markers of iron metabolism with early mortality in patients with decompensated cirrhosis.

Our study did not look at the relationship of transferrin as a marker for predicting mortality and thus we are unable to comment on its utility in our patient group. Apart from predicting early mortality in patients with decompensated cirrhosis, serum ferritin has recently been shown to be associated with increased long-term mortality not only in patients with hemochromatosis and iron overload but also those with non-alcoholic fatty liver disease.[12,13] This shows that serum ferritin is an important marker for predicting survival in liver disease. Further studies involving full spectrum of patients from acute liver failure to decompensated cirrhosis as well as acute on chronic liver failure are needed to further characterise this association.

CONCLUSION

Serum ferritin levels greater than 400 ng/dl can predict mortality in patients with advanced cirrhosis as early as one month.

AUTHORS' CONTRIBUTION

NU conceived and designed the study. SKK carried out the data collection. MUM drafted the manuscript and supervised the write up of the study with substantial input in its improvement. NAJ did help in data analysis and reviewed the manuscript. All authors read and approved the final manuscript

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