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To Study the Serum Ferritin Level in Chronic Liver Disease and it's Correlation with Child Turcotte Pugh Score

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ABSTRACT

Liver cirrhosis has been established as the condition where normal liver parenchyma is replaced with connective tissue producing nodule formation. Child-Pugh score has been used to assess the severity of liver dysfunction in clinical work. Serum ferritin is universally available biochemical parameter and is elevated in several clinical conditions including patients with chronic liver disease. To estimate the serum ferritin level in liver Cirrhosis and to assess any significant correlation between ferritin level and CTP score. The present study was carried out in the Department of General Medicine, KIMS, Hubballi. Patients who were clinically diagnosed with CLD and were eligible for the study according to the above-mentioned eligibility criteria were included in the study after informed consent from the patient. All necessary investigations were performed and the severity of CLD was defined as per CTP Criteria. In the study, the mean age of the subjects was 45.16 years. The most common grade of hepatic encephalopathy was Grade 2 (16.7%). The mean CTP Score among the subjects was 10.2 Majority belonged to Class c (49.1%). The mean MELD score among the subjects was 22.90. The mean serum ferritin score among the subjects was 364. The mortality rate in the study was 10.5%. There is a significant and positive correlation between serum ferritin levels and CTP score is evident among liver cirrhosis patients. In this study, CTP classification which was done to access severity and prognosis of cirrhosis also showed higher ferritin levels with increasing class. Hence, as the severity of the liver disease increases, it is associated with increased in serum ferritin levels. These findings point toward a possible prognostic value of serum ferritin in CLD.

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Key Words
Serum ferritin, chronic liver disease, child pugh score, alcoholic liver disease

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INTRODUCTION

Liver cirrhosis has been established as the condition where normal liver parenchyma is replaced with connective tissue producing nodule formation[1]. CLD and its complications are becoming a major health problem and posing as a big challenge to the health economy[2]. Decompensated cirrhosis is characterized by striking and life-threatening complications, like variceal haemorrhage and spontaneous bacterial peritonitis (SBP). Once decompensation has occurred, mortality without liver transplantation (LT) can be as high as 85% over 5 years[3]. Liver cirrhosis has a high morbidity and mortality and it is the 14th most common cause of death all over the world and the 4th in central Europe[4].

The primary version of Child-Pugh score includes ascites, hepatic encephalopathy (HE), nutritional status, total bilirubin and albumin. Pugh et al5 modified the Child-Pugh classification by adding prothrombin time (PT) or international normalized ratio (INR) and removing nutritional status. Child-Pugh score has been widely used to assess the severity of liver dysfunction in clinical work[4].

In general, there is a need for an easily derived markers that provide accurate prediction for decompensated cirrhosis patients. Serum ferritin is a universally available biochemical parameter which is elevated in several clinical conditions, including patients with both acute and chronic liver diseases3.

Ferritin synthesis is induced by macrophages and hepatocytes and raised levels is seen in iron overload conditions or in several pathologies, inflammation, infection and liver diseases[3]. Thus, this study was done to assess any significant correlation between ferritin levels and Child-Turcotte-Pugh score.

MATERIALS AND METHODS

Single Centre Prospective Observational Study was conducted Patients with history of chronic liver disease admitted under the department of General Medicine, Karnataka Institute of Medical Sciences, Hubballi during the study period i.e December 2020 to November 2022 for a duration of 2 years.

Sample Size Calculation: In the study area, the total number of IP admissions under General Medicine in the year 2019 was 13562. The total number of patients with chronic liver disease admitted in the study area in the same year was 1046. That makes the prevalence of chronic liver disease in the studyarea as 7.71%. Keeping the absolute precision at 5.0%, with 95.0% confidence level and 80.0% power, the sample size was calculated using the following formula.,

$$n = \frac{Z^2_{1-\frac{\alpha}{2}} * p(1-p)}{d^2}$$

The sample size was estimated to be 114.

Sampling Method: Simple Random Sampling.

Inclusion Criteria: Patients who are newly diagnosed or a diagnosed case of chronic liver disease with clinical and radiological evidence of cirrhosis of liver.

Exclusion Criteria:

- Patients with malignancy
- End-stage renal disease
- Chronic pulmonary obstructive disorder
- Blood transfusion in the previous three months
- Patients <18 years.

Methodology: Patients who were clinically diagnosed with chronic liver disease and were eligible for the study according to the above mentioned eligibility criteria were included in the study after informed consent from the patient.

All patients were subjected to clinical and laboratory evaluation as per proforma. The following investigations will be done in the selected patient.

- CBC.
- Liver function test.
- PT, INR.
- Renal function tests.
- Serum electrolytes.
- HCV, HBsAg serology.
- Serum ferritin.
- ECG, Chest X Ray.
- USG abdomen and pelvis.
- Ascitic fluid analysis.

Severity of CLD was defined as per Child Turcotte Pugh criteria and MELD system. Serum level of serum ferritin was measured by venous sampling.

Statistical Analysis: Data was entered into Microsoft excel data sheet and was analysed using SPSS 22 version software. Normality of the continuous data was tested by Kolmogorov-Smirnov test and the Shapiro-Wilk test. Continuous data was represented as mean and standard deviation. Independentt test was used as test of significance to identify the mean difference between two quantitative variables.

Categorical data was represented in the form of Frequencies and proportions. Chi- squaretest was used as test of significance for qualitative data. Fischer's exact test was used as test of significance for qualitative data which does not fulfil the criteria for Chi-square test (2x2 tables only). Yates correction was applied wherever chi-square rules were not fulfilled (for 2x2 tables only). p-value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

RESULTS AND DISCUSSIONS

Out of 114 patients >half, 64 (56.1%) were 30-45 years, 44 (38.6%) belonged to 46-50 years and 6 (5.3%) were more than 60 years. Of all the participants, 100 (87%) were men and 14 (12.3%) were women.

Out of 114 patients, 97 (85%) had ascites, 99 (86.8%) were presented with jaundice, 60 (52.6%) had hepatic encephalopathy, 45 (39.5%) had pain in the abdomen, 32 (28.1%) had GI bleed and 23 (20.2%) had fever.

Table 1: Distribution of the Study Subjects Based on the Severity of Hepatic Encephalopathy.

Grade	Number	Percentage
0	54	47.4
1	15	13.2
2	19	16.7
3	14	12.3
4	12	10.5
Total	114	100.0

Out of all the participants, 54 (47.4%) belonged to hepatic encephalopathy grade 0, 15 (13.2%) were grade I, 19 (16.7%) were in grade II, 14 (12.3%) were in grade III and 12 (10.5%) were in grade IV. Of 114, 56 (49.1%) were belonged to child Pugh Class C, 43 (37.7%) were class B and 15 (13.2%) were in child Pugh Class A.

The aetiology of hepatic encephalopathy for majority (81.6%) of the participants was alcohol, followed by viral in 15 (13.2%), cryptogenic in 5 (4.4%) and auto immune in 1 (0.9%).

Table: 2 Distribution of the Study Subjects Based on Ferritin Levels.

Ferritin categories	Number	Percentage
Ferritin<200	21	18.4
Ferritin 200-400	43	37.7
Ferritin>400	50	43.9
Total	114	100.0

Out of 114 patients, 50 (43.9%) had a ferritin level of >400, 43 (37.7%) had ferritin level of 200-400 and 21 (18.4%) had ferritin level of <200. Of total 114 participants, 102 (89.5%) were discharged and 12 (10.5%) were expired.

Table: 3 Comparison of Age Group and Ferritin Levels in Study Subjects

Age groups	Ferritin <200		Ferritin 200-400		Ferritin >400		P-value
(years)	n	%	n	%	n	%	
30-45	10	47.6	24	55.8	30	60	
46-60	9	42.9	18	41.9	17	34	0.667
>60	2	9.5	1	2.3	3	6	
Total	21	100.0	43	100	50	100	

In ferritin <200 group, nearly half of them (47.6%) were 30-45 years of age, 9 (42.5%) were 46-60 years and 2 (9.5%) were>60 years of age. In Ferritin 200-400, more than half (55.8%) were 30-45 years, 18 (41.9%) were 46-60 years and 1 (2.3%) were >60years. In Ferritin >400 group, 30 (60%) were 30-45 years, 17 (34%) were 46-60 years and 3 (6%) were more than 60 years. There was no significant difference in age was observed between the ferritin categories.

Table: 4 Comparison of Gender and Ferritin Levels in Study Subjects

Gender	Ferritin<200		Ferritin 200-400		Ferritin>400		P-value
	n	%	n	%	n	%	
Male	14	66.7	40	93	46	92	
Female	7	33.3	3	7	4	8	0.005
Total	21	100.0	43	100	50	100	

In all the ferritin subgroups, majority were men. The proportion of males was as follows: 14 (66.7%) in ferritin <200, 40 (93%) in ferritin 200-400 and 46 (92%) in ferritin >400 groups. The proportion of females were high in ferritin<200 group when compared to 200-400 and >400 and this was significant with the p value of 0.005.

Table:5 Comparison of Clinical Features and Ferritin Levels in Study Subjects

Variable	Ferritin<200		Ferritin 200-400		Ferritin>400		P- value
	n	%	n	%	n	%	
Ascites							
Yes	11	52.4	39	90.7	47	94.0	
No	10	47.6	4	9.3	3	6.0	<0.001
Jaundice							
Yes	11	52.4	39	90.7	49	98.0	<0.001
No	10	47.6	4	9.3	1	2.0	
Alcohol history							
Yes	17	81.0	35	81.4	46	92.0	0.260
No	4	19.0	8	18.6	4	8.0	
Total	21	100.0	43	100	50	100	

About 11 (52.4%) of the participants in ferritin <200 group had ascites, 39 (90.7%) in ferritin 200-400 and 47 (94%) ferritin >400 group had ascites. The proportion of participants having ascites was higher in ferritin>400 group when compared to 200-400 and <200 groups. About 11 (52.4%) of the participants in ferritin <200 group had jaundice, 39 (90.7%) in ferritin 200-400 and 49 (98%) ferritin >400 group had jaundice. The proportion of participants having jaundice was higher in ferritin>400 group when compared to 200- 400 and <200 groups (98% Vs 90.7 and 52.4%). This difference was statistically significant with the p value of <0.001 Majority of the hepatic encephalopathy patients (90%) had a ferritin level of >400, followed by 11 (25.6%) in ferritin 200-400 group and 4 (19%) <200 group. There was a difference in the presence of hepatic encephalopathy between the ferritin groups and this was significant with the p<0.001.

Table: 6 Comparison of Child Pugh Class and Ferritin Levels in Study Subjects

Child Pugh	ClassFerritin<200		Ferritin 200-400		Ferritin>400		P-value
	N	%	n	%	n	%	
A	11	52.4	3	7.0	1	2.0	
B	6	28.6	33	76.7	4	8.0	<0.001
C	4	19.0	7	16.3	45	90.0	
Total	21	100.0	43	100	50	100	

In ferritin <200 group, more than half of the participants (52.4%) had child pugh class A, 6 (28.6%) were in class B and 4 (19%) were in class C. In ferritin 200-400 group, 33 (76.7%) were in class B, 7 (16.3%) were in class C and 3 (7%) in class A. In ferritin >400 group, 45 (90%) were in class C followed by 4 (8%) in class B and 1 (2%) were in child pugh class A. When the ferritin level was low, majority of the patients were in

child pugh score of class A and when the ferritin level was high (>400), majority of the patients were in child pugh score of class C There was an association was observed between the child pugh class scores and ferritin categories (p<0.001).

Table: 7 Comparison of Aetiology and Ferritin Levels in Study Subjects

Aetiology	Ferritin<200		Ferritin 200-400		Ferritin>400		P-value
	N	%	n	%	n	%	
Alcohol	14	66.7	36	83.7	43	86.0	
Auto immune	1	4.8	0	0	0	0.0	0.257
Cryptogenic	2	9.5	2	4.7	1	2.0	
Viral	4	19.0	5	11.6	6	12.0	
Total	21	100.0	43	100	50	100.0	

Alcohol was the main aetiology in all the ferritin subgroups. In ferritin <200 group, 19% of the participants had viral cause, followed by 2 (9.5%) had cryptogenic cause. In Ferritin 200-400, 5 (11.6%) of the participants had viral cause followed by 2 (4.7%) of the patients had cryptogenic cause. In Ferritin>400 group, 6 (12%0 had viral aetiology and 1 (2%) had cryptogenic. Only one patient ibn ferritin <200 group had auto-immune aetiology for the disease. There was no association observed between the aetiology and ferritin categories with the p value of 0.257. The mean (SD) Child Pugh score was 8.1 (3) in ferritin <200 group, 9.1 (1.6) in ferritin 200-400 and 12 (1.9) in ferritin >400 group. There was a significant difference in mean Child Pugh score was observed between the ferritin subgroups (p<0.001).

The mean (SD) MELD score was 18.2 (12.4) in ferritin <200 group, 17.9 (9.3) in ferritin 200-400 and 29.3 (13) in ferritin >400 group. There was a difference in MELD was observed between the ferritin subgroups and the difference was significant (p<0.001).

Table 8: Comparison of Bio-Chemical Parameters with Ferritin Levels in Study Subjects

Parameter	Ferritin<200		Ferritin 200-400		Ferritin>400		P-value
	Mean	SD	Mean	SD	Mean	SD	
Haemoglobin	11.3	1.9	11.3	1.3	9.9	1.5	<0.001
Total protein	6.1	1	5.8	0.7	6.4	7	0.8631
Total bilirubin	4.4	3.1	5.3	2.4	8	2.8	<0.001
Serum albumin	3.4	0.5	3.1	0.5	2.7	0.6	<0.001
Serum creatinine	1.8	1.9	1.3	1.2	2.7	2.1	0.001
INR	1.6	0.8	1.5	0.7	2.5	1.7	<0.001

The mean (SD) Haemoglobin of the participants in Ferritin<200 was 11.3 (1.9), 11.3 (1.3) in Ferritin 200-400 and 9.9 (1.5) mg/dl in Ferritin>400 group. The mean (SD) total protein was 6.1 (1) in Ferritin<200, 5.8 (0.7) in Ferritin 200-400 and 6.4 (0.7) mg/dl in Ferritin >400 group. Total bilirubin was 4.4 (3.1) in Ferritin <200 was 5.3 (2.4) in Ferritin 200-400 and 8 (2.8) mg/dl in Ferritin >400 group. Serum albumin was 3.4 (0.5) in Ferritin <200, 3.1 (0.5) in Ferritin 200-400 and 2.7 (0.6) mg/dl in Ferritin>400 group. Serum creatinine was 1.8 (1.9) in Ferritin<200, 1.3 (1.2) in Ferritin 200-400 and (2.1) in Ferritin>400 group. There was a significant difference in mean haemoglobin, total bilirubin, serum albumin and serum creatinine between the ferritin subgroups with the p<0.001.

The mean (SD) age of the participants in Ferritin<200 was 45.1 (9.5), 45 (7.5) years in Ferritin 200-400 and 45.3 (8.4) years in Ferritin>400 group. All the groups were similar regarding with the age and there was no significant difference (p=0.983).

In the present study, majority of the subjects belonged to the age group of 30 to 45 years (56.1%, n=64). The next common age group was 46 to 60 years (38.6%, n=44). On comparison with the previous literature, the CLD was found to be more common in younger when compared with other studies[1,3,6].

Majority of the subjects in the present study were males (87.7%, n=100) and the remaining were females (12.3%, n=14). This sort of male predominance was present in most of the previous studies[1,3,6,7].

Table: 9 Comparison of Etiology (in%) in Different Studies

Studies	Alcohol : viral: others
Present study	81.6:13.2:5.2
Theodora Oikonomou, *et al*[3]	25:48:27
Naseer Umer *et al*[6]	5:87:8
Walker NM *et al*[7]	20:51:29
Maiwall R *et al*[8]	33:17:50

The most common etiology of the liver disease in the present study was found to be alcohol(81.6%, n=93). The other causes were viral infection (13.2%, n=15) and autoimmune condition (0.9%, n=1). Remaining 4.4%(n=5) cases were observed to have uncertain origin. In the other studies viral etiology found to be more predominant. Alcohol being the main etiology in our study might be due to multiple factors like lack of awareness regarding the harmful effects of alcohol, many patients becoming addicted to alcohol, low socioeconomical status, failure in detection and treating early stages of alcoholic liver disease diagnosis, lack of routine virological screening. This might also explain development of chronic liver disease in early age in our study.

The mean Child Pugh Score among the subjects in the present study was 10.2. Majority of the subjects belonged to Class C (49.1%, n=55) with significant compromise of liver functions. This can be compared with the previous literatures[1,6,8].

In the present study, the mean MELD score among the subjects was 22.96 which was higher than 15±6 in Taufik Sungkar[1] and the value of MELD score in different category of serum ferritin is higher when compared with other study and increase in MELD score was associated with increasing serum ferritin levels.

In the study, the significant and positive correlation between serum ferritin levels and CTP score was evident among decompensated liver cirrhosis patients in the study, which was comparable with other studies. Along with increasing CTP score the serum ferritin was also increasing.

The present study found statistically significant association of gender, ascites, jaundice, hepatic encephalopathy, CTP score, MELD score and different

biochemical parameters like hemoglobin, total bilirubin, serum albumin and serum creatinine of the subjects with respect to the serum ferritin levels, thereby suggesting that serum ferritin level might have prognostic value in chronic liver disease patients. This mimics the association observed in the studies such as Taufik Sungkar[1], Theodora Oikonomou[3], Naseer Umer[6], Walker[7] and Maiwall[8] which have signified the importance of characteristics of the subjects with hyperferritinemia. Statistically significant association of severity of hepatic encephalopathy was established in the present study with respect to the serum ferritin levels, thereby suggesting that serum ferritin level increases significantly with increase in the severity of hepatic encephalopathy which co related with other studies.

CONCLUSION

In this study, factors responsible for decompensation of liver cirrhosis like serum albumin hepatic encephalopathy were also associated with increased serum ferritin levels. Child-Turcotte-Pugh classification which was done to access severity and prognosis of cirrhosis also showed higher ferritin levels with increasing class. Hence, as the severity of the liver disease increases, it is associated with increased in serum ferritin levels. These findings points towards possible prognostic value of serum ferritin in chronic liver disease.

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