Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v30i19.3603

"TO STUDY IRON PROFILE IN CHRONIC LIVER DISEASE IN A TERTIARY CARE HOSPITAL IN MANIPUR."

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Abstract:

Introduction: Chronic liver disease (CLD) is progressive deterioration of liver functions for more than six months. Chronic liver disease is one of the frequent causes of death, especially in the developing world. The severity of liver disease can be graded by Child Pugh Score. The liver plays a major role in iron homeostasis. Hepatic inflammation and dysfunction in CLD interferes with iron metabolism (including synthesis and clearance). Excess iron deposition in the liver is known to be hepatotoxic and exacerbate liver injury.CLD also decreased synthetic functions of liver including decreased hepcidin level causing ultimately iron overload and deposits in liver and higher levels of non-transferrin-bound iron in the bloodstream. Iron combined with reactive oxygen species leads to an increase in hydroxyl radicals, which are responsible for phospholipid peroxidation, oxidation of amino acid side chains, DNA strain breaks, and protein fragmentation. Iron deficiency as well as excess of iron, both have harmful effects on the body. Not much studies have been conducted in north-eastern part of India, so we conducted this study to evaluate the iron profile in patients with CLD and its correlation with severity of CLD.

Methods: This cross sectional study enrolled 134 chronic liver disease patients above 18 years of age who visited the Medicine outpatient department, Liver clinic or admitted to the medicine ward, Regional institute of Medical Sciences (RIMS), Imphal from 1st January, 2021 to 31st October 2022. Data were collected randomly using predesigned performa and the severity of liver disease were assessed using Child Pugh Score. Routine haematological and radiological investigations including serum iron, serum ferritin, total iron binding capacity (TIBC), unsaturated iron binding capacity (UIBC) and USG abdomen were done. ANOVA test was performed to test the significance level. A p value < 0.005 was considered significant.

Results: A total of 134 patients with chronic liver disease (CLD) were included whose mean age was 48.04 ± 15.67 years with male: female was 4:1. In this study, as per Child Pugh Turcotte Score, majority 67 (50%) of the CLD patients had decompensated liver disease classified as group C, 49 (36.6%) in group B and 13.4% in group A. The mean serum Iron level was 71.9 with SD of 47.28 mcg/dL with majority 79 (59%) having normal serum Iron levels (50-175 mcg/dL) while 51 (38.1%) of the patients had iron deficiency. Most of the participants 68 (50.7%) had TIBC levels below the normal range of 240 – 450 mcg/dL, maximum patients 82 (61.2%) had UIBC level within the normal range of 111-343 mcg/dL. But, the majority 69 (51.5%) had serum ferritin levels above the normal range of 25-336 mcg/L. Serum Iron level, TIBC, UIBC were highest in child group A and lowest in Child Pugh C which is more severe form of disease while serum ferritin was highest in child group C indicating more rapid increase in the levels of serum ferritin with increase in severity of liver disease. There was no significant association between severity of liver disease and serum iron levels (p value = 0.606) while there were statistically significant associations between serum TIBC,UIBC and serum ferritin with the severity of liver disease (p value <0.05) . The above study finding demonstrated that iron metabolism was hampered because of chronicity of liver damage in chronic liver diseases.

Conclusions: The study concluded that iron profile was deranged in chronic liver diseases where serum ferritin and total iron binding capacity has increased in relation to the severity of liver disease .This finding guided the management of chronic condition of liver damage.

Keywords: *Serum iron, TIBC, UIBC, serum ferritin, chronic liver disease.*

INTRODUCTION

CLD is a continuous process of inflammation, destruction, and regeneration of liver parenchyma, which leads to fibrosis and cirrhosis of liver.[1]The functions of liver include synthesis of clotting factors, other proteins, metabolism of fats, proteins and carbohydrates, detoxification of harmful products of metabolism, storage of vitamins and minerals and excretion of bile. The spectrum of aetiologies of CLD is broad, which includes toxins, alcohol abuse for a prolonged time, infection such as Hepatitis B, Hepatitis C, autoimmune diseases, genetic and metabolic disorders.

Cirrhosis is a final stage of chronic liver disease that results in disruption of liver architecture, the formation of widespread nodules, vascular reorganization, neo-angiogenesis(formation of new blood vessels) and deposition of an extracellular matrix.[1]The underlying mechanism of fibrosis and cirrhosis at a cellular level is the recruitment of stellate cells and fibroblasts, resulting in fibrosis, while parenchymal regeneration relies on hepatic stem cells.[1]The severity of liver disease can be graded by using a scoring system called Child Pugh Score, also known as Child Pugh Turcotte Score.[2]

In all living organisms, iron exists both in free form and as compounds in blood, such as protoporphyrin, or other cell enzymes; it plays an essential role as a cofactor for electron transporting enzymes in oxidative metabolism, and as oxygen transporter.[3] Iron is an essential micronutrient for the human body. Iron is crucial to humans' biological functions and cellular biochemical processes.[4]The human body has an average of 2–4 g of iron, of which 80% is bound in haemoglobin. There is tight control of systemic iron levels by means of iron absorption, storage, and recycling[2]. The liver plays a major role in iron homeostasis. This is of vital importance to the well-being of the body. Thus, in patients with chronic liver disease, iron regulation may be disturbed. Liver being the major storage organ, approximately one-third of the body's total iron is deposited in hepatocytes, sinusoidal mesenchymal cells, and reticuloendothelialcells.[4,5,6]

Iron deficiency – anaemia causes difficulty in oxygen transport in the body causing cellular hypoxia at severe grades of iron deficiency anaemia. Anaemia, glossitis and neurological symptoms can

subsequently occur in chronic liver disease patients.[7]In a prospective study of 213 patients with compensated cirrhosis, anaemia was found in up to 21%.[8]

Iron overload, on the other hand, which is common in chronic HBV-related diseases, hereditary hemochromatosis, but also in those with alcoholic liver disease, non-alcoholic fatty liver disease and hepatitis C viral infection, is associated with oxidative stress and subsequent tissue damage and chronic inflammation in the liver. According to the literature, chronic alcohol consumption in moderate to excessive amounts is associated with elevation of serum ferritin concentration and transferrin saturation, and can result in increased hepatic iron stores. Additionally, increased intestinal iron absorption has been documented in patients with ALD.[9]So the deficiency of Iron as well as excess of iron, both have harmful effects on the body.[10,11,12]So, liver plays a vital role in iron homeostasis, as it produces transferrin, hepcidin, ferritin – the hormones playing key role in maintaining the iron levels in the body. And chronic liver disease due to any pathology, alcoholic liver disease, Hepatitis B, Hepatitis C and so on can hamper the functions of the liver and disrupt the normal regulation of Iron levels.[13,14]Many indices of iron metabolism such as hepatic iron levels, serum iron and ferritin levels and transferrin saturation have been commonly used as diagnostic tools for iron overload as a risk factor for liver fibrosis.[9,15,16]

Not many significant studies have been conducted in India, more so in the context of the state of Manipur in aid of better understanding Iron profile in patient with CLD and its associations with the severity of liver disease.

MATERIAL AND METHODS

This study was conducted at the Department of Medicine in collaboration with Department of Biochemistry of Regional institute of Medical Sciences (RIMS), Imphal, India, from 1stJanuary, 2021 to 31st October 2022. Serum iron profile was measured in 134 diagnosed patients of CLD and its correlation studied with the severity of liver disease as measured by Child Pugh Score.

Inclusion Criteria

Included chronic liver disease patients more than 18 years of age visiting the Medicine outpatient department, Liver clinic or admitted to the medicine ward, RIMS, Imphal and giving consent for the study.

Exclusion criteria

Included patients suffering from other systemic diseases (Chronic Kidney Disease, Malignancies, Stroke, Hemoglobinopathies, Hemochromatosis or other disease which can alter absorption, metabolism or defect in excretion) and those not giving consent for the study.

Study variables

The study included demographic data such as age, sex, occupation, h/o alcohol intake, duration of CLD, co-infection with hepatitis B or C and detailed physical examination was done after informed consent. The severity of liver disease was assessed using Child Pugh Score. Serum iron profile which includes serum iron, serum ferritin, total iron binding capacity (TIBC) and unsaturated iron binding capacity (UIBC) were measured. USG abdomen was done for diagnosis for CLD.

Study tool :

Estimation of serum iron, TIBC, UIBC were measured by Photo colorimetric method and serum ferritin by enzyme linked immunosorbent assay.

Operational definitions:

a)Chronic Liver Disease diagnosed as : Diffuse disruption of liver architecture with fibrosis and nodule formation by USG/ Fibro-scanThe normal values for iron profile were given here under as:-

b)Serum Iron Level[17] Male: 70 – 175µg/dL,Female: 50 – 170µg/dL
c)Total iron binding capacity: 240 – 450µg/dL[18]
d)Unsaturated iron binding capacity: 111 – 343µg/dL[18]
e)Serum ferritin[19] -Men: 24-336mcg/L,Cyclic women: 11-307mcg/L,Menopausal women: 24-280 mcg/L.
f) Child Pugh Turcotte Score:

Critical and Lab Criteria	Points		
	1	2	3
Encephalopathy	None	Mild to Moderate(Grade 1 or 2)	Severe (Grade 3 or 4)
Ascites	None	Mild to Moderate(diuretic responsive)	Severe (diuretic unresponsive)
Bilirubin (mg/dl)	<2	2-3	>3
Albumin (g/dl)	>3.5	2.8-3.5	<2.8
Prothrombin time	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3

Child-Turcotte-Pugh Class (obtained by adding score for each parameter, i.e., total score) Class A = 5-6 points (least severe liver disease)Class B = 7-9 points (moderate severe liver disease) Class C = 10-15 points (severe liver disease)

Sample size:
Based on the study conducted by Dhillon.et al[33] sample size was calculated as $N=4PQ/l^2$; Where P is prevalence = 14%; Q is (100-P) = 86,L is the absolute allowable error = 6% at 95% confidence interval .Thereby substituting the values ,N= 4x(14)x(86)/ 36 = 133.77.Therefore sample size is taken as 134.

Statistical analysis:
SPSS Software 21.0 (IBM Corp., Armonk, NY, United States) was used for analysis. Descriptive statistics was done for the demographic details, iron profile. One-way ANOVA test was used to determine the association between Child Pugh Group of Liver disease of the patients and iron profile. A p value < 0.05 was considered as statistically significant.

Approval of Research Ethics Board and Informed consent:
The study was approved by Research Ethics Board Regional Institute of Medical Sciences, Imphal.(Reference No- A/206/REB-Comm (SP)/RIMS/2015/712/54/2020).

RESULTS
A total of 134 patients with chronic liver disease were included in the study. The demographic patterns of the participants were given in table I. The mean age of the study participants was 48.04± 15.67 years with majority males ,106 (79.1%) while female constituted 28 (20.9%). Distribution of CLD patients based on severity of the liver damage based on Child Pugh Score, was shown in figure I. Majority patients, 67 (50%) had decompensated liver disease (group C), significant functional compromised (group B) in 49 (36.6%) study subjects and well decompensated liver disease (group A) in13.4%.Serum iron profile in chronic liver disease were shown table II. The mean Serum Iron level was 71.9 $\pm$ 47.28 mcg/dL with most of them, 79 (59%) having normal serum Iron levels while 51 (38.1%) patients had serum Iron levels below the normal range. The mean TIBC level was 251.63 $\pm$ 103.19 mcg/dL with maximum patients, 68 (50.7%) having TIBC levels below the normal range of 240 – 450 mcg/dL and 63 (47%) of the CLD patients had normal TIBC levels. The mean UIBC level was 182.1 $\pm$ 114.38 mcg/dL, majority 82 (61.2%) of the CLD

patients had UIBC level within the normal range of 111-343 mcg/dL. However, 36 (26.9%) had low UIBC level. But, the majority 69 (51.5%) had Serum Ferritin levels above the normal range of 25-336 mcg/L. 55 (41%) had Serum Ferritin levels within the normal range. Mean Serum Ferritin level was 488.8 ±393.1 mcg/L.

The mean comparison of iron profile based on severity of the liver damage based on Child Pugh Score was given in table III. The association of Serum Iron profile with severity of CLD shows that serum iron levels, TIBC, UIBC were higher in Child Pugh A, slightly lower in Child Pugh B and lowest in Child Pugh C which is more severe form of disease, indicating greater decrease in the levels with severity of liver disease. In contrast, the serum ferritin level is lower in Child Pugh A; is slightly higher in Child Pugh B and highest in Child Pugh C which is more severe form of disease (681.75 mcg/L ± 270.30) indicating more rapid increase in the levels of serum ferritin with increase in severity of liver disease. There was no significant association between severity of liver disease and serum Iron levels while statistically significant associations existed for serum TIBC,UIBC and serum ferritin with the severity of liver disease (p value <0.05).

Table I: Demographic patterns of the study participants (N=134)

Demographic variables	N(%) / Mean ± SD
Age in completed years	48.04 ± 15.67
Age group: <40 years 40-60 years >60 years	 54 (40.3) 51 (38.0) 29 (21.7)
Sex: (male:female)	4:1
H/o alcohol intake	98(73.1)
Duration of chronic liver disease (median)	13 years
History of Hepatitis B infection	3 (2.3)
History of Hepatitis C infection	12 (9.0)

Table II: Distribution of Iron profile among the participants (N=134)

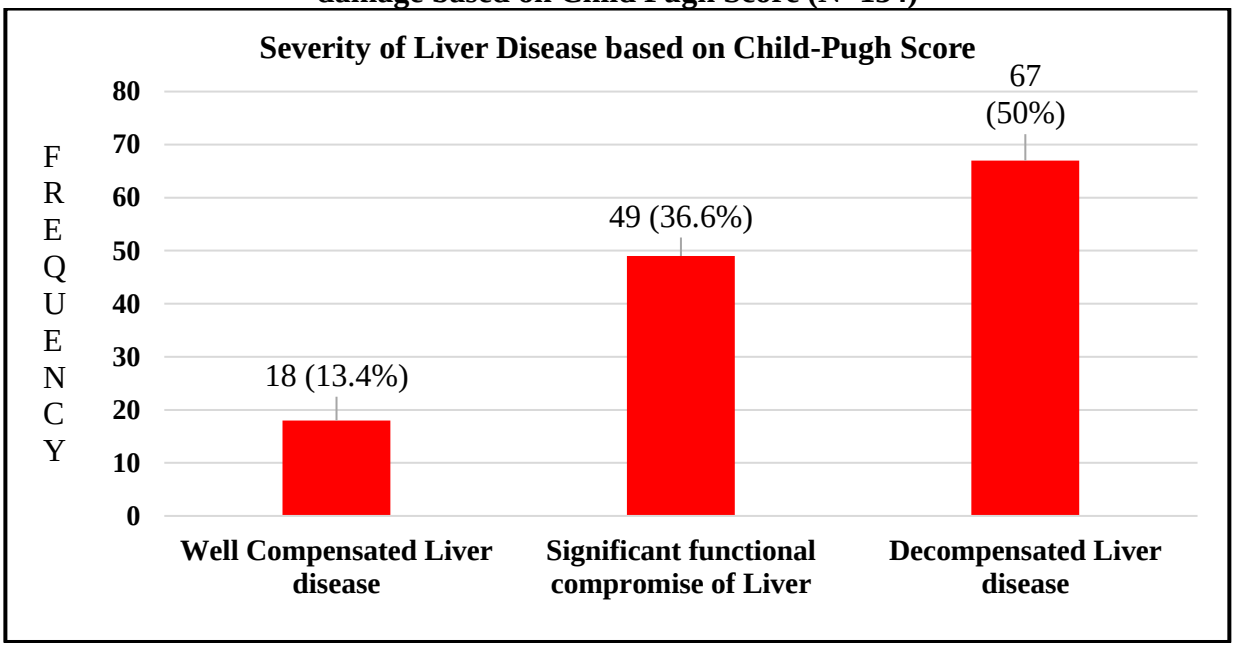
Iron profile	N(%)
Serum iron level: Below normal range Within normal range Above normal range	 51 (38.1) 79 (59.0) 4 (2.9)
Total iron binding capacity: Below normal range Within normal range Above normal range	 68 (50.7) 63 (47.0) 3 (2.3)
Unsaturated iron binding capacity: Below normal range Within normal range Above normal range	 36 (26.9) 82 (61.2) 16 (11.9)
Serum ferritin: Below normal range Within normal range Above normal range	 10 (7.5) 55 (41.0) 69 (51.5)

Table III: Mean comparison of iron profile based on severity of the liver damage based on Child Pugh Score (N=134)

Iron profile in chronic liver disease	Child Pugh Score (Severity of liver damage) (mean ± SD)			P value
	Group A	Group B	Group C	
Serum Iron level (mcg/dl)	79.39± 40.25	74.33±44.14	68.10 ± 31.23	0.606
Serum total iron binding capacity (mcg/dl)	331.72±67.50	274.47±109.85	213.42±88.8	0.001
Serum unsaturated iron binding capacity	252.17± 57.07	187.57±129.05	159.31± 107.31	0.008

(mcg/dl)				
Serum ferritin (mcg/dl)	213.08± 97.66	389.29± 79.79	681.75± 270.30	0.001

Figure I: Distribution of patients with chronic liver disease based on severity of the liver damage based on Child Pugh Score (N=134)



DISCUSSION

A total of 134 CLD patients were enrolled in the study. The mean age of the study participants was 48.04± 15.67 years, which was similar to the studies by Mao WL et al[4]and Paternostro R et [al8](mean age of 46 years),Wei Y et al[20](mean age ± SD of Chronic Hepatitis B patients was 40±12 years, of HBV related Liver Cirrhosis was 42±14 years and of HBV related Hepatocellular Carcinoma (HCC) was 47.7±7 years). This finding was similar to the study conducted by Dhillon BK et al.[21]

In our study majority of the study participants were males106 (79.1%); females were 29 (20.9%). Male to female ratio was 3.7:1, which was comparable to Hollebecque, A[22](108 males,20 females)and Wei Y et al,[20](72.2 % males,27.8% females). Our study shows that majority 67 (50%) of the CLD patients had decompensated liver disease as per Child Pugh Score (Child Pugh C). 49 (36.6%) had significant functional compromise of Liver (Child Pugh B) and 18 (13.4%) had well Compensated Liver disease (Child Pugh A). Similar result was seen in a study by Paternostro R et al[8] where majority 78.1% had decompensated cirrhosis and 21.9% had compensated liver cirrhosis. Study by Jamil Z et al[23]showed 38 (30.4%) had advanced liver disease and were in Child Pugh C, 39 (31.2%) were CP class B 48 (38.4%) were Child Pugh A. Our study shows that serum TIBC and ferritin were significantly associated with severity of liver condition which was measured by Child Pugh Score which is quite similar to the study conducted by Prieto J et al[24], Maras JS et al[25], Tung BY et al[26], Di Bisceglie AM et al[27], Kowdley K.V et al[28], and Buzzetti E et al.[29]

Majority of our patients i.e. 79 (59%) had normal Serum Iron levels (50-175 mcg/dL) while iron deficiency anemia was present in 51 (38.1%) patients. Serum iron level is higher in Child Pugh A (mean79.39±40.25 mcg/dL); is slightly lower in Child Pugh B (74.33±44.14 mcg/dL) and lowest in Child Pugh C (68.1±51.34mcg/dL).However, there was no significant association between severity of liver disease and serum iron levels (p value = 0.606) which was consistent with the findings by Çam H et al[10],Paternostro R et al[8]and Mao WL et al[4].

Excess iron can be harmful to the organism, in part through the generation of oxygen radicals, and is potentially lethal.[14,15]Excessive iron deposition in the liver leads to further injuries by triggering

hepatocellular necrosis, inflammation, fibrosis [16,23], and even carcinoma.[4]Several studies reported significant prognostic impact of hyperferritinaemia for mortality and decompensation.[6,30,31]

Tanaka H et al[32]conducted a study on excessive reactive iron impairs hematopoiesis by affecting both immature hematopoietic cells and stromal cells which shows that ferrous ammonium sulphate (FeAS)induced growth arrest and apoptosis in immature hematopoietic cells, which was mediated via reactive oxygen species (ROS) activation of p38MAPK and JNK pathways. In in-vitro haematopoiesis derived from embryonic stem cells (ES cells), FeAS enhanced the development of dysplastic erythroblasts but inhibited their terminal differentiation; in contrast, it had little effect on the development of granulocytes, megakaryocytes, and B lymphocytes. In addition to its direct effects on hematopoietic cells, iron overload altered the expression of several adhesion molecules on stromal cells and impaired the cytokine production profile of these cells. Therefore, excessive iron would affect whole haematopoiesis by inflicting vicious effects on both immature hematopoietic cells and stromal cells.

TIBC is a test that measures the blood's capacity to bind iron with transferrin. It is a measure of the maximum amount of iron that it can carry, which indirectly measures transferrin. TIBC reflects the availability of iron binding sites on transferrin. Values increase in iron deficiency and decrease in iron overload[33]. Our study shows that majority 68 (50.7%) of the CLD patients had TIBC levels below the normal range of 240 – 450 mcg/dL, which is consistent with the study by Gao YH et al[9]. TIBC level is higher in Child Pugh A (mean of 331.72 $\pm$ 67.5 mcg/dL); is slightly lower in Child Pugh B (274.47±109.85 mcg/dL) and lowest in Child Pugh C (213.42$\pm$88.8 mcg/dL). Significant association present between severity of liver disease and TIBC levels (p value <0.001). However in a study by Çam H et al,[10]no significant differences in total iron binding capacity among patients in different stages of fibrosis.

UIBC is a measurement of the unsaturated fraction of serum transferrin. In contrast to transferrin saturation, which requires two analytical steps, UIBC is a single-step chemical assay that can be easily automated. Because transferrin saturation involves two separate assays to give the ratio of serum iron and TIBC, the laboratory errors are compounded[33]. Our study shows that majority 82 (61.2%) of the CLD patients had normal UIBC level (111-343 mcg/dL while 36 (26.9%) had low UIBC level. UIBC level was higher in Child Pugh A (mean of 252.17$\pm$ 57.07 mcg/dL); is slightly lower in Child Pugh B (187.57±129.05 mcg/dL) and lowest in Child Pugh C (159.31$\pm$107.35mcg/dL).Significant association present between severity of liver disease and UIBC levels(p value 0.008)were found which is similar to the study by Paternostro R et al[8].

In our study majority 69 (51.5%) had elevated serum ferritin levels (above the normal range of 25-336 mcg/L). There was statistically significant association between serum ferritin level and different Child Pugh groups (p value <0.001) (highest in Group C with mean of 681.75±370.3mcg/L). Similar findings were noted in the studies by Gao YH et al[9], Di Bisceglie AM et al[27], Tung BY et al[26].In study by Çam H et al[10],higher fibrosis stages were associated with higher serum ferritin levels. However in a study conducted by Silva et al[34] noticed that ferritin is an inadequate marker of hepatic iron content because it increases in acute and chronic inflammatory processes with or without liver damage.

Limitations

In the present study, **s**ample size was relatively less and may not depict the full picture. Iron profile was not repeated, so result could have been under estimated or over estimated. Repetitive measurements could have increased the robustness of the study. Hepcidin which plays a key role in iron homeostasis could not be studied due to financial constraint. This study could not prove causality however directed to conduct randomized contrail trials with adequate sample.

CONCLUSION

Iron profile was deranged in chronic liver diseases where serum ferritin and total iron binding capacity has increased in relation to the severity of liver disease .The findings may guide the complete management of chronic condition of liver damage. A comparative multicentric study with higher sample size controlling the confounders will give better clinical picture.

Funding:
No funding sources

Conflict of interest:
None declared

Ethical Approval:
The study was approved by the Institutional Ethics Committee.

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