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ORIGINAL RESEARCH

A Cross-Sectional Analysis of Iron Metabolism Markers and Cirrhosis Severity in Patients at a Tertiary Care Hospital

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Abstract:
Background: Cirrhosis represents the terminal stage of chronic liver disease, characterized by progressive hepatic dysfunction and systemic metabolic derangements, including disruptions in iron metabolism. This study investigates the relationship between iron metabolism markers and the severity of cirrhosis among patients in a tertiary care setting in Northeast India.
Methods:A prospective cross-sectional study was conducted from March to August 2024, involving 112 cirrhotic patients from Tripura Medical College. The severity of cirrhosis was classified using the Child-Pugh scoring system. Serum iron, ferritin, total iron-binding capacity (TIBC), and haemoglobin levels were analyzed. Statistical comparisons were made using ANOVA.
Results: The study cohort (mean age 51.1 ± 7.3 years) exhibited a male predominance (83%). Cirrhosis severity was categorized as Class A (28.6%), Class B (40.2%), and Class C (31.3%). Significant alterations in iron metabolism markers were observed with increasing disease severity. Serum iron and ferritin levels increased progressively ($p < 0.001$), while haemoglobin and TIBC levels declined ($p < 0.001$).
Conclusion: Progressive cirrhosis severity is associated with significant dysregulation of iron metabolism. These findings highlight the potential utility of monitoring iron markers to assess disease progression and guide clinical management. Further research is needed to elucidate the underlying mechanisms and explore therapeutic implications.
Key-words: Cirrhosis, Child-Pugh score, ferritin, iron metabolism,liver disease

Introduction:

Cirrhosis of the liver represents the terminal stage of chronic liver disease, characterized by irreversible scarring and architectural disruption of hepatic parenchyma. This pathological state results in the formation of widespread nodules, vascular remodelling, neo-angiogenesis (formation of new blood vessels), and excessive deposition of extracellular matrix components.[1] At a cellular level, the progression to cirrhosis is primarily driven by the activation and recruitment of hepatic stellate cells and fibroblasts, leading to the development of fibrosis. Concurrently, parenchymal regeneration is facilitated by hepatic stem cells, which attempt to restore liver architecture[1]. The severity of liver dysfunction in cirrhotic patients can be evaluated using established scoring systems, with the Child-Pugh Score (also known as the Child-Pugh-Turcotte Score) serving as a

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widely accepted tool for grading disease severity and guiding clinical management.[2]

Iron is an essential micronutrient that plays a pivotal role in numerous biological functions and cellular processes. It acts as a critical cofactor for electron transport enzymes involved in oxidative metabolism and as a key component in oxygen transport via haemoglobin. The human body contains an average of 2–4 grams of iron, with approximately 80% of this iron bound within haemoglobin. To maintain optimal physiological function, systemic iron levels are tightly regulated through mechanisms governing iron absorption, storage, and recycling. The liver, as a central organ in iron homeostasis, plays a crucial role in regulating these processes. It serves as the primary storage site for iron, with approximately one-third of the body's total iron content being deposited in hepatocytes, sinusoidal mesenchymal cells, and reticuloendothelial cells.[3–8]

In patients with chronic liver disease, the liver's ability to regulate iron homeostasis becomes progressively impaired. This dysfunction is particularly pronounced in advanced stages of cirrhosis, where the liver's capacity to store iron, synthesize ferritin, and produce transferrin is significantly diminished. These alterations in iron metabolism lead to disturbances in systemic iron regulation. Elevated serum ferritin levels, for instance, are often indicative of iron overload and systemic inflammation, while reduced total iron-binding capacity (TIBC) frequently reflects impaired hepatic synthesis of transferrin. These disruptions in iron markers are not only indicative of altered iron homeostasis but also serve as potential indicators of disease progression and severity in cirrhotic patients.[9–11]

Despite the critical interplay between iron metabolism and liver function, there is a paucity of studies examining the relationship between iron profile parameters and the severity of cirrhosis in specific regional contexts, such as Northeast India, including the state of Tripura. So, this study aims to bridge this gap by investigating the relationship between iron markers and the severity of cirrhosis in patients attending a tertiary care center in Tripura.

Material and Methods:

Study designand setting: This prospective observational cross-sectional study was done at the Department of Medicine in association with Department of Biochemistry of Tripura Medical College between March and August 2024.

Inclusion andexclusion criteria: Cirrhotic patients aged 18 years and above who attended the Medicine outpatient department or were admitted to the Medicine ward at Tripura Medical College (TMC), Agartala, and who provided informed consent to participate in the study were included. Patients were excluded if they had concurrent systemic diseases, such as chronic kidney disease, malignancies, stroke, hemoglobinopathies, or hemochromatosis, or any other conditions that could alter iron absorption, metabolism, or excretion. Additionally, patients who refused to provide informed consent for participation in the study were also excluded.

Sample size andsampling: A total of 112 patients diagnosed with cirrhosis, admitted to the Medicine ward, were recruited for the study after fulfilling the inclusion and exclusion criteria. Participants were selected using a convenient sampling method.

Data collection and analysis: Patient demographic and biochemical details were recorded using a semi-structured proforma. The severity of cirrhosis was classified using the Child-Pugh scoring system, categorizing patients into three groups: Class A (mild), Class B (moderate), and Class C (severe). Blood samples were obtained to evaluate serum iron, total iron-binding capacity (TIBC), ferritin, and haemoglobin levels. Statistical analyses were conducted using SPSS software (version 26).Continuous data were presented as mean and standard deviation, while qualitative data was presented as frequency and percentages. ANOVA was applied to see the difference in mean values.

Results:

The mean age of the participants was 51.1 ± 7.3 years, with half of the cohort falling within the 30–60 years age range. A male predominance was observed among the participants. Based on the Child-Pugh classification, 28.6% of patients were Class A (mild), 40.2% were Class B (moderate), and 31.3% were Class C (severe).

Table 1: Basic characteristics of patients

Gender	Frequency	Percentage
Male	93	83.0%
Female	19	17.0%
Age-group	**Frequency**	**Percentage**
<30	17	15.2%
30-60	56	50.0%
>60	39	34.8%
Total	**112**	**100%**

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Figure 1: Distribution of participants according to cirrhosis severity

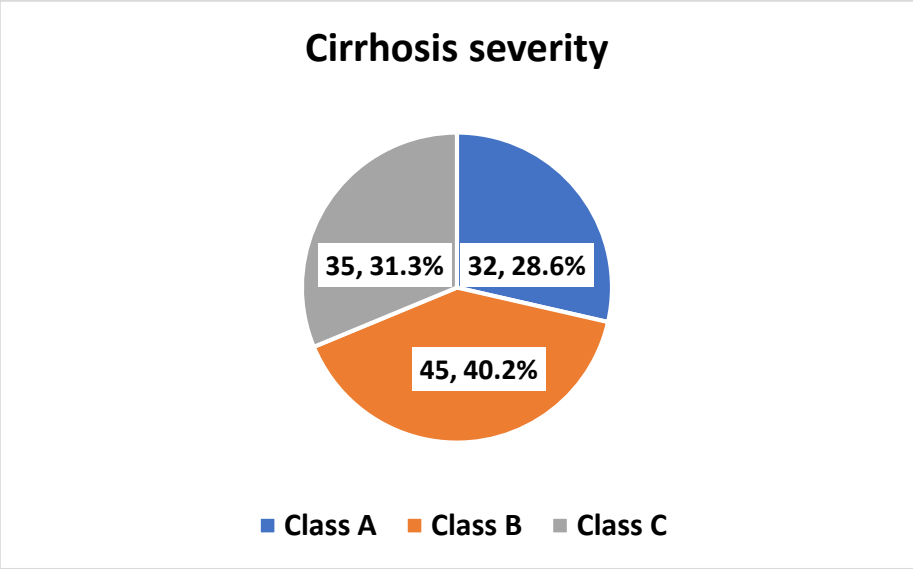

Table: Association of cirrhosis grade and iron markers

Marker	Class A	Class B	Class C	p-value[#]
Haemoglobin (g/dL)	12.5 ± 2.0	11.0 ± 2.5	9.5 ± 2.8	<0.001*
Serum Iron (µg/dL)	150 ± 28	170 ± 30	200 ± 40	<0.001*
TIBC (µg/dL)	380 ± 40	340 ± 50	280 ± 45	<0.001*
Ferritin (ng/mL)	250 ± 50	300 ± 60	450 ± 70	<0.001*

[#]ANOVA, [*]Statistically significant

This study identified significant alterations in iron metabolism markers with increasing cirrhosis severity, as classified by the Child-Pugh scoring system (Classes A, B, and C). Haemoglobin levels decreased progressively, from 12.5 ± 2.0 g/dL in Class A to 9.5 ± 2.8 g/dL in Class C ($p < 0.001$). Whereas, serum iron levels showed a progressive increase from 150 ± 28 µg/dL in Class A to 200 ± 40 µg/dL in Class C, while ferritin levels rose from 250 ± 50 ng/mL to 450 ± 70 ng/mL ($p < 0.001$ for both). In contrast, total iron-binding capacity (TIBC) declined significantly, from 380 ± 40 µg/dL in Class A to 280 ± 45 µg/dL in Class C ($p < 0.001$).

Discussion:

This study was done to find the association between iron metabolism markers and cirrhosis severity by examining patients admitted to a tertiary care center in Tripura and a total of 112 patients diagnosed with cirrhosis were recruited from the Medicine ward.Haemoglobin levels exhibited a significant decline with advancing cirrhosis severity, highlighting the progression of anaemia in these patients. The mean haemoglobin level in Class A cirrhosis was 12.5 ± 2.0 g/dL, which decreased to 11.0 ± 2.5 g/dL in Class B and further to 9.5 ± 2.8 g/dL in Class C. This decline reflects the multifactorial nature of anaemia in cirrhosis. Contributing factors may include reduced erythropoietin production due to impaired renal function, chronic systemic inflammation leading to hepcidin-mediated iron sequestration, and impaired iron utilization resulting from altered iron homeostasis. Serum iron levels demonstrated a significant upward trend with increasing cirrhosis severity. The mean serum iron level was 150 ± 28 µg/dL in patients with Class A cirrhosis, rising to 170 ± 30 µg/dL in Class B, and further increasing to 200 ± 40 µg/dL in Class C. This pattern suggests progressive iron accumulation as liver dysfunction advances. Similar findings have been reported in previous studies, which also observed serum iron overload in patients with cirrhosis.[11] However, contrasting evidence from Tlau et al. indicates no significant association between the severity of liver disease and serum iron levels, highlighting the need for further investigation to clarify these discrepancies.[12]

Ferritin is classically considered the main marker of iron homeostasis. The hepatocyte is the major site for ferritin synthesis, but also for synthesis of transferrin, which represents the major iron-binding protein.[13]Ferritin levels increased significantly with advancing cirrhosis severity, reflecting progressive iron storage as liver function deteriorated. The mean ferritin level in patients with Class A cirrhosis was 250 ± 50 ng/mL, rising to 300 ± 60 ng/mL in Class B and further to 450 ± 70 ng/mL in Class C. Similar trends have been reported in different studies, which also observed elevated ferritin levels in cirrhosis.[12,14] However, Silva et al. highlighted that ferritin might be an inadequate marker of hepatic iron content due to its elevation in acute and chronic inflammatory

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conditions, irrespective of liver damage.[15] Total iron-binding capacity (TIBC) showed a significant decline with increasing cirrhosis severity. The mean TIBC was 380 ± 40 µg/dL in Class A cirrhosis, decreasing to 340 ± 50 µg/dL in Class B and further to 280 ± 45 µg/dL in Class C, indicating reduced iron-binding capacity in advanced liver disease. These findings align with the study by Tlau et al., which emphasized that TIBC reflects the blood's capacity to bind iron with transferrin. TIBC values decrease in iron overload, as observed in cirrhosis, and increase in iron deficiency.[12] However, Çam and Yılmaz reported no significant differences in TIBC.[16] Serum iron and ferritin levels increased significantly with advancing disease severity, suggesting potential iron dysregulation in the context of worsening liver function. Conversely, TIBC and haemoglobin levels exhibited significant reductions, reflecting impaired iron-binding capacity and anaemia in more advanced stages of cirrhosis.

This study highlights a significant relationship between cirrhosis severity and disruptions in iron metabolism. As liver function declines in cirrhosis, the liver's capacity to regulate iron homeostasis is compromised, resulting in elevated serum iron and ferritin levels, alongside a reduction in total iron-binding capacity and worsening anaemia. Increased ferritin levels observed in advanced stages of cirrhosis may indicate iron overload or a systemic inflammatory response, complicating its utility as a specific marker of iron storage. The observed decrease in TIBC is likely attributable to impaired hepatic synthesis of transferrin, a critical protein for iron transport. These findings underscore the potential value of monitoring iron metabolism markers and haemoglobin levels to enhance understanding of cirrhosis progression and inform clinical management strategies.

The present study had certain limitations. The relatively small sample size may not fully represent the broader population, potentially limiting the generalizability of the findings. Additionally, the iron profile was assessed only once, which may have led to an underestimation or overestimation of the results. Repeated measurements could have enhanced the study's robustness. Hepcidin, a key regulator of iron homeostasis, could not be analyzed due to financial constraints. While this study does not establish causality, it highlights the need for future randomized controlled trials with larger sample sizes. Furthermore, incorporating data on personal habits, underlying liver diseases, and adjusting for these variables when analyzing iron marker levels would significantly enhance the depth and applicability of future research.

Conclusion:

This study demonstrates that cirrhosis progression is closely associated with significant alterations in key iron metabolism markers. Regular monitoring of these markers could enhance the assessment of liver function and anaemia, offering a more comprehensive understanding of disease progression. These findings underscore the need for further research to clarify the pathophysiological mechanisms and explore the prognostic and therapeutic potential of iron metabolism markers in managing cirrhosis.

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