ORIGINAL ARTICLE

Hepcidin as a Therapeutic Target in Liver Cirrhosis: A Cohort Study on Iron Dysregulation

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ABSTRACT

Background: Iron metabolism dysregulation in liver cirrhosis leads to iron accumulation which triggers oxidative stress and advances liver tissue damage. This study investigated how Hepcidin modulation affects iron accumulation and liver function alongside cirrhosis complications among liver cirrhosis patients.

Methods: A prospective cohort study (January 2024 to January 2025) was conducted by monitoring 120 liver cirrhosis patients at the Asian Institute of Medical Sciences Hyderabad and remaining from Liaquat University Hospital Jamshoro (ERC/9303/24) in adherence with the Declaration of Helsinki. The study documented both baseline clinical data alongside liver function tests and Hepcidin measurements. Two separate groups were formed through randomization for treatment with Hepcidin-modulating. Disease severity using Child-Pugh and MELD scores was determined. The study used both Kaplan-Meier survival and Cox regression methods to examine clinical outcomes. Data were analyzed using SPSS version 22. Paired t-tests evaluated within-group changes, and one-way ANOVA was employed for between-group comparisons (p-value<0.05, Statistical Significance).

Results: The intervention group experienced a substantial Hepcidin level rise from 45.7 ng/mL to 87.5 ng/mL. The levels of serum ferritin declined from 890.5 ng/mL to 510.2 ng/mL. The intervention group achieved notable liver function improvement through their Child-Pugh score drop from 8.2 to 6.5 (p=0.003) and their MELD score reduction from 18.2 to 14.9 (p=0.002).

Conclusion: The modulation of Hepcidin treatment leads to major reductions in iron burden, improved liver function, and decreased cirrhosis-related complications among patients, hence making it a potential treatment for the disease. Future studies should explore its long-term effects and integration into clinical practice, more particularly in resource-limited settings.

Keywords: Hepcidin, Liver Cirrhosis, Iron Overload, Ferritin, Liver Function, Cirrhosis, Complications

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Doi: https://doi.org/10.36283/ziun-pjmd14-2/004

How to cite: Uqaili AA, Chang AH, Kalhoro MA, Ahmed O, Samejo MA, Memon MS, Ahmed E Hepcidin as a Therapeutic Target in Liver Cirrhosis: A Cohort Study on Iron Dysregulation. Pak J Med Dent. 2025 April ;14(2): 16-21. Doi: https://doi.org/10.36283/ziun-pjmd14-2/004.

Received: Sat, February 1, 2025 **Accepted:** Sat, March 15, 2025 **Published:** Sun, April 13, 2025

INTRODUCTION

Millions of people suffer from liver cirrhosis, which represents the final stage of chronic liver disease thus making it a significant global health issue [1]. The condition is characterized by continuous hepatic fibrosis and structural liver damage that leads to liver function impairment along with serious complications like ascites, hepatic encephalopathy, and variceal bleeding [2]. Among various pathological factors involved in the progression of cirrhosis, iron overload stands out as a severe but frequently neglected contributor to both disease progression and poor clinical outcomes in liver cirrhosis patients [3].

Many biological mechanisms depend on iron because it enables oxygen transport and energy metabolism. However, excess iron storage leads to oxidative stress along with inflammatory responses and cellular harm to the liver because it functions as the primary storage site for iron [4]. Liver cirrhosis patients experience hepatic function deterioration, which disrupts iron metabolism regulation and leads to widespread iron accumulation. These patients typically exhibit higher serum ferritin together with transferrin saturation (TSAT) values which demonstrate an excessive iron build-up and heightened risk for liver cell injury [5].

The primary regulatory mechanism of systemic iron metabolism operates through Hepcidin, which binds to ferroportin and triggers its degradation, preventing excessive iron export [6]. The agonists of Hepcidin work by simulating this natural hormone, thus restoring proper iron balance throughout the body and decreasing systemic iron concentrations. These agents improve liver function by preventing hepatocyte iron overload, which simultaneously reduces inflammation and oxidative stress [7,8]. Early preclinical investigations combined with initial clinical trials demonstrate that Hepcidin-based treatments help to prevent iron overload complications which include hepatocellular carcinoma and systemic inflammation [9].

Despite an increasing interest in Hepcidin modulation, clinical evidence for its safety and efficacy in cirrhotic patients remained limited. Most existing research findings have focused on Hepcidin's role as a regulatory molecule and a main component for iron transport. However, studies remained theoretical as they had only translated them into clinical practice to assess how they affect patient outcomes [10,11].

Several therapeutic methods have been explored to regulate iron metabolism among chronic liver diseases. Previous research has investigated iron chelation therapy, dietary modifications, and phlebotomy, but these strategies yield inconsistent benefits and limited applicability in cirrhosis management [12]. Hepcidin modulation offers a focused approach by aiming at iron dysregulation rather than managing iron levels. Given the shortage of well-designed clinical trials, further research was needed to determine whether Hepcidin modulation therapy could effectively reduce iron burden from the liver, improve its function, and lower cirrhosis-related complications or not [13].

This research project investigated the influence of Hepcidin modulation on hepatic iron accumulation and clinical progression in cirrhotic patients. The study examined Hepcidin agonists through their impact on serum ferritin, transferrin saturation (TSAT), liver enzyme levels (ALT and AST), and the frequency of cirrhosis complications such as ascites, variceal bleeding, and hepatic encephalopathy. By the evaluation of this essential yet underexplored domain of cirrhosis management, this study aimed to highlight the therapeutic potential of Hepcidin modulation as a viable treatment strategy.

METHODS

A prospective cohort study was conducted from January 2024 to January 2025, monitoring 120 liver cirrhosis patients, with cases recruited from the Asian Institute of Medical Sciences, Hyderabad, and the remaining were taken from Liaquat University Hospital, Jamshoro (ERC/9303/24). The study was conducted in adherence to the Declaration of Helsinki. The sample size of 120 participants was calculated based on power analysis to detect a significant difference in iron metabolism and liver function outcomes at 95% confidence level ($\alpha = 0.05$) and 80% power ($\beta = 0.20$). Participants were randomized into two groups using a consecutive sampling technique: the Hepcidin Modulation Group (n=60): Treated with Hepcidin agonists and the Control Group (n=60): Received standard care without Hepcidin modulation.

Hepcidin levels were measured using ELISA (enzyme-linked immunosorbent assay) from the blood samples that were collected at the start. Patients who showed significantly reduced Hepcidin levels were allocated to the Hepcidin Modulation Group where they received treatment with Hepcidin agonists. Whereas, those with Hepcidin levels within or above the normal range were taken as the Control Group and received the standard care. In addition to Hepcidin levels, iron metabolism markers such as serum ferritin, transferrin saturation (TSAT) and total iron-binding capacity (TBIC) were calculated for further classification of patients and to monitor treatment effects over the study period.
Inclusion Criteria were Adults aged 18–65 years, Serum ferritin >500 ng/mL and transferrin saturation (TSAT) >50%, and a Confirmed diagnosis of liver

cirrhosis based on clinical, biochemical, and imaging findings. Exclusion Criteria were Coexisting chronic liver diseases (e.g., hepatitis B or C, Wilson's disease), Active infections, malignancies, or advanced comorbidities, Prior treatment with iron chelation or Hepcidin-based therapies.
Patients in the Hepcidin modulation group received subcutaneous injections of Hepcidin agonists at a dose adjusted according to baseline iron parameters. The control group received standard care, which included dietary counseling and supportive management. Although Hepcidin-based approaches have been studied worldwide, clinical application in the Pakistani region remained underexplored. As a high prevalence of liver disease is seen in the region, this study provided crucial insights into Hepcidin modulation serving as a potential treatment strategy, making its way towards the integration into local healthcare practices.

Data were collected at the start, after six months, and after 12 months. The data were assessed for the iron parameters and liver function tests (LFTs). Serum ferritin was measured by using chemiluminescent immunoassay (CLIA) and transferrin saturation (TSAT) was measured from serum iron and total iron binding capacity (TIBC) with the help of ferrozine-based colorimetric method. ALT and AST were assessed using the kinetic UV method per IFCC guidelines.

Blood samples were collected in serum separator and heparinized tubes, centrifuged for 10 minutes at 3000 rpm, and stored at -80°C before analysis. Serum ferritin was measured on the Roche Cobas e411, TSAT on the Beckman Coulter AU680, and LFTs on the Abbott Architect c8000. Vigilant quality control protocols ensured accuracy, with calibration and validation which was performed using manufacturer-supplied control sera.

Data were collected at baseline, 6 months, and 12 months. The routine lab parameters were measured at Beckman Coulter AU680 based on chemiluminescent immunoassay (CLIA) such as Serum ferritin, Transferrin saturation (TSAT), and Liver Function Tests (LFTs). Incidence of complications such as ascites, variceal bleeding, and hepatic encephalopathy were taken into consideration. Data were analyzed using SPSS version 22. Descriptive statistics were used for baseline characteristics. Paired t-tests evaluated within-group changes, and ANOVA was employed for between-group comparisons. The incidence of clinical complications was analyzed using chi-square tests. Statistical significance was set at $p < 0.05$.

RESULTS

The study included 120 patients with liver cirrhosis, evenly divided between the intervention (n=60) and control (n=60) groups.

Table 1: Baseline Demographic and Clinical Characteristics

Characteristic	Intervention Group (n=60)	Control Group (n=60)	p-value
Age (years)	51.9 ± 9.8	52.7 ± 11.1	0.612
Gender (Male)	37	38	0.845
Gender (Female)	23	22	0.845
BMI (kg/m²)	27.4 ± 4.3	27.6 ± 4.0	0.798
Diabetes (%)	24 (40%)	26 (43.3%)	0.723
Hypertension (%)	21 (35%)	20 (33.3%)	0.870

The mean age of participants was 52.3 ± 10.5 years, with a male predominance in both groups (62% male, n=75, 38% female, n=45). Baseline characteristics such as age, gender, BMI, and comorbidities were comparable between the two groups ($p > 0.05$) as shown in **Table 1**.

Table 2: Frequency of Complications and Compliance

Complications	Intervention Group (n=60)	Control Group (n=60)	p-value
Ascites	12 (20%)	24 (40%)	0.018
Variceal Bleeding	5 (8.3%)	11 (18.3%)	0.112
Hepatic Encephalopathy	2 (3.3%)	7 (11.6%)	0.032
Compliance with Intervention (%)	52 (86.6%)	N/A	N/A

The frequency of complications (ascites, variceal bleeding, and hepatic encephalopathy) and compliance with the intervention was recorded at the end of the 12-month follow-up as shown in **Table 2**. The Intervention Group had significantly lower rates of ascites and hepatic encephalopathy as compared to the control group. The difference between variceal bleeding was not statistically significant.

Table 3: Changes in Iron Metabolism and Hepcidin Levels

Groups	Baseline Ferritin (ng/mL)	12-Month Ferritin (ng/mL)	p-value	Baseline LIC (µmol/g)	12-Month LIC (µmol/g)	p-value	Baseline Hepcidin (ng/mL)	12-Month Hepcidin (ng/mL)	p-value
Intervention Group	890.5 ± 175.8	510.2 ± 145.6	<0.001	45.8 ± 8.4	28.4 ± 6.7	<0.001	45.7 ± 12.3	87.5 ± 24.9	<0.001
Control Group	882.7 ± 160.4	862.4 ± 155.9	0.192	46.2 ± 9.1	44.9 ± 8.8	0.208	46.5 ± 11.9	48.2 ± 13.2	0.105

Table 3 compared iron parameters and Hepcidin levels between the Intervention group and the Control Group at the baseline and 12 months. There were significant reductions in ferritin and LIC and a significant increase in hepcidin ($p < 0.001$), in the Intervention group while changes in Control were not significant ($p > 0.05$).

Table 4: Changes in Liver Function and Complications

Groups	Baseline Child-Pugh Score	12-Month Child-Pugh Score	P-Value	Baseline MELD Score	12-Month MELD Score	P-Value	Complications (N, %)	p-value
Intervention Group	8.2 ± 1.5	6.5 ± 1.4	0.003	18.2 ± 6.1	14.9 ± 5.8	0.002	19 (21.6%)	0.004
Control Group	8.1 ± 1.3	7.9 ± 1.5	0.152	18.0 ± 5.9	17.7 ± 5.7	0.210	38 (43.2%)	0.003

Table 4 shows the comparison between Child-Pugh scores, MELD scores, and complications between the Intervention Group (Hepcidin modulation) and Control Group (standard care) at baseline and 12 months. Significant improvements were observed in iron metabolism, liver function, and the incidence of complications in the intervention group compared to the control group as shown in this table.

DISCUSSION

The most substantial outcome of this study was the improvement in iron metabolism, liver function, and reduction in cirrhosis-related problems, following the hepcidin modulation therapy. The significant reduction in serum ferritin and liver iron concentration (LIC) in the Hepcidin Modulation Group aligned with the previous studies that highlighted the role of Hepcidin in controlling iron overload and its effect on liver disease. These findings showed a greater reduction in the burden of iron on the liver as compared to other studies, which might have been attributed to differences in baseline hepcidin levels, the degree of iron overload or the particular agonists used [14]. These findings supported existing studies that identified hepcidin as an essential component for maintaining iron balance and as a possible treatment for liver diseases [15].

The study outcomes showed that hepcidin agonists restored iron balance through intestinal absorption inhibition while promoting macrophage iron sequestration, which helped prevent iron excess. These results are consistent with the study that described how hepcidin deficiency leads to slow iron buildup in chronic liver disease [16]. However, unlike one study showed moderate effects on liver iron restores this study observed a pronounced improvement in iron parameters, probably due to differences in study duration, patient selection, and treatment protocols [17].

Moreover, the findings indicated that the sustained modulation of hepcidin not only improved homeostasis of the body but also reduced hepatic oxidative stress significantly, which is a crucial factor in cirrhosis progression [18]. The reductions observed in serum ferritin and iron concentration within the liver reinforced the concept that targeted hepcidin therapies could become an important aspect of future cirrhosis management. Additionally, the improved liver function test scores and decreased MELD scores in an intervention group suggested that there was a direct hepatoprotective effect of hepcidin-based treatments [19]. It was notable that

patients who received hepcidin modulation reported better outcomes for quality of life, indicating that iron overload is not only a laboratory marker to detect clinical complications but has broader implications. These points called for further exploration in larger, multicenter clinical trials [20].

Hepatic performance showed substantial improvement in the intervention group as proven by enhanced Child-Pugh and MELD scores. Modulating hepcidin emerges as a therapeutic approach to ease liver inflammation and fibrosis by minimizing iron-driven oxidative damage which leads to liver cell injury[21,22]. Current research shows that reduced hepcidin expression during cirrhosis links to greater hepatic iron stores and worsening disease conditions which suggests hepcidin activation as a potential medical therapy [23,24].

The therapeutic use of hepcidin agonists to address iron overload will lower the risk of complications enhanced by oxidative damage from excess iron and hepatic decompensation. The connection between iron imbalance and negative outcomes in liver disease cases has been confirmed by previous studies [25,26].

Upcoming studies need to extend follow-up durations to test persistent hepcidin modulation effects alongside advanced imaging techniques for accurate hepatic iron and fibrosis evaluation and investigate potential combination therapies to boost clinical results in liver cirrhosis patients.

CONCLUSION

This study demonstrated that Hepcidin modulation significantly reduced iron overload, improved liver function, and reduced cirrhosis-related consequences. This indicated its promise as a treatment method. Effective iron sequestration, reduced oxidative stress, and lower hepatic inflammation have led to improved clinical outcomes. Future research should focus on long-term follow-ups and interaction with other therapy modalities. Given Pakistan's high incidence of liver cirrhosis, this study laid the effective groundwork for the development of cost-effective, regionally tailored treatment procedures.

LIST OF ABBREVIATIONS

ALT – Alanine Aminotransferase
AST – Aspartate Aminotransferase
BMI – Body Mass Index
CLDQ – Chronic Liver Disease Questionnaire
ERC – Ethical Review Committee
LIC – Liver Iron Concentration
LFTs – Liver Function Tests
MELD – Model for End-Stage Liver Disease
SPSS – Statistical Package for the Social Sciences
TSAT – Transferrin Saturation

ACKNOWLEDGMENTS

None

CONFLICT OF INTEREST

None

FUNDING SOURCE

None

ETHICAL APPROVAL

The ethical approval for the current study was taken from the Institutional Review Board at the Asian Institute of Medical Sciences AIMS, Hyderabad (ERC/9303/24).

AUTHORS' CONTRIBUTIONS

AAU, AHC conceived the idea and designed the research work, **AAU, AHC, MAK** did data analysis, **MAK, OA, and MAS** did the manuscript writing, **MSM** and **EA** did proofread and editing, and all authors agreed to be accountable for all aspects of the research.

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