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(RESEARCH ARTICLE)

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Role of Serum ferritin as a marker of decompensated cirrhosis and its correlation with CTP, MELD and MELD-Na scores

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Abstract

Objectives: Liver cirrhosis, when decompensated; is associated with considerable morbidity and mortality. Scoring systems used to define the severity of cirrhosis and predict mortality include several clinical and biochemical parameters. Serum ferritin is a universally available biomarker, elevated in inflammatory conditions including hepatic necroinflammation. The study aimed to analyze whether serum ferritin has a role as a biomarker of decompensation and correlation with severity in cirrhotic patients.

Methods: 131 patients with cirrhosis; both compensated and decompensated admitted at Gastroenterology, BIRDEM General Hospital, Dhaka, Bangladesh from November 2019 to March 2022 were included in this cross-sectional study. To determine severity, Child-Turcotte-Pugh (CTP), Model for End-Stage Liver Disease (MELD) and MELD-sodium (MELD-Na) were estimated. Comparison of ferritin between and among different groups was done and the relationship with severity was assessed.

Results: Serum ferritin was significantly higher in decompensated (mean 474.20±769.53 ng/mL) than in compensated (80.85±35.31) cirrhosis patients (P<0.001). Ferritin levels among different CTP grading differed significantly (P<0.001). It was higher in grade C (694.14±975.57) than in grade B (213.02±219.17) and A (80.85±35.31) as per pairwise comparison. Moderate positive correlations were observed between ferritin and MELD along with MELD-Na scores. Receiver operating characteristic (ROC) analysis of serum ferritin for predicting hepatic decompensation gave a significant area under the curve (AUC) value (0.821) and the best cut-off value was 105.5 ng/mL (sensitivity 76.2%, specificity 84.6%).

Conclusion: The study suggests serum ferritin can be used as an alternate biomarker for screening hepatic decompensation and stratifying severity.

Keywords: Cross-sectional study; Cirrhosis; Decompensated cirrhosis; Child-Turcotte-Pugh score; Model for End-Stage Liver Disease score; MELD-sodium score; Serum ferritin

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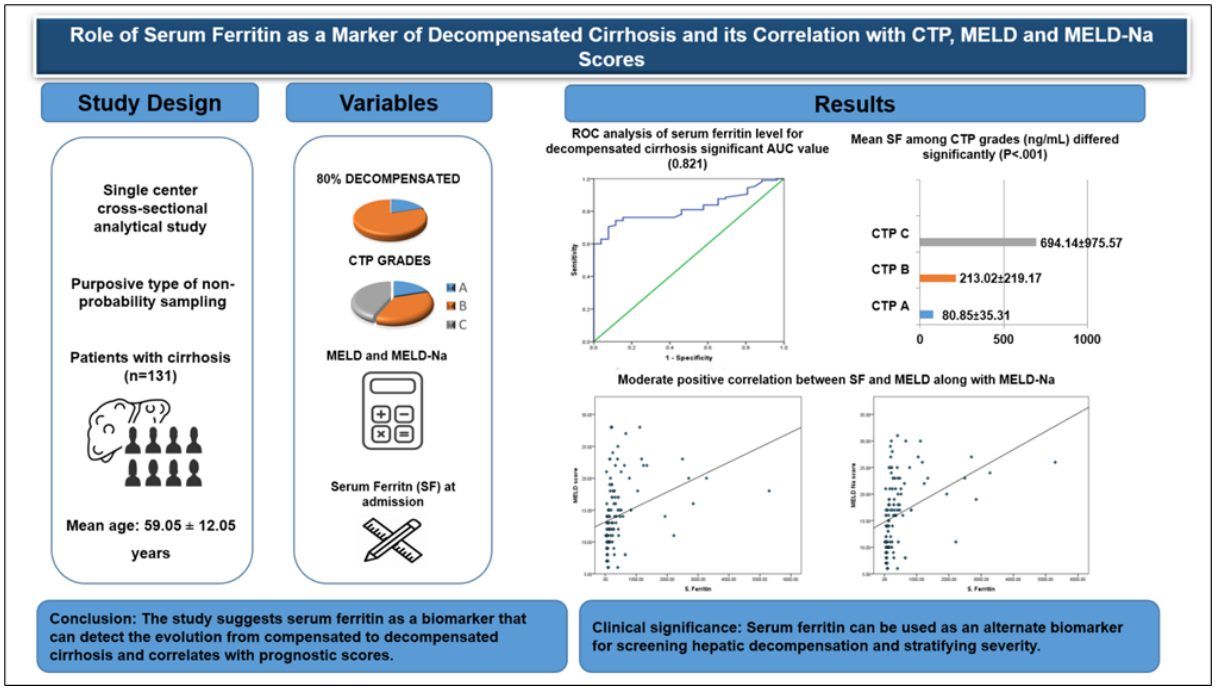
Graphical abstract



1. Introduction

Cirrhosis is the sequelae of chronic liver inflammation where connective tissue replaces liver parenchyma disrupting liver function[1]. It is the 16th cause of disability-associated life-years (DALY)[2]. In 2017, 112 billion cases of compensated and 10.6 billion cases of decompensated cirrhosis were reported globally[3]. The transition rate to decompensation (ascites, encephalopathy, jaundice and bleeding varices) is 5-7% per year[4]. Chronic viral hepatitis B and C, non-alcoholic and alcoholic fatty liver diseases are the commonest etiologies[5]. Liver disease significantly affects the health status and economy of Bangladesh. It is the 3rd leading cause of mortality in tertiary care hospitals. Hepatitis B (HBV) is the predominant cause of all forms of liver disease[6] and cirrhosis[7] as Bangladesh belongs to the intermediate zone of HBV prevalence[8].

Due to short-term survival (3–5 years) after decompensation, liver transplant evaluation should be done if there is no contraindication[9]. The management strategies and costs related to compensated and decompensated cirrhosis vary greatly. Allocation for transplant depends further on the severity of decompensation.

CTP, MELD and MELD-Na are the universally applied scoring systems to stratify cirrhotic patients by prognosis[10].

CTP score does not need computational analysis and can be measured with three biochemicals (albumin, international-normalized ratio, bilirubin) and two clinical indicators (ascites and hepatic encephalopathy). It stratifies cirrhotic patients into risk grades A (score <7), B (7-9) and C (>9). Higher grades correspond with a worse prognosis and more mortality[11].

Model for End-stage Liver Disease (MELD) is a linear numerical scale computed using three biomarkers; serum creatinine, bilirubin and international normalized ratio (INR). It correlates with risk of short-term mortality and is thereby used to prioritize transplantation candidacy[12]. MELD-sodium (MELD-Na) score was published in 2008 and put in practice for the allocation of liver transplants in 2016 since hyponatremia was found to be a strong and independent mortality predictor among waitlist patients[10,13].

If a single, easy and reliable marker can be established for severity stratification, it can cover a large number of cirrhotic populations and will also become easily acceptable to patients.

The liver has a prominent place in iron storage and homeostasis. The iron carrier protein transferrin and iron metabolism-regulating hormone hepcidin are produced by the liver[14,15]. Iron deposition in cirrhotic liver accelerates oxidative damage and fibrosis[16,17,18]

Ferritin; a 24-subunit iron storage protein, is elevated in serum in patients with increased body iron, hepatic necro-inflammation, systemic inflammations and malignancy. In acute liver failure, the serum level is raised as a feature of macrophage activation[19,20]. Its correlation with raised alanine aminotransferase (ALT) implicates its release from the cytoplasm of damaged hepatocytes. Ferritin might be regarded as an alternate biomarker of liver iron deposit and necroinflammation[21].

In recent years, several studies found the predictive capacity of serum ferritin concentration in liver-related morbidities and mortality in cirrhosis[22,23]. It emerges to be a simple prognostic marker of cirrhosis and is widely available. The study intended to assess the association of serum ferritin level with decompensation of the liver and the correlation of ferritin with CTP, MELD and MELD-Na scores in patients admitted to a tertiary care hospital in Bangladesh.

2. Material and methods

The cross-sectional study was conducted on adult cirrhotic patients admitted at the Department of Gastroenterology, BIRDEM (Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders) General Hospital, Dhaka, Bangladesh from November 2019 to March 2022. Ethical clearance of the research protocol was obtained from the Institutional Review Board (IRB) of BIRDEM Academy. A purposive type of non-probability sampling was applied for enrolment. Patients with infection (including COVID-19), Acute on chronic liver failure (ACLF), acute bleeding (except variceal), iron deficiency (Haemoglobin < 8 gm/dL, Transferrin saturation < 20%), iron overload (blood transfusion in previous 3 months, evidence of hemochromatosis, thalassemia, sideroblastic anemia), End stage renal disease (ESRD), chronic inflammatory conditions, malignancy and pregnancy were excluded. Diagnosis of cirrhosis was based on clinical, biochemical (done within 24 hours of admission) sonographic and endoscopic findings. Serum albumin, bilirubin, creatinine, sodium, prothrombin time (PT), international normalized ratio (INR), complete blood count and ferritin reports (Reference. Male: 30-400 ng/mL, Female: 15-150 ng/mL) were documented along with CTP, MELD and MELD-Na scores of the patients. Serum ferritin was measured with ARCHITECT using 6K41-02 Quantia Ferritin reagent by immune turbidometry method, (Abbott, Germany). Statistical analysis was done using Statistical Packages for Social Sciences version 25 (SPSS 25). Numerical variables were expressed with means and standard deviations and categorical variables with frequencies and percentages. Comparisons of the mean serum ferritin between compensated and decompensated cirrhosis and among different Child-Pugh grading were done using Mann Whitney U and Kruskal Wallis test respectively. Correlation between ferritin and MELD along with MELD- Na scores were assessed using Spearman correlation and expressed using scatter diagrams. Receiver Operating Characteristic (ROC) analysis of serum ferritin for decompensated cirrhosis was done and the cut-off value was determined with the Youden index.

3. Results

Among 163 cirrhotic patients screened; 131 were finally enrolled. The mean age of participants was 59.05 ± 12.05 years. More than half of them were female (52.7%). About 64 (48.9%) cases presented with Non-B Non-C cirrhosis. 48 (36.6%) patients had HBV, 17 (13.0%) had HCV-related cirrhosis, 1 (0.8%) had alcohol and 1 (0.8%) had biliary cirrhosis as etiology. 80.1% of patients had decompensated cirrhosis and 19.9% were in compensated state. Most of the patients presented with ascites (61.8%), followed by hepatic encephalopathy (27.5%), jaundice (13.0%) and variceal bleeding (13.0%). 43.5% of patients belonged to CTP grade C, 36.6% and 19.9% to CTP grade B and A respectively (Table 1).

Table 1 Demographic features of the participants (n=131)

	Frequency (f)	**Percentage (%)**
Age (years)		
18-30	3	2.3
31-40	4	3.1
41-50	22	16.8
51-60	50	38.2
61-70	32	24.4
71-80	15	11.5

>80	5	3.8
Mean± SD	59.05±12.05	
Gender		
Male	62	47.3
Female	69	52.7
Aetiology		
HBV	48	36.6
HCV	17	13.0
Alcohol	1	0.8
Secondary Biliary cirrhosis	1	0.8
Non-B Non-C (NBNC)	64	48.9
Hepatic Compensation		
Decompensated	105	80.1
Compensated	26	19.9
Clinical Symptoms		
Ascites	81	61.8
Jaundice	17	13.0
Variceal Bleeding	17	13.0
Hepatic Encephalopathy	36	27.5
CTP scores		
CTP A	26	19.9
CTP B	48	36.6
CTP C	57	43.5

Table 2 Laboratory parameters and the prognostic scores of the study population. (n=131)

Parameters	**Minimum**	**Maximum**	**Mean**	**Std. Deviation**
Haemoglobin (gm/dL)	8.00	15.10	10.40	1.54
Platelet (/cmm)	11000	272000.00	106354.96	49932.55
WBC (/cmm)	2110	13830.00	6083.05	2735.11
S. Creatinine (mg/dL)	0.40	3.80	1.24	0.64
TIBC (µmol/L)	15.00	61.30	33.64	10.37
Serum Iron (µmol/L)	6.00	79.00	11.66	8.07
TSAT (%)	20.14	88.77	33.87	16.76
S. Ferritin (ng/mL)	26.00	5297.00	381.00	688.00
S. Bilirubin (mg/dL)	0.40	13.90	2.27	2.21
S. Albumin (gm/L)	14.20	41.90	27.30	5.33
Na (mmol/L)	119.00	144.00	133.91	4.70

PT (s)	11.20	28.10	16.62	3.67
INR	0.93	2.34	1.33	0.28
CTP score	5.00	14.00	9.24	2.49
MELD score	6.00	28.0	14.07	5.10
MELD-Na score	6.00	31.00	16.10	6.50

Table 2 demonstrates the laboratory parameters and mean CTP, MELD and MELD-Na scores of the studied patients.

Table 3 Comparison of serum ferritin between compensated and decompensated cirrhosis patients

Parameter	**All patients n= 131**	**Compensated n= 26 (19.9%)**	**Decompensated n= 105 (80.1%)**	**P value[a]**
Serum ferritin (ng/mL)	Mean=381.00±688.00, Median=167.00 Range=26 - 5297	80.85±35.31	474.20±769.53	<0.001

[a]P value obtained from the Mann-Whitney U test.

The Mean serum ferritin level of the decompensated cirrhosis group in comparison to compensated cirrhosis was significantly higher (P<0.001).

Table 4 Comparison of serum ferritin among different Child-Turcotte-Pugh grading

Parameter	**Grade A n=26 (20%)**	**Grade B n= 48 (37%)**	**Grade C n=57 (43%)**	**P value[a]**
Serum ferritin (ng/mL)	80.85±35.31	213.02±219.17	694.14±975.57	<0.001

[a]P value obtained from the Kruskal Wallis test.

Serum ferritin levels among Child-Pugh grades differed significantly (P<0.001). It was higher with higher grades as per pairwise comparison.

Table 5 Correlation of serum ferritin levels with MELD and MELD-Na scores

Parameters	**Correlation coefficient of serum ferritin (r)**	**P value[a]**
MELD score	0.549	<0.001
MELD-Na score	0.585	<0.001

MELD: Model for end-stage liver disease; **r:** Correlation coefficient; [a]P-value obtained from Spearman correlation test

There are moderate positive correlations between serum ferritin levels and MELD along with MELD-Na scores.

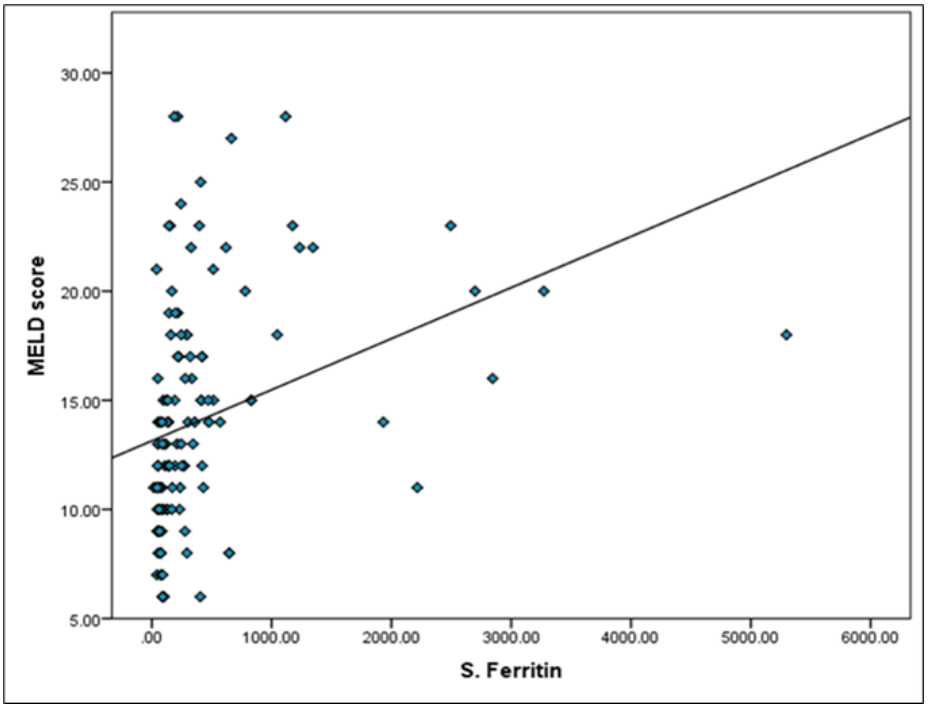


Figure 1 Scatter diagram between serum ferritin levels and MELD scores

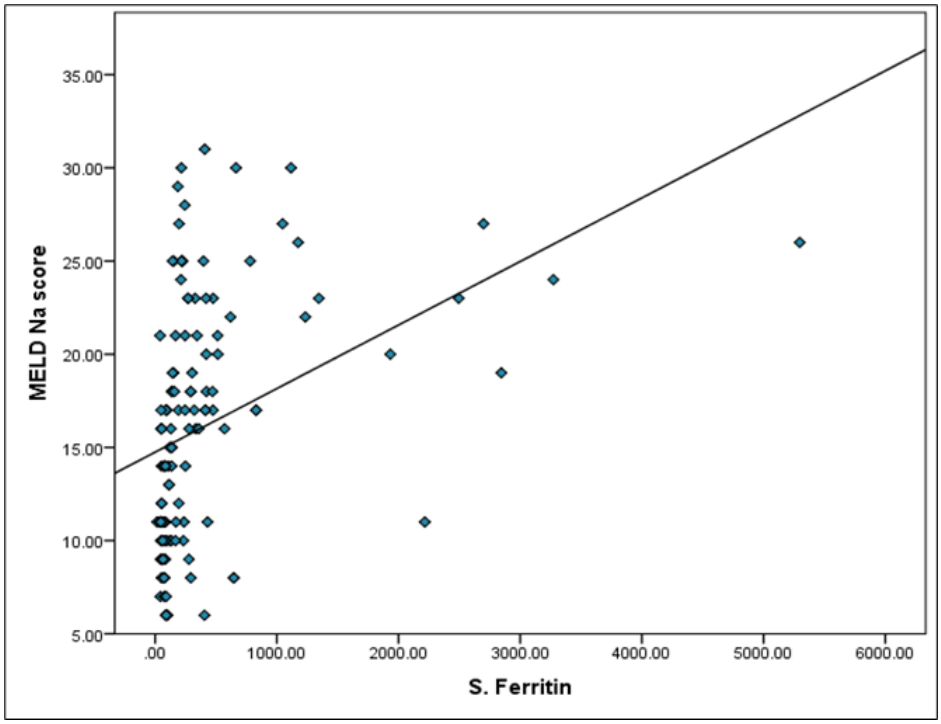


Figure 2 Scatter diagram between serum ferritin levels and MELD-Na scores

Positive relationships are shown between serum ferritin and MELD as well as MELD-Na scores in the scatter diagrams (Figures 1 and Figure 2).

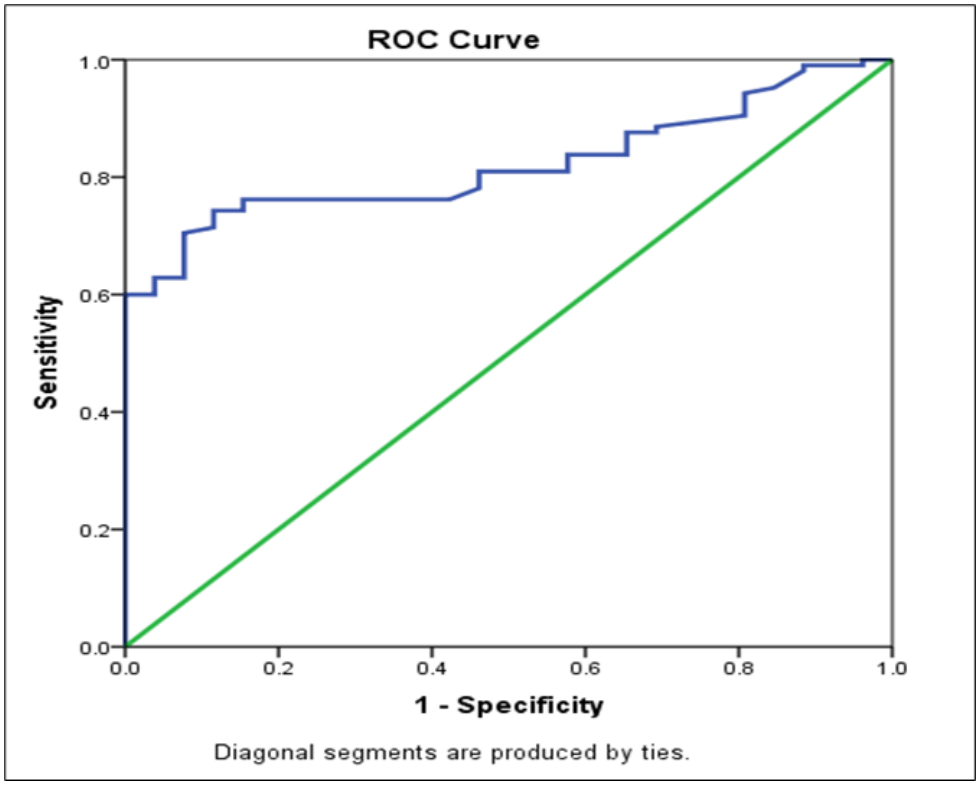


Figure 3 ROC (Receiver Operating Characteristic) analysis of serum ferritin level for decompensated cirrhosis

Table 6 Area Under the Curve (AUC)

Test Result Variable(s): Serum ferritin				
Area	**Std. Error**	**P value**	**Asymptotic 95% Confidence Interval**	
			Lower Bound	**Upper Bound**
0.821	0.036	<0.001	0.751	0.891

ROC analysis of serum ferritin for hepatic decompensation in cirrhotic patients found an AUC value of 0.821 (P<0.001). A cut-off value of ≥105.50 ng/mL showed the highest Youden index (0.608) with 76.2% sensitivity and 84.6% specificity. In addition, the accuracy was 77.9%, the positive predictive value (PPV) was 95.2% and the negative predictive value (NPV) was 46.8%.

4. Discussion

We assessed whether serum level of ferritin could discriminate patients with decompensated from compensated cirrhosis and correlate with prognostic scores that are proven to predict mortality of cirrhotic patients.

The present study included a total of 131 participants with liver cirrhosis. Among them, roughly 80 percent of patients were diagnosed as having hepatic decompensation. In the acute medical unit, patients with acute decompensation are frequently admitted because of their complex medical needs and significant mortality risk[24]. The appearance of ascites, encephalopathy, variceal bleeding and jaundice defines liver decompensation[25]. The mortality is raised to 85% in 5 years after decompensation without transplantation of liver[26]. In this study, 81 presented with ascites, 17 had jaundice, 17 had variceal bleeding, 36 had hepatic encephalopathy and 40 patients had more than 1 sign of decompensation. Other studies also found similar presentations in decompensated cirrhosis patients[22,27]. Alcoholism is the dominant etiology of cirrhosis in different states of India[28,29]. In Bangladesh, the leading cause remains Hepatitis B; followed by Hepatitis C and NASH[7]. Most of our study participants had Non-B Non-C cirrhosis (48.9%), followed by hepatitis B (36.6%) and C (13.0%). As this study was conducted in a diabetic and metabolic disease hospital, Non-B Non-C cirrhosis predominates other etiologies.

Despite being an intracellular protein, ferritin is present in the serum in trace amounts. High serum level is encountered either due to accelerated synthesis or release from injured cells[22]. Iron overload has been revealed in advanced liver disease of different etiologies[30,31,32].

Ferritin plays a defensive role against inflammatory stress and hence is an acute phase reactant[21]. It is elevated in inflammation and malignancy. Besides hereditary hemochromatosis; raised levels of ferritin are seen in NAFLD and viral hepatitis[33]. Moreover, it has been shown in various studies that serum ferritin level increases as liver disease advances[27,33,34].

Hepatic necroinflammation, macrophage activation, and release from damaged liver tissue contribute to high serum ferritin in liver injury. A serum concentration of more than 500 µgm/L was found to be an independent risk factor for death in a study by Walker et al.[31]. In a study by Umer et al. 1-month mortality of cirrhotic patients with serum ferritin <200, 200-400 and >400 ng/mL were 0%, 50% and 93% respectively[33]. Our study suggests serum ferritin to be a reliable marker for hepatic decompensation as its level was significantly higher in participants with decompensated cirrhosis compared to those with compensated cirrhosis. A cut-off value of ferritin ≥105.50 ng/mL in detecting decompensated cirrhosis showed 76.2% sensitivity and 84.6% specificity and the AUC was 82.1%. 80 out of 105 patients with decompensation had serum ferritin values greater than this cut-off. In the study of Oikonomou et al., a cut-off value of serum ferritin for predicting death or liver transplant within a median follow-up period of 12 months was >55 ng/mL (sensitivity 85.3% and specificity 44.2%)[27].

In addition, ferritin is a universally accessible serum marker. It is elevated in acute and chronic inflammatory states including hepatic necroinflammation[27,34]. Walker et al. in a dual-center retrospective study found that increased serum level is related to increased complications and levels more than 200 µgm/L can predict mortality among liver transplant waitlist patients independently, while Maiwall et al. found that ferritin could independently predict early liver-related death in hospitalized decompensated cirrhosis patients[22,31].

Acharya et al. showed that CTP, MELD and MELD-Na scores could significantly predict 3 months mortality among cirrhosis patients[10]. In our cross-sectional study, we assessed the correlation of ferritin with these established prognostic tools. Among the participants in the present study, most had a CTP grade of C (43.5%) followed by 36.6% grade B patients. All the patients having compensated cirrhosis belonged to Child-Pugh grade A. Several studies confirmed higher CTP scores in decompensated cirrhosis, which supports the findings of the present study[22,34,35]. In our study, the mean ferritin level among different Child-Pugh grades was significantly different. It was higher with higher CTP grades. Ripoll et al., and Sungkar et al. also found a correlation of ferritin level with CTP scores[34,35].

In complicated and advanced liver disease, MELD scores accurately assess the severity and prognosis[36]. The mean score of our participants was 14.05±5.12. Oikonomou et al. found a mean MELD score of 15±6 in decompensated cirrhosis patients and Walker et al. found a 15.4±5.1 MELD score among patients awaiting liver transplant[27,31].

The MELD includes total bilirubin, creatinine and INR to rank the priority of liver transplantation (LT) candidates[37]. The present study targeted to determine an association of MELD score with serum ferritin.

A weak correlation between serum ferritin and MELD score was established by Ripoll et al. (r=0.293, P=0.041)[35]. Our study found a moderate correlation between MELD score and serum ferritin level (correlation coefficient value r=0.549, P<0.001). In the study of Maiwall et al., the MELD score differed significantly with the rise in ferritin concentration[22]. Walker et al. also found high serum ferritin concentration with increased MELD score[31]. The MELD-Na score incorporates serum sodium for a more accurate prediction of mortality[13]. In our participants, Serum ferritin was correlated moderately also with the MELD-Na score (r=0.585). Thus, the present study suggests serum ferritin as a reliable biomarker for hepatic decompensation and severity of cirrhosis. Being an inflammatory marker, serum ferritin is affected by many conditions. Multi-center studies with larger sample sizes are recommended to determine an accurate cut-off value. Further longitudinal research regarding the mortality of cirrhotic patients is required.

5. Conclusion

Ferritin is an important biomarker suggesting the evolution from compensated to decompensated cirrhosis and also correlates with prognostic scores. According to the findings, it may be considered as a single parameter of the severity and prognosis of cirrhotic patients. Longitudinal investigations must offer actual cut-off values related to prognosis and outcome.

Compliance with ethical standards

Acknowledgments

Doctors, nurses and laboratory staff of BIRDEM General Hospital.

Clinical Significance

Decompensated cirrhosis is a chronic inflammatory state that persuades increased ferritin production and elevated iron absorption. Serum ferritin can be used as an alternate biomarker for screening hepatic decompensation and prognosis prediction.

Disclosure of conflict of interest

No conflict of interest is to be disclosed.

Statement of ethical approval

Ethical clearance was obtained from the Institutional Review Board (IRB) of BIRDEM Academy.

Statement of informed consent

Informed written consent was obtained from all individual participants included in the study.

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