

Serum iron parameters in liver cirrhosis

G A Siregar^{1*} and W Maail²

¹Division of Gastroenterohepatology, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, H. Adam Malik Hospital, Medan, Indonesia

²Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

*Corresponding author: gontarsir@gmail.com

Abstract. The liver plays a fundamental role in iron homeostasis. Iron parameters change, especially ferritin, need to be evaluated in patients with liver cirrhosis. Serum ferritin could predict the prognosis of patients with decompensated cirrhosis since it reflects immune-mediated and infectious stimuli. Ferritin could express the severity of liver disease and possible subsequent complications. Finally, it might reflect an iron overload condition resulting in significant morbidity and early mortality. 70 patients with decompensated liver cirrhosis divided into three Child-Pugh subgroups. Serum iron parameters include serum iron (SI), total iron binding capacity (TIBC) and ferritin was measured in these groups. From these 70 patients, 30 (42.9%) with HbsAg positive, 26 (37.1%) with anti-HCV positive and 14 (20%) with both HbsAg and anti-HCV positive. Of the 70 patients, 14 (20%) had CTP Class A cirrhosis, 17 (24.3%) had CTP Class B cirrhosis, and 39 (55.7%) had CTP C cirrhosis. The median (range) value of serum iron was 36 (10-345) µg/dl, TIBC was 160 (59-520) µg/dl, Ferritin was 253.5 (8-6078) ng/ml and the transferrin saturation was 22.9 (3.65-216.98) %. We found a significant difference in serum ferritin level with CTP score. Ferritin levels increased as Child-Pugh class progressed (p<0.001).

1. Introduction

Liver cirrhosis is an important cause of liver-related mortality worldwide. Various modifiable and non-modifiable factors are involved in the pathogenesis and complications of liver cirrhosis.[1] Almost one-third of the total serum iron is in the portal system, sinusoidal mesenchymal cells and in the reticuloendothelial cells.[1,2,3] Liver disorders can disturb iron homeostasis.[4]

Serum iron (SI), Total Iron Binding Capacity (TIBC) and ferritin are important tests for evaluating iron abnormalities. Other parameters are transferrin saturation.[3] Ferritin is an iron-containing protein in the human body and transferrin is a protein that acts as an iron transport protein. Ferritin is an acute phase protein and levels elevated in response to iron overload and systemic inflammation. The accumulation of iron in the liver will initiate a radical reaction that will ultimately damage the liver cells.[4]

Studies have shown that removal of excess iron from the body can improve post-liver transplant (LT) survival in patients with decompensated liver cirrhosis. These lines of evidence suggest that iron is an important culprit in the pathogenesis of liver cirrhosis.[5,6]

In some previous studies, it has been shown that increased ferritin has significant prognostic value in chronic liver disease. Serum ferritin level has recently been reported to associate with early mortality in patients with liver cirrhosis.[7] A recent study also showed that ferritin behaving as a



cytokine might also directly induce the fibrogenic process by activating hepatic stellate cells. Their lines of evidence suggest that iron may be an important co-factor in the progression of liver cirrhosis.[8]

Ferritin synthesis is induced by macrophages, and hepatocytes and raised levels can be seen either in iron overload conditions or several pathologies, inflammation, infection and liver diseases.[9] Walker et al. showed that serum ferritin could be an independent predictor of mortality in cirrhosis patients awaiting LT and high levels associated with the higher frequency of liver-related complications.[10]

Serum ferritin could be such a prognostic marker in patients with liver diseases. Moreover, ferritin could express the severity of liver disease and possible subsequent complications. Finally, it might reflect an iron overload condition resulting in significant morbidity and early mortality.[8]

Examination of iron parameters especially ferritin is a simple and inexpensive examination, but so it can be used to find out iron homeostasis that can predict the occurrence of complications and determine the prognosis of patients with cirrhosis hepatic so that precautions can be an option so that no further life-threatening complications.

2. Materials and Methods

2.1. Participants

The study was a retrospective study of adults patients admitted with decompensated liver cirrhosis to Adam Malik Hospital Medan between January 1st 2016 and 31st June 2016. The Obtained clinical data included patient demographics and disease etiology. 70 consecutive adult patients with liver cirrhosis divided into three Child-Pugh subgroups. Cirrhosis was diagnosis based on the clinical, laboratory and ultrasonography findings. Fasting plasma or serum samples for Iron, TIBC, ferritin, and parameters necessary for determining Child-Pugh scores [11] were from the patients in the morning.

2.2. Exclusion Criteria

Exclusion criteria for the patients included malignant disease other than hepatoma, chronic infectious or inflammatory diseases, acute bleeding or red blood cell transfusion within the last three months, previous history of hematological and coagulation disorder other than chronic liver disease, pregnancy, patient on drug which cause in defect parameters such as glucocorticoid, synthetic estrogens, aspirin, tamoxifen, methotrexate and patient with chronic renal failure. We exclude these patients based on their medical records and also the anamnesis.

2.3. Statistics

The Statistical Package for the Social Sciences (SPSS) 22.0 for the analysis of the data. All continuous variables were expressed as mean value \pm standard deviation (SD) or median (range), and categorical data as percentages. Differences in variables were analyzed using ANOVA and student t-test (for normally distributed data) or the Kruskal-Wallis and Mann Whitney U-tests (for non-normally distributed data). The Spearman's correlation analysis calculated Correlations between iron parameters and the Child-Pugh classification. Statistical significance was defined a P value lower than 0.05.

3. Results

We studied 70 consecutive adult patients with decompensated cirrhosis. Demographic and laboratories data of the patients are in Table 1. Of the 70 patients, 40 (57.1%) were male, and 30 (42.9%) were female. The mean age of these 70 patients was 50.91 ± 12.37 years.

From these 70 patients, 30 (42.9%) with HbsAg positive, 6 (8.6%) with anti-HCV positive and 1 (1.4%) with both HbsAg and anti-HCV positive. Of the 70 patients, 14 (20%) had CTP Class A cirrhosis, 17 (24.3%) had CTP Class B cirrhosis, and 39 (55.7%) had CTP C cirrhosis. The median

(range) value of serum iron was 36 (10-345) µg/dl, TIBC was 160 (59-520) µg/dl, Ferritin was 253.5 (8-6078) ng/ml and the transferrin saturation was 22.9 (3.65-216.98)%.

We found a significant difference in serum ferritin level with CTP score (Table 2). Ferritin levels increased as Child-Pugh class progressed ($p < 0.001$).

Table 1. Baseline clinical and laboratory characteristics of the patients.

Variable	n = 70
Sex	
Male	40 (57.1%) ^a
Female	30 (42.9%)
Age	50.91 ± 12.37 ^b
Child-Pugh	
A	14 (20%) ^a
B	17 (24.3%)
C	39 (55.7%)
Viral Marker	
HbsAg (+)	30 (42.9%) ^a
Anti HCV (+)	26 (37.1%)
HbsAg and Anti-HCV (+)	14 (20 %)
Serum Iron Parameters	
Serum Iron (µg/dl)	36 (10-345) ^c
TIBC (µg/dl)	160 (59-518)
Ferritin (ng/ml)	253.5 (8-6078)
Transferrin Saturation (%)	22.29 (3.65-216.98)

^acategorical: n(%)

^bnumeric: mean ± SD

^cnumeric: median (minimum – maximum)

Table 2. Serum iron parameters in different cirrhosis groups.

Iron Parameters	Child Pugh A (n = 15)	Child Pugh B (n = 17)	Child Pugh C (n = 48)	P
Serum Iron	37 (11 – 100)	37 (12 – 160)	36 (10 – 345)	0.942
TIBC	289.5 (102 – 520)	195 (112 – 490)	150 (59 – 480)	0.070
Ferritin	79 (8 – 400)	393 (21.81 – 1249.5)	535.6 (40.8 – 6078) ^a	<0.001 ^b
Transferrin Saturation	13.75 (3.65 – 98.04)	25.48 (5.49 – 65.65)	21.77 (6.25 – 216.98)	0.334

^aChild Pugh C vs Child-Pugh A $p < 0.05$

4. Discussion

In the present study of 70 consecutive patients with liver cirrhosis, males are predominant with 57.1 %. In a study done by Khare et al. males are predominant with 72 %. In the present study, the mean age of all patients was 50.91 ± 12.37 years.[4] This almost comparable with a study of M. Radicheva et al. that means age overall was 49.90 ± 12.2 years.[12]

Iron might be important for progression of liver fibrosis in Chronic Liver Disease. Serum Iron reflects hepatic iron accumulation and disease severity. In the current study was found that all iron parameters in patients with liver cirrhosis experienced changes or disorders. In this study obtained that cirrhotic patients of any Child-Pugh class had deviations from normal results. It is research conducted by several previous studies that explained the associations of aberrant serum iron tests with an advanced stage of liver disease, defined by increased fibrosis and or cirrhosis.[13,14,15] This study found decreased of Serum Iron, but the SI level did not change between Child-Pugh groups. TIBC also declined with the increase of Child-Pugh class. It is in line with research conducted by Büyükaşık et al.[13]

The findings of our study reveal that high ferritin level was a common phenomenon in patients with decompensated liver cirrhosis. In this study, ferritin increased in all Child-Pugh classes. It is in line with research conducted by Olmes et al. and Büyükaşık et al.[3,13]

Oikonomou et al showed that the best cut-off point for the outcome was ferritin >55 ng/ml with sensitivity 85.3% and specificity 11.2% and patients with ferritin > 55 had a worse outcome, compared to those with ferritin ≤ 55 ng/ml.[8] In this study, there was an increase in ferritin levels along with worsening of disease characterized by an increase in the Child-Pugh class.

We acknowledge that there are some limitations, including that it is a single-center study while no other markers such as hepcidin and transferrin had an evaluation.

5. Conclusions

Serum ferritin could predict the prognosis of patients with decompensated cirrhosis since it reflects immune-mediated and infectious stimuli. Moreover, ferritin could express the severity of liver disease and possible subsequent complications. Finally, it might reflect an iron overload condition resulting in significant morbidity and early mortality.

In this study, significant differences were between serum ferritin levels with CTP score. Ferritin levels increased as Child-Pugh class progressed.

Assessment of serum ferritin is easy for routine use and could provide additional information to determine a strategy for our patients. Regular monitoring of iron parameters is necessary for better patient management and to minimize the morbidity and mortality related to liver injury.

References

- [1] Noor M T, Tiwari M and Kumar R 2016 Non-HFE iron overload as a surrogate marker of disease severity in patients of liver cirrhosis *Indian J. Gastroenterol.* **35** 33
- [2] Vagu C, Sultana C and Ruta S 2013 Serum iron markers in patients with chronic hepatitis C infection *Hepat. Mon.* **13**(10)
- [3] Olmez S, Alan M, Saritas B, Yalcin MS, Tas A and Balaharogou R 2016 Serum ferritin levels in patients with HBV and HDV-related cirrhosis *Acta Medica Mediterranea* **32** 1813
- [4] Khare S and Garg V K 2015 Serum iron and TIBC parameters in chronic liver disease **3** 2128-31
- [5] Weismüller T J, Kirchner G I, Scherer M N, Negm A A, Schnitzbauer A A, Lehner F and Strassburg C P 2011 Serum ferritin concentration and transferrin saturation before liver transplantation predict decreased long-term recipient survival *Hepatology*. **54**(6) 2114–24
- [6] Recalcati S, Invernizzi P, Arosio P and Cairo G 2008 New functions for an iron storage protein: The role of ferritin in immunity and autoimmunity *J. Autoimmun.* **30**(1–2) 84–9
- [7] Kowdley K V, Brandhagen D J, Gish R G, Bass N M, Weinstein J, Schilsky M L and Polissar N 2005 Survival after liver transplantation in patients with hepatic iron overload: The national hemochromatosis transplant registry *Gastroenterol.* **129**(2) 494–503
- [8] Oikonomou T, Goulis I, Soulaïdopoulos S, Karasmani A, Doumtsis P, Tsioni K and Cholongitas E 2017 High serum ferritin is associated with worse outcome of patients with decompensated cirrhosis *Ann. Gastroenterol.* **30**(2) 1–8
- [9] Walker N M, Stuart K A, Ryan R J, Desai S, Saab S, Nicol J A and Crawford D H G 2010 Serum ferritin concentration predicts mortality in patients awaiting liver transplantation *Hepatology*. **51**(5) 1683–91
- [10] Manousou P, Kalambokis G, Grillo F, Watkins J, Xirouchakis E, Pleguezuelo M and Burroughs A K 2011 Serum ferritin is a discriminant marker for both fibrosis and inflammation in histologically proven non-alcoholic fatty liver disease patients *Liver Int.* **31**(5) 730–9
- [11] Child C G and Turcotte J G 1964 Surgery and portal hypertension *The liver and portal hypertension* ed C G Child (Philadelphia: Saunders) pp 50–64
- [12] Radicheva M 2011 Comparative evaluation of iron overload in patients with chronic liver

- disease *Trakia J. Sci.* **9(1)** 10-6
- [13] Büyükaşık N Ş, Nadir I, Akin F E, Çakal B, Kav T, Ersoy O and Büyükaşık Y 2011 Serum iron parameters in cirrhosis and chronic hepatitis: detailed description *Turk. J. Gastroenterol.* **22(6)** 606–11
- [14] Casaril M, Stanzial A M and Tognella P 2000 Role of iron load on fibrogenesis in chronic hepatitis C *Hepatogastroenterol.* **47** 220-5
- [15] Fabris C, Toniutto P and Scott C A 2001 Serum iron indices as a measure of iron deposit in chronic hepatitis C *Clin. Chim. Acta* **304** 49-55