ORIGINAL PAPER

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Cutoff Values for Serum Ferritin in Predicting Cirrhosis Severity due to Cholestatic Jaundice in Vietnamese Children

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ABSTRACT

Background: High serum ferritin levels are associated with liver cirrhosis severity and worse outcomes for hepatopathies. This study determined the serum ferritin cutoff values for predicting cirrhosis severity in children with cholestatic jaundice. **Methods:** A retrospective study was performed, including all cases diagnosed with cirrhosis in children aged 1 month to 16 years at Children's Hospital 2-Vietnam between 2016 and 2021. Receiver operating characteristic (ROC) curve analysis was used to estimate ferritin cutoff values for predicting disease severity. **Results:** The study included 95 patients with cirrhosis due to cholestatic jaundice. Decompensated cirrhosis accounted for the majority (74.7%) of cases. Increased serum ferritin concentrations predicted cirrhosis severity in children, and the optimal ferritin cutoff value for predicting decompensated cirrhosis was determined to be 195 µg/l, resulting in a sensitivity of 65.22%, a specificity of 95.83%, and an area under the ROC curve (AUC) or 0.82. The Child–Pugh C group had higher ferritin levels than the Child–Pugh A and B group (p < 0.001), and the ferritin cutoff value for distinguishing between Child–Pugh classifications was 195 µg/l, resulting in a sensitivity of 71.2%, a specificity of 87.9%, and an AUC of 0.80. **Conclusions:** Serum ferritin levels are significantly associated with decompensated cirrhosis and disease severity (as assessed by Child–Pugh score). Routine serum ferritin testing may contribute to predicting cirrhosis severity in children.
Keywords: serum ferritin, cirrhosis, decompensated cirrhosis, compensated cirrhosis, prognosis of cirrhosis

1. BACKGROUND

Cirrhosis is characterized by the excessive deposition of extracellular matrix, resulting in the development of fibrous tissue hyperplasia and regenerative nodules, disrupting normal liver function. Irreversible histopathological damage is considered the end stage of various chronic liver diseases. During the decompensation stage, more than 50% of patients experience complications associated with conservative prognosis and reduced survival rates [1].

Ferritin has classically been considered the primary intracellular iron storage molecule in the body and plays a critical role in iron homeostasis. Ferritin concentrations correlate with tissue iron stores, which are released in a controlled manner. The liver, spleen, and bone marrow are the main organs that produce soluble ferritin, which can be found in many tissues, particularly the liver, endothelial reticulum system, and intestinal mucosa. Elevated serum ferritin is an indicator of necrotizing inflammation due to liver damage. Cirrhosis may induce iron dysregulation, disrupting iron homeostasis and leading to excess iron concentrations, which promote further liver damage [2–4].

Meier *et al.* conducted a cohort study at the Department of Gastroenterology and Hepatology of the University Hospital of Muenster, Germany, which included 279 patients, 59.5% of whom were men, and 40.5% of whom were women. The median age of the patient cohort was 58 years (49–65 years). The most frequent reasons for hospital admission were ascitic decompensation (35.6%), underlying infection (33%), hepatic encephalopathy (19.3%), and hepatorenal syndrome (15.4%). In total, 64 (22.9%) patients died during the study period, including 36 patients who died within 90 days. The median serum ferritin concentration of the study population was 222 mg/L (73–632 mg/L). Serum ferritin levels were significantly increased in the <90-day sur-

vival group (861 mg/L [244.3–1876.5 mg/L]) compared with the >90-day survival group (190 mg/L [63.5–456 mg/L], p < 0.001). Serum ferritin and transferrin values were identified as significant independent predictive factors for death due to end-stage liver disease. Serum ferritin levels >1030.5 mg/L are associated with a 50% risk of death within 11 days and are associated with a reported mortality rate of 83% within 90 days. In addition, serum ferritin levels were significantly different between patients who survived <90 days than in those who survived>90 days (p<0.001) [5].

Parikh *et al.* conducted a study including 250 patients with non-alcoholic fatty liver disease and reported a serum ferritin cutoff value of 48.0 μg/L as a predictor of cirrhosis grade. The area under the curve (AUC) for a serum ferritin cutoff of 48.0 ng/mL was 0.779, and ferritin levels were closely associated with the assessment of cirrhosis using the ultrasound-based FibroScan method [6]. Ample evidence supports a role for increased serum ferritin in determining the degree of cirrhosis and contributing to advanced liver disease in adults [7]. Currently, the ferritin cutoff values used to assess outcomes in cirrhotic patients are not widely published, particularly those used to evaluate cirrhotic children. In this study, we examined the utility of ferritin cutoff values for predicting disease severity in children with cirrhosis due to cholestatic jaundice.

2. MATERIAL AND METHODS

2.1 Study subjects

Children who met the criteria for a diagnosis of cirrhosis due to cholestatic jaundice were hospitalized for treatment at the Department of Gastroenterology- Children's Hospital 2, Vietnam, from 2016 to 2021. All patients were clinically examined, and data were obtained for levels of albumin, protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelets, hemoglobin (Hb), iron, and ferritin. Children enrolled in the study were divided into two groups based on the cirrhosis stage. Compensated cirrhosis was defined as early-stage cirrhosis, characterized by liver damage but the continued ability to perform necessary bodily functions. Decompensated cirrhosis was defined as end-stage cirrhosis, manifested as diffuse fibrotic lesions, in which the uninjured liver cells are no longer able to compensate for damaged cells to maintain liver function, resulting in the clinical manifestation of symptoms such as ascites, gastrointestinal bleeding, and hepatic encephalopathy [8].

Disease severity was assessed according to Child–Pugh scores: 5–6 points were classified as Child–Pugh A, representing mild cirrhosis with good prognosis; 7–9 points were classified as Child–Pugh B, representing moderate cirrhosis with conservative prognosis; and 10–15 points were classified as Child–Pugh C, representing severe cirrhosis with poor prognosis.

2.2 Data processing and statistical analysis

All data analysis was performed using Excel 2010 and SPSS 20.0 software. Receiver operating characteristic (ROC) curve analysis was used to estimate the ferritin index cutoff point. Each cutoff point was assessed for sensitivity, specificity, and AUC. A p-value < 0.05 was considered significant.

2.3 Ethical issues

This study was approved by the Medical Ethics Committee of Children's Hospital 2 (Ref: 1651/BVNĐ2-CĐT dated 2 December 2020).

3. RESULTS

3.1 Characteristics of the study population and causes of liver cirrhosis

This study enrolled 95 eligible, 53.7% of whom were girls and 46.3% of whom were boys. The median age of enrolled patients was 8.8 months. The youngest age was 1.2 months, and the oldest age was 180 months. The most common causes of cholestatic jaundice were biliary atresia (47.4%) and hepatitis (14.7%) (Table 1).

3.2 Characteristics of cirrhosis

We divided our patients into compensated and decompensated groups. The majority of cases were defined as decompensated cirrhosis (74.7%), as displayed in Table 2.

3.3. Child–Pugh classification

The severity of liver cirrhosis was determined according to the Child–Pugh category. Only 1 patient was assessed as Child–Pugh A (1.1%), whereas 32 patients (34.0%) were assessed as Child–Pugh B, and the majority of cases were assessed as Child–Pugh C (61 patients, 64.9%), as shown in Table 3.

| Causes	Frequency (n)	Percentage (%)
Biliary atresia	45	47.4
Hepatitis	14	14.7
Sepsis	5	5.3
Metabolic disease	4	4.2
Progressive familial intrahepatic cholestasis (PFIC)	4	4.2
Byler's disease	3	3.2
Caroli's disease	2	2.1
Common bile duct cyst	2	2.1
Sclerosing cholangitis	2	2.1
Autoimmune hepatitis	2	2.1
Alagille syndrome	1	1.1

Table 1. Causes of liver cirrhosis due to cholestatic jaundice (n = 95)

| Classification	Frequency (n)	Percentage (%)
Decompensated cirrhosis	71	74.7
Compensated cirrhosis	24	25.3

Table 2. Classification of compensated and decompensated cirrhosis (n=95)

Child–Pugh	Frequency (n)	Percentage (%)
A	1	1.1
B	32	34.0
C	61	64.9

Table 3. Child–Pugh classification
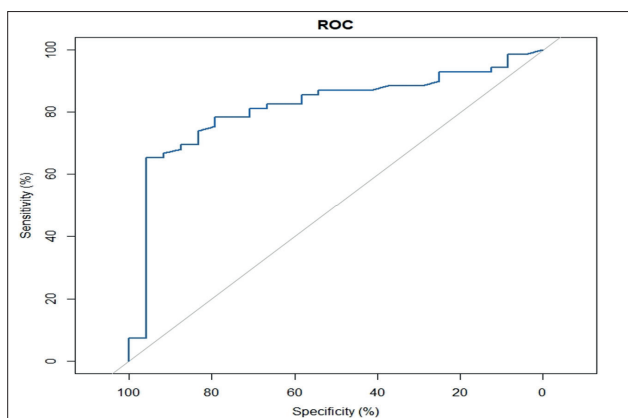
Figure 1. Receiver operating characteristic curve showing the ability of ferritin levels to predict decompensated cirrhosis
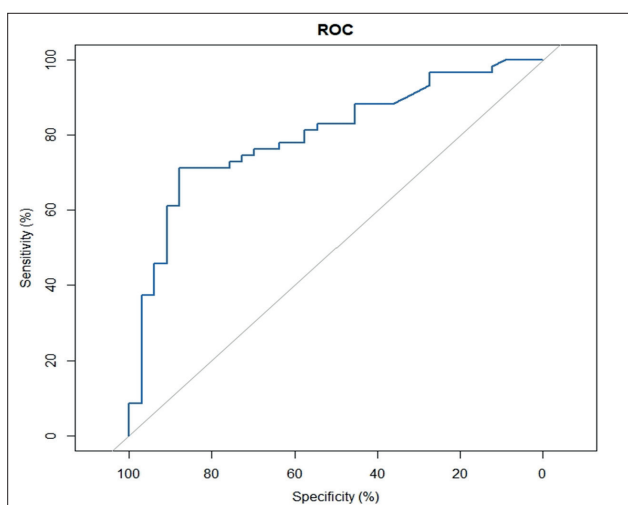
Figure 2. Receiver operating characteristic curve showing the ability of ferritin concentrations to predict worse outcomes as assessed by the Child–Pugh scale.

3.4 The ferritin level cutoff value for predicting decompensated cirrhosis

A ferritin concentration cutoff value of 195 µg/L was found to have a sensitivity of 65.22% and a specificity of 95.83%. A Youden index value of 0.61 was used to determine the optimal cutoff value for predicting decompensated cirrhosis. The AUC for 195 µg/L ferritin was 0.82 (95% confidence interval [CI] 0.72–0.91, Figure 1).

3.5 The ferritin level cutoff value for predicting poor prognosis according to Child–Pugh classification

A ferritin concentration cutoff value of 195 µg/L had a sensitivity of 71.2% and a specificity of 87.9% for predicting poor outcomes according to the Child–Pugh classification. A Youden index value of 0.59 was used to determine the optimal cutoff value, resulting in an AUC of 0.80 (95% CI 0.71–0.89, Figure 2).

4. DISCUSSION

In the present study, the majority of included patients presented with decompensated cirrhosis (74.7%). Among the enrolled patients, the majority were classified as Child–Pugh C (64.9%), followed by Child–Pugh B (34%), whereas only 1 patient was classified as Child–

Pugh A (1.1%). The Child–Pugh scale is widely used to classify cirrhosis severity. Survival rates are inversely related to the Child–Pugh scale; close medical monitoring is necessary for patients with Child–Pugh scores above 10, patients with Child–Pugh scores ≥12 often require hospitalization due to manifestations of liver dysfunction, and patients with Child–Pugh scores of 13 or 14 often require intensive care, with most patients dying before reaching a Child–Pugh score of 15 [1].

Siregar *et al.* conducted a study of 70 patients with decompensated cirrhosis, divided into three Child–Pugh subgroups. The largest proportion of patients was classified as Child–Pugh C (55.7%). Similar findings were reported in the present study and in the study conducted by Meier *et al.*, who followed 286 patients with end-stage liver disease for 2 years and found patients with Child–Pugh C grade represented the largest proportion (51%)[9].

The median serum ferritin levels in the present study was 190.0 µmol/L (4.0–3300.0 µmol/L). The mean value of our study was much higher than the upper limit of the normal range, and 55.9% of patients in our study had serum ferritin levels above the normal range. Our results are similar to the findings reported by Behairy *et al.* in 2019 in Egypt, in which the average serum ferritin concentration was 159.8 µmol/L [10]. Serum copper, iron, and ferritin levels and transferrin saturation were significantly higher in a group with chronic liver disease (CLD) than in the control group. Cytotoxic or inflammatory elevations in ferritin levels can be initiated by bacterial translocation or infections, resulting in subclinical effects [11].

A prospective study conducted by Cakir *et al.* in 2014 in Turkey enrolled 34 children with established biliary atresia with newly diagnosed CLD, including 15 girls and 19 boys with a mean age of 8.9 ± 5.4 years. A control group of healthy children with normal laboratory parameters, including 7 girls and 8 boys, had a mean age of 8.5 ± 5.5 years. Serum ferritin levels were higher among patients with CLD than among control patients (100.1 ± 98.2 ng/mL vs. 50.5 ± 32.2 ng/mL, p = 0.016). No significant difference was found in hepcidin levels. However, hepcidin levels in children with CLD were positively correlated with ferritin levels ($r = 0.75$, p = 0.001), and the pediatric end-stage liver disease (PELD) score ($r = 0.56$, p = 0.001) but negatively correlated with albumin levels ($r = -0.45$, p = 0.008) [12].

Siregar *et al.* studied 70 patients with decompensated cirrhosis divided into three subgroups according to Child–Pugh classification and quantified serum iron and ferritin levels, and transferrin saturation levels, revealing the significant elevation of ferritin levels to 253.5 µmol/L [9], which is higher than the mean concentration identified in our study. This difference is likely due to the selected sample consisting only of patients with decompensated cirrhosis in late-stage cirrhosis, which may be associated with a higher ferritin concentration.

In turn, these last two causes can lead to severe infection, and general inflammation and iron-induced toxicity can also trigger the progression of hepatocellular car-

cinoma and associated terminal comorbidities, leading to an increase in overall mortality [13, 14]. In patients diagnosed with liver disease, iron should be routinely assessed, especially transferrin and ferritin, to detect potential iron overload. Even in patients with liver damage associated with hepatitis C or B, non-alcoholic fatty liver disease, alcoholic liver disease, or end-stage liver disease, iron assessments should be included in routine screening.

Our data revealed that cases with decompensated cirrhosis were significantly more likely to present with increased serum ferritin levels than cases with compensated cirrhosis (p < 0.001). A ferritin concentration cutoff value of 195 µg/L was able to differentiate decompensated from compensated cirrhosis with a sensitivity of 65.22% and a specificity of 95.83%. A Youden's index value of 0.61 was used to establish the optimal cutoff point for predicting decompensated cirrhosis, resulting in an AUC pr 0.82 (95% CI 0.72–0.91). A study by Oikonomou *et al.*, including 192 cases with stable, decompensated cirrhosis, applied multivariate analysis to show that ferritin levels were significantly associated with poor outcomes (hazard ratio 1.001, 95% CI 1.00–1.002, p = 0.005), although ferritin levels were not found to be a good prognostic indicator of poor outcomes (AUC 0.61, sensitivity 85.3%, and specificity 44.2%) when using a cutoff value of 55 µg/L [15].

El Nakeeb *et al.* examined 113 cases, including 52 cases of acquired cirrhosis due to non-alcoholic fatty liver disease, and found that patients with non-alcoholic fatty liver disease had significantly higher ferritin levels than healthy controls, with an AUC of 0.658 at a ferritin cutoff value of 51.95 µmol/L (sensitivity 65%, specificity 60%) [7]. By comparison, our study identified a ferritin cutoff value with a higher AUC and specificity.

In the study by Parikh *et al.*, including 250 patients with non-alcoholic fatty liver disease, serum ferritin was shown to have good predictive value for determining cirrhosis outcomes. The AUC for a serum ferritin cutoff value of 48.0 ng/mL was 0.779, and ferritin levels correlated well with the degree of cirrhosis determined by ultrasound elastography [6].

A report by Cakir *et al.* found high ferritin levels in children with CLD compared with healthy controls, and positive correlations were identified between serum hepcidin levels and PELD scores and between ferritin levels and total antioxidant status in children with CLD, but inverse correlations were identified between serum ferritin and albumin levels and between serum ferritin and a low hepcidin ratio. Serum ferritin concentrations serve as a potential marker for advanced liver disease in patients classified as Child–Pugh grade B or C and as a marker of severe fibrosis in children classified as Child–Pugh grade B [12].

Another study followed 244 cirrhotic patients for 2 years, reported by Tornai *et al.*, which found that high ferritin levels were associated with an increased risk of infection in patients with acquired decompensated cirrhosis (hazard ratio 2.335, 95%, CI 1.193–4.568, p = 0.013) [16].

In 2019, a similar investigation of adult patients in India found that serum ferritin levels correlate with hepatocellular failure and predict early mortality in patients with decompensated liver disease [3]. Our study was entirely conducted in children and did not include a long-term follow-up, which prevented us from assessing the relationship between ferritin concentrations and survival in children.

The 2019 Behairy *et al.* study in Egypt measured serum ferritin levels in 75 infants, including 50 diagnosed with neonatal cholestasis and 25 diagnosed with sepsis. Increased serum ferritin was significantly associated with hepatic iron grades (r = 0.536, p < 0.0001), and serum ferritin levels were significantly elevated in children with intrahepatic cholestasis (p < 0.001). The authors concluded that serum ferritin ≥ 803.5 ng/mL could predict higher grades of iron deposition; however, the contributions of elevated serum ferritin and intrahepatic iron to disease progression remain controversial [10].

In addition, our study further noted an association between ferritin levels and decompensated cirrhosis, suggesting that the evaluation of ferritin levels at the time of hospital admission might predict cirrhosis severity.

We identified significantly more cases with elevated serum ferritin concentrations in children classified as Child–Pugh C than in those classified as Child–Pugh A or B groups (p < 0.001). Ferritin concentrations greater than 195 µg/L were able to detect severe cirrhosis as assessed by the Child–Pugh scale with an AUC of 0.80 (95% CI 0.71–0.89), a sensitivity of 71.2%, and a specificity of 87.9%, using a Youden index value of 0.59.

The Child–Pugh score has been validated as both a predictor of postoperative mortality and a predictor of overall mortality risk associated with other major surgeries. After abdominal surgery, patients classified as Child–Pugh A have a mortality rate of 10%; the mortality rate increases to 30% among patients classified as Child–Pugh B and increases further, to as high as 70%–80%, among patients classified as Child–Pugh C. Surgical procedures are generally considered safe in patients classified as Child–Pugh A, and the Child–Pugh score can contribute to predicting the risk of all-cause mortality and the development of other complications due to liver dysfunction, such as gastrointestinal bleeding. Similar scores, including the model of end-stage liver disease (MELD) and PELD scores, can also be combined with the Child–Pugh scale to assess the severity of liver disease. The MELD score is applicable to patients older than 12 years, whereas the PELD scale is applied to children younger than 12 years. The MELD and PELD scores assess serum bilirubin, the international normalized ratio, and serum creatinine to evaluate renal function. Clinical physicians can use any of these scores to determine whether a patient is a good candidate for liver transplantation when a donor liver is available, with transplantation priority commonly given to the patient with the highest MELD or PELD score with the same blood type as the donor.

Siregar *et al.* surveyed 70 patients with decompensated cirrhosis, divided into three Child–Pugh subgroups, and

measured serum iron parameters, including serum iron and ferritin. In this cohort, 30 patients (42.9%) were positive for hepatitis B serum antigen (HBsAg), 26 patients were positive for hepatitis C antibodies (37.1%), and 14 (20%) patients were positive for both HBsAg and hepatitis C antibodies. The numbers of patients classified as Child–Pugh A, B, and C were 14 (20%), 17 (24.3%), and 39 (55.7%), respectively. The mean serum iron concentration was 36 µg/dL, the mean ferritin concentration was 253.5 ng/mL, and transferrin saturation was 22.9%. This study found significant differences in serum ferritin levels according to the Child–Pugh score, with ferritin levels increasing with higher Child–Pugh grades ($p < 0.001$) [9]. Thus, recent studies have indicated that patients with cirrhosis classified as Child–Pugh C have higher ferritin levels than those classified as Child–Pugh A or B. High serum ferritin levels predict complications and death due to liver disease (cirrhosis) among patients awaiting liver transplantation. Furthermore, serum ferritin levels are good predictors of liver transplantation outcomes and post-transplantation patient survival. In addition to identifying decompensations, the severity of liver disease should be assessed using one of several available mortality predictors, such as the MELD score combined with sodium and Child–Turcotte–Pugh scores [17].

These findings indicate that more severe liver disease is associated with higher serum ferritin concentrations, likely because liver damage affects iron metabolism in the body. Under healthy conditions, iron is obtained from ferritin in the liver during red blood cell synthesis; however, when the liver becomes damaged, it loses the ability to extract iron from ferritin, resulting in the accumulation of ferritin in the liver, which increases with increasing liver damage severity. Iron from other tissues is also transported to the liver, leading to increased ferritin levels in the blood. Thus, in our opinion, the assessment of serum ferritin levels in patients can be used as an indicator of disease severity.

Our study has a few limitations. First, we reported data from a retrospective analysis. Second, our data were obtained from a single-center study, and our study lacks a validation cohort. A prospective, multicenter study with a larger sample size remains necessary to validate these findings.

5. CONCLUSION

All cirrhotic patients with high ferritin levels are subject to increased severity risk and require closer follow-up. Although the underlying mechanism of this association requires further exploration, these findings support the need to include ferritin among the routinely monitored markers used to evaluate disease progression in patients with cirrhosis.

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