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Original Article

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Evaluating the Association between Anemia and the Severity of Liver Disease in Children with Cirrhosis: A Cross-Sectional Study from 2015 to 2020

Seyed Mohsen Dehghani,[1] **Iraj Shahramian**,[2] **Hamideh Salehi**,[1] **Leila Kasraian**,[3] **Maryam Ataollahi**,[1] **and Masoud Tahani** [4]

[1]Shiraz Transplant Research Center, Shiraz University of Medical Science, Shiraz, Iran
[2]Department of Pediatrics, School of Medicine, Namazi Teaching Hospital, Abu Ali Sina for Medicine & Organ Transplant, Shiraz University of Medical Sciences, Shiraz, Iran
[3]Blood Transfusion Research Centre, Higher Institute for Research and Education in Transfusion Medicine, Shiraz, Iran
[4]Pediatric Gastroenterology and Hepatology Research Center, Zabol University of Medical Sciences, Zabol, Iran

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Correspondence to
Iraj Shahramian
Department of Pediatrics, School of Medicine, Namazi Teaching Hospital, Abu Ali Sina for Medicine & Organ Transplant, Shiraz University of Medical Sciences, Namazi Educational and Therapeutic Center, Namazi Square, Zand Street, Shiraz 7193613311, Iran.
Email: ir_buper@yahoo.com

ORCID iDs
Seyed Mohsen Dehghani
https://orcid.org/0000-0001-5930-0110
Iraj Shahramian
https://orcid.org/0000-0002-3760-7717
Hamideh Salehi
https://orcid.org/0009-0009-4996-0698
Leila Kasraian
https://orcid.org/0000-0002-7155-4049
Maryam Ataollahi
https://orcid.org/0000-0003-1876-5266
Masoud Tahani
https://orcid.org/0000-0002-0213-9087

ABSTRACT

Purpose: Liver cirrhosis is a major cause of hospital admission and mortality among children. Understanding the factors that influence disease severity is essential for preventing and reducing mortality. This study explored the association between hemoglobin levels and liver disease severity in children with cirrhosis.

Methods: This cross-sectional study included 326 children with cirrhosis admitted to Namazi Teaching Hospital between 2015 and 2020. Clinical data, Child–Turcotte–Pugh (CTP) scores, and pediatric end-stage liver disease/model for end-stage liver disease (PELD/MELD) scores were collected to assess disease severity. Anemia was defined based on age, sex, and hemoglobin levels.

Results: Among the children with cirrhosis, 275 (84.4%) were anemic, with a mean age of 5.4±4.8 years. The overall mean hemoglobin level was 9.2±2.1 g/dL. A significant inverse correlation was observed between hemoglobin levels and CTP and PELD/MELD scores in children with anemia (p<0.001). Moreover, lower hemoglobin levels were associated with more higher CTP classes (p<0.001).

Conclusion: According to the data analysis, a significant correlation was observed between hemoglobin level and the severity of liver disease, and hemoglobin level decreased with increasing severity of liver disease. According to CTP class, the mean hemoglobin level decreased progressively as the disease progressed. A comparison of the mean CTP scores between children with and those without anemia revealed that those with anemia had more severe disease than those without anemia.

Keywords: Anemia; Liver cirrhosis; Child; Hemoglobins; Liver diseases

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Conflict of Interest
The authors have no financial conflicts of interest.

INTRODUCTION

Liver cirrhosis is a major cause of hospitalization and mortality among children, often resulting from various factors such as infections, metabolic disorders, genetic conditions, and abnormal developmental disorders [1]. In a study involving children with cirrhosis in southern Iran, Wilson's disease was the leading cause of cirrhosis, with other contributors including biliary atresia and autoimmune hepatitis; these children often experience complications such as jaundice, ascites, gastrointestinal bleeding, and hepatic encephalopathy [2]. Anemia is a prevalent manifestation among children with advanced liver disease, occurring in approximately 75% of cases and being more common in those with hepatic encephalopathy [3]. In a study including 88 children with cirrhosis in southern Iran, 54.5% had anemia, including cases of iron-deficiency anemia [4]. Anemia in liver disease is multifactorial, stemming from issues such as blood loss from varices and peptic ulcers, erythrocyte membrane defects, hypersplenism, malnutrition, malabsorption, and impaired blood coagulation due to decreased hepatocyte production of coagulation factors [3,5]. Another factor contributing to anemia in liver disease is a structural or functional deficiency in erythrocyte lipid membranes, which leads to the formation of acanthocytes (spur cells) with a short lifespan, making them susceptible to splenic destruction. In addition, hypersplenism, which is often induced by portal hypertension, can result in pancytopenia, further contributing to anemia. Other factors include malnourishment, malabsorption, and folate and vitamin B12 deficiency, leading to macrocytic anemia, especially in cases of alcoholic liver disease. Hepcidin secretion, which regulates iron homeostasis, is also relevant as it commonly leads to iron deficiency anemia in advanced liver disease. Impaired blood coagulation, stemming from reduced hepatocyte production of coagulation factors, is another causative element [3,5]. Child–Turcotte–Pugh (CTP) score is a clinical scoring system used to assess the severity of liver disease in patients with cirrhosis. It considers several clinical and laboratory parameters including the presence of ascites, hepatic encephalopathy, prothrombin time (PT), bilirubin levels, and serum albumin levels. This scoring system categorizes patients into three classes, A, B, and C, with class C indicating the most severe disease [6]. The 1-year survival rates in patients with cirrhosis and CTP A, B, and C are 100%, 80%, and 45%, respectively [7]. Model for end-stage liver diseases (MELD) score predicts the severity of liver disease based on the patient's serum creatinine, total bilirubin, and international normalized ratio (INR) [8] and helps predict the mortality rate in patients with compensated or uncompensated cirrhosis [9]. Using MELD score, the 3-month survival rate in patients with cirrhosis can be predicted regardless of the cause [8]. A study including 181 patients with liver cirrhosis revealed a significant relationship between CTP class and hemoglobin level, with the lowest level observed in CTP class C. Additionally, hemoglobin level and MELD score decreased with increasing liver disease severity. Of the 58 patients with macrocytosis, 77.6% had a MELD score >12, whereas only 22.4% had a score <12. This suggests that anemia and hemoglobin levels can be used to determine the severity of liver disease because they indicate the hemoglobin level in the patient [10]. Another study was conducted involving 494 patients with advanced chronic liver diseases (ACLD), which showed that 324 people (66%) were anemic, having a higher MELD score than that of those who were not anemic (p<0.001) and were mostly in stage B. C was in the CTP category (p<0.001). This study showed that two-thirds of patients with ACLD suffer from anemia, which is related to decompensation, acute-on-chronic liver failure, and increased mortality. According to these studies, the rate of hospitalizations during the follow-up period is related to the level of anemia. Only 57% of patients without anemia were hospitalized during this period, whereas 69% of patients with mild anemia, 81% with moderate anemia, and 92% with severe

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anemia required hospitalization [3,11,12]. A study including 88 patients with alcoholic liver cirrhosis, aged 18–75 years, showed a significant relationship between hemoglobin levels and MELD scores. Patients were divided into five groups based on their MELD scores, and their hemoglobin levels were compared. As the MELD scores increase, hemoglobin levels progressively decrease in each category [11,13]. Given the ease, affordability, and accessibility of anemia diagnosis, and along with studies involving adults revealing a strong statistical association between liver disease severity and anemia [3,10,11], we aimed to investigate this relationship in children with cirrhosis. Our study aimed to assess whether anemia levels can serve as an indicator of liver disease severity, aiding in prognosis determination and patient prioritization for liver transplantation. Establishing a substantial association between anemia and disease severity could facilitate rapid diagnosis and improved anemia control, potentially preventing the worsening of liver disease in patients.

MATERIALS AND METHODS

In this study, all children under the age of 18 years who were diagnosed with liver cirrhosis (based on clinical, radiological, or histological evidence) and admitted to the Pediatric Gastroenterology and Liver Department at Namazi Teaching Hospital affiliated with Shiraz University of Medical Sciences, between 2015 and 2020, were enrolled. Among the 676 children hospitalized during this period, those with a history of blood transfusion in the last 3 months were excluded from the study. In addition, children currently being treated for anemia, those with chronic kidney disease, and those with anemia due to any cause not directly or indirectly related to liver cirrhosis (such as tuberculosis anemia, thalassemia, and leukemia) were excluded from the study. Several children were also excluded from the study due to incomplete hospitalization records, incomplete tests, and missing data. In addition, for children who had multiple hospitalizations during the study period, only the data from their first hospitalization were evaluated.

Finally, 326 children were included in the study. At the time of hospitalization, consent was obtained from the children's guardian. The following data were collected: age, sex, cause of liver disease, presence of ascites, hepatic encephalopathy, bleeding from the upper gastrointestinal tract, and paraclinical data including complete blood count, PT, INR, serum creatinine, serum electrolytes, liver function test (total and direct bilirubin, albumin, alanine transaminase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase).

Pediatric end-stage liver disease (PELD)/MELD scores were assessed using a standard formula that is accessible online, and CTP scores were calculated based on five variables (hepatic encephalopathy, INR, ascites, bilirubin, and albumin). These scores were calculated at the time of hospitalization for each children. MELD score can be used in children aged ≥12 years.

CTP score includes three continuous variables (bilirubin, albumin, and PT) and two qualitative variables (encephalopathy and ascites).

PELD score is calculated using the following formula:

$$PELD\ score = 0.480 \times Log\ (bilirubin\ mg/dL) + 1.857 \times Log\ (INR) - 0.687 \times Log\ (albumin\ g/dL).$$

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If the children is less than 1 year old, the number obtained is added by 0.436; if the children has growth failure (less than –2 standard deviations), it is added by 0.667. The obtained number is then multiplied by ten and rounded off to the nearest whole number. To calculate PELD score, laboratory measurements of less than one are considered as one.

MELD score is calculated using the following formula:

$$MELD\ score = 0.957 \times Log\ (creatinine\ mg/dL) + 0.378 \times Log\ (bilirubin\ mg/dL) + 1.120 \times Log\ (INR) + 0.6431.$$

The obtained number is then multiplied by ten and rounded off to the nearest whole number. To calculate MELD score, laboratory measurements of less than one are considered as one.

Anemia is characterized by a decrease in hemoglobin levels, leading to a reduced oxygen-carrying capacity of the blood. Age-specific cutoff values for anemia can vary, but a commonly used reference is the World Health Organization (WHO) guidelines for hemoglobin levels. According to the WHO, anemia is typically defined as a hemoglobin concentration of 11 g/dL in children aged 6 months to 6 years, 12 g/dL in children aged 7–14 years, 13 g/dL in adult males aged >15 years, 11 g/dL in pregnant females, and 12 g/dL in non-pregnant females [14]. Individuals with anemia were identified based on established references and considering the age and sex of the children [15]. Children were categorized into classes A, B, and C based on their CTP scores. Data analysis was performed using SPSS version 25 software (IBM Co.). Quantitative data were measured using the *t*-test of independent samples or one-way analysis of variance and expressed as mean±standard deviation. The frequency of qualitative data is calculated, and the relationship between them was assessed using the chi-square test. Pearson's correlation coefficient was used to determine the association of PELD/MELD scores and CTP classes with blood hemoglobin levels. The *p*-value was calculated using the two-tailed test. The results were considered statistically significant if the *p*-value was <0.05.

Ethical approval was obtained from the Ethics Committee of Shiraz University of Medical Sciences, and the information of individuals and their outcomes were kept confidential (IR.SUMS.MED.REC.1400.004).

RESULTS

This study included 326 children with liver cirrhosis, including 176 girls (54.0%) and 150 boys (46.0%), with an average age of 5.4 years (ranging, 0.92–17.83 years). Of these children, 275 (84.4%) had anemia, whereas 51 (15.6%) did not have anemia. The average PELD/MELD scores were 21.6±15.1, and the average CTP score was 9.7±2.3. Notably, 42, 94, and 190 children were in CTP classes A, B, and C, respectively. Biliary atresia was the most common cause of liver disease (n=119; 36.5%). In addition, 248 children (76.1%) had at least one cirrhotic complication. Of the 326 children, 243 survived and 83 (25.5%) died (**Table 1**).

The average hemoglobin level of the study population was 9.27±2.10 g/dL (9.36±2.2 g/dL in girls and 9.16±2.1 g/dL in boys) (**Table 2**). A total of 275 (84.4%) children had anemia, including 145 (52.7%) girls and 130 (47.3%) boys.

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Table 1. mographic characteristics of children with cirrhosis

Variable	All	Anemic	Non-anemic	*p*-value
Number	326 (100)	275 (84.4)	51 (15.6)	
Age (yr)	5.4±4.8	5.5±4.9	4.9±4.5	0.468
Sex				0.289
Female	176 (54.0)	145 (52.7)	31 (60.8)	
Male	150 (46.0)	130 (47.3)	20 (39.2)	
Hemoglobin (g/dL)	9.27±2.1	8.7±1.8	12.3±1.1	<0.001
CTP score	9.7±2.3	9.92±1.7	8.49±1.2	<0.001
CTP class A	42 (12.9)	28 (10.2)	14 (27.5)	<0.001
CTP class B	94 (28.8)	75 (27.3)	19 (37.3)	
CTP class C	190 (58.3)	172 (62.5)	18 (35.3)	
PELD/MELD score	21.6±15.1	22.9±15.1	14.8±15.1	<0.001
Underlying disease				0.004
Biliary atresia	119	104	15	
Wilson's disease	44	35	9	
Tyrosinemia	44	36	8	
PFIC	34	31	3	
AIH	26	23	3	
INH	21	20	1	
Metabolic disease	4	3	1	
Others	34	23	11	
Complication				0.049
Yes	248 (76.1)	215 (78.2)	33 (64.7)	
No	78 (23.9)	60 (21.8)	18 (35.3)	
Survive				0.382
Yes	243 (74.5)	202 (73.5)	41 (80.3)	
No	83 (25.5)	73 (26.5)	10 (19.7)	

Values are presented as number (%) or mean±standard deviation.
CTP: Child–Turcotte–Pugh, PELD: pediatric end-stage liver disease, MELD: model for end-stage liver disease, PFIC: progressive familial intrahepatic cholestasis. AIH: autoimmune hepatitis, INH: idiopathic neonatal hepatitis.

Table 2. Comparison of laboratory parameters in the anemic and non-anemic groups

Parameter	Number	Mean±SD	Anemic	Non-anemic
AST (U/L)	320	263.00±342.94	266.60±351.40	244.20±296.30
ALT (U/L)	321	139.97±249.79	134.10±249.60	170.60±250.30
ALKP (U/L)	321	1,000.49±1,140.47	994.10±1,182.50	1,033.90±894.00
Total BILI (mg/dL)	326	15.83±14.35	16.30±14.50	13.00±13.00
Direct BILI (mg/dL)	325	8.05±7.49	8.40±7.00	5.90±6.90
Total protein (g/dL)	325	6.00±1.20	5.90±1.10	6.00±1.30
Albumin (g/dL)	326	3.10±0.83	3.00±0.80	3.40±0.80
INR	326	3.14±2.80	3.30±2.90	2.20±1.90
Creatinine (mg/dL)	324	0.33±0.60	0.30±0.60	0.30±0.30
Na (mEq/dL)	323	135.89±6.30	135.00±6.10	137.00±6.80
White blood cell	326	11.58±8.30	11.70±8.80	10.90±5.20
Hemoglobin (g/dL)	326	9.27±2.10	8.70±1.80	12.30±1.10
MCV	325	87.56±12.50	87.80±13.20	85.90±7.40
MCHC	325	31.27±2.60	30.90±2.50	33.20±1.60
MCH	325	27.34±4.50	27.10±4.70	28.60±3.00
Platelet	326	170.95±141.90	165.00±138.00	200.00±159.50

SD: standard deviation, AST: aspartate aminotransferase, ALT: alanine transaminase, ALKP: alkaline phosphatase, BILI: bilirubin, INR: international normalized ratio, Na: sodium, MCV: mean corpuscular volume, MCHC: mean corpuscular hemoglobin concentration, MCH: mean cell hemoglobin.

To investigate the association between hemoglobin levels and the severity of liver disease, we compared hemoglobin levels with CTP and PELD/MELD scores using Pearson's test. A statistically significant inverse relationship was observed between hemoglobin blood levels and CTP scores (p<0.001). Thus, with an increase in CTP score, hemoglobin level decreased significantly.

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According to the Pearson's test results, no statistically significant association was observed between hemoglobin level and CTP score in children without anemia (p=0.759); however, in those with anemia, a clear and significant statistical relationship was observed. In children with anemia, with an increase in CTP score, the amount of hemoglobin decreased significantly (p<0.001).

A statistically significant and inverse relationship was observed between PELD/MELD scores and hemoglobin level in the entire study population (p<0.001), as hemoglobin levels decreased with an increase in PELD/MELD scores.

According to further investigations, an inverse and significant statistical relationship was observed between hemoglobin level and PELD/MELD scores in children with anemia (p=0.01), such that with increasing PELD/MELD scores, hemoglobin decreased significantly, whereas no significant association was observed in those without anemia (p=0.119).

Among the 326 children, 42, 94, and 190 were in CTP classes A, B, and C, respectively. The average hemoglobin levels in classes A, B, and C were 10.6±1.7 g/dL, 9.6±2.5 g/dL, and 8.8±1.9 g/dL, respectively, indicating a decrease in hemoglobin level with advancing class. This difference in the numerical value of hemoglobin levels in different classes of CTP was statistically significant (p<0.001).

In this study, children were categorized into the anemic and non-anemic groups, and their average CTP scores were compared. The average CTP score was 9.9±2.3 in the anemic group and 8.5±2.5 in the non-anemic group. The anemic group had a statistically significant higher CTP scores than the non-anemic groups (p<0.001).

In CTP class A, 28 of the 42 (66.7%) children; in class B, 75 of the 94 (79.8%) children; and in class C, 172 of the 190 (90.5%) children were anemic. Among the children with anemia, 10.2% were in class A, 27.3% in class B, and 62.5% in class C. This difference was statistically significant (p<0.001).

Notably, 145 (54%) of children with anemia were girls and 130 (46%) were boys. The frequency of anemia in children with cirrhosis did not significantly differ between the male and female groups (p=0.182).

The average hemoglobin levels in girls and boys were 9.36±2.22 g/dL and 9.17±2.1 g/dL, with no significant difference (p>0.05).

To investigate the association between anemia and disease severity based on sex, an independent t-test was performed, and an association was observed between anemia and CTP score (p<0.05) and PELD/MELD scores (p<0.05) in the female group.

In the female group, the mean CTP and PELD/MELD scores were significantly higher in children with anemia than in those without anemia.

In the male group, the association between anemia and CTP score was significant (p<0.05), indicating that boys with anemia had a higher CTP score than those without anemia. However, no significant difference in the mean PELD/MELD scores was observed between boys with and those without anemia (p>0.05) (**Table 3**).

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Table 3. Association between anemia and disease severity based on sex

Sex		Anemia	Number	Mean±SD	*p*-value
Female	CTP score	No	31	8.58±2.39	<0.05
		Yes	145	9.98±2.33	
	PELD/MELD scores	No	31	13.97±12.31	<0.05
		Yes	145	22.84±14.85	
Male	CTP score	No	20	8.35±2.71	<0.05
		Yes	130	9.87±2.28	
	PELD/MELD scores	No	20	16.00±15.02	>0.05
		Yes	130	22.91±15.40	

SD: standard deviation, CTP: Child–Turcotte–Pugh, PELD: pediatric end-stage liver disease, MELD: model for end-stage liver disease.

Table 4. Association between anemia and underlying diseases

Underlying disease	Non-anemic	Anemic	Total
Biliary atresia	15	104	119
NH	1	20	21
PFIC	3	31	34
AIH	3	23	26
Wilson's disease	9	35	44
Tyrosinemia	8	36	44
Metabolic disease	1	3	4
Others	11	23	34
Total	51	275	326

NH: neonatal hepatitis, PFIC: progressive familial intrahepatic cholestasis, AIH: autoimmune hepatitis.

The association between children's age and anemia was investigated, and no relationship was observed between them. The average age of children with and those without anemia was 5.5±4.9 years and 4.9±4.5 years, respectively, which was not significantly different (p=0.468).

Of the 326 children, 119 had biliary atresia. Among them, 104 had anemia and 15 did not. Twenty-one children were diagnosed with neonatal hepatitis and twenty were diagnosed with anemia. Moreover, 34 children had progressive familial intrahepatic cholestasis, 26 had autoimmune hepatitis, 44 had Wilson disease, 44 had tyrosinemia type 1, 4 people had other metabolic diseases, and 34 had other underlying diseases (**Table 4**).

The frequency of anemia in children with different underlying diseases was compared, and the difference in prevalence of anemia in different underlying diseases was significant (p<0.05).

We compared hemoglobin levels in different underlying diseases separately. The results showed a significant difference (p<0.001) in hemoglobin levels in different underlying diseases. The lowest hemoglobin level was observed in children with neonatal hepatitis and the highest in children with Wilson's disease (**Table 5**).

To investigate the association between underlying disease and disease severity, CTP and PELD/MELD scores were compared for different underlying diseases, but no significant relationship was observed among them (CTP score, p=0.944; PELD/MELD scores, p=0.540).

Ascites was the only complication that exhibited a significant association with anemia (179 [88.2%] of 203 children with ascites were anemic). Other complications of cirrhosis did not exhibit significant association with anemia.

To investigate the association between anemia and mortality, mortality rates was compared between children with and those without anemia. Of the 83 children who died, 73 (87.9%) were

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Table 5. Hemoglobin levels in various underlying diseases

Underlying disease	Number	Mean±SD	95% confidence interval for mean	
			Lower bound	Upper bound
Biliary atresia	119	8.99±1.91	8.64	9.33
NH	21	7.92±2.13	6.96	8.89
PFIC	34	8.71±1.77	8.09	9.32
AIH	26	9.80±2.50	8.79	10.81
Wilson's disease	44	10.45±2.14	9.80	11.10
Tyrosinemia	44	9.45±1.89	8.88	10.03
Metabolic	4	9.47±1.45	7.16	11.79
Others	34	9.50±2.84	8.50	10.49
Total	326	9.27±2.17	9.03	9.51

SD: standard deviation, NH: neonatal hepatitis, PFIC: progressive familial intrahepatic cholestasis, AIH: autoimmune hepatitis.

Table 6. Association between disease severity and mortality rate

	Mortality	Number	Mean±SD	*p*-value
CTP score	Died	83	11.20±2.22	<0.001
	Survived	243	9.19±2.23	
PEDL/MELD scores	Died	83	30.31±14.90	<0.001
	Survived	243	18.63±14.00	

SD: standard deviation, CTP: Child–Turcotte–Pugh, PELD: pediatric end-stage liver disease, MELD: model for end-stage liver disease.

anemic. In contrast, of the 243 children who survived, 202 (83.1%) were anemic. No statistically significant difference was observed between mortality rates in children with and those without anemia (p=0.382).

The association of CTP and PELD/MELD scores with mortality rate was investigated using the independent sample t-test, and it was observed that the scores were higher for deceased children than that for those who survived, and this difference was statistically significant (p<0.001) (**Table 6**).

The association between the presence of anemia and other laboratory parameters was investigated by comparing the levels of various laboratory parameters in the anemic and non-anemic groups. The results showed that only INR, albumin level, and direct bilirubin level differed significantly between the two groups (p<0.05). No significant difference in other laboratory parameters was observed between the two groups.

Furthermore, a significant difference between hemoglobin level, mean corpuscular hemoglobin (MCH), creatinine level, ALT level, age, and weight in different diseases (p<0.05).

The mean of hemoglobin level, white blood cell (WBC) count, mean corpuscular volume (MCV), MCH, sodium (Na) levels, INR, total protein level, total and direct bilirubin levels, and AST level were significantly different between children who died and those who survived (p<0.05).

DISCUSSION

The present study revealed a statistically significant association between anemia and the severity of liver disease in children with liver cirrhosis. The results revealed that with an increase in disease severity, hemoglobin level decreases.

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The frequency of anemia in children with cirrhosis was unrelated to sex, and no correlation was observed between sex and the presence of anemia. Therefore, sex had no effect on the presence of anemia. A study conducted in 2014 to investigate the prevalence of anemia in 88 children with liver cirrhosis (46 girls and 42 boys) reported that 54.5% of the children had anemia. However, no correlation was observed between sex and the presence of anemia (p=0.3) [4]. In addition, by comparing the average hemoglobin levels in the male and female groups, it can be concluded that there is no relationship between hemoglobin levels and sex.

No correlation was observed between age and anemia in children with liver cirrhosis. In other words, the prevalence of anemia in children with liver cirrhosis was not affected by age. In a study conducted including patients with ACLD and children with cirrhosis, no association was found between patients' age and anemia (p=0.23) [3,4].

Owing to the existence of a statistically significant and inverse relationship between hemoglobin level and CTP score, it can be concluded that in patients with anemia, an increase in CTP score corresponds to a decrease in hemoglobin level. This relationship does not exist in patients without anemia, making it unlikely to establish a relationship between hemoglobin level and disease severity in individuals without anemia.

In addition, by analyzing and comparing the average hemoglobin levels across different CTP classes, it was observed that as the CTP classes progressed from A to C and disease severity increased, the average hemoglobin level decreased significantly. Therefore, it can be concluded that hemoglobin levels are lower in patients with more severe disease (**Fig. 1**). In 2020, a study was conducted to investigate the relationship between anemia and disease severity in adults. In this study, the lowest hemoglobin level was observed in CTP Class C, and the difference in hemoglobin level in different classes of CTP was significant, indicating a relationship between disease severity and blood hemoglobin levels [10].

The average CTP score was higher in children with anemia than in those without anemia, which indicates a greater disease severity among patients with anemia.

In addition, the prevalence of anemia was higher in children with severe diseases. With an increase in disease severity, an increase in the number of children with anemia was observed, which indicates an association between anemia and disease severity.

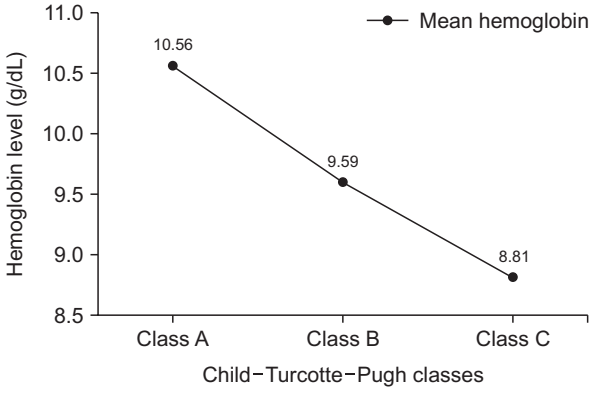

Fig. 1. Hemoglobin level in different Child–Turcotte–Pugh classes.

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Furthermore, 62.5% of the children with anemia were in CTP class C, indicating an increase in the number of children with anemia in higher CTP class; this shows a direct association between anemia and disease severity.

In addition, the statistical analysis revealed a statistically inverse association between hemoglobin level and PELD/MELD scores in the entire population, indicating that with a decrease in hemoglobin levels, disease severity increases. As reported by Jain et al. (2016) [15], hemoglobin levels decrease progressively with increasing MELD scores. This inverse statistical association was observed in the anemic group. However, no statistically significant association between hemoglobin level and MELD/PELD scores was observed in the non-anemic group. Therefore, a drop in hemoglobin level is expected with increasing disease severity in patients with anemia; however, in patients without anemia, hemoglobin level changes are not related to disease severity. In another study conducted in 2020 involving adults, a statistically significant association between hemoglobin levels and MELD scores was observed [10]. This finding suggests a statistical relationship exists between anemia and liver disease severity in both children and adults. Another study including patients with ACLD showed that those with anemia had significantly higher MELD scores than those of individuals without anemia [3,16].

The association between anemia and CTP and PELD/MELD scores were significant in girls. Thus, girls with anemia had higher disease severity. In boys, a significant association was observed between anemia and CTP scores, but anemia did not significant correlated with PELD/MELD scores. Other studies involving patients with cirrhosis have shown that anemia is not related to sex; however, male sex can be considered a risk factor for developing anemia in patients with cirrhosis [3,17].

Biliary atresia is the most common underlying disease in the general population and in patients with anemia. By comparing the proportion of patients with anemia with different underlying diseases, a statistically significant relationship between the underlying cause of cirrhosis and the prevalence of anemia was observed, suggesting a significant association between the underlying disease and anemia. The prevalence of anemia differs among patients with different underlying diseases. Therefore, the underlying cause of cirrhosis is effective in causing anemia. In a study including adult patients with cirrhosis, the most common underlying cause was alcoholic cirrhosis, which has a significant relationship with anemia [3,18]. Considering that the study was conducted including adults, differences can be seen in determining the most common cause of cirrhosis. Studies conducted including 106 children with cirrhosis showed that Wilson disease and biliary atresia were the most common causes of cirrhosis [4,19]. In another study including children with cirrhosis, biliary atresia was identified as the most common cause of liver cirrhosis [7,20]. In addition, hemoglobin levels in different underlying diseases was significantly different; the lowest hemoglobin level was noted in neonatal hepatitis and the highest level was observed in Wilson's disease. Therefore, it can be concluded that the presence of anemia is influenced by the underlying disease.

However, when CTP and PELD/MELD scores in different underlying diseases were compared, no significant association was observed between disease severity and the underlying cause. Therefore, it is not possible to predict disease severity based on the underlying cause.

This study also showed that anemia effectively contributes to the development of ascites as a complication of liver cirrhosis. This means that patients with anemia have a higher chance

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of developing ascites and that anemia is a risk factor for the occurrence of ascites in patients with liver cirrhosis. No statistically significant association was observed between anemia and other complications caused by liver cirrhosis. In the present study, no clear association was observed between mortality rate and anemia, suggesting that that anemia does not affect patient mortality. However, in another study, the overall survival was lower in patients with anemia and in those without anemia, and the mortality rate related to liver disease was higher. CTP and PELD/MELD scores were higher in children who died than in those who survived, indicating an association between mortality and disease severity. Investigations have shown significant differences in laboratory parameters including INR, albumin level, and direct bilirubin level between children with anemia and those without anemia, indicating the effects of anemia on these parameters. In addition, the mean hemoglobin level, WBC count, MCV, MCH, Na level, INR, total protein level, total and direct bilirubin levels, and AST level were significantly different between children who died and those who survived, indicating the impact of these factors on patient mortality.

In conclusion, this study demonstrated an inverse and statistically significant relationship between blood hemoglobin levels and the severity of liver disease in children with anemia and cirrhosis. Moreover, children with anemia had more severe diseases, and the percentage of anemia was higher in children with more severe disease, indicating a correlation between anemia and disease severity. This relationship was observed in boys and girls. Considering that children's age was not related to anemia, the underlying cause was not related to disease severity. Therefore, the association between anemia and disease severity cannot be evaluated based on age and the underlying cause of cirrhosis. Although the underlying cause of the disease does not affect its severity, it may still contribute to the occurrence of anemia in these patients.

Study limitations

This study benefits from its substantial sample size, comprehensive data collection, rigorous statistical analysis, and ethical approval, providing a robust foundation for the findings. However, the study is limited by its single-center design and wide age range of the participants. Further research is needed to explore additional factors influencing anemia and disease outcomes in this patient population.

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