



Original Research Article

Correlation Of Anemia with Severity of Liver Cirrhosis as Assessed by Model for End-Stage Liver Disease Score

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ABSTRACT

Background: Anemia is common in liver cirrhosis, yet its relationship with disease severity remains incompletely understood.

Objective: To investigate the correlation between anemia and liver cirrhosis severity as assessed by the Model for End-Stage Liver Disease (MELD) score.

Methods: This prospective observational study included 60 cirrhotic patients with anemia. Demographic data, clinical features, hematological parameters, and liver function tests were analyzed. The MELD score was calculated to assess liver disease severity.

Result: A significant negative correlation was found between hemoglobin and MELD score ($r=-0.481$, $p=0.001$). Severe anemia was significantly more prevalent in patients with high MELD scores (50.00%) compared to moderate (12.90%) and low (0.00%) MELD scores ($p=0.001$). Mean hemoglobin levels decreased significantly with increasing MELD scores: 10.76 ± 0.78 g/dL in low MELD, 9.41 ± 1.33 g/dL in moderate MELD ($p=0.029$), and 8.17 ± 1.96 g/dL in high MELD ($p=0.001$). Multivariate analysis identified MELD score >19 as the only independent predictor of severe anemia (OR=3.86, 95% CI 1.18-12.64, $p=0.025$).

Conclusion: Anemia severity correlates significantly with liver cirrhosis severity as measured by the MELD score. This relationship is independent of clinical features, portal hypertension manifestations, or cirrhosis etiology, highlighting the multifactorial nature of anemia in liver cirrhosis.

Keywords: Anemia; Liver cirrhosis; MELD score; Normocytic anemia; Macrocytic anemia; Microcytic anemia; Portal hypertension; Liver function.

INTRODUCTION

Anemia is a frequently observed hematological abnormality in patients with liver cirrhosis, reflecting both the severity and the progression of the disease. The intricate relationship between anemia and liver cirrhosis has been extensively studied, primarily because anemia can exacerbate both the clinical manifestations and outcomes of cirrhosis. This thesis aims to explore the correlation between anemia and the severity of liver cirrhosis, as assessed by the Model for End-Stage Liver Disease (MELD) score.

The MELD score, initially developed for predicting mortality in patients undergoing transjugular intrahepatic portosystemic shunt (TIPS) procedures, has become a pivotal tool in assessing the severity of liver disease and prioritizing patients for liver transplantation [1]. It incorporates serum bilirubin, serum creatinine, and the international normalized ratio (INR) for prothrombin time, offering a quantitative measure of liver function. However, how anemia correlates with these parameters and, consequently, with the MELD score, remains an area ripe for further investigation.

Previous studies have demonstrated that anemia in cirrhotic patients is not only a marker of disease severity but also significantly contributes to morbidity and mortality. For instance, anemia has been associated with an increased risk of hepatic encephalopathy, variceal bleeding, and poor outcomes post-liver transplantation [2]. The prevalence of anemia in cirrhotic patients ranges widely, reported to be between 15% to 75%, depending on the study population and the criteria used for defining anemia [3].

Moreover, the liver's role in the metabolism of drugs and vitamins critical for hematopoiesis is compromised in cirrhosis, potentially leading to deficiencies in vitamin B12, folate, and iron, all of which are essential for red blood cell production. The liver also produces EPO, and in advanced cirrhosis, this production can be significantly reduced, contributing to anemia [4].

The MELD score, by integrating parameters that reflect liver synthetic function and renal function, indirectly captures some of these pathophysiological changes. However, the direct correlation between the severity of anemia and the MELD score has not been uniformly established across studies. Some research suggests a direct correlation, where higher MELD scores are associated with more severe anemia, possibly due to the cumulative effects of the aforementioned mechanisms [5]. Conversely, other studies show less clear or no association, highlighting variability due to different etiologies of cirrhosis, patient demographics, and variations in anemia definitions [6].

In conclusion, understanding the correlation between anemia and the severity of liver cirrhosis through the lens of the MELD score could enhance our prognostic capabilities, improve therapeutic strategies, and optimize patient outcomes in this complex patient group.

Material and Methods

This prospective observational study was conducted on patients admitted to the wards and ICU of SDM College of Medical Sciences and Hospital, Sattur, Dharwad. Ethical clearance was taken from the institution's Ethics Committee.

Inclusion Criteria

- Liver cirrhosis patients aged over 18 years, irrespective of etiology.
- Patients with hemoglobin levels <13 g/dL in males and <12 g/dL in females.

Exclusion Criteria

- Patients who had received a blood transfusion within the past three months. Patients diagnosed with chronic kidney disease.
- Patients with any other cause of anemia not directly or indirectly related to liver cirrhosis.

Sampling

- Sampling Population
- Patients diagnosed with cirrhosis of the liver who were admitted to SDM College of Medical Sciences were included.

Sample Size Calculation

The sample size was calculated using the formula:

Sample size

$$Zx^2PQ/e^2$$

$Z_x = 1.96$ for a 95% confidence interval

$P = 75\%$ (prevalence of anemia in cirrhosis from literature ⁷)

$Q = 25\%$ $e = 12\%$

This calculation resulted in a sample size of 60.

Sampling Technique

Over the last three years, an average of 346 cirrhosis patients per year were treated at SDM. Out of these, 60 patients were selected using simple random sampling. Those fulfilling the inclusion criteria were enrolled.

Data Collection Method

Participants were screened for eligibility. Those eligible were briefed about the study, and written informed consent was obtained.

Demographic data including age, sex, and history of comorbidities (e.g., hypertension, diabetes mellitus), along with personal habits like alcohol consumption and smoking, were recorded.

A thorough physical examination included checking vitals and performing a systemic examination.

Diagnosis of liver cirrhosis was confirmed with ultrasound findings, blood investigations, and other relevant tests, which were documented on a pre-designed, pre-tested proforma.

Investigations

Complete haemogram, blood group, random blood sugar, blood urea, serum creatinine, serum electrolytes, liver function tests, PT-INR and viral markers were evaluated for each patient.

Additional procedures like ascitic fluid analysis, upper GI endoscopy, ultrasonography, colonoscopy, and CT abdomen

were performed where clinically indicated and feasible.

MELD Score

The MELD score was calculated for each patient to assess the severity of liver disease.

Statistical Analysis: Data analysis was performed using SPSS version 20. Data were collected on a periodic basis throughout the inpatient stay, with all entries made into an MS Excel spreadsheet. Descriptive statistics were used for demographic data. Pearson's correlation was employed to explore the relationship between anemia and the severity of liver cirrhosis. The Chi-square test was used for comparing categorical variables. A p-value less than 0.05 was considered statistically significant.

RESULTS

The study included 60 patients with a mean age of 48.85 ± 9.97 years, ranging from 32 to 72 years. The age distribution showed that the largest proportion of participants (33.33%, n=20) were in the 40-49 years category, followed by 30.00% (n=18) in the 50-59 years category, and 21.67% (n=13) in the 30-39 years category. The 60-69 years age group comprised 13.33% (n=8) of the participants, while only 1.67% (n=1) were ≥ 70 years of age. This distribution indicates that middle-aged individuals (40-59 years) represented the majority (63.33%) of the study population.

There was a striking gender disparity in the study population, with males constituting 90.00% (n=54) of the participants, while females represented only 10.00% (n=6). This male predominance is consistent with the epidemiological pattern of liver cirrhosis, particularly that associated with alcoholic etiology.

Based on MCV values, normocytic anemia was the most prevalent type, affecting 65.00% (n=39) of the patients. Macrocytic anemia was found in 20.00% (n=12), while microcytic anemia was present in 15.00% (n=9). The predominance of normocytic anemia suggests that multiple mechanisms, including chronic disease and hemolysis, may contribute to anemia in liver cirrhosis.

Table 1: Severity of Anemia by Gender

Anemia Severity	Males (n=54)	Females (n=6)	p-value
Mild	9 (16.67%)	2 (33.33%)	0.321*
Moderate	30 (55.56%)	3 (50.00%)	0.796*
Severe	15 (27.78%)	1 (16.67%)	0.548*

*p-value calculated using Fisher's exact test due to small cell counts

Among males (n=54), moderate anemia was most common, affecting 55.56% (n=30), followed by severe anemia in 27.78% (n=15) and mild anemia in 16.67% (n=9). In females (n=6), moderate anemia was also most prevalent (50.00%, n=3), followed by mild anemia (33.33%, n=2) and severe anemia (16.67%, n=1). Fisher's exact test revealed no statistically significant differences in anemia severity between genders (p=0.321 for mild, p=0.796 for moderate, p=0.548 for severe anemia), indicating that gender did not influence the severity of anemia in this cohort.

The mean total bilirubin level was 4.71 ± 5.23 mg/dL, with a wide range from 0.18 to 24.60 mg/dL, reflecting varying degrees of liver dysfunction. The mean INR was 1.63 ± 0.42 , ranging from 0.99 to 2.99, indicating impaired coagulation function. The mean MELD score was 17.23 ± 5.49 , with a range from 7 to 31, suggesting moderate to severe liver disease in the majority of patients.

Table 2: MELD Score Categories

MELD Score Category	Number (%)
Low (<10)	5 (8.33%)
Moderate (10-19)	31 (51.67%)
High (>19)	24 (40.00%)

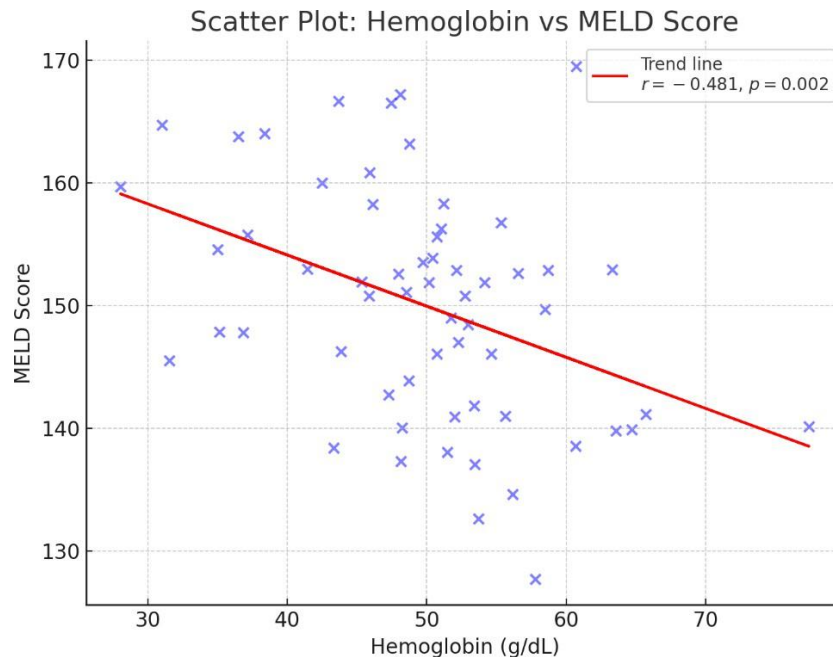
The majority of patients (51.67%, n=31) had moderate MELD scores (10-19), followed by 40.00% (n=24) with high MELD scores (>19). Only 8.33% (n=5) had low MELD scores (<10). This distribution indicates that most patients had significant liver dysfunction, with a substantial proportion having severe disease.

Ascites was the most common manifestation of portal hypertension, present in 88.33% (n=53) of the patients, followed by varices on endoscopy in 58.33% (n=35) and portal hypertensive gastropathy (PHG) in 48.33% (n=29). The high prevalence of these features indicates advanced liver disease with significant portal hypertension in the study population.

Table 3: Correlation Between Hemoglobin and MELD Score

Correlation	Pearson's r	p-value
Hemoglobin vs MELD Score	-0.481	0.001*

*Statistically significant ($p < 0.05$)



A significant negative correlation was found between hemoglobin levels and MELD scores ($r = -0.481$, $p = 0.001$), indicating that as MELD scores increased (reflecting worse liver function), hemoglobin levels decreased. This supports the hypothesis that anemia severity is related to the severity of liver dysfunction.

Table 4: Anemia Severity Across MELD Score Categories

Anemia Severity	MELD <10 (n=5)	MELD 10-19 (n=31)	MELD >19 (n=24)	p-value
Mild (n=11)	3 (60.00%)	6 (19.35%)	2 (8.33%)	0.008*
Moderate (n=33)	2 (40.00%)	21 (67.74%)	10 (41.67%)	0.093
Severe (n=16)	0 (0.00%)	4 (12.90%)	12 (50.00%)	0.001*

*Statistically significant ($p < 0.05$) by Chi-square test

There was a significant association between anemia severity and MELD score categories. Mild anemia was more common in patients with low MELD scores (60.00%, $n=3/5$) compared to those with moderate (19.35%, $n=6/31$) and high (8.33%, $n=2/24$) MELD scores ($p=0.008$). Conversely, severe anemia was significantly more prevalent in patients with high MELD scores (50.00%, $n=12/24$) compared to those with moderate (12.90%, $n=4/31$) and low (0.00%, $n=0/5$) MELD scores ($p=0.001$). There was no significant difference in the prevalence of moderate anemia across MELD categories ($p=0.093$). These findings further support the relationship between anemia severity and liver dysfunction severity.

No significant association was found between alcohol intake and anemia severity. Among patients with alcohol intake ($n=47$), mild anemia was present in 14.89% ($n=7$), moderate in 55.32% ($n=26$), and severe in 29.79% ($n=14$). In those without alcohol intake ($n=13$), mild anemia was present in 30.77% ($n=4$), moderate in 53.85% ($n=7$), and severe in 15.38% ($n=2$). The p-values for comparisons were 0.187 for mild, 0.925 for moderate, and 0.299 for severe anemia, indicating that alcohol intake did not significantly influence anemia severity.

Table 5: Hemoglobin Levels Across MELD Score Categories

MELD Score Category	Mean Hemoglobin (g/dL)	p-value
Low (<10) (n=5)	10.76 $\pm$ 0.78	Reference

Moderate (10-19) (n=31)	9.41 ± 1.33	0.029*
High (>19) (n=24)	8.17 ± 1.96	0.001*

*Statistically significant (p<0.05) compared to MELD <10 category by ANOVA with post-hoc analysis

Mean hemoglobin levels decreased significantly with increasing MELD scores, from 10.76 ± 0.78 g/dL in the low MELD category to 9.41 ± 1.33 g/dL in the moderate category (p=0.029 compared to low) and 8.17 ± 1.96 g/dL in the high category (p=0.001 compared to low). This progressive decline in hemoglobin with worsening liver function further supports the relationship between anemia and liver dysfunction severity.

Total bilirubin levels differed significantly across MCV categories: 2.36 ± 2.49 mg/dL in microcytic, 4.08 ± 4.76 mg/dL in normocytic, and 8.57 ± 6.54 mg/dL in macrocytic anemia patients (p=0.007). This finding further supports the association between macrocytosis and more severe liver dysfunction. Hemoglobin levels (8.29 ± 1.54 g/dL in microcytic, 9.07 ± 1.82 g/dL in normocytic, and 9.70 ± 1.78 g/dL in macrocytic anemia, p=0.197), INR (1.56 ± 0.38 in microcytic, 1.59 ± 0.43 in normocytic, and 1.80 ± 0.38 in macrocytic anemia, p=0.232), and serum creatinine (1.27 ± 0.66 mg/dL in microcytic, 1.02 ± 0.53 mg/dL in normocytic, and 1.08 ± 0.59 mg/dL in macrocytic anemia, p=0.483) did not differ significantly across MCV categories.

Table 6: MELD Score Distribution Among Patients With Different Anemia Types

MELD Score Category	Microcytic (n=9)	Normocytic (n=39)	Macrocytic (n=12)	p-value
Low (<10) (n=5)	2 (22.22%)	3 (7.69%)	0 (0.00%)	0.120
Moderate (10-19) (n=31)	5 (55.56%)	22 (56.41%)	4 (33.33%)	0.354
High (>19) (n=24)	2 (22.22%)	14 (35.90%)	8 (66.67%)	0.073

No statistically significant differences were found in MELD score distribution across anemia types, although there was a trend towards higher MELD scores in macrocytic anemia. Low MELD scores were present in 22.22% (n=2/9) of microcytic, 7.69% (n=3/39) of normocytic, and 0.00% (n=0/12) of macrocytic anemia patients (p=0.120). Moderate MELD scores were present in 55.56% (n=5/9) of microcytic, 56.41% (n=22/39) of normocytic, and 33.33% (n=4/12) of macrocytic anemia patients (p=0.354). High MELD scores were present in 22.22% (n=2/9) of microcytic, 35.90% (n=14/39) of normocytic, and 66.67% (n=8/12) of macrocytic anemia patients (p=0.073). The near-significant trend for high MELD scores in macrocytic anemia (p=0.073) is consistent with the findings from Tables 25 and 30, suggesting an association between macrocytosis and more severe liver disease.

DISCUSSION

This prospective observational study explored the relationship between anemia and liver cirrhosis severity as assessed by the Model for End-Stage Liver Disease (MELD) score. Our findings revealed a significant negative correlation between hemoglobin levels and MELD scores (r=-0.481, p=0.001), indicating that anemia worsens with increasing severity of liver disease. This relationship remained robust in multivariate analysis, with high MELD scores (>19) emerging as an independent predictor of severe anemia (OR=3.86, 95% CI 1.18-12.64, p=0.025).

Our finding of a significant negative correlation between hemoglobin levels and MELD scores (r=-0.481, p=0.001) is supported by several studies. Singal et al. examined 114 cirrhotic patients and found that the prevalence of anemia increased progressively with MELD score, from 40% in patients with MELD <10 to 75% in those with MELD >18 (p<0.01) [8]. Similarly, Singh et al. reported a significant correlation between anemia severity and MELD score (r=-0.462, p<0.001) in their study of 252 cirrhotic patients [9].

In our study, mean hemoglobin levels decreased significantly with increasing MELD scores, from 10.76 ± 0.78 g/dL in patients with low MELD scores (<10) to 9.41 ± 1.33 g/dL in those with moderate scores (10-19) (p=0.029) and 8.17 ± 1.96 g/dL in those with high scores (>19) (p=0.001). This stepwise decline aligns with findings from Scheiner et al., who observed mean hemoglobin levels of 13.4 g/dL in patients with compensated cirrhosis compared to 11.7 g/dL in those with decompensated disease (p<0.001) [10].

The multivariate analysis in our study identified MELD score >19 as the only independent predictor of severe anemia (OR=3.86, 95% CI 1.18-12.64, p=0.025), emphasizing the strong relationship between liver dysfunction severity and anemia. This is consistent with findings from Paternostro et al., who examined 338 patients with chronic liver disease and found that anemia was independently associated with decompensated cirrhosis (OR=4.71, 95% CI 2.49-8.89, p<0.001) [11].

The biological mechanisms underlying this correlation are multifaceted. Advanced liver disease is associated with increased portal hypertension, which can lead to splenomegaly and hypersplenism, resulting in peripheral sequestration and destruction of red blood cells [12]. Giannini et al. demonstrated that splenomegaly is an independent predictor of anemia in cirrhosis (OR=2.52, 95% CI 1.05-6.05, p=0.039) [13]. Additionally, patients with advanced cirrhosis often have

reduced erythropoietin production and response. Piscaglia et al. showed that despite elevated serum erythropoietin levels in cirrhotic patients compared to controls (29.5 ± 11.4 mU/ml vs. 17.2 ± 5.3 mU/ml, $p < 0.01$), the levels were inadequate relative to the degree of anemia, suggesting impaired erythropoietin response [14].

Furthermore, patients with high MELD scores often have elevated bilirubin levels, which can contribute to anemia. Our correlation matrix showed a significant negative correlation between hemoglobin and total bilirubin ($r = -0.315$, $p < 0.05$). This relationship has been mechanistically explained by Lang et al., who demonstrated that conjugated bilirubin can trigger eryptosis (programmed death of erythrocytes) through oxidative stress and calcium influx [15].

Our study demonstrates a significant correlation between anemia severity and liver cirrhosis severity as assessed by the MELD score. The predominance of normocytic anemia, consistent with anemia of chronic disease, highlights the multifactorial nature of anemia in liver cirrhosis. The association between macrocytic anemia and more severe liver dysfunction suggests that MCV could serve as a simple prognostic marker in cirrhotic patients.

The identification of MELD score >19 as an independent predictor of severe anemia emphasizes the close relationship between liver function and erythropoiesis. However, the lack of significant associations between anemia and clinical manifestations or portal hypertension features underscores the complex interplay of multiple mechanisms in the development of anemia in liver cirrhosis.

CONCLUSION

This prospective observational study provides compelling evidence of a significant correlation between anemia and liver cirrhosis severity as measured by the MELD score. Our findings demonstrate that as liver function deteriorates, reflected by increasing MELD scores, hemoglobin levels progressively decline, with a strong negative correlation ($r = -0.481$, $p = 0.001$). This relationship is further substantiated by the significantly higher prevalence of severe anemia in patients with high MELD scores (50.00%) compared to those with moderate (12.90%) or low (0.00%) MELD scores ($p = 0.001$), and by multivariate analysis identifying MELD score >19 as an independent predictor of severe anemia (OR=3.86, 95% CI 1.18-12.64, $p = 0.025$).

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