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Are Hematological Parameters Associated with Disease Severity in Cirrhotic Patients?

E. Krithiga*, Chokka M. Kiran, Anita Ramdas***, Thomas Alexander******

*Assistant Professor **Associate Professor ***Professor, Department of Pathology, ****Professor, Department of Gastroenterology, Pondicherry Institute of Medical Sciences, Kalapet, Puducherry 605014, India and Perundurai Medical College and Hospital, Perundurai, Tamilnadu, 638053, India.

Abstract

Background: Hematological abnormalities are quite frequent in cirrhotic patients and commonly include various types of anemias, thrombocytopenia and increased PT/INR. Some of these parameters are used as prognostic markers in scoring systems like Child-Pugh and Model for End Stage Liver Disease (MELD). *Aim*: We aimed to assess the various hematological parameters in cirrhotic patients and correlate them with disease severity based on Child-Pugh and MELD scoring systems. *Materials and Methods*: 87 patients diagnosed with cirrhosis irrespective of etiology were studied over a period of 2 years. Complete blood count, peripheral smear and coagulation parameters were noted along with relevant clinical history. Variations in these were compared with Child-Pugh and MELD scoring systems. *Results*: Macrocytic anemia and spur cell anemia were seen in 33 and 7 patients respectively. Thrombocytopenia was noted in 33 patients. 67 patients had prolonged PT. According to Child-Pugh classification, 65.5% of patients came under Grade C, 27.6% under Grade B and 6% under Grade A respectively. According to MELD score, 24% of patients had a score < 15 and 76% had a score of ≥ 15. Hematological parameters like MCH, MCHC and Total count showed a significant positive correlation with both Child-Pugh and MELD scoring systems with $p < 0.05$. Hemoglobin, RBC count and RDW showed a negative correlation with both Child-Pugh and MELD scoring systems with p value < 0.05. Coagulation parameters PT and PT/INR showed a significant positive correlation with both Child-Pugh and MELD scoring with p value < 0.001. *Conclusions*: Although a number of hematological abnormalities are seen in cirrhotic patients, only few of them show significant correlation with disease severity. Hence it is suggested that these parameters be used for prognostication in cirrhotics.

Keywords: Child-Pugh; Cirrhosis; Hematological; MELD.

Introduction

Liver cirrhosis is defined as necrosis of the liver followed by fibrosis and regeneration [1]. It causes significant morbidity and mortality in both developed and developing countries and is the 14th most common cause of death in adults worldwide. India ranks 27th in the world in mortality due to cirrhosis [2]. Viral hepatitis is the leading cause of cirrhosis in the developing countries, where as in developed countries Alcoholic liver disease (ALD), Hepatitis C virus (HCV) and Non-alcoholic steato-hepatitis (NASH) are the most common causes. The mean age at diagnosis is around 60 years and the male female ratio ranges from 1.3-4:1 [3].

Abnormalities in hematological parameters are common in cirrhotic patients. The various pathogenetic mechanisms include portal hypertension induced splenic sequestration, alterations in bone marrow stimulating factors mainly erythropoietin, viral and toxin induced bone marrow suppression and increased blood loss [4].

Microcytic hypochromic anemia, macrocytic anemia, sideroblastic anemia and spur cell anemia are the different types of anemias encountered frequently [5,6,7,8]. Thrombocytopenia, pancytopenia and disseminated intravascular coagulation (DIC) are the other abnormalities [6,9]. Deranged coagulation parameters include prolonged prothrombin time (PT), activated partial thromboplastin time (aPTT) and decreased fibrinogen [10,11,12].

Corresponding Author: C.M. Kiran, Associate Professor, Dept. of Pathology, Pondicherry Institute of Medical Sciences, Kalapet, Puducherry 605014, India.
E-mail: kirencm@yahoo.com

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The severity of liver disease can be assessed by scoring systems like Child-Pugh and MELD score. The Child-Pugh classification is designed to predict hepatic reserve and mortality associated with cirrhotic liver based on serum bilirubin, albumin, PT, presence of ascites and encephalopathy. This system classifies patients into class A, B and C respectively in relation to best, moderate or worst prognosis [13].

The MELD score has been developed to predict the prognosis of patients with end stage liver disease undergoing Transjugular Intrahepatic Porto-systemic Shunt (TIPS) procedure. The score ranges from 8 to 40 and the 3-month mortality rate increases as the score increases [14].

Literature on hematological aspects in patients with cirrhosis is sparse, particularly in south India. Our interest in revisiting this problem was aroused because of an increasing number of patients with end stage liver disease often manifesting with intractable anemias.

Materials and Methods

This was a descriptive study in Department of Pathology of our institute during the period May 2013 and April 2015. The Institutional Ethics Committee of our institute approved the research study and informed consent was obtained from the patients in accordance with the Declaration of Helsinki. 87 patients diagnosed with cirrhosis from Department of Gastroenterology were taken up for the study. The diagnosis of cirrhosis was confirmed by ultrasound examination and liver biopsy. All patients with cirrhosis irrespective of age, sex and etiology were included in the study. Patients with hepatocellular carcinoma and other malignancies were excluded from the study.

Two millilitres of EDTA venous blood sample was collected from the patients under aseptic precautions for hematological investigations. An automated haematology analyser, Horiba ABX Pentra DF 120, France was used for recording the various hematological parameters like hemoglobin, RBC count, total WBC count, differential leucocyte count, red cell indices, hematocrit and platelet count. A peripheral blood smear was prepared and stained with Leishman stain for studying the RBC and WBC morphology. Supravital staining technique using New Methylene Blue was done to determine the reticulocyte count. The coagulation parameters like PT/INR and aPTT were analyzed by Sysmex O automated blood coagulation analyzer CA-500. Liver function tests and other relevant tests like serum ferrtin, serum iron, total iron binding capacity (TIBC), serum vitamin B12 and folate, serum ceruloplasmin, serum lactate dehydrogenase (LDH), serum alpha-fetoprotein (AFP), lipid profile, HbsAg and anti HCV were performed wherever necessary.

Essential clinical information like hematemesis, epistaxis, ascites, splenomegaly and features of hepatic encephalopathy were obtained. The severity of liver disease in each patient was assessed by both Child-Pugh classification system and MELD scoring system. For Child-Pugh system, the patients were categorized into one of the three classes in accordance with the five parameters (encephalopathy, ascites, serum bilirubin, serum albumin and INR). For MELD scoring system, the patients were categorized into two groups (score < 15 and score > 15). A correlation between the various hematological parameters and severity of liver disease was made. Statistical analysis was done using SPSS software version 20. Mean, standard deviation (SD), percentage and Spearman and Pearson correlation were determined.

Results

A total of 87 cirrhotic patients were analyzed. The mean age of presentation was 51 years with a M:F ratio of 7.7:1. Alcoholism accounted for the commonest cause of cirrhosis in males (89.6%) and cryptogenic cirrhosis was common in females (60%). Anemia was seen in 77 patients (88.5%). Microcytic hypochromic anemia with MCV < 80 was seen in 7 patients (8%) and macrocytic anemia with MCV > 100 was seen in 33 patients (37.9%). Spur cell anemia characterized morphologically by the presence of spur cells (Figure 1) with multiple thorn-like projections similar to acanthocytes was a significant finding and was seen in 7 patients (8 %). Normocytic normochromic anemia was seen in 30 patients (34.4%). The typing and sex wise distribution of anemias is shown in Table 1.

Leucopenia and leucocytosis were seen in 9 and 37 patients respectively (10.3% and 42.5%). Thrombocytopenia was present in 33 patients (37.9%). 58.6% of patients had increased MCH and 31% of patients had normal MCH. 2.3% of patients had increased MCHC and 83.9% of patients had normal MCHC. 47.1% of patients had increased RDW.

Among the coagulation parameters, PT was prolonged in 67 patients (77 %). The liver profile of the patients is shown in table 2. Ascites was seen in 84 patients (96.5%). Splenomegaly and hepatomegaly

Table 1: Typing and sex wise distribution of various anemias

Type of Anemia	Male (N)	Female (N)	Total N (%)
NCNC	27	3	30 (34.4 %)
MCHC	5	2	7 (8 %)
Macrocytic anemia	28	5	33 (37.9 %)
Spur cell anemia	7	0	7 (8 %)

NCNC - Normocytic normochromic
MCHC - Microcytic hypochromic

Table 2: Liver profile of study patients

Liver parameters	Normal range		Increased		Decreased	
	%	(N)	%	(N)	%	(N)
Total bilirubin	19.5 %	(17)	80.5 %	(70)	-	
Direct bilirubin	11.5 %	(10)	88.5 %	(77)	-	
Indirect bilirubin	42.5 %	(37)	57.5 %	(50)	-	
SGOT	21.8 %	(19)	78.2 %	(68)	-	
SGPT	66.7 %	(58)	33.3 %	(29)	-	
Serum protein	57.5 %	(50)	5.7 %	(5)	36.8 %	(32)
Serum albumin	12.6 %	(11)	-		87.4%	(76)
Serum globulin	31.1 %	(27)	67.8 %	(59)	1.1%	(1)
ALP	64.4 %	(56)	35.6 %	(31)	-	
GGT	58.1 %	(51)	41.9 %	(36)	-	

Table 3: Additional vital signs

Signs	Percentage of patients	
	Present	Absent
Anemia	27.6 %	72.4 %
Jaundice	72.4 %	27.6 %
Fever	21.8 %	78.2 %
Spider naevi	3.4 %	96.6 %
Gynecomastia	3.4 %	96.6 %
Clubbing	6.9 %	93.1 %
Pedal edema	70.1 %	29.9 %

Table 4: Correlation of hematological parameters with Child-Pugh score

Hematological Parameters		Child-Pugh Class			p value
		A	B	C	
Hemoglobin	≤5	0	1	1	0.11
	5.1-11	3	17	47	
	≥11	3	6	9	
RBC count	<4.5	2	18	43	0.02
	4.5-5.5	4	6	14	
MCV	<80	1	4	1	0.12
	80-100	3	11	34	
	>100	2	9	22	
MCH	<26	2	5	2	0.05
	26-32	2	7	18	
	>32	2	12	37	
MCHC	<32	2	7	3	0.001
	32-38	4	17	52	
	>38	0	0	2	
RDW	<11.5	0	2	7	0.003
	11.5-14.5	2	6	29	
	>14.5	4	16	21	

Anemia	NCNC	2	7	26	
	MCHC	2	4	2	
	Macrocytic	2	11	24	0.16
	Spur cell	0	2	5	
Total count	< 4000	2	2	5	
	4000-11000	4	16	21	0.002
	>11000	0	6	31	
Platelet count	< 1 lakh	1	10	21	0.14
	>1 lakh	5	13	35	
PT	<12.0	3	2	0	
	12.0 - 16.0	3	8	4	<0.001
	>16.0	0	14	53	
PT/INR	< 1.7	6	20	23	
	1.7 - 2.3	0	3	22	<0.001
	>2.3	0	1	12	

Table 5: Correlation of hematological parameters with MELD score

Hematological parameters		MELD score		p value
		<15	≥15	
Hemoglobin	≤5	0	2	
	5.1-11	13	54	0.03
	≥11	8	10	
RBC count	<4.5	12	51	0.08
	4.5-5.5	9	15	
MCV	<80	2	4	
	80-100	11	37	0.23
	>100	8	25	
MCH	<26	4	5	
	26-32	7	20	0.09
	>32	10	41	
	<32	5	7	
MCHC	32-38	16	57	0.001
	>38	0	2	
RDW	<11.5	1	8	
	11.5-14.5	7	30	0.04
	>14.5	13	28	
Anemia	NCNC	6	29	
	MCHC	4	4	
	Macrocytic	9	28	0.24
	Spur Cell	2	5	
Total count	< 4000	3	6	
	4000-11000	13	28	<0.001
	>11000	5	32	
Platelet count	< 1 lakh	5	27	0.32
	>1 lakh	15	38	
PT	<12.0	5	0	
	12.0 - 16.0	7	8	<0.001
	>16.0	9	58	
PT/INR	< 1.7	21	28	
	1.7 - 2.3	0	25	<0.001
	>2.3	0	13	

Table 6: Comparison of spectrum of anemias with other studies

Author	Year	Number of patients	NCNC	Macrocytic	MCHC	Spur cell nemia
Berman et al[21]	1949	25	14 %	76 %	10 %	-
Riedler GF et al[33]	1975	256	-	67 %	-	-
Vassiliadis T et al[24]	2010	56	-	-	-	48 %
Kumar EH et al[20]	2014	100	52.3 %	17.4 %	27.9 %	-
Present study	2015	87	34.4 %	37.9 %	8 %	8 %

NCNC - Normocytic normochromic, MCHC - Microcytic hypochromic

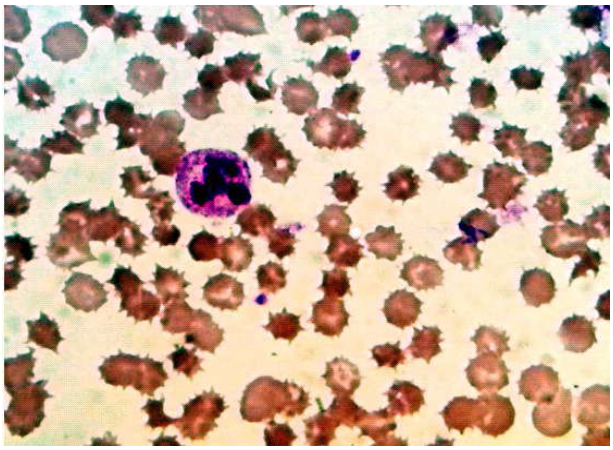

Fig. 1: Spur cells with thorn-like projections (Leishman, x400).

were seen in 48 and 28 patients respectively (55.1% and 32.1%). Hepatic encephalopathy was seen in 70 patients (80.5%). The other vital signs are shown in Table 3.

Child-Pugh scoring showed 6 patients (6.9%) with Grade A, 24 patients (27.6%) with Grade B and remaining 57 patients (65.5%) with Grade C. According to MELD scoring system, 66 patients (76%) had a score ≥ 15 and 21 patients (24%) had a score < 15.

The correlation of hematological parameters with Child-Pugh system is shown in table 4 and correlation of the same with MELD score is shown in Table 5. Among the red cell indices MCH and MCHC showed a statistically significant positive correlation with both Child-Pugh and MELD scoring systems whereas RDW showed a negative correlation. Total leucocyte count showed a positive correlation with both the scoring systems. Platelet count showed no significant correlation. PT and PT/INR also once again showed a significant positive correlation with both the scoring systems.

Discussion

Abnormalities in hematological parameters in cirrhotic patients were studied by few researchers but the literature pertaining to correlation of these parameters with disease severity is meagre. Alcoholism was the commonest cause of cirrhosis in our study followed by cryptogenic cirrhosis. This is in correlation with some of the Indian studies done by Ahmed et al in Assam and Nagarajaiah et al in Bangalore where alcoholism accounted for 69% and 75% of cirrhotic cases respectively [15,16]. A study by Andreu et al from Spain also showed alcoholism as the most common cause [17].

However, studies by Ghadir MR et al from Iran and Suk KT et al from Korea showed HBV infection as the most common cause of cirrhosis followed by alcoholism [18,19].

The most common type of anemia encountered in our study was macrocytic anemia followed by normocytic normochromic anemia. Kumar EH et al assessed the prevalence of anemias in cirrhotic patients in South India (Chennai) and concluded that normocytic normochromic anemia constituted about 52% and it is more prevalent than other types of anemias [20].

Berman et al state that anemia of macrocytic normochromic or normocytic normochromic type is a common occurrence in cirrhotic patients [21].

Microcytic hypochromic anemia was not commonly encountered in our study as most of our patients did not manifest with acute gastrointestinal haemorrhage.

One significant type of anemia, but accounting for a small proportion noted in our study was spur cell anemia. The cut-off for diagnosing spur cell anemia in peripheral smear was 20% [22].

Spur cells are morphologically similar but chemically distinct from acanthocytes. They are distinguished from acanthocytes by elevated membrane free cholesterol content with an increased cholesterol : phospholipid ratio. These spur cells gets sequestered by the splenic macrophages resulting in spur cell hemolytic anemia [23].

Vassiliadis T et al assessed the incidence of spur cell anemia in 56 patients with advanced liver disease and concluded that patients presenting with > 5 % spur cells in peripheral smear were associated with poor prognosis [24].

Our study did not show any statistically significant correlation of spur cell anemia with both the scoring systems. The comparison of spectrum of anemias with other studies is shown in Table 6.

Leucocytosis was more common than leucopenia in our study. Majority of our patients had ascites and had undergone paracentesis which might have contributed to leucocytosis. The other possible explanation could be due to spontaneous bacterial peritonitis. A study done by Berman et al in 1949 on blood and bone marrow of cirrhotic patients suggests that some patients may present with normal leucocyte count, while others experience leucocytosis after paracentesis, infections or surgical procedures [21].

Hypersplenism and bone marrow suppression by interferon therapy might be the possible causes for leucopenia.

Hemostatic abnormalities occur in cirrhotic patients due to disturbances in clotting and activation of fibrinolytic system in primary hemostasis [25].

PT is commonly increased in liver disease because of the decreased production of clotting factors like factors 2, 5, 7 and 10, including those involved in extrinsic pathway leading to prolongation of aPTT [11].

In advanced cirrhosis both aPTT and PT are prolonged with prolongation of PT exceeding that of aPTT [26]. Prolonged PT has been used as prognostic parameter in scoring systems like Child-Pugh and MELD. Degree of PT impairment also predicts the severity of portal hypertension and oesophageal varices [12].

Siddique SA et al [12], Devaranjani BR et al [27], and Arif S et al [28] showed that around 70% to 80% of cirrhotic patients presented with prolonged PT which was also seen in our study. PT/INR also showed significant correlation with the severity of the liver disease.

Child-Pugh and MELD scoring systems are used for assessing the severity of underlying liver disease. The predictive value of Child-Pugh score has been recently challenged because of subjective variables such as ascites and encephalopathy with interobserver variability, as well as the ceiling effect of the CP score [29]. Yet it is followed because of its simplicity with no need for computation or statistical analysis. MELD scoring was initially designed in 1999 to predict the risk of mortality in patients undergoing TIPS surgery. Now it is being used as a predictor of survival irrespective of whether the patient is undergoing liver transplant or not. The MELD score ranges from 8 to 40. Botta et al in his study concluded that MELD score is an excellent predictor of both short and medium term survival. An increase in MELD score is associated with a decrease in residual liver function. It has certain limitations like need for computation, absence of well defined cut-off value for patient categorization, inability to calculate at the bedside and more complex than calculation of CP score [30]. A recent study done in the US by Wedd JP et al in 2013 used MELD score of 15 as a cut-off point because balance between the risk of death on the transplant list versus risk of death with transplant surgery reverses around a MELD score of 15, with scores lower than 15 favouring staying on the transplant list and higher scores favouring accepting the risk of the surgery [31,32].

However, our study had certain limitations. Most of the patients were treated on out-patient basis rendering follow-up difficult. Some of the tests like lipid profile, vitamin B12, folate and ferritin could not be done in few patients because of poor follow-up and financial constraints.

Conclusion

Abnormalities in haematological parameters are quite often in cirrhotic patients with some of them having an immense prognostic significance. These parameters show a statistically significant correlation with disease severity as assessed by scoring systems like Child-Pugh and MELD, thus forming a fundamental tool in haematological evaluation. The notable ones amongst these are red cell indices and coagulation parameters. Moreover, there has been a steady increase in liver cirrhosis mortality in India since 1980 because of increased alcohol consumption, prevalence of hepatitis B and C and diabetes (a major risk factor for non-alcoholic fatty liver disease) with an estimated 1,88,575 liver cirrhosis deaths in 2010 accounting for almost one-fifth (18.3%) of the global liver cirrhosis death toll. Hence, there is a need to improve prevention and control of cirrhosis risk factors. Despite certain minor limitations, our study highlights the significance of hematological parameters in cirrhotic patients and emphasizes their association with disease severity.

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