Original Research Article

Coagulation profile and Hematological parameters in patients with Alcoholic Liver Disease and its association with the disease severity (A study of 230 cases)

Pankti I. Macwan[1],Hena D. Sodha[2], Kirit Jadav[3],Sivaranjini N[4]

[1] Senior Resident, Department of Pathology, Medical college Baroda, Vadodara,India
[2]Senior Resident, Department of Pathology, Medical college Baroda, Vadodara,India
[3]Associate professor, Department of Pathology, Medical college Baroda, Vadodara,India
[4] Senior Resident, Department of Pathology, Medical college Baroda, Vadodara,India

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Abstract

Introduction: Alcoholic liver disease is a term that encompasses the liver manifestation of long-term alcohol consumption, including fatty liver, alcoholic hepatitis, and liver cirrhosis. Abnormalities in hematological parameters are common in patients with alcoholic liver disease. The pathogenesis of abnormal hematological parameters in cirrhosis is multifactorial and includes portal hypertension-induced sequestration, alterations in bone marrow stimulating factors, viral- and toxin-induced bone marrow suppression. Excess alcohol intake itself causes direct bone marrow suppression leading to toxic effects on the cell lineages and cause hematological disturbances causing anemia, leucocytosis, leucopenia, and thrombocytopenia. Abnormalities in hematological parameters are associated with an increased risk of complications, including bleeding and infection. All three parameters determine a greater extent of morbidity and mortality in these patients.**Materials and Methods:** In the present study, patients were grouped into Group 1 to 5 based on the Model for End-stage Liver Disease scoring, and individual hematological parameters were studied. The onset of anemia, leucocytosis or leucopenia, and thrombocytopenia in the MELD group was studied so that corrective measures can be taken at the earliest.**Results:** Maximum number of patients fell into Group 2 of MELD score and hemoglobin, total count and platelets were studied in each group. Patients followed a pattern of reduced hemoglobin as the MELD score as well as group increased with significant p value and increase total count with increase in MELD group with significant p value.**Concluison:** The results obtained from the study have clear implications regarding the prediction of what the hematological spectrum does an individual patient has when he falls into a particular group of MELD score. This speculation could persuade the treating physicians to correct these hematological indices so that further disease progression could be delayed or nullified.

Keywords: Alcohol, MELD, Anemia, Leucocytosis, Leucopenia, Thrombocytopenia.

Introduction

Alcohol is a psychoactive substance with dependence-producing properties and causes a social and economic burden. Alcoholic hepatitis is an acute inflammation of the liver, accompanied by the destruction of individual hepatocytes, and can progress to cirrhosis. Symptoms may include fever, jaundice, an increased white blood cell count, an enlarged, tender liver, and spider-like veins in the skin [1]. It may develop due to a large amount of alcohol for an extended period, and the outcome may range from abnormal liver functions with no symptoms to hepatic encephalopathy [2].The principal goal is to establish a single score resulting from the sum of a subset of individual variables (predictive variables), each being supposed to weigh on the disease's progression. More recent scores (including the MELD score) are based on a subset of variables shown to be significantly and independently correlated to the outcome by multivariate analysis.Among a series of new prognostic scores reported in the literature [3,4,5,6] MELD (for Model for End-Stage Liver Disease) score was proposed as the most promising alternative to Child-Pugh score [7].

**Correspondence*
Dr. Pankti I. Macwan
Senior Resident, Department of Pathology, Medical college Baroda, Vadodara,India
E-mail: panktimac123@gmail.com

MELD Score (Model for End-stage Liver Disease Score) [8,9]
MELD score=9.6 $\log_e$ (creatinine mg/dl) +3.8 $\log_e$ (bilirubin mg/dl) +11.2 $\log_e$ (INR) +6.4

Hepatic steatosis may cause hepatomegaly, with mild elevation of serum bilirubin and alkaline phosphatase levels. In contrast, alcoholic hepatitis tends to appear acutely, usually following a bout of heavy drinking. Symptoms and laboratory manifestations may range from minimal to those that mimic acute liver failure. These two extremes are the nonspecific symptoms of malaise, anorexia, weight loss, upper abdominal discomfort, and tender hepatomegaly, and the laboratory findings of hyperbilirubinemia, elevated serum aminotransferases and alkaline phosphatase, and often a neutrophilic leukocytosis. In contrast to the other chronic liver diseases where serum A.L.T. tends to be higher than serum A.S.T., serum A.S.T. levels tend to be higher than serum A.L.T in a ratio of 2:1 or higher in alcoholic liver disease. This can be helpful in the differential diagnosis of chronic liver injury when adequate history is not available.

Hematological Manifestation of Alcohol Consumption

Alcohol is the most commonly used drug whose consumption includes dose-dependent suppression of blood cell production or hematopoiesis, also may suffer from nutritional deficiencies of folic acid and other vitamins that play a role in blood cell development.Chronic excessive alcohol ingestion reduces the number of blood cell precursors in the bone marrow and causes characteristic structural abnormalities in these cells, resulting in

fewer than normal or non-functioning mature blood cells. As a result, alcoholics may suffer from moderate anemia, characterized by enlarged, structurally abnormal R.B.C.'s increased or mildly reduced numbers of WBC's,mainly of neutrophils and moderately to severely reduced numbers of platelets.[10] Although this generalized reduction in blood cell numbers usually is not progressive or fatal and is reversible with abstinence.The severity of anemia according to hemoglobin levels is graded as follows [11] -

Mild Anemia- 11-13 gm/dl

Moderate Anemia- 8-11 gm/dl

Severe Anemia- <=8 gm/dl

Sideroblastic and megaloblastic anemia is a common complication in severe alcoholics.

Under conditions of folic acid deficiency, precursor cells cannot divide properly, and large immature and nonfunctional cells, megaloblasts, accumulate in the bone marrow and the bloodstream. This impaired hematopoiesis affects mainly R.B.C.'s, but also WBC's and platelets. The resulting deficiency in R.B.C.'s, WBC's, and platelets has numerous adverse consequences for the patient, including weakness and pallor from anemia, infections resulting from reduced neutrophil numbers, and bleeding as a result of the lack of platelets. Alcoholic ingestion itself may accelerate the development of folic acid deficiency by altering the absorption of folic acid from food.

Causes of Anemia in Alcoholics: Alcohol and alcohol cirrhosis leads to decreased R.B.C. production. Hypersplenism, a condition characterized by an enlarged spleen and deficiency of one or moreblood cell types, can induce premature R.B.C. destruction. Blood loss occurs primarily in the gastrointestinal tract, e.g., at the peptic ulcer sites, and increased in patients with reduced platelets. Folic acid deficiency impairs R.B.C. production and results from decreased ingestion, decreased absorption, and abnormal folic acid metabolism.Because alcoholics commonly develop bacterial infections, much research has focused on alcohol's effects on neutrophils, the primary cell of defense against bacterial invasion. However, alcohol also impairsmonocytes and macrophages' function, which attack bacteria and other microorganisms, and lymphocytes, which mediate the immune response. Patients with a White blood cell count of more than 11,000/cumm were at increased risk of infections. [12] Alcohol interferes with the monocyte-macrophage system. Compared with healthy subjects, alcoholics are less resistant to infection by microorganisms that normally are eradicated by monocytes and macrophages, such as the bacteria that causes tuberculosis and various forms of pneumonia.

Thrombocytopenia is a frequent complication of alcoholism, affecting 3-43 percent of non-acutely ill, well-nourished alcoholics and 14-81 percent of acutely-ill, hospitalized alcoholics. Platelet count <1,50,000 is considered value to grade thrombocytopenia in chronic alcoholics. [12] Thus, apart from acquired immune deficiency syndrome (AIDS), alcoholism probably is the leading cause of thrombocytopenia. Except for the most severe cases, however, the patients generally do not exhibit manifestations of excessive bleeding. Moreover, alcohol-related thrombocytopenia is typically transient, and platelet counts usually return to normal within one week of abstinence. Therefore, patients generally require no therapeutic interventions other than that needed to ease alcohol withdrawal. Only in patients whose thrombocytopenia is severe and associated with excessive bleeding is platelet transfusion indicated.

Materials and Methods

The present study was carried out at S.S.G. Hospital, Baroda, from December 2018 to November 2019 on the indoor patients of Alcoholic Liver Disease,Department of Medicine, S.S.G. Hospital, Baroda and with permission from the Scientific Research Committee. A total of 230 patients with Alcohol Liver Disease were selected for the study. The criterion for selecting patients was the patients with a history of chronic alcohol consumption and those diagnosed with Alcoholic Liver Disease clinically. The exclusion criteria were patients with a known case of primary coagulation disorders or primary abnormality of hemostatic function.

After selecting cases for the study, careful history and detailed clinical examination were carried out in each patient about Alcoholic Liver Disease. The quantity and duration of alcohol consumption were also noted.The following investigations were done-

Complete Blood Count (C.B.C.),Liver Function Tests, Serum Creatinine, Ultrasonography.Complete Blood Count was done by collecting 2 ml of the patient's blood in EDTA vacuette in a five-part hematological analyzer (Horiba), and values of Hemoglobin, total count, and platelets were obtained.Coagulation profile was done by collecting 3ml of the patient's blood in an automated machine (stago) and was done manually in emergency cases with the waterbath technique. Values of Prothrombin time, Internationalized Normalized Ratio (INR), and Activated Partial Thromboplastin Time were obtained.Blood was collected in plain vacuttee, and a semi-auto analyzer obtained serum Bilirubin and Serum Creatinine values.From the values obtained of Serum total bilirubin, INR, and serum creatinine, the Model for End-stage Liver Disease (MELD) score was derived. Patients were grouped according to the MELD scoring calculation from group 1 to group 5.The calculation for the derivation of MELD Score is as follows-

MELD Score= 3.78xlog(Serum total bilirubin)+11.2x log (INR)+9.57x log (Serum Creatinine)+6.43

With the values derived fromthe MELD Score, the patients were grouped as follows-

- 40 or more — group 5
- 30–39 — group 4
- 20–29 —group 3
- 10–19 — group 2
- <9 — group1

Observation

Out of 230 cases of Alcoholic Liver Disease, 95.22% of the patients were males and 4.78% were females.

Age distribution among 230number of cases of Alcoholic Liver Disease is as follows-

Table 1: Distribution of number of cases in age groups

Age group	Number of cases	Percentage (%)
20-29 yrs	42	18.26
30-39 yrs	77	33.48
40-49 yrs	61	26.52
50-59 yrs	33	14.35
>60 yrs	17	7.39
Total	230	100.00

The majority were in the age group of 30-39 years (33.48%). 26.52% of the patients belonged to the age group of 40-49 years. 18.26% of the patients belonged to the age group of 20-29 years. 14.35% of the patients belonged to the age group of 50-59 years, and 7.39% belonged to the age group of >60 years of age.Incidence of Anemia in Alcoholic Liver Disease-

Table 2: Incidence of severity of anemia in alcoholics

Severity of Anemia	Number of cases	% of cases
Mild (11-13g/dl)	32	13.91
Moderate (8-11g/dl)	92	40.00
Severe (<8 g/dl)	74	32.17
Total	198	86.09

Thirty-two number cases had Hemoglobin>13 g/dl (13.91%). Anemia was present in 198 cases out of 230 cases (86.09%) of alcoholic liver disease. Mild anemia was found in 13.91% of cases. Moderate anemia was present in 40.00% of cases, while severe anemia was present in 32.17%. The maximum number of patients presented with moderate anemia.

Table 3: Alcoholic Liver Disease cases and platelet count

Platelet Count	No of cases	Percentage %
Normal count (>1,50,000/cumm)	118	51.30
Thrombocytopenia (<1,50,000/cumm)	112	48.70
Total	230	100.00

48.70% of cases showed the presence of thrombocytopenia. 51.30% of patients had a normal platelet count.

The various leucocyte count assessed were as follows-

Table 4: No. of cases with normal, high and low leucocyte count

Total Count	No. of cases	Percentage
>11,000 /cumm	81	35.22
4,000-11,000 /cumm	137	59.57
<4,000 / cumm	12	5.22
Total	230	100.00

35.22% of cases presented with leucocytosis (higher than 11,000/cumm), equated to higher infections in patients of alcoholic liver disease cases. Leucopenia was present in 5.22% of cases, and normal leukocyte count was observed in 59.57% of cases.

Results

Model for End-stage Liver Disease (MELD) scoring was done for each study subject assessing the chronicity of the liver disease. Patients were divided into five different groups based on the scoring system. Group 1 with scores 0-9, group 2 consisted of patients with scores 10-19, group 3 with scores of 20-29, group 4 with scores of 30-39, and group 5 with scores >40 and above.Among 230 cases of Alcoholic Liver Disease studied, MELD group 1 had 24cases, group 3 had 73 cases, group 4 had 30 cases, and group 5 had 9 cases. The maximum number of cases- 94 fell into group 2 with a MELD score between 10-19.

Table 5: The following case distribution into different MELD groups according to the MELD score was obtained

MELD Group	MELD Score	No. of cases	Percentage of cases (%)
1	<9	24	10.43
2	10-19	94	40.87
3	20-29	73	31.74
4	30-39	30	13.04
5	>=40	9	3.91
Total		230	100.00

The maximum number of cases fell into group 2 with a MELD score of 10-19. Among the 230 cases studied, the mean Hemoglobin of the study population was 9.5±3.02g/dl. Mean Hemoglobin in different groups of MELD score was as follows-

Table 6: Incidence of anemia in different MELD groups

MELD Group	Anemia Mean (SD)
1	10.01 (±3.73)
2	10.04 (±2.98)
3	9.21 (±2.98)
4	8.53 (±2.56)
5	8.07(±1.93)
Mean Hemoglobin (overall)	9.5(±3.02)

10.01± 3.73 g/dl in group 1, 10.04±2.98 in group 2, 9.21±2.98 in group 3, 8.53± 2.56 in group 4, group 5 had mean hemoglobin of 8.07±1.93. All five groups showed anemia, but it was severe in group 4 and 5 patients with average Hemoglobin of 8.53 and 8.07 g/dl, respectively, in groups 4 and 5. In group 1,2and 3, patients had moderate anemia. So, all patients who had MELD score >=20 had moderate to severe anemia. The relationship between mean Hemoglobin among different MELD groups was significant with $p<0.05$. The pattern of hemoglobin variation is shown in figure 1.

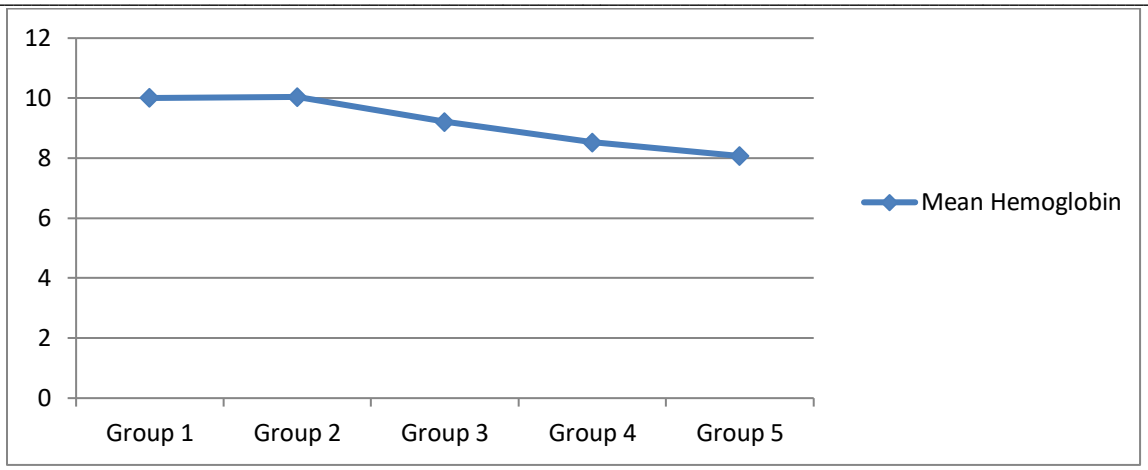

Fig 1: Line graph showing the relationship between Hemoglobin and MELD score group

The mean leukocyte count of the population was 10,472/cumm. Mean leucocyte count in different groups of MELD score is as follows-

Table 7: Mean Total leucocyte count in different MELD groups

MELD Group	Total Count Mean (SD)
1	6450 (±3161.59)
2	8928.72 (±3912.2)
3	12739.04 (±6722.03)
4	12506.67 (±6977.5)
5	12138 (±7165.27)
Overall mean total count	10471.74 (±5860.75)

In group 1 mean leucocyte count was 6,450/cumm; in group 2, it was 8,929/cumm; in group 3, it was 12,739/cumm; in group 4, it was 12,507/cumm, and it was 12,138/cumm in group 5. The mean total count among different MELD groups was statistically significant with $p<0.05$.

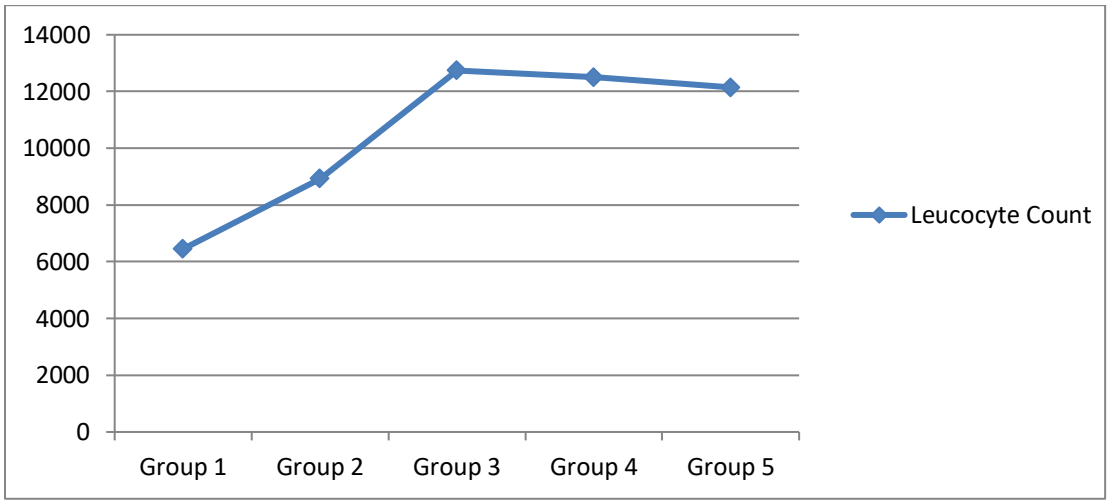

Fig 2: Shows a line graph showing a variation of leucocyte count in patients in different MELD score groups

The mean platelet count among the study subjects was 1,53,503/microlitre. Mean platelet count in the individual MELD score groups was as follows-

Table 8: Mean platelet count in different MELD groups

MELD Group	Platelet Count Mean (SD)
1	140916.67 (±75171.64)
2	156675.53 (±80209.43)
3	168880.82 (±126801.24)
4	110000 (±68365.65)
5	174222.22 (±71855.37)
Overall mean platelet count	153503.47 (±96792.25)

In group 1, mean platelet count was 1,40,916/microlitre in group 2, it was 1,56,675/microlitre, in group3,it was 1,68,880/microlitre, group 4 had 1,11,000/microlitre and group 5 had 1,74,222/microlitremean platelet count. Among the 230 subjects studied, 112 had thrombocytopenia. Out of 24 cases of group 1, 11 cases (45.83%) had thrombocytopenia, 40 cases (42.55%) out of 94 cases of group 2 had thrombocytopenia, and 36cases (49.31%) out of 73 cases of group 3 had thrombocytopenia, 20 cases (66.66 %) out of 30 cases in group 4 had thrombocytopenia. In comparison, group 5 had 4(44.44%) out of 9 cases who had thrombocytopenia. The platelet count among different MELD group was statistically insignificant with p>0.05.

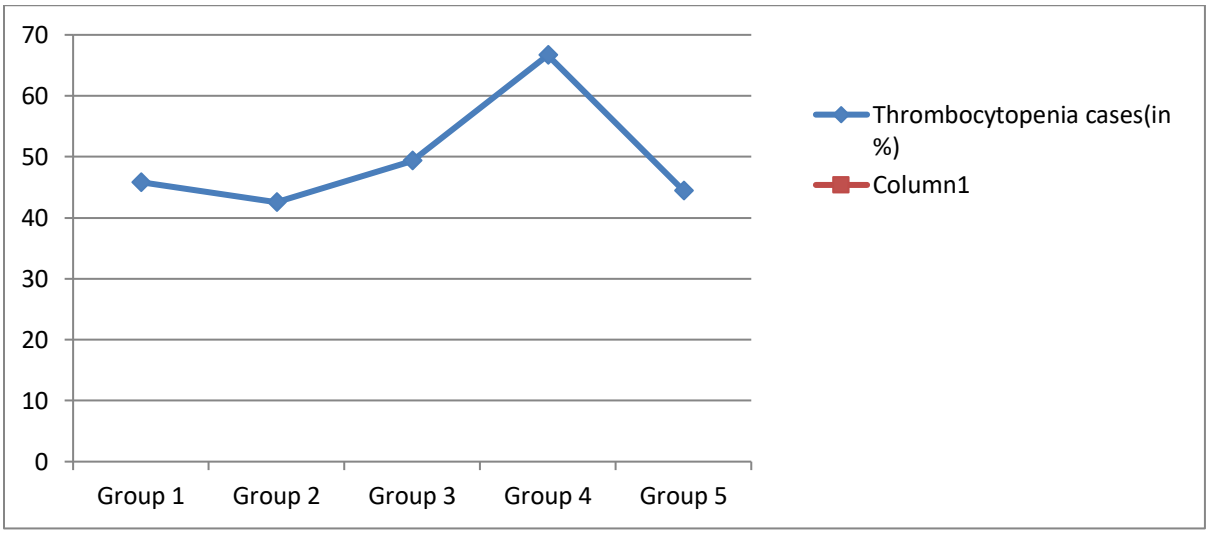

Fig 3: shows the variation of thrombocytopenia in study subjects in different MELD score groups

Discussion:

Alcohol causes complex aberrations in Hematological indices, leading to fatal complications, increasing these patients' mortality rate.

Our study observed a progressive fall in hemoglobin levels on par with the increase in MELD score. Group 1 had a mean Hemoglobin of 10.01, which progressively reduced to mean Hemoglobin of 8.07 in group 5, and this difference was significant with p<0.05.

These findings in Hemoglobin correlated with the study of Deepak Jain and colleagues. [12]

George N.Ioannov and colleagues proved that chronic alcohol intake causes gastrointestinal bleeding and increased risk of iron deficiency anemia. [13]

Joyce Kaferle and colleagues stated that alcoholism is the cause in as many as 80% of patients with macrocytosis in some populations. [14]

Anemia was noted from MELD group 1itself, and all the patients in groups 2-5 had anemia. In patients who have MELD scores representing MELD group ≥2, expeditious management of anemia should be undertaken. Investigations including upper gastrointestinal endoscopy should be undertaken by the treating physicians to look for bleed varices so that timely intervention at this stage could prevent the further deterioration of hemoglobin status in these patients.

Alcoholic hepatitis, the major determinant of leukocytosis, is distinct from cirrhosis caused by long-term alcohol consumption. Also, the superadded infections in any stage of the alcoholic liver disease spectra can lead to leukocytosis.

In the present study, leukocytosis predominated in MELD group 3,4, and 5 patients. It did notsettle down to nil in higher groups.

The possible underlying mechanism could be the defense mechanisms in the body, including various cytokines, interleukins, and defensins that are active against the infections until group 3. After this stage, these mechanisms get exhausted, and the body's ability to withstand the incoming pathogens would come to a standstill. So, in the higher groups of MELD score, leukopenia is the predominant picture.

This finding is in contrast to Deepak Jain and colleagues in which leucocytosis predominated in MELD group 2 and 3 while leucopenia predominated in MELD group 4 and 5. [12]

Low platelet counts can result from decreased platelet production, enhanced splenic sequestration, or platelet consumption.

Our study noted that the occurrence of thrombocytopenia started in MELD group 4 patients, excluding all the patients of groups 1,2,3, and 5.

In contrast to the present study, Deepak Jain and colleagues stated that the incidence of thrombocytopenia increased as the MELD group increase with a significant p value. [12]

Peltz S studied the causes of thrombocytopenia in hospitalized patients, which may be caused by splenomegaly, folate deficiency, and a direct toxic effect on production, survival time, and function of platelets. [15]

Arvind R. Murali and colleagues stated that platelet count decreases with an increase in alcohol consumption, and alongwith INR, has good diagnostic accuracy for identifying cirrhosis in alcoholics.

The likely explanation for this is that the platelets' splenic sequestration starts only after features of portal hypertension are well established. Another proposed mechanism for this is, platelets are more resistant to the splenic hyperactivity than R.B.C.s. This would retain the quantitative and qualitative activity of the thrombocytes to the higher stage of the MELD group. However,thrombocytopenia was present only in 44% of cases of MELD group 5, while it predominated with 66% in MELD group 4. This difference in platelet counts amongst various MELD groups was insignificant with p>0.05.

The hypocellular bone marrow characterizes pancytopenia associated with alcoholic liver disease in relation to the occurrence of hepatitis. This syndrome's main feature is an injury to or loss of pluripotent hematopoietic stem cells in the absence of infiltrative disease of the bone marrow. [16] The incidence of bicytopenia in the study is evident at group 4 MELD score. This is explained by the prolonged oxidative injury to the bone marrow caused by alcohol, which has affected all the cell lines in these patients.

Conclusion

We have used the MELD grouping approach in defining the hematological parameters in this category of patients. The results obtained from the study have clear implications regarding the prediction of what the hematological spectrum does an individual patient has when he falls into a particular group of MELD score. This speculation could persuade the treating physicians to correct these hematological indices so that further disease progression could be delayed or nullified. Although the MELD score has been used in previous studies for therapeutic purposes and mortality prediction, this novel idea gives an edge to the MELD score as its importance could also be utilized in the prevention and progression of the disease.

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