Research Article

Hematological spectrum in patients with alcoholic liver cirrhosis: a model of end-stage liver disease score based approach

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ABSTRACT

Background: Patients with alcoholic liver cirrhosis have anaemia, leucocytosis as well as leukopenia and thrombocytopenia in various proportions, which are, to a greater extent, determine mortality and morbidity among them. There is a growing need of a scale to determine the stages at which these hematological parameters could be corrected so as to decrease their adverse impacts on the patients’ lives. The model of end-stage liver disease (MELD) score is built to predict survival in cirrhotic patients undergoing transplantation and to assign priority for liver transplantation. To simplify the task of early identification and management of patients with deranged blood indices, we studied the relationship between various hematological parameters and MELD score.

Methods: This was a prospective observational study in which spectrum of various hematological indices and complications of alcoholic liver disease were observed in 88 patients with stigmata of chronic liver failure on clinical examination substantiated by histopathological evidence and imaging. Hematological parameters including anaemia, leucocyte count and platelet count were assessed in the subjects and were categorized under the different groups of MELD score. The relationship of these variables with MELD score was studied and statistical analysis was done.

Results: We observed a progressive fall in hemoglobin levels with the increase in MELD score. All the patients in group 1 had normal leucocyte count. Leukocytosis predominated in MELD group 2 and 3 patients. In group 4, leukopenia was more prevalent. All the patients in group 5 had leukopenia. Group 1 and 2 patients did not have thrombocytopenia. Thrombocytopenia started occurring in MELD group 3 patients, while involving all the patients of group 4 and 5.

Conclusions: The statistically significant association between the variables and the groups shows that MELD score grouping system could be an important tool in the assessment of these patients. This association strongly depicts that the clinicians could effectively apply the classification in predicting the hematological complications in these patients and take precautions early in preventing the further progression of the disease thus decreasing the mortality in these patients.

Keywords: Anaemia, Cirrhosis, Leukocytosis, Leukopenia, Thrombocytopenia, MELD score

INTRODUCTION

Alcohol is the most commonly used drug whose consequences include the suppression of hematopoiesis. Because its toxic effects are dose dependent, significantly impaired hematopoiesis usually occurs only in people with severe alcoholism. These patients also may suffer from nutritional deficiencies of folic acid and other vitamins that play a role in hematopoiesis. As a result, alcoholics may suffer from moderate to severe anemia, characterized by enlarged, structurally abnormal RBC’s, mildly reduced numbers leukocytes and neutrophils and moderately to severely reduced numbers of platelets. Although this generalized reduction in blood cell
numbers (i.e., pancytopenia) usually is not progressive or fatal and is reversible with abstinence, complex aberrations of hematopoiesis can develop over time that may cause death.¹

Anemia of diverse etiology occurs in about 75% of patients of chronic liver disease.² The frequent association of anemia with alcoholic liver disease and/or hepatocellular failure provides a rationale for examining the role of the liver in the formation and destruction of red blood cells.

Indeed, a variety of different mechanisms may be implicated in the development of anemia in patients with liver disease. These include iron deficiency, hypersplenism, anemia due to chronic disease, folic acid and vitamin B₁₂ deficiencies.

There is a variable manifestation of leukocytosis and leukopenia in patients with alcoholic liver cirrhosis. Incidence of high rate of infections, impaired defense mechanism and direct bone marrow suppressive effect of alcohol contribute to the differential presentation of leukocyte count. Even though the causes of the varied presentation are known, studies are needed to determine the stage at which emergent intervention could help in the recovery.

In chronic liver disease and cirrhosis, alterations in primary platelet hemostasis (platelet adhesion, activation and aggregation) have received less attention than changes in secondary hemostasis (coagulation). Regarding platelet count, an increased intra-splenic platelet breakdown with variable roles of decreased platelet production and splenic pooling appear to be the most important determinants. Regarding the functional change, there is a decreased aggregability attributable to defective (trans-membrane and intracellular) signaling, a storage pool defect and an up regulation of the inhibitory pathways.³

While child score was originally designed for assessing the prognosis of cirrhotic patients undergoing surgical treatment of portal hypertension, MELD score was designed for assessing the prognosis of cirrhotic patients undergoing transjugular porto-systemic intrahepatic shunt (TIPS).⁴ Four variables namely bilirubin, creatinine, INR had an independent impact on survival, were included in determining the MELD score. To lessen the influence of extreme values, the natural logarithm of bilirubin, INR and creatinine were entered into the model. In the original series, the resulting score was slightly more accurate than child-pugh score for predicting survival after TIPS. MELD score has been adopted since 2002 for organ allocation to patients listed for liver transplantation.⁵

Alteration in the hematological indices is a telltale sign of chronicity of alcoholic liver disease. Efforts can be made to normalize the hematological parameters so that, the morbidity and mortality in these patients could be effectively reduced. This could also extend help in increasing the longevity in transplant awaiting patients. We, through our study, have made an attempt to group the patients with deranged hematological indices using MELD score and analyzed the variation of these indices in accordance. This could have clear therapeutic implications in managing these patients and reducing the adverse events.

METHODS

This was a prospective observational study in which spectrum of various hematological indices and complications of alcoholic liver disease were observed in 88 patients from 2013-14 who were admitted in department of general medicine, PGIMS, Rohtak. Written informed consent was obtained from all the patients included in the study. The study was approved by ethical committee of university of health sciences.

Inclusion criteria

1) Male patients within age group 18 and 75 years.
2) Patients of alcoholic liver cirrhosis with stigmata of chronic liver cell failure on clinical examination substantiated by any of the following: histopathological evidence and imaging.

Exclusion criteria

1) Patients with age <18 and >75 years.
2) Patients with chronic liver disease due to causes other than alcohol as etiology.

After due consideration into inclusion and exclusion criteria, detailed history and clinical examination was undertaken in all subjects. History regarding any previous/concomitant illness and intake of drugs (prescriptional as well as recreational) history were recorded if deemed relevant. They underwent routine laboratory investigations including baseline radiographic and biochemical evaluation.

Following this, each patient was assessed for the complications of alcoholic liver disease as proved on the basis of history, radiographic and biochemical investigations.

In the present study, anemia was defined with a value of hemoglobin <13 g/dl, leukocytosis with a value >11,000/mm³, leukopenia <4000/mm³ and thrombocytopenia with a value <150×10⁹/µl and increased prothrombin time as value >5 seconds of the control.

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. Group 1 constituted patients with scores of 1-9, group 2 consisted patients with scores of 10-19, group 3 with scores of 20-29, group 4 with scores of 30-39 and group 5 with scores >40 and above.

Hematological parameters including anemia, leukocyte count and platelet count were assessed in the subjects and were categorized under the different groups of MELD score. The relationship of these variables with MELD score was studied and statistical analysis was done.

**Statistical analysis**

Chi-square test and Independent t tests were employed for statistical analysis using SPSS for windows version 20. A p value of <0.05 was considered significant. The continuous data were given as mean value±standard deviation.

**RESULTS**

Among the 88 male study subjects, the mean hemoglobin of the study population was 9.4±2.9 g/dl. Mean hemoglobin in different groups of MELD score were as follows; 13.4±0.5 g/dl in group 1, 11.6±1.7 g/dl in group 2, 7.9±1.9 g/dl in group 3, 7.5±2.3 g/dl in group 4 and 5.4±1.4 g/dl in group 5. There was no anemia in patients who had MELD scores of 1-9 and 25 (73.5%) patients had anemia in MELD score group 2. All the patients who had MELD scores ≥20 had anemia. The pattern of hemoglobin variation is shown in Figure 1. The relationship between the MELD score group and the hemoglobin was statistically significant with p value of <0.01.

Median leukocyte count of the population was 7500 cells per mm$^3$. Median leukocyte count in different groups of MELD score is as follows; in group 1 it was 7700 cells/mm$^3$, in group 2 it was 7950 cells/mm$^3$, in group 3 it was 11500 cells/mm$^3$, in group 4 it was 3550 cells/mm$^3$ and in group 5 it was 2400 cells/mm$^3$. All the patients in group 1 had normal leukocyte count. Among 34 patients in group 2, 11 (32.3%) patients had leukocytosis and 1 (2.9%) patient had leukopenia. Among 27 group 3 patients, 14 (51.9%) patients had leukocytosis and 2 (7.4%) patients had leukopenia. In group 4, only 2 (11.1%) of 18 patients had increased leukocyte count but 13 (72.2%) patients had leukopenia. All the patients who constituted group 5 had leukopenia (Figure 2).

Median platelet count among the study subjects was 150×103/µl. Median platelet count in the individual MELD score groups was as follows; in group 1 it was 380×103/µl, in group 2 it was 315×103/µl, in group 3 it was 130×103/µl, in group 4 it was 105×103/µl and in group 5 it was 100×103/µl. Among 88 study subjects, 43 had thrombocytopenia. MELD score group 1 and 2 patients did not have thrombocytopenia. Of 27 patients in group 3, 20 (74.1%) patients had thrombocytopenia. All the patients in group 4 and 5 had thrombocytopenia (Figure 3). The variation of thrombocytopenia among different groups was statistically significant with p value of <0.01.

**Figure 1: Line graph showing relationship between hemoglobin and MELD score group.**

**Figure 2: Line graph shows variation of leukocyte count in patients in different MELD score group.**

**Figure 3: Line graph shows variation of thrombocytopenia in study subjects in different MELD score classes.**

Mean prothrombin time in different MELD score groups was; 12.8±1.1 seconds in group 1, 19.4±4.1 seconds in group 2, 27.1±8.3 seconds in group 3, 38.9±11.5 seconds in group 4 and 56.3±17.8 seconds in group 5. Mean INR in different MELD score groups was; 0.9±0.1 in group 1, 1.6±0.4 in group 2, 2.4±0.9 in group 3, 3.7±1.3 in group 4 and 5.8±2.2 in group 5. As INR is an independent variable determining MELD score, the statistical analysis
to study its association with the MELD score was not done.

**DISCUSSION**

Abnormalities in hematological parameters are common in patients with alcoholic liver cirrhosis. The pathogenesis of abnormal hematological indices (HIs) 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 blood cell lines. Indirectly, it affects the nutritional biology of the patient resulting in production of functionally immature cells. Alcohol causes nutritional abnormalities in HIs leading to fatal complications, increasing the mortality rate in these patients. Abnormalities in HIs are associated with an increased risk of complications including bleeding and infection.

In our study, we observed a progressive fall in hemoglobin levels in par with the increase in MELD score. Hemoglobin, an iron-containing substance present in RBCs, is essential for oxygen transport. In patients with alcoholic liver disease, the iron is not incorporated properly into the hemoglobin molecules. Instead, it is converted into a storage form called ferritin, which can accumulate in RBC precursors, forming granules encircling the nucleus causing functional immaturity.

Blood cell precursors require folic acid and other B vitamins for their continued production. Under conditions of folic acid deficiency, precursor cells cannot divide properly due to defective DNA synthesis and large immature nonfunctional cells (i.e. megaloblasts) accumulate in the bone marrow as well as in the bloodstream. In our study, about 14.7% of the patients had red blood cell indices and peripheral blood smear study pointing towards the megaloblastosis confirmed by the measurement of folic acid and vitamin B12 level measurement. Rest 52% of the patients had normocytic normochromic anemia, the most common type of anemia in alcoholic liver cirrhosis, which could be attributed to the nutritional deprivement in alcoholics.

Portal hypertension gastropathy, a common complication of alcoholic liver cirrhosis, may be associated with slow chronic loss of blood into the gut and development of chronic iron deficiency anemia. About 33.3% of the total patients in the study had red blood cell indices and peripheral film picture showing evident iron deficiency anemia.

The presence of anemia was first noted in MELD group 2 and all the patients in the group 3-5 had anemia. In patients who have MELD scores that represent MELD group ≥2, an expeditious management of anemia should be undertaken. Investigations including upper gastrointestinal endoscopy should be undertaken by the treating physicians to look for the presence of 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. Alcoholic hepatitis can occur in patients with chronic alcoholic liver disease and alcoholic cirrhosis. Some alcoholics develop acute hepatitis as an inflammatory reaction to the cells affected by fatty change. This is not directly related to the dose of alcohol. This is called alcoholic steatonecrosis and the inflammation probably predisposes to liver fibrosis. Here, the neutrophilic invasion is triggered by the necrotic changes and presence of cellular debris within the lobules. In addition, the superadded infections in any stage of the alcoholic liver disease spectra can lead to the leukocytosis.

Alcohol interferes with the normal production and function of WBC’s, which form the body’s defense against microorganisms and other foreign substances. Because alcohols 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 impairs the function of monocytes and macrophages, which attack bacteria and other microorganisms, and of lymphocytes, which mediate the immune response. The observed neutropenia may be related to impaired neutrophil development in the bone marrow. Thus, bone marrow analysis of alcoholic patients during the neutropenic stage demonstrated that virtually none of the neutrophil precursors had matured beyond an early developmental stage. Moreover, the neutrophil stores that are maintained in the bone marrow to allow a quick response to a bacterial infection were depleted more rapidly in active alcoholics than in healthy control subjects. Alcohol interferes with the function of the monocyte-macrophage system, with clinically significant consequences. For example, compared with healthy people, alcoholics are less resistant to infections by microorganisms that normally are eradicated by monocytes and macrophages, such as the bacteria that cause tuberculosis and various forms of pneumonia.

In the present study, leukocytosis predominated in MELD group 2 and 3 patients. It gradually settled down to nil in higher groups. The possible underlying mechanism could be the defense mechanisms in the body including various cytokines, interleukins and defensins 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. Most patients in group 4 and all the patients of group 5 have leukopenia. In the higher groups of the MELD score, the bone marrow suppressive effect of alcohol as well as
immaturity of these cells could be responsible for the manifestation of leukopenia.

Lowered platelet counts can be the result of decreased platelet production, enhanced splenic sequestration or platelet consumption. Kinetic studies with radiolabelled platelets in cirrhosis and chronic liver disease indicate that there is a decreased platelet survival. Depending on the ability of the bone marrow to increase platelet production, platelet counts can be reduced or normal depending on the ability of the bone marrow to increase the platelet production. The main site of platelet consumption is in the spleen. As the liver is the major site of thrombopoietin (TPO) production, it is reasonable to expect its decreased plasma level in cirrhosis. Indeed, TPO mRNA levels in the liver are slightly decreased in cirrhosis. Liver transplantation is known to resolve thrombocytopenia due to an increase in serum TPO and increased platelet production. As splenomegaly is an important feature of portal hypertension, it is not surprising that splenic platelet sequestration is thought to be an important mechanism in the etiology of thrombocytopenia. Kinetic radiolabelled platelet studies do suggest splenic pooling, but they also report shorter platelet survival time, indicative of splenic destruction rather than mere splenic pooling. In chronic liver disease, platelet-associated IgG's are markedly elevated as well as the number of B cells producing antibodies against the major auto-antigen of platelets, GPIIb/IIIa. Others found an increased fibrinogen and plasminogen turnover suggesting platelet consumption. Soluble P-selectin levels, a marker of in vivo platelet activation, are increased in chronic liver disease.

In our study, we noted the occurrence of thrombocytopenia started in MELD group 3 patients involving all the patients of groups 4 and 5. The likely explanation for this is that, the splenic sequestration of the platelets starts only after features of portal hypertension are well established. Other proposed mechanism for this is, platelets are more resistant to the splenic hyperactivity than RBCs. This would retain the quantitative and qualitative activity of the thrombocytes till the higher stages of MELD group.

Blood clotting, or coagulation, an important physiological process that ensures the integrity of the vascular system, involves the platelets, or thrombocytes as well as several proteins dissolved in the plasma. When a blood vessel is injured, platelets are attracted to the site of the injury, where they aggregate to form a temporary plug. The liver secretes several proteins (i.e., clotting factors) that together with other proteins either secreted by surrounding tissue cells or present in the blood-initiate a chain of events that result in the formation of fibrin. Fibrin is a stringy protein that forms a tight mesh in the injured vessel; blood cells become trapped in this mesh, thereby plugging the wound. Fibrin clots, in turn, can be dissolved by a process that helps prevent the development of thrombosis (i.e., fibrinolysis).

Alcohol can interfere with these processes at several levels. Hepatic injury caused by alcohol could cause diminished synthesis of the clotting factors. Prothrombin time represents the activity of extrinsic pathway of coagulation assessing the activity of coagulation factors I (fibrinogen), II (prothrombin), V, VII and IX. In the study, as the INR formed an independent variable of the MELD score, its individual association with the scoring was not analyzed.

Pancytopenia associated with alcoholic liver disease is characterized by hypo cellular bone marrow in relation to the occurrence of hepatitis. The main feature of this syndrome is injury to or loss of pluripotent hematopoietic stem cells, in the absence of infiltrative disease of the bone marrow. The incidence of pancytopenia in the study is evident at group 4 and 5 of 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.

From the literature there are few studies classifying MELD score into different groups to study the mortality in end stage liver disease patients. For the first time, we have used this grouping approach in defining the hematological parameters in this category of patients. The results obtained from the study have clear implications regarding prediction of what hematological spectrum does an individual patient has when he falls into particular group of MELD score. This speculation could persuade the treating physicians to take steps in correcting these hematological indices so that, further progression of the disease could be delayed or nullified. Although MELD score has been used in the previous studies for therapeutic purposes and mortality prediction, this novel idea gives an edge to MELD score as its importance could also be utilized in the prevention of the disease.

**Limitations**

Although the results of this prospective study had convincing explanations from the literature, there were some limitations. 1) The cause of anemia in individual patients has not been extensively studied which could make a difference in the specific treatment approach. 2) The differential components of leucocyte count have not been compared with the progression of the MELD score. 3) Only patients with alcoholic liver disease have been considered in the present study. Studies are needed to apply this approach in patients having end stage liver disease due to other causes. 4) As this is the first study assessing relation of the hematological spectrum with MELD score, only 88 patients have been studied. Further studies with more number of patients are needed to support the results of the study.
CONCLUSION

Numerous clinical observations support the notion that alcohol adversely affects the production and functioning of virtually all types of blood cells. Long-term excessive alcohol consumption leads to liver cirrhosis which interferes with various physiological, biochemical, and metabolic processes involving the blood cell production and maturation. The medical consequences of these adverse effects can be severe which include anemia, an increased risk of serious bacterial infections and impaired blood clotting and fibrinolysis.

In this study, patients with end stage liver disease secondary to alcohol consumption were divided into various MELD score groups. Various hematological parameters and complications associated with the disease were studied in these different classes. The statistically significant association between the variables and the groups shows that MELD score grouping system could be an important tool in the assessment of these patients. This association strongly depicts that the clinicians could effectively apply the classification in predicting the hematological complications in these patients and vigorously takes precautions in preventing the further progression of the disease thus decreasing the mortality in these patients. To the best of our knowledge, this is the first study categorizing the MELD score into different groups and utilizing it for studying the hematological spectra and alcohol related complications in patients with alcoholic liver disease.

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REFERENCES


