“CORERELATION BETWEEN HEMATOLOGICAL ABNORMALITIES AND MELD SCORE IN PATIENTS WITH CIRRHOSIS OF LIVER”

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ABBREVIATIONS

PT - PROTHROMBIN TIME

INR - INTERNATIONAL NORMALISED RATIO

MELD - MODEL FOR END STAGE LIVER DISEASE

CTP – CHILD PUGH SCORE

HB – HEMOGLOBIN

CLD – CHRONIC LIVER DISEASE

HE- HEPATIC ENCEPHALOPATHY

SBP- SPONTANEOUS BACTERIAL PERITONITIS

TLC – TOTAL LEUCOCYTE COUNT

ABSTRACT

INTRODUCTION: Abnormal values of various haematological indices are commonly observed in cirrhosis of liver. Multiple factors contribute to this observation. According to a number of studies, cirrhosis has a bad prognosis when haematological cytopenias are present.

AIMS & OBJECTIVES: To assess the correlation between haematological abnormalities and MELD score in patients with cirrhosis of liver.

MATERIALS AND METHODS: This is a Cross-sectional observational study. Data will be collected from patients with CIRRHOSIS OF LIVER who are admitted in B.L.D.E. (D.U.)'s Shri B.M. Patil Medical College Hospital & Research Centre, Vijayapura. The period of study is from January 2021 to June 2022.

RESULTS: we conducted the study on 60 patients with chronic liver disease to examine the haematological anomalies. 58(98%) patients had anaemia. Most patients had Macrocytic anaemia. Next normocytic normochromic anaemia was common after that. 24 patients had thrombocytopenia. 37 patients had increased INR and PT. In comparison to individuals without anaemia, those with anaemia had MELD scores that were higher than 15%. Patients with a MELD score greater than 20% had mean platelets 1.5 lakh/dL higher than those with a lower score.

CONCLUSION: we can conclude that there is significant correlation between Hb and PT with MELD score. Deranged haematological indices contribute to the worse prognosis of the patient. Hence the need to correct them to improve morbidity and mortality among cirrhosis patients.

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INTRODUCTION

Blood homeostasis is majorly maintained by the liver. It is the primary haematopoiesis site in foetus and maintains haematological parameters after birth. Liver secretes clotting factors and inhibitors and stores iron, folic acid, and vitamin B12. The liver parenchyma is damaged in cirrhosis of the liver. A variety of haematological disorders result from the loss of liver function. Haematological abnormalities in many chronic diseases like chronic kidney disease increase morbidity and mortality.[1]

According to some research, thrombocytopenia could act as a non-invasive indicator of oesophageal varices. The risk of infection could be increased by leukopenia. Any hemorrhagic episode's prognosis is made more unsatisfactory by chronic anaemia .[2]

Hepatic decompensation and death are at an increased risk due to anaemia, which is a substantial risk factor. Increased splenic sequestration brought on by portal hypertension, altered bone marrow stimulating factors, and suppression of bone marrow suppression by various toxins, alcohol, hepatitis B, and C are all factors leading deranged haematological parameters in cirrhotics .[3]

The three-month mortality of cirrhosis patients is determined by the MELD score. The MELD score is used to allocate organs to patients posted for liver transplantation. The calculation of the MELD score considers creatinine, bilirubin, and INR.

Numerous studies have shown that lower haemoglobin (Hb) levels are linked to worse prognosis and higher MELD scores. A change in the haematological indicators indicates that the liver illness is chronic.

In order to decrease mortality and morbidity and increase longevity in transplant-awaiting patients, efforts should be made to normalise the haematological indices .[4]

To reduce comorbidity in patients when treated early, it is necessary to determine if haematological and haemostatic abnormalities in liver disease can be associated to the standard prognostic ratings of cirrhosis.

REVIEW OF LITERATURE

CLD is among the major cause of increased deaths across the globe. It also decreases the quality of life. Mortality rate worldwide increased by 46% between 1980 to 2013 due to CLD. This indicates the public health importance of CLD.[5] One of the frequent aetiologies is alcohol. Alcohol liver disease is the leading cause of death about 2.5 million/yr. The pathology of cirrhosis include increased fibrosis, distortion of architecture and emergence of regenerative nodules. In decompensated cirrhosis of liver, the 5-year survival rate ranges from 14 to 35 percent while in compensated cirrhosis it is 84 percent.[6]

Cirrhosis of liver:

Cirrhosis is Defined as "anatomically as a diffuse process with fibrosis and nodule formation."

It is final stage of progressive hepatic fibrosis with hepatic architecture distortion followed by the development of regenerative nodules. It is irreversible in its late stages, when liver transplantation may be the only option left. Following the therapy of the underlying cause, cirrhosis has been reversed if it is in its early stages. Patients with cirrhosis develop several problems and have shorter life expectancies.

Incidence:

According to autopsy studies prevalence of cirrhosis ranges from 4.5% to 9.5% of the world population. According to estimates cirrhosis claimed lives of 771,000 people globally in 2001, ranking 14th and 10th as the leading cause of mortality globally and developed countries, respectively.[7] Cirrhosis-related deaths are estimated to rise, making it the 12th leading cause of death by 2020.[8] According to estimates from the World Health Organization's Global Health Observatory, cirrhosis leads to 22.2 deaths for 1lakh people in India.[9]

Etiologies

Cirrhosis can be caused by a variety of liver diseases, including chronic hepatic inflammation and cholestasis. Hepatitis C, alcoholic liver disease and non-alcoholic fatty liver disease are the major frequent causes of cirrhosis in United states. They accounted for approximately 80% of patients waiting for liver transplantation between 2004 and 2013.[10]

In developed countries, common causes are[11];

- Hepatitis B infection
- Hepatitis C infection
- Alcoholic liver disease
- Haemochromatosis
- NAFLD

other frequent causes of the cirrhosis are

- Wilson disease
- Celiac disease
- Sclerosing cholangitis
- Alpha-1 antitrypsin deficiency
- Autoimmune hepatitis
- Granulomatous liver disease
- Biliary cirrhosis
- Medication like methotrexate and isoniazid
- Right sided heart failure
- Polycystic portal fibrosis

- Veno-occlusion disease
- Hereditary haemorrhagic telangiectasia

Classification

Cirrhosis is either micronodular, macronodular, or mixed.[12] Alcohol, hemochromatosis, cholestasis and obstruction of hepatic venous outflow were thought to cause micronodular cirrhosis, with nodules lesser than 3 mm in diameter. Macronodular cirrhosis, described by nodules lesser than 3 mm in size, is caused by chronic viral hepatitis.

Pathogenesis

The hallmark pathological characteristic is chronic severe hepatocyte damage accompanied by extensive fibrosis with nodule formation of normal liver tissue. This is primarily due to hepatocyte necrosis, reticular network degradation, and nodule regeneration of healthy liver tissue. The pathogenesis is common for all the aetiologies of cirrhosis of liver.

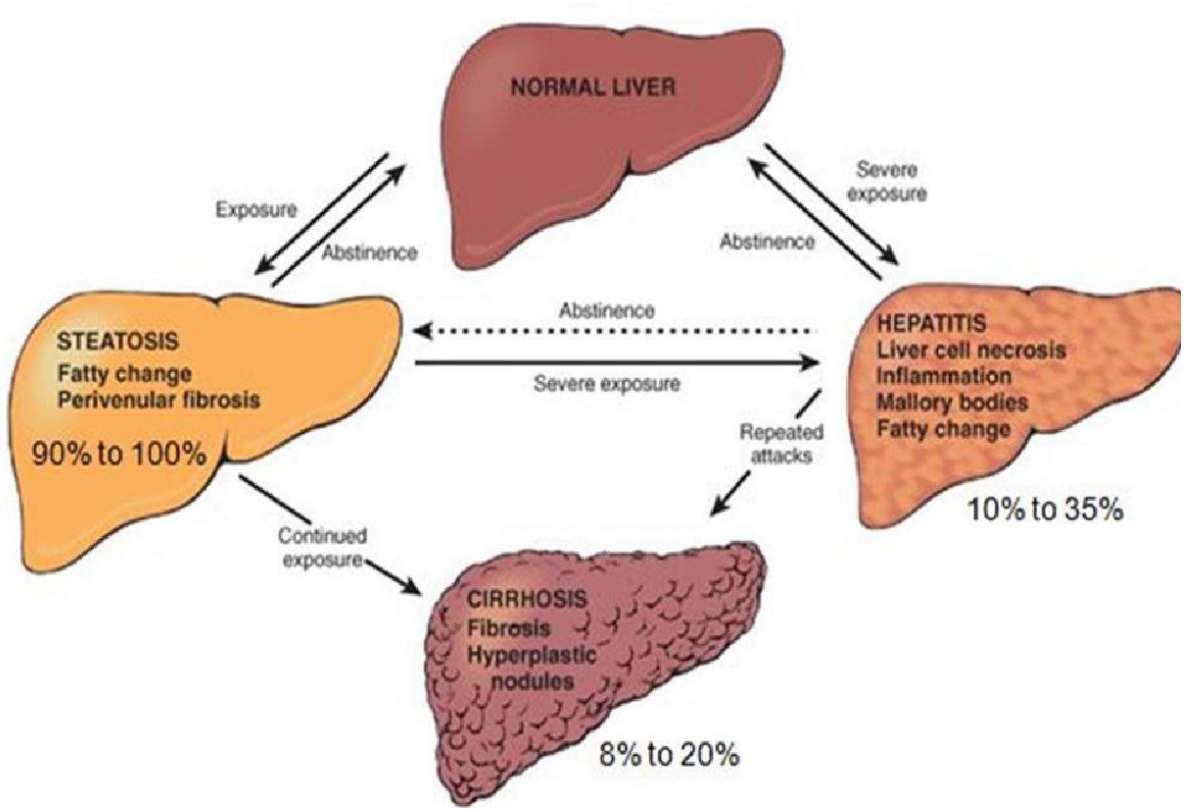


Figure 1: Hepatic repair and regeneration

Collagen and other extracellular matrix components are produced in greater amounts as a result of the activation of hepatic stellate cells to myofibroblasts, leading to architectural distortion, decreased function, and bulk.

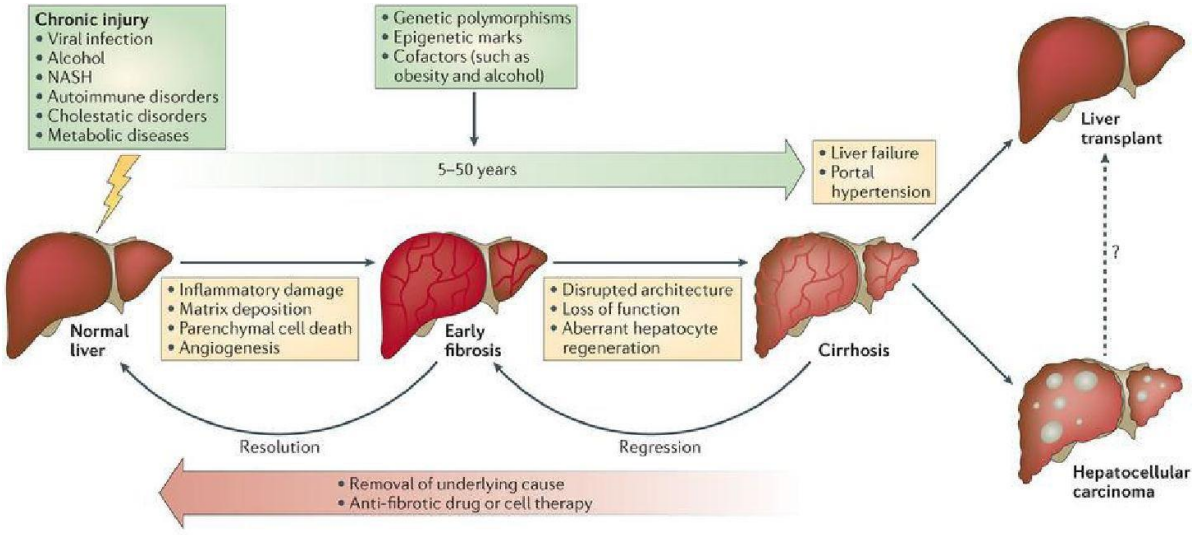


Figure 2: Pathogenesis of hepatic cirrhosis

Clinical features

The common clinical features of cirrhosis are anorexia, weight loss fatigue or signs and symptoms of decompensation of liver function.

Cirrhotic patients can also show a many different signs and symptoms, indicating the liver's vital role in the homeostasis of a variety of body functions. Additionally, they may have chrachteristics as a result of the aetiology of cirrhosis, (cryoglobulinemia from hepatitis C, diabetes mellitus or extrahepatic autoimmune disorders).

ARTERIAL SPIDERS

PALMAR ERYTHEMA

LEUCONYCHIA

CLUBBING

DUPUYTRENS CONTRACTURE

SARCOPENIA

FOETOR HEPATICUS

HYPOGONADISM

GYNECOMASTIA IN MALES

HEPATOMEGALY

SPLEENOMEGALY

PAROTID GLAND ENLARGEMENT

LOSS OF AXILLARY AND CHEST HAIR IN MEN

JAUNDICE

CAPUT MEDUSA

ACITES

ASTEREXIS

TERRY AND MUEHRCKE NAILS

Jaundice is a yellow discoloration of the skin and mucous membranes caused by an increase in bilirubin levels in the serum. It is visible when the bilirubin level exceeds 2 mg/dL. Cola colored urine is seen due to increased bilirubin levels.

Spider angiomas are vascular lesions that has a central arteriole surrounded by several feeding arterioles. They are common on the chest and back, ears, and upper limbs. When the central arteriole pulsated when squeezed with a glass slide. After blanching, blood flows to the central arteriole first, then to the peripheral tips of each neck. The erythema that surrounds the lesion typically has numerous radiating legs and may cover the entire lesion or just its centre.

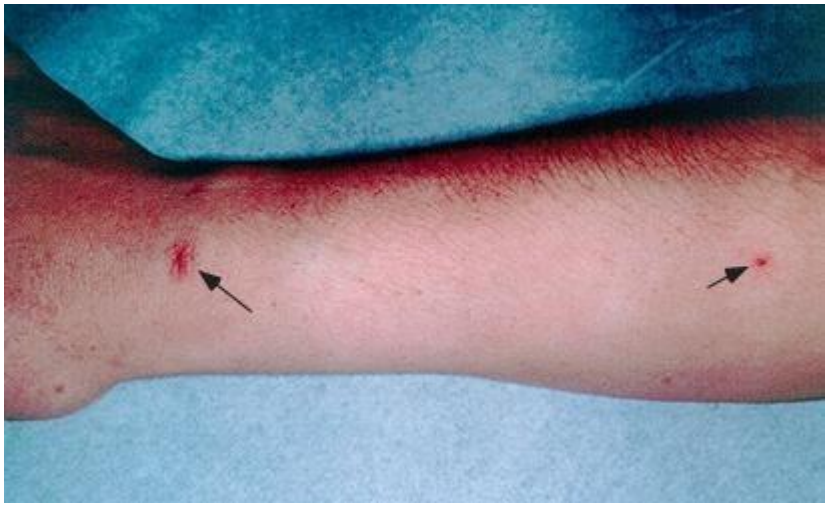


Figure 3: Showing the spider angiomas on arms

Enlarged Parotid gland is common in alcoholic liver disease patients, It is caused by alcohol rather than cirrhosis. It is due to infiltration of fat, edema and fibrosis. Cirrhotic patients' breath has a sweet, pungent smell called fetor hepaticus. High levels of dimethyl sulphide, which are a sign of severe portal-systemic shunting, are the cause.[14]

On chest, gynecomastia is seen in up to two-thirds of cirrhotic patients. It might be brought on by increased androstenedione production in the adrenal glands, increased androstenedione aromatization to estrone, and increased estrone conversion to estradiol.[15] Men can also acquire traits linked to feminization, such as axillary or chest hair loss, as well as an inversion of the typical male pubic hair pattern.

Cirrhotic livers may be normal, increased or small in size.

The cirrhotic liver is firm and nodular in consistency when palpated. With dimensions of 21 to 23 centimetres in horizontal direction and 14 to 17 cm in vertical direction, the liver is the largest internal organ in an adult person. The size of liver varies depending on the body type, height, and gender.

Normally, the lower abdominal wall veins drain into the iliofemoral veins and the upper abdominal wall veins drain superiorly into axillary veins. The umbilical vein, which is often obliterated in childhood, can reopen when cirrhosis produces portal hypertension. In order to reach the umbilical vein and finally the abdominal wall veins, blood from the portal venous system may be shunted through the periumbilical veins. This aspect has been compared with that of the head of the Gorgon Medusa (caput). Hence the name caput medusae.

Dupuytren's contracture is caused by the palmar fascia thickening and shortening, resulting in flexion contracture of digits (picture 3). It is due to excessive production of fibroblasts and deposition of collagen disorderly with thickening of fascia. The pathogenesis could be due to free radical formation secondary to oxidative metabolism of hypoxanthine.[16]

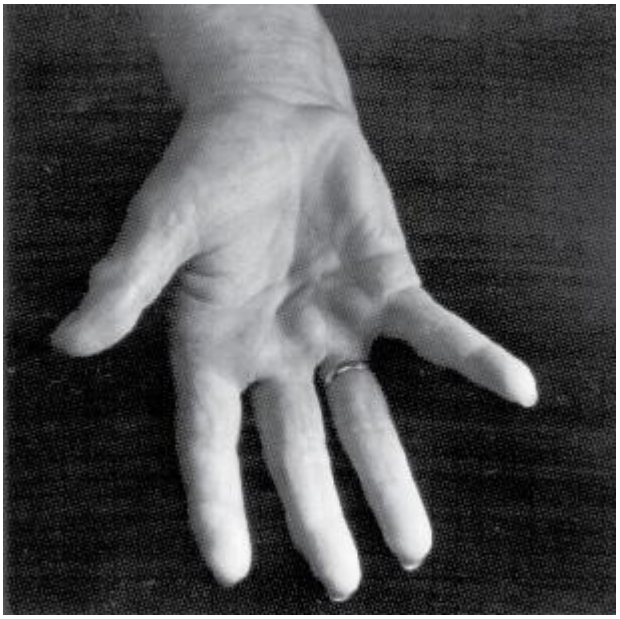


Figure 4: Features of Dupuytren's contracture

Major complications

The common complications of the cirrhosis includes the

- Ascites
- Variceal Bleed
- Hepatic encephalopathy
- Hepato-cellular carcinoma
- Hepato-renal syndrome
- Hepato-pulmonary syndrome
- Hepatic hydrothorax
- Porto-pulmonary hypertension
- Cirrhotic cardiomyopathy
- Thrombosis of the portal vein

- Spontaneous bacterial peritonitis (SBP)

Patients suffering with decompensated cirrhosis are those that experience these complications. Multiple factors can predispose a cirrhotic patient to decompensation. Bleeding, inflammation, alcohol use, medicines, dehydration, and constipation are all risk factors for decompensation.[17–19] Furthermore, patients who are obese are at a greater risk of decompensation.[20] Patients that have developed decompensation should be considered for liver transplantation.

Many complications of cirrhosis are due portal hypertension. Portal Hypertension is increased pressure in the porto caval system. When the portal circulation is obstructed, collateral circulation develops to carry the portal blood into the systemic veins The major sites of porto-systemic or porto-caval shunts are lower part of esophagus, umbilicus, rectum .

Complications of portal hypertension:

- Hepatic encephalopathy
- Ascites
- Spontaneous bacterial peritonitis
- Variceal hemorrhage
- Hepatorenal syndrome
- Portal hypertensive gastropathy
- Hepatopulmonary syndrome
- Portopulmonary hypertension
- Cirrhotic cardiomyopathy
- Hepatic hydrothorax

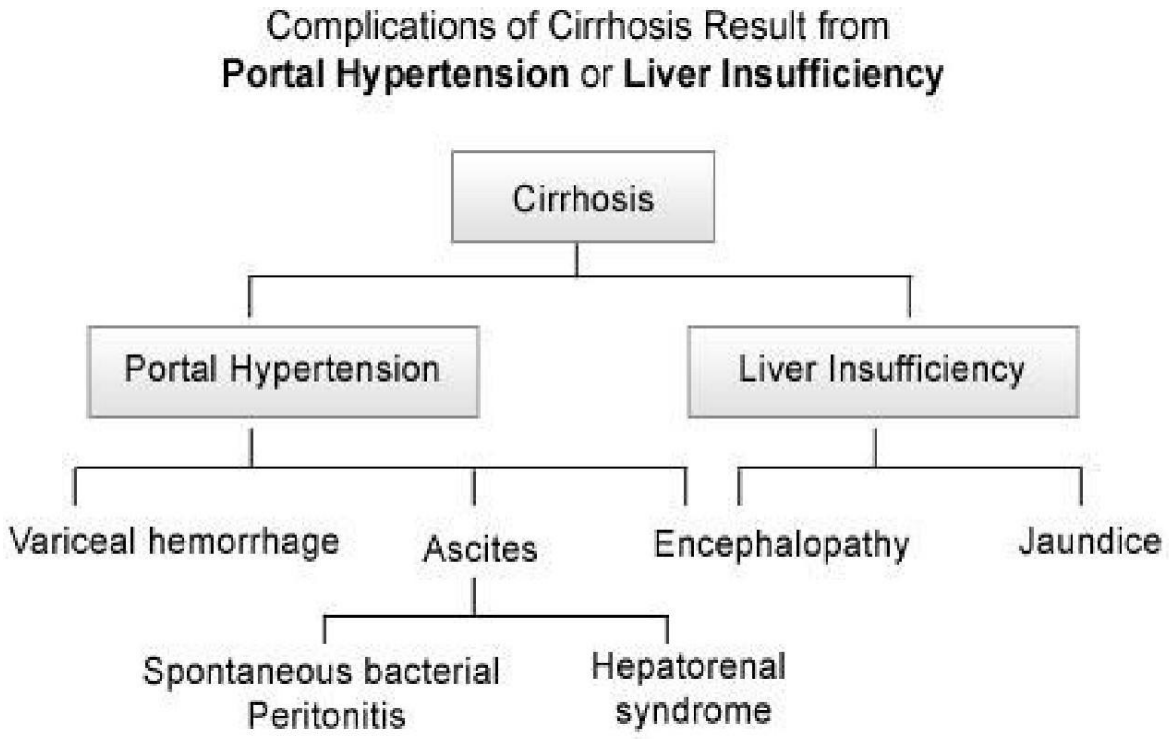


Figure 5: Complications of cirrhosis

Ascites and variceal haemorrhage are effects of the portal hypertension. The portal hypertension is due to either pre-hepatic, post-hepatic, and intra-hepatic cause.

Portal hypertension affects about 60% of cirrhotic patients.

Portal hypertension leads to ascites, bleeding varices, splenomegaly, hypersplenism, and other consequences. Congestion brought on by elevated portal pressure results in splenomegaly. Hypersplenism with decreased platelet count could be the the initial sign of portal hypertension.

.

Pathogenesis:

Portal hypertension occurs as a result of increased intra-hepatic resistance and portal blood flow. Hepatic compliance decreases as hepatic resistance increases. Tiny variations in blood flow are caused by an increase in portal pressure. A healthy liver adapts to these variations.

In addition to vascular architecture distortion and remodelling that take place in the systemic and splanchnic vascular systems in response to the persistent increases in flow and shear stress that characterise the hyperdynamic circulatory state, mechanical factors also include cirrhotic fibrosis and liver nodularity.

The hyperdynamic circulation is distinguished by peripheral and splanchnic vasodilation, decreased mean arterial pressure, and increased cardiac output. Vasodilation, especially in the splanchnic bed, allows more systemic blood to enter the portal circulation. Splanchnic vasodilatation is primarily caused by splanchnic arteriole relaxation and the resulting

splanchnic hyperemia.

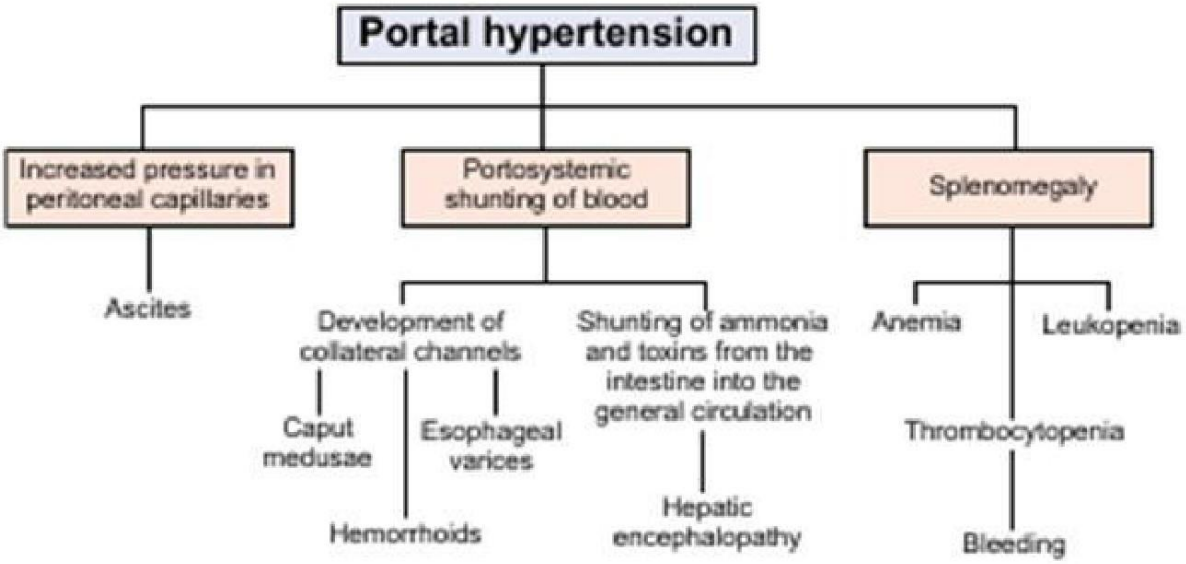


Figure 6: Portal Hypertension

Findings on laboratory tests:

Several abnormalities in the laboratory tests are seen in patients with cirrhosis. Sometimes laboratory abnormalities are the first thing that indicates that a patient has cirrhosis.

Table 1: Laboratory tests used in cirrhosis patients

Investigations
Increased aminotransferase levels (AST:ALT ratio >1)
Increased alkaline phosphatase
Elevated gamma-glutamyl transpeptidase
Thrombocytopenia
Leukopenia/neutropenia
Anaemia
Low serum albumin
Prolonged prothrombin time/elevated INR
Hyperbilirubinemia
Hyponatremia
Elevated serum creatinine

Liver function tests (LFT) :

They include serum aminotransferases, alkaline phosphatase and gamma glutamyl transpeptidase, serum bilirubin and serum albumin concentration and Prothrombin time.

Aminotransferases – both Aspartate aminotransferase (AST) and alanine aminotransferases (ALT) are usually increased in patients with cirrhosis. The AST is frequently increased more than the ALT. Most often chronic hepatitis other than the alcoholic liver disease have ratio of AST / ALT less than one. The ratio of AST to ALT will be inverted in chronic hepatitis patients that develop to cirrhosis. [21,22]

Alkaline phosphatase is normally increased in patients with cirrhosis. It is often less than twice or thrice the upper limit of normal value. Greater levels can be seen in patients with primary biliary cirrhosis or primary sclerosing cholangitis which cause cholestasis.

Gamma glutamyl transpeptidase (GGT): levels are non-specifically correlated with alkaline phosphatase in liver disease. GGT levels are normally significantly greater in alcoholic liver disease than in other aetiologies. This is attributed to hepatic microsomal GGT to leak[23] or GGT leak from hepatocytes secondary to alcohol[24].

Bilirubin – Bilirubin levels in well-compensated cirrhosis can be normal. They do, however, rise as the cirrhosis progresses. In patients with primary biliary cirrhosis, an increase in blood bilirubin indicates bad prognosis[24].

Prothrombin time (PT) – The liver produces most of the proteins involved in the coagulation process. As a result, the length of the prothrombin time indicates the severity of hepatic synthetic malfunction. As the cirrhotic liver's capacity to synthesize clotting factors decreases, PT rises. Therefore, the degree of hepatic dysfunction correlates with worsening coagulopathy.

Albumin is only produced in the liver. Serum albumin levels decrease as cirrhosis progresses and the liver's capacity for synthesis declines. Therefore, serum albumin levels can be utilised to categorise the severity of cirrhosis more accurately. In addition to liver illness, other medical diseases such as the nephrotic syndrome, heart failure, malnutrition and protein-losing enteropathy can also cause hypoalbuminemia.

The most frequent cause of thrombocytopenia is portal hypertension with congestive splenomegaly. A splenic enlargement may result in the temporary sequestration of up to 90% of the circulating platelet mass. However, platelet counts less than 50,000/mL are unusual, and unless complicated by coexisting coagulopathy, it is rarely a clinical concern.

Hematological disorders seen in Cirrhosis of liver

Cirrhosis of liver is associated with presence of hypersplenism and diminished RBC lifespan. The problem is made worse by dietary inadequacies, alcoholism, improper protein synthesis, bleeding, and coagulation disorders.

Patients with ascites secondary to cirrhosis have increased plasma volume. This may lead to low peripheral erythrocyte levels. The total haemoglobin will be reduced to half in the patients.

Anaemia in cirrhosis

- The following mechanism causes anaemia in people with cirrhosis:
- Haemodilution caused by increase in plasma volume

- Decreased lifespan of red cell due to hypersplenism
- Decreased erythropoietin concentration leads to decreased bone marrow response to anaemia.
- Bone marrow suppression secondary to Chronic inflammation and increased level of inflammatory cytokines.
- Bone marrow suppression due to the virus (hepatitis B and C) or alcohol consumption

67 patients with varying degrees of cirrhosis were evaluated by Yang et al.[25] They observed plasma erythropoietin levels in cirrhotic patients were substantially greater than in controls.

Additionally, they observed that those who were anaemic had higher amounts of erythropoietin. They found a positive correlation among erythropoietin and HVPG and a negative correlation among erythropoietin and hepatic blood flow.

According to Bruno et al.,[26] cirrhotic people with anaemia only had an increase in erythropoietin when their haemoglobin levels were lower than 12 mg/dL.

The authors hypothesized that the response of erythropoietin was muted in contrast to anaemia due to iron deficiency and others.

Granulocyte colony-stimulating factor and granulocyte macrophage colony-stimulating factor role in decreased leucocytes in cirrhotics is poorly understood.

They are produced by the immune cells to stimulate the development of the bone marrow and the circulation of stemcells and granulocytes in the blood.The development and operation of neutrophils also involve them.

According to Gurakar et al.,[27] seven days of GM-CSF therapy increased the WBC count in people with cirrhosis and leukopenia.

In addition, there was no rise in the percentage of leukocytes trapped within the spleen.

Cirrhosis frequently co-occurs with viral hepatitis B or C, binge drinking, drug use, and increased pancytopenia risk due to bone marrow suppression brought on by hypoplasia of the bone marrow. Patients with cirrhosis who take certain drugs, such as azathioprine, interferon and mycophenolate mofetil, run the risk of developing pancytopenia..[28]

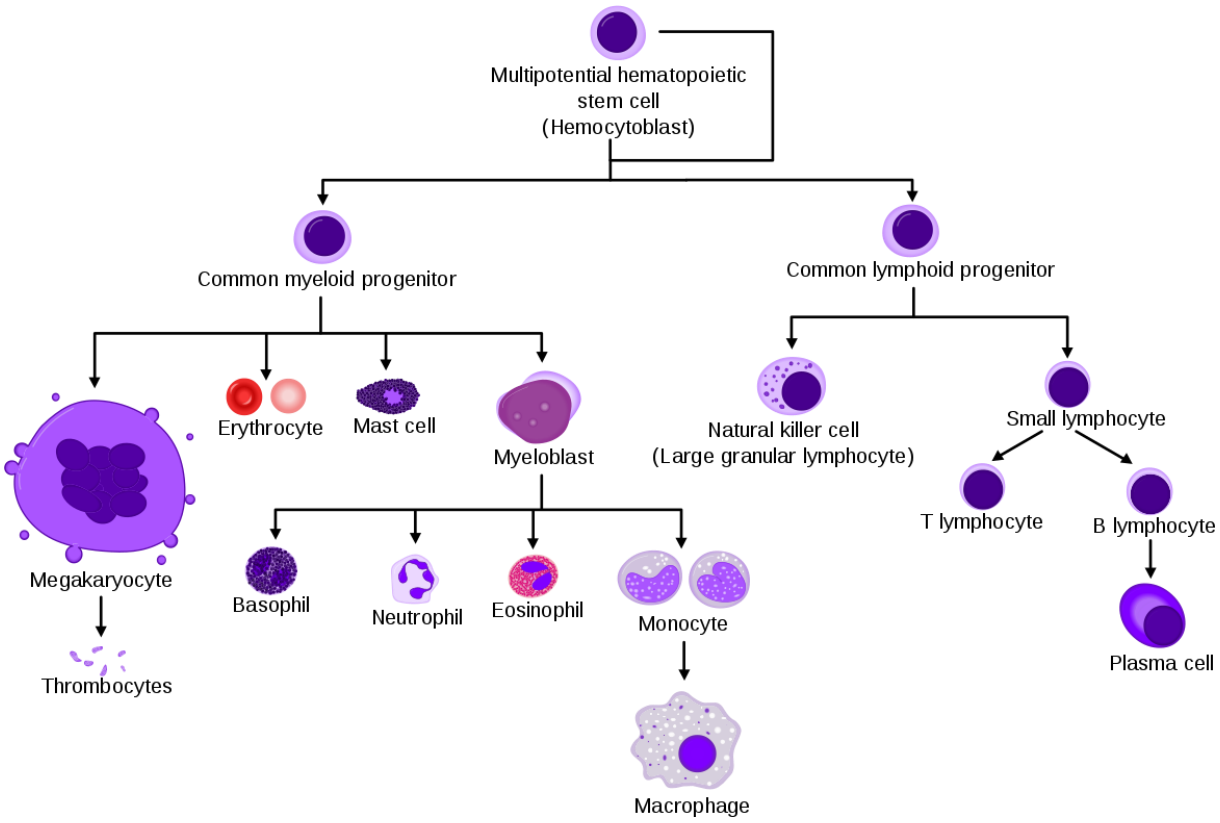


Figure 7: Stage of haematopoiesis

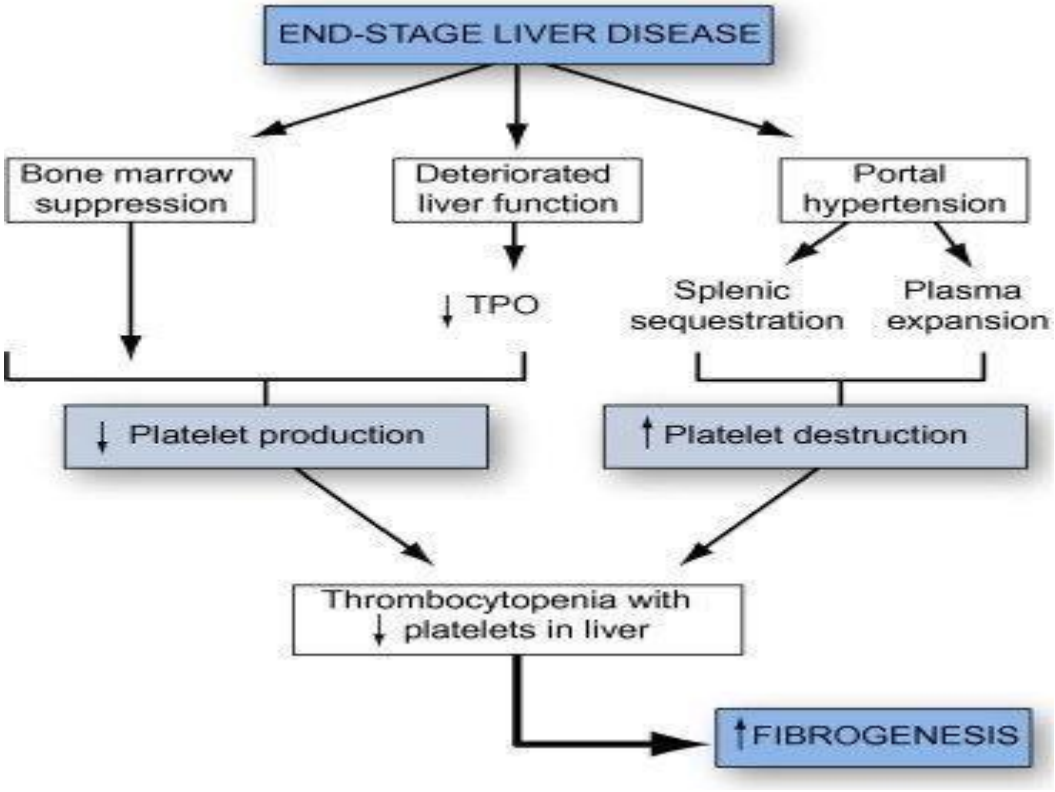
Normocytic erythrocytes are typical. This may be a combination of the macrocytosis seen in people with liver illness and the microcytosis brought on by ongoing blood loss. The cholesterol and phospholipid content and their ratio in the erythrocyte membrane change as a result, leading to morphological flaws including target cells and thin macrocytes. Spur cells include distinct, prickly projections. Acanthocytes are another name for them. They are related to severe liver disease, which most frequently affects alcoholics. Haemolysis and severe anaemia are also present. Their presence suggests a dismal outlook.

In uncomplicated cirrhosis, decreased or normal serum iron concentrations with decreased or normal total iron binding capacity are common. Alcohol has a toxic impact and lowers bone marrow in alcohol-induced liver disease, although also promotes iron absorption from the GI tract. Serum ferritin levels rise in response to hepatic inflammation and necrosis. The increase in MCV that occurs as a result of Chronic Liver Disease and alcohol use hides the deficit in iron levels. Serum iron binds to beta globulin transferrin, which is produced in the liver; overall iron binding capacity is heavily dependent on transferrin content. Iron shortage is indicated by a high total iron binding capacity. TIBC is frequently reduced in CLD patients due to decreased transferrin production. The levels of serum transferrin receptor are a more accurate laboratory indicator of iron insufficiency.

The liver converts folate to tetrahydrofolate which is its active form of storage.in alcoholic liver disease, Folate deficiency is common. This is mainly due to lack of nutrients in the diet. The level of folate in the blood is low. Folate treatment is beneficial. Vitamin B12 is also stored in the liver. In liver disease, hepatic levels are lowered. When hepatocytes die, vitamin B12 is released into the bloodstream, resulting in elevated serum B12 levels.

Thrombocytopenia in CLD patients is due to various reasons. They include hepatocellular cancer and chemotherapy, portal hypertension and the ensuing hypersplenism. Direct

myelosuppressive effects of HCV infection, bone marrow suppression, and decreased level of platelet growth factor activity.



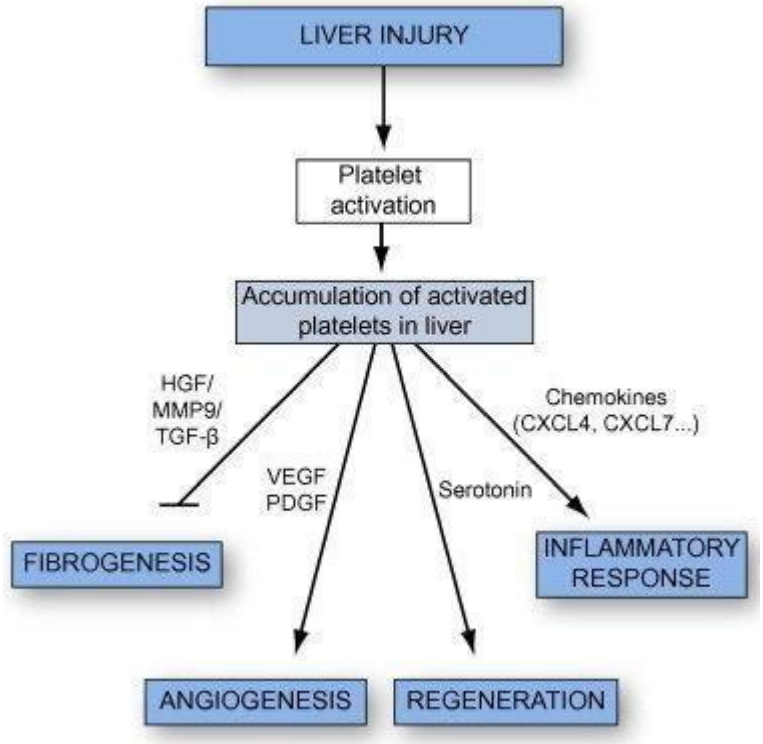


Figure 8: Thrombocytopenia in cirrhosis of liver

Impaired blood coagulation in hepatobiliary disease patients is a complicated procedure. This is because alterations in the pathways that lead to fibrin formation occur concurrently with alterations in the fibrinolytic process.

But there is no connection between inaccurate clotting tests and the chance of bleeding. More important than the severity of prothrombin time anomalies may be platelet quantity and function in determining the risk of bleeding during invasive procedures. Vitamin K-dependent factors, factor VIII, factors XI and XII, labile factor V fibrinogen and fibrin stabilizing factor are primarily produced in hepatocyte.

Clotting abnormalities, are frequent in individuals with decompensated cirrhosis and acute liver failure. Coagulopathy is frequently caused by liver injury and loss of liver synthetic activity, resulting in a decreased capacity to manufacture clotting factors (factors I, II, V, VII, IX, X,

XI, protein C, and antithrombin) and higher potential of bleeding. In haemostasis, Platelets have two roles.

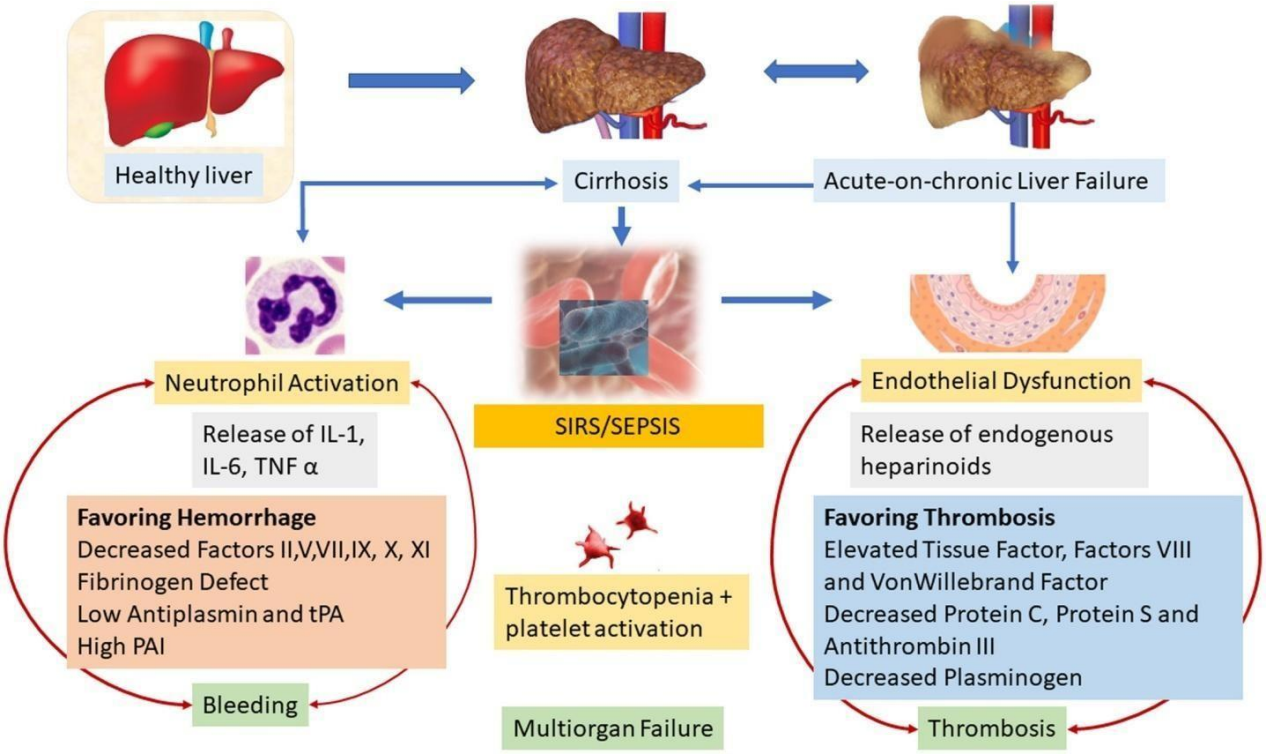


Figure 9: Dynamic coagulation profile changes in cirrhosis

During secondary haemostasis, platelets expose negatively charged phospholipids on their surface that serve as receptors for coagulation factors in plasma and promote thrombin production, formation of fibrin and stability of platelet plug.

Pancytopenia in alcoholic liver disease is due to hypersplenism, deficient B12 vitamin and bone marrow suppression. The damage or loss of hematopoietic stem cells is the primary defining feature of pancytopenia in the absence of primary suppression of bone marroe.

Various articles discussing haematological changes in cirrhosis of liver

According to a study on hemotalogical abnormalities done by Solomon R et al., in patients with chronic liver disease, the anaemia of diverse aetiology occurs in about 75% of patients with chronic liver disease. Only 12% of individuals with thrombocytopenia had a longer bleeding time, demonstrating that BT is an insensitive test of platelet quantity and function. In 72% of patients, the PT-INR was high. But only 25% of patients with a prolonged PT-INR had upper Gastrointestinal bleeding, suggesting that alternative mechanisms, such as a rebalanced haemostatic system, were at work. However, this needs to be confirmed with more thorough research. With regard to treating coagulopathy in cirrhotic patients, this observation emphasises the significance of focusing on the patient's clinical condition as opposed to lab results. [29]

An analysis of 213 patients followed for nine years by Qamar showed that 84% of them with Child-Pugh Class A and B cirrhosis had aberrant haematological indices.[28]

In a study conducted by ferlitsch et al., (2020) the prevalence of anaemia increased with Child-Pugh score (C.P.S.). Patients suffering with decompensated cirrhosis showed anemia of greater rates than compensated Cirrhosis. Individuals with compensated cirrhosis were more likely to have iron deficiency anaemia (I.D.A.) than non-Iron deficiency anaemia. Additionally, compared to patients without IDA, patients with I.D.A had considerably lower MELD ratings. Anemia was shown to be a significant risk factor in the development of hepatic decompensation and death in both the validation and derivation cohorts (aSHR: 1.65, P = 0.008), as well as an independent risk factor for hepatic decompensation and/or mortality in compensated patients (aHR: 4.91, P = 0.004). Cirrhosis is linked with a high rate of anaemia. IDA appears to be the most likely cause of anaemia in compensated cirrhosis, CPS A and B, and poor MELD. Furthermore, anaemia is linked to an increased chance of hepatic decompensation or death during long-term.[30]

In a retrospective cross-sectional study done by Yang et al., to assess the macrocytic anemia association with severity of liver disease in patients with decompensated Cirrhosis due to hepatitis B. MELD scores were greater in patients with macrocytic anaemia (10.8±6.6) than in those with normocytic anaemia (8.0±5.5) or microcytic anaemia (6.3±5.1). After controlling for age, gender, smoking, drinking, and total cholesterol, the link remained strong (β= 1.94, CI: 0.81–3.07, P<0.001). In individuals with decompensated cirrhosis due to HBV , macrocytic anaemia was observed to be correlated with the degree of liver damage and may be an indicator of increased mortality.[31]

Yoon et al., has done a study in which elevated MCV levels were correlated with more significant mortality in men. According to the findings, higher MCV levels in non-anemic cancer-free persons were linked to increased all-cause mortality in both men and women, as well as cancer mortality, namely liver cancer mortality in males. Prospective investigations are needed in the future to confirm our findings. [32]

According to a study done by Scheiner B et al., higher MELD score is seen in anemic patients, and the severity of anemia increased with the MELD score. Found that Anemia affects two-thirds of ACLD patients. The severity of anaemia is related to the degree of hepatic dysfunction and portal hypertension. Anaemia is linked to decompensation, ACLF, and higher mortality in ACLD patients.[33]

Jain D et al., studied alcoholic liver cirrhosis in 88 patients where they found that anemia and leucopenia were frequent in group with high MELD score . Study noticed a steady decrease in haemoglobin levels as the MELD score increased. Group 1 patients all had normal leukocyte counts. In MELD groups 2 and 3, leukocytosis predominated. Leukopenia was more common in group 4. Group 5 patients all exhibited leukopenia. Patients in Groups 1 and 2 did not experience decreased platelet count. It first appeared in group 3 patients and then spread to

group 4 and group 5. This significant statistical relationship among the groups and the factors suggests that the grouping method by using MELD score could be a useful aid in assessing the cirrhotic patients. [34]

According to a study done by Jha S et al., in north Bihar, anemia that is normocytic normochromic is frequently seen. Iron deficiency results due to Blood loss from varices, gastric antral vascular ectasia, portal hypertensive gastropathy. Chronic inflammatory state can also result in iron deficiency anemia. Normocytic, Normo-chromic Anaemia, Macrocytic primarily in alcoholics, leucocytosis was more common than leukopenia and thrombocytopenia, increased prothrombin time and APTT were among the haematological abnormalities reported. Every chronic liver disease patient should be screened for haematological abnormalities and treated as soon as feasible. The picture is of microcytic hypochromic anemia. Macrocytosis is also one of the common abnormalities seen in Cirrhosis.[35]

Efforts can be made to normalize the haematological indices to reduce mortality and morbidity and extend help in increasing the longevity in transplant waiting patients.

AIMS & OBJECTIVES

Aim:

To assess the correlation between hematological abnormalities and MELD score in patients with cirrhosis of liver

Objective:

- To assess the hematological changes seen in patients with liver cirrhosis which includes R.B.C, WBC, platelets and coagulation profile.
- To measure the severity of liver cirrhosis using Model for End-stage Liver Disease score (MELD).
- Correlate the haematological abnormalities with severity of the liver cirrhosis defined by the Model for End-stage Liver Disease score (MELD).

MATERIAL & METHOD

Type of study: Cross-sectional observational study

Source of data:

- Data will be collected from patients suffering with CIRRHOSIS OF LIVER who are admitted in B.L.D.E. (D.U.)'s Shri B.M. Patil Medical College Hospital & Research Centre, Vijayapura.
- The period of study is from January 2021 to June 2022.

Inclusion Criteria:

All the patients who are admitted in medical wards of Shri. B. M. Patil Medical College with Cirrhosis of the liver, diagnosed with:

- The history was given by the patient and his/her attenders.
- Patients having signs and symptoms of Cirrhosis of the liver.
- Patients having ultrasonographic findings of Cirrhosis with the shrunken liver.

Exclusion Criteria:

- Patients having primary hemostatic function abnormalities or primary coagulation disorder.
- Patients who undergone transfusion of blood in the last three months.
- Patients on treatment for anemia.
- Presence of any etiology of anemia not attributable directly or indirectly to Cirrhosis of the liver.

Sample size calculation

With 95% confidence level and margin of error of ±7.5%, a sample size of 60 subjects will allow the study to determine **"**Correlation Between MELD Score And Hematological Abnormalities In Patients With Cirrhosis Of Liver**"** with finite population correction (N=200). By using the formula:

$$n = z^2p(1-p)/ {}_d2$$

where

Z= z statistic at 5% level of significance d is a margin of error p is anticipated prevalence rate (50%)

METHODOLOGY:

1. Subjects fulfilling the inclusion criteria are taken for the study.
2. Complete hemogram, Coagulation profile, S. Bilirubin, S. Creatinine values are investigated on admission.
3. MELD SCORE is calculated using the formula 0.957 x Log e (creatinine mg/dL) + 0.378 x Log e (bilirubin mg/dL) + 1.120 x Log e (INR) + 0.6431 for each patient.
4. Values of the various hematological indices are correlated with the MELD score.

STATISTICAL ANALYSIS

All the obtained data were entered in a Microsoft Excel sheet and statistical analysis was performed using statistical package for the social sciences (Version 20). Results were summarised as Mean (Median) ±SD, counts and percentages and represented using tables, figures, bar diagram and the pie chart. The mean difference between the continuous variable was done with the help of unpaired t-test and categorical variables using chi-square test. Statistical significance was defined as p- value less than 0.005..

OBSERVATIONS AND RESULTS

FIGURE 11: DISTRIBUTION OF AGE AMONG SUBJECTS

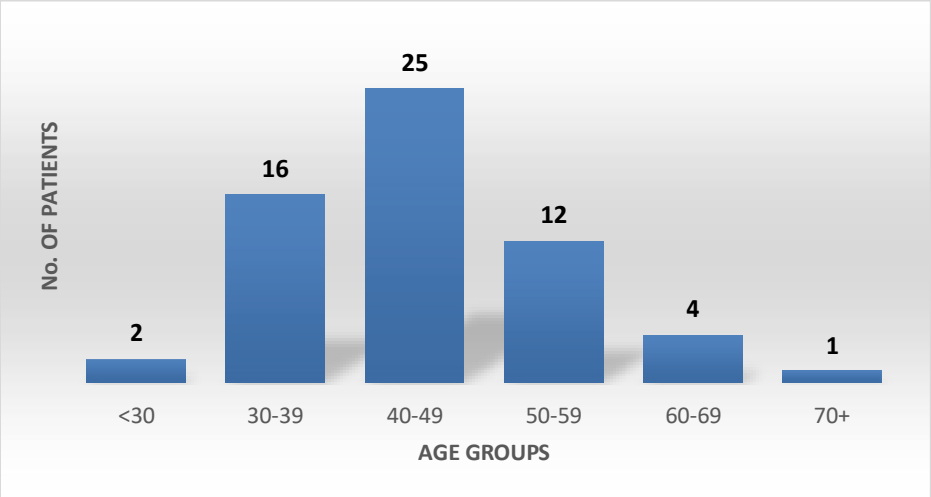
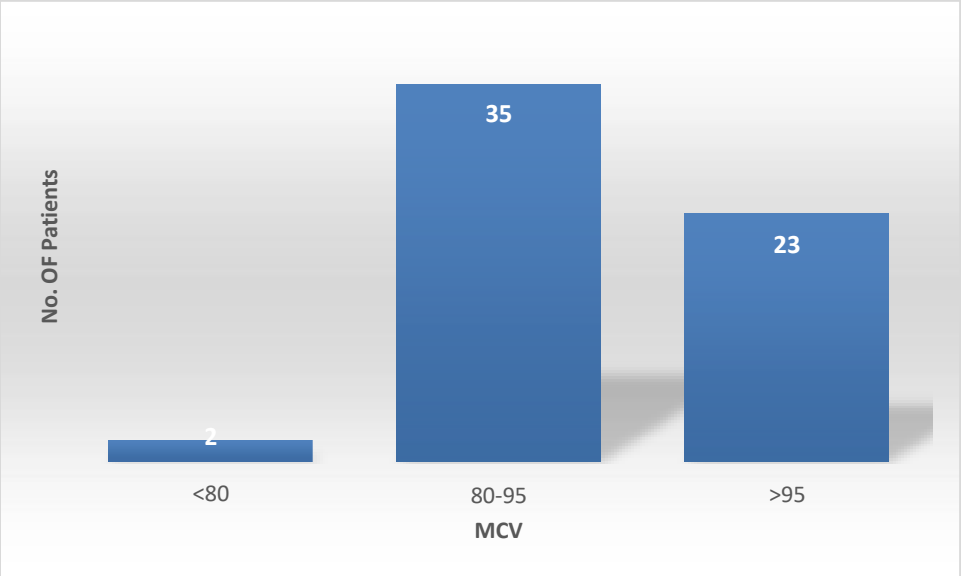


TABLE 3 MEAN AGE DISTRIBUTION:

	Minimum	Maximum	Mean	Std Deviation
AGE	22	70	43.55	9.898

40- 49 years old were the highest affected age group

figure 12: DISTRIBUTION OF MCV AMONG SUBJECTS



23 patients had mcv greater than 95.

TABLE 4: MEAN MCV DISTRIBUTION

	Minimum	Maximum	Mean	Std Deviation
MCV	69.0	113.8	93.47	7.444

FIGURE 13: DISTRIBUTION OF HAEMOGLOBIN AMONG SUBJECTS

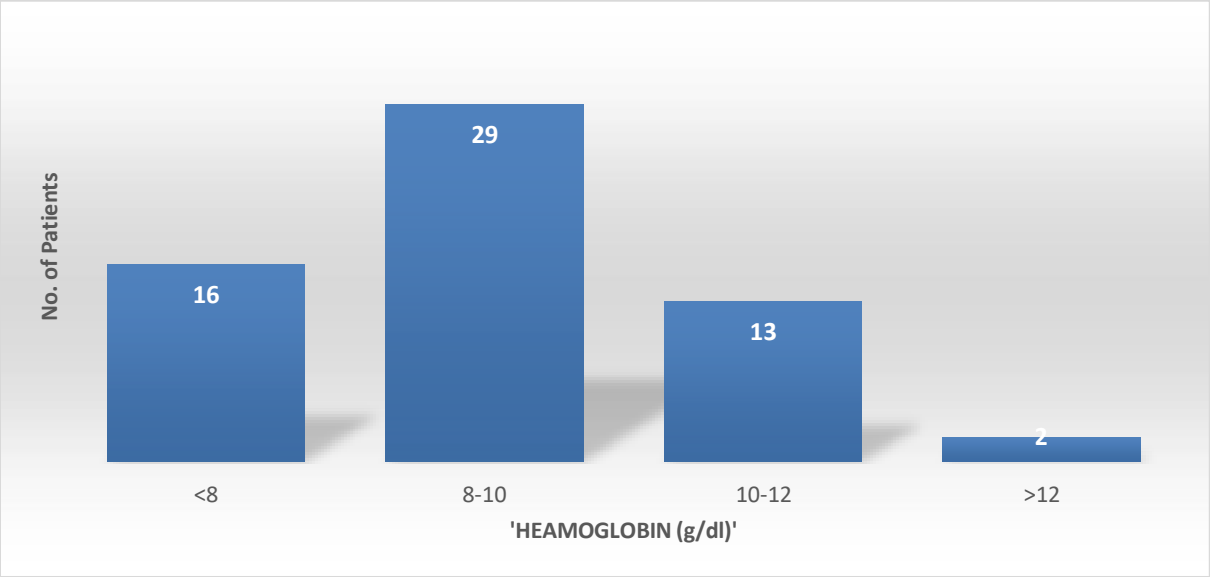


TABLE 5: MEAN Hb DISTRIBUTION

	Minimum	Maximum	Mean	Std Deviation
'HEAMOGLOBIN (g/dl)'	5.8	13.1	9.035	1.546

FIGURE 14: DISTRIBUTION OF PT AMONG SUBJECTS

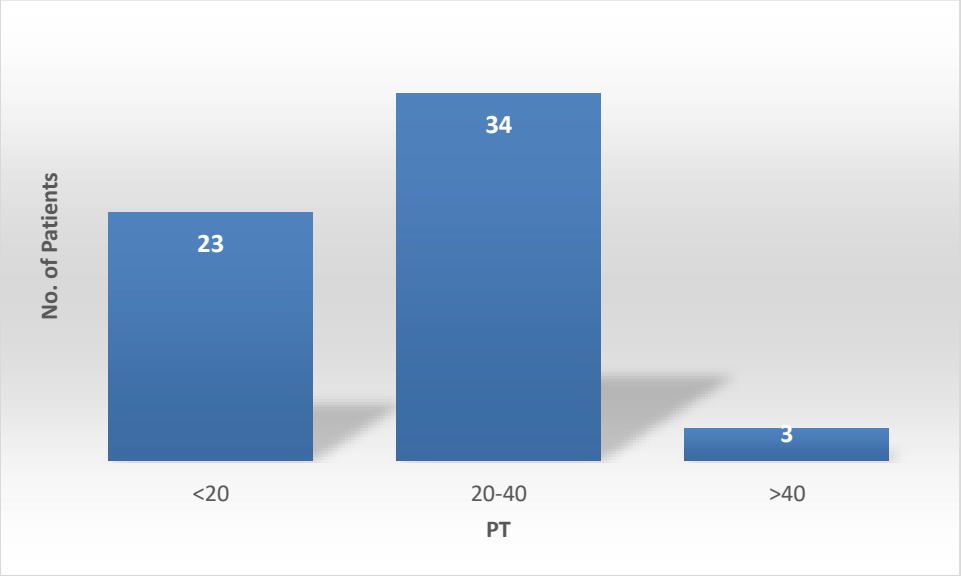


TABLE 6: MEAN PT DISTRIBUTION

	Minimum	Maximum	Mean	Std Deviation
PT	11.0	100.0	23.258	12.090

FIGURE 15. DISTRIBUTION OF INR IN SUBJECTS

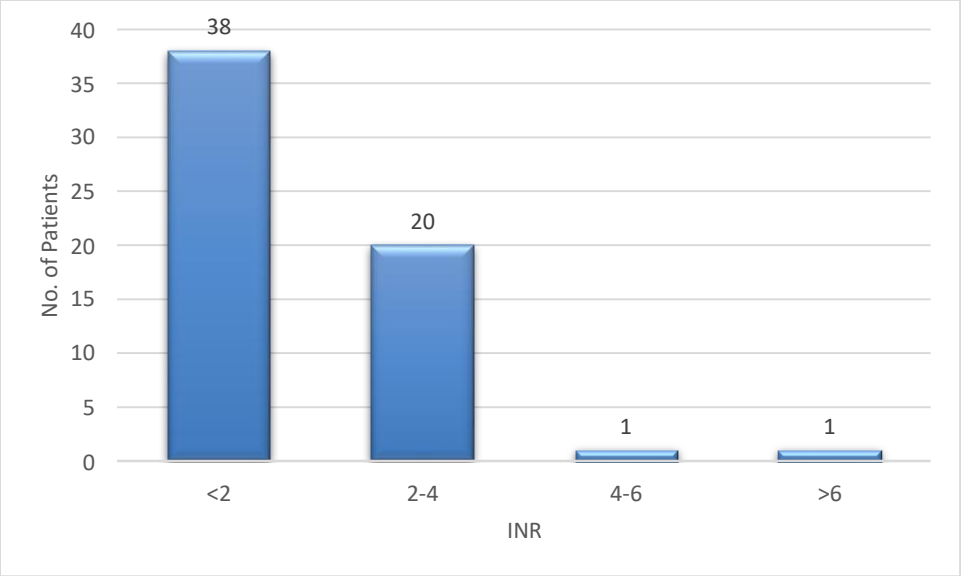


TABLE 7 MEAN INR DISTRIBUTION

	Minimum	Maximum	Mean	Std Deviation
INR	0.8	8.0	1.926	1.042

FIGURE 16 : DISTRIBUTION OF ALBUMIN AMONG PATIENTS

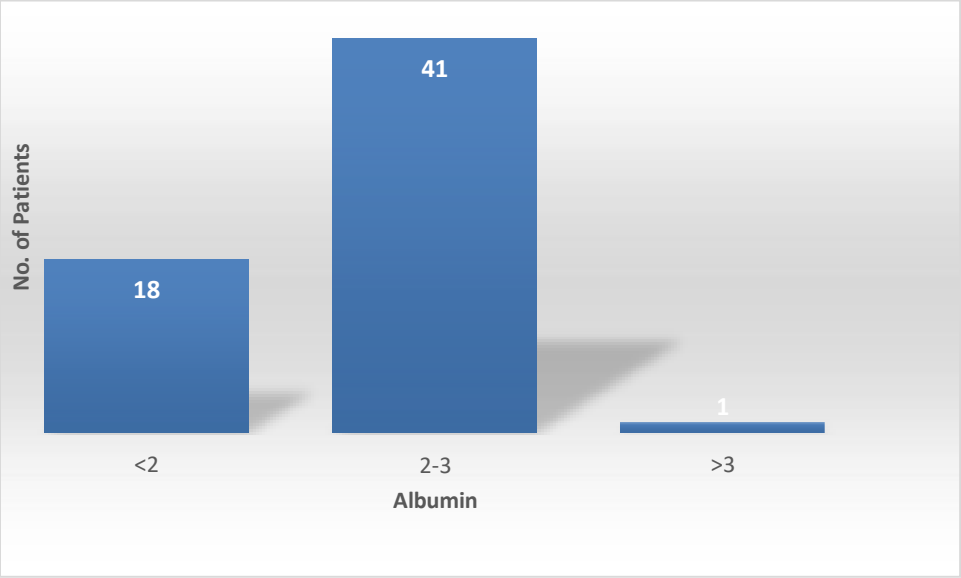


TABLE 8: MEAN ALBUMIN DISTRIBUTION

	Minimum	Maximum	Mean	Std Deviation
Albumin	1.0	3.7	2.238	0.4847

FIGUE 17 : DISTRIBUTION OF SODIUM

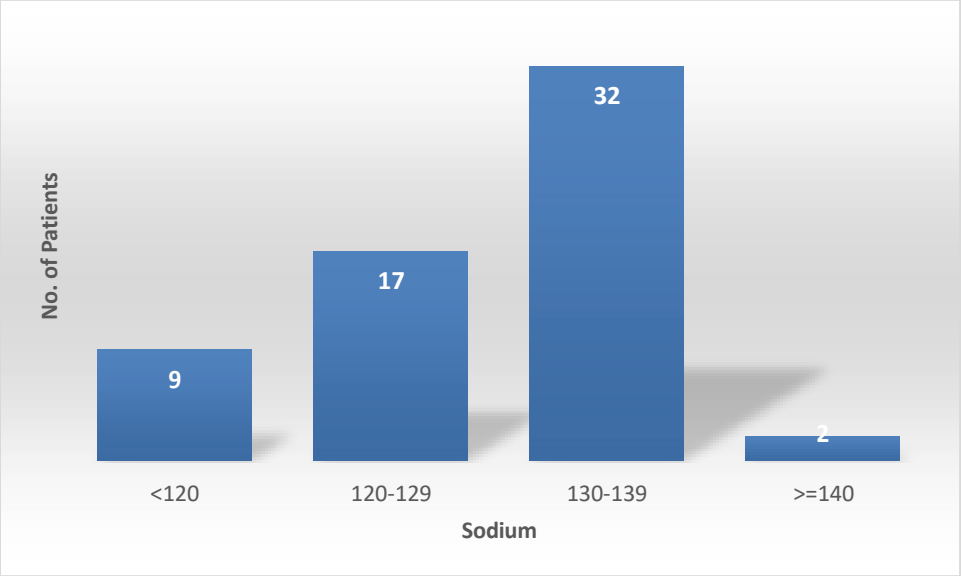


TABLE 9: MEAN SODIUM DISTRIBUTION:

	Minimum	Maximum	Mean	Std Deviation
Sodium	109	141	128.4	8.3406

FIGURE 18 : DISTRIBUTION OF PLATELETS

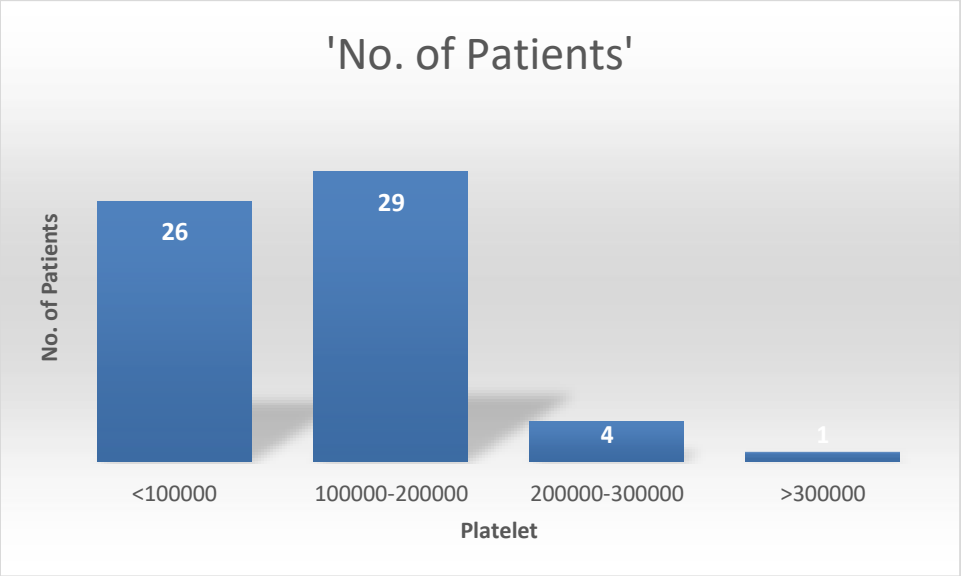


TABLE 10: MEAN DISTRIBUTION OF PLATELETS:

	Minimum	Maximum	Mean	Std Deviation
Platelet	24000	362000	116233	61166

FIGURE 19: DISTRIBUTION OF TOTAL LEUCOCYTE COUNT

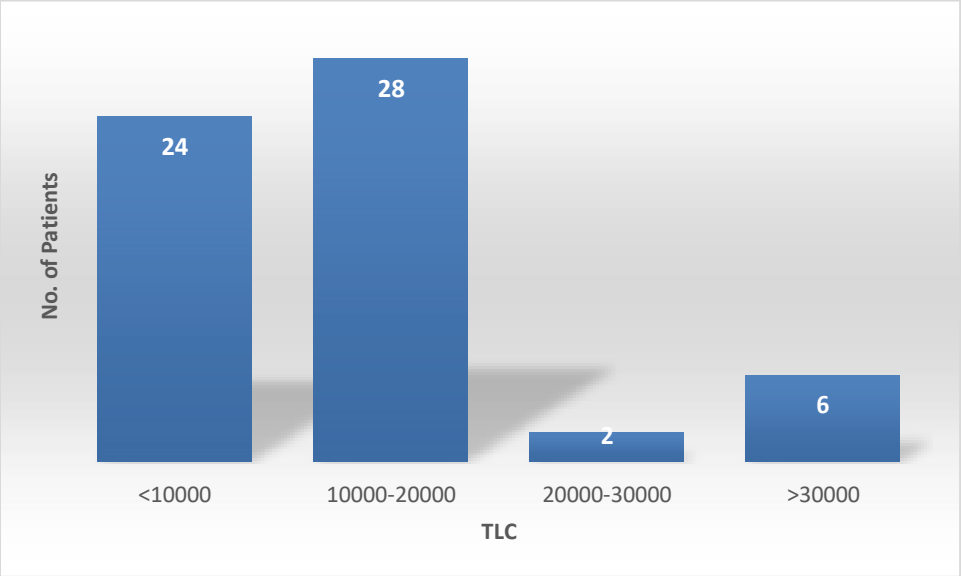


TABLE 11 MEAN TLC DISTRIBUTION:

	Minimum	Maximum	Mean	Std Deviation
TLC	3900	38470	13189	8102

FIGURE 20: DISTRBUTION OF MELD SCORE IN PATIENTS

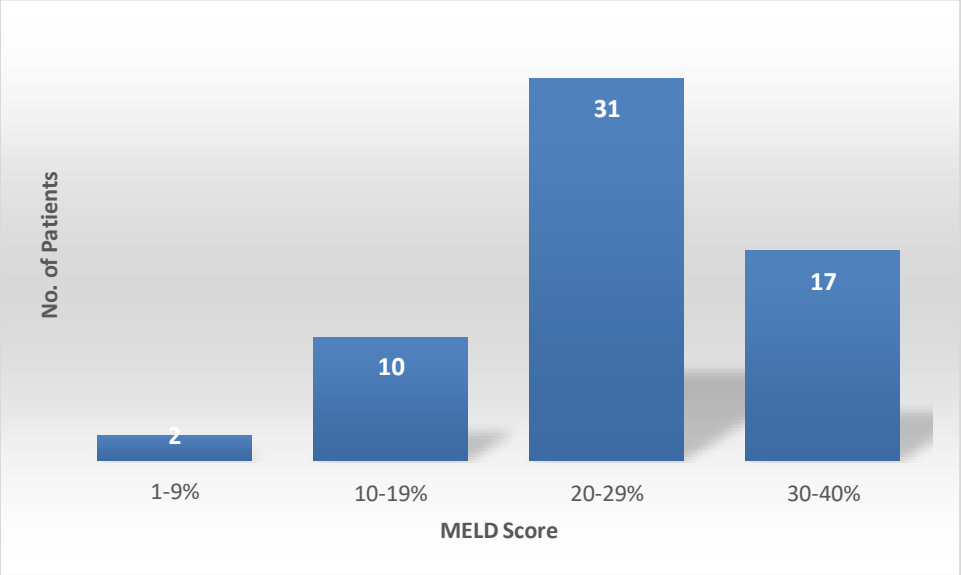
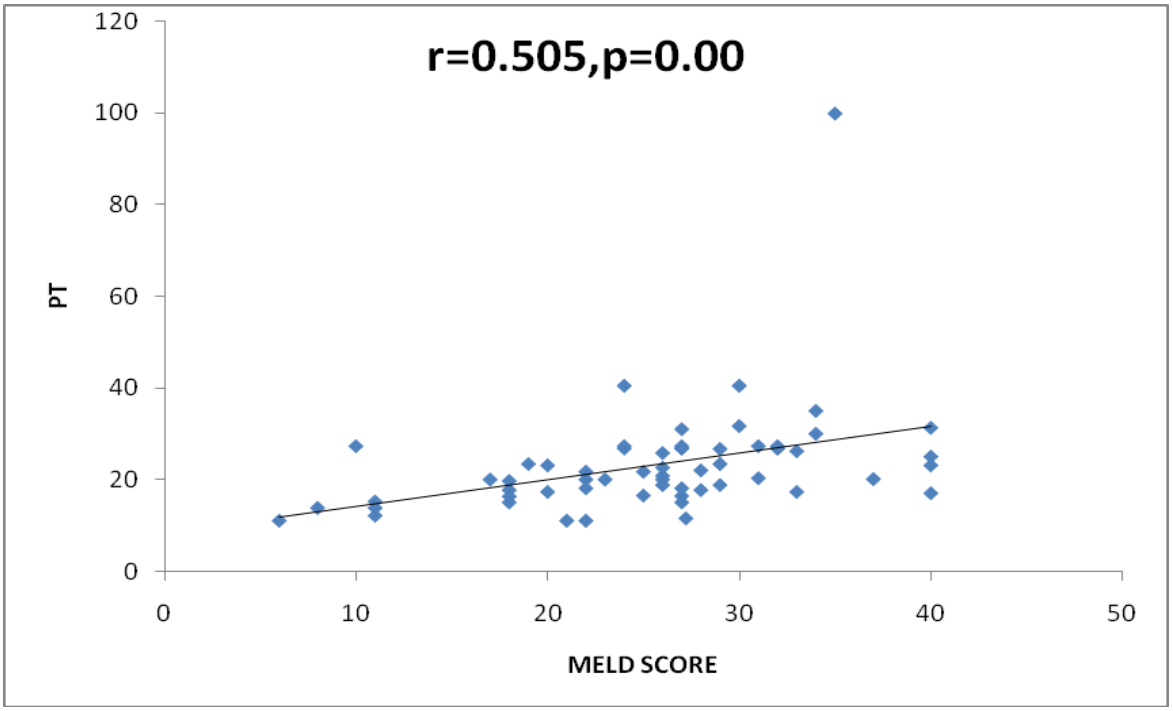


TABLE 12 :MEAN MELD DISTRIBUTION:

	Minimum	Maximum	Mean	Std Deviation
MELD SCORE	6.0	40.0	25.537	7.8736

FIGURE 21 :CORRELATION BETWEEN MELD SCORE AND PROTHROMBIN TIME

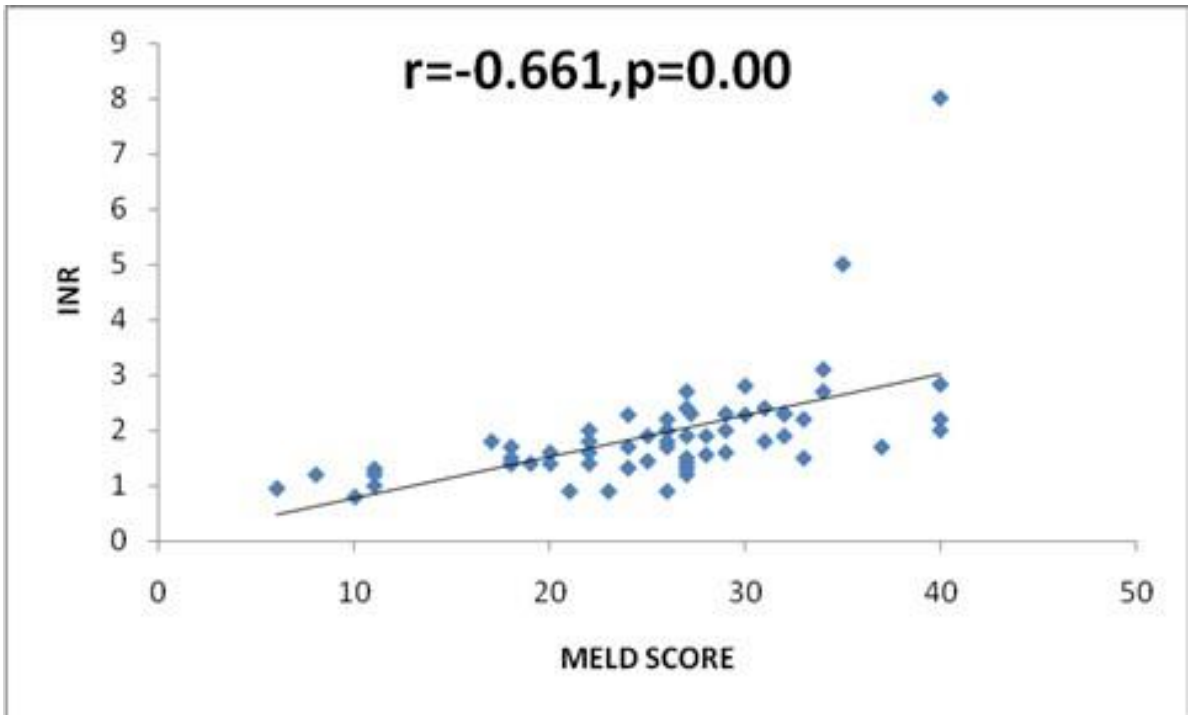


Statistical analysis shows significant correlation between MELD score and prothrombin time (p=0.00)

TABLE 13

	r value	P value	remark
MELD SCORE AND PT	0.505	0.00	significant

FIGURE 22: CORRELATION BETWEEN MELD SCORE AND INR

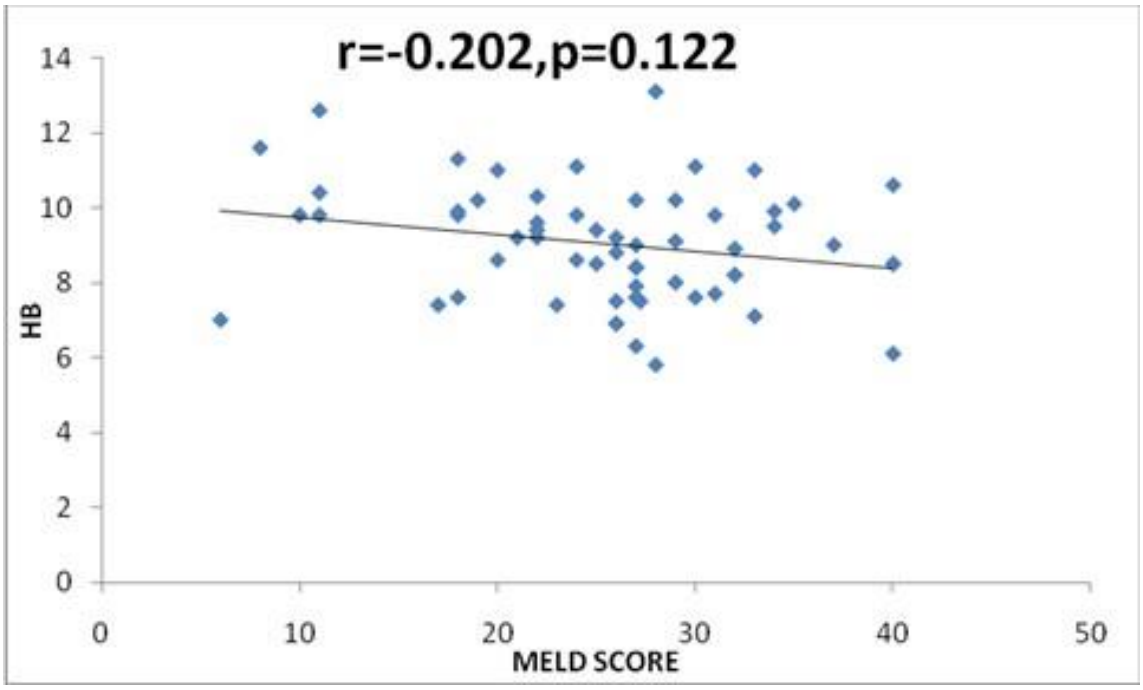


Statistical analysis shows correlation between MELD score and INR (p=0.00)

TABLE 14

	r value	P value	remark
MELD SCORE AND INR	0.661	0.00	significant

FIGURE 23: CORRELATION BETWEEN MELD SCORE AND HEMOGLOBIN

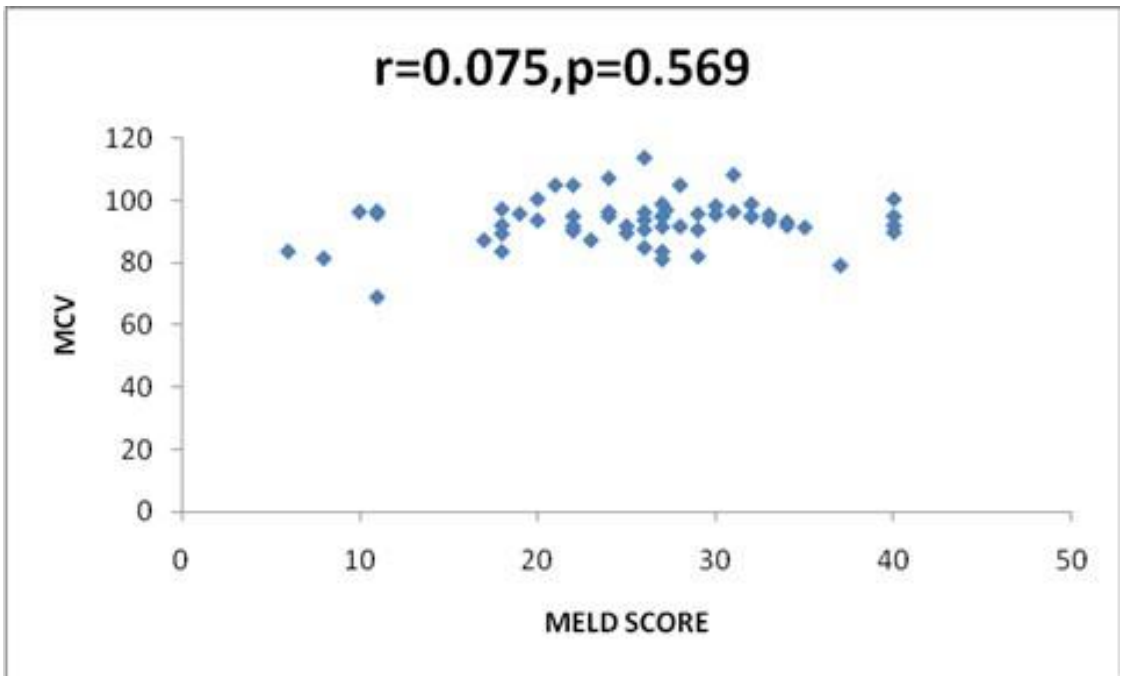


Statistical analysis shows correlation between MELD score and hemoglobin levels (p= 0.122)

TABLE 15

	R value	P value	remarks
MELD SCORE AND HB	-0.202	0.122	Not significant

FIGURE 24: CORRELATION BETWEEN MELD SCORE AND MCV

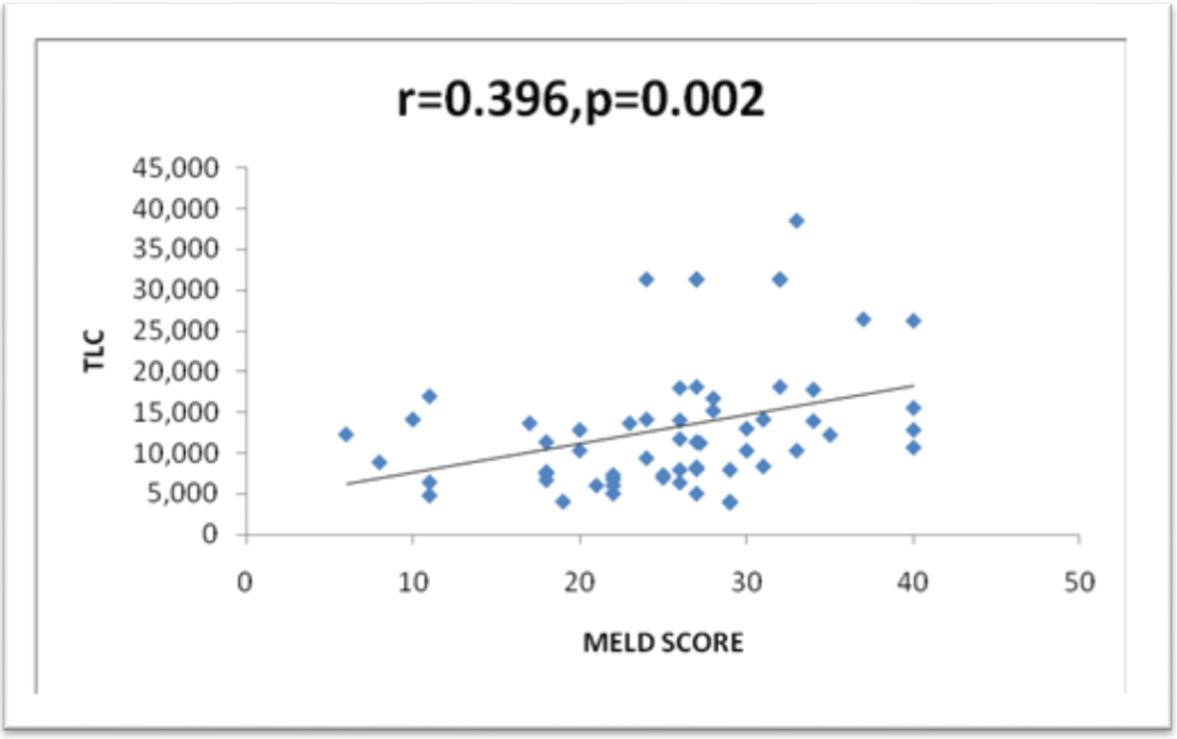


Statistical analysis shows correlation between MELD score and MCV (p=0.569)

TABLE 16

	R value	P value	Remarks
MELD SCORE AND MCV	0.075	0.569	Not significant

FIGURE 25: CORRELATION BETWEEN MELD SCORE AND TOTAL LEUCOCYTE COUNT

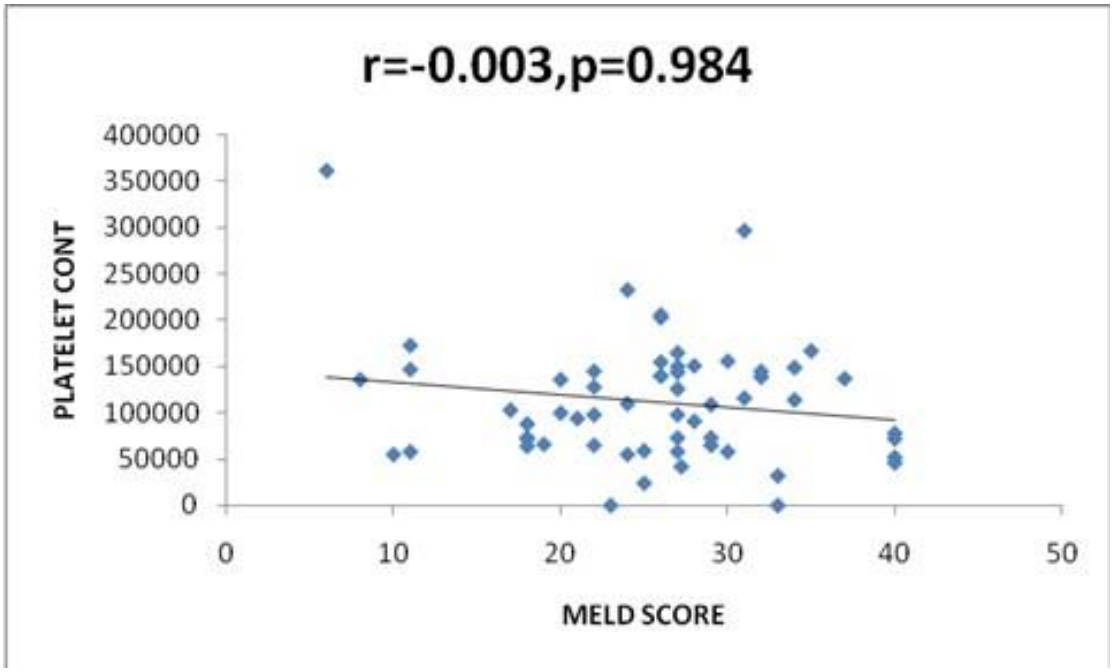


Statistical analysis shows correlation between MELD score and total leucocyte count

TABLE 17

	R value	P value	remarks
MELD SCORE AND TLC	0.396	0.002	significant

FIGURE 26: CORRELATION BETWEEN MELD SCORE AND PLATELET COUNT



Statistical analysis shows weak correlation between MELD score and platelet count (pvalue= 0.984)

TABLE 18

	R value	P value	remarks
MELD SCORE AND PLATELET COUNT	-0.003	0.984	Not significant

DISCUSSION

In our study, we observed thrombocytopenia, leucocytosis, anaemia as the three major haematological abnormalities.

Abnormal haematological indices in cirrhosis are due to

a. Increased splenic sequestration due to portal hypertension
b. Decrease in thrombopoietin, erythropoietin, hematopoietic stimulating factor
c. Suppression of bone marrow mediated toxins like alcohol, hepatitis B and C
d. Increased blood loss with gastrointestinal bleeds or haemolysis.

These abnormalities cause poor prognosis of the disease affected patients as seen by increased MELD score. There is also significant relation observed between increased PT and increased MELD score.

Thrombocytopenia and increased PT lead to increased GI bleed risk. GI bleed leads to high chance of hepatic encephalopathy. There is high mortality seen in patients with hepatic encephalopathy[9,10]

According to a study done by Solomon R et al., 72% of patients had high PT-INR. 50% of the patients had low platelets. Majority of patients with low platelets in the study had increased PT[29].

An analysis of 213 patients followed for nine years by Qamar showed that 84% of them with Child-Pugh Class A/B cirrhosis had aberrant haematological indices[28].

Jain D et al., studied alcoholic liver cirrhosis in 88 patients. It was observed that haematological abnormalities like leukopenia and anaemia were frequent in greater MELD score group. They noticed a steady decline in haemoglobin levels as the MELD score increased. All Group 1 patients had leucocyte counts within the normal limit. In MELD groups 2 and 3, leucocytosis predominated. Leukopenia was more common in group 4.group 5 patients all exhibited leukopenia. Thrombocytopenia first appeared in group 3 patients and spread to group 4 and 5 patients[34].

In a study done by Jha S et al., the most common type of anaemia is normocytic normochromic. Normocytic normochromic anaemia, macrocytic anaemia is commonly seen in alcoholics. Leucocytosis is more common than leukopenia and thrombocytopenia[35].

CONCLUSION

Alteration in haematological parameters and serum albumin, which represent the liver's synthetic activity, are obvious markers of chronic liver illness. In order to lower the mortality and morbidity of these individuals, efforts might be undertaken to normalise the haematological parameters.

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IEC/00-09/2021
Date- 22/01/2021

B.L.D.E. (DEEMED TO BE UNIVERSITY)

(Declared vide notification No. F.9-37/2007-U.3 (A) Dated. 29-2-2008 of the MHRD, Government of India under Section 3 of the UGC Act, 1956)

The Constituent College

SHRI. B. M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Institutional ethical committee of this college met on 11-01-2021 at 11am to scrutinize the synopsis of Postgraduate students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has been accorded Ethical Clearance

Title: Study of correlation between meld score and hematological abnormalities in patients with cirrhosis of Liver

Name of PG student: Dr K Sweta Sri, Department of Medicine

Name of Guide/Co-investigator: Dr Mallanna Mullimani, Professor of Medicine

DR.S.V.PATIL
CHAIRMAN
Institutional Ethical Committee
B L D E (Deemed to be University)
Shri B.M. Patil Medical College,
VIJAYAPUR-586103 (Karnataka)

Following documents were placed before Ethical Committee for Scrutinization:

1. Copy of Synopsis / Research project
2. Copy of informed consent form
3. Any other relevant documents.

10

ANNEXURE

INFORMED CONSENT FORM

BLDEU'S S.H.R.I. B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR- 586103

TITLE OF THE PROJECT - " CORRELATION BETWEEN MELD SCORE AND HEMATOLOGICAL ABNORMALITIES IN PATIENTS WITH CIRRHOSIS OF LIVER"

PRINCIPAL INVESTIGATOR : **DR. SWETHA SRI KORLAPATI**

8919710555

P.G. GUIDE NAME : **DR. MALLANNA S.MULIMANI**

PROFESSOR OF MEDICINE

08352-, Ext-2148

All aspects of this consent form are explained to the patient in the language understood by him/her.

1) INFORMED PART

1) PURPOSE OF RESEARCH:

I have been informed about this study. I have also been given a free choice of participation in this study.

2) PROCEDURE:

I am aware that in addition to routine care received, I will be asked a series of questions by the investigator. I have been asked to undergo the necessary investigations and treatment, which will help the investigator in this study.

3) RISK AND DISCOMFORTS:

I understand that I may experience some pain and discomfort during the examination or my treatment. This is mainly the result of my condition, and the procedure of this study is not expected to exaggerate these feelings associated with the usual course of treatment.

4) BENEFITS:

I understand that my participation in this study will help to patient's survival and better outcome.

5) CONFIDENTIALITY:

I understand that the medical information produced by this study will become a part of Hospital records and will be subject to confidentiality and privacy regulation. Information of

a sensitive personal nature will not be a part of the medical records but will be stored in the investigator's research file and identified only by code number. The code-key connecting name to numbers will be kept in a separate location. If the data are used for publication in the medical literature or teaching purposes, no name will be used, and other identifiers such as photographs and audio or videotapes will be used only with my special written permission. I understand that I may see the pictures and videotapes and hear the audiotapes before giving this permission.

6) REQUEST FOR MORE INFORMATION:

I understand that I may ask questions about the study at any time. Dr. .SWETHASRI KORLAPATI is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation. If during the study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me. A copy of this consent form will be given to me to keep for careful reading.

7) REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital. I also understand that Dr. K.SWETASRI may terminate my participation in the study after she has explained the reasons for doing so and has helped arrange for my continued care by my own physician or physical therapist if this is appropriate.

8) INJURY STATEMENT:

I understand that in the unlikely event of injury to me resulting directly from my participation in this study if such injury were reported promptly, the appropriate treatment would be available to me, but no further compensation would be provided. I understand that by my agreement to participate in this study, I am not waiving any of my legal rights. I have explained the purpose of the research, the procedures required, and the possible risks and benefits to the best of my ability in the patient's own language.

_____ _____

Date Dr. SWETHASRI KORLAPATI

Principal Investigator

I) STUDY SUBJECT CONSENT STATEMENT:

I confirm that Dr.K.SWETHA SRI has explained the purpose of research, the study procedures that I will undergo, the possible risks and discomforts, and benefits that I may experience in my own language. I have read, and I understand this consent form. Therefore, I agree to give consent to participate in this research project.

---------- ----------

Participant / guardian Date

---------- ----------

Witness signature Date