

A Study on Hematological Abnormalities in Chronic Liver Diseases

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Abstract

Aim Of The Study: To assess the hematological profile of patients with chronic liver disease and their correlation in patients with GI Bleed.

Materials And Methods: To assess the hematological abnormalities in chronic liver disease, a cross sectional analytical study was conducted All patients taken up for the study were evaluated in detail. Oral consent was obtained for clinical examination and lab investigations. Written consent was obtained for procedures such paracentesis, Upper GI endoscopy and viral marker studies.

Inclusion Criteria

1. All patients with liver disease whose symptoms and signs persists for more than 6 months
2. Alcoholic cirrhosis, post-necrotic cirrhosis, metabolic causes of liver diseases were taken up for the study

Exclusion Criteria

1. Patients with underlying malignancy or known primary hepatocellular carcinoma were excluded
2. Patients with primary coagulation disorder or primary abnormalities of haemostatic function were excluded.
3. Acute hepatic failure was excluded
4. Patients with preexisting anemia due to other causes were excluded.
5. Patients suffering from end stage medical diseases like COPD, Coronary artery disease, cardiac failure, CKD were excluded

Observation & Data Analysis: A descriptive study to assess the hematological abnormalities in chronic liver disease was conducted at Department of Digestive Health and diseases, Kilpauk medical college , Chennai from August 2016 to January 2017. 50 patients with chronic liver disease were taken for the study; this included 43 males (86%) and 7 females (14 %).

The age range was from 24 to 70. The average age of the patients in the study was 48 yrs. 70 % of the patients were between 40 and 60 years.

52% of the patients had alcoholic cirrhosis were males. The aetiology of chronic liver disease could not be determined in 24 % of cases but all of them had clinical and radiological features of cirrhosis. 6 patients had Hepatitis B and 2 had Hepatitis C; all these 8 patients had cirrhosis. Autoimmune hepatitis and cirrhosis were present in 2 females

Results: 50 % of the patients had thrombocytopenia (<1 lakh). Of the 13 patients who had an upper GI bleed 3 patients had normal platelet counts and the rest had counts below 1 lakh. The average platelet count of patients who experienced an upper GI bleed was 92000 vs. 1.2 lakh in patients without a GI bleed. The bleeding time was prolonged only in 6 patients with thrombocytopenia indicating BT as an insensitive test. 36 patients had a prolonged INR. Among the 13 patients with upper GI bleed 9 had prolonged INR; indicating other factors play a role in GI bleed

Conclusions: Many conclusive results regarding the hematological abnormalities in chronic liver disease were obtained with this limited study involving 50 patients with cirrhosis

- ⇒ 50 % of patients had thrombocytopenia.
- ⇒ The average platelet count of patients with an upper GI bleed was 92000 compared to 1.2 lakh to those without an upper GI bleed; suggesting other factors such functional platelet defects may play a role as well. These need to be confirmed with platelet functional studies.
- ⇒ Bleeding time was prolonged only in 12 % of patients with thrombocytopenia indicating BT as an insensitive test of platelet number and function.
- ⇒ The PT-INR was elevated in 72 % of patients. However only 25 % of patients with a prolonged PT-INR had upper GI bleed indicating other factors such as a rebalanced hemostatic system at work, however this

needs to be confirmed with more extensive studies. This result underlines the fact that clinical status of the patient and not lab values have to be treated, when correcting coagulopathy in a patient with cirrhosis.

From this study we can conclude that various hematological alterations are very common in cirrhosis patients that needs to be identified and corrected early to reduce morbidity and mortality.

Keywords: Liver cirrhosis, Hematological abnormalities, Platelets, PT/INR.

I. Introduction

The liver is the largest organ in the body and one of the most complex functioning organs with a wide array of functions. It plays a major role in carbohydrate, protein, lipid metabolism; inactivation of various toxins, metabolism of drugs, hormones, synthesis of plasma proteins & maintenance of immunity (Kupffer cells). Right from being a primary site of haematopoiesis in fetal life to maintenance of hematological parameters in postnatal life; the liver has an extremely important role in maintenance of blood homeostasis. It acts as a storage depot for Iron, Folic acid & Vitamin B12, secretes clotting factors and inhibitors. Hence it's not surprising to see a wide range of hematological abnormalities in liver diseases. In chronic liver disease the presence of jaundice, liver cell failure, portal hypertension and hypersplenism, reduced red cell half-life all influence peripheral blood picture. Both Liver cell failure & cholestasis can derange the coagulation system. Dietary deficiencies, bleeding, alcoholism and abnormalities in hepatic synthesis of proteins used for blood formation or coagulation add to the problem liver disease. This study was undertaken to describe the coagulation abnormalities in chronic liver disease so that measures could be taken to correct them and reduce morbidity.

Aim Of The Study

To assess the hematological profile of patients with chronic liver disease and their correlation in patients with GI bleed.

II. Materials And Methods

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All patients taken up for the study were evaluated in detail. Oral consent was obtained for clinical examination and lab investigations. Written consent was obtained for procedures such paracentesis, Upper GI endoscopy and viral marker studies.

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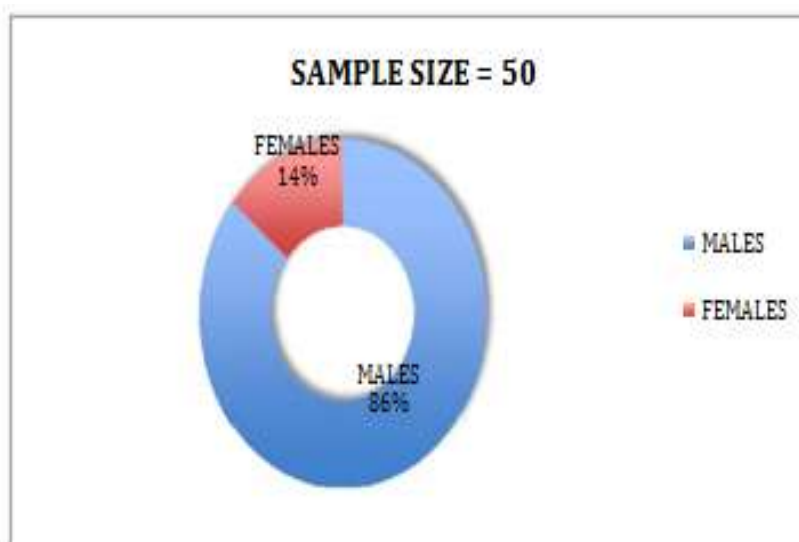
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III. Observation & Data Analysis

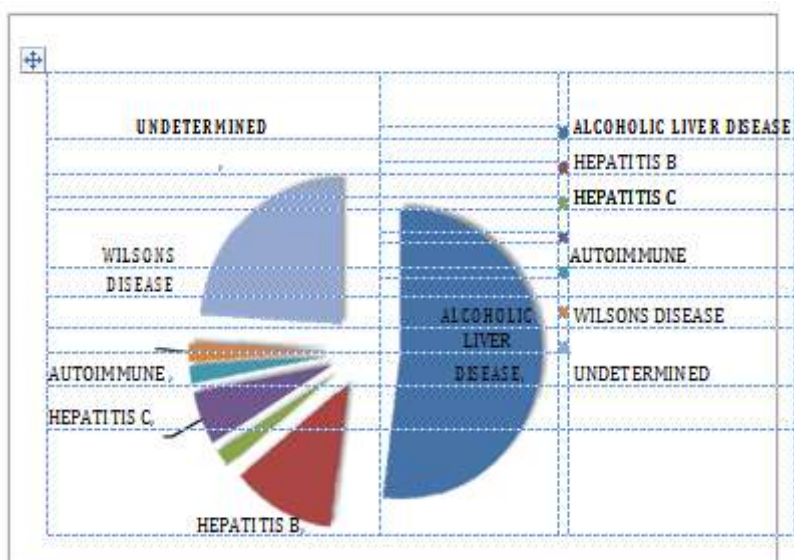
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Age Distribut Ion Of Case S

Age	Males	Females	Total	%
20 to 30	2	0	2	4
30 to 40	4	3	7	14
40 to 50	16	2	18	36
50 to 60	17	0	17	34
>60	4	2	6	12

The age range was from 24 to 70. The average age of the patients in the study was 48 yrs. 70 % of the patients were between 40 and 60 years of age



Aetiology Of Chronic Liver Disease

AETIOLOGY OF CIRRHOSIS			
Aetiology of cirrhosis	Males	Females	Total
Alcoholic liver disease	26	1	27
Hepatitis B	5	1	6
Hepatitis C	2	0	2
Autoimmune	0	2	2
Wilson's disease	0	1	1
Undetermined	9	3	12

2% of the patients had alcoholic cirrhosis were males. The aetiology of chronic liver disease could not be determined in 24 % of cases but all of them had clinical and radiological features of cirrhosis. 6 patients had Hepatitis B and 2 had Hepatitis C; all these 8 patients had cirrhosis. Autoimmune hepatitis and cirrhosis were present in 2 females

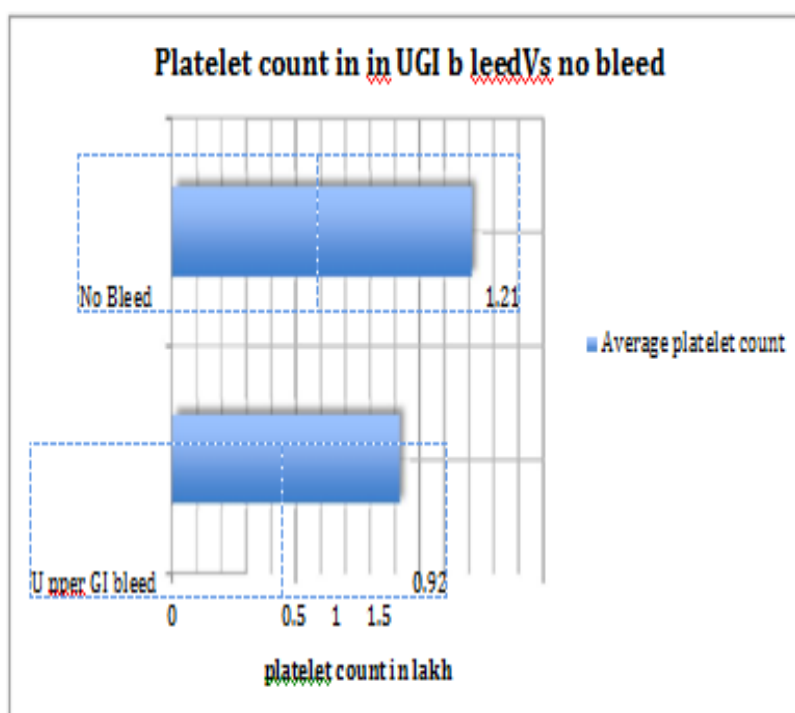
Past History Of Jaundice

Of the 50 patients with Cirrhotic liver only 14 patients gave past history of jaundice. Serology proved that 4 patients had hepatitis B and 2 had hepatitis C. One female patient had recurrent history of jaundice and was diagnosed as a case of Wilson's disease.

Platelet Abnormalities

50 % of the patients had thrombocytopenia (<1 lakh) Of the 13 patients who had an upper GI bleed 3 patients had normal platelet counts and the rest had counts below 1 lakh. The average platelet count of patients who experienced an upper GI bleed was 92000 vs. 1.2 lakh in patients without a GI bleed.

Comparison Of Platelet Counts In Patients With And Without Upper GI Bleed



The bleeding time was prolonged only in 6 patients with thrombocytopenia indicating BT as an insensitive test.

Coagulation Profile

The liver secretes all clotting factors except VIII & VWBf. Coagulation profile was assessed using aPTT, PT-INR and fibrinogen levels. 36 patients had a prolonged INR. Among the 13 patients with upper GI bleed 9 had prolonged INR; indicating other factors play a role in GI bleed.

INR VALUES	
INR	Number
1.3 to 1.6	17
1.7 to 2	10
2 to 2.5	7
>2.5	2

IV. Discussion

This study conducted at Department of digestive health and diseases hospital, Kilpauk medical college involving 50 patients has thrown light on many of the hematological abnormalities that is seen in chronic liver disease.

Platelet Abnormalities

Several studies on platelet defects in CLD have been done before. According to an interesting article by Jody L Kujovich MD – “Haemostatic defects in end stage liver disease”; Critical care clinics 21 (2005) - mild to moderate thrombocytopenia occurs in 49 to 64 % of patients with DCLD. The platelet count is rarely less than 30 to 40 thousand. The etiology of thrombocytopenia is multifactorial –

- Splenic sequestration of platelets
- Low Thrombopoietin levels
- Hypersplenism
- Reduced platelet half-life related to autoantibodies
- Folate deficiency
- Alcohol induced bone marrow suppression
- DIC
- Sepsis
- Drugs

Functional platelet defects are well described in several studies. Escolar G et al reports that platelet aggregation seems to be particularly affected in as much as 46% of patients with DCLD. The possible mechanisms have been postulated by a study by Ballard HS, Marcus AJ et al - “Platelet aggregation in portal cirrhosis”; Arch Intern Med 1996. They include

- Reduced availability of arachidonic acid for prostaglandin synthesis
- Reduced platelet ATP and serotonin
- Circulating factors that inhibits platelet aggregation - FDP and D- dimers, plasmin degradation of platelet receptors, dysfibrinogenemia, and excess nitric oxide synthesis.
- Nitric oxide is a powerful vasodilator and inhibitor of platelet adhesion and aggregation produced by vascular endothelial cells.
- HDL isolated from cirrhotic patients inhibit ADP induced platelet aggregation
- Platelet binding domains are abnormal thus preventing efficient binding to Von Willi Brand factor during adhesion.

Comparison of various studies showed conflicting reports regarding bleeding time as a test to assess platelet function adequately. Blake JC et al.” Bleeding time in patients with hepatic cirrhosis”. BMJ 1990 reports that bleeding time is prolonged in as much as 40% of patients with cirrhosis. However another study by Basili S et al. “Bleeding time does not predict gastrointestinal bleeding in patients with cirrhosis”; J Hepatol (1996) reports bleeding time as an inadequate and ineffective test for platelet function and correlates poorly with bleeding tendency. In our particular study 50% of patients had thrombocytopenia (< 1 lakh) of which 80% had mild to moderate thrombocytopenia (50 to 100 thousand). This conforms to the article by Jody L

Kujovich mentioned earlier. The rest 20 % had severe thrombocytopenia (below 50000).

In our study, of the 13 patients who had an upper GI bleed, 3 patients had normal platelet counts and the rest had average platelet count of 92000. The bleeding time was prolonged only in 12% of patients with thrombocytopenia. This clearly indicates that bleeding time as an insensitive test for platelet function conforming to the result shared by Basili S et al; and functional abnormalities probably play a role. However due to lack of facilities platelet functional studies could not be taken up.

Coagulation Abnormalities

A deranged coagulation system is very common in chronic liver disease. There is reduced synthesis of all coagulation factors (except factor VIII & Von Willibrand factor), Vitamin K deficiency, Hyperfibrinolysis & dysfibrinogenemia, all contributing to increased bleeding tendency. Tripodi et al HEPATOLOGY 2005 through an elegant study have shown in addition to the diminished hepatic synthesis of clotting factors, patients also have a profound deficit of natural anticoagulants, mainly of protein C (a protein synthesized by the liver), and also of anti-thrombin, which may counterbalance the bleeding tendency caused by the deficiency in procoagulants. This was the concept of the Rebalanced Haemostatic system, which can be tipped in favor of bleeding or thrombosis depending on the clinical situation.

In our particular study as much as 72% of patients had a prolonged PT-INR, though only 25 % of these patients had an upper GI bleed. This may suggest a rebalanced coagulation system in action to prevent bleed, however we did not have any patient with DCLD who presented with thrombosis. Individual assessment of procoagulants & endogenous anticoagulants were not possible due to lack of facilities and are definitely warranted for more conclusive results. Thus from this limited study of 50 patients with chronic liver disease we were able to draw many inferences regarding the haematological abnormalities that contribute to the morbidity of patients. Many of the results obtained conform to previously done studies mentioned earlier but whether these results can be extrapolated to the larger population of cirrhotic patients as a whole is not definitely known and needs larger, more comprehensive studies with a wider range of patient selection.

V. Conclusions

Many conclusive results regarding the haematological abnormalities in decompensated chronic liver disease were obtained with this limited study involving 50 patients with decompensated cirrhosis

- ⇒ 50 % of patients had thrombocytopenia.
- ⇒ The average platelet count of patients with an upper GI bleed was 92000 compared to 1.2 lakh to those without an upper GI bleed; suggesting other factors such as functional platelet defects may play a role as well. These need to be confirmed with platelet functional studies.
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Bibliography

- [1]. Review of Medical Physiology: William F Ganong 22nd edition, Regulation of gastrointestinal function, page 500, Functions of liver.
- [2]. Sherlocks textbook of liver diseases 12th edition; Haematological disorders of the liver, Pramod K Misry and Dhanpat Jain, Para 1.
- [3]. Sherlocks textbook of liver diseases 12th edition; Chapter 5: Haematological disorders of the liver, Pramod K Misry and Dhanpat Jain, Para 2.
- [4]. Sherlocks textbook of liver diseases 12th edition; Chapter 1: Anatomy and Function, Jay H. Lekowitch, Anatomy of liver, page 1.
- [5]. Boyd E. Normal variability in weight of the adult human liver and spleen. ArchPathology 1933.
- [6]. Sherlocks textbook of liver diseases 12th edition; Chapter 1: Anatomy and Function, Jay H. Lekowitch, Anatomy of liver, page 1, Para 3.
- [7]. Couinaud C. Le foie. Etudes anatomiques et chirurgicales. 1957, Paris, Masson
- [8]. Bismuth H. Surgical anatomy and anatomic surgery of liver; World Journal of surgery, 1982; 6:3 to 9
- [9]. Sherlocks textbook of liver diseases 12th edition; Chapter 1: Anatomy and Function, page 9, Para 4, Jay H. Lekowitch
- [10]. Kiernan F. Anatomy of liver. 1833; 123: 711 to 770
- [11]. Rappaport AM. The microcirculatory acinar concept of liver. Beitr. Pathol. 1976

- [12]. Schiff Hepatology 2012; Chapter 5: physioanatomic considerations, Ian R Wanless, Page 89, Para 2
- [13]. Review of Medical Physiology: William F Ganong 22nd edition, Regulation of gastrointestinal function, page 500, Functions of liver- table 26-7
- [14]. Robbins & Cotran: pathologic basis of disease; 8th Edition; chapter 18, liver and biliary tract - James M Crawford, Chen Liu, page 837, para 1
- [15]. Sherlocks textbook of liver diseases 12th edition; Hepatic cirrhosis, P Aiden McCormick, page 106, Para 2.
- [16]. Gines P, Quintero E, Arroyo V et al. Compensated cirrhosis: natural history and prognostic factors. Hepatology 1987: 122 to 128
- [17]. Sherlocks textbook of liver diseases 12th edition; Hepatic cirrhosis, P Aiden McCormick, table 7.2 – histopathology and aetiology of cirrhosis.
- [18]. Schiff Hepatology 2012; Chapter 12: Hepatic Fibrosis, Scott I Friedman, Page 299, Para 5
- [19]. Gressner et al. Comparative Hepatology 2007 6:7
Davidson principles and practice of internal medicine; 21st Edition, Chapter 23: Liver and Biliary tract: J D Collier, G Webster, page 942,