CIRRHOSIS: NON-INVASIVE PARAMETERS FOR PREDICTING THE OCCURRENCE OF OESOPHAGEAL VARICES

S. M. Sujatha1, G. Vasumathi2, P. Sampath Kumar3, A. Ramalingam4, P. Kishore Chander5, K. Valarmathi6

1Senior Assistant Professor, Department of Medicine, Stanley Medical College, Chennai.
2Associate Professor, Department of Medicine, Stanley Medical College, Chennai.
3Post Graduate, Department of Medicine, Stanley Medical College, Chennai.
4Senior Assistant Professor, Department of Medicine, Stanley Medical College, Chennai.
5Post Graduate, Department of Medicine, Stanley Medical College, Chennai.
6Associate Professor, Department of Pathology, Stanley Medical College, Chennai.

ABSTRACT

BACKGROUND
Cirrhosis of liver results in portal venous hypertension and oesophageal varices when decompensated. The present study aims to study the non-invasive clinical, biochemical and ultrasonographic parameters to predict the risk of oesophageal varices to correlate platelet count/splenic diameter ratio with grade of varices and to study the type of anaemia picture in cirrhatics.

MATERIALS AND METHODS
50 patients (25 female, 25 male) of cirrhosis between 20-60 years of age, presenting to the Medicine Department OPD/Ward, Stanley Hospital, Chennai, during March-August 2013, diagnosed by ultrasonography and biochemical parameters were investigated, classified under Child Pugh’s and results analysed in SPSS 14 version for statistics.

RESULTS AND OBSERVATION
Out of 50 patients 26, 46, 28 were the respective percentages in Child Pugh’s A, B, C. The mean platelet count in cirrhotics with no, small, large oesophageal varices were 153.64, 132.94 and 90.27 respectively. Platelet count can predict oesophageal varices with a sensitivity of 74.36%, specificity of 72.73% with a mean of 132.9 x 1000/cmm. The mean portal vein diameter in cirrhotics were 153.64, 132.94 and 90.27 respectively. Platelet count can predict varices with 74.35% sensitivity and 65.63% specificity with a mean of 143.7 mm. The platelet count/splenic diameter ratio were 1.09, 0.94, 0.52 respectively in cirrhotics with no, small, large varices.

CONCLUSION
Study predicts the large oesophageal varices with 100% specificity and 100% positive predictive value. Hence, non-invasive parameters can predict the presence of varices in cirrhotics.

KEYWORDS
Cirrhosis, Oesophageal Varices, Platelet Count, Splenic Diameter, Peripheral Smear.


INTRODUCTION
Cirrhosis is a histopathological condition characterized by the formation of fibrosis, which leads to architectural distortion and the development of regenerative nodules presenting with different kinds of clinical manifestations and complications, some of them are life threatening. Cirrhosis results in a decrease in hepatocellular mass and its function and causes changes in blood flow leading to portal hypertension.

Portal hypertension is an important feature of decompensate liver disease.(1) Portal hypertension is characterized by an increase in the pressure gradient in the hepatic vein of more than 5 mmHg.

The development of portal hypertension is usually revealed by the presence of thrombocytopenia; the appearance of an enlarged spleen or the development of ascites, encephalopathy and/or oesophageal varices with or without bleeding.

Low platelet count, ascites and splenic enlargement are important non-invasive predictors of oesophageal varices. Our aim is to identify the markers, which can indicate the occurrence of bleeding oesophageal varices.

AIM AND OBJECTIVES
- To predict the presence of varices of oesophagus in cirrhotic patients by studying the non-invasive clinical, biochemical and ultrasonographical parameters,(2)
- Correlate platelet count/splenic diameter ratio with grade of varices.(3)
- To study the various type of anaemia picture in cirrhotic patients.
REVIEW OF LITERATURE/CIRRHOSIS

Definition
Cirrhosis is described as hepatic process in which there is fibrosis of liver parenchyma, which is usually ending up with the variable chronic hepatic dysfunction in the form of varying disease presentation. The term cirrhosis was coined by Laennec. Cirrhosis, a Greek word, which means tawny surface or orange. It is concluded that it is an irreparable disease in its end stages at which treatment of choice is transplantation of the cirrhotic liver. However, reversal of cirrhosis (In its earlier stages) has been documented in several forms of hepatic dysfunction following treatment of the underlying aetiology.(6)

Prevalence of Cirrhosis
The worldwide percentage of old and new cases of disease is not known. The percentage of old and new cases of hepatic cirrhotic disease was measured as 0.16% or 4 lakhs in United States. Its contribution for mortality is more than 25,000 in 2001.

There is similarity in the prevalence of cirrhosis in Europe and higher prevalence is noted in African and Asian continent, where chronic hepatitis B viral infection or chronic hepatitis C viral infections found in increasing numbers. A few of the compensated hepatic cirrhotic disease often goes unnoticed for longer duration; a rough measure of 1% of population exhibit features of cirrhosis histologically.

CLINICAL MANIFESTATIONS OF CIRRHOSIS AND PORTAL VENOUS HYPERTENSION
Patients with cirrhosis may have a variable presentation. They might have signs of liver disease identified on clinical examination.

Physical Findings
A number of physical findings have been described in patients with cirrhosis. Spider nevi, Palmar erythema, Changes in nail – Muehrcke’s nails, Terry nails, Clubbing and hypertrophic osteoarthropathy, Dupuytren’s contracture, Gynecomastia, Testicular atrophy, Splenomegaly, Ascites, Caput medusae Cruveilhier-Baungarten murmur, Fetor hepaticus, Jaundice, Asterixis. Other general features that may be seen include - Excessive weakness, lethargy, loss of appetite, loss of weight, symptoms of malnutrition, pigment gallstones resulting from haemolysis, fifteen to thirty percentage of cirrhotic patients have diabetes.

LABORATORY FINDINGS
Haematologic Abnormalities
• Anaemia
Anaemia is usually multifactorial in origin; acute and chronic gastrointestinal blood loss, folate deficiency, direct toxicity due to alcohol, hypersplenism, bone marrow suppression (as in hepatitis-associated aplastic anaemia), the anaemia of chronic disease (inflammation) and haemolysis may all contribute.
• Thrombocytopenia
Low platelet count is mainly caused by increased portal venous pressure with attendant congestive splenomegaly. An enlarged spleen can result in temporary sequestration of up to 90 percent of the circulating platelet mass. However, this uncommonly results in platelet counts less than 50,000/mL. Decreased thrombopoietin levels may also contribute to thrombocytopenia. On multivariate analysis, low platelet count and presence of a palpable spleen were found to have independent predictive value, coagulative deficiencies.

Liver Function Tests
Bilirubin, Transaminases, Alkaline Phosphatase, Gamma-Glutamyl Transpeptidase, Albumin, Globulins, Prothrombin time, Serum sodium.

RADIOGRAPHIC FINDINGS
• Ultrasonography — Ultrasonography is routinely used during the evaluation of the cirrhotic patient.(9) It is non-invasive, well tolerated, widely available and provides valuable information. In advanced cirrhosis, the liver may appear small and nodular. Surface nodularity and increased echogenicity with irregular appearing areas are consistent with cirrhosis, but can also be seen with hepatic steatosis. Findings of portal hypertension include an increased portal vein size and the visible collateral formation, “stiffness” measurement in advanced fibrosis. Computed tomography — CT findings may suggest the occurrence of cirrhosis, but it is not diagnostic. Magnetic resonance imaging, Nuclear studies.

Diagnosis of Cirrhosis
The confirmative diagnosis of cirrhosis is made out with the help of the post-mortem examination of liver or following liver transplantation, during which the architecture of the entire liver can be appreciated. Clinical diagnosis of cirrhosis is confirmed with the histopathological examination of liver during which a liver tissue is collected by either a transcutaneous, transjugular, laparoscopic or ultrasonogram or CT-guided fine-needle biopsy based on the clinical scenario.(5)

MELD score is one of the scoring systems, which was developed to determine the various factors which determined the extent of severity of the liver disease in patients with cirrhosis and during liver transplantation to assess the subjects prior to the procedure. It is based on many factors like bilirubin level, creatinine values and also prothrombin time. There is also a recent addition of sodium level to this scoring system, having comparable results with the previous scoring (MELD).

Upper Gastrointestinal Endoscopy
Till recent times, endoscopy has remained as the best modality for the detection of oesophageal varices.

Endoscopy remains the mainstay in the diagnosis of oesophageal varices, although the role of capsule endoscopy also remains as an important diagnostic aid. Capsule endoscopy is reserved for those patients who cannot undergo endoscopy. Whenever both procedures cannot be performed in patients for predicting the presence of varices, platelet count/splenic diameter is used as an important predictive marker for varices.
Endoscopic Grading of Oesophageal Varices in Cirrhosis

Size - Classification system based on Japanese Research Society of Portal Hypertension.

Grade I: Small oesophageal varices with minimal luminal protrusion.

Results of Studies showing Relationship of Various Parameters Associated with the Occurrence of Large Sized Oesophageal Varices

<table>
<thead>
<tr>
<th>Author</th>
<th>Amarsapurkar</th>
<th>Chalasani</th>
<th>Ng</th>
<th>Pilette</th>
<th>Schepis</th>
<th>Zaman</th>
<th>Madhota</th>
<th>Thomopoulos</th>
<th>Giannini</th>
<th>Bressler</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>India</td>
<td>USA</td>
<td>China</td>
<td>France</td>
<td>Italy</td>
<td>USA</td>
<td>USA</td>
<td>Greece</td>
<td>Italy</td>
<td>Canada</td>
</tr>
<tr>
<td>Number of patients studied</td>
<td>257</td>
<td>782</td>
<td>92</td>
<td>116</td>
<td>143</td>
<td>300</td>
<td>184</td>
<td>184</td>
<td>266</td>
<td>235</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Platelet count</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ascites</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Spiders</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Serum bilirubin</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Prothrombin time or index</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>N</td>
</tr>
<tr>
<td>Child's score or class</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Aetiology other than NASH</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>N</td>
</tr>
<tr>
<td>Portal vein diameter</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>N</td>
</tr>
<tr>
<td>Platelet count/spleen diameter</td>
<td>N0</td>
<td>N0</td>
<td>N0</td>
<td>N0</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>N</td>
</tr>
</tbody>
</table>

Yes indicates presence of relationship and No indicates that the relationship was either not studied or not found.

NASH, Non-Alcoholic Steatohepatitis.

Clinical Predictors of Bleeding from Oesophageal Varices

Variceal haemorrhage accounts for an important cause of mortality in patients with portal hypertension. The rate of occurrence of varices in patients having cirrhosis is 55 to 60%. The size of the varices was directly proportional to the risk of bleeding with larger varices carrying greater risk.

Gastroesophageal varices are present in 50-60% of cirrhotic patients, 30% of patients with cirrhosis have a risk of developing an episode of variceal haemorrhage within one year of diagnosis of varices. Larger varices bleed more often than smaller varices. Several studies stated that low platelet count, ascites and splenomegaly are important predictors of varices in cirrhotic patients and recent studies have shown association among these parameters in predicting bleeding.

Non-Invasive Parameters in Predicting the Occurrence of Varices

Portal hypertension and oesophageal varices are the two important complications occurring in cirrhosis. For patients having an increased risk of variceal bleeding, it is imperative to screen using endoscopy. The screening by endoscopy, though effective, is not affordable to be implemented as a screening procedure and is also an invasive procedure. Therefore, there is a need for non-invasive measures which can effectively predict the occurrence of varices.

Other non-invasive parameters, which are being used for the prediction of oesophageal varices are presence of ascites, splenic diameter, diameter of the portal vein greater than or equal to 13 mm, average velocimetry of the portal vein (Ranging between 20 cm/s and 12 cm/s).

Comparision of Variceal Size and Risk of Bleeding

<table>
<thead>
<tr>
<th>Author</th>
<th>Size</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peglioro al et al 1993 (132)</td>
<td>- 6 - 6 - 6 - 26</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
<td>120</td>
<td>140</td>
</tr>
<tr>
<td>Buroughs et al 1986(78)</td>
<td>- 10 - 10 - 10 - 36</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
<td>120</td>
<td>140</td>
</tr>
<tr>
<td>Vitzel al 1986 (131)</td>
<td>22 36 15 54 19 85</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
<td>120</td>
<td>140</td>
</tr>
<tr>
<td>Kock et al 1987 (130)</td>
<td>22 36 - 11 22</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
<td>120</td>
<td>140</td>
</tr>
<tr>
<td>NIEC 1988 (95)</td>
<td>160 18 112 29 49 49</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
<td>120</td>
<td>140</td>
</tr>
<tr>
<td>Benedeto-Stojanov et al (129)</td>
<td>- - 5 50 17 65.38</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
<td>120</td>
<td>140</td>
</tr>
</tbody>
</table>
MATERIALS AND METHODS
50 diagnosed cases of cirrhotic (25 female, 25 male) patients, aged between 20 yrs. to 60 yrs., confirmed by Ultrasonography and other Biochemical parameters are selected from the Medical OPD and Medical ward in the period of March 2013 - August 2013 and they underwent the following investigations. The patients were selected according to inclusion and exclusion criteria.

Place of Study
Department of Medicine, Medical OPD, Medical ward, Stanley Medical College and Hospital.

Duration: March 2013 to August 2013.

Study Design: Prospective Observational Study Patient.

SELECTION CRITERIA
Inclusion Criteria
- Age more than 20 years and below 60 years.
- All patients with cirrhosis of the liver detected by USG.

Exclusion Criteria
- Age below 20 years and above 60 yrs.
- Hepatocellular carcinoma detected by USG.
- Primary haematological disorder.
- Active UGI bleed on admission.
- Taking B-Blocker for primary prophylaxis of oesophageal varices.
- All diagnosed diabetes mellitus.
- Taking alcohol in the past 6 months.
- History of pyrexia in the past 4 weeks.

All patients underwent the following investigations and the patients were classified according to Child-Pugh’s Classification.

Peripheral smear picture for comment with platelet count, Liver profile (Including liver enzymes, serum bilirubin and prothrombin time), serum albumin, ultrasonography for liver architecture, spleen diameter, portal vein diameter and free fluid, upper GI endoscopy.

The following Parameters were defined
Cirrhosis
Detected by USG (Altered Coarse Echotexture of the liver parenchyma with surface micronodularity in the setting CLD).

Splenomegaly
Spleen bipolar diameter more than 100 mm by USG.

Normal Platelet Count
150-450x103/µl. mm.

Size of Oesophageal Varices
1. Large sized varices occupying the lower one-third portion of the oesophagus occupying one-third lumen, having oesophageal lumen protrusion and does not flatten with insufflations.
2. Small: Varices similar to large sized except that it occupies less than one-third lumen of oesophagus.

Platelet count/splenic diameter ratio: Platelet count 103/splenic diameter in mm.

All the data were analysed in the SPSS 14 version for windows and mean standard deviation, Pearson’s correlation efficient and independent T-test were used to identify the significance of study.

OBSERVATIONS

Distributions of Cases According to Child-Pugh’s Classification

Non-Invasive Predictors for the Occurrence of Varices of Esophagus

CORRELATION OF PORTAL VEIN DIAMETER WITH ESOPHAGEAL VARICES

CORRELATION OF PLATELET COUNT WITH ESOPHAGEAL VARICES
DISCUSSION
Non-Invasive Parameters for Predicting the Occurrence of Oesophageal Varices

In our study, out of 50 patients 13 patients (26%) were in the class A, 23 patients (46%) were in the class B and 14 patients (28%) were in the class C. On correlation of platelet count alone with oesophageal varices, cirrhotic patients with no oesophageal varices showed the mean platelet count of 153.64 with SD±28.02, patients with small oesophageal varices showed the mean platelet count of 132.94 with SD±16.49 and patients with large oesophageal varices showed the mean platelet count of 90.27 with SD±19.32. The correlation was significant with a Pearson correlation coefficient r=-0.801 with a 2-tailed significance of sig. (2-tailed) of 0.000. (Correlation is significant at the 0.01 level (2-tailed)). Platelet count alone with a mean value of 132.9 (x10^3/cu.mm) can predict the oesophageal varices showing a sensitivity of 74.36%, specificity 72.73%, positive predictive value of 90.62% and negative prediction value 44%.

On correlation of portal vein diameter alone with oesophageal varices, cirrhotic patients with no oesophageal varices showed the mean portal vein diameter of 12.9 with SD±1.93, patients with small oesophageal varices showed the mean portal vein diameter of 14.24 with SD±2.20 and patients with large oesophageal varices showed the mean portal vein diameter of 15.80 with SD±2.05. The correlation was significant with a Pearson correlation coefficient r=-0.570 with a 2-tailed significance of sig. (2-tailed) of 0.000. (Correlation is significant at the 0.01 level (2-tailed)). Portal vein diameter alone with a mean of 14.23 mm can predict the oesophageal varices having sensitivity of 69.23%, specificity of 81.8% and positive predictive value of 93.11% and negative predictive value of 42.8%.

On correlation of spleen diameter alone with oesophageal varices, cirrhotic subjects with no oesophageal varices showed mean spleen diameter of 141.80 with SD±19.52, subjects with small oesophageal varices showed mean spleen diameter of 143.70 with SD±15.64 and subjects with large oesophageal varices showed the mean spleen diameter of 178.18 with SD±22.12. The correlation was significant with a Pearson correlation coefficient r=0.679 with a 2-tailed significance of sig. (2-tailed) of .000. (Correlation is significant at the 0.01 level (2-tailed)). Spleen diameter alone with a mean of 143.7 mm can predict the oesophageal varices having sensitivity of 74.35%, specificity...
of 63.63%, positive predictive value of 87.87% and negative predictive value about 41.17%.

On correlation of ratio of platelet count and splenic diameter with oesophageal varices, subjects who did not have oesophageal varices showed a mean platelet count/splenic diameter ratio of 1.09 with SD±0.20, subjects having small oesophageal varices showed the mean platelet count/spleen diameter ratio of 0.94 with SD±0.16 and patients with large oesophageal varices showed the mean platelet count/splenic diameter ratio of 0.52 with SD±0.15. The correlation was significant with a Pearson correlation coefficient r=-0.900 with a 2-tailed significance of sig. (2-tailed) of 0.000. (Correlation is significant at the 0.01 level (2-tailed)).

When the platelet count and splenic diameter ratio had mean of .93 (x103) can predict the varices of esophagus with a sensitivity of 79.5%, specificity of 72.73%, positive predictive value of 91.18% and negative predictive value of 50%.

So the non-invasive parameters cannot be an alternative of upper GI endoscopy, but the platelet count/splenic diameter of mean value of 0.52 can predict the large oesophageal varices with 100% specificity, also with 100% of positive predictive value.

REFERENCES
3. Philip Abraham- Cirrhosis of liver, API textbook of Medicine,8th ed;11:697.