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 cirrhotics.

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 with no, small, large oesophageal varices were 12.9, 14.24 and 15.80 mm respectively. It alone can predict varices with 69.23% sensitivity and 81.8% specificity with a mean of 14.23 mm. The mean splenic diameter in cirrhotics were 141.80, 143.70 and 178.18 mm in no, small and large varices respectively. It alone predicts 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. It predicts varices with 79.5% sensitivity and 91.18% specificity with a mean of 0.93.22; out of 50, 44% had dimorphic, 24% had microcytic hypochromic, 22% haemolytic, 4% had pancytopenia, 4% had thrombocytopenia and 2% had normal blood picture in peripheral smear.

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.

HOW TO CITE THIS ARTICLE: Sujatha SM, Vasumathi G, Kumar PS, et al. Cirrhosis: Non-invasive parameters for predicting the occurrence of oesophageal varices. J. Evolution Med. Dent. Sci. 2016;5(40):2460-2465, DOI: 10.14260/jemds/2016/574

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.

Financial or Other, Competing Interest: None.

Submission 02-03-2016, Peer Review 04-04-2016,

Acceptance 11-04-2016, Published 19-05-2016.

Corresponding Author:

S. M. Sujatha,
No. 1, 8th Street,
Balaji Nagar,
Nanganallur,
Chennai-61.

E-mail: smsuja2011@yahoo.com

DOI: 10.14260/jemds/2016/574

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. Scirrhosis, 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.⁽⁴⁾

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-Baumgarten murmur, Fetus 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.

Grade II: Moderate sized varices.

Grade III: Large sized varices.

Grade IV: Extremely large varices that do not flatten on insufflations and completely obscure the gastrooesophageal junction.

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

Author	Amara-purkar	Chalasani	Ng	Pilette	Schepis	Zaman	Madhotra	Thomopoulos	Giannini	Bressler
Year	1994	1999	1999	1999	2001	2002	2002	2003	2003	2005
Country	India	USA	China	France	Italy	USA	USA	Greece	Italy	Canada
Number of patients studied	257	782	92	116	143	300	184	184	266	235
Splenomegaly	No	Yes	Yes	No	No	No	Yes	Yes	Yes	N
Platelet count	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Y
Ascites	No	No	Yes	No	No	No	No	Yes	No	N
Spiders	No	No	No	Yes	No	No	No	No	No	N
Encephalopathy	No	No	Yes	No	No	No	No	No	No	N
Serum albumin	No	No	No	No	No	No	No	No	No	Y
Serum bilirubin	No	No	No	No	No	No	No	No	No	Y
Prothrombin time or index	No	No	No	Yes	No	No	No	No	No	N
Child's score or class	No	No	No	No	No	Yes	No	No	Yes	N
Aetiology other than NASH	No	No	No	No	No	No	No	No	No	N
Portal vein diameter	No	No	No	No	No	No	No	No	No	N
Platelet count/spleen diameter	No	No	No	No	No	No	No	No	Yes	N

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.

Gastrooesophageal 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.⁽⁶⁾

Comparison of Variceal Size and Risk of Bleeding

Author	Size					
	1		2		3	
	No.	%	No.	%	No.	%
Pecgioro et al 1993 (132)	-	6	-	-	-	26
Burroughs et al 1986(78)	-	10	-	-	-	36
Vitzel et al 1986 (131)	22	36	15	54	19	85
Kock et al 1987 (130)	22	36	-	-	11	22
NIEC 1988 (95)	160	18	112	29	49	49
Benedeto-Stojanov et al (129)	-	-	5	50	17	65.38

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).

Splenic diameter per se is proved to be an independent predictive measure of varices.^(7,8) Thrombocyte count has also been reported to have a major predictive role for varices. Increased bilirubin, splenomegaly, presence of spider angiomas, prolongation of prothrombin time, thrombocyte count/splenic diameter are some of the other important non-invasive parameters used for the prediction of varices. These parameters yet cannot be substituted for endoscopy in clinical practice.

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/cu. 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

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 $SD \pm 28.02$, patients with small oesophageal varices showed the mean platelet count of 132.94 with $SD \pm 16.49$ and patients with large oesophageal varices showed the mean platelet count of 90.27 with $SD \pm 19.32$. 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 ($\times 10^3/\text{cu. mm}$) can predict the oesophageal varices showing a sensitivity of 74.36%, specificity 72.73%, positive predictive value of 90.62% and negative prediction 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 $SD \pm 1.93$, patients with small oesophageal varices showed the mean portal vein diameter of 14.24 with $SD \pm 2.20$ and patients with large oesophageal varices showed the mean portal vein diameter of 15.80 with $SD \pm 2.05$. 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 $SD \pm 19.52$, subjects with small oesophageal varices showed mean spleen diameter of 143.70 with $SD \pm 15.64$ and subjects with large oesophageal varices showed the mean spleen diameter of 178.18 with $SD \pm 22.12$. The correlation was significant with a Pearson correlation coefficient $r = 0.679$ with a 2-tailed significance of sig. (2-tailed) of 0.000. (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 $SD \pm 0.20$, subjects having small oesophageal varices showed the mean platelet count/spleen diameter ratio of 0.94 with $SD \pm 0.16$ and patients with large oesophageal varices showed the mean platelet count/splenic diameter ratio of 0.52 with $SD \pm 0.15$. 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 ($\times 10^3$) 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 a specificity of 100% and positive predictive value of 100%.

Anaemia Profile in Cirrhosis

In our study, we found 22 patients out of 50 patients were having Dimorphic picture (44%), 12 patients (24%) were having microcytic hypochromic picture, 11 patients (22%) were having haemolytic picture, 2 patients (4%) were having pancytopenia, 2 patients (4%) were having normal picture with thrombocytopenia and 1 patient (2%) was having normal picture.

SUMMARY AND CONCLUSION

Non-invasive Parameters for Prediction of Oesophageal Varices

Even though parameters that are non-invasive can predict the presence of varices in oesophagus, the negative predictive

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

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