TO EVALUATE THE REPRODUCIBILITY AND VALIDITY OF NON-INVASIVE PARAMETER PLATELET COUNT SPLENIC DIAMETER RATIO TO PREDICT ESOPHAGEAL VARICES IN INDIAN POPULATION WITH HEPATIC CIRRHOSIS

By

DR. V. KISHORE

DISSERTATION SUBMITTED TO SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTER, KOLAR, KARNATAKA

In partial fulfillment of the requirements for the degree of

DOCTOR OF MEDICINE

IN

GENERAL MEDICINE

Under the Guidance of

Dr. RAVEESHA. A MD

Professor and Head of the department

SDUMC, KOLAR

DEPARTMENT OF GENERAL MEDICINE,

SRI DEVARAJ URS MEDICAL COLLEGE,

TAMAKA, KOLAR-563101

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH

TAMAKA, KOLAR-563101, KARNATAKA

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation/thesis entitled **"TO EVALUATE THE REPRODUCIBILITY AND VALIDITY OF NON INVASIVE PARAMETER PLATELET COUNT SPLENIC DIAMETER RATIO TO PREDICT ESOPHAGEAL VARICES IN INDIAN POPULATION WITH HEPATIC CIRRHOSIS"** is a bonafide and genuine research work carried out by me under the guidance of **Dr.RAVEESHA.A**, Professor and head of the Department of General Medicine, Sri Devaraj Urs Medical College, Tamaka, Kolar.

This work has not formed the basis for the award of any other degree or diploma to me previously by any other university.

Date: **DR V. KISHORE**

Place: Kolar

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION,

TAMAKA, KOLAR, KARNATAKA

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled **"TO EVALUATE THE REPRODUCIBILITY AND VALIDITY OF NON-INVASIVE PARAMETER PLATELET COUNT SPLENIC DIAMETER RATIO TO PREDICT ESOPHAGEAL VARICES IN INDIAN POPULATION WITH HEPATIC CIRRHOSIS"** is a bonafide and genuine research work done by **Dr. V. KISHORE** in partial fulfillment of the requirement for the degree of **M.D IN GENERAL MEDICINE.**

Date :

Place :

Dr. RAVEESHA . A

Professor, and head of department

Department of General Medicine,

Sri Devaraj Urs Medical College,

Tamaka, Kolar.

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTER, TAMAKA, KOLAR, KARNATAKA

ENDORSEMENT BY THE HOD, PRINCIPAL / HEAD OF THE INSTITUTION

This is to certify that the dissertation entitled **"TO EVALUATE THE REPRODUCIBILITY AND VALIDITY OF NON INVASIVE PARAMETER PLATELET COUNT SPLENIC DIAMETER RATIO TO PREDICT ESOPHAGEAL VARICES IN INDIAN POPULATION WITH HEPATIC CIRRHOSIS"** is a bonafide and genuine research work done by Dr.V. KISHORE under the guidance of **Dr.RAVEESHA A**. Professor, Department of General Medicine, Sri Devaraj Urs Medical College, Tamaka, Kolar.

Dr. RAVEESHA A
Professor & HOD
Department of General Medicine,
Sri Devaraj Urs Medical College,
Tamaka, Kolar

Date:
Place: Kolar

Dr.P N SREERAMULU .
Principal,
Sri Devaraj Urs Medical College
Tamaka, Kolar

Date:
Place: Kolar

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTER, TAMAKA, KOLAR, KARNATAKA

ETHICS COMMITTEE CERTIFICATE

This is to certify that the Ethical committee of Sri Devaraj Urs Medical College & Research Center, Tamaka, Kolar has unanimously approved

Dr.V KISHORE

Post-Graduate student in the subject of

GENERAL MEDICINE

at Sri Devaraj Urs Medical College, Kolar to take up the Dissertation work entitled **"TO EVALUATE THE REPRODUCIBILITY AND VALIDITY OF NON-INVASIVE PARAMETER PLATELET COUNT SPLENIC DIAMETER RATIO TO PREDICT ESOPHAGEAL VARICES IN INDIAN POPULATION WITH HEPATIC CIRRHOSIS"** *to be submitted to the* SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTER, TAMAKA, KOLAR, KARNATAKA.

Date:

Place: Kolar

Member Secretary

Sri Devaraj Urs Medical College,

& Research Center, Tamaka, Kolar–563101

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION

TAMAKA, KOLAR, KARNATAKA

COPY RIGHT

DECLARATION BY THE CANDIDATE

I hereby declare that the Sri Devaraj Urs Academy of Higher Education and Research Center, Kolar, Karnataka shall have the rights to preserve, use and disseminate this dissertation/thesis in print or electronic format for academic / research purpose.

Date:

Place: Kolar **DR V KISHORE**

ACKNOWLEDGEMENT

I would like to take this opportunity to thank all those who have been a part of this wonderful journey that has culminated in the completion of this thesis.

I am deeply indebted and grateful to my guide**, Dr.RAVEESHA A**, Professor,and head of Department of General Medicine, Sri Devaraj Urs Medical College, for his able guidance, support, timely advice and constant encouragement throughout the period of the study.

I convey my sincere thanks to **DR. V.LAKSHMAIAH, DR. B.N. RAGHAVENDRA PRASAD, DR.PRABHAKAR, DR.VIDYA SAGAR C R, DR. SRINIVASA S V, DR NIVEDITHA, DR JAYAPRASAD V, DR ANITHA A, DR VISHWANATH REDDY, DR PRASANNA,DR SINDHU,DR THANUJ REDDY** for their advice and encouragement throughout the study.

I offer my salutations and thank all my teachers who have not only guided me through the maze of new information and skills but also shaped my personality by chiseling out all the rough edges.

I am thankful to my postgraduate **colleagues DR M SASI SHEKAR, DR SREENATH , DR DHRUVA ,DR SANMITA RAM. S ,DR DEEPTHI ,DR CHARCHITH and DR MEGHASR**I for their motivation and for being a constant source of strength.

If I have learnt to see far it is only by standing on the shoulders of my great teachers.

I am thankful to all my seniors especially **DR SAMBA SHIVA RAO, DR JITHENDRA, DR POOJITHA, DR DWARAK, DR MAHARAJ, DR RAGAVENDRA** and dear juniors for their love, motivation and help.

At the foremost I offer my gratitude and seek blessings from my parents, **V**

SRIRAMULU, V VENKATA SUBBAMA, my sisters **V SRI DEVI** and brother **V RAJA** whose countless sacrifices and endless love has made me who I am today in life.

I am highly indebted to my patients for providing me an opportunity to carry out this study.

Last but not least, I am thankful to all Technical Staff and non-teaching staff for theirinvaluable help without which this study would not have been possible.

Date: **Dr V KISHORE**

Place

Sri Devaraj Urs Academy of Higher Education and Research

Certificate of Plagiarism Check for Dissertation

Author Name	Dr.VARDHINENI KISHORE
Course of Study	MD.GENERAL MEDICINE
Name of Major Supervisor	DR.RAVEESHA.A
Department	GENERAL MEDICINE
Acceptable Maximum Limit	10%
Submitted By	librarian@sduu.ac.in
Paper Title	TO EVALUATE THE REPRODUCIBILITY AND VALIDITY OF NON INVASIVE PARAMETER PLATELET COUNT SPLENIC DIAMETER RATIO TO PREDICT ESOPHAGEAL VARICES IN INDIAN POPULATION WITH HEPATIC CIRRHOSIS
Similarity	8%
Paper ID	190198
Submission Date	2020-12-01 14:19:52

Signature of Student

Signature of Major Advisor
Prof & HOD of Medicine
SDUMC, Tamaka, Kolar

Head of the Department
Prof & HOD of Medicine
SDUMC, Tamaka, Kolar

University Librarian

Director Of Post Graduate Studies
Director
PG STUDIES
Sri Devaraj Urs Medical College
Tamaka, KOLAR-563 101

* This report has been generated by DrillBit Anti-Plagiarism Software

ABSTRACT

Background: Esophageal varices (EV) are engorged veins in the esophagus. The prevalence of EV in cirrhosis patients is nearly 3-12%, and around 8 to 12% of subjects show the advancement of EV from small to large veins.

Aim: To evaluate the reproducibility or validity of non - invasive parameter platelet count/splenic diameter ratio to predict esophageal varices in Indian population with hepatic cirrhosis

Materials and methods: All the cirrhosis patients irrespective of etiology, attended to the outpatient ward in the department of General Medicine at R.L. JALAPPA hospital and research centre Tamaka, Kolar. Who fulfils the inclusion criteria were considered as the study population? The current study was a cross-sectional study.

Results: A total of 52 subjects were included in the final analysis. The mean age was 50.1 ± 13.97in the study population, ranged between was 25 years to 78 years in the study population. Among the study population,44(84.62%) participants were male and remaining 8(15.38%) participants were female. Relationship between non-invasive parameters like Age, Serum Bilirubin, Serum albumin, Haemoglobin, Platelet count, Spleen Bipolar diameter,PC/SD ratio to the presence of varices was studied and were not statistical significance. The mean spleen bipolar diameter was 119.1 ± 31.09 in the study population. The mean Platelet tospleen diameter Ratio was 1201.3 ± 941.54. No significant values were obtained on the comparison of varices with Platelet to spleen diameter ratio. Predictive validity of Platelet to spleen diameter ratio in predicting varices had a sensitivity of 47.83%; specificity was 33.33%.

Conclusion: This study indicates that it may be possible to predict the presence of large esophageal varices using simple and non-invasive tools like a clinical examination for the presence of a palpable spleen and platelet count with a fairly high degree of accuracy.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Glossary	Abbreviations
AIH	Autoimmune hepatitis
ALT	Alanine aminotransferase
APRI	Aspartate aminotransferase-to-platelet ratio index
APRI	Ast to platelet ratio index
ARFI	Acoustic radiation force impulse imaging
AST	Aspartate aminotransferase
AUC	Area under the curve
CI	Confidence interval
CRC	Cirrhosis related complications
EGD	Esophagogastroduodenoscopy
EV	Esophageal varices
EVB	Esophageal variceal bleeding
FI	Fibrosis index
FIB-4	fibrosis-4-index
GOV	Gastroesophageal varix
HVPG	Hepatic venous pressure gradient
IGV	Isolated gastric varix
MELD	Model for end-stage liver disease
NASH	Non-alcoholic steatohepatitis
PBC	Primary biliary cirrhosis
PC/SD	Platelet count/spleen diameter ratio
PSC	Primary sclerosing cholangitis
PV	Portal vein
QOL	Quality of life
RD	Renal dysfunction
ROC	Receiver operative curve
SWE	Shear wave elastography
WHO	World health organization
WHVP	Wedged hepatic venous pressure

INTRODUCTION

INTRODUCTION:

Esophageal varices (EV) are engorged veins in the esophagus. This is caused by an obstruction in the blood flow by portal vein carrying through intestine, pancreas, spleen and tothe liver. Liver cirrhosis subjects with portal hypertension mainly develop EV. The prevalence of EV in cirrhosis patients is nearly 3-12%, and around 8 to 12% of subjects show the advancement of EV from small to large veins.[1] Following alcohol withdrawal, there canbe an immediate regression of EV of small veins.[2,3]

A most important complication of EV is variceal bleeding with mortality rate reported to be 11.1 to 40%.[4,5] Vital predictors of variceal bleeding are the size of varices, the existence of red spots and severity of cirrhosis.[6] Variceal bleeding treated by β-blockers can reduce the chance of bleeding in nearly half of subjects with large and medium varices.[7,6] The diagnosis of EV and the size of varices can be estimated by esophagogastroduodenoscopy (EGD). However, EGD consist of complications related to endoscopy, requiring general anaesthesia and relatively expensive procedure.[8, 6] Hence, with these disadvantages, new diagnostic tools wereresearched to detect varices. Several non and minimally invasive tools have been suggested asa substitute to EGD for examining EV.[9] Recent guidelines by Baveno VI suggested the use ofEGD can be circumvented in subjects with (cACLD) compensated advanced chronic liver disease presenting with <20 kPa liver stiffness and >150,000/μL of platelet count.[9]

Presently non-invasive approaches have a discrete role in patients with (CSPH) clinically significant portal hypertension in subjects with cACLD.[9] Non- invasive approach is beneficial in subjects with viral infected cACLD to suspect CSPH, significant in a set of subjects at the peril of possessing endoscopic signs of portal hypertension.[9]

EV can be detected using liver stiffness assessed by transient elastography alone or with combined platelet count and spleen size.[10]

Additionally, collateral circulation identified on imaging is sufficient to rule-in CSPH in patients with cACLD of all etiologies. Non-invasive methods do not yet have a well- established role in the follow up of patients with varices.

THE NEED FOR THE STUDY:

The most common cause of mortality in cirrhosis subjects is a progression of esophageal varices and portal hypertension. The esophageal varices are commonly presented by the gold standard method "gastrointestinal endoscopy". The role of gastrointestinal endoscopy is crucial in cirrhotic patients due to high prevalence (60% -80%) of varices in liver cirrhosis, and these varices mature to bleeding in nearly 40% of cirrhotic subjects.[11,12] According to the guidelines, endoscopy should be done most regularly.[9]

In India, most of the interventional procedure are not cost-effective and hence non -invasive methods which are more affordable becomes a requirement. Endoscopy plays a vital role in predicting the size of varices and thus bleeding. Therefore, non-invasive methods in predicting size and bleeding could be a benefit to subjects. Several studies have attempted to study various non-invasive test to foresee EV. Most frequently studied non-invasive methods are the spleen diameter and platelet count ratio. Hence our study intended to study the practical use of platelet count and spleen diameter ratio in predicting EV in cirrhosis patients.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES:

- To evaluate the reproducibility or validity of non - invasive parameter platelet count/splenic diameter ratio to predict esophageal varices in Indian population with hepatic cirrhosis.

REVIEW OF LITERATURE

REVIEW OF LITERATURE:

Global burden of Hepatic Cirrhosis:

The worldwide chief cause of the deaths related to liver diseases is because of the Cirrhosis.[13] The architecture of the liver is lost in the end stage of the fibrosis of the liver.[14] during the beginning of the disease the compensation is done for any the cirrhosis. Hence there is only the incidental finding of the initial stages. So, the prevalence rates are biased for compensated cirrhosis. "Decompensation in patients with compensated cirrhosis is usually defined as the first occurrence of ascites, oesophageal variceal bleeding, hepatic encephalopathy, and, in some individuals, increased bilirubin concentration".[15,16] Due to these reasons reports of decompensated cirrhosis prevalence are accurate than compensated cirrhosis prevelance.[15] as it goes unnoticed the death rate may increase up to 80% in the decompensation.[17,18] The mortality and morbidity that occurs due to the liver diseases may be said in the decompensated conditions. In these patients, they need thorough medical care and hospitalizations that may be frequent and long.[19] Also, there may be a need for transplant that puts the burden on the health-care systems, patients, and governance health financing.[19] However, in the Compensated cirrhosis, a life expectancy similar to that of healthy adults is expected. [17] To achieve that the identification of the initial stages is important.[15,20]

According to the latest statistics cirrhosis lead to greater than 1.32 million mortality globally in 2017, where mortality in men accounted for about 440 000 and in women was 883 000. The mortality rate in 2017 worldwide constituted 2.4%. This statistic was higher whencompared to 1.9% in 1990. However, when the age-standardised death rate worldwide witnessed a low from 21 per 1000000 people in 1990 to 16.5 per 1000000 in 2017. Further, the age-standardised death rate decrease was much appreciated in the high-income region (10.1 per 100 000) in 2017 and in contrast was greatest in low income sub- Saharan African region with 32.2 per 100 000 in the same from 1990-2017.

During 1990-2017 mortality was the same in the men and women in the same age groups. But the men surpassed women later globally.[14] In 2017, cirrhosis led to around 41.4 million DALYs. During 1990 and 2017, mortality in the same age groups, DALYs were less among women than men.

Usually, women have a low percentage of mortality rates due to alcoholism and hepatitis B than men but have a higher rate due to various causes, including NASH. This tendency could be determined by a lower frequency of high-risk behaviours; hormonal factors; the higher occurrence of obesity;[21] less consumption of alcohol;[22] and diseases that are seen in females like autoimmune hepatitis, that responds well to treatment and has lower mortality.[23]

"Non-Viral Cirrhosis and Chronic Liver Diseases":

„Alcohol"

3.8% of the world"s mortality and 4.6% of DALYs are alcohol-related in the reports of WHO. 9.5% of alcohol-related DALY"s globally are due to Liver disease but are different in different regions. France and Spain of Europe have the highest liver-related death due to Alcohol nearly 30 in one lakh in a year. Mortality due to alcohol as a cause of death is less reported due to legal issues. Also, the classification of liver diseases is not well establisheddue to a poor drafted national questionnaire. Alcohol has become the chief cause of liver failure related deaths even in developing countries like India.[24]

"Non-Alcoholic steatohepatitis (NASH)"

In 2005 WHO"s report the over one billion are overweight, & thirty million people as obese that is again on a gradual rise. Internationally, NASH prevalence ranges from six to thirty-five percent.[25] Prevalence rates are in US 10-35%, Japan14%, China 5%, and. India 5-28%. [26] NASH Clinical Research Network"s data shows the individuals with NAFLD have lower QOL that was enhanced in patients with cirrhosis, diabetes and obesity.[27]

„Cryptogenic"

Many of the subjects with cirrhosis may also have diabetes and obesity like patients with NASH and signifies end-stage NASH. Some of the cryptogenic cirrhosis patients may represent Autoimmune Hepatitis (AIH) in a "burnt-out" stage. Prevalence of HCC among cryptogenic cirrhosis patients is 6.9-29% and reportedly increasing.[27]

"Cholestatic and autoimmune liver disease."

The incidence and prevalence of primary biliary cirrhosis (PBC) in Europe and the US, has been measured as 2-3 (peak incidence of 4-6 in women 40 years of age) and 21-40 (59-65 in adult women) per a lakh persons per year, and mortality rate of 0.5 per lakh per year.[28] The incidence and prevalence of primary sclerosing cholangitis (PSC) of 1.3 and 8.5 per 100,000 per year, respectively, and mortality rates were the same as that for PBC were calculated from the Data from Norway.[29]

Indian burden of Hepatic Cirrhosis:

WHO"s 2018 reports show that Liver Disease Deaths in India reached 264,193 or 3.00% of total deaths. The Death Rate was 23.00 per 100,000 of population among the subjects at a similar age, that ranks India #62 in the world. The burden of liver ailments in India is large, with 22.2 deaths per 100,000 people only contributed to cirrhosis.[30] Jain et al[31], studies showed 1-year mortality rate in subjects with cirrhosis of the liver with 27.7%. It was greater in subjects with advanced liver disease as demonstrated by greater MELD score and greater frequency of CRC (cirrhosis related complications) at registering. Those with RD (renal dysfunction) had poor rates of survival. Patients with variceal bleeding in their first visit had poor survival. Past the 4th admission onwards, almost all CRCs were related with pooroutcomes. It can be hence inferred among patients with advanced liver condition should be of priority for liver transplantation.[31]

Pathophysiology of Esophageal varices:

Portal hypertension has increased portal inflow as well as increased outflow resistance.[32] Even though direct measurement of portal pressure gives accurate condition, the clinical application is limited due to the invasiveness of portal venous catheterization. The Hepatic venous catheterization is a common technique to measure portal pressure. Wedged hepatic venous pressure (WHVP) mirrors the sinusoidal pressures, and hepatic venous pressure gradient (HVPG) is the difference between WHVP and free hepatic venous pressure, being a good predictor for the severity of portal hypertension. Portal hypertension leads to the development of collateral vessels, which are the route blood returning to the systemic circulation from the portal system detouring the liver.[33]

CLASSIFICATION OF GASTRIC VARICES:

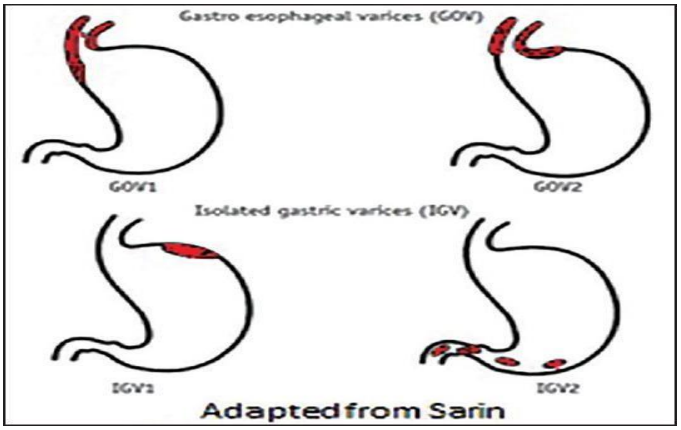
There are three types of classification commonly used for GV.[34]

1. Sarin's classification
2. Hashizome classification
3. Arakawa's classification.

Most commonly used classification is Sarin's classification of GV.

SARIN'S CLASSIFICATION:

Figure 1: Gastric varices can be grouped into four types based on the relationship with esophageal varices, as well as by their location in the stomach.[35]



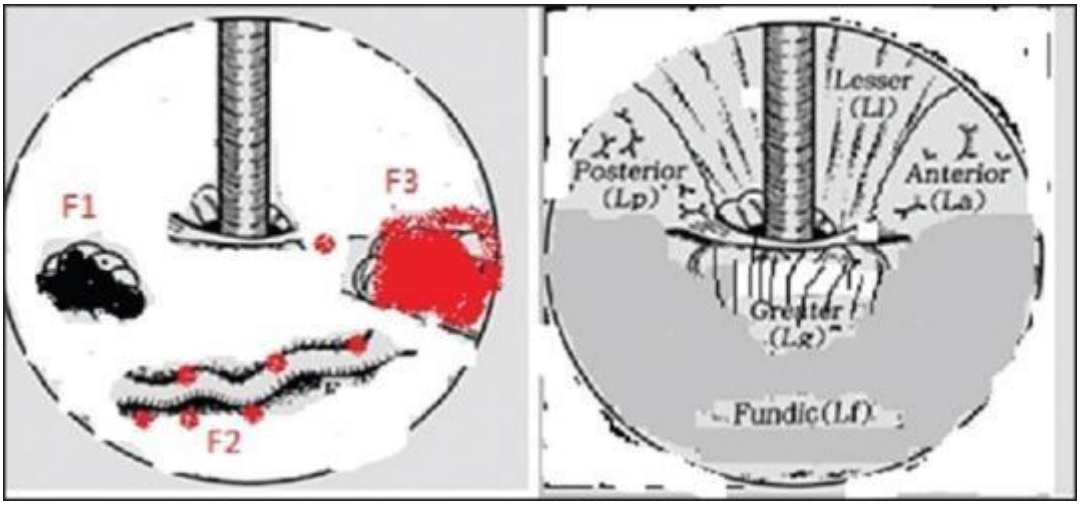
a. Gastroesophageal varix (GOV) type 1: Extension of esophageal varices along lesser
b. Gastroesophageal varix type 2: Extension of esophageal varices along great curve
c. Isolated gastric varix (IGV) type 1 and
d. Isolated gastric varix type 2: Varices in stomach or duodenum as shown in the figure.

Gastroesophageal varix type 1 is the most common type, accounting for 74% of all GV. However, the incidence of bleeding is highest with IGV type 1, followed by GOV type 2. On the whole, the good predictor of haemorrhage is the varices size, with the highest danger of the first haemorrhage (15%/year) seen in those with the large varices. Other predictors of haemorrhage are decompensated cirrhosis (Child B or C) and the endoscopic presence of red wale marks.[36]

HASHIZOME CLASSIFICATION:

Created on clinically significant endoscopic findings, and particularly from the perspective of findings associated with the light risk of rupture, similar to the classification of esophageal varices. (Figure 2). Thus, endoscopic findings of GV were classified according to their form, location, and color. [37]

Figure 2: The form was classified into three types:



a. Tortuous (F1).

b. Nodular (F2).

c. Tumorous (F3).

The location was categorized as five types and depended on hemodynamic factors;

a. Anterior (La).

b. Posterior (Lp).

c. Lesser curvature (Ll).

d. Greater curvature (Lg) of the cardia and.

e. Fundic area (Lf).

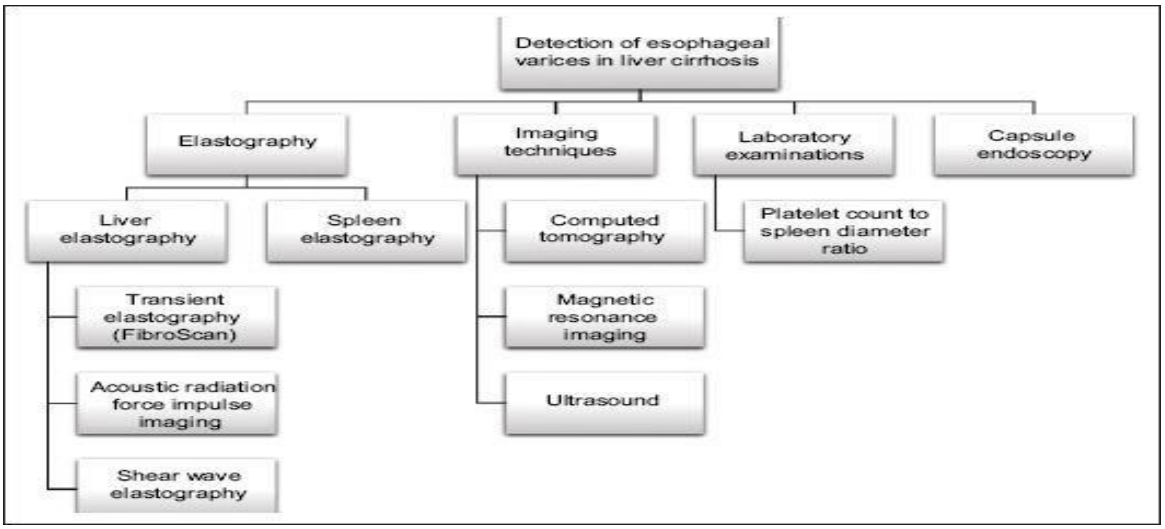
The colors can be classified in (a) white (Cw) or (b) red (Cr). The glossy, thin-walled focal redness on the varix was defined as red color spot (RC spot). The Hashizume group reported that the RC spot and larger forms were related to a significantly higher risk of gastric variceal bleeding. The form and location of Hashizome classification are shown in Figure 2.

Arakawa's classification[38]", type I: Branches within the stomach wall are very few, and the supplying vessel, varix and draining vessel form a single continuous vein of a nearly unchanged caliber."

- Ia: "A single supplying vessel forms fundic varix."
- Ib: "Plural supplying vessels join and form varix that drains into a single draining vessel".
- Type II: "Beside the main supplying and the draining vessels, there are many branching vessels that exist within the stomach wall, namely varix has communications with vessels within the stomach wall."

Non-invasive methods of screening Esophageal varices:

Figure 3: Diagnostic non-invasive methods for detection of esophageal varices among the subjects with liver cirrhosis are as follows.[6]



1.Elastography

1a. Liver elastography

Transient elastography (Fibro Scan)

"Acoustic radiation force impulse imaging."

"Shear wave elastography."

1b. Spleen elastography

2. Imaging techniques include

- Computed tomography
- Magnetic resonance imaging
- Ultrasound

3. Laboratory test

The ratio of the Platelet count to spleen diameter

1. capsule endoscopy

Liver and spleen elastography:

At present, there are three different elastography techniques that measure liver and spleen stiffness. TE (Fibro Scan) uses a mechanical wave generated by a special transducer, while "acoustic radiation force impulse imaging" (ARFI) and "shear wave elastography" (SWE) use sound waves. TE has technical limitations, of which the main ones are ascites, obesity, and narrow intercostal spaces. Though there are new probes that enhanced the TE in obesepatients[6] and patients with narrow intercostal spaces, such as children[6] TE remains unfeasiblein patients with ascites.[39] ARFI and SWE have partly overcome these limitations and have shown higher success rates.[40,41] The diagnostic accuracy of all three methods is similar, butTE has been validated in more studies. The above methods have been used to correlate spleen and liver stiffness with the incidence of varices.[6]

Many non-invasive methods have been investigated regarding screening for EV. Some simple parameters were identified as being associated to the presence of varices: "platelet count, spleen diameter, portal vein diameter, the presence of ascites, the presence of telangiectasias, prothrombin activity, albumin, alanine aminotransferase, the Child-Pugh classification, among others".[42,43] Nevertheless, their performance in predicting the existence of EV was not sufficient. "Aspartate aminotransferase-to-platelet ratio index" (APRI) was also evaluated in this context.

APRI was first described for the prediction of liver fibrosis in patients with hepatitis C.[44] The fact of being a predictor of liver fibrosis, which is itself related to the origin of portal hypertension in cirrhosis, and the fact of using the count of the platelet on its denominator, a variable independently associated to the presence of EV, have led regarded for screening method for EV. The first study to evaluate APRI for this purpose demonstrated that it was associated to the presence of EV in the univariate analysis, but not in the multivariate one.[34] Berzigotti et al[43], demonstrated an association between APRI and clinically significant portal hypertension, but not directly to the occurrence of EV. When evaluating patients with compensated cirrhosis related to hepatitis C, Castéra et al[45], found that APRI had a sensitivity of only 68% for predicting EV. Stefanescu et al[46], found that APRI had a sensitivity of 66.24% for predicting EV, while Wang et al[47], found a sensitivity of 71%. It was also studied that APRI in patients with cirrhosis and found a sensitivity of 64.7%and a negative predictivevalue (NPV) of only 43.2% for predicting EV.[48] Considering the presented evidence, one can easily realize that APRI is not a suitable method for screening for EV. Until recently, the moststudied and promising non-invasive method for screening for EV was platelet count/spleen diameter ratio (PC/SD). It was proposed by Giannini et al[49], who identified an NPV 100% equally in a training set of 145 cirrhotic patients and in a validation cohort of 121 patients, using a cut-off point of909 for PC/SD. According to that study, using a PC/SD above 909 to predict the absence of EV would have saved 27.4% of endoscopies in the whole sample of 266 patients.[50] The rationale for PC/SD is correcting thrombocytopenia, which has many causes associated to liver diseases, by spleen diameter, since splenomegaly is mostly associated to portal hypertension in these patients.[50] Moreover, besides the impressive results in first published papers on PC/SD, this method would have the advantage of not increasing costs of the assistance of patients with cirrhosis, since both platelet count and abdominal ultrasound are already part of the routine workup of these patients.

Giannini et al[51], suggested that PC/SD could be used to follow-up patients without varices over time and tested PC/SD in a multicenter validation cohort of 218 cirrhotic patients, but their results were not as impressive as in the original study (sensitivity of 91.5% and NPV of 87.0%).[52] At that time, an editorial questioned if the results of the multicenter validation cohort study were not biased by a significant part of patients being enrolled by the center where PC/SD had been developed.[53]

Seeing the significance of platelet count and trying to increase its weight in the index, as well as considering the possible benefit of including APRI in the formula, it was also evaluated the platelet count squared/spleen diameter-aspartate aminotransferase ratio, which had a sensitivity of 95.8%, but an NPV of only 66.7%.[54]

Some systematic reviews have evaluated PC/SD. In 2012, the two first meta-analyses on this issue were published, and they presented contradictory conclusions.[55, 56] Ying et al[55], performed a meta-analysis of 20 studies (3063 patients), in which PC/SD had pooled sensitivity of 92%. Despite a significant heterogeneity among the included studies, the authors concluded that endoscopy could be avoided according to PC/SD. On the other hand, Chawla et al[56], only included seven studies in their meta-analysis (1169 patients), reaching a pooled sensitivity of89%, but the evidence was considered to be of low quality, and there was heterogeneity among included studies, and authors concluded that PC/SD still could not replace endoscopy for screening for EV among those with cirrhosis.

More recently, a systematic review including 67 studies on adult patients evaluated the performance of spleen length and platelet count individually, as well as that of PC/SD for the prediction of EV. Platelet count, for a cut-off value around 120,000/mm3had a pooled sensitivity of 77% for the prediction of any varices.

Spleen length, for a cut-off value around 110 mm had a pooled sensitivity of 85% for the calculation of any varices. PC/SD, for a cut-off value of 909 had a pooled sensitivity of 93% for calculation of any varices. The hierarchical summary of receiver operating characteristic model was used to compare the three non-invasive methods of screening for EV, an PC/SD had higher overall accuracy than both other parameters used individually ($p < 0.001$). The performance of the three methods was also evaluated regarding the prediction of high-risk varices, and PC/SD performed better than the others also in this context ($p < 0.01$), with a pooled sensitivity of 85%. Authors concluded that considering high-risk EV, none of the studied non-invasive methods was accurate enough to replace endoscopy. On the other hand, they suggested that future assessments of new non-invasive methods for screening for varices should include a comparison with PC/SD.[57]

Doppler ultrasonography:

Various indexes measured by Doppler ultrasonography have been proposed as non-invasive prognosticators of the presence of esophageal varices. In a study that compared several Doppler indexes[58], portal vascular resistance ([0.066 × splenic artery pulsatility index - 0.044] × portal blood flow), hemodynamic liver index (portal vein [PV] diameter/PV mean velocity) and splenoportal index (SPI = spleen long diaameter × spleen short diameter/mean velocity in the PV) were the best predictors for the occurrence of esophageal varices, with sensitivities of 76%, 65% and 63% and specificities of 92%, 92% and 92%, respectively.[58] However, all these parameters failed to accurately predict the incidence of large varices. Liver elastographyin this study was superior to all the Doppler indexes and had a 95% sensitivity and 100% specificity for the detection of varices. SPI has been proved to be a good predictor of incidence of varices in several other studies[59], with a sensitivity up to 96% [60] but relatively low specificity.

Contrast-enhanced ultrasound:

In a recent study, contrast-enhanced ultrasound was evaluated for the detection of varices.[61] Although direct visualization of esophageal varices was not feasible; the parameters measured produced high sensitivity and specificity in the detection of varices. Ultrasound has low cost and no ionizing radiation or iodinated contrast material, so these promising results have to be validated by further studies.[61]

Laboratory tests A wide range of laboratory tests have been evaluated as predictors for the presence of varices. The most investigated parameter is PC: SD.[55] The advantage of this parameter is the fact that a constant cutoff value (909) has been used in many of the studies, which enables its use in clinical practice. A recent meta-analysis, which included 20 studies and 3063 patients[55], showed pooled sensitivities and specificities of 92% and 87%, respectively, at the verge of 909, with a positive predictive value of 86% and a negative predictive value of 90%. These results were validated in subgroups of patients with specific etiologies of cirrhosis, including hepatitis C[62] and schistosomiasis.[63] However, several studies failed to reproduce the above encouraging results.[64]

Laboratory tests:

A wide range of laboratory tests has been evaluated as predictors for the occurrence of varix. The most investigated parameter is the PC: SD.[55] The benefit of this parameter is the fact that a constant cutoff value (909) has been used in most of the studies, which enables its use in clinical practice. A recent meta-analysis, which included 20 studies and 3063 patients[55],showed pooled sensitivities and specificities of 92% and 87%, respectively, at the threshold of909, with a 86% positive predictive value and a negative predictive value of 90%. These results have been validated in subgroups of patients with specific etiologies of cirrhosis, including hepatitis C[55], and schistosomiasis.[55] However, several studies failed to reproducethe above encouraging results.[64,63]

The spleen volume and the right liver lobe volume, measured by MRI, have also been proposed along with platelet count as screening methods in detecting esophageal varices[65],but the benefit of such a complicated measurement is doubtful, compared to the measurement of the spleen diameter by ultrasound. Additionally, the platelet count alone may predict the presence of large varices, although less accurately, which could be a cheap and readily available screening method in countries with limited resources.[66] In a comparative study of several parameters, the platelet to spleen diameter ratio and the PV diameter measured by CT were the most accurately prognostic factors for the incidence of large varix in cirrhotic patients with hepatitis C.[67] Various combinations of laboratory findings with demographic parameters and ultrasound parameters[68], serum liver fibrosis markers[69], or even fibrosis parameters from liver biopsy[70], have been shown to correlate with the presence of esophageal varices, but these results have not been validated. A meta-analysis of various non-invasive laboratory findings yielded only moderate accuracy, especially for large varices.[67] In conclusion, although correlations between several laboratory parameters and the presence of varices have been demonstrated, none were strong enough to allow a finding of varices with a single laboratory test. As discussed on liver elastography above, the combination of the platelet count with liver stiffness measurements has proven to be a valuable predictor of the presence of varices. Other laboratory measurements need further validation, especially in combination with liver stiffness, and may produce even better results in the future.

Capsule endoscopy:

Wireless video capsule endoscopy was originally designed as a small-bowel imaging device. It was approved by the USFDA in November 2004 as an alternative technique for thedetection of esophageal varices.[71] The diagnostic pooled sensitivity 83% and 85% specificity were achieved in a recent meta-analysis of 17 studies.[71] The pooled sensitivity and specificity for the grading of medium to large varices were 72% and 91%, respectively.

The diagnostic correctness of this method, especially after taking into consideration its high cost[72], is moderate and not comparable to classic endoscopy. The capsule had the special strings, which help control its movement, has yielded the highest accuracy.[73] The sensitivity and specificity in this study reached 96% and 100%, respectively. However, these results weren't confirmed by another string capsule study, which showed 84% sensitivity and 72% specificity.[74] Nevertheless, it has been shown that string capsule endoscopy improves visualization of the distal esophagus, which may potentially have an impact on the detection of esophageal varices.[75] A more recent study using the PillCam capsule in 62 patients[76], showed even less satisfactory results, with a sensitivity and specificity of 92% and 50% varices detection and 55% and 91% in large varices detection, respectively. In the given studycapsule endoscopy couldn‟t identify gastric varices in all 13 patients.[76] Capsule endoscopy was preferred to EGD by the patients[76,77], although a few patients in some studies had difficulty swallowing it.[78,79] Capsule endoscopy may have a role in cases of patient refusal or contraindications for EGD and may also improve compliance with endoscopic follow up, but the accuracy of the method remains moderate, despite the advances in the capsule technology. String capsule endoscopy needs to be further evaluated as it holds the potential to yield higher accuracy rates.

Recent studies:

GLOBAL STUDIES:

A prospective study by Kassim A et al[80] 2018, aimed to study the non-invasive method to detect esophageal varices in cirrhosis patients in Yemen. A total of 103 subjects with chronic liver disease were involved. Among the study population, 60 were men, and 43 were females with a mean age of 42.69 ± 16.96 years. Among the study population, 59.95% had esophagealvarices, 58% were small, and 42% were large.

The specificity was 33.3%, and sensitivity was 79.7% for spleen diameter whereas platelet count the sensitivity was 87.2% and 26.6%, and for PV diameter it was 47.4% and 39% for right lobe diameter/albumin ratio was 82% and 23.4%, for spleen diameter/platelet count ratio was 74.4% and 37.5% and for AST/ALT ratio was 51.3% and 53.1%. This study showed none non-invasive tests with high sensitivity or specificity for determining esophageal varices and hence concluded that endoscopy as best and gold standard method to determine the grading and diagnosis of esophageal varices.

A systematic review by Karatzasa et al[6] 2018, aimed to find the predictive value of the less invasive method to predict esophageal varices in cirrhosis patients against gold standard endoscopy. A non-invasive method such as spleen and liver elastography, magnetic resonance imaging, computed tomography and ultrasound, capsule endoscopy and laboratory tests are discussed. The accuracy of each method was analyzed. From the analysis, it was found that, though there was supporting studies for PC & liver stiffness to predict variceal esophagus, had low specificity. However, spleen elastography had found to be promising and superior to liver elastography but has be further tested.

A systematic review by Colli, A et al[57] 2017, aimed to evaluate the accuracy of spleen length, platelet count and their ratio in predicting esophageal varices in both paediatric and adults with longstanding liver diseases. This analysis included 71 research papers, but only 67 were included. The results of this study showed PC having sensitivity and specificity of 71% and 80% with a cut off value of 150,000/mm^3 from 140,000 to 150,000/mm^3 with 10 studies involving 2054 subjects. Results showed spleen length having a specificity of 54% and sensitivity of and sensitivity of 85% with cut off values of 110 to 112.5 mm from 13studies, with 1489 subjects.

The prediction for any size showed sensitivity and specificity of 93% and 84% in 17 studies involving 2637 subjects having cut off value for platelet count-to-spleen length ratio of 909 (n/mm^3)/mm. ROC showed that of 3index test platelet count and spleen length ratio to be more accurate test compared to platelet count and spleen length alone. Hence this study concluded that Platelet count-to-spleen length ratio to be a good predictor for esophageal varices.

A meta-analysis by Chen R et al[81] 2017, aimed to access the PC: SD (PSR) non-invasive method of diagnosis esophageal varices. Totally 49 studies were involved in the analysis. The AUSROCs of PSR were 0.8719 for any varices and 0.8132for high-risk varices. Whereas PSR sensitivities for any varices were 0.84 and 0.78. Summary specificities of PSR were 0.78 any varices and 0.67high-risk varices. The „AUSROC of PSR for any varices at the threshold of 909 was 0.8867. The AUSROC of PSR for any varices in viral liver cirrhosis was 0.8675". Hence this meta-analysis showed PSR to be an important non-invasive predictor for esophageal varices of any size.

A study by Shibata, S et al[82] 2016, aimed to find the predictive value of LSPS counts in recognising in the chronic liver disease, the high-risk esophageal varices. This study involved 230 subjects with liver disease and the clinical relationship between clinical and LSPS. The LSPS were compared with other non-invasive methods with ROC. It was shown that LSPS was correlated well with Esophageal varices (EV)and were superior to other non-invasive indices in determining EV. In addition, LSPS was found to be an independent predictor for EV. The optimal cut-off values of LSPS for EV and the high risk EV were 1.1 and 2.2, respectively, at which AUC, negative predictive value, and accuracy were 0.821 [95 %confidence interval (CI) 0.743–0.899], 91.9, and 84.3 % and 0.859 (95 % CI 0.736–0.981), 95.5&76.9 %, respectively. The results showed LSPS to be a „useful, non-invasive, accurate" method to detect EV and a high EV risk in Japanese patients with CLD.

A cross-sectional study by González-Ojeda, et al[83] 2014, aimed to access the predictive value platelet count/spleen size ratio in EV among liver cirrhosis patients. Totally 91 patients were analysed where the mean age among the subjects was 53.75 ± 12 years; 54.9% were men, and 45.0% women. The PC: SD in esophageal varices detection free of the grades, presented with a cut-off score of ≤ 884.3, had 84% sensitivity, 70% specificity, and 94% positive and 40% negative predictive values. This study results suggested PC: SD as a good adjuvant in esophageal varices detection in patients with hepatic cirrhosis.

A meta-analysis by Ying, L et al[55] 2012, aimed to find the non -invasive method to diagnose EV. Nearly 20 studies were included with 3063 subjects. The HSROC of PSR was 0.95 at several edges. The summary 0.92sensitivities and 0.87specificities, HSROC 0.95, at the threshold of 909. If PSR was below 909 for EV ("positive" result), the post-test probability was 87% (if pre-test probability was 50%), while if PSR was at or over 909 ("negative"result), 9% was the post-test probability. PSR showed good precision in EV diagnosis in patients with compensated cirrhosis. PSR could diagnose EV in cirrhosis with the greatest accuracy.

Indian studies:

A prospective study by Kumar P et al[84] 2020, aimed to find the predictive value of the non-invasive method to detect EV in cirrhosis of the liver patients. A total number of subjects recruited in the study were 50. Less platelet count showed to predict the existence of a large EV with $p<0.05$. however, no other hematological value could predict EV. From the ultrasonographic test spleen size, splenic large vein size portal vein size and existence of collateral portal systems showed significant presence of large EV. Hence this study results showed the value of hematological parameters, with radiological parameters in predicting EV among patients of the cirrhosis.

A study by Bitey S et al[85] 2019, aimed to evaluate and recognise the biochemical, clinical and sonographic EV predictors in cirrhosis. Included in study 200 patients‟ adults without gastric bleeding. Among the 100 subjects, 80% were found to have EV, Grade I was 33%, andgrade II 34% varices predominate. Widely patients belonged to child-pugh class C, with 68% followed by class B (28). Mean PC and SD among patients with varices was 115300±66077/cm and 123±32.23mm while among those without varices was 158750±52711/cm and 90±11.21mm respectively. The sensitivity of PC: SD of <909 in predicting the presence of esophageal varices was 74% with 86% positive predictive value (PPV). The PC/SD cut off of <957 had a 78.75% sensitivity and 95.92%PPV. So it can be said that thrombocytopenia and lower PC: SD determine the incidence of higher grades varices, and so recognize those who need endoscopy for the prophylactic management of esophageal varices.

A cross-sectional study by Kraja et al[86] 2017, aimed to assess the non-invasive predictors for EV among cirrhotic patients. A total of 100 subjects were analysed. Model for end-stage liver disease (MELD), aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio (AST/ALT), AST to platelet ratio index (APRI), PC/SD, fibrosis-4-index (FIB-4), fibrosis index (FI) and King's Score were measured for all subjects. The major endpoint was the first esophageal variceal bleeding (EVB) event. The only strong and significant "predictor" of esophageal varices is FIB-4 (multivariable-adjusted OR = 1.57 for one-unit increment; 95% CI: 1.15-2.14). Furthermore, a cut-off value of 3.23 for FIB-4 was a significant predictor of esophageal varices, with a sensitivity of 72%, 58%specificity and a proportion of area under the curve (AUC) of 66%. During the follow-up (median: 31.5 mo; interquartile range: 11-59 mo), 34 patients (24%) experienced a first EVB. FIB-4 was a poor predictor of EVB (the AUC was only 51%) for a cut-off value of 5.02.

Furthermore, the AUC of AST/ALT, APRI, PC/SD, FI, MELD and King's Score ranged from 45% to 55%. None of the non-invasive markers turned out to be a useful predictor of EVB. Despite the low diagnostic accuracy, FIB-4 appears the most efficient non-invasive liver fibrosis marker, which can be used as an initial screening tool for cirrhosis.

In a systematic review by Chawla S et al[56] 2012, aimed to review the diagnostic accuracy 0f 909 ratios. (PC/SD less than 909) in predicting EV. Around 8 studies met the inclusion criteria with 1275 subjects. Meta-analysis yielded a pooled sensitivity of 89% and a pooled specificity of 74% (95% CI 70-78%; I2 statistic 94.5%). The pooled positive LR was 3.5 (95% CI 1.92-6.25; I2 statistic 94.0%) and the pooled negative LR was 0.12 (95% CI 0.05-0.32; I2 statistic 90.8%). The quality of the evidence calculated by the GRADE methodology was low. Hence the results of this study show PC/SD of 909 to be inconclusive to predict EV due to poor quality studies.

A cross-sectional study Grace et al[87] 2016, aimed to find out the usefulness of PC/SD to predict EV. This study involved 60 patients with liver cirrhosis analysed whether a ratio of PC/SD lower than 909 could be used in the subjects predict varices. This study showed no signs of PC/SD of less than 909. However, regression analysis elevated bilirubin and splenomegaly more than 10.5cm were found to be useful to predict the presence of varices (OR 9.95 95% CI 1.32-74 and OR 6.18 95% CI 0.99-38 respectively). Spleen size more than 93 mm in bipolar diameter had 91.7% sensitivity, 50% specificity, 88% PPV, 60% NPV, 1.83 LR+ and 0.16 LR- to predict the presence of varices. PC/SD ratio below 1097 had 60% sensitivity 75% specificity, 90.6% PPV, 32% NPV, 2.4+LR and 0.5-LR for varices presence. Thus, this study concluded that Platelet counts to spleen diameter ratio to be less useful to in varices prediction in cirrhosis.

A study by Tiwari D et al[88] 2016, among 100 subjects to assess the predictive value of platelet count, spleen diameter and their ratio with EV in liver cirrhosis. Both the Biochemical, ultrasound tests were used. The platelet count/spleen diameter (PC/SD) ratio was assessed to check for EV predictability. The gold standard was taken as Upper gastrointestinal endoscopy. 80% were men, and the mean age was 45±13 years, 68% had alcoholism. 66% had EV. The platelet count/spleen diameter ratio to detect EV independent of the grade showed using a cut-off value of ≤ 909, had 81.8% sensitivity, 100% specificity, 100%positive and 73.91%negative predictive value. Hence it can be said PC/SD ratio can be employed in the patient identification varix high risk even in a PHC set up by avoiding endoscopy.

A prospective study by Manohar TP et al[89] 201, aimed find if non - invasive method could predict EV in cirrhosis patients. This study involved 100 incident subjects with cirrhosis. Demographic, clinical, biochemical and ultrasonographic parameters were recorded. Esophageal varices were classified endoscopically as small and large. Nearly 69% of patients had small, and 31% had large varices. Univariate analysis revealed significant differences between the grade of the spleen, blood parameters, platelet count, international normalized ratio, serum albumin, spleen size, PVD & PC/SD ratio in the two groups. Multivariateanalysis revealed that INR [OR: 2.432 (95% CI: 1.192 – 4.958)], splenomegaly at USG [OR: 2.138 (95% CI: 0.662 – 6.911)] and PVD [OR: 1.318 (95% CI: 0.937 - 1.853)] were the most significant predictors for large varices. Hence, Multivariate prediction of large varices based using various non- endoscopic parameters could be employed in place of single parameter-based predictions.

A prospective study by Cherian, J e al[90] 2011, aimed at identifying non-endoscopic parameters that could predict the presence and EV grades. A total of 229 newly diagnosed patients with liver cirrhosis, without an account of variceal bleeding, were included.

Demographic, clinical, biochemical and ultrasonographic parameters were recorded. Esophageal varices were classified as small and large, at endoscopy. Of the 229 patients (141 males; median age 42 years; range 17-73 years) with liver cirrhosis, 97 (42.3%) had small and 81 (35.4%) had large varices. On multivariate analysis, low platelet count (Odd‟s Ratio [OR], 4.3; 95% confidence interval [CI], 1.2-14.9), Child-Pugh class B/C (OR, 3.3; 95% CI, 1.8-6.3), spleen diameter (OR, 4.3; 95% CI, 1.6-11.9) and portal vein diameter (OR, 2.4; 95% CI, 1.1-5.3) were varices presence independent predictors. Likewise, for the occurrence of large esophageal varices, low platelet count (OR, 2.7; 95% CI, 1.4-5.2), "Child-Pugh class B/C" (OR, 3.8; 95% CI, 2.3-6.5) and spleen diameter (OR, 3.1; 95% CI, 1.6-6.0) were the independent risk factors. The presence and higher grades of varices can be predicted by a low platelet count, Child-Pugh class B/C and the diameter of the spleen. These may be considered as non-endoscopic predictors for the diagnosis and management of large grade varix.

LACUNAE OF LITERATURE:

Esophageal varices are the most common problem among Indians. In majority of patient‟s invasive methods are used in diagnosing esophageal bleeding, however non-invasive methods such as platelet count and spleen diameter are also used. But its use has to be validated for general population. There have been extensive studies in regarding the non- invasive methods especially platelet indices and spleen diameter in EV but there‟s lack in the uniformity of results in its predicting esophageal bleeding.

MATERIALS & METHODS

Materials and Methods:

Study site: This study was conducted in the department of General Medicine at R.L. JALAPPA hospital and research centre Tamaka, Kolar

Study population: All the cirrhosis patients irrespective of etiology, attended to the outpatient ward in the department of General Medicine at R.L. JALAPPA hospital and research centre Tamaka, Kolar. Who fulfils the inclusion criteria were considered as the study population.

Study design: The current study was a cross-sectional study

Sample size: Sample size was calculated assuming the incidence of zinc deficiency as 56.2% as per the study by Ayman E. Eskander **e**t al.[91] The other parameters considered for sample size calculation were 5% absolute precision and 95% confidence level. The following formulawas used for sample size calculation.[92]

$$n = \frac{Z^2 P(1 - P)}{d^2}$$

Where *n* = Sample size

Z= Z statistic for a level of confidence,

P = Expected prevalence of proportion

(If the expected prevalence is 56.2%, then *P*= 0.562), and

d = Precision (If the precision is 10%, then *d*=0.1).

The required number of subjects as per the above-mentioned calculation was 95 To account for a non-participation rate of about 20% (19subjects) , it was decided to sample about 114 subjects in to the study. [91]

Sampling method: All the eligible subjects were recruited into the study consecutively by convenient sampling till the sample size is reached.

Study duration: The data collection for the study was done between January 2019 to June 2020 for a period of 1.5 years.

Inclusion Criteria:

- All cirrhosis patients irrespective of etiology.

Exclusion criteria:

- Patients who are not stable in particular those who had active intestinal bleeding at admission.
- A patient who had previously undergone sclerosis and band ligation of oesophageal varies.
- Trans jugular intrahepatic porto systemic stent shunt.
- Surgery for portal ligation.
- Patient taking drugs for primary prophylaxis of variceal bleeding.

Ethical considerations: Study was approved by the institutional human ethics committee. Informed written consent was obtained from all the study participants, and only those participants willing to sign the informed consent were included in the study. The risks and benefits involved in the study and the voluntary nature of participation were explained to the participants before obtaining consent. Confidentiality of the study participants was maintained.

Data collection tools: All the relevant parameters were documented in a structured study proforma.

Methodology:

This study was conducted in R.L. JALAPPA hospital in patients who fulfill inclusion and exclusion criteria from outpatients and inpatients of R.L. JALAPPA hospital.

A cross-sectional study was planned. After obtaining approval from the ethical committee board and taking informed consent, Patients were screened for routine hematological andbiochemical parameters depending on the inclusion criteria.

Investigations:

- COMPLETE HEMOGRAM
- LIVER FUNCTION TESTS
- PT, APTT, INR
- ULTRASOUND ABDOMEN AND PELVIS
- UPPER GI ENDOSCOPY

Statistical methods:

Varices were considered as the primary outcome variable. Platelet to spleen diameter Ratio was considered as Primary explanatory variable. Demographic parameter, Age, gender, diagnosis, Signs of liver cell failures, Ascites, Distended Veins, Hepatomegaly, Splenomegaly, Encephalopathy, lap parameter like (haemoglobin, platelet count, S. Bilirubin)cirrhosis, spleen bipolar diameter and ascites were considered as study relevant variable.

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Data was also representeddiagrams like a bar diagram, pie diagram and staked bar diagram.

The association between explanatory variables and categorical outcomes was assessed by cross tabulation and comparison of percentages. Odds ratio, along with 95% CI, is presented. Chi square test was used to test statistical significance.

The utility of platelet to spleen diameter in predicting outcome was assessed by Receiver Operative curve (ROC) analysis. The area under the ROC curve along with its 95% CI and p value are presented. Basing on the ROC analysis, it was decided to consider <909 and >=909 as the cut off values. The sensitivity, specificity, predictive values and diagnostic accuracy of the screening test with the decided cut off values along with their 95% CI were presented.

P value < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.[93]

RESULTS

Results:

A total of 52 subjects were included in the final analysis.

Table 1: Descriptive analysis of age in study population (n=52)

Parameter	Mean ± SD	Minimum	Maximum
Age	50.1 ± 13.97	25.00	78.00

The mean age was 50.1 ± 13.97in the study population, ranged between was 25 years to 78 years in the study population. (Table 1)

Table 2: Descriptive analysis of gender in the study population (n=52)

Gender	Frequency	Percentages
Male	44	84.62%
Female	8	15.38%

Among the study population,44(84.62%) participants were male and remaining 8(15.38%) participants were female. (Table 2 & Figure 4)

Figure 4: Pie chart of gender in the study population (n=52)

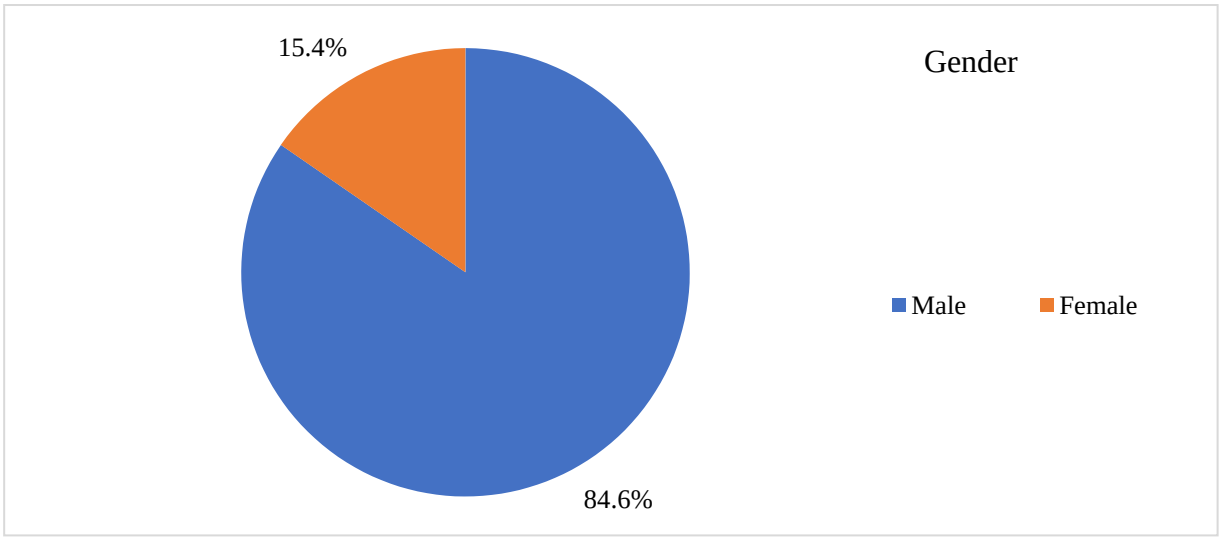


Table 3: Descriptive analysis of jaundice in the study population (n=52)

Diagnosis	Frequency	Percentages
Icterus	45	86.54%
Pedal Edema	45	86.54%
Abdominal Distension	45	86.54%
Alcoholism	40	76.92%
Pedal Oedema	37	71.15%
Fatigue	35	67.31%
Jaundice	32	61.54%
Abdominal Pain	28	53.85%
Pallor	28	53.85%
Weight Loss	25	48.08%
Vomiting /Nausea	16	30.77%
Symptoms of Hepatic encephalopathy	9	17.31%
Oliguria	6	11.54%

Among the study population, 45(86.54%) people had icterus, 45(86.54%) people had pedal Edema, 45(86.54%) people had abdominal distension, 40(76.92%) people had alcoholism, 37(71.15%) people had pedal odema, 35 (67.31%) people had fatigue, 32 (61.54%) people had jaundice, 28(53.85%) people had abdominal pain and pallor, 25(48.08%) people had weight loss, 16(30.77%) people had vomiting/nausea, 9(17.31%) people had symptoms of hepatic encephalopathy and 6(11.54%) people had oliguria. (Table 3)

Table 4: Descriptive analysis of signs of liver cell failures in the study population (n=52)

Signs of liver cell failures	Frequency	Percentages
Scanty Axillary	16	30.77%
Parotid Swelling	15	28.85%
Spider Naevi	15	28.85%
Asterixis	10	19.23%
Pubic Hair	9	17.31%
Gynaecomastia	8	15.38%
Alopecia	6	11.54%
Absent	2	3.85%

Among the study population,16(30.77%) people had scanty axillary, 15(28.85%) people had parotid swelling and spider naevi, 10(19.23%) people had asterixis, 9(17.31%) people had pubic hair, 8(15.38%) people had gynaecomastia, 6(1154%) people had alopecia and 2(3.85%) people had absent. (Table 4)

Table 5: Descriptive analysis of ascites in the study population (n=52)

Ascites	Frequency	Percentages
Positive	46	88.46%
Negative	6	11.54%

Out of 52 people, 46(88.46%) participants had ascites. (Table 5 & Figure 5)

Figure 5: Bar chart of ascites in the study population (n=52)

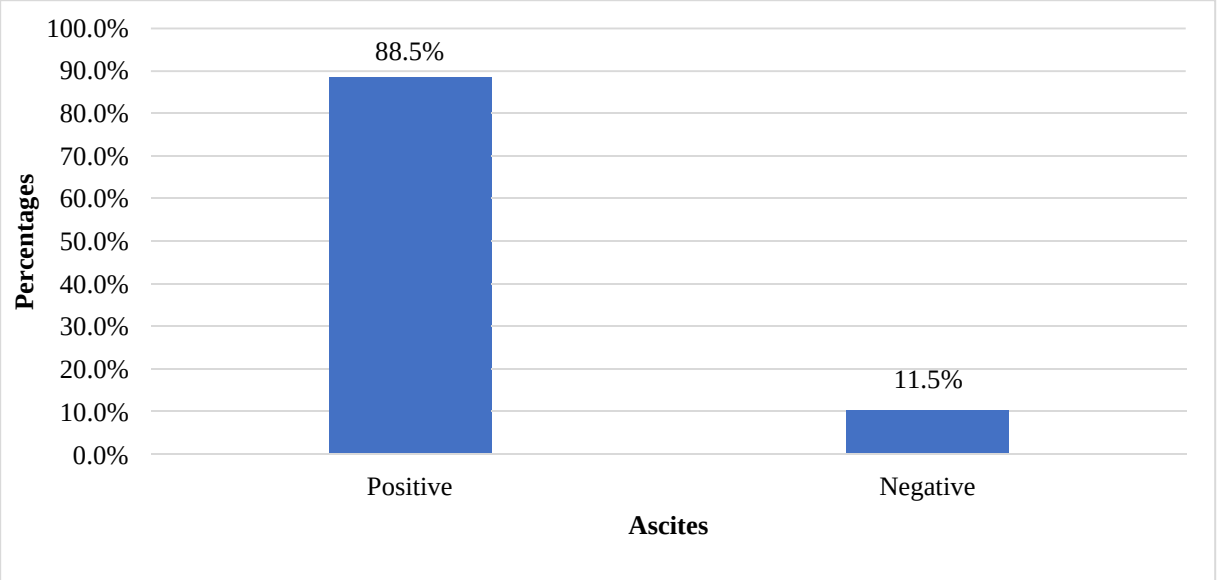


Table 6: Descriptive analysis of distended veins in the study population (n=52)

Distended Veins	Frequency	Percentages
Positive	20	38.46%
Negative	32	61.54%

Out of 52 people, 20(38.46%) participants had distended veins. (Table 6 & Figure 6)

Figure 6: Pie chart of distended veins in the study population (n=52)

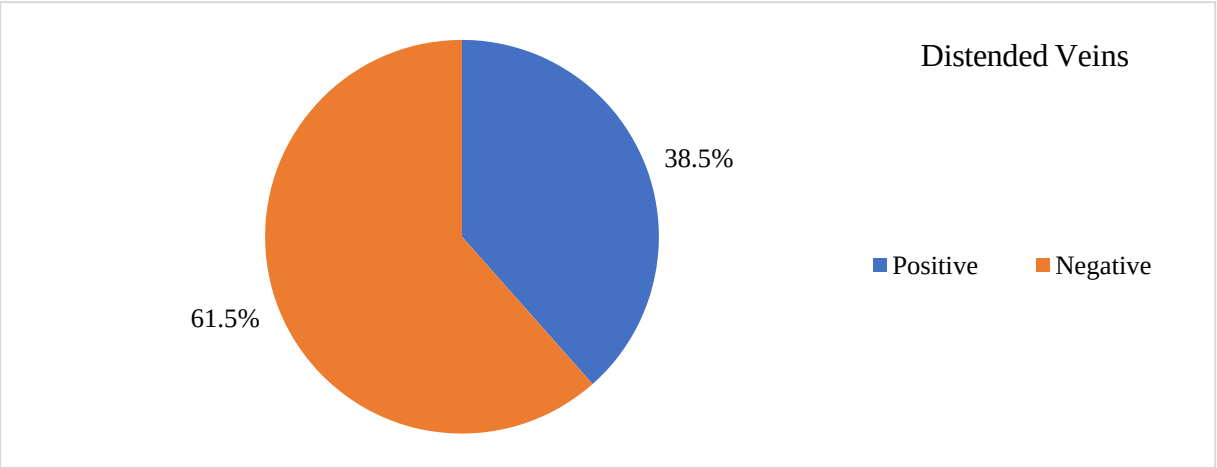


Table 7: Descriptive analysis of hepatomegaly in the study population (n=52)

Hepatomegaly	Frequency	Percentages
Positive	10	19.23%
Negative	42	80.77%

Out of 52 people, 10(19.23%) participants had hepatomegaly. (Table 7 & Figure 7)

Figure 7: Pie chart of hepatomegaly in the study population (n=52)

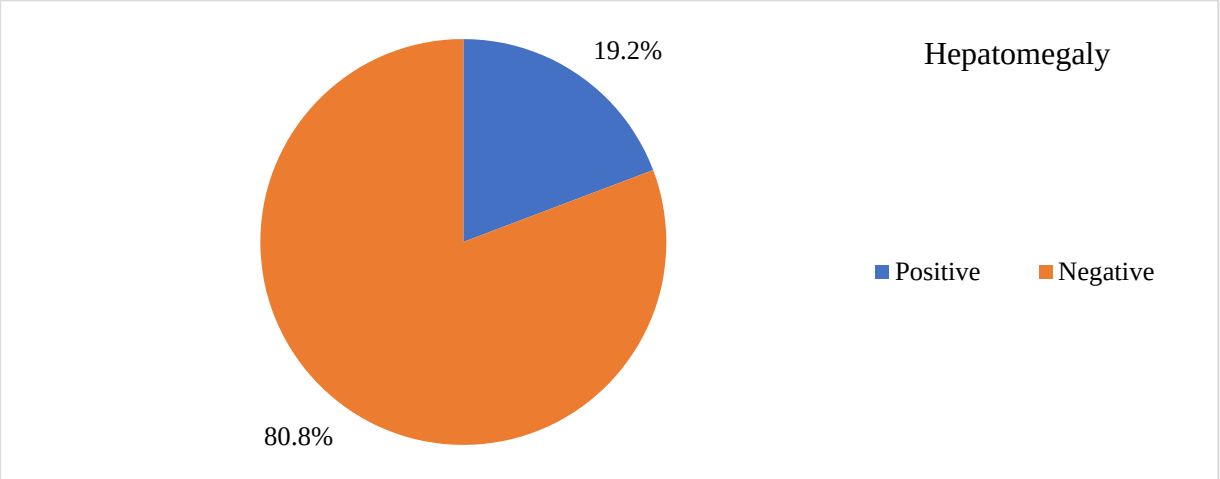


Table 8: Descriptive analysis of splenomegaly in the study population (n=52)

Splenomegaly	Frequency	Percentages
Positive	24	46.15%
Negative	28	53.85%

Out of 52 people, 24(46.15%) participants had splenomegaly. (Table 8 & Figure 8)

Figure 8: Bar chart of splenomegaly in the study population (n=52)

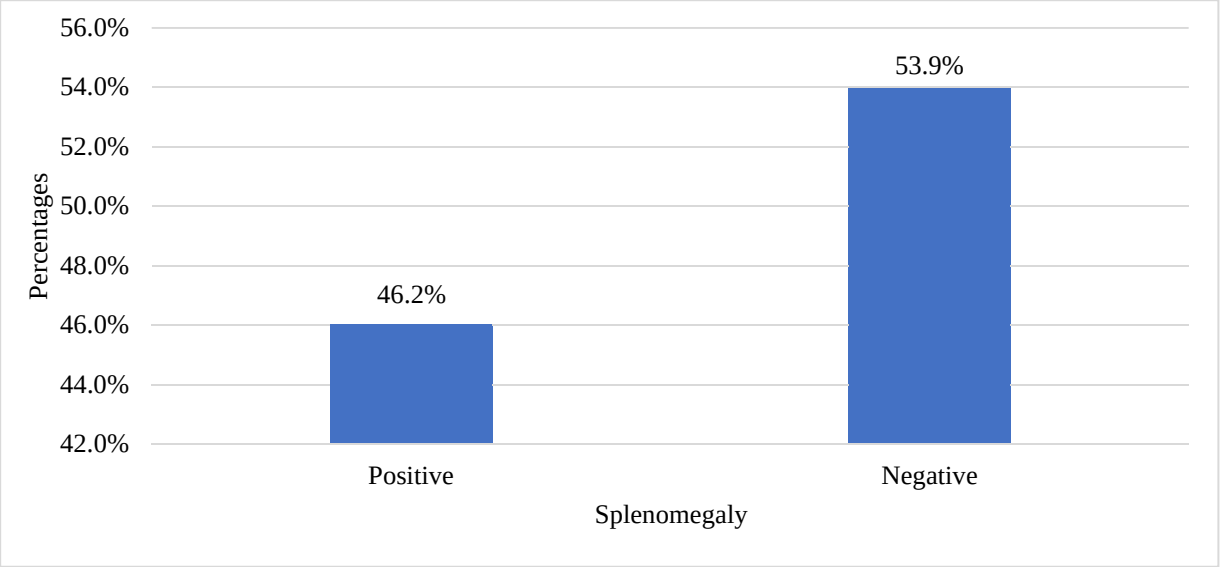


Table 9: Descriptive analysis of encephalopathy in the study population (n=52)

Encephalopathy	Frequency	Percentages
Positive	11	21.15%
Negative	41	78.85%

Out of 52 people, 11(21.15%) participants had encephalopathy. (Table 9 & Figure 9)

Figure 9: Pie chart of encephalopathy in the study population (n=52)

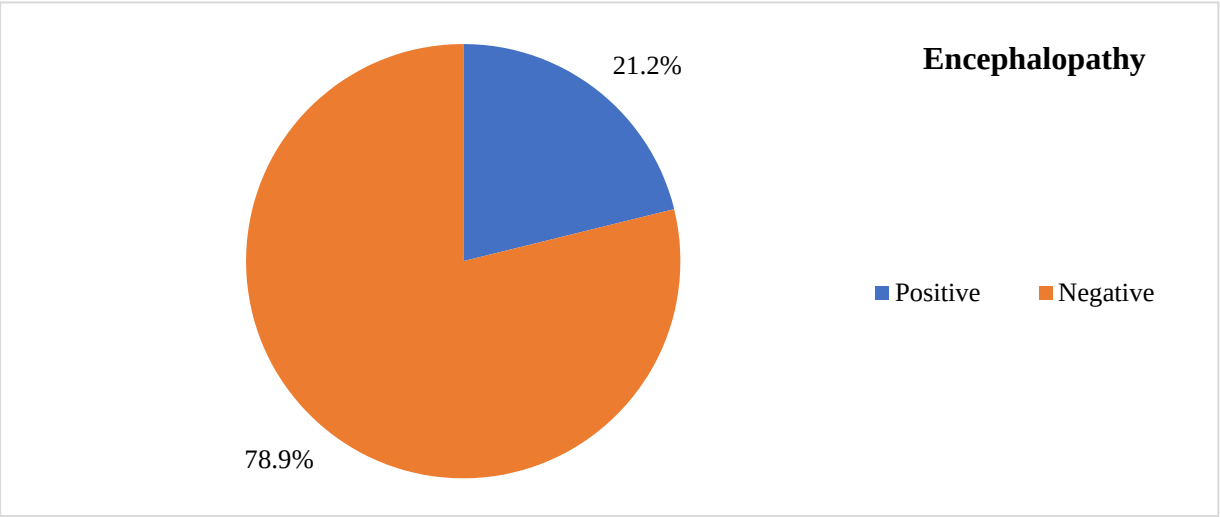


Table 10: Descriptive analysis of lab parameter in the study population (n=52)

Lab Parameter	Mean ± SD	Minimum	Maximum
Haemoglobin	10.65 ± 2.48	5.1	16.2
Platelet Count	97000 ± 62525.29	18000.0	353000.0
Total Bilirubin	6.94 ± 9.08	0.3	37.2
Direct Bilirubin	5.28 ± 7.15	0.1	29.4
SGOT	79.98 ± 62.47	14.0	304.0
SGPT	40.92 ± 66.23	10.0	485.0
ALK.PH	139.25 ± 58.8	64.0	300.0
Total Protein	6.61 ± 0.92	4.5	8.6
Serum Albumin	2.47 ± 0.53	1.5	4.2
Prothrombin	23.98 ± 8.54	14.0	59.0
INR	1.87 ± 0.63	1.1	4.0

The mean haemoglobin was 10.65 ± 2.48 in the study population, ranged between was5.1(g/dL) and 16.2(g/dL) in the study population. The mean platelet count was 97000 ± 62525.29in the study population, ranged between was 18000.0 (µL) and 353000 (µL) in the study population. The mean S. Bilirubin was 6.94 ± 9.08in the study population, ranged between was 0.3 (mg/dl) and 37.2(mg/dl) in the study population. The mean D. Bilirubin was

5.28 ± 7.15in the study population, ranged between was 0.1 (mg/dl) and 29.4(mg/dl) in the study population. The mean SGOT was 79.98 ± 62.47in the study population, ranged between was 14 (IU/L) and 304(IU/L) in the study population. The mean SGPT was 40.92 ± 66.23 in the study population, ranged between was 10 (IU/L) and 485(IU/L) in the study population. The mean alkaline phosphatase was 139.25 ± 58.8in the study population, ranged betweenwas 64 (U/L) and 300(U/L) in the study population. The mean T. Protein was 6.61 ± 0.92 in the study population, ranged between was 4.5 (g/dl) and 8.6(g/dl) in the study population. Themean S. Albumin was 2.47 ± 0.53in the study population, ranged between was 1.5 (g/dl) and 4.2(g/dl) in the study population.

The mean prothrombin time was 23.98 ± 8.54 in the study population, ranged between was 14 and 59 in the study population. The mean International normalized ratio was 1.87 ± 0.63 inthe study population, ranged between was 1.1 and 4 in the study population. (Table 10)

Table 11: Descriptive analysis of spleen bipolar diameter in the study population (n=52)

Parameter	Mean ± SD	Minimum	Maximum
Spleen Bipolar Diameter	119.1 ± 31.09	69.00	171.00

The mean spleen bipolar diameter was 119.1 ± 31.09 in the study population, ranged between was 69mm and 171mm in the study population. (Table 11)

Table 12: Descriptive analysis of ascites in the study population (n=52)

Ascites	Frequency	Percentages
Positive	47	90.38%
Negative	5	9.62%

Out of 52 people, 47(90.38%) participants had ascites. (Table12 & Figure 10)

Figure 10: Bar chart of ascites in the study population (n=52)

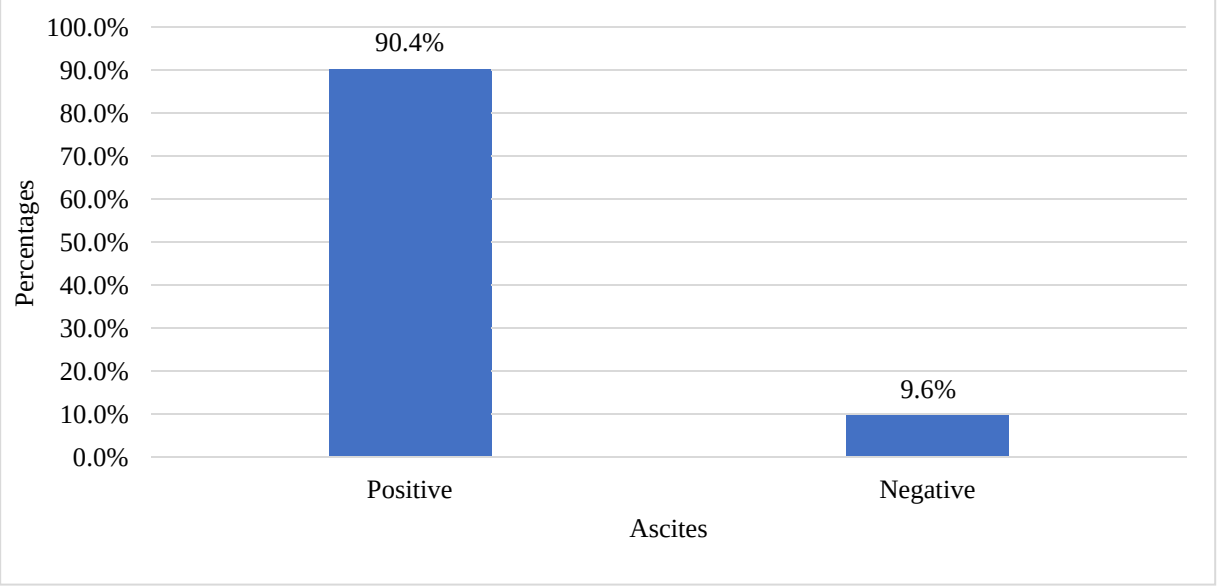


Table 13: Descriptive analysis of varices in the study population (n=52)

Varices	Frequency	Percentages
Positive	46	88.46%
Negative	6	11.54%

Out of 52 people, 46(88.46%) participants had ascites. (Table13 & Figure 11)

Figure 11: Pie chart of varices in the study population (n=52)

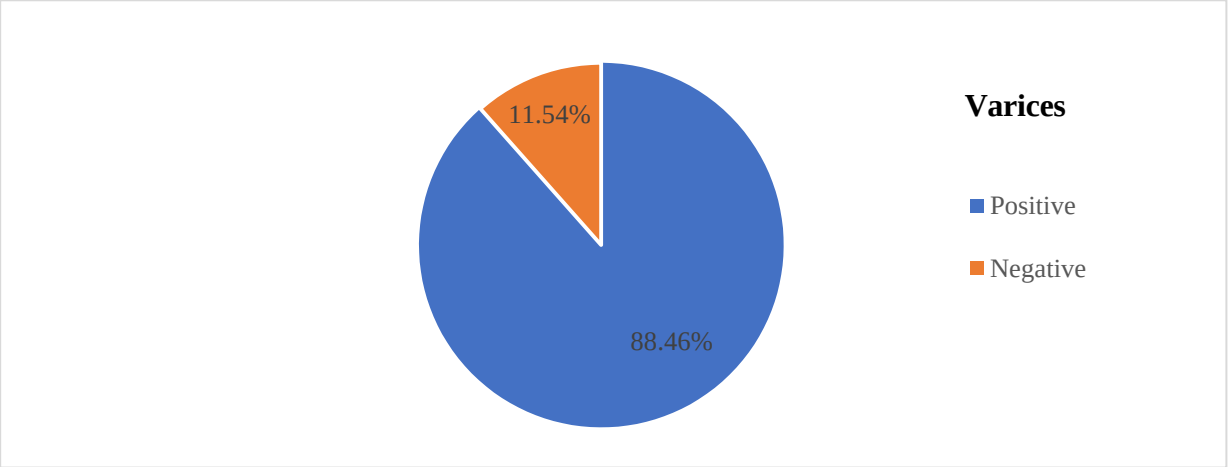


Table 14: Descriptive analysis of platelet to spleen diameter ratio in the study population (n=52)

Parameter	Mean ± SD	Minimum	Maximum
Platelet to spleen diameter Ratio	1201.3 ± 941.54	620.92	6788.46

The mean Platelet to spleen diameter Ratio was 1201.3 ± 941.54 in the study population, ranged between was 620.92 and 6788.46 in the study population. (Table 14)

Table 15: Comparison of varices with platelet to spleen diameter ratio (n=52)

Platelet to Spleen Diameter	Varices		Chi square	P value
	Positive (n=46)	Negative (n=6)		
Low (<909)	22 (47.83%)	4 (66.67%)	0.754	**0.385**
High (>=909)	24 (52.17%)	2 (33.33%)		

Among the people with varices positive group, 22 (47.83%) people had low (<909) and 24 (52.17%) people had high (>=909). Among the people with varices negative group, 4 (66.67%) people had low (<909) and 2 (33.33%) people had high (>=909). the difference in the proportion of platelet to spleen diameter ratio between varices was statistically not significant (p value 0.358) (Table 15 & Figure 12)

Figure 12: Staked bar chart of comparison of varices with Platelet to spleen diameter ratio (n=52)

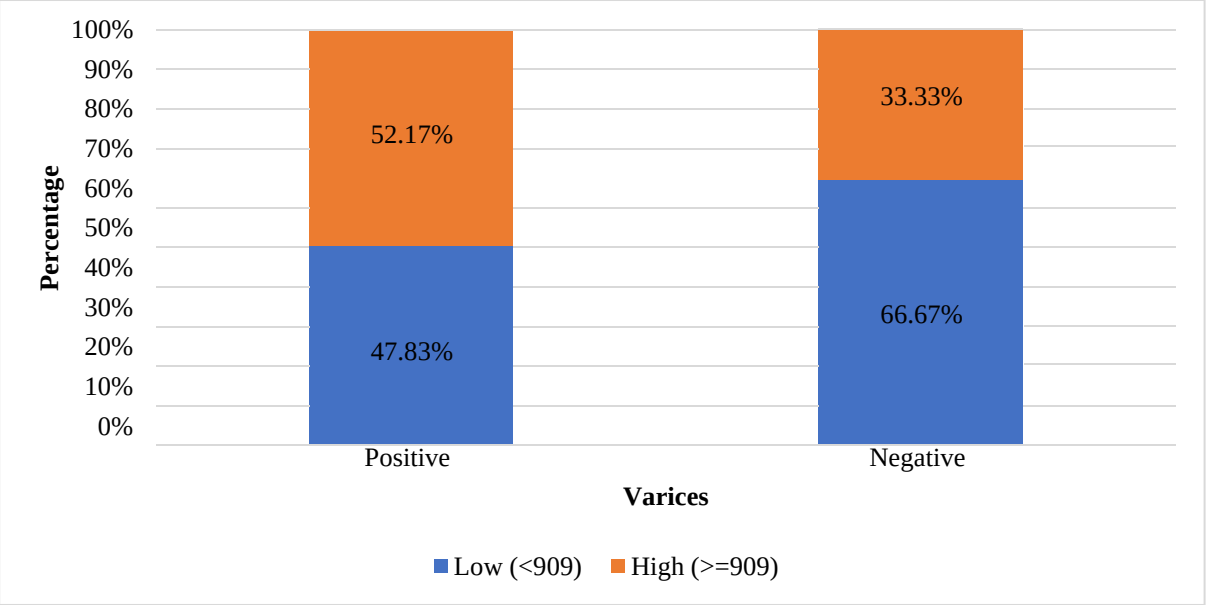


Table 16: Predictive validity of platelet to spleen diameter ratio in predicting varices(n=52)

Parameter	Value	95% CI	
		Lower	Upper
Sensitivity	47.83%	32.89%	63.05%
Specificity	33.33%	4.33%	77.72%
False positive rate	66.67%	22.28%	95.67%
False negative rate	52.17%	36.95%	67.11%
Positive predictive value	84.62%	65.13%	95.64%
Negative predictive value	7.69%	0.95%	25.13%
Diagnostic accuracy	46.15%	32.23%	60.53%

The platelet to spleen diameter ratio had sensitivity of 47.83% (95% CI 32.89% to 63.05%) in predicting varices. specificity was 33.33% (95% CI 4.33%to 77.72%), false positive rate was 66.67% (95% CI 22.28% to 95.67%), false negative rate was 52.17% (95% CI 36.95% to 67.11%), positive predictive value was 84.62% (95% CI 65.13% to 95.64%), negative predictive value was 7.69% (95% CI 0.95% to 25.13%), and the total diagnostic accuracy was 46.15% (95% CI 32.23% to 60.53%). (Table 16)

DISCUSSION

DISCUSSION:

The obstruction of by portal vein carrying through intestine, pancreas, spleen and to the liver gives the origin to the Esophageal varices (EV). Esophageal varices are distended veins in the esophagus that can be seen in the patients with the cirrhosis of the Liver, who ultimately develop portal hypertension.[1] However, when there is the cessation of the alcohol intake, the Esophageal varices seem to regress.[2],[3]

In the EV patients bleeding from the varices is the chief cause of the mortality. Literature reports the incidence to be approximately 40%.[4, 5] The size of varices, the existence of red spots and severity of cirrhosis are the Vital predictors of variceal bleeding.[6] β-blockers may lessen the bleeding among those with the EV. [7,6] The esophagogastroduodenoscopy (EGD) aid in the diagnosis of EV and the size of varices. But there are complications related to endoscopy, requiring general anaesthesia and relatively expensive procedure when doing the EGD.[8,6] to overcome these complications there have been few researches. Minimally invasive and non-invasive tools are designed to overcome the complications associated with the ECD.[94] Hence, a need for a non-invasive predictor for the presence of EVs to ease the social, medical, and economic burden of the disease arose. There are multiple studies that have used various non-endoscopic variables for detecting the varices. Hence in the current study, we used only easily available, simple, reproducible parameters in Indian population with hepatic cirrhosis.

Baseline sociodemographic variables:

We did a hospital-based cross-sectional study among 52 cases of cirrhosis patients irrespective of aetiology attending the outpatient and inpatient services conducted in R.L. JALAPPA hospital who fulfil inclusion and exclusion criteria. The study was conducted for 1

½ year from Jan 2019 to June 2020 after getting ethical clearance. Varices were considered as the primary outcome variable. PC/SD ratio was considered as Primary explanatory variable.

Demographic parameter, Age, gender, diagnosis, Signs of liver cell failures, Ascites, Distended Veins, Hepatomegaly, Splenomegaly, Encephalopathy, lab parameter like (haemoglobin, platelet count, S. Bilirubin…) cirrhosis, spleen bipolar diameter and ascites were considered as study relevant variable. The Objectives of our study were similar to that ofKassim A et al.[80] (2018) Karatzasa et al.[6] (2018) Colli, A et al.[57] (2017) Chen R et al.[81] (2017)Shibata S et al.[82] (2016) Giannini et al.[39] (2003)

Clinical & anthropometric variables:

Age and sex: 50.1 ± 13.97 were the mean age, with the majority male subjects 44 (84.62%) participants and remaining 8 (15.38%) participants were females. However mean age was fifty-one years in the study of Baig et al[95], mean age was 42 in a study by Cherian et al, [90] and in the study of Sarangapani et al[64] mean age was 45. 25 years was the age of the Youngest patient, and the oldest was 78 years. Males were seen more among the various age groups studied.

Cirrhosis was present among all in the present study. 76.92% of subjects had alcoholism. The clinical signs seen were most commonly Ascites, constituting 88% and Pedal edema along with Icterus, fatigue, jaundice, pain abdomen and pallor, weight loss, vomiting/nausea and oliguria. 38.46% of participants had distended veins, 10(19.23%) participants had hepatomegaly, 24(46.15%) participants had splenomegaly, 11(21.15%) participants had encephalopathy

The liver cell failure was identified by the scanty axillary, parotid swelling and spider naevi, asterixis, gynaecomastia, alopecia.

The mean haemoglobin was 10.65 ± 2.48. The mean platelet count was 97000 ± 62525.29. The mean S. Bilirubin was 6.94 ± 9.08. The mean D. Bilirubin was 5.28 ± 7.15. The mean SGOT was 79.98 ± 62.47. The mean SGPT was 40.92 ± 66.23. The mean alkaline phosphatase was 139.25 ± 58.8. The mean T. Protein was 6.61 ± 0.92. The mean S. Albumin was 2.47 ± 0.53. The mean prothrombin time was 23.98 ± 8.54; The mean International normalized ratio was 1.87 ± 0.63 in the study population. The Relationship between "non- invasive parameters like Age, Haemoglobin, Serum albumin, Serum Bilirubin, Platelet count, Spleen Bipolar diameter, PC/SD ratio to the presence of varices" was studied and was not significant statistical.

Thrombocytopenia is caused by the defects in consumptive, productive, distributional mechanisms, usually seen due to the platelet associated IgG-mediated pooling and destruction of platelets in the spleen. May also be caused due to lower thrombopoietin, that may be due to compromised production / rapid degradation. Hence can be said that multiple factors, along with portal hypertension, may lead to the differences in the platelet count. Garcia- Tsao et al. [17], (180 patients), K.C. Thomopoulos et al.[6] (184 patients) have shown in their studies that thrombocytopenia can be a prediction varix as an independent factor. 40% patients belonged to the group with the platelet count 50,000 - 1,00,000/mm3. Mean PC was 97000 ± 6252/mm3.

Zaman A et al. [52] identified platelet count <88,000 was the only parameter recognized by univariate/multivariate analysis ($p < 0.05$) shows large EV or gastric varices. The PC/SD ratio was shown to be the suitable parameter to be used as splenomegaly is associated in thrombocytopenia of liver cirrhosis with the size of the spleen being in reverse associatedwith PC.

PC/SD ratio normalizes platelet count to splenic sequestration since platelet count alone can‟t alone be seen associated with portal hypertension. Our study shows that the platelet to spleen diameter ratio had a sensitivity of 47.83% in predicting varices. Specificity was 33.33%, the false positive rate was 66.67%, false-negative rate was 52.17%, positive predictive value was 84.62%, negative predictive value was 7.69%, and the overall diagnostic accuracy was 46.15%. Giannini et al.[49] found that the 100% negative predictive value of PC/SD ratio 909 in145 cirrhosis patients. Agha et al.[62] achieved 100% negative predictive value and a 93.8% positive predictive value of for the diagnosis of EV among 144 patients with compensated HCV related cirrhosis 909. Baig et al.[95] achieved 1014 cut-off, with 95.4% positive and 95.1%, negative predictive values.

In E Giannini et al.‟s[49] study of 266 patients, the prevalence rates of OV were 61% and 58% in the first and second groups of patients, respectively. The PC/SD ratio was the only parameter which associated independently with OV in a multivariate analysis. A PC/SD ratio cut off value of 909 had 100% negative predictive value for a diagnosis of OV. This resultwas reproduced in the second group of patients as well as in patients with the compensated disease. In a cost-benefit analysis, among those with the liver cirrhosis according to the PC/SD was far more cost-effective compared with the “scope all strategy”. The mean PC/SD 1201.3 ± 941.54 in the subjects, that was between the 620.92 and 6788.46.

Among subjects‟ positive group for varix, 22 (47.83%) people had low (<909) and 24(52.17%) people had high (>=909). Among the people with varices negative group, 4 (66.67%) people had low (<909) and 2 (33.33%) people had high (>=909). the difference in the proportion of platelet to spleen diameter ratio between varices was not significant (p value0.358).

Zaman et al. [52] has shown that in the patients without varices, they had a higher mean platelet count (≈1,28,500) than those who had varices that are small (≈1,07,800) and an increase of EV by 2 and a half folds if the platelet count of <90,000 fold. The restrictions of their study were „retrospective analysis and exclusive liver transplant patients". Sarwar et al. has shown that PC <88,000 as large EV"s, independent risk factor. showed that platelet count of <1,50,000 to be a predictor of EV.

Spleen bipolar diameter"s mean was 119.1 ± 31.09 in the present study, with ranges of 69mm and 171mm. Higher esophageal varices in cirrhosis of the liver were associated with thrombocytopenia. US of Spleen"s bipolar diameter may indicate higher grades of esophageal varices.

Table 17: Comparative studies.

Variable	Present study	Kassim A et al.[80] (2018)	Giannini et al. [49] (2005)	Baig et al.[95] (2008)
Sample size	52	103	145	150
Age in years	50.1±13.97	50.1±13.97	61	50
Sex ratio	44:8	60:43	103:42	88:18
Platelet count, $\times 10^9$/L	97000	94000	79820	90500
Spleen diameter, mm, median (range)	120	142	155	140
Platelet count to spleen diameter ratio, median (range)	1201.3	462	533	702
Sensitivity	47.83%	79.7	100	80
Specify	33.33%	33.3	93	89

In our study out of 52 people, 46(88.46%) participants had varices. Large esophageal varices excessively associated with low platelet count, an enlarged spleen, as observed globally. And multivariate analysis depicted the US measurement of the spleen, and splenic vein size, portal vein size was also associated with large esophageal varices, which are likely to cause a significant bleed. According to K. C.

Thomopoulos et al[6], study, esophageal varices were present in 92 patients (50%), and large varices in 33 patients (17.9%). 22 Variables seen in large esophageal varices on univariate analysis were the presence of ascites and splenomegaly either by clinical examination or by ultrasound ($p<0.01$) and bilirubin ($p=0.01$).

This study indicates that it may be possible to envisage the occurrence of large esophageal varices using simple and non-invasive tools like a clinical examination to check for palpable spleen and platelet count with a fairly high degree of accuracy. The high accuracy rates may preclude endoscopy‟s need in these patients, restricting the use of this costly and invasive procedure to only those patients.

CONCLUSIONS:

- Among the 52 subjects, the mean age was 50.1 ± 13.97, with the majority of male subjects than females.
- Ascites (88%) and Pedal edema along with Icterus, fatigue, jaundice, abdominal pain and pallor, weight loss, vomiting/nausea and oliguria were seen in the subjects. All the subjects had cirrhosis. The majority had varices. However, only 20(38.46%) participants had distended veins, 10(19.23%) participants had hepatomegaly, 24(46.15%) participants had splenomegaly, 11(21.15%) participants had encephalopathy
- The liver cell failures were shown by the scanty axillary, parotid swelling and spider naevi, asterixis, gynaecomastia, alopecia among the subjects.
- "Relationship between non-invasive parameters like Serum Bilirubin, Age, albumin, Platelet count, Hemoglobin Spleen Bipolar diameter, PC/SD ratio to the presence of varices" was not statistical significance.
- Spleen bipolar diameter mean was 119.1 ± 31.09, The mean PC/SD Ratio was 1201.3 ± 941.54 among the subjects.
- No significant values were obtained on the comparison of varices with PC/SD ratio
- Predictive validity of PC/SD ratio in predicting varices had a sensitivity of 47.83%; specificity was 33.33%

LIMITATIONS AND RECOMMENDATIONS:

This study has certain limitations. Our study group represented a select group of patients attending a hospital and included patients with relatively advanced disease. It would be best applied in patients attending large hospitals and may not perform as well in primary care settings. The variable being predicted, that is, the large esophageal varices presence is not completely objective and is subject to interobserver variation.

SUMMARY:

This study indicates that possibility to envisage the presence of large esophageal varices using simple and non-invasive tools like a clinical examination for palpable spleen and platelet count with a fairly high degree of accuracy. The high accuracy rates may obviate the need for endoscopy in these patients, restricting the use of this costly and invasive procedure to only those patients with intermediate scores. Such an approach would reduce both hospital costs and the workload of endoscopy units.

BIBLIOGRAPHY

REFERENCES:

1. Khan Sarin AS, Le Mair A. Esophageal Varices WGO 2014. Czech Republic) Prof Michael Fried Prof A Gangl Prof AG Khan Prof D Bjorkman Prof R Eliak Prof R Bektaeva Prof SK Sarin Prof S Fedail Drs JH Krabshuis (Fr. 2014;(2).
2. Merli M, Nicolini G, Angeloni S, Rinaldi V, De Santis A, Merkel C, et al. Incidence and natural history of small esophageal varices in cirrhotic patients. J Hepatol. 2003 Mar;38(3):266–72.
3. Franchis R, Dell'Era A. Non-invasive diagnosis of cirrhosis and the natural history of its complications. Best Pract Res Clin Gastroenterol. 2007;21:3–18.
4. Burroughs AK, Triantos CK. Predicting failure to control bleeding and mortality in acute variceal bleeding. J hepatol. 2008;48(2)185–8.
5. Abraldes JG, Villanueva C, Bañares R, Aracil C, Catalina MV, Garci A-Pagán JC, et al. Hepatic venous pressure gradient and prognosis in patients with acute variceal bleeding treated with pharmacologic and endoscopic therapy. J Hepatol. 2008 Feb;48(2):229–36.
6. Karatzas A, Konstantakis C, Aggeletopoulou I, Kalogeropoulou C, Thomopoulos K, Triantos C. Non-invasive screening for esophageal varices in patients with liver cirrhosis. Ann Gastroenterol. 2018;31(3):305–14.
7. Tursi T. Use of ß-blocker therapy to prevent primary bleeding of esophageal varices. J Am Acad Nurse Pract. 11/09. 2010;22(12):640–7.
8. Lichtenstein DR, Jagannath S, Baron TH, Anderson MA, Banerjee S, Dominitz JA, et al. Sedation and anesthesia in GI endoscopy. Gastrointest Endosc. 2008 Nov;68(5):815–26.

9. de Franchis R. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension.J Hepatol. 2015 Sep;63(3):743–52.

10. Vizzutti F, Arena U, Romanelli RG, Rega L, Foschi M, Colagrande S, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. Hepatology. 2007;45(5):1290–7.

11. Drastich P, Lata J, Petrtyl J, Bruha R, Prochazka V, Vanasek T, et al. Endoscopic variceal band ligation compared with propranolol for prophylaxis of first varicealbleeding. Ann Hepatol. 2011;10(2):142–9.

12. Jensen DM. Endoscopic screening for varices in cirrhosis: findings, implications, and outcomes. Gastroenterology. 2002;122(6):1620–30.

13. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1736–88.

14. Sepanlou SG, Safiri S, Bisignano C, Ikuta KS, Merat S, Saberifiroozi M, et al. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol. 2020;5(3):245–66.

15. Fleming KM, Aithal GP, Card TR, West J. The rate of decompensation and clinical progression of disease in people with cirrhosis: A cohort study. Aliment Pharmacol Ther. 2010;32(11–12):1343–50.

16. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013;144(7):1426–37, 1437.e1-9.

17. D‟Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. J Hepatol. 2006;44(1):217– 31.
18. Fleming KM, Aithal GP, Card TR, West J. All-cause mortality in people with cirrhosis compared with the general population: a population-based cohort study. Liver Int. 2012;32(1):79–84.
19. Ge PS, Runyon BA. Treatment of Patients with Cirrhosis. N Engl J Med. 2016;375(8):767–77.
20. Arthur MJP. Reversibility of liver fibrosis and cirrhosis following treatment for hepatitis C. Gastroenterology. 2002;122(5):1525–8.
21. Afshin A, Reitsma MB MC. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med. 2017;377(15):1496–7.
22. Griswold MG, Fullman N, Hawley C, Arian N, Zimsen SRM, Tymeson HD, et al. Alcohol use and burden for 195 countries and territories, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2018;392(10152):1015–35.
23. Guy J, Peters MG. Liver disease in women: The influence of gender on epidemiology, natural history, and patient outcomes. Gastroenterol Hepatol. 2013;9(10):633–9.
24. Garg V, Garg H, Khan A, Trehanpati N, Kumar A, Sharma BC, et al. Granulocyte colony-stimulating factor mobilizes CD34+ cells and improves survival of patients with acute-on-chronic liver failure. Gastroenterology. 2012;142(3):505-512.e1.
25. Amarapurkar DN, Hashimoto E, Lesmana LA, Sollano JD, Chen PJ, Goh KL. How common is non-alcoholic fatty liver disease in the Asia-Pacific region and are there local differences? J Gastroenterol Hepatol. 2007;22(6):788–93.

26. Vernon G, Baranova A, Younossi ZM. Systematic review: The epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34(3):274–85.

27. David K, Kowdley K V., Unalp A, Kanwal F, Brunt EM, Schwimmer JB, et al. Quality of life in adults with nonalcoholic fatty liver disease: Baseline data from the nonalcoholic steatohepatitis clinical research network. Hepatology. 2009;49(6):1904– 12.

28. Kim WR, Brown RSJ, Terrault NA, El-Serag H. Burden of liver disease in the United States: summary of a workshop. Hepatology. 2002;36(1):227–42.

29. Boberg KM, Aadland E, Jahnsen J, Raknerud N, Stiris M, Bell H. Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population. Scand J Gastroenterol.1998;33(1):99–103.

30. Who. Global Health Observatory data repository [Internet]. World Health Organization. 2016 [cited 2020 Oct 30]. Available from: https://apps.who.int/gho/data/node.home

31. Jain M, Varghese J, Kedarishetty C, Srinivasan V, Venkataraman J. Incidence and risk factors for mortality in patients with cirrhosis awaiting liver transplantation. Indian J Transplant. 2019;13(3):210.

32. Sanyal AJ, Bosch J, Blei A, Arroyo V. Portal Hypertension and Its Complications. Gastroenterology. 2008 May;134(6):1715–28.

33. Maruyama H, Yokosuka O. Pathophysiology of portal hypertension and esophageal varices. Int J Hepatol. 2012;2012:895787.

34. Wani ZA, Bhat RA, Bhadoria AS, Maiwall R, Choudhury A. Gastric varices: Classification, endoscopic and ultrasonographic management. J Res Med Sci. 2015;20(12):1200–7.

35. Sarin SK, Lahoti D, Saxena SP, Murthy NS, Makwana UK. Prevalence, classification and natural history of gastric varices: A long- term follow- up study in 568 portal hypertension patients. Hepatology. 1992;16(6):1343–9.

36. Brocchi E, Caletti G, Brambilla G, La Mantia L, Lupinacci G, Pisano G, et al. Prediction of the First Variceal Hemorrhage in Patients with Cirrhosis of the Liver and Esophageal Varices. N Engl J Med. 1988;319(15):983–9.

37. Hashizume M, Kitano S, Yamaga H, Koyanagi N, Sugimachi K. Endoscopic classification of gastric varices. Gastrointest Endosc. 1990;36(3):276–80.

38. Arakawa M, Masuzaki T, Okuda K. Pathomorphology of esophageal and gastric varices. Semin Liver Dis. 2002;22(1):73–82.

39. Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, et al. Transient elastography: A new noninvasive method for assessment of hepatic fibrosis.Ultrasound Med Biol. 2003;29(12):1705–13.

40. Ferraioli G, Tinelli C, Zicchetti M, Above E, Poma G, Di Gregorio M, et al. Reproducibility of real-time shear wave elastography in the evaluation of liver elasticity. Eur J Radiol. 2012;81(11):3102–6.

41. Elkrief L, Rautou P-E, Ronot M, Lambert S, Dioguardi Burgio M, Francoz C, et al. Prospective comparison of spleen and liver stiffness by using shear-wave and transient elastography for detection of portal hypertension in cirrhosis. Radiology. 2015;275(2):589–98.

42. Burton JR, Liangpunsakul S, Lapidus J, Giannini E, Chalasani N, Zaman A. Validation of a multivariate model predicting presence and size of varices. J Clin Gastroenterol. 2007;41(6):609–15.

43. Berzigotti A, Gilabert R, Abraldes JG, Nicolau C, Bru C, Bosch J, et al. Noninvasive prediction of clinically significant portal hypertension and esophageal varices in patients with compensated liver cirrhosis. Am J Gastroenterol. 2008;103(5):1159–67.

44. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology. 2003;38(2):518–26.

45. Castéra L, Bail B Le, Roudot-Thoraval F, Bernard PH, Foucher J, Merrouche W, et al. Early detection in routine clinical practice of cirrhosis and oesophageal varices in chronic hepatitis C: Comparison of transient elastography (FibroScan) with standard laboratory tests and non-invasive scores. J Hepatol. 2009;50(1):59–68.

46. Stefanescu H, Grigorescu M, Lupsor M, Maniu A, Crisan D, Procopet B, et al. A new and simple algorithm for the noninvasive assessment of esophageal varices in cirrhotic patients using serum fibrosis markers and transient elastography. J Gastrointestin Liver Dis. 2011;20(1):57–64.

47. Wang JH, Chuah SK, Lu SN, Hung CH, Chen CH, Kee KM, et al. Transient elastography and simple blood markers in the diagnosis of esophageal varices for compensated patients with hepatitis B virus-related cirrhosis. J Gastroenterol Hepatol. 2012;27(7):1213–8.

48. Mattos AZ de, Alves de Mattos A, Daros LF, Musskopf MI. Aspartate aminotransferase-to-platelet ratio index (APRI) for the non-invasive prediction of esophageal varices. Ann Hepatol. 2013;12(5):810–4.

49. Giannini E, Botta F, Borro P, Risso D, Romagnoli P, Fasoli A, et al. Platelet count/spleen diameter ratio: Proposal and validation of a non-invasive parameter to predict the presence of oesophageal varices in patients with liver cirrhosis. Gut. 2003;52(8):1200–5.

50. Mattos ÂZ, Schacher FC, John Neto G, Mattos AA. Screening for esophageal varices in cirrhotic patients – Non-invasive methods. Ann Hepatol. 2019;18(5):673–8.

51. Giannini EG, Botta F, Borro P, Dulbecco P, Testa E, Mansi C, et al. Application of the platelet count/spleen diameter ratio to rule out the presence of oesophageal varices in patients with cirrhosis: a validation study based on follow-up. Dig liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver. 2005 Oct;37(10):779–85.

52. Giannini EG, Zaman A, Kreil A, Floreani A, Dulbecco P, Testa E, et al. Platelet count/spleen diameter ratio for the noninvasive diagnosis of esophageal varices: results of a multicenter, prospective, validation study. Am J Gastroenterol.2006;101(11):2511–9.

53. De Franchis R. Noninvasive diagnosis of esophageal varices: Is it feasible? Am J Gastroenterol. 2006;101(11):2520–2.

54. de Mattos ÂZ, Daros LF, de Mattos AA. Razão da contagem de plaquetas ao quadrado/diâmetro do baço-aspartato aminotransferase: Avaliação de um novo método não-invasivo para a predição de varizes esofágicas. Arq Gastroenterol. 2017;54(3):222–4.

55. Ying L, Lin X, Xie Z-L, Hu Y-P, Shi K-Q. Performance of platelet count/spleen diameter ratio for diagnosis of esophageal varices in cirrhosis: a meta-analysis. Dig Dis Sci. 2012;57(6):1672–81.

56. Chawla S, Katz A, Attar BM, Gupta A, Sandhu DS, Agarwal R. Platelet count/spleen diameter ratio to predict the presence of esophageal varices in patients with cirrhosis: A systematic review. Eur J Gastroenterol Hepatol. 2012;24(4):431–6.

57. Colli A, Gana JC, Yap J, Adams-Webber T, Rashkovan N, Ling SC, et al. Platelet count, spleen length, and platelet count-to-spleen length ratio for the diagnosis ofoesophageal varices in people with chronic liver disease or portal vein thrombosis. Cochrane Database Syst Rev. 2017;2017(4):CD008759.

58. Binţinţan A, Chira RI, Binţinţan VV, Nagy GA, Mânzat-Săplăcan MR, Lupşor-Platon M, et al. Value of hepatic elastography and Doppler indexes for predictions of esophageal varices in liver cirrhosis. Med Ultrason. 2015;17(1):5–11.

59. Mahmoud HS, Mostafa EF, Mohammed MAW. Role of portal haemodynamic parameters in prediction of oesophageal varices in cirrhotic patients. Arab J Gastroenterol. 2014;15(3–4):130–4.

60. Chakrabarti R, Sen D, Khanna V. Is non-invasive diagnosis of esophageal varices in patients with compensated hepatic cirrhosis possible by duplex Doppler ultrasonography? Indian J Gastroenterol. 2016;35(1):60–6.

61. Qiu L, Zhang X, Liu D, Qian L, Hu X. Contrast-Enhanced Ultrasonography Diagnostic Evaluation of Esophageal Varices in Patients with Cirrhosis. Ultrasound Q. 2016;32(2):136–43.

62. Agha A, Anwar E, Bashir K, Savarino V, Giannini EG. External validation of the platelet count/spleen diameter ratio for the diagnosis of esophageal varices in hepatitis C virus-related cirrhosis. Dig Dis Sci. 2009;54(3):654–60.

63. Cammà C, Petta S, Di Marco V, Bronte F, Ciminnisi S, Licata G, et al. Insulinresistance is a risk factor for esophageal varices in hepatitis C virus cirrhosis. Hepatology. 2009;49(1):195–203.

64. Sarangapani A, Shanmugam C, Kalyanasundaram M, Rangachari B, Thangavelu P, Subbarayan JK. Noninvasive prediction of large esophageal varices in chronic liver disease patients. Saudi J Gastroenterol Off J Saudi Gastroenterol Assoc. 2010;16(1):38–42.

65. Chen XL, Chen TW, Zhang XM, Li ZL, Zeng NL, Zhou P, et al. Platelet count combined with right liver volume and spleen volume measured by magnetic resonance imaging for identifying cirrhosis and esophageal varices. World J Gastroenterol. 2015;21(35):10184–91.

66. Abd-Elsalam S, Habba E, Elkhalawany W, Tawfeek S, Elbatea H, El-Kalla F, et al. Correlation of platelets count with endoscopic findings in a cohort of Egyptian patients with liver cirrhosis. Medicine (Baltimore). 2016;95(23):e3853.

67. Deng H, Qi X, Guo X. Diagnostic Accuracy of APRI, AAR, FIB-4, FI, King, Lok, Forns, and FibroIndex Scores in Predicting the Presence of Esophageal Varices in Liver Cirrhosis: A Systematic Review and Meta-Analysis. Medicine (Baltimore). 2015;94(42):e1795–e1795.

68. Cho EJ, Kim MY, Lee JH, Lee IY, Lim YL, Choi DH, et al. Diagnostic and prognostic values of noninvasive predictors of portal hypertension in patients with alcoholic cirrhosis. PLoS One. 2015;10(7):e0133935–e0133935.

69. Qi X, Li H, Chen J, Xia C, Peng Y, Dai J, et al. Serum liver fibrosis markers for predicting the presence of gastroesophageal varices in liver cirrhosis: A retrospective cross-sectional study. Gastroenterol Res Pract. 2015;2015:274534.

70. Wu Q-M, Zhao X-Y, You H. Quantitative fibrosis parameters highly predict esophageal-gastro varices in primary biliary cirrhosis. Eur Rev Med Pharmacol Sci. 2016;20(6):1037–43.

71. McCarty TR, Afinogenova Y, Njei B. Use of Wireless Capsule Endoscopy for the Diagnosis and Grading of Esophageal Varices in Patients With Portal Hypertension: A Systematic Review and Meta-Analysis. J Clin Gastroenterol. 2017;51(2):174–82.

72. Spiegel BMR, Esrailian E, Eisen G. The budget impact of endoscopic screening for esophageal varices in cirrhosis. Gastrointest Endosc. 2007;66(4):679–92.

73. Ramirez FC, Hakim S, Tharalson EM, Shaukat MS, Akins R. Feasibility and safety of string wireless capsule endoscopy in the diagnosis of esophageal varices. Am J Gastroenterol. 2005;100(5):1065–71.

74. Stipho S, Tharalson E, Hakim S, Akins R, Shaukat M, Ramirez FC. String capsule endoscopy for screening and surveillance of esophageal varices in patients with cirrhosis. J Interv Gastroenterol. 2012;2(2):54–60.

75. Chen W-S, Zhu L-H, Li D-Z, Chen L, Wu Y-L, Wang W. String esophageal capsule endoscopy with real-time viewing improves visualization of the distal esophageal Z-line: a prospective, comparative study. Eur J Gastroenterol Hepatol. 2014;26(3):309– 12.

76. Krok KL, Wagennar RR, Kantsevoy S V., Thuluvath PJ. Esophageal capsule endoscopy is not the optimal technique to determine the need for primary prophylaxisin patients with cirrhosis. Arch Med Sci. 2016;12(2):365–71.

77. Sacher-Huvelin S, Calès P, Bureau C, Valla D, Vinel JP, Duburque C, et al. Screening of esophageal varices by esophageal capsule endoscopy: Results of a French multicenter prospective study. Endoscopy. 2015;47(6):486–92.

78. Lapalus MG, Dumortier J, Fumex F, Roman S, Lot M, Prost B, et al. Esophageal capsule endoscopy versus esophagogastroduodenoscopy for evaluating portal hypertension: A prospective comparative study of performance and tolerance. Endoscopy. 2006;38(1):36–41.

79. Frenette CT, Kuldau JG, Hillebrand DJ, Lane J, Pockros PJ. Comparison of esophageal capsule endoscopy and esophagogastroduodenoscopy for diagnosis of esophageal varices. World J Gastroenterol. 2008;14(28):4480–5.

80. Kassim A, Ameen S, Musead M. Non-Invasive Assessment of Esophageal Varices in Cirrhotic Yemeni Patients. Int J Med Sci Public Heal. 2018;7(7):119–26.

81. Chen R, Deng H, Ding X, Xie C, Wang W, Shen Q. Platelet Count to Spleen Diameter Ratio for the Diagnosis of Gastroesophageal Varices in Liver Cirrhosis: A Systematic Review and Meta-Analysis. Gastroenterol Res Pract. 2017;2017:7407506.

82. Shibata S, Joshita S, Umemura T, Yamazaki T, Fujimori N, Ichikawa Y, et al. Liver stiffness-spleen size-to-platelet ratio risk score detects esophageal varices in chronic liver disease. Springerplus. 2016;5(1):1–6.

83. González-Ojeda A, Cervantes-Guevara G, Chávez-Sánchez M, Dávalos-Cobián C, Ornelas-Cázares S, Macías-Amezcua MD, et al. Platelet count/spleen diameter ratio to predict esophageal varices in Mexican patients with hepatic cirrhosis. World J Gastroenterol. 2014;20(8):2079–84.

84. Chowdhury S, Chakraborty P pratim. Universal health coverage - There is more to it than meets the eye. J Fam Med Prim Care. 2017;6(2):169–70.

85. Bitey S, Bitey A, Dhokade L. Non-invasive predictors of esophageal varices in patients with cirrhosis of liver. Int J Biol Med adv Res. 2019;10(4):1–5.

86. Kraja B, Mone I, Akshija I, Koçollari A, Prifti S, Burazeri G. Predictors of esophageal varices and first variceal bleeding in liver cirrhosis patients. World J Gastroenterol. 2017;23(26):4806–14.

87. Grace M, Sebastian S, Sajeev M. Platelet Count to Spleen Diameter Ratio in the Prediction of Varices in Cirrhosis in Indian Patients - An Analytical Cross Sectional Study. 2016;3(12):3491–4.

88. Tiwari D, Kumar S, Lahariya D, Jacob J. Comparison between Platelet Count , Spleen Diameter and Their Ratio with Esophageal Varices in Patients with Liver Cirrhosis. Am J Med Med Sci. 2016;6(1):29–33.

89. Manohar TP, Patil V, Salkar HR. Combination of non-endoscopic parameters as predictors of large esophageal varices. Trop Gastroenterol. 2014;35(3):173–9.

90. Cherian J V., Deepak N, Ponnusamy RP, Somasundaram A, Jayanthi V. Non-invasive predictors of esophageal varices. Saudi J Gastroenterol. 2011;17(1):64–8.

91. Eskander A, Sherif L, Nabih M, El Baroudy N, Marcos G BE. Serum Zinc Level and Its Correlation with Vesikari System Scoring in Acute Pediatric Diarrhea. Open Access Maced J Med Sci. 2017;5(5):677–80.

92. Kirkwood BR, Sterne JA. Essential medical statistics. John Wiley & Sons; 2010 Sep 16.

93. IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

94. Kamath PS, Mookerjee RP. Individualized care for portal hypertension: Not quite yet. J Hepatol. 2015;63(3):543–5.

95. Baig WW, Nagaraja M V., Varma M, Prabhu R. Platelet count to spleen diameter ratio for the diagnosis of esophageal varices: Is it feasible? Can J Gastroenterol. 2008;22(10):825–8.

ANNEXURES

PROFORMA FOR DATA COLLECTION

NAME: IP NO:

AGE:

SEX:

OCCUPATION:

DETAILED HISTORY:

JAUNDICE

PEDAL EDEMA

ABDOMINAL DISTENSION

NAUSEA

VOMITING

ABDOMINAL PAIN

GENERAL PHYSICAL EXAMINATION:

PULSE: RR: TEMPERATURE

BLOOD PRESSURE:

ICTERUS CLUBBING PEDAL EDEMA

PALLOR CYANOSIS

BMI:

SYSTEMIC EXAMINATION:

ABDOMINAL EXAMINATION

CVS

COMPLETE HEMOGRAM. LFT. PT/INR

USG ABDOMEN. UPPER GI ENDOSCOPY. PC/SD

SPLENIC DIAMETER

INFORMED CONSENT FORM

SUBJECT‟S NAME: **HOSPITAL NUMBER:**

TITLE: TO EVALUATE THE REPRODUCIBILITY AND VALIDITY OF NON-INVASIVEPARAMETER PLATELET COUNT SPLENIC DIAMETER RATIO TO PREDICT ESOPHAGEAL VARICES IN INDIAN POPULATION WITH HEPATIC CIRRHOSIS

If you agree to participate in the study we will collect information (as per proforma) from you or a person responsible for you or both. We will collect the treatment and relevant details from your hospital record. This information collected will be used for only dissertation and publication. This study has been reviewed by the institutional ethical committee. The care you will get will not change if you don‟t wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

I understand that I remain free to withdraw from the study at any time and this will not change my future care. I have read or have been read to me and understood the purpose of the study, the procedure that will be used, the risk and benefits associated with my involvement in the study and the nature of information that will be collected and disclosed during the study. I have had the opportunity to ask my questions regarding various aspects of the study and my questions are answered to my satisfaction. I, the undersigned agree to participate in this study and authorize the collection and disclosure of my personal information for publication.

Subject name:

(Parents / Guardians name)

DATE: **SIGNATURE /THUMB IMPRESSION**

'cRA å& S d' 2eå32cನ

o 'cR 6 ' 63: .9 & 'cR

o ' ð ' 63: .c ¸ ¸ ¸e',2 3 o 'cR ನ d'ROd,-

&,Ro'RS e6 28 ed e'R ' 'cR8 e Ao'.

e'c &g SS6 ' 63: ,2 o ', :

ನ 33&,R /&,R2å33n' . ce. 9 ¸ ¸e',ð8 3 ' e fi3å 63S e ,ð3d8 33 33

'R& ¸ e fi3S d3 cod3 33n' e x fi3S c 'ð8 9S& e Ao'.

ईo 'cR ನ e ,ð3d8 e'c & 333 33 .....9 e Ao'. ईo be'ð8 63S2 &åð3e ,ð3d8

e'c & u'Rd'Re u'R 'RCOr3d33 9 x& 3 33n' ನ6 fi3S d3.

,o 3 o 'cR ನco8n' ನ 33 ईe ,ð3d' oro8 doe' 33 e332 3fi&33 ¸ ¸ 8 co8o'ನ.

ईe ,ð3d8 e'c &g Soe' 33n' c9 e Ao' d'od 'ನ 33e xe 2 3do fi&33 µ 'e 3e' Rನ.

33 6 d 2 d&ð33 n'c 3 8 d &Rą'fi n'9Sx& 3 ನ 33 . o 99 eS63 93oå 3e'R ನ2 3

e8d 6S33 9R 3e'Rನ.d'&A3 33 &ð3 e x 'cRfi, Sęå 6&od &Rą'ð e33 c fi&g,e ðfi&g

2 3 &åfi&33 33 ęi n'9S& e Ao' cod3 33 eoARd 6S33 6ci 3 o'

c fiS& 39d' o µax A .ðo ',R& A63 o' 2 3 2 d& ofi, 'n' ð So'R ad 3 Så

& .

ce &Rą 8e o fi&33 'ed,&Rð n ,e'£o8n' &fiå e fi3 o' 2 3 d 3c93efi ,9d ' 'c6

3 8 ð So'R 'c6A3S&n'r&6ofi 8 3S 8 .

33 n ,e' 9Sx& ¸ 3SS 'n' 'ed,&Rð &Rą',

&Rą'ð2 ,2 3 e & ad A 33 2 d&ð3 r& 333 si¸n'ð33 9R 3e' R ನ

ನ 33 ಈ e ,ð38od ð S o'R 2ðd8 &oe'n'd3d'c& 323 A63e' R ನ2 3 ad3 33 23o83d &

9ð33 rd8 3S 8 cod3 e x2 8d'co8o' R ನ

'cRAð 2 &å ,S3 ನ 3398o' R ನ 2 3 ,åð33 .R & o' R '.ಈo be'ð8 sdA d2 &åð33
ನ

ನ 33e x2 8d'co8o' R ನ 2 3 &Rą',

,&,δ, oro8 d e ð 2 3 ð xðfi& rn' 33 'ര8ϭ3S , ' fi&33 d'R& 3

33n' eSd 8¸ e Ao'.

' ϭ3 2 3 & / 'u' ϭ&gfi3ϭ3 3 8ನo :

R ϭ / ϭ ' ϭ3 / 'u' ϭ&g fi3ϭ3 3 8ನo :

si¸n' e'n'd3d'c&g S S,& ð & 8ನo

PATIENT INFORMATION SHEET

Study Title: TO EVALUATE THE REPRODUCIBILITY AND VALIDITY OF NON-INVASIVE PARAMETER PLATELET COUNT SPLENIC DIAMETER RATIO TO PREDICT ESOPHAGEAL VARICES IN INDIAN POPULATION WITH HEPATIC CIRRHOSIS

Principal investigator: Dr. V KISHORE

Study site :R.L Jalappa Hospital and Research Center attached to Sri Devaraj Urs Medical College, Tamaka, Kolar.

Purpose of the study: To evaluate the reproducibility or validity of non-invasive parameter platelet count /splenic diameter to predict esophageal varices in Indian population with hepatic cirrhosis

Voluntary Participation: Your participation in this study is entirely voluntary. There is no compulsion to participate in this study. You will be no way affected if you do not wish to participate in the study. You are required to sign only if you voluntarily agree to participate in this study. Further you are at a liberty to withdraw from the study at any time. We assure you that your withdrawal will not affect your treatment by the concerned physician in any way.

Procedure: we will take detailed history and send your blood samples for complete hemogram , liver function test , PT /APT INR and USG abdomen , upper GI endoscopy .

Confidentiality: All information collected from you will be strictly confidential & will not be disclosed to anyone except if it is required by the law. This information collected will be used only for research. This information will not reveal your identity.

We would not compel you any time during this process; also we would greatly appreciate your cooperation to the study. We would like to get your consent to participate in the study.

For any information you are free to contact investigator. This study has been approved by the Institutional Ethics Committee & has been started only after their formal approval. The sample collected will be stored in the institute and I request you to permit us to store and use this sample for any future study.

MASTER SHEET

S.no	UHID NO	Age	Gender	Jaundice	Pedal oedema	Abdominal distension	Abdominal pain	Vomiting /nausea	Gi bleeding	Fatigue	Weight loss	Oliguria	Symptoms of hepatic encephalopathy	Alcoholism	Pallor
1	751477	52	Male	Negative	Negative	Positive	Positive	Negative	Negative	Negative	Negative	Negative	Negative	Positive	Positive
2	749712	39	Male	Positive	Positive	Positive	Negative	Negative	Negative	Negative	Negative	Positive	Negative	Positive	Positive
3	745287	52	Male	Positive	Positive	Positive	Negative	Positive	Negative	Positive	Negative	Negative	Negative	Positive	Positive
4	862960	60	Male	Positive	Positive	Positive	Negative	Negative	Negative	Negative	Positive	Negative	Negative	Positive	Negative
5	641243	64	Male	Positive	Positive	Positive	Negative	Negative	Negative	Positive	Positive	Negative	Negative	Positive	Positive
6	857067	60	Female	Positive	Positive	Positive	Negative	Negative	Negative	Positive	Positive	Negative	Negative	Negative	Positive
7	871240	52	Male	Negative	Positive	Positive	Positive	Negative	Negative	Positive	Negative	Negative	Negative	Positive	Negative
8	785566	78	Male	Negative	Positive	Positive	Positive	Negative	Negative	Negative	Negative	Negative	Negative	Positive	Positive
9	860713	55	Male	Positive	Negative	Positive	Positive	Negative	Negative	Negative	Negative	Negative	Negative	Positive	Negative
10	558098	61	Male	Negative	Negative	Negative	Negative	Positive	Negative	Positive	Positive	Negative	Negative	Positive	Positive
11	863659	60	Male	Positive	Positive	Positive	Negative	Negative	Negative	Positive	Positive	Negative	Negative	Positive	Positive
12	770398	72	Male	Positive	Positive	Negative	Negative	Positive	Negative	Positive	Negative	Negative	Negative	Negative	Positive
13	746923	35	Male	Negative	Negative	Positive	Negative	Negative	Negative	Negative	Positive	Negative	Negative	Positive	Negative
14	862964	45	Male	Positive	Negative	Negative	Positive	Negative	Negative	Positive	Negative	Negative	Negative	Positive	Negative
15	867234	47	Male	Positive	Positive	Positive	Negative	Negative	Negative	Negative	Negative	Positive	Negative	Positive	Negative
16	747887	58	Female	Positive	Positive	Positive	Negative	Negative	Negative	Negative	Positive	Negative	Positive	Negative	Positive
17	748648	48	Male	Positive	Negative	Positive	Negative	Negative	Negative	Positive	Positive	Negative	Positive	Positive	Negative
18	707346	48	Male	Positive	Negative	Negative	Positive	Negative	Negative	Negative	Negative	Negative	Negative	Positive	Negative
19	764766	75	Female	Negative	Positive	Positive	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Positive
20	763310	52	Male	Negative	Positive	Positive	Positive	Negative	Negative	Positive	Negative	Negative	Negative	Positive	Positive
21	763248	32	Male	Positive	Positive	Positive	Negative	Negative	Negative	Positive	Negative	Negative	Negative	Positive	Positive
22	849385	61	Male	Negative	Negative	Positive	Negative	Negative	Negative	Positive	Positive	Negative	Positive	Positive	Positive
23	769332	37	Male	Negative	Positive	Positive	Positive	Positive	Negative	Positive	Negative	Negative	Negative	Negative	Positive
24	769364	35	Male	Positive	Positive	Positive	Positive	Negative	Negative	Negative	Negative	Negative	Negative	Positive	Positive
25	861693	64	Male	Negative	Positive	Positive	Positive	Negative	Negative	Negative	Negative	Negative	Negative	Positive	Positive
26	767210	35	Male	Negative	Positive	Negative	Negative	Negative	Negative	Positive	Positive	Positive	Positive	Positive	Negative

27	842229	52	Female	Negative	Positive	Positive	Positive	Positive	Negative	Positive	Negative	Negative	Negative	Negative	Positive
28	852855	75	Female	Negative	Negative	Negative	Positive	Positive	Negative	Positive	Negative	Negative	Negative	Negative	Positive
29	865785	34	Male	Positive	Negative	Positive	Positive	Negative	Negative	Positive	Negative	Negative	Positive	Positive	Negative
30	838145	55	Male	Positive	Positive	Positive	Positive	Negative	Negative	Positive	Negative	Negative	Negative	Positive	Negative
31	805500	70	Male	Negative	Negative	Positive	Positive	Positive	Negative	Negative	Negative	Negative	Negative	Positive	Negative
32	857050	51	Male	Negative	Positive	Negative	Positive	Positive	Negative	Negative	Negative	Negative	Negative	Negative	Negative
33	801866	45	Male	Positive	Positive	Positive	Negative	Negative	Negative	Negative	Negative	Positive	Negative	Positive	Negative
34	815133	48	Male	Positive	Positive	Positive	Positive	Positive	Negative	Positive	Positive	Negative	Negative	Positive	Positive
35	815525	53	Male	Positive	Positive	Positive	Negative	Positive	Negative	Positive	Positive	Negative	Positive	Positive	Negative
36	801866	27	Male	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Positive	Negative	Negative	Positive	Negative
37	825506	33	Male	Positive	Positive	Positive	Positive	Negative	Negative	Positive	Positive	Negative	Negative	Positive	Negative
38	854655	65	Male	Negative	Positive	Positive	Negative	Positive	Negative	Positive	Positive	Negative	Positive	Negative	Positive
39	830850	53	Male	Positive	Positive	Positive	Positive	Positive	Negative	Positive	Positive	Negative	Positive	Positive	Positive
40	789282	45	Male	Negative	Positive	Positive	Positive	Negative	Negative	Positive	Negative	Negative	Negative	Positive	Negative
41	806627	35	Male	Positive	Positive	Positive	Negative	Negative	Negative	Positive	Positive	Negative	Negative	Positive	Positive
42	831151	38	Male	Positive	Negative	Positive	Positive	Negative	Negative	Positive	Positive	Negative	Negative	Positive	Negative
43	834637	25	Female	Positive	Positive	Positive	Negative	Negative	Negative	Positive	Positive	Negative	Negative	Negative	Negative
44	832035	35	Male	Negative	Negative	Positive	Positive	Negative	Negative	Positive	Negative	Negative	Negative	Positive	Negative
45	836332	48	Male	Negative	Positive	Positive	Positive	Negative	Negative	Negative	Positive	Negative	Negative	Positive	Negative
46	838057	26	Male	Positive	Negative	Positive	Positive	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
47	634758	31	Male	Positive	Positive	Positive	Positive	Positive	Negative	Positive	Positive	Negative	Positive	Positive	Positive
48	825508	38	Male	Positive	Positive	Positive	Positive	Positive	Negative	Positive	Positive	Negative	Negative	Positive	Positive
49	899277	71	Male	Positive	Positive	Positive	Positive	Negative	Negative	Positive	Positive	Negative	Negative	Positive	Positive
50	879569	70	Female	Negative	Positive	Positive	Positive	Negative	Negative	Positive	Positive	Negative	Negative	Negative	Negative
51	859055	45	Male	Positive	Positive	Positive	Negative	Negative	Negative	Negative	Negative	Positive	Negative	Positive	Positive
52	750583	60	Female	Positive	Positive	Positive	Negative	Negative	Negative	Positive	Positive	Negative	Negative	Negative	Positive

S.no	Icterus	Pedal edema	Absent	Spider naevi	Scanty Axillary	Pubic hair	Asterixis	Parotid swelling	Gynaecomastia	Alopecia	Ascites	Distended veins	Hepatomegaly	Splenomegaly	Encephalopathy
1	Positive	Positive	Yes	No	No	No	No	No	No	No	Positive	Negative	Negative	Negative	Negative
2	Positive	Positive	No	Yes	No	No	No	No	No	No	Positive	Negative	Negative	Negative	Negative
3	Positive	Positive	No	No	Yes	Yes	No	No	No	No	Positive	Positive	Negative	Positive	Negative
4	Positive	Positive	No	No	No	No	Yes	No	No	No	Positive	Negative	Negative	Negative	Positive
5	Positive	Positive	No	No	Yes	No	No	Yes	Yes	No	Positive	Negative	Negative	Negative	Negative
6	Positive	Positive	No	No	Yes	Yes	No	No	No	No	Positive	Negative	Negative	Negative	Negative
7	Negative	Positive	Yes	No	No	No	No	No	No	No	Positive	Positive	Negative	Positive	Negative
8	Negative	Positive	No	No	Yes	Yes	Yes	No	No	No	Positive	Negative	Negative	Negative	Positive
9	Negative	Positive	No	Yes	Yes	Yes	No	No	No	No	Positive	Negative	Negative	Negative	Negative
10	Positive	Positive	No	No	Yes	Yes	No	No	Yes	No	Positive	Negative	Negative	Positive	Negative
11	Positive	Positive	No	No	No	No	No	Yes	Yes	No	Positive	Positive	Negative	Positive	Negative
12	Positive	Positive	No	No	No	No	No	No	No	No	Negative	Negative	Negative	Positive	Negative
13	Positive	Negative	No	No	No	No	No	No	No	No	Positive	Negative	Negative	Positive	Negative
14	Positive	Positive	No	Yes	No	No	No	No	No	No	Negative	Negative	Positive	Positive	Negative
15	Positive	Positive	No	No	No	No	No	No	No	No	Positive	Negative	Negative	Negative	Negative
16	Positive	Positive	No	No	No	No	No	No	No	No	Positive	Negative	Negative	Negative	Positive
17	Positive	Negative	No	No	No	No	Yes	No	No	No	Positive	Negative	Positive	Positive	Positive
18	Positive	Positive	No	Yes	No	No	No	Yes	No	No	Negative	Negative	Negative	Negative	Negative
19	Negative	Negative	No	No	Yes	Yes	No	No	No	No	Positive	Negative	Negative	Negative	Negative
20	Positive	Positive	No	No	No	No	No	Yes	No	No	Negative	Negative	Negative	Negative	Negative
21	Positive	Positive	No	No	No	No	No	Yes	No	No	Positive	Positive	Negative	Positive	Negative
22	Positive	Positive	No	No	Yes	No	Yes	No	No	No	Positive	Negative	Positive	Negative	Positive
23	Positive	Positive	No	No	Yes	No	No	No	No	No	Positive	Positive	Negative	Positive	Negative
24	Positive	Positive	No	No	Yes	No	No	Yes	No	No	Positive	Positive	Positive	Negative	Negative

25	Positive	Positive	No	No	Yes	No	No	Yes	No	No	Positive	Negative	Positive	Positive	Negative
26	Positive	Positive	No	Yes	Yes	Yes	Yes	No	Yes	No	Positive	Positive	Positive	Negative	Positive
27	Positive	Positive	No	No	No	No	No	No	No	No	Positive	Positive	Negative	Negative	Negative
28	Positive	Positive	No	No	No	No	No	No	No	No	Negative	Negative	Negative	Positive	Negative
29	Positive	Negative	No	Yes	No	No	Yes	No	No	No	Positive	Negative	Negative	Positive	Positive
30	Positive	Positive	No	No	No	No	No	No	No	No	Positive	Positive	Positive	Negative	Negative
31	Negative	Negative	No	No	No	No	No	No	No	No	Positive	Negative	Negative	Negative	Negative
32	Positive	Positive	No	No	No	No	No	No	No	No	Negative	Negative	Negative	Negative	Negative
33	Positive	Positive	No	Yes	No	No	No	Yes	No	No	Positive	Positive	Negative	Positive	Negative
34	Positive	Positive	No	Yes	No	Yes	No	Yes	No	Yes	Positive	Positive	Negative	Positive	Negative
35	Positive	Positive	No	Yes	Yes	No	Yes	No	No	No	Positive	Negative	Negative	Negative	Positive
36	Positive	Positive	No	No	No	No	No	No	No	No	Positive	Positive	Negative	Positive	Negative
37	Positive	Positive	No	No	No	No	No	No	No	No	Positive	Positive	Negative	Negative	Negative
38	Positive	Positive	No	Yes	No	No	Yes	Yes	Yes	Yes	Positive	Positive	Negative	Positive	Positive
39	Positive	Positive	No	Yes	No	No	Yes	Yes	Yes	No	Positive	Positive	Negative	Positive	Positive
40	Positive	Positive	No	No	No	No	No	No	No	No	Positive	Negative	Positive	Positive	Negative
41	Positive	Positive	No	Yes	No	No	No	Yes	Yes	No	Positive	Positive	Negative	Positive	Negative
42	Positive	Positive	No	No	No	No	No	Yes	No	No	Positive	Negative	Positive	Positive	Negative
43	Positive	Positive	No	No	No	No	No	No	No	Yes	Positive	Positive	Negative	Negative	Negative
44	Negative	Negative	No	No	No	No	No	Yes	No	Yes	Positive	Negative	Negative	Negative	Negative
45	Negative	Negative	No	No	No	No	No	No	No	No	Positive	Negative	Negative	Negative	Negative
46	Positive	Positive	No	No	No	No	No	No	No	No	Positive	Negative	Positive	Positive	Negative
47	Positive	Positive	No	No	No	No	No	No	No	No	Positive	Positive	Negative	Positive	Negative
48	Positive	Positive	No	No	No	No	No	Yes	Yes	No	Positive	Negative	Negative	Positive	Negative
49	Positive	Positive	No	Yes	Yes	No	No	No	No	Yes	Positive	Positive	Negative	Negative	Negative
50	Positive	Positive	No	Yes	Yes	No	Yes	No	No	Yes	Positive	Positive	Negative	Negative	Positive
51	Positive	Positive	No	Yes	No	No	No	No	No	No	Positive	Negative	Negative	Negative	Negative
52	Positive	Positive	No	No	Yes	Yes	No	No	No	No	Positive	Negative	Negative	Negative	Negative

S.no	HB%	PLT COUNT	S. BILIRUBIN	D. BILIRUBIN	SGOT	SGPT	ALK.PH	T. PROTEIN	S. ALBUMIN	PT	INR	CIRRHOSIS	SPLEEN BIPOLAR DIAMETER	ASCITES	VARICES	Platelet to spleen diameter Ratio
1	8.9	1,21,000	3.5	2.9	63	25	101	7.6	2	24.1	1.98	Positive	135	Positive	Positive	896.31
2	10.1	75,000	2.8	2.2	122	55	113	5.1	2	19	1.52	Positive	70	Positive	Positive	1,071.43
3	7	1,12,000	7.3	7	82	10	274	6.7	1.9	30.1	2.47	Positive	130	Positive	Negative	861.54
4	10.6	78,000	4.3	4.1	107	25	300	8.6	2	17.3	1.57	Positive	96	Positive	Positive	812.5
5	5.1	78,000	1.6	1	64	21	111	6	3	20.5	1.57	Positive	81	Positive	Positive	962.96
6	11.2	1,20,000	1.4	0.9	79	46	227	6.4	2.9	19.7	1.5	Positive	136	Positive	Positive	882.34
7	10.6	85,000	3.4	2.7	43	19	134	6.8	2	28.1	2.28	Positive	85	Positive	Positive	1,000.00
8	8.8	73,000	1.3	0.7	25	12	64	6.1	2.4	36.8	3.1	Positive	74	Positive	Positive	986.49
9	12.6	1,08,000	11.5	8.6	72	40	123	7.1	2.9	14	1.3	Positive	143	Positive	Positive	754.13
10	8.8	1,07,000	1.1	0.9	16	16	104	7.7	2.5	18.8	1.4	Positive	139	Positive	Positive	769.14
11	11.3	94,000	5	2.5	46	16	150	7.2	2.3	27.6	2.2	Positive	120	Positive	Positive	783.21
12	10.5	95,000	16.2	13.7	51	31	249	7.5	2	19.7	1.5	Positive	153	Negative	Positive	620.92
13	11.7	1,32,000	11.5	10.4	236	33	182	7.1	2.4	21	1.65	Positive	151	Positive	Negative	874.5
14	11.3	2,05,000	31.4	23	62	44	177	5.5	2.6	26.3	2.1	Positive	157	Negative	Positive	1,305.73
15	13.3	1,12,000	4.3	3.8	262	68	201	8.5	2.4	26.8	2.1	Positive	141	Positive	Positive	794.33
16	8	1,74,000	17.2	15.1	41	17	143	5.8	2	19.3	1.46	Positive	138	Positive	Positive	1,260.87
17	12.2	1,63,000	37.2	29.4	57	19	235	6.3	2.9	26	2.08	Positive	137	Positive	Positive	1,189.78
18	16.2	1,20,000	19.7	15.2	304	485	135	5.5	2.2	19.6	1.49	Positive	74	Negative	Negative	2,553.19
19	12.3	1,03,000	0.6	0.3	57	13	87	7	3.1	19.5	1.48	Positive	84	Positive	Positive	1,907.41
20	9.2	75,000	3.1	1.7	21	10	148	6.6	2.1	23.4	1.83	Positive	71	Positive	Positive	1,500.00
21	5.6	1,20,000	3.7	2	111	45	134	6.2	2.1	20.2	1.54	Positive	152	Positive	Positive	789.31
22	7.1	1,27,000	2.8	2.4	33	15	74	5.9	1.5	27.1	2.17	Positive	129	Positive	Positive	984.47
23	8.8	85,000	2.4	1.7	35	11	232	6.4	2	15.3	1.11	Positive	120	Positive	Positive	708.33
24	10.3	1,12,000	5.9	3.7	163	51	84	7.3	2.9	27.1	2.17	Positive	128	Positive	Positive	875.21
25	10.6	90,000	3.2	2.4	65	27	114	6.8	2.8	27.6	2.23	Positive	121	Positive	Positive	743.8
26	11	3,53,000	2.5	2	122	22	177	6.4	2.6	17.6	1.31	Positive	90	Positive	Positive	6,788.46

27	5.6	2,50,000	0.3	0.1	22	13	113	6.9	3.8	17.3	1.28	Positive	77	Positive	Positive	3,246.75
28	9.7	1,01,000	2.9	1.1	47	22	83	5.3	2	33.2	2.77	Positive	136	Negative	Negative	742.18
29	13.1	1,09,000	23.1	17.1	127	61	99	5	2.7	50.4	4.03	Positive	110	Positive	Positive	990.91
30	12.7	94,000	10.8	10.1	126	43	114	5.7	2.1	24.2	1.71	Positive	100	Positive	Positive	940
31	14.2	99,000	2.2	1.3	80	24	220	6	2.6	15.6	1.13	Positive	92	Positive	Positive	1,903.85
32	13.5	1,30,000	1.2	0.8	24	15	88	6.1	2.6	17.1	1.27	Positive	104	Positive	Positive	2,031.25
33	10.6	1,17,000	5.7	3.6	104	32	105	7.5	2.4	23.9	1.87	Positive	152	Positive	Positive	769.12
34	9.4	90,000	3.1	2	66	15	117	7.6	2.4	27.4	2.21	Positive	112	Positive	Positive	803.57
35	10	1,79,000	1.8	1.1	47	23	85	6.7	2.4	21.7	1.68	Positive	90	Positive	Positive	1,988.89
36	13.5	1,13,000	1	0.4	44	28	83	6.9	2.5	19.4	1.47	Positive	149	Positive	Positive	758.12
37	12	1,23,000	9.7	5.2	65	58	195	6.1	2.7	36.2	3.07	Positive	163	Positive	Positive	754.14
38	11.6	1,27,000	0.5	0.3	28	22	129	7.2	2	17.3	1.28	Positive	129	Positive	Positive	984.53
39	8.8	1,25,000	3.1	2.2	37	122	100	6.5	2.7	20.5	1.57	Positive	159	Positive	Positive	786.32
40	13.8	2,28,000	1	0.8	125	43	214	7.7	2.5	20.1	1.53	Positive	133	Positive	Positive	1,714.29
41	7.8	79,000	8.6	7.3	160	74	110	6.1	2	28.6	2.32	Positive	106	Positive	Positive	745.32
42	14.9	1,23,000	1.5	0.4	14	34	93	7.3	4.1	14.6	1.05	Positive	154	Negative	Positive	798.21
43	9.7	1,30,000	33.9	26.1	107	67	71	4.5	2.6	59	2.92	Positive	121	Positive	Negative	1,074.38
44	16.2	77,000	0.4	0.1	18	10	67	5.2	2.7	15.1	1.09	Positive	98	Positive	Negative	785.71
45	13.8	1,64,000	1.3	0.6	32	24	88	7.7	4.2	15.7	1.14	Positive	100	Positive	Positive	1,640.00
46	11.5	1,38,000	28.3	21.7	177	22	208	6.8	2.5	28.1	2.28	Positive	142	Positive	Positive	971.83
47	9.7	1,17,000	2.1	1.5	62	24	120	6.9	2.5	25.5	2.03	Positive	133	Positive	Positive	879.21
48	9.8	1,15,000	2.7	1.9	24	45	104	7.5	2.5	22	1.91	Positive	154	Positive	Positive	746.23
49	9.6	1,19,000	3.5	2.9	63	25	101	7.6	2	24.1	1.98	Positive	123	Positive	Positive	967.12
50	8.5	80,000	3.3	2.9	24	11	125	7.6	1.9	39.3	3.38	Positive	81	Positive	Positive	987.23
51	9.8	73,000	2.7	2.1	119	50	110	4.9	1.9	19	1.52	Positive	69	Positive	Positive	1,057.97
52	10.9	1,21,000	1.3	0.8	78	45	226	6.3	2.8	19	1.4	Positive	167	Positive	Positive	724.31