European Journal of Molecular & Clinical Medicine (EJMCM)
ISSN: 2515-8260 Volume 07, Issue 09, 2020

Original research article

A study on clinical, biochemical and sonological parameters in predicting and grading esophageal varices (ev) in compensated cirrhosis in a tertiary care hospital

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Abstract

Background: Liver cirrhosis and portal hypertension causes esophageal variceal (EV) formation, which can cause variceal bleed with significant mortality. But, endoscopic screening, in a resource constrained setup like India,is not feasible for entire cirrhotic population. Hence there has always been a need for noninvasive predictive factors of EV and hence, umpteen studies have been done in this regard.

Materials and Methods: This cross sectional study was conducted in 70 patients with compensated cirrhosis. We assessed parameters like Model of end stage liver disease (MELD) score, fasting blood ammonia, platelet count (PC)and platelet count/bipolar spleen diameter ratio(PC/SD).

Results: All these four parameters were found to have significant association in prediction of presence or absence of EV in the study group{ 9.46 ± 1.46 vs 7.56 ± .70, (81.19Umol/l) ± 10.59 vs (52.11Umol/l) ± 9.70, 119346 ± 30986 vs 189611 ± 37595 and 856 ± 140 vs 1460 ± 204, } respectively (p values <.001).Also, they have significant association in EV grading ,if present, in the univariate analysis (p values <.001).The cut off values of all these markers were calculated using a receiver operating characteristic(ROC) curve.

Conclusion: All these non-invasive parameters can be a useful tool in identifying & targeting cirrhotic with large EV who should undergo screening esophagogastroduodenoscopy (EGDscopy).

Keywords: Esophageal varices(EV), portal hypertension, serum ammonia, cirrhosis.

Introduction

Cirrhosis of liver usually progresses to end stage liver damage causing fibrosis leading to distortion and destruction of normal hepatic parenchyma. Portal Hypertension (PHTN) caused by increase in portal pressure is one of the complication of cirrhosis. Varices are formed when Hepatic Vein Pressure Gradient (HVPG) exceeds 10 mm Hg and they tend to bleed when it exceeds 12 mm Hg. EV prevalence ranges from 60% to 80% in cirrhotics ,and the mortality from variceal bleed is around 20% .The Baveno VI Consensus Conference advocate that all cirrhotics must have endoscopic variceal evaluation during time of diagnosis. Also,it recommends repeat endoscopy in patients without EV, every 2-3 years and every 1-2 years in patients having small EV [1].In a country like India which is not fully developed and where most of the population still resides in rural areas,, with a relative absence of endoscopic facilities, the implementation of these recommendations looks

unattainable and not ideal for clinical practice. To curtail the unnecessary endoscopies in cirrhotics without varices, several studies have evaluated possible non-invasive markers of EV. Most of them concluded that, by selecting patients on basis of a few laboratory and/or ultrasonographical parameters, an good number of screening endoscopies can be safely avoided, while also keeping the rate of undiagnosed EV, with a risk of bleed, acceptably low[2]. However, the predictability of most if not all non-invasive parameters, is still unsatisfactory, and none of them till now are recommended for use in practice.

Thrombocytopenia often seen in association with chronic liver disease and EV, is probably a reflection of the degree of portal hypertension. Splenic sequestration and antibody-mediated destruction platelet culling has been implicated as the major causative factors. Alternate mechanisms involved are reduction in production of liver-specific thrombocytopoietic growth factor. presence of antithrombocytic antibodies and thrombocyte associated immunoglobulin. The use of splenic diameter (SD) to predict variceal presence has several advantages. It can be easily calculated at routinely biannual US screening for Hepatocellular carcinoma(HCC) in cirrhotics, and also can be easily done on outpatient basis. platelet count(PC) alone as a non-invasive predictor of EV can sometimes cause confounding results as the cause cannot sometimes be solely attributed to portal hypertension. Hence using, PC/SD ratio negates this disadvantage because it "normalizes" platelet count to splenic sequestration [3,4].

From the last decade, various studies have emerged which indicate that serum ammonia can be used as a predictor of EV. Normal range of the fasting venous ammonia is 20-65 µmol..Probable mechanism is by the fact that portal hypertension contributes to slow, but progressive hepatic insufficiency. High serum ammonia levels are significant, because they are an ominous pointer to impending hepatic decompensation; In other words, less blood reaches the liver causing diminished hepatic reserve. Ammonia also augments vascular tone by promoting influx of extracellular calcium via voltage-dependent calcium channel.[5] The present study was intended to see the correlation of aforementioned parameters in predicting and grading of EV, if present in compensated cirrhotics of different etiologies in a tertiary care hospital in a city by the name of Kochi,in ,South India.

Materials & Methods

This was a single centre cross sectional observational study conducted in department of gastroenterology, Medical Trust Hospital Kochi, Kerala over a period of one year (January 2017 to January 2018). After obtaining approval from institutional ethics committee and obtaining informed consent from the patient, 70 consecutive adult compensated cirrhotic (both inpatients and outpatients)in gastroenterology and other departments were recruited for the study. Compensated Cirrhosis was detected by physical, laboratory and radiological evaluation. Patients with decompensated liver disease or malignancy (hepatocellular carcinoma or HCC), recent upper GI(gastrointestinal) bleed, who underwent previous medical, endoscopic or surgical intervention for portal hypertension, were excluded. Also excluded were patients having portal vein thrombosis on ultrasonography, patients with advanced co morbidities like cardiopulmonary and renal diseases

For all patients included in the study, etiological work up for cirrhosis was done. Serological tests for viral hepatitis (hepatitis B&C), serum ferritin levels, serum ceruloplasmin and ANA (antinuclear antibody) were done for all patients and other autoimmune profile done in relevant patients.

Laboratory examination included complete blood count including platelet count, complete liver function tests. MELD (Model for end stage liver disease) score and Child Pugh Turcotte staging were done for all patients [6,7]. Fasting venous blood ammonia was quantified for all subjects. 5ml of peripheral venous blood was obtained from each subject without tourniquet and collected into an EDTA evacuated tube. Ammonia level was quantified in plasma by

vitros amon slide method. All patients had endoscopic examination done by an expert gastroenterologist using Olympus Evis Exera III clv-190 system and were evaluated for EV. EV was graded according to the Japan Research Society for Portal Hypertension system [8]. After this, Doppler ultrasound examination was performed by an expert radiologist using 3.5Mhz transducer (Toshiba Nemio,30). It was conducted upine position during quiet respiration ,and splenic bipolar diameter measured in cm and platelet count/splenic diameter ratio was charted. Both gastroenterologist and radiologist were blinded to each other's results.

Statistical Methods

As per published reports, prevalence of EV among cirrhotics is taken as 60 to 80% with a confidence rate of 95% with an error estimate of 12%The minimum sample size worked up for this study was 65 using the formula N=Z2*P*Q/D2 where N=sample size Z=confidence coefficient. Chi-square test or Fisher's Extract test was used to compare the categorical variables with Oesophageal varices. Independent t-test of Mann-whitney U test was used to compare the continuous variables by Oesophageal varices. One-way ANOVA with post hoc Tukey was used to compare the continuous variable by oesophageal varices Grade. Receiving Operating Characteristic Curve (ROC Curve) was used to find best cut-point of diagnostic values that maximize sensitivity and specificity. The Analysis was done using IBM software SPSS version 20.0 for windows.A p value <0.05 was considered statistically significant.

Results

A total of 70 compensated cirrhosis cases were enrolled of which 52 patients (74%) had oesophageal varices & 18 (26%) did not have varices. Of the total cases 83% were male patients & 17% were female patients. No significant gender distribution was noted in our study. Major etiologic factor for cirrhosis was alcohol consumption & NASH (Non Alcoholic steatohepatitis). T. 63% of Child Stage A & 100% of Stage B developed varices. Mean age of the enrolled cases was 53.71 years. No significant difference was found among those with and without varices. The mean MELD score was higher in variceal group compared to the non variceal group (p-value <.001) (Table 1). The mean platelet count was much lower in the variceal group cpmapred to those without varices (p-value <.001). The mean PC/SD ratio value was significantly lower in those who had varices as compared to those who did not have varices. ie (p value <.001) Likewise fasting serum ammonia was significantly high in those who had varices when compared to non variceal group (p value <.001)(Table 1)

Table 1: Univariate analysis of various non-invasive predictors of Oesophageal varices(EV) and association between presence and absence of EV

Variables	**EsophagealVarices Present (n=52)**		**EsophagealVarices Absent (n=18)**		**P value**
	Mean	**SD**	**Mean**	**SD**	
Age	54.42	7.47	51.67	6.03	0.162
MELD Score	9.46	1.46	7.56	0.70	<0.001
PLC/SD	856.62	140.53	1460.28	204.74	<0.001
PLT count(lakhs/mm^3)	119346.15	30986.96	189611.11	37595.59	<0.001
Fasting Ammonia (μmol/l)	81.19	10.59	52.11	9.70	<0.001

There was statistical significance between serum ammonia values and grade of varices (p <0.001). The relationship between MELD score and variceal grading were directly proportional statistically significant (p<0.001). There is statistically significant correlation between platelet count and grades of varices (p<0.001). The mean platelet count in non variceal group was much higher than non variceal group and it was seen that there was an inverse relationship between platelet count and grade of varices (Table2)

Table 2: Univariate Analysis of Association Between Various Non Invasive Predictors of Esophageal Varices And Grades Of Varices

	Esophageal varices Grade								**p value**
	0 (n=18)		**1 (n=17)**		**2 (n=24)**		**3 (n=11)**		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
MELD Score	7.6	0.7	8.6	1.3	9.7	1.4	10.4	1.1	<0.001
PLC/SD	1460.3	204.7	904.9	89.1	890.5	131.2	708.2	132.2	<0.001
Plt count	189611.1	37595.6	145882.4	19277.2	117666.7	24767.9	82000.0	12385.5	<0.001
Fasting Ammonia µmol/l	52.1	9.7	76.4	7.9	78.6	8.5	94.2	8.1	<0.001

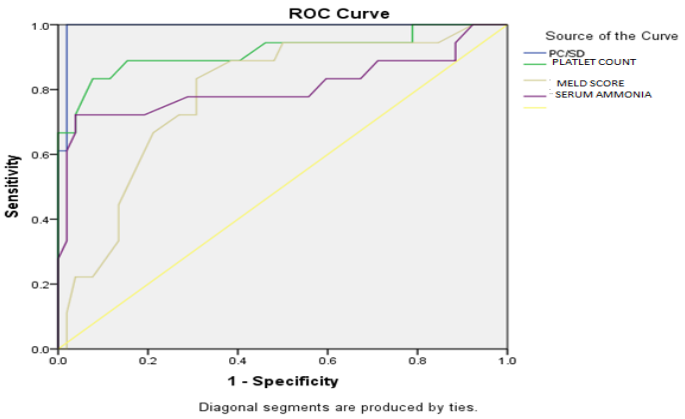

Figure 1: ROC CURVE used to calculate cut off values for various noninvasive parameters

ROC CURVE AND DETERMINING CUT OFF FOR VARIOUS PARAMETERS

A receiver operator curve (ROC) was used to determine the cut off levels of various parameters that were ascertained as significant predictors of presence of varices and their grading. The following values were obtained for various parameters, as a cut off for predicting the presence or absence of EV..A cut-off of 64 micromol/L was obtained for serum ammonia with a sensitivity of 98.1% and specificity of 88.9%. The cut off for MELD score was 8.5 with a sensitivity, specificity of 71.2%, 88.9% respectively. The mean platelet count

which predicted the presence or absence of varices was 1,67,500 with sensitivity and specificity of 92.3% and 83.3% respectively. .The mean cut off for PC/SD (platelet count/spleen diameter) was calculated as 1124.5 with sensitivity, specificity of 98.1% and 94.4%, respectively.

Discussion

Several studies have been published on the non-invasive diagnosis of EV in patients with chronic liver disease.[9,10] Our study was aimed at identifying different clinical, laboratory, ultrasonic and doppler parameters in addition to identifying different indices and scores which can be used in prediction of the presence or absence of EV and their grades in our cirrhotic patients for the purpose of avoiding unnecessary endoscopy.[11] In this hospital based study conducted over a one year period, the prevalence of esophageal varices was found to be 74%. This is comparable with various studies which estimate that prevalence of EV in newly detected cirrhotics range from 60-80%..Of the 70 compensated cirrhotics,majority were males A male preponderance could be explained by the fact that increased incidence of ethanol induced liver disease in this study group. .Ethanol abuse was the most common etiology to be implicated (52%) followed by NASH and 4% each for Hepatitis B and C.We also had a single case of hemochromatosis as etiological agent .As far as other etiologies were concerned, they were not be found as causative factor for cirrhosis in our study. There was no evidence of coexisting aetiologies in our study. This is in agreement with etiological distribution shown in other studies from this part of the world .Chang MH et al found out that in a population of 736 subjects, 42.4% of cirrhosis etiology was ethanol abuse followed by viral hepatitis (41%) [15].The lower incidence of viral hepatitis may be explained the fact that sample size was low in our study.

MELD score was significantly associated with prediction and grading of varices (p<. oo1). The cut off MELD score for predicting varices was 8.5. This is in concordance with studies conducted by SafwatEslam et al who postulated that MELD was significantly increased in patients with EV. The lesser cut off value for MELD could be explained by the fact that our study included only compensated cirrhotics[16]. Our study also showed that thrombocytopenia was significantly correlating with presence and grading of EV. By using ROC curve analysis, cut off value for predicting varices was 167500. (sensitivity-91 and specificity-88%). Previous studies had suggested that platelet count can predict EV presence in cirrhotics, although discriminating threshold for varices varies used to vary widely, ranging from 68,000 to 160,000 with sensitivity from 62% to 100% and specificity of 18 to 77%[3,4]. It has also been shown that PC/SD ratio is the one marker that has been consistently and independently associated with variceal presence. Giannini postulated that a PC/SD ratio cut off value of 909, had 100% negative predictive value in diagnosing EV presence.[3] Significantly, this result was also extrapolated in a sub group of compensated cirrhotics (PC/SD) ratio has a significant association with presence and grading of EV. The mean cut off for PC/SD was 1124.55 in our study.Jijo V Cherian et al postulated that in a subset of mainly alcoholic cirrhotics,the mean PC/SD cut off ratio for predicting varices was 666[17] . The higher cut off obtained in our study may be due to the fact that our subjects included only compensated cirrhotics.

The most sensitive noninvasive predictor tested in our study was fasting ammonia level. By analyzing the receiver operating characteristic (ROC) curve, the cut off levels of ≥64 mmol/L was found to predict the presence of EV with a sensitivity of 93.2% and a specificity of 94.6% .Studies by Tarantino et al and Hassan et al have noted that serum ammonia levels were significantly higher in cirrhotics with EV than those without, and ,ammonia levels above 65 μmol/L predicted the presence of EV with 100% sensitivity and 95% specificity[5,13].Khonadker et al also had same results in similar setting. They postulated that

blood ammonia levels of 63mmol and above had 95% sensitivity and 50%specificty in predicting large EV in compensated cirrhosis[14].

Our study has some unique features and strengths. To the best of our knowledge ,this was the first study done from this part of India where the study population was composed only of compensated cirrhotics as against similar such studies which included both decompensated and compensated cirrhotics. The prevalence of portal hypertension is low in compensated cirrhosis; hence the predictability of these parameters in compensated cirrhosis is more crucial. In the past such studies have focused on ability of these parameters in prediction of the presence and/or absence of EV in cirrhotics.There are very few studies which measured the ability of these parameters in grading the EV.Our study, does in fact investigate the role of these parameters in grading EV .And last but not the least all these parameters were studied are simple, bedside, cheap, noninvasive, objective,and easily reproducible in a resource constrained environment and ideal for follow up. Our study does have a few limitations.The sample size was relatively low. But this was because compensated cirrhotics rarely seek treatment themselves. And most of the cases were accidentally picked up and only a few volunteered to undergo all the battery of tests in the study. Also cirrhosis was diagnosed on clinical and sonological basis without the confirmation of a liver biopsy. But in our setting it is cumbersome to do a liver biopsy to confirm the diagnosis in all cirrhotics

CONCLUSIONS AND RECOMMENDATIONS

Esophagogastroduodenoscopy (EGDscopy) has been and will remain the gold standard for detecting and grading of EV in cirrhosis. It seems possible that by using non-invasive predictors we could restrict the use of endoscopy to those cirrhotic patients who are high risk for bleeding. On the practical aspect, this implies that these simple tests can enhance the efficacy of endoscopic variceal screening,even though they cannot obviate the need for screening endoscopy in all cirrhotics

In this era, where cirrhosis is increasingly being detected at a very early asymptomatic stage by non-invasive methods, this strategy may act as game changer. However,more such studies are needed before we can embark up on a method so as to do triaging system in which only the cirrhotics with maximum risk of developing EV need to undergo screening endoscopy.

Disclosure Statement: The authors have no conflicts of interest to declare.
Funding Sources: No kind of research funding received.

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