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Sensitivity, specificity and predictive values of noninvasive markers of esophageal varices in cirrhosis of liver

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Abstract

Objective: To assess the sensitivity, specificity, positive predictive values and negative predictive values of non invasive markers of esophageal varices in liver cirrhosis.

Methodology: This two year validation study was started on 1st January 2010 after approval of ethical review committee. 739 cases of cirrhosis of liver underwent upper GI endoscopy after informed written consent. Radiological parameters (liver size, portal vein, splenomegaly and ascites) and biochemical/hematological parameters (bilirubin, INR, albumin, platelet count) was documented in all case. Data regarding grades of varices and non invasive parameters was analyzed using SPSS 19.

Results: Serum albumin = 2.8 g/dl was 90.9% specific for varices in cirrhosis. Platelet count < 50,000/µL had specificity and PPV of 98.9% and 96.7% with p value < 0.001 and odds of 8.19 (95% CI: 5.74 – 11.69). Serum bilirubin = 3 mg/dl was 33.4% and 78.9% sensitive and specific for varices and the PPV and NPV was 63.7% and 51.6% respectively. INR > 2.2 had high predictive value for varices with sensitivity, specificity, PPV and NPV of 60.4%, 91.7%, 89.0% and 67.6% respectively (p < 0.001) with odds of 16.89 (95% CI: 10.97 – 25.99). Portal vein diameter > 15 mm, ascites, liver span < 8 cms and spleen size > 15 cms was 64.0%, 12.6%, 77.4% and 69.2% specific for varices (p < 0.001).

Conclusion: Platelet count < 50,000/µL is highly specific and sensitive predictive of varices, as is INR > 2.2. Biochemical markers have more significant predictive value than radiological. Platelet count and INR may be used as a predictor of varices in cirrhosis of liver.

Key Words: Sensitivity, Specificity, Positive Predictive Values, Negative Predictive Values, Non Invasive Markers, Esophageal Varices, Cirrhosis.

INTRODUCTION

Esophageal varices (EV) are dilated, tortuous and fragile vessels that connect portal venous with systemic venous circulation and located in sub mucosa of lower esophagus. Worldwide the most common cause of EV is portal hypertension secondary to cirrhosis of liver. Their most dangerous presentation is upper gastrointestinal bleeding. At the time of diagnosis 30% of cirrhotic patients have EV that increase to 90%, after 10 years. Varices strongly correlated with deteriorating hepatic function. In Child Turcot Pugh (CTP) class A, 40% cirrhotic harbors varices, which reach to 85% in CTP class C.

Approximately 30% of cirrhotic will bleed in first year after diagnosis and mortality of single episode depend on severity of liver disease. Some 10% cirrhotic in CTP class A and 70% in CTP class C die due to bleeding. The risk of variceal bleeding is also related to the size of esophageal varices, with large esophageal varices (LEV) being at a greater risk due to a higher variceal wall tension in LEV. Thus, annual incidence of gastrointestinal bleeding is only 1-2% in patients without varices, 5% in those with small esophageal varices and 15-20% in patients with LEV.[1]

It is recommended that all patients of cirrhosis at the time of diagnosis should undergo endoscopic evaluation for presence of EV. In compensated cirrhosis if no varices are detected, next review should be 2 – 3 years later. If small varices detected, repeat endoscopy should be done at 1 – 2 years. In patients with decompensated cirrhosis, follow should be yearly. The main aim of this surveillance endoscopy is to prevent bleeding from varices to improve survival of by therapeutic or endoscopic intervention [1, -]These recommendations imply a large workload on endoscopic units and a significant cost burden on patients with liver cirrhosis. As the prevalence of varices at time of diagnosis is only 30%, a large number of invasive endoscopic procedures turn out to be negative. Thus, there is a need for non-invasive means to diagnose or predict the presence or absence of EV.[1] Availability of such methods may help limit the number of endoscopic procedures performed for detection of EV and save a huge amount of resources. These recourses can be diverted for prevention of epidemic of HBV and HCV. Several studies have evaluated possible non-invasive markers of EV in patients with cirrhosis and have found platelet count, splenomegaly, advanced Child status, serum albumin and high portal vein diameter to be useful for this purpose.[-12] The predictive accuracy of these predictive factors is still unsatisfactory.

So, our study aims to evaluate the diagnostic validity i.e. sensitivity, specificity, positive predictive values and negative predictive values of four radiological (splenomegaly, ascites, portal vein diameter, shrunken liver) and four biochemical/hematological (serum bilirubin, serum albumin, INR, platelet count) non invasive markers EV.

METHODOLOGY

Design

This was a hospital based validation (cross-sectional) study.

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Duration

Two years from January 2010 till December 2011.

Setting

The patients were enrolled from wards of medicine department and weekly hepatology clinic of Medicine Department, Chandka Medical College (C.M.C), Larkana.

Sampling Technique

Purposive sampling.

Inclusion Criteria

All known patients of liver cirrhosis of either sex admitted in medical wards or visiting hepatology clinic of C.M.C Larkana for evaluation and management of cirrhosis of liver were enrolled.

Exclusion Criteria

Patients younger than 15 years and older than 75 years. Past history of bleeding per mouth.or propranolol or received endoscopic intervention for variceal hemorrhage. Previous interventions for portal hypertension as TIPSS or Shunts. Ultrasonography proven Hepato Cellular Carcinoma or Alpha Feto Protein = 10 times the normal limit.Haemodynamically unstable patients. Patients with advanced chronic disorders as COPD, CCF and heamatological disorders.Patients with medical contraindications to upper gastrointestinal endoscopy like shock, atlanto-axial subluxation, any coagulation disorder.

Data Collection

Informed written consent was taken from each case to draw blood sample, undergo ultrasonological evaluation and endoscopic examination. Blood samples were taken and sent to central laboratory C.M.C Larkana for detection of serum bilirubin (normal value 0.2 – 1 milligram per deciliter (mg/dL), serum albumin (normal value 3.5 – 7.5 gram per deciliter (g/dL), international normalized ratio (INR) and platelet count (normal values greater than 150,000/µL). Ultrasound (US) examination of abdomen was done for liver size, portal vein (PV) size, spleen size and the presence of ascites. Ultrasound examination of abdomen was done by a senior radiologist with more than 10 years experience, at the Radiology Department C.M.C Teaching Hospital. Toshiba SSA-70 U/S machine was used to carry out U/S examination. The U/S findings recorded were: liver was regarded as normal in size if it was 8 - 12 centimeters (cms), enlarged if it was more than 12 cms, decreased if it was less than 8 cms; spleen was regarded as enlarged when it was more than 12 cms; portal vein was regarded as dilated when it was more than 1.2 cms.

Endoscopic evaluation of all patients was done by a gastroenterologist having 10 year experience in endoscopy and were graded as

Grade 1: Varix is flush with the wall of the esophagus.Grade 2: Protrusion of the varix but not more than half way to the lumen center

Grade 3: Protrusion more than halfway to the center.

Grade 4: The varices are so large that they meet at the midline.

A separate Performa was filled for each patient entered into the study to record the data of these investigations and demography. All investigations were performed at the laboratory of CMC teaching hospital.

Data Analysis

The collected data was transferred to and analyzed using SPSS version 19. Means and SD (standard deviation) of numeric response variables as age, serum bilirubin, serum albumin, INR, platelet count, portal vein diameter and spleenic size were calculated. Frequencies and percentages were calculated for categorical response variables such as age (15 – 29 years, 30 – 44 years, 45 – 59 years, 60 – 74 years), gender, liver size (normal, decreased, increased), portal vein diameter (normal, dilated), ascites (present, absent) spleen size (= 13cms, = 15cms, mild splenomegaly, moderate splenomegaly, massive splenomegaly) serum bilirubin (<2 mg/dl, 2 – 3 mg/dl, > 3 mg/dl), serum albumin (>3.5 g/dl, 2.8 – 3.5 g/dl, < 2.8 g/dl), INR (< 1.7, 1.7 – 2.2, > 2.2) and platelet count (< 150,000/µL, < 100,000/µL, 50,000/µL, > 150,000/µL). Sensitivity, specificity, negative predictive values and positive predictive values of radiological and biochemical variables were calculated. The data was also compared in patients with and without varices by Chi-square test and T-test, when and where applicable. Odd ratios (OR) and 95% Confidence Interval (CI) were calculated. Probability value (p-value) of less than 0.05 (<0.05) was considered to be statistically significant

RESULTS

A total of 739 patients were studied with mean age of 45.81 ± 15.13 years and 481 (65.1%) male. Varices were documented in 52.6% patients. Grade 1 varices was documented in 58 (7.8%), grade 2 varices in 45 (6.1%), grade 3 varices in 162 (21.9%) and grade 4 varices in 124 (16.7%) participants. There demography is outlined in table 1.

Portal vein > 13mm had a sensitivity and specificity of 64.5% and 51.7%, for predicting varices with p value of 0.001. Presence of ascites ($p < 0.001$) had a sensitivity of 82.8% for varices. Decreased liver span < 8 cms ($p < 0.001$) had sensitivity, specificity, PPV and NPV of 48.3%, 77.4%, 70.4%, and 57.4% respectively with odds of 3.20 (95% CI: 2.33 – 4.41). With the increase in size of spleen the specificity of predicting varices in cirrhosis increases but sensitivity decreased. The specificity of spleen size > 13cms, spleen size > 15cms, mild splenomegaly, moderate splenomegaly and massive splenomegaly was 25.1%, 69.2%, 50.6%, 80.6% and 94.0% respectively. The sensitivity of spleen size > 13cms, spleen size > 15cms, mild splenomegaly, moderate splenomegaly and massive splenomegaly was 83.5%, 48.8%, 40.4%, 35.2% and 8.00% respectively. The details of predictive values of radiological parameters for varices in cirrhosis are detailed in table 2.Sensitivity of serum albumin fell from 66.8% to 32.1%, when serum albumin fell to < 2.8 g/dl. In contrast specificity increased from 70.6% to 90.9% when serum album fell from < 3.5 g/dl to < 2.8 g/dl with odds of 4.70 (95% CI: 3.08 – 7.17). Serum bilirubin > 3 mg/dl ($p < 0.001$) had sensitivity, specificity, PPV and NPV of 33.4%, 78.9%, 63.7%, and 51.6% respectively with odds of 1.87 (95% CI: 1.34 – 2.60). INR > 2.2 ($p < 0.001$) had sensitivity, specificity, PPV and NPV for varices in cirrhosis of 60.4%, 91.7%, 89.0% and 67.6% respectively with odds of 16.89 (95% CI: 10.97 – 25.99). The details of predictive values of biological parameters for varices in cirrhosis are detailed in table 3.

Platelet count < 150,000/µL ($p < 0.001$) had sensitivity, specificity, PPV and NPV of 76.6%, 52.0%, 63.9%, and 66.7% respectively with odds of 0.28 (95% CI: 0.28 – 0.38). When the platelet count was decreased the specificity and PPV sharply increased but sensitivity sharply decreased. Platelet count < 50,000/µL ($p < 0.001$) had sensitivity, specificity, PPV and NPV of 30.1%, 98.9%, 96.7%, and 56.0% respectively with odds of

Table no:1. Demographic profile of 739 cirrhotic patients under study

CHARACTERISTICS	NUMBER	PERCENTAGE
AGE		
Mean ±SD	**45.81 ±15.13 years**	
Range (Max - Min)	**55 (74 – 19)**	
GENDER		
Male	**481**	**65.1 %**
Female	**258**	**34.9 %**
AGE CATEGORIES		
15 – 29 years	**163**	**22.1 %**
30 – 44 years	**125**	**16.9 %**
45 – 59 years	**296**	**40.1 %**
60 – 74 years	**155**	**21.0 %**
VARICES		
Present	**389**	**52.6 %**
Absent	**350**	**47.4 %**
INDICATION OF ENDOSCOPY		
Hematemesis	**158**	**21.4 %**
Malena	**186**	**25.2 %**
Surveillance	**238**	**32.2 %**
Anemia	**157**	**21.2 %**
GRADES OF VARICES		
Grade 1	**58**	**7.8 %**
Grade 2	**45**	**6.1 %**
Grade 3	**162**	**21.9 %**
Grade 4	**124**	**16.7 %**

Table no: 2. Diagnostic validity of radiological parameters in esophageal varices

PARAMETER	SENSITIVITY	SPECIFICITY	PPV	NPV
PORTAL VEIN (PV)				
PV > 13 mm	**64.5 %**	**51.7 %**	**59.8 %**	**56.7 %**
PV > 15 mm	**33.7 %**	**64.0 %**	**51.0 %**	**46.5 %**
P value & OR (95% CI)	**< 0.001**		**1.41 (1.21 – 1.64)**	
ASCITES				
Present	**82.8 %**	**12.6 %**	**51.3 %**	**39.6 %**
P value & OR (95% CI)	**< 0.077**		**0.69 (0.45 – 1.04)**	
LIVER SPAN				
Decreased (< 8cms)	**48.3 %**	**77.4 %**	**70.4%**	**57.4 %**
P value & OR (95% CI)	**< 0.001**		**3.20 (2.33 – 4.41)**	
Increased (> 12 cms)	**20.6 %**	**81.7 %**	**55.6 %**	**48.1 %**
P value & OR (95% CI)	**< 0.435**		**1.15 (0.80 – 1.66)**	
SPLEEN SIZE (SS) &	**ENLARGEMENT**			
SS > 13 mm	**83.5 %**	**25.1 %**	**55.4 %**	**57.9 %**
P value & OR (95% CI)	**< 0.004**		**1.70 (1.18 – 2.44)**	
SS > 15 mm	**48.8 %**	**69.2 %**	**59.4 %**	**52.5 %**
P value & OR (95% CI)	**< 0.001**		**1.61 (1.20 – 2.16)**	
Mild splenomegaly	**40.4 %**	**50.6 %**	**47.6 %**	**43.3 %**
P value & OR (95% CI)	**< 0.013**		**0.69 (0.51 – 0.92)**	
Moderate splenomegaly	**35.2 %**	**80.6 %**	**66.8 %**	**52.8 %**
P value & OR (95% CI)	**< 0.001**		**2.25 (1.61 – 3.15)**	
Massive splenomegaly	**8.00 %**	**94.0 %**	**59.6 %**	**47.9 %**
P value & OR (95% CI)	**< 0.296**		**1.35 (0.76 – 2.40)**	

Table no: 3. Diagnostic validity of biochemical / heamatological parameters in esophageal varices

PARAMETER	SENSITIVITY	SPECIFICITY	PPV	NPV
SERUM ALBUMIN (ALB)				
ALB = 3.5 g/dl	66.8 %	70.6 %	71.6 %	65.7 %
P – value & OR (95% CI)	< 0.001		0.20 (0.15 – 0.28)	
ALB = 2.8 g/dl	32.1 %	90.9 %	79.6 %	54.6 %
P – value & OR (95% CI)	< 0.001		4.70 (3.08 – 7.17)	
ALB = 2.8 – 3.5 g/dl	34.7 %	79.7 %	65.5 %	52.3 %
P – value & OR (95% CI)	< 0.001		2.08 (1.49 – 2.91)	
PLATELET COUNT (PLAT)				
PLAT < 150,000 / µL	76.6 %	52.0 %	63.9 %	66.7 %
P – value & OR (95% CI)	< 0.001		0.28 (0.20 – 0.38)	
PLAT < 100,000 / µL	59.4 %	84.9 %	81.3 %	65.3 %
P – value & OR (95% CI)	< 0.001		8.19 (5.74 – 11.69)	
PLAT < 50,000 / µL	30.1 %	98.9 %	96.7 %	56.0 %
P – value & OR (95% CI)	< 0.001		37.20 (13.56 – 102.07)	
SERUM BILIRUBIN (BILI)				
BILI = 2 mg/dl	62.2 %	46.6 %	56.4 %	52.6 %
P – value & OR (95% CI)	< 0.016		0.69 (0.52 – 0.93)	
BILI = 3 mg/dl	33.4 %	78.9 %	63.7 %	51.6 %
P – value & OR (95% CI)	< 0.001		1.87 (1.34 – 2.60)	
BILI = 2 – 3 mg/dl	28.8 %	67.7 %	49.8 %	46.1 %
P – value & OR (95% CI)	< 0.303		0.84 (0.62 – 1.16)	
INTERNATIONAL NORMALIZED RATIO (INR)				
INR > 1.7	77.4 %	70.3 %	74.3 %	73.7 %
P – value & OR (95% CI)	< 0.001		0.12 (0.08 – 0.17)	
INR > 2.2	60.4 %	91.7 %	89.0 %	67.6 %
P – value & OR (95% CI)	< 0.001		16.89 (10.97 – 25.99)	
INR = 1.7 – 2.2	17.2 %	78.6 %	47.2 %	46.1 %
P – value & OR (95% CI)	< 0.147		0.76 (0.52 – 1.10)	

DISCUSSION

Upper gastrointestinal bleed is a catastrophic presentation of esophageal varices. Prognosis of patient critically depends on liver function of patient. Endoscopy has been the gold standard for diagnosis and treatment of varices for decades, but with each passing day, demand to develop noninvasive methods to diagnose varices is increasing. Researchers worldwide evaluated radiological, biochemical and hematological parameters for predicting varices.[11–15] Our study targeted four radiological and four biochemical parameters. We found that predictive values of biochemical non invasive parameters were much stronger than radiological. Of these, platelet count < 50,000 / µL, INR > 2.2, serum bilirubin > 3 mg / dl and serum albumin < 2.8 g /dl had very high sensitivity and specificity. Platelet count less than 50,000 /µL had specificity and PPV for esophageal varices of 98.9% and 96.7% respectively. Besides, the odd risk of cirrhotic patient to have varices in presence of platelet count < 50,000 / µL was 37.20 (95% CI: 13.56 – 102.07). Similar results were obtained in patients with INR > 2.2. It had sensitivity, specificity, PPV and NPV for varices in cirrhosis of 60.4%, 91.7%, 89.0% and 67.6%. The odd risk of cirrhotic patients to have varices in presence of INR > 2.2 was 16.89 (95% CI: 10.97 – 25.99).

Farooqi JI et al., in 2007 reported that platelet count less than < 65,000 / µL, serum albumin < 2.2 g / dl and portal vein > 13 mm had very high predictive value for presence of varices. He and his colleagues were of the view that patients having all of these parameters must undergo endoscopy, as chances of picking up varices in such patient are near 100%. Khurram M et al., was of the opinion that ratio of platelet count and spleenic index was even more sensitive and specific than either alone. Similarly, Gill ML et al., reported that portal vein > 13 mm, platelet count < 100,000 / µL and INR > 1.5 has a sensitivity of picking up varices in chronic hepatitis of 70%.[11].

Platelet count has been reported as most sensitive and specific non invasive parameter for predicting varices. A count of less than 68000 / µL was 71% sensitive and 73% specific for large esophageal varices. Enlarged spleen had a sensitivity and specificity of 75% and 58%, respectively. When both parameters were analyzed the sensitivity and specificity drastically fell to 4% to 34%. Sen S et al., reported the sensitivity and specificity of platelet count to be 78% and 61% respectively and splenomegaly of 82% and 65% respectively. Sheikh NA et al., reported that platelet count of 76,000 and spleen size of 120 mm had a sensitivity and specificity of 90% and 100%, and 70% and 86% respectively.[12]

Another non invasive parameter commonly advocated for prediction of varices is platelet count and spleenic size or spleenic index ratio. This ratio has been reported to be more specific and sensitive than spleen size and platelet count separately. Giannini EG et al., reported that platelet count / spleen size ratio of 909 had sensitivity, specificity, positive predictive value and negative predictive value of 91.5%, 67.0%, 76.6% and 87.0% respectively. Legasto GMA et al., evaluated the same ratio. He concluded that if the ratio is decreased to < 160, the specificity, positive predictive

value and negative predictive value increased to 80.2%, 79.2% and 89.0% respectively.

The above studies show that non invasive parameters have very good predictive values for varices in cirrhosis of liver. But the main limitation is that, it does not have therapeutic arm attached to endoscopy. So, it is difficult to apply them universally for predicting varices. These parameters may be more useful in poor, developing and third world countries, where endoscopy is not freely available. These non invasive parameters may be used at basic health units or filter clinics to refer patients for endoscopy. These parameters may be used as indication to start beta – blockers in patients who cannot undergo endoscopy due to financial constrains or unavailability. More studies showed be performed, so that combination of these parameters me be evaluated for their predictive values.

CONCLUSION

Our study was an attempt to evaluate the diagnostic validity of non invasive parameters for predicting varices in cirrhotic patients. Radiological parameters were more sensitive but biochemical parameters had more specificity. Over all, platelet count less than 50,000 / µL and INR > 2.2 highly sensitive and specific for predicting varices in cirrhosis of liver. These non invasive parameters may be used as alternate of endoscopy for diagnostic purpose, but they cannot replace endoscopy at present, that is the gold standard test for esophageal varices.

REFERENCES

1. Dite P, Labrecque D, Fried M, Gangl A, Khan AG, Bjorkman D, et al. Esophageal varices: World Gastroenterology Organisation practice guideline 2007. Accessed online 01/02/12. Available from URL: http://www.worldgastroenterology.org/.
2. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis: Practice Guidelines Committee of the American Association for the Study of Liver Diseases; Practice Parameters Committee of the American College of Gastroenterology. *Hepatol.* 2007;46:922–38;
3. Sharara AI, Rockey DC. Gastroesophageal variceal hemorrhage. N Engl J Med. 2001;345:669–81.