Non-invasive markers as predictors of oesophageal varices in cirrhotic patient in a teaching hospital in Ghana

Amoako Duah[1], Kofi N. Nkrumah[2] and Kenneth Tachi[2]

[1]Department of Medicine, St. Dominic Hospital, Akwatia, Ghana.
[2]Department of Medicine and Therapeutics, School of Medicine and Dentistry, College of Health Science, University of Ghana

Corresponding author: Dr Amoako Duah   **E-mail:** amoakoduah@yahoo.com
Conflict of interest: None declared

SUMMARY

Introduction: Oesophageal variceal (OV) bleeding is a potentially fatal consequence of portal hypertension in patients with liver cirrhosis. Upper GI endoscopy is recommended for screening for varices in cirrhotics for early detection and treatment, however, this is invasive. The purpose of this study was to assess the predictive values of the non-invasive tests in detecting the presence of OV.
Methods: A cross-sectional hospital-based study involving 149 patients with liver cirrhosis was carried out at the Korle-Bu Teaching Hospital from 1st November 2015 to 25th November 2016. Relevant clinical parameters assessed included Child-Pugh class, ascites and splenomegaly. Full blood count and liver function tests, abdominal ultrasound and gastroscopy were done for all the participants. Receiver operating characteristic curve was generated to determine the cut-off values for the best sensitivity, specificity, negative and positive predictive values of the variables (serum albumin, platelet count (PC), aspartate aminotransferase (AST)/alanine aminotransferase (ALT), PC/Spleen diameter(SD)) with regard to the presence of OV.
Results: On gastroscopy, 135 (90.60%) had OV and 14 patients (9.40%) had no OV. One hundred and eleven of the varices (82.22%) were large varices and the rest (17.78%) small varices. The overall mean of serum albumin, PC and PC/SD were not significant predictors of the presence of OV. However, the overall mean of AST/ALT significantly predicted the presence of OV. A PC/SD cut off value of ≤833.3 had 72.62% diagnostic accuracy for diagnosing all OV.
 Conclusion: PC/SD cut-off could be used to screen cirrhotics for OV and treatment initiated in geographical areas lacking endoscopy facilities

Keywords: oesophageal varices, non-invasive, predictors, platelet/spleen
Funding: None declared

INTRODUCTION

Oesophageal variceal (OV) bleeding is a potentially fatal consequence of portal hypertension in patients with liver cirrhosis. Varices are present in 40%and 60% of patients with clinically compensated and decompensated chronic liver disease respectively.[1] Over the course of their disease, 90% of cirrhotics will develop oesophageal varices.[2] Variceal bleeding accounts for 80% to 90% of bleeding episodes in cirrhotic patients and oesophageal varices have a 25-35% risk of bleeding.[4,5,6] Bleeding caused by rupture of OV is associated with a high mortality rate of 30%,[3]and therefore is a qualifying criteria for liver transplantation. The poor outcome of variceal bleeding makes identification of those at high risk and prevention of a first bleeding episode critically important.[7]

Early diagnosis of varices before the first bleed is essential as studies of primary prophylaxis with non-selective beta blockers have clearly shown reduction in bleeding risk by 50% to about 15% for large oesophagealvarices.[8]

Current guidelines recommend that all cirrhotic patients should undergo endoscopic screening for varices, and patients identified with medium and large varices treated to prevent bleeding. For all other patients, regular periodic endoscopic surveillance is required to detect subsequent developments of OV.[9] Baseline endoscopy and subsequent follow-up endoscopies are not feasible in Ghana and most African countries due to the lack of or poor availability of endoscopy facilities[10] and high cost.

Endoscopy is also an invasive and time consuming procedure and therefore puts a heavy burden upon the few endoscopy units and health professionals in the country. It is anticipated that this social and medical burden will further increase due to the greater number of patients with chronic liver disease and their improved survival. Therefore, the use of accurate and specific non-invasive tools to diagnose OV will likely avoid some of the problems associated with endoscopy.

Several studies have reported that non-invasive markers like platelet count (PC), spleen diameter (SD), and their ratio (PC/SD), portal vein diameter, albumin level, aspartate aminotransferase (ALT) and alanine aminotransferase ratio (AST/ALT), and Child–Pugh score are strongly associated with the presence of OV in cirrhotic patients.[8,11,12,13,14] These are readily available and cheaper. This study was to assess these non-invasive markers [PC, PC/SD, serum albumin level, AST/ALT] as predictors of OV in patients with liver cirrhosis.

METHODS
This was a cross-sectional hospital-based study, carried out at the Department of Medicine, Korle-Bu Teaching Hospital (KBTH), Accra from 1st November 2015 to 25th November 2016. All cirrhotic patients undergoing upper GI endoscopy who gave their consent and were undergoing their first screening endoscopy for varices were recruited. Their medical records were reviewed to confirm the diagnosis of liver cirrhosis.

Diagnosis of liver cirrhosis was based on the presence of two or all three of the following:[7]
1. Clinical signs of chronic liver disease (clubbing, palmar erythema, spider naevi, gynaecomastia, distended abdominal veins, female pubic hair pattern, encephalopathy, splenomegaly or ascites)
2. Impaired liver function test consistent with cirrhosis (elevated INR, and low serum albumin)
3. Ultrasound diagnosis of cirrhosis (Shrunken or enlarged nodular liver with increased echotexture, a blunt edge, and distorted architecture, with or without a dilated portal vein, thickened gallbladder wall, splenomegaly or ascites)

The following were the exclusion criteria;
1. Clinically unstable patient
2. Previous oesophageal band ligation or sclerotherapy.
3. Patients on B-blockers for primary prophylactic treatment for variceal bleeding or on any surgical treatment for portal hypertension
4. Patients with abdominal tuberculosis, liver abscess, hematological malignancies and sickle cell anemia
5. Refusal of consent

Patients who met the criteria above were selected using the convenience sampling method.

Data Collection
After thoroughly explaining the study to patients and gaining consent, questionnaire administration was performed (socio-demographic data and clinical history including alcohol use of the patients were obtained). Alcoholic aetiology was made when patient's declared alcohol consumption was more than 21 units of alcohol for men or 14 units for women per week when measurable or local alcohol beverage consumption was three times per week in the past five years and correlated with biological abnormalities related to alcohol consumption.[14]

Blood tests
Ten (10)mls of blood was taken on a single occasion for haematological, biochemical and serological workup. Haematological and biochemical workup included measurement of haemoglobin, total leukocyte count, platelet count, prothrombin time/INR, and serum concentrations of bilirubin (total and conjugated), protein, albumin, alanine aminotransferase and aspartate aminotransferase. For each patient, a modified Child-Pugh score was calculated.[15]All patients were tested for HBsAg and anti-HCV Ab to determine the cause of liver cirrhosis. Serum antinuclear antibodies (ANA), anti-smooth muscles antibodies (ASMA), serum IgG and anti-liver kidney microsomal (LKM) tests were carried out for patients with suspected autoimmune hepatitis. Viral aetiology of cirrhosis was considered when one of these serological tests of HBV (HBsAg) or HCV (HCV Ab) was positive.

Ultrasound scan
All patients underwent abdominal ultrasound scan after an overnight fast and the following details were recorded: Maximum vertical span of the liver; nodularity of liver surface; spleen size (Length of its longest axis); and presence of ascites.

Endoscopic evaluation
All patients underwent upper GI endoscopy for assessment of oesophageal and gastric varices and any other upper gastrointestinal lesions. The presence and size of OV were recorded if present. The sizes of the varices were subdivided into two classes, small and large. Small OV defined as varices that flatten with insufflation or minimally protrude into the oesophageal lumen, while large OV defined as varices that protrude into the oesophageal lumen and touch each other (presence of confluence), or that fill at least 50% of the esophageal lumen. This semiquantitative approach was used because it provides better interobserver agreement as compared with quantitative grading.[16] An optic and video endoscope (GIF XQ 10 Olympus) was used.

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 18 data entry template was used for statistical analysis. Descriptive statistics was run for all the variables and data presented in appropriate graphs and tables. Proportion of OV was determined and further analysis was done to determine if there were any association between OV and the clinical/laboratory parameters. Chi square test and t-test statistics were used to determine the level of association. Data are presented as frequencies and percentages. Categorical data were analyzed using chi-squared statistics at 95% confidence intervals. Continuous data were analyzed using t-test statistic at 95% confidence interval. A p-value of <0.05 was considered significant. A multivariate logistic regression analysis was done for selected binary variables to determine if any of them was a predictor of OV.

Receiver operating characteristic (ROC) curve was generated to determine the cutoff values for the best sensitivity and specificity of the variables (serum albumin, PC, AST/ALT, PC/SD) with regard to the presence of oesophageal varices. Also, the ROC curve was used to identify the cut-off prevalence-adjusted negative and positive predictive values for the presence of OV. All p-values for this work was two-tailed with p<0.05 as significant.

Ethical Approval

The study was approved by the Ethical and Protocol Committee of the University of Ghana School of Medicine and Dentistry with protocol identification number CHS-Et/M.3–P 3.8/2015-2016. The nature of the study was fully explained to potential participants. Participants who agreed to participate signed an informed consent form.

RESULTS

One hundred and forty-nine patients with liver cirrhosis were included in this study. This consisted of 33 female and 116 male patients with a male to female ratio of 3.5:1. The mean age of the patients was 45 ±12.28years (Table 1). Out of this number of participants, Child Pugh score was not calculated for 2 patients because their INR reports were not retrieved. PC/SD was not calculated for 3 patients because platelet count and spleen size were not done for 2 and 1 patients respectively. AST/ALT was not calculated for 2 patients because AST results for them were not retrieved.

On gastroscopy, 135 (90.60%) patients had OV and 14 patients (9.40%) had no varices. One hundred and eleven of the varices (82.22%) were large varices and the rest (17.78%) small varices. Based on Child-Pugh Classification to determine severity of liver disease, 12 (8.16%) patients were classified as class A, 64 (43.54%) as class B, and 71 (48.3%) as class C (Table 1).

Chronic HBV infection was the cause of liver cirrhosis in 44.3% when acting alone and 48.33% when in combination with alcohol and HCV infection. Alcohol alone accounted for 32.89% of causes of liver cirrhosis and 39.61% when combined with HBV and HCV infections. HCV mono-infection, autoimmune hepatitis and fatty liver were uncommon causes. Clinical features noted to be associated with presence of OV are illustrated in Table 1. Jaundice, haematemesis, melena stools, weight loss and anorexia were found to be associated with presence of OV. On multivariate analysis none of these clinical features were found to be statistically significant. The following laboratory parameters; AST, ALP, GGT, AST/ALT were found to be associated with presence of OV among the cirrhotic patients as shown in Table 2. However, none of these were statistically significant on multivariate analysis except AST/ALT (Table 3).

Prediction of all oesophageal varices

Pairwise comparisons of AUROCs show that there is a difference between the model AST/ALT (0.714 ± 0.0626; p=0.0006) and PC/SD (0.690 ± 0.0807; p=0.0182) for the prediction of all OV in the patients (Table 7). However, serum albumin and PC were not statistically significant in predicting OV among cirrhotic patients. The application of the respective cutoffs, the sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) and diagnostic accuracies in the sample are as follows:

AST/ALT cutoff value of ≤2.2 gave a sensitivity of 66.9% and specificity of 78.6%. PPV and NPV were 96.8% and 19.8% with diagnostic accuracy of 68.0%. PC/SD cutoff value of ≤833.3 gave a sensitivity of 73.5% and specificity of 64.3%. PPV and NPV were 95.2% and 20.1% with diagnostic accuracy of 72.6%. Serum PC gave a sensitivity of 62.96%, 64.29% specificity, 94.4% PPV, 15.0% NPV and diagnostic accuracy of 63.09 with the cut off value of ≤98000/mm³. For serum albumin, a cutoff value of >22.6g/l gave a sensitivity of 75.56%, 57.14% specificity, 93.6% PPV, 17.5% NPV and diagnostic accuracy of 73.83%. Table 4

Prediction of large oesophageal varices alone

Pairwise comparisons of AUROCs did not show any difference between all the parameters for the prediction of large OV alone in the cirrhotic patients. For prediction of large OV a cut of value of ≤789.1 for PC/SD gave a sensitivity of 68.81%, specificity of 56.52%, PPV, NPV and diagnostic accuracy of 88.0%, 28.2% and 66.62% respectively. For platelet count a cut off value of ≤176000/mm³ gave a sensitivity of 93.69%, 20.83% specificity, 84.6% PPV, 41.7% NPV and a diagnostic accuracy of 80.74%.

For AST/ALT to predict large OV a cut off value of ≤4.2 gave a sensitivity of 95.45%, 17.39% specificity, 84.2% PPV, 45.3% NPV and diagnostic accuracy of 81.57%.

Serum albumin cut off value ≤22g/l gave a sensitivity of only 25.23%, 83.33% specificity, 87.50% PPV, 19.4% NPV and 35.64% diagnostic accuracy (Table 5).

Table 1 Association of demographic and clinical features of cirrhotic patients with the presence of varices

Demographic and clinical characteristics	All (n=149)	Patients with Oesophageal Varices n=135	Patients Without Oesophageal Varices n=14	p-value
Mean age (years)*	45 ± 12.28	135 (90.60%)	14(9.40%)	0.197
Sex				
Male	116	106 (91.38%)	10(8.62%)	0.84
Female	33	29 (87.88%)	5(12.12%)	
Clinical findings [n (%)]				
Ascites	122 (81.88)	109 (89.34)	13 (10.66)	0.263
Jaundice	59 (39.60)	50 (84.75)	13 (10.66)	0.047†
Haematemesis	85 (57.05)	83 (97.65)	2 (2.35)	0.001†
Melaena stool	74 (49.66)	73 (98.65)	1 (1.35)	0.001†
Weight Loss	59 (39.60)	50 (84.75)	9 (15.25)	0.047†
Pedal oedema	60 (40.27)	55 (91.67)	5 (8.33)	0.715
Hepatic encephalopathy	28 (18.79)	26 (92.86)	2 (7.14)	0.65
Anorexia	35 (23.49)	27 (77.14)	8 (22.86)	0.002†
Child Pugh Score*	9.57 ± 2.26	9.53 ± 2.30	10.0 ± 1.88	0.4577
Child Pugh Class A	12 (8.16)	12 (100.0)	0.0 (0.0)	0.491
Child Pugh Class B	64 (43.54)	57 (89.06)	7.0(4.70)	
Child Pugh Class C	71 (48.3)	64 (90.14)	7.0(4.70)	
Systolic BP*	112.70 ±15.67	112.63 ± 16.09	113.29 ± 11.36	0.883
Diastolic BP*	68.44 ± 12.82	68.46 ± 13.13	68.21 ± 9.74	0.9453
BMI*	24.35 ± 3.40	24.41 ± 3.50	23.87 ± 2.25	0.5765

* Data expressed as Mean ± SD

Table 2 Laboratory parameters of cirrhotic patients with and without oesophageal varices

Laboratory Parameters	All (n=149)	Patients with Oesophageal Varices n=135	Patients Without Oesophageal Varices n=14	p-value
HB g/l*	9.19 ± 2.76	9.17 ± 2.81	9.4 ± 2.23	0.7670
Platelet count (mm3)*	98788.77 ± 60825.83	96644.44 ± 59790.61	119466.10 ± 69016.34	0.1824
WBC *	7.29 ± 4.65	7.28 ± 4.66	7.35 ± 4.75	0.9569
AST*	155.06 ± 203.84	141.23 ± 167.12	288.41 ± 404.99	0.0097†
ALT*	65.12 ± 48.52	63.73 ± 47.08	78.56 ± 61.18	0.2778
S. Albumin*	26.46 ± 6.52	26.79 ± 6.33	23.27 ± 7.63	0.0545
Total Prot*	69.82 ± 12.72	69.86 ± 12.81	69.35 ± 12.14	0.9035
Total Bilirubin*	63.74 ± 80.34	62.69 ± 80.83	73.79 ± 77.58	0.6244
Ind. Bilirubin*	26.46 ± 38.20	27.35 ± 39.65	16.84 ± 12.96	0.3851
Dir. Bilirubin*	42.56 ± 61.18	42.73 ± 62.39	40.765 ± 49.50	0.9158
ALP*	216.73 ± 235.57	188.16 ± 132.50	484.14 ± 594.88	<0.0001†
GGT*	206.58 ± 212.96	179.22 ± 164.58	460.66 ± 391.25	<0.0001†
INR*	1.87 ± 0.57	1.87 ± 0.59	1.92 ± 0.43	0.7550
AST/ALT*	2.23 ± 1.22	2.14 ± 1.11	3.08 ± 1.85	0.0058†
Spleen Size (mm)*	138.28 ± 32.70	138.80 ± 33.13	133.27 ± 28.80	0.5489
PC/SD RATIO*	855.36 ± 1062.70	825.0653 ± 1093.294	1140.96 ± 674.09	0.2918

* Data expressed as Mean ± SD

Table 3: Multiple Logistic regression model of independent risk factors of oesophageal varices

Independent Risk factors	Adjusted Odds Ratio (OR)	Standard error	p-value	95% CI
Jaundice	1.5821	1.2822	0.571	0.3231 to 7.7462
Haematemesis	1.3137	1.4560	0.806	0.1496 to 11.5328
Mealena Stools	38.9512	82.1518	0.082	0.6241 to 2431.003
Weight Loss	0.7736	0.6942	0.775	0.1333 to 4.4906
Anorexia	0.199	0.1760	0.068	0.0351 to 1.1267
AST	0.9981	0.0019	0.305	0.9944 to 1.0018
ALP	0.9981	0.0017	0.272	0.9948 to 1.0015
GGT	0.9972	0.0017	0.098	0.9939 to 1.0005
AST/ALT*	0.6605	0.2102	0.0484	0.4375 to 0.9972

LR Chi[2]: Likelihood Ratio Chi-squared. p-value of <0.05 was considered to be significant

Table 4 Sensitivity, Specificity, Positive and Negative Predictive Values, and Cutoff Values in Predicting Presence of oesophageal varices

Variable	Total	AUROC ± SE	p-value	Cut-off Value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	DA(%)
All Oesophageal Varices									
Serum Platelet count (mm³)	149	0.623 ± 0.0872	0.1575	≤98000	62.96	64.29	94.4	15.0	63.09
Serum Albumin (g/l)	149	0.641 ± 0.0943	0.1354	>22.6	75.56	57.14	93.6	17.5	73.83
AST/ALT	147	0.714 ± 0.0626	0.0006	≤2.2	66.92	78.57	96.8	19.8	68.02
PC/SD	146	0.690 ± 0.0807	0.0182	≤833.3	73.48	64.29	95.2	20.1	72.62

Note: AUROC: area under receiver operating characteristic curve, SE: standard error, PC/SD: platelet count-spleen diameter ratio, PPV: positive predictive value, NVP: negative predictive value, DA: diagnostic accuracy. Prevalence of Oesophageal varices: 90.6%.

Table 5 Sensitivity, Specificity, Positive and Negative Predictive Values, and Cutoff Values in predicting presence of oesophageal varices

Variable	Total	AUROC ± SE	p-value	Cut-off Value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	DA (%)
Large OV alone									
Serum Platelet count (mm³)	135	0.531 ± 0.0728	0.6706	≤176000	93.69	20.83	84.6	41.7	80.74
Serum Albumin (g/l)	135	0.514 ± 0.0627	0.8177	≤22	25.23	83.33	87.5	19.4	35.64
AST/ALT	133	0.506 ± 0.0696	0.9344	≤4.2	95.45	17.39	84.2	45.3	81.57
PC/SD	132	0.564 ± 0.0770	0.4042	≤789.1	68.81	56.52	88.0	28.2	66.62

Note: AUROC: area under receiver operating characteristic curve, SE: standard error, PC/SD ratio: platelet count-spleen diameter ratio, PPV: positive predictive value, NVP: negative predictive value, DA: diagnostic accuracy. Prevalence of Oesophageal varices: 90.6%

DISCUSSION

Several studies have previously reported PC/SD as an excellent non-invasive predictor for the presence of both all OV and large OV alone.[14,18,19,20] In this study however, there was no association noted between PC/SD and the presence of OV on both binary and multivariate regression analysis. Moreover, the best cut-off value of ≤833.3 determined by the ROC curve was an independent predictor of all OV. The diagnostic accuracy of this cut off value was 72.62% with a sensitivity of 73.48%. This cut-off value misclassified 27.38% in the study population. The prevention of variceal bleeding is an important goal to be achieved in cirrhotic patients with large OV by implementing prophylactic treatment.[17] Therefore this can be used as part of tools to monitor cirrhotic patients and consider treatment in geographical areas lacking endoscopic facilities. However, upper endoscopy remains the more reliable means to monitor cirrhotic patients. These findings compare quite well with a similar study conducted in Cote d'Ivoire by Mahassadi et al.,[14] PC/SD of ≤ 868 had a diagnostic accuracy of 81.1%% in predicting OV. However, a study by Giannini et al.,[18] found that PC/SD yielded a higher diagnostic accuracy to predict the presence of OV. This was confirmed by Agha et al.,[19] using the same cutoff of 909. Abu El Makarem et al.,[20] found an optimal cutoff value of ≤ 939.7 for this ratio, which gave a diagnostic accuracy of 96.5%.

The best explanation for the differences in the sensitivities and the diagnostic accuracies could be due to the aetiology and the severity of liver cirrhosis.

In this study the major causes of liver cirrhosis were hepatitis B virus and alcohol while the major causes of cirrhosis in the studies reporting higher sensitivities and diagnostic accuracies were mainly hepatitis C, apart from Mahassadi et al.[14] Also the severity of liver cirrhosis could be a contributing factor; the participants in this study were mainly in Child- Pugh class B and C but class A in the other studies. For prediction of large OV the best cut off value of ≤789.1 as determined by ROC curve was not an independent predictor of large OV. This is in contradiction to report from Mahassadi et al.[14] This may be due to the differences in aetiology as reported by Sens et al.[21] Data from this study suggest that PC/SD is not effective non-invasive marker for predicting the presence of large OV alone and should not replace upper GI endoscopy for the diagnosis of large OV.

Low PC has often been suggested as a marker of portal hypertension and OV in patients with liver cirrhosis. This is because platelet levels are affected during the pathogenesis of cirrhosis. Thrombocytopenia results from pooling in the spleen and decreased production of thrombopoeitin. Aetiological agents such as alcohol and hepatitis virus also have suppressive effects on bone marrow platelet production.[22,23]

Low PC was not a significant predictor of all OV and large OV alone in the overall mean in this study. Also the best cut-off value of ≤98000/mm³ and ≤176000/mm³ determined by the ROC curve for the PC were not independent predictors for all OV and large OV alone respectively.

This may be due to the direct effect of the causes of liver cirrhosis as the cause of thrombocytopenia and not mainly related to splenic sequestration as a complication of portal hypertension–induced splenomegaly (that is, hypersplenism). The findings in this study is similar to one conducted by Qamar et al.[24] Many other studies have reported significant association between PC and the presence of OV with good sensitivities and diagnostic accuracies with different cut-off values.[14] The difference may be as a result of non-aetiologically uniform subjects and severity of liver cirrhosis patients were different in these studies.

Some studies have found low serum albumin to be a predictor of both the presence of all OV and large OV alone. Low serum albumin is an indicator of hepatic function derangement. The extent of hepatic dysfunction is likely to be correlated with the development of portal hypertension and thus the development of varices. Schepis et al.,[25] and Sarwar et al.,[26] reported cut-off value of < 29.5g/l to be independent marker for the presence of esophageal varices. Farooqi et al.,[7] also found cut-off value of less than 22g/l to be a predictor of OV and Khan et al.,[27] reported <35g/l of albumin as a predictor of OV. However, the results of this study differ significantly from the above reports. The overall mean of serum albumin was not a predictor of OV. With ROC curve analysis, no serum albumin cut off value could also be identified that accurately predicted the presence of all or large OV. This makes serum albumin a poor predictor of OV based on this study and cannot be recommended as a non-invasive predictor of OV. Similar conclusions have been reported in studies conducted by Tafarel et al.,[28] and Mahassadi et al.[14] The reason for these differences may be due to the high prevalence rate of OV in this study, patients with either normal or low serum albumin had OV. The severity and the aetiologies of participants were different from above studies and this may also accounted for the differences. Furthermore, hypoalbuminaemia can be caused by other conditions such as malnutrition, kidney disease, protein losing enteropathy etc. and therefore not specific to liver cirrhosis.

Based on the concept that the development of portal hypertension is caused by the progression of liver fibrosis, non-invasive biomarkers of liver fibrosis such as AST/ALT have been used to predict the presence of varices in cirrhotic patients. The sensitivity and specificity of AST/ALT has been shown to vary with the different cut-off values used. The mean AST/ALT was the only parameter that was statistically significant in detecting OV in the multivariate analysis in this study. The best cut-off value of ≤2.2 was an independent predictor of all OV but ≤4.2 determine by ROC curve was not a predictor of large OV.

The cut-off values of AST/ALT ≤2.2 and ≤4.2 put diagnostic accuracy for detecting all OV and large OV as 68.0% and 81.57% respectively in this study. This is similar with studies conducted by Cast´era et al.,[29] and Treeprasertsuk et al.,[30] but with different cut off values. Cast´era, et al.,[29] in their study, AST/ALT cut-off ≥1.0 was an independent predictor with good sensitivity and specificity for detecting both mild and large OV. In Treeprasertsuk et al.,[30] cut-off value of AST/ALT >1.12 was significantly associated with the presence of varices at initial endoscopy.

The ratio ≥1.0 is consistent with studies that suggest that AST/ALT ≥1.0 correlate with advance liver fibrosis or cirrhosis and to some extent portal hypertension and OV.[31,32] This means the relevance of using the ratio obtained in this study in clinical practice may need further evaluation. The reason for this may be due to the high prevalence rate of OV in this study and most of the patients were having AST/ALT ratio below 2.2 for detecting all varices and ≤4.2 for detecting large varices alone. The aetiologies were different and the severities of the liver cirrhosis in the patients involved in these studies were also different. In this study, although AST/ALT was an independent predictor of all OV, it cannot be recommended as a non-invasive marker to determine the presence of OV. This is because the lower limits of the best cut off values were not defined.

Limitations
The diagnosis of liver cirrhosis was based mainly on clinical, laboratory and radiologic examinations. This method of diagnosis without any histologic basis may be less accurate as other causes of portal hypertension such as portal vein thrombosis, Budd-Chiari syndrome, early stage schistosomiasis etc. leading to OV could have been included. The mode of sampling had the potential of introducing selection bias; nevertheless, all patients who satisfied the inclusion criteria and did not have any of the exclusion criteria were selected.

CONCLUSION
The overall mean of AST/ALT significantly predicted the presence of OV, but the lower limit was not defined and could not be recommended as a predictor of OV in this study. PC/SD of ≤833.3 can be used as a non-invasive tool to predict varices in cirrhotic patients and for making decision on treatment of varices in geographical areas lacking endoscopy facilities.

REFERENCES

1. El-Tawil AM. Trends on gastrointestinal bleeding and mortality: where are we standing? *WJG*.2012; 18(11):1154-8.
2. Weinstein WM HawkeyCJ, Bosch J. Portal hypertension. *Clinical Gastroenterology and Hepatology.*2005:707-14.
3. DeDombal FT, Clarke JR, Clamp SE, et al. Prognostic factors in upper GI bleeding. *Endoscopy*. 1986; 18 suppl 2:6-10.
4. Groszmann RJ, Bosch J, Grace ND, et al. Hemodynamic events in a prospective randomized trial of Propranolol versus placebo in the prevention of a first variceal hemorrhage. *Gastroenterology* 1990; 99(5): 1401-7.
5. The North Italian Endoscopic `Club for the Study and `Treatment of Esophageal Varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices: a prospective multicenter study. *N Engl J Med.* 1988; 319: 983-989.
6. Gores GJ, Wiesner RH, Dickson ER, et al. Prospective evaluation of esophageal varices in primary biliary cirrhosis: development, natural history, and influence on survival. *Gastroenterology*. 1989; 96(6): 1552-9.
7. Farooqi JI, Ahmed H, Ikramullah Q et al. Predictors of esophageal varices in patients of liver cirrhosis. *JPMI*. 2007; 21(01): 60-64.
8. D 'Amico G, Pagliaro L, Boch J, et al. Pharmacological treatment of portal hypertension: An evidence-based approach," *Seminars in Liver Disease.* 1999; 19: 475-505.
9. Garcia-Tsao G, Sanyal AJ, Grace ND, et al. Prevention and management of gastroesophagealvarices and variceal hemorrhage in cirrhosis. *Hepatology.*2007; 46(3):922-38.
10. Mandeville KL, Krabshuis J, Ladep NG, et al. "Gastroenterology in developing countries: issues and advances," *World Journal of Gastroenterology*. 2009; 15(23): 2839–2854.
11. Graham DY, Smith JL. The course of patients after variceal hemorrhage. *Gastroenterology* 1981; 80(4):800-9
12. Koransky JR, Galambos JT, Hersh T, et al.The mortality of bleeding esophageal varices in a Private University Hospital. *Am J surg*. 1978; 136(3): 339-41.
13. The Veterans Affairs Cooperative Variceal Sclerotherapy Group, Prophylactic Sclerotherapy for esophageal varices in men with alcoholic liver disease: a randomized, Single-blind, multicenter clinical trial. *N Eng J Med.* 1991; 324: 1779-84
14. Mahassadi AK, Bathaix FY, Assi C, et al. Usefulness of noninvasive predictors of oesophagealvarices in black African cirrhotic patients in Cote d'Ivoire (West Africa). *Gastroenterology Research and Practice*. Volume 2012, Article ID 216390, 10 pages.
15. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for the bleeding of the oesophagealvarices. *Br J Surg*. 1973;60(8):646-9.
16. Cales P, Zaboto B, Meskens C, et al. Gastro-esophageal endoscopic features in cirrhosis: Observer variability, inter-associations and relationship to hepatic dysfunction. *Gastroenterology*. 1990;98(1):156-62
17. deFranchis R. Updating consensus in portal hypertension: Report of the Bevano III consensus workshop on definitions, methodology and therapeutic strategies in portal hypertension. *J Hepatol*. 2000;33:846-851
18. Giannini EG, Botta F, Borro P, et al. Application of the platelet count/spleen diameter ratio to rule out the presence of oesophagealvarices in patients with cirrhosis: a validation study based on follow-up. *Dig Liver Dis.* 2005; 37(10):779-85
19. Agha A, Anwar E, Bashir K, et al. 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.
20. Abu El Makarem MA, Shatat ME, Shaker Y, et al. Platelet count/bipolar spleen diameter ratio for the prediction of esophageal varices: The special Egyptian situation. *Hepat Mon.*2011; 11(4):278-84.
21. Sen S, Griffiths WJH. Non-invasive prediction of oesophagealvarices in cirrhosis. *World J Gastroenterol*. 2008; 14(15): 2454-2455.
22. Peck-Radosavljevic M. Hypersplenism*. Eur J Gastroenterol Hepatol*. 2001;13(4):317-323.
23. Peck-Radosavljevic M. Thrombocytopenia in liver disease. *Can J Gastro-enterol* 2000;14(Suppl D):D60-D66
24. Qamar AA, Grace ND, Groszmann RJ, et al. Platelet count is not a predictor of the presence or development of gastroesophageal varices in cirrhosis. *Hepatology*. 2008;47(1):153–159
25. Schepis F, Camma C. Niceforo D. Which patients with cirrhosis should undergo endoscopic screening for esophageal varices detection? *Hepatology.* 2001; 33(2): 333-8.
26. Sarwar S, Khan AA, Alam A, et al. Non-endoscopic prediction of presence of esophageal varices in cirrhosis. *J Coll Physicians Surg Pak.* 2005; 15(9):528-31.
27. Khan H, Iman N. Hypoalbuminemia: a marker of esophageal varices in chronic liver disease due to hepatitis B and C. *Rawal Med J*. 2009;34(1):98-101.
28. Tafarel JR, Tolentino LH, Correa LM, et al. Prediction of esophageal varices in hepatic cirrhosis by

noninvasive markers. *Eur J Gastroenterol Hepatol*. 2011;23(9):754–758

29. Castéra L, Le Bail B, Roudot-Thoraval F, 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.

30. Treeprasertsuk S, Kowdley KV, Luketic VAC et al., "The predictors of the presence of varices in patients with primary sclerosing cholangitis." *Hepatology*. 2010; 51(4): 1302-1310.

31. Angulo P, Keach JC, Batts KP, et al. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. *Hepatology.* 1999;30(6):1356-62.

32. Giannini E, Botta F, Fasoli A, et al. Progressive liver functional impairment is associated with an increase in AST/ALT ratio. *Dig Dis Sci.* 1999;44(6):1249-53.