Expediency of Platelet (Thrombocyte) count estimate to Spleen diameter ratio as a non-invasive tool in the prediction of Esophageal Varices among Liver Cirrhotic patients.

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ABSTRACT

Objective: To assess the early benefit and usefulness of platelet count to diameter of spleen ratio as a non-invasive parametric tool in detection of esophageal Varices in liver cirrhosis.
Study Design: Prospective observational study.
Place and Duration: Department of Medicine, Hamdard University Hospital, Karachi from February 06, 2019 to August 31, 2019.
Methodology: Among cirrhotic patients, ultrasound technique was employed for platelet count and spleen bipolar ratio. The patients were also screened for esophageal varices. Patients who had active bleeding from upper gastro-intestinal tract were excluded from study. Ratio of Platelet count to diameter of spleen was determined and estimated for all subjects and analyzed.
Results: Among 85 liver cirrhotics, 68.2% were male and esophageal varices were found in 63.5% patients. The cut-off value for ratio of platelet count to spleen diameter was 1014 with 76% sensitivity and 67.1% specificity. Among all, 83.33% was estimated by positive predictive value and 80.65% by negative predictive value. The diagnostic accuracy was 82.35%.
Conclusion: There is noticeable advantage and usefulness in early detection and advance prediction of esophageal varices in liver cirrhotic subjects by employing non-invasive method of ratio of platelet count to spleen diameter.
Keywords: Cirrhosis, Platelet count, Splenic (spleen) diameter, Endoscopy, Esophageal varices, Diagnosis.

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INTRODUCTION

It is recognized since decades that bleeding is a serious a life threatening complication in liver cirrhotic patients[1,2]. Endoscopic monitoring, timely clinical procedural follow up and investigation based surveillance of esophageal varices (EV) in patients suffering from cirrhosis of liver is financially expensive and might not be acceptable to all the patients in terms of discomfort[2,3]. At the time when hepatic cirrhosis is diagnosed, the guidelines recommendation requires invasive screening of people with esophageal varices through cumbersome upper GI esophageal and gastro-duodenoscopy[4,5].

Clinical and ultrasonographic evidence of enlarged spleen size with low platelet count are exclusive factors to predict the existence of varices of esophagus in subjects having cirrhosis. Platelet count-to-spleen length ratio is one of these non-invasive test,[6] which may assist in decreasing the financial cost and unpleasant distress for these affected patients in addition to concern of work load on endoscopy procedural facilities. More implications for using this non-invasive technique are; standardized follow-up monitoring, periodic annual/biannual abdominal ultrasonography for the evaluation of hepatocellular complications[6,7]. These parameters may also be beneficial in identifying subjects who show a low chance of varices in esophagus and might not be an early candidate for Upper Gastrointestinal Endoscopy[8], therefore to avoid the need for

invasive tests, a non- invasive test is required to establish the diagnostic evidence of esophageal varices. Therefore, there is a definite need of employing noninvasive predictors for EV which are valuable, cost effective and more acceptable[3,9]

Rationale of current study is to establish and propose a non-invasive test which is easy and acceptable and could be performed on bedside with least financial burden and minimum logistics involved. Due to this reason a study has been planned, keeping in view the objective, to establish the benefit and usefulness of ratio of Platelet count to diameter of spleen as non-invasive parametric tool in establishing the diagnosis of esophageal varices in liver cirrhotics. So this study was conducted with an objective to assess the early benefit and usefulness of ratio of Platelet count to diameter of spleen as a non-invasive parametric tool in detection of esophageal varices in liver cirrhosis.

METHODOLOGY

This prospective observational study was conducted in Department of Medicine, Hamdard University Hospital, a tertiary care hospital in Karachi. Mean duration of study is six months from February 06, 2019 to August 31, 2019.

After taking patient consent, liver cirrhosis was diagnosed on the integrated interpretation of physical examination data, clinical indicators, laboratory investigational data along with radiological/ultrasonography findings. All subjects had gone through a careful clinical evaluation, assessment, laboratory investigations; such as total bilirubin, alanine (ALT) aminotransferase, aspartate (AST) aminotransferase, serum level of albumin and estimation of prothrombin time/INR. Child-Pugh numerical score was also evaluated. Upper gastrointestinal endoscopic procedure was performed with ultrasonography of abdomen to measure the maximal diameter (bipolar) of spleen and also to identify the manifestations showing portal hypertension signs (ascites, enlarged spleen and increased diameter of portal vein). The investigator who performed the procedure of upper gastrointestinal endoscopy was kept unaware and blind to the laboratory and the ultrasound results when the findings of the esophageal varices were documented.

Criteria for Inclusion in the study was the patients less than 18 years of age, low platelet count, having Portal hypertension, portal vein diameter more than 13mm, and enlarged splenic size. In the similar way, criteria for Exclusion; active bleeding from upper Gastrointestinal tract, patients suffering from malignancies of hematological system, megaloblastic anemia, aplastic anemia, patients who had gone through ligation and application of bands or who underwent sclerotherapy for esophageal varices, subjects taking medicines which can result in low platelet count. Patients not willing or unable to undergo invasive endoscopic procedure, pregnancy, advanced or acute cardiac or pulmonary disease and major bleeding disorders in which endoscopy is not possible.

Data analysis: SPSS 20 was used for statistical workup. Chi-square analysis was done with 2x2 contingency tables. Ratio attributed to platelet count to spleen diameter was described as the ratio of platelet numbers/mm^3 divided by maximum splenic bipolar diameter as measured in millimeters by the Ultrasound. A platelet count cutoff of 150,000/cubic mm, spleen diameter (length) of 110 mm and 13 mm portal vein size were preferred because they offered the appropriate discrimination. The ratio 1014 was considered the cut-off value. Ratio of platelet estimated count to diameter of spleen ≤1014 showed the presence of existing varices in esophagus and >1014 the absence of varices.

RESULTS

Eighty five subjects (n=85) were evaluated in this study. The calculated mean age was 50 years. Among these subjects, the cause of Liver cirrhosis was Hepatitis C in 62 patients, Hepatitis B in 20 patients and 3 patients were alcoholic.

In overall liver 85 cirrhotic patients, male and female patients are 58 (68.2 %) and 27 (31.7 %) respectively. Esophageal varices were found to be present in 54 (63.5%) and absent in 31 (36.4%) patients. In ratio of platelet count to spleen diameter 1014 was taken as a cut-off value, which produced a sensitivity 76.0%, specificity 67.1%, positive predictive value 83.33%, negative predictive value 80.65%. The diagnostic accuracy was 82.35%.

Patients who had large size of varices also had low thrombocyte counts compared to those patients who had small varices (136635/mm3 V/s 199574/mm3; p=0.01), large spleen diameter (148 mm V/s 110 mm; p=0.0001), diameter of Portal vein (13.8 mm V/s 11.3 mm; p= 0.001). There was not much differences in the findings of detected ascites (through imaging), collaterals, and size of liver in two groups. The independent predicting factors to show the presence of large existing esophageal varices on logistic regression evaluation for multiple variables were platelet count (less than) <150,000 /mm^3, spleen palpable on clinical examination, splenic size >13 cm and size of portal vein >13 mm.

Table-I: Platelet count v/s Spleen diameter ratio in comparison to Endoscopy Findings. (N=85)

Platelet Count / Spleen Diameter	Endoscopy Findings		Total	Significance
	Varices +ve	Varices –ve	Marginal Row Totals	
PC/SD < 1014	45 (True +ve)	9 (False +ve)	54	p=0.0001
PC/SD > 1014	6 (False –ve)	25 (True –ve)	31	
Marginal Column Totals	51	34	85	

p-value is significant at <0.05

Sensitivity 76.0%, displayed specificity 67.1%. The estimated positive (+ve) predictive value (PPV) for this data 83.33%, negative (-ve) predictive value (NPV) was found as 80.65%. The diagnostic accuracy being 82.35%.

The results of 85 subjects for platelet count v/s Spleen diameter ratio in comparison to Endoscopy Findings are 63% (54) were positive and 36% (31) were negative. (45) 53% were true positive and (25) 29% were true negative. 10% (9) were false positive and 7% (6) were false negative, p=0.0001. (Table-I)

Similarly in 85 subjects, spleen diameter via Ultrasound V/S Endoscopy Findings, 60% (n=51) were true positive, 28% (n=24) were true negative. 10% (n=9) were false positive and 1% (n=1) was false negative, p=0.0001. (Table-II)

Table-II: Spleen diameter via Ultrasound V/S Endoscopy Findings (N-85)

Ultrasound	Endoscopy Findings		Total	Significance
	Varices +ve	Varices –ve	Marginal Row Totals	
Spleen Diameter > 110 mm	51 (True +ve)	9 (False +ve)	60	p=0.0001
Spleen Diameter < 110 mm	1 (False – ve)	24 (True – ve)	25	
Marginal Column Totals	52	33	85	

p-value is significant at <0.05

Sensitivity was 98%, Specificity 73%, PPV (positive predictive value) 85%. NPP (negative predictive value) 96% and Diagnostic accuracy was 88.5%

In findings of platelet count in comparison to Endoscopy of 85 subjects, 60% (n=51) were true positive, 27% (n=23) were true negative. 5% (n=4) were false negative and 8% (n=7) were false positive, p=0.0001. (Table-III)

Table-III: Platelet count in comparison to Endoscopy Findings (N-85)

Platelet count	Endoscopy Findings		Total	Significance
	Varices +ve	Varices –ve	Marginal Row Totals	
Platelet count < 150,000	51 (True +ve)	7 (False +ve)	58	p=0.0001
Platelet count > 150,000	4 (False – ve)	23 (True – ve)	27	
Marginal Column Totals	55	30	85	

p-value is significant at <0.05

Sensitivity was 93%, Specificity 77%, PPV (positive predictive value) 88%. NPP (negative predictive value) 85% and Diagnostic accuracy was 87%.

The Child Turcott Pugh (CTP) class of severity of liver (cirrhotic) disease with relation to the score was observed as follows: CTP-A-33, 38.8 %; CTP-B - 36, 42.3 %; and CTP-C-16, 18.8%. Among the 54 positive cases; 20 (37%) patients had grade I EV (Esophageal Varices), 21 (38.8%) patients had grade II EV, 11 (20.3%) patients had grade III EV (Endoscopic grade) in esophagus and 02 (3.0 %) patients had grade IV EV.

DISCUSSION

Current study has shown outcomes comparable to national and international studies. Chen et al also noticed that thrombocyte count, diameter of spleen and ratio of platelet estimated count to bipolar diameter of spleen in subjects having Varices of esophagus were noticeably different from the individuals who did not have Esophageal Varices[7]. Current study used the same cut-off ratio of estimated platelet count/diameter (bipolar/length) of spleen as established and followed by Baig *et al*.[10] which was 1014, the current study reveals same results and showed a positive (+ve) predictive value (PPV) of 95.4% while negative (-ve) predictive value (NPV) 95.1%. In another study by Amin et al[11] in which subjects having liver cirrhosis with ratio to platelet (Thrombocyte) count to diameter (bipolar/length) of spleen had high sensitivity. A number of studies have depicted, ratio of "platelet count/spleen diameter" (PC/SD) a considerably important tool used in non-invasive prediction and diagnosing the existence of esophageal varices[10,11].

Interestingly, current study shared the same outcome as done by Giannini *et al* [12]. in which more than 140 patients who had compensated HCV associated cirrhosis, a 909 cut-off value resulted in negative (-ve) predictive value (NPV) as 100% and a positive (+ve) predictive value (PPV) as 93.8% for the confirmation of the diagnosis of Varices in esophagus. Study results of Agha *et al*[13] found that patients affected as compensated cirrhosis, the ratio of platelet estimated count/(bipolar) measured diameter of spleen (SD) with a cut-off value of 909 produced negative predictive value (NPV) of 100% and estimated positive predictive value (PPV) of 93.8% for diagnostic presence of Varices in esophagus, which further endorse the direction of current study. A different study inferred that ratio attributed to platelet count to diameter (bipolar/length) of spleen is helpful predicting factor to know the existence of higher and severe grades of varices[14]. Results of current study are also supported by Levick et al[15] who reported that in cirrhosis, ratio of platelet/spleen volume was helpful in the identification of portal hypertension with the highest accuracy (AUROC 0.79)[15]. In addition to the non-invasiveness, ratio of estimated platelet count to bipolar diameter (length) of spleen is a considerably low cost investigation as two tests of thrombocyte count and ultrasonography of abdomen would be routinely done in all patients of cirrhosis usually as part of their clinical workup,[16] which is also supporting the recommendation of current study.

Zaman et al[17] conclusions were also in the support of current study and stated that a higher value of thrombocyte count (mean estimated thrombocyte value: 128500) was observed in groups without varices in comparison to the group who had small size esophageal varices (mean estimated thrombocyte count: 107800) and thrombocyte count with the value of <90,000 showed substantial risk of harboring any esophageal varices. He further concluded that patients who are in C-Turcotte-Pugh class B or class C was related to an almost 3-times increased risk of having esophageal varices as compared to the patients who are in in C-Turcotte-Pugh class A. Low thrombocyte count estimation of 80×103/µL or further less than that was linked with a close to 2.5 times increased risk of harboring large esophageal varices on endoscopic procedure of upper gastrointestinal tract. Patients who are in C-Turcotte Pugh class B or class C were linked with an approximately three-times increased risk of harboring large esophageal varices in comparison to subjects who are in C-Turcotte Pugh class A[18].

Sarwar et al mentioned that thrombocyte count of <88000 is a risk stratification factor which is independent for the identification of large varices in esophagus[18]. Current study also showed results in same direction yet with a little less sensitivity and specificity than Khadka et al who studied 191 patients affected by liver cirrhosis. Varices in esophagus were found in

125 subjects (65.4%). Pre-determined cutoff value of ≤909 was set for the ratio of platelet estimated count/diameter of spleen to detect Varices in esophagus regardless of endoscopic grade of esophageal varices. They found sensitivity of 93% and specificity 100%. Garcia- Tsao *et al* observed that to identify the presence of varices in esophagus, thrombocytopenia is a recognized as a separate risk component[19]. Pilette *et al*[20] discovered low count of thrombocyte in 116 patients having varices in esophagus, which is also comparable to current study.

This non-invasive marker not only can help in advance identification of the subgroup of the subjects at probable risk of having esophageal varices but also lowering the excess work load on the endoscopy procedural units. It may also results in reduction of cost incurred to the patients in the management of bleeding varices[13,14].

Advancements in genetics showed that selected serum and genetic markers C(+405)G GG, C(+936)T TT, higher risk genotype of VEGF, and Val(-297) Ile Ile/Ile, a higher risk genotype of VEGFR2 are at increased risk of developing Varices in esophagus[21].

CONCLUSION

There is noticeable advantage and usefulness in early detection and advance prediction of esophageal varices in liver cirrhotic subjects by employing non-invasive method of ratio of platelet count estimate to splenic diameter.

Recommendations: The ratio of platelet estimated count to calculated spleen length (bipolar) diameter may prove a considerably dependable non-intrusive tool for diagnostic identification of “Esophageal varices” in affected subjects with liver cirrhosis. Study will facilitate by controlling the increasing work load on endoscopy units with an approximate idea of referral time for a certain subset of liver cirrhotic patients suggested by non-intrusive methods.

AUTHOR’S CONTRIBUTION

Jami A: Conception and study design, Introduction, Discussion.
Fouzia S: Manuscript drafting, contribution to discussion.
Kumar K: Critical review and evaluation.
Imran M: Data collection and processing.
Khaliq SA: Statistical analysis and interpretation of results.

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