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RESEARCH ARTICLE

THE PLATELET/SPLEEN DIAMETER RATIO; REPRESENT AN ACCEPTABLE SURROGATE PARAMETER FOR SCOPE ALL STRATEGY FOR DETECTION OF ESOPHAGEAL VARICES IN PATIENTS WITH LIVER CIRRHOSIS

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Abbreviations:

EV, Esophageal varices,
GV, Gastric varices,
CTP, Child- pugh class,
TIPS, Transjugular intrahepatic,
Porto systemic shunting, PV,
Portal vein, P/S diameter,
Portal splenic diameter,
No EV, No esophageal varices.

ABSTRACT

Background: Variceal bleeding is a frequent and life-threatening complication of portal hypertension. The first episode of variceal bleeding is not only associated with a high mortality, but also with a high recurrence rate in those who survive. Therefore, many studies and randomized clinical trials have focused on different strategies aiming to prevent the first episode of variceal bleeding (primary prophylaxis).

Aims: to identify clinical, biochemical, and ultrasonographic parameters which might non-invasily predict the presence of esophageal varices and to evaluate the reproducibility of different non-invasive parameters like P/S dimeter ratio, portal vein diameter, splenic diameter and platelet count cut off values in diagnosing the presence of varices.

Methods: In the first part of this study we retrospectively included 284 patients referred to our unit in National Liver Institute, Menoufiya University. Non-invasive diagnostic parameters for the presence of varices which included portal vein diameter, splenic diameter, platelets count and P/S diameter ratio were analyzed. In the second part, we analyzed prospectively 83 patients for the smae non-invasive diagnostic parameters.

Results: Among the 289 patients included in the 1st retrospective part who underwent upper endoscopy, overall 177 (61%) patients had endoscopic evidence of EV, 85 (29%) patients had both EV and GV and only 5(2%)patients had gastric patients, while 17 (6%) patients had gastric erosions. Different non invasive diagnostic parameters for dtection of varices were studied as shown in table (5): PV diameter was was 11.3571±2.22 for non-EV patients and 13.9125±3,55 for EV patients (p=0.006). Platelet count was 235,363.64±11420.88 for non-EV patients and 120,080.15±61,673.88 for EV patients (p<0.0001) with significantaly higher number in EV group. Splenic diameter count was 137.73±46.08 for non-EV patients and 175.43±34.07 for EV patients (p<0.0001) with significantaly higher number in EV group and finally, P/S diameter ratio was 1952.6405±1180.35 for non-EV patients and 738.2708±456.12 for EV patients (p<0.0001) with significantaly higher cut-off in non-EV group. In the 2nd part, 83 patients were prospectively studied; splenic diameter was ≥ 142.50 (sensitivity: 86.36%, specificity: 41.28%, +ve predictive value: 85.07% and -ve predictive value: 43.75%), platelet count was ≤ 183,500 (sensitivity: 92.42%, specificity: 29.41%, +ve predictive value: 83.56% and -ve predictive value: 50%) and P/S diameter ratio was ≤ 1313.9400 (sensitivity: 95.45%, specificity: 29.41%, +ve predictive value: 84% and -ve predictive value: 62.5%). P/S diameter ratio cut off was (≤ 1313) the only indepenent parameter for detection of esophageal varices but, not for predicting the presence or absence of gastric varices.

Conclusions: Upper endoscopy is still the essential tool for diagnosing and directing management of variceal bleeding. The use of P/S diameter ratio cut off value is promising and might be benificial and an important substitute for endoscopy and cost effective. Future studies are needed to predict its role in diagnosing which patient will have attack of bleeding.

INTRODUCTION

The prevalence of esophageal varices (EV) is very high: when cirrhosis is diagnosed, varices are present in about 40% of compensated patients and in 60% of those with ascites (Schepis *et al*., 2001; D'Amico and Luca, 1997). After initial diagnosis of cirrhosis, the expected incidence of newly developed varices is about 5% per year (D'Amico *et al*., 1999). Once developed, varices increase in size from small to large at an overall rate of 10–15% per year (D'Amico *et al*., 1999).

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Progression of liver failure seems to be the factor withthe greatest influence on overall growth (Zoli *et al*., 2000). On the other side, improvement in liver function may result in decrease or even disappearance of varices (Vorobioff *et al*., 1996). The 1996 the American Association for the study of Liver Disease single topic symposium stated that cirrhotic patients should be screened for the presence of EV when portal hypertension is diagnosed (Grace *et al*., 1998).

Also, Baveno III Consensus Conferance on poratl hypertension recommended that all cirrhotic patients should be screened for the presence of E V when liver cirrhosis is diagnosed (D'Amico *et al*., 2001). Other studies have suggested repeating upper endoscopy at 2-3 year intervals in patients without varices and 1-2 year intervals for patients with small varices (Cales *et al*., 1990).

Many syudies that included different clinical, biochemical and ulrrasonographic parameters have shown good predictive power for non-invasive assessing the presence or absence of varices, so decreasing the burden on gastrointestinal endoscopy (Chalasani *et al*., 1999; Zaman *et al*., 1999; Pilette *et al*., 1999).

Patients and methods

1st part of the study

In the first part of this study we retrospectively included 284 patients referred to our unit in National Liver Institute, Menoufiya University between January 2006 and September 2007.

Exclusion criteria:

1- Patients with active bleeding at admission
2- Patients who had undergone sclerotherapy or band ligation
3- Patients who had undergone transjugular intrahepatic portosystemic shunting (TIPS)
4- Patients who undergone surgical shunting
5- Patients taking drugs for primary prophylaxis of variceal bleeding

The total number of included patients was 284 and were 222 male and 62 female patients.

The etiology of their liver disease was as follow;

Each patient had a complete biochemical and clinical examination. All patients were classified according to Child classification, 19 patients were Child A, 127 were Child B and 138 were Child C. All patients underwent upper endoscopy and abdominal ultrasonography to evaluate the presence of signs of portal hypertension (presence and degree of esophageal varices, splenomegaly and ascites).

For the purpose of the study, patients were divided two groups according to the presence/absence of varices. Abdominal ultrasonography was carried out to detect the maxicum splenic bipolar diameter in millimeters (mm). Platelet count/spleen diameter ratio was calculated for all patients to detect the exact cut off for diagnosing the presence or absence of varices.

2nd part of the study

In the second part of the study we evaluated whether the predictive criteria identified in the first part of the study were able to reproduce their predictive ability in a subsequent different, but related, group of patients who represented the same populations. Eighty-three patients were prospectively evaluated to detect the platelet count/spleen diameter ratio.

Statistical analysis

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation, analysis of variance [ANOVA] test, Chi-square roc curve test t. test , SPSS V11.

1. Mean $= \frac{\Sigma x}{n}$

Where Σ = sum & n = number of observations.

2. Standard Deviation [SD] :

$$SD = \sqrt{\frac{\Sigma |x - x|^2}{n-1}}$$

Chi-square the hypothesis that the row and column variables are independent, without indicating strength or direction of the relationship. Pearson chi-square and likelihood-ratio chi-square. Fisher's exact test and Yates' corrected chi-square are computed for 2x2 tables.

RESULTS

1st part of the study

Among the 289 patients who underwent upper endoscopy**,** 19 (7%) patients were Child A, 127 (45%) were Child B and 138 (48%) were Child C. Overall 177 (61%) patients had endoscopic evidence of EV, 85 (29%) patients had both EV and GV and only 5(2%)patients had gastric patients, while 17 (6%) patients had gastric erosions. The included patients were classified into 4 groups according to endoscopic findings (group 1: patients with GV, group 2: patients with gastric erosions, group 3: patients with EV and group 4: patients with both EV and GV). For group 1; 5 (100%) patients were males, group 2; 9 (52.94%) patients were males, group 3; 140 (79.1%) were males and group 4; 68 (80%) patients were males.

The mean age was 60 ± 16 for group 1, 57.06±12.15 for group 2, 51.76±10.17 for group 3 and for 49.99±13.04 group 4 with no significant difference. Also, CTP score was calculated in all groups: For group 1; 1 (20%) patient was Child A, 3 (60%) were Child B and 1 (20%) was Child C For group 2; 5 (29.41%) patient was Child A, 10 (58.82%) were Child B and 2 (11.7%) was Child C For group 3; 8 (4.52%) patient was Child A, 78 (44.07%) were Child B and 91 (51.41%) was Child C For group 4; 5 (5.88%) patient was Child A, 36 (42.35%) were Child B and 44 (51.77%) was Child C as shown in Table (1).

Multivariate logestic regression analysis was performed on different parameters like P/S diameter ratio between 4 groups using ANOVA test and reflectd that 1503±127.61 for group 1,

2058.42±1171.35 for group 2, 764.06±469.24 for group 3 and 684.57±425.17 for group 4 with significant differnces (p value <0.00001) and portal vein diameter; 12±1.87for group 1, 11.16±2.34 for group 2, 14.12±3.59 for group 3 and 13.49±3.44 for group 4 without sinificant difference (p= 0.006) as shown in Table (2).

120,080.15±61,673.88 for EV patients (p<0.0001) with significantaly higher number in EV group. Splenic diameter count was 137.73±46.08 for non-EV patients and 175.43±34.07 for EV patients (p<0.0001) with significantaly higher number in EV group and finally, P/S diameter ratio was 1952.6405±1180.35 for non-EV patients and 738.2708±456.12

Table 1. Comparison between 4 groups regarding sex and Child score using Chi-Square test

		GV	Erosions	EV	EV& GV	ᵡ2	P
Sex	Male	5 (100%)	9 (52.94%)	140 (79.1%)	68 (80%)	7.993	0.046
	Female	0	8 (47.06%)	37 (20.9%)	17 (20%)		
Child Score	A	1 (20%)	5 (29.41%)	8 (4.52%)	5 (5.88%)	22.964	0.001
	B	3 (60%)	10 (58.82%)	78 (44.07%)	36 (42.35%)		
	C	1 (20%)	2 (11.77%)	91 (51.41%)	44 (51.77%)		

Table 2. Comparisons between 4 groups using ANOVA test

	GV	Erosions	EV	EV& GV	F	P
Age	60.60±16.64	57.06±12.15	51.76±10.17	49.99±13.04	3.007	0.028
P/S diameter ratio	1503±127.61	2058.42±1171.35	764.06±469.24	684.57±425.17	35.279	<0.0001*
P V diameter	12±1.87	11.16±2.34	14.12±3.59	13.49±3.44	4.211	0.006

*: means Significant p value

Table 3. Comparisons between 4 groups using Post Hoe Tukey HSD test

Compared groups		Age	P/S diameter ratio	PV diameter
Gastric varices (GV)	Erosions	0.943	0.330	0.965
	EV	0.312	0.004	0.532
	EV& GV	0.175	0.002	0.788
Erosions	EV	0.209	<0.0001*	0.006
	EV& GV	0.069	<0.0001*	0.066
Esophageal varices (EV)	EV & GV	0.644	0.682	0.518

*: means Significant p value

Table 4. Comparison between EV and Non-EV groups (Chi-Square test)

		No EV (N=22)	EV (N=262	ᵡ2	P
Sex	Male	14(63.6%)	208 (79.4%)	2.951	0.086
	Female	8 (36.4%)	54 (20.6%)		
Child Score	A	6 (27.3%)	13 (4.96%)	22.119	<0.0001*
	B	13 (59.1%)	114 (43.51%)		
	C	3 (13.6%)	135 (51.53%)		

*: means Significant p value

Table 5. Comparison between EV and Non-EV groups (t-test)

	No EV (N=22)	EV (N=262	T	P
Age	58.09±12.89	51.19±11.18	2.747	0.006
PV diameter	11.3571±2.22	13.9125±3,55	-3.245	0.001
Platelet count	235,363.64±11420.88	120,080.15±61,673.88	4.681	<0.0001*
Splenic diameter	137.73±46.08	175.43±34.07	- 4.838	<0.0001*
P/S diameter ratio	1952.6405±1180.35	738.2708±456.12	4.796	<0.0001*

*: means Significant p value

Another analysis comparing the 4 groups using Post Hoe Tukey HSD test which revealed P/S diameter was significantly different between EV as shown in Table (3). Another classification was done according to presence or absence of varices (262 patients with EV and 22 patients with Non-EV) and were compared regarding sex and CTP acore as shown in Table (4) with significantly higher score for EV group. Different non invasive diagnostic parameters for dtection of varices were studied as shown in table (5): The age for non-EV patients was 58.09±12.89 and 51.19±11.18 for EV patients (p=0.006). PV diameter was was 11.3571±2.22 for non-EV patients and 13.9125±3,55 for EV patients (p=0.006). Platelet count was 235,363.64±11420.88 for non-EV patients and

for EV patients (p<0.0001) with significantaly higher cut-off in non-EV group. We then used ROC curves to assess the P/S diameter ratio cut off values for different studied parameters with the best sensitivity and specificity for diagnosis of EV as shown in Table (6).

Table 6. Proposed cut off levels for detection of EV

	Cut off (+ve if)	Sensitivity	Specificity
	≥ 10.50	84.3%	42.9%
PV diameter	≥ 11.15	73.3%	47.6%
Splenic diameter	≥ 142.50	85.1%	72.7%
Platelet count	≤ 183,500	87%	72.7%
	≤ 1196.8750	87%	77.3%
P/S diameter ratio	≤ 1313.9400	89.3%	72.7%

- PV diameter cut off value was ≥ 10.50 (sensitivity: 84.3% and specificity: 42.9%)

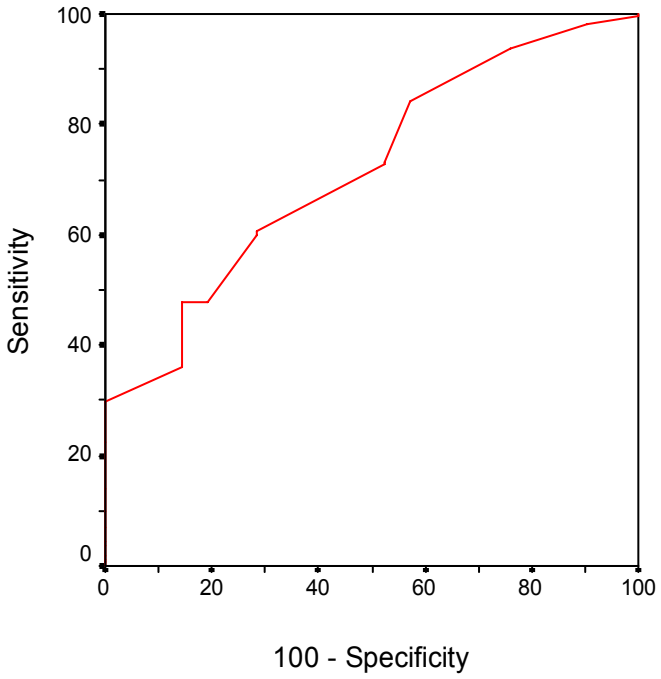
- Splenic diameter was ≥ 142.50 (sensitivity: 85.1% and specificity: 72.7%)

- Platelet count was ≤ 183,500 (sensitivity: 87% and specificity: 72.7%)

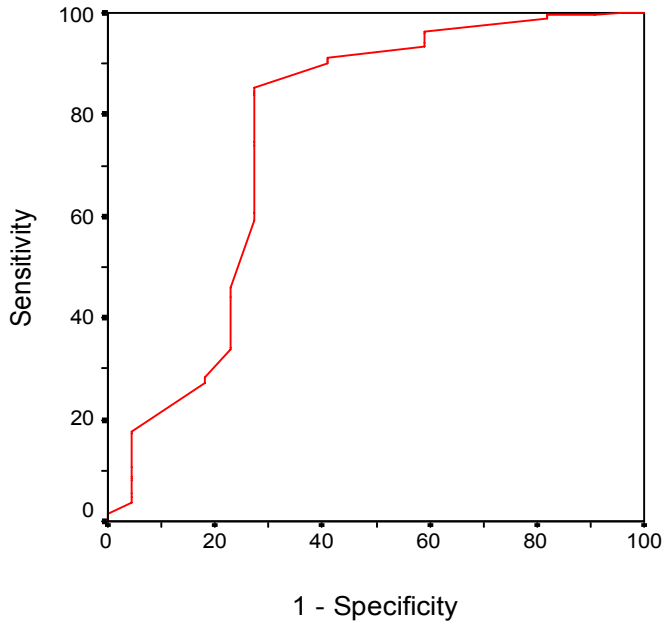
-P/S diameter ratio was ≤ 1313.9400 (sensitivity: 89.3% and specificity: 72.7%)

ROC curves

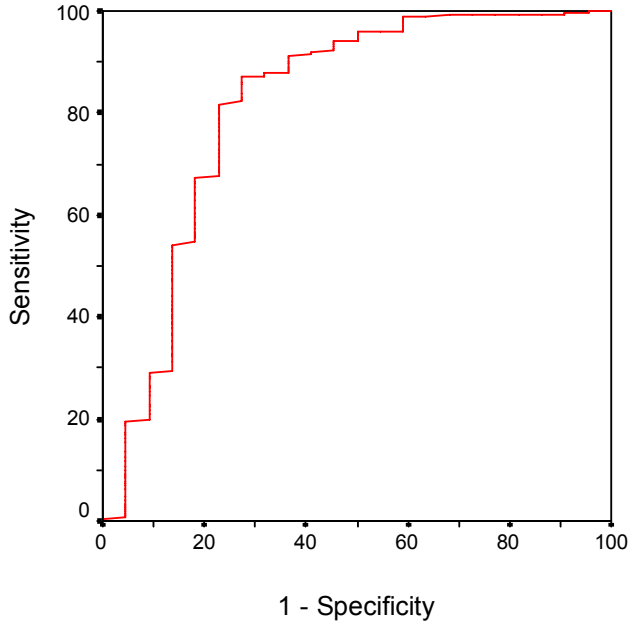
ROC curve 1. PV diameter



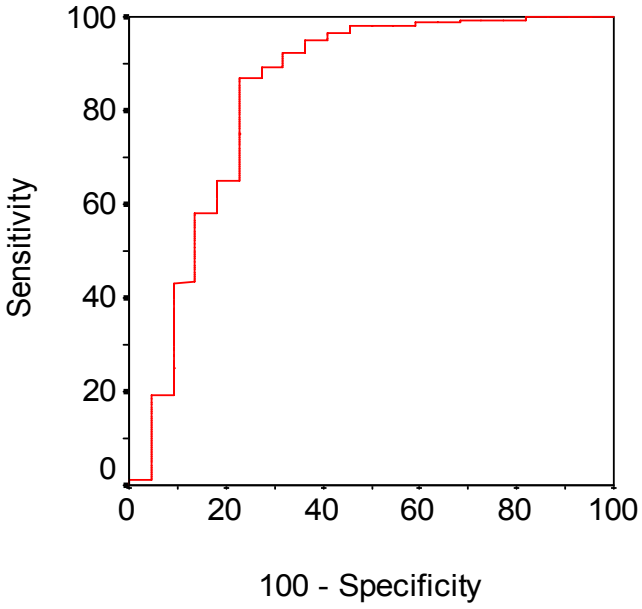
ROC curve 2. Splenic diameter (mm)



ROC curve 3. Platelet count (/mm^3)



ROC curve 4. Platelet count (/mm^3) Splenic diameter (mm) ratio



Area under the Curve

	Area	P	95% Confidence Interval
PV diameter	0.719	0.001*	0.617 - 0.820
Splenic diameter	0.760	<0.0001*	0.624 - 0.896
Platelet count	0.814	<0.0001*	0.694 - 0.934
Platelet splenic ratio	0.835	<0.0001*	0.718 - 0.952

Proposed Cut off levels for detection of EV

	Cut off (+ve if)	Sensitivity	Specificity
PV diameter (mm)	≥10.50	84.3%	42.9%
	≥11.15	73.3%	47.6%
Splenic diameter (mm)	≥142.50	85.1%	72.7%
Platelet count (/mm^3)	≤183,500	87%	72.7%
Platelet count (/mm^3) splenic diameter (mm) ratio	≤1196.8750	87%	77.3%
	≤1313.9400	89.3%	72.7%

Cut off level for detection of EV by measuring PV diameter with acceptable sensitivity and specificity is below the level of upper limit of normal of PV diameter. Consequently it is lacking a reliable sensitivity and specificity as a reliable parameter for detection of EV.

2-2nd part of the study

In this part of the study we evaluated the reproducibility of the predictive criteria in the first part of the study which included 83 patients as shown in Table (7):

- Splenic diameter was ≥ 142.50 (sensitivity: 86.36%, specificity: 41.28%, +ve predictive value: 85.07% and -ve predictive value: 43.75%)
- Platelet count was ≤ 183,500 (sensitivity: 92.42%, specificity: 29.41%, +ve predictive value: 83.56% and -ve predictive value: 50%)
- P/S diameter ratio was ≤ 1313.9400 (sensitivity: 95.45%, specificity: 29.41%, +ve predictive value: 84% and -ve predictive value: 62.5%)

Table 7. Prospective part of the study

	P/S diameter ratio		Platelets	Splenic diameter
	≤ 1313	≤ 1196	≤ 183,5	≥ 142.5
Sensitivity	95.45%	93.94%	92.42%	86.36%
Specificity	29.41%	35.29%	29.41%	41.28%
+ve predictive value	84%	84.93%	83.56%	85.07%
-ve predictive value	62.5%	60%	50%	43.75%

DISCUSSION

Portal hypertension is a common complication of liver cirrhosis which develops as a result of a combination of increased resistance to portal venous flow (Backward Theory) and increased splanchnic blood flow (Forward Theory) (Genecin and Groszmann, 1994). Although portal hypertension plays a role in the pathogenesis of ascites and hepatic encephalopathy, variceal bleeding is its major and life-threatening complication, representing a major therapeutic challenge with up to 50% mortality (Saunders *et al*., 1981; D'Amico *et al*., 1986).

We studied our patients' characteristics including age, sex and CTP score and there was no age or sex significant difference but CTP score was higher for patients with varices. Also, multivariate analyses of randomized studies, mortality from esophageal variceal hemorrhage increases with age and **CTP** class—particularly related to ascites and encephalopathy. Therefore, the potential of preventing first variceal hemorrhage offers the promise of reducing mortality, morbidity, and associated health care costs (Kleber *et al*., 1991; Andreani *et al*., 1990; The Northern Italian Endoscopic Club, 1988). For prediction of first variceal hemorrhage in patients who have never bled, different classifications have been developed by using clinical data (such as CTP class), laboratory results (such as coagulation tests), endoscopic findings (including size, color, stigmata, and location of esophageal varices), or combinations of these. The natural history of cirrhosis and its complications such as variceal hemorrhage have been studied in reference to these classifications (Jensen, 1999).

Multiple studies have been published concerning the validity of non invasive diagnostic predictors of presence or absence of EV (Zaman *et al*., 1999; Pilette *et al*., 1999; Ng *et al*., 1999). These predictors should be simple, reproducible, and commonly available because we beleive that other features that were studeid as non invasive predictors were less reproducible in clinical practice (Valletta *et al*., 1993).

Almost all of the studies were retrospective, although the only prospective one study obtaind results that were not different from those obtained from retrospective analysis (Schepis *et al*., 2001). The P/S diameter ratio was chosen as a parameter in this study because it could identify the degree of thromocytopenia which most likely depends on hypersplenism. The splenic bipolar diameter was measured using the ultrasonography. The study population was distrubited homogeneousily and was representive of the population of liver cirrhosis. Diagnosis and classification of EV was made in the same endoscopy unit and using a single classification. In this study, we focused on the presence or absence of varices rather than the size of varices or, presence of risky signs. In the first part of the study, we analysed the parameters linked to portal hypertension (platelet count and splenic diameter) and parameters linked to hepatic dysfunction (CTP score).

The P/S diameter ratio showed very good good results in distinguishing between the presence or absence of varices and this agrees with the results obtained by Giannini *et al*. 2003 who proved that P/S diameter ratio cut off 909 was the only independent predictor for the presence of varices either esophageal or gastric and had 100% negative predictive value (Giannini *et al*., 2003). The rational for use of this ratio is supported by both clinical and statistical reasons: the first one from clincal point of view, platelet count may decrease due to several reasons in cirrhotic patients. The second reason from statisrical point of view, the use of P/S diameter ratio cut off was **(≤ 1313)** the only indepenent parameter for detection of esophageal varices but, not for predicting the presence or absence of gastric varices.

In the second part of the study, the aim was to evaluate whether the predictive power of P/S diameter ratio cut off identified in the first part of the study was able prospectively to be reproducible and efficient in detecting the presence or absence of varices and the results showed that P/S diameter ratio cut off was **(≤ 1313)** the only indepenent parameter for detection of esophageal varices

Conclusions

Endoscopy is essential for diagnosing variceal bleeding as well as directing management and providing therapy but it is an invasive technique so the non-invasive modalities including P/S diameter ratio cut off might be an important substitute which also is cost effective. The use of P/S diameter ratio in detection of possibility of first bleeding attack is highly recommended in future studies.

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