Non-Endoscopic Predictors of Esophageal Varices and Portal Hypertensive Gastropathy

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Abstract: Liver cirrhosis has been associated with portal hypertension as a common complication with subsequent development of esophageal varices (OV) and portal hypertensive gastropathy (PHG). Screening endoscopy repeated at certain intervals had been suggested for early detection and evaluation of progression of OV and PHG in cirrhotic patients with portal hypertension .However that approach had its limitations being an invasive technique and its cost- effectiveness was graded. Our study was undertaken to identify and evaluate non –invasive parameters as predictors of OV and PHG in cirrhotic patients. **Methods:** Fifty patients was in rolled in this study diagnosed as cases of liver cirrhosis with no past history of gastrointestinal tract (GIT) bleeding, all patients had complete blood count, liver profile (Alanine transferase (ALT), Aspartate Transferase (AST), s.Albumin and s. Bilirubin), Abdominal ultrasound[for portal vein diameter (PVD)., splenic bipolar diameter, and Ascites),Platelet count/Splenic diameter ratio and upper Gastrointestinal tract (GIT)endoscopy for evaluation of the presence and grade of OV and PHG . **Results:** The study showed that OV grade had a significant inverse correlation ($P<0.05$) with WBCs count, Platelets count as well as Platelet count/Splenic diameter ratio and a positive significant correlation ($P<0.05$) with Mean splenic bipolar diameter(MSBD), PVD ,and Child Pugh's classification grade. **Conclusion**: Platelet count, MSBD, PVD, and Platelet count/ Splenic diameter ratio can be used as non-invasive predictors of OV in patients with liver cirrhosis. [Nature and Science 2010;8(6):43-50]. (ISSN: 1545-0740).

KEY WORDS: esophageal varices, portal gastropathy,platelet/spleen ratio, PVD.

Introduction

Liver cirrhosis is a major health problem; it represents the final conmen pathway for wide variety of chronic liver diseases **(WOLF, 2004).**

Portal hypertension commonly accompanies liver cirrhosis with the development of esophageal varices (OV) and portal hypertensive gastropathy (PHG) as major complications **(De franchis and Primignani ,2001**)

Sever PHG probably accounts for most of non-variceal bleeding episodes in patients with cirrhosis and portal hypertension, PHG bleeding is a serious complication which is usually chronic and insidious but occasionally maybe massive and life threatening (**Perez-Ayurso et al., 1991**).

Variceal hemorrhage is not confined to patients with large OV although they are more liable to bleed than patients with small OV. **(Jenesn 2002)**

The American association for the study of liver disease single topic symposium stated that cirrhotic patients should be screened for the presence of OV when portal hypertension is diagnosed **(Grace et al., 1998).**

It had been suggested for endoscopy to be repeated at 2-3 years interval in patients without varices and at 1-2years interval in patients with small varices to evaluate the development and / or progression of OV (**Calés et al., 1990, and D'Amico,et al.,1995).**However this approach has some limitations as endscopy is an invasive procedure, the cost-effectiveness is questionable also only 9%-36% of patients with cirrhosis found to have varices on screening endoscopy **(Brennan et al., 2003).**

It may be more cost – effective to routinely screen patients at high risk for the presence of varieces to reduce the increasing burden and procedure cost of endoscopy unit **(Zoli et al., 1996).**

Identification of non –invasive predictors of OV and PHG will allow upper gastrointestinal tract(GIT) endoscopy to be carried out only in selected group of patients thus avoid un-necessary intervention and at the same time not to miss patients at risk of bleeding **(Sarwar et al.,2004)**

Patients and methods

This study was preformed at Ain Shams University Hospital, where 50 patients were recruited from the internal medicine and hepatology out patient clinics during the period between March and October 2009

Diagnosis of cirrhosis was based on standered clinical, biochemical, ultrasonographic and pathological data if possible.

All patients included in the study were subjected to

1- Full history and clinical examination.

2- Routine laboratory investigations including complete blood picture, liver function tests (serum bilirubin, ALT, AST, Alkaline phosphatase and serum albumin), Prothrombine time (PT) and INR.

3- Abdominal ultrasonography: to detect maximum spleen bipolar diameter(MSBD), portal vein diameter(PVD) and presence of ascites.

4- Classification according to Child-Pugh'criteria

Parameter	**1 point**	**2 points**	**3points**
Bilirubin(mg/dl)	<2	2-3	>3
Albumi(gm/dl)	>3.5	2.8-3.5	<2.8
Prothrombin time increase(sec)	1-3	4-6	>6
Ascites	None	Slight	Moderate
Encephalopathy	None	1-2	3-4

The grades are:

A for 5-6 points
B for7-9 points
C for10-15 points

(Pugh et al., 1973).

5- Ultrasonography of the abdomen especially for signs of portal hypertension:

-Splenomegaly with detection of the maximum bipolar diameter (MBDS) in mm.
-The presence of ascites.
-Portal vein diameter (PVD).

6- The platelet count / spleen diameter ratio calculation.

7- Upper GIT endoscopy (after consent) for, evaluation of the presence and grade of OV and PHG.

▪ OV classified into:

-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.

(Westbay et al., 1983)

▪ PHG classified into:

-Mild (Grade 1): Mosaic like pattern .

-Sever (Grade 2): Mosaic like pattern with superimposed red sings.

(**De Franchis, 2000)**

Patients with past history of upper GIT bleeding were excluded from the research.

Statistical analysis:

Analysis of data was done using IBM computer using SPSS (statistical program for social science)

-Quantitative variables were descried as mean, SD and rang, while qualitative variables were described as no and %.

- Chi-square test, unpaired t-test, or Mann Whitney U-test were used when appropriate

-Correlation coefficient test to rank different variables positively or inversely in linear correlations.

-Logistic regression model was used to find the most important independent predictors for OV.

-ROC (Receiver operator characteristic curve) was used for best cut-off value of different predictors as well as sensitivity and specificity at each cut- off value, together with calculation of area under the curve which represent the overall productivity of the test.

P- Value >0.05: insignificant.
<0.05: significant.
<0.01: highly significant.

Results

This study was carried on fifty (50) cases, 37 males (74%) and 13 female (26%), their ages ranged between39years and67 years with a mean of 49.6±8.8. The etiology of liver cirrhosis was hepatitis C virus in 35 patients (70%), hepatitis B in 10 patients (20%) and combined hepatitis C and B in 5 patients(10%).

Laboratory findings showed total bilirubin ranging between0.3 -5.1 mg/dl with a mean of 2 ± 1.4, AST ranging between 28-258 IU /dl with a mean of 78.1± 37, ALT ranging between 18 - 168 IU/dl with a mean of 57.2 ± 32.3, serum albumin ranging between 1.8-4.3 gm/dl with a mean of 2.8± 0.5, PT ranging between 11.4-21.7 sec with a mean of 15.9 ± 2.5,INR ranging between 1-2.4 with a mean of 1.4± 0.3 . WBCs count ranging between 1.2- 9.6 $\times 10^3$ with a mean of 5± 2.4 and platelet count ranging between 29 – 298 $\times 10^3$ with a mean of 110.8 ± 55.7.

Among the studied cases, 19 were child-Pugh's class A (38%), 21 were class B (42%) and 10 were class C (20%).

Endoscopic findings showed 6 patients with no OV (12%), 14 patients with grade1 (28%), 13 patients with grade 2 (26%), 16 patients with grade 3 (32%) and 1 patient with grade 4 (2%). As regard PHG, 21 patients had no PHG (42%), 24 patients with mild PHG (48%) and 5 patients with sever PHG (10%).

In sonographic examination, PVD ranged between11.2-23 mm with a mean of 15.2 ±2.6 , MSBD ranged between 114-221 mm with a mean of 155.9 ±28.8 and platelet count / spleen diameter ratio ranged between 142 -2504 with a mean of 746.7± 454.

Relations of endoscopic findings and laboratory parameters;

OV grade showed statistically inverse correlation versus WBCS ($P<0.05$) and platelets count($P<0.05$),on the other hand; no statistically significant correlation was found between PHG grade versus WBCS or platelet count.(Table-1) .Also there were no significant correlation between OV or PHG grade and any of the liver profile data. (Table - 2).

Relations of endoscopic findings and sonographic data;

There were significantly positive correlation between OV grade versus PVD and MSBD ($P<0.05$), and an inverse correlation ($P<0.05$) between the OV grade and platelet/splenic diameter ratio (Table-3).

In this study; platelet count and platelet/splenic diameter ratio were lower, while PT, PVD, MSBD were higher in cases with OV(OV+ve) when compared with cases without OV(OV –ve) with statistically significant difference inbetween, while no statistically significant difference could be detected between OV+ve or –ve cases as regard other laboratory data (Tab-4). Also no statistically significant difference could be detected between cases with +ve or-ve PHG as regard all laboratory data (Tab-5).

Relations between endoscopic findings and Child-Pugh's classifications;

A statistically significant positive correlation was found between OVgrade and Child-Pugh's classification grades i.e., the higher grade of OV the more advanced grade of Child's classification. On the other hand, no statistically significant associations were found between PHG grade and Child's classification grade (Tab-6).

This study showed that platelet count $<100\times10^3$, MSBD >145 mm, PVD >135 mm and platelet count/ spleen diameter ratio < 820 were considered the most significant independent predictors of worse outcome or OV presence (Tab-7).

When the sensitivity, spicificty, and predictive value of platelet count, MSBD, PVD,and, platelet count /splenic diameter ratio were studied in prediction of OV; MSBD and platelet count /splenic diameter ratio showed the best sensitivity for OV prediction,but overall, the non–endoscopic parameters can be considered a good positive rather than negative predictors i.e positive results allow early OV prediction, while negative result can not exclude the possibility of OV except with other confirmatory test(s). (Tab-8), (Fig-1-2-3-4).

Table (1) Correlation between endoscopic parameters versus hematological parameters:

Variables	OV		PHG	
	R	p	r	p
WBCs	-0.25	<0.05	0.15	>0.05
Platelets	-0.25	<0.05	0.21	>0.05

Table (2) Correlation between endoscopic parameters versus liver profile parameters:

Variables	OV		PHG	
	r	p	r	p
Total bilirubin (mg/dl)	0.11	>0.05	0.15	>0.05
AST IU/dl	0.1	>0.05	0.23	>0.05
ALT IU/dl	0.2	>0.05	0.14	>0.05
Serum Albumin (gm/dl)	0.17	>0.05	0.17	>0.05
PT (second)	0.19	>0.05	0.2	>0.05
INR	0.22	>0.05	0.18	>0.05

Table (3) Correlation between endoscopic parameters versus sonographic findings:

Variables	OV		PHG	
	r	p	r	p
PVD(mm)	0.29	<0.001	0.12	>0.05
MSBD	0.29	<0.001	0.2	>0.05
Platelets/Spleen	-0.27	<0.001	0.1	>0.05

Table (4) Relation between OV versus other variables (laboratory & sonographic):

Variables	OV		t	p
	Negative	Positive		
Total bilirubin (mg/dl)	2.4 ± 1.8	1.95 ± 1.3	0.7	>0.05
AST IU/dl	81 ± 46	77.7 ± 37	0.2	>0.05
ALT IU/dl	50.7 ± 30	58 ± 32	0.5	>0.05
Serum Albumin (gm/dl)	3.1 ± 0.6	2.8 ± 0.52	1.3	>0.05
PT (second)	15.9 ± 2.9	18.9 ± 2.5	2.8	<0.05
INR	1.4 ± 0.29	1.4 ± 0.3	0.25	>0.05
WBCs	6.1 ± 1.5	4.8 ± 2.4	1.2	>0.05
Platelets	116.2 ± 93	100.9 ± 50	2.3	<0.05
PVD(mm)	13.8 ± 2.7	15.3 ± 2.4	2.6	<0.05
MSBD	147.8 ± 33	166.9 ± 24	2.8	<0.05
Platelets/Spleen	962.5 ± 834	700.9 ± 390	2.7	<0.05

Table (5) Relation between PHG versus other variables (laboratory & sonographic):

Variables	PHG		t	p
	Negative	Positive		
Total bilirubin (mg/dl)	2.3 ± 1.2	1.91 ± 1.3	0.9	>0.05
AST IU/dl	79 ± 35.6	72.7 ± 37	0.5	>0.05
ALT IU/dl	55.7 ± 32.3	57 ± 32.3	0.4	>0.05
Serum Albumin (gm/dl)	3.4 ± 0.4	2.9 ± 0.54	1.6	>0.05
PT (second)	15.9 ± 2.9	16.5 ± 2.5	1.8	>0.05
INR	1.5 ± 0.22	1.3 ± 0.23	0.45	>0.05
WBCs	6.58 ± 1.5	5.8 ± 2.4	1	>0.05
Platelets	116.2 ± 93	110.9 ± 54	1.1	>0.05
PVD(mm)	13.9 ± 2.2	14.3 ± 2.5	1.6	>0.05
MSBD	145.8 ± 31	156.9 ± 22.3	1.8	>0.05
Platelets/Spleen	862.5 ± 814	720.9 ± 310	1.7	>0.05

Table (6) Relation between endoscopic parameters versus Child classification:

Variables	Child's A	Child's B	Child's C	X^2	P
O.V					
Negative	4 (66.7 %)	0	2 (33.3 %)	6.7	<0.05
Grade I	5 (35.7 %)	7(50 %)	2 (14.3 %)		
Grade II	5 (38.5 %)	6 (46.2 %)	2 (15.4 %)		
Grade III	5 (31.3%)	7 (43.8 %)	4 (25 %)		
Grade IV	0	1 (100 %)	0		
PHG					
Negative	7 (33.3 %)	10 (47.6 %)	4 (19 %)	2.3	>0.05
Grade I	9 (37.5 %)	9 (37.5 %)	6 (25 %)		
Grade II	3 (60 %)	2 (40 %)	0		

Table (7) Relation between OV versus all parameters by using logistic regression model:

Independent Predictors	Beta coefficient	P	Odd's (95% CI)
Platelets ≤ 100 X 10^3	-0.25	<0.05	3 (0.5-3.5)
MSBD ≥ 145	0.45	<0.05	3.5 (0.2-5.9)
PVD ≥ 13.5	0.32	<0.05	2 (0.2-4)
Platelets/Spleen ≤ 820	-0.21	<0.05	1.9 (0.1-3.5)

Table (8) Sensetivity,specificity and predictive value of platelets, MSBD , PVD, and platelet count / spleen ratio in prediction of OV :

Independent Predictors	Best cut off value	Sensitivity	Specificity	Overall predictivity
Platelets	100 X 10^3	78%	63%	67%
MSBD	145	82%	60%	75%
PVD	13.5	80%	55%	75%
Platelets/Spleen	820	85%	54%	80%

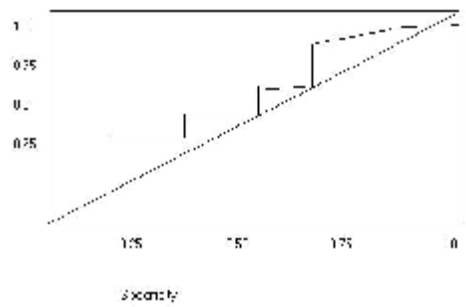

Figure (1) ROC (Receiver operator characteristic curve) to find out the best cut off value of platelet count & detection of sensitivity & specificity value at this point that could predict OV .
Area under the curve = 0.67
X: sensitivity; Y: Specificity

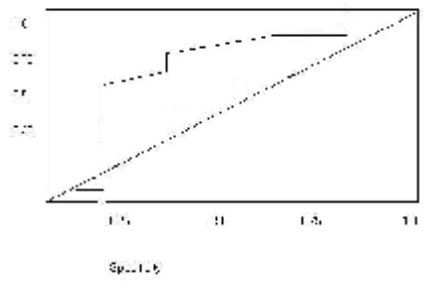

Figure (2) ROC (Receiver operator characteristic curve) to find out the best cut off value of PVD & detection of sensitivity & specificity value at this point that could predict OV .
Area under the curve = 0.75
X : sensitivity; Y : Specificity

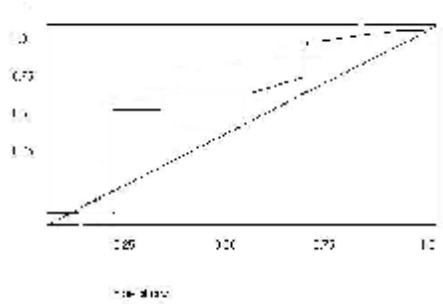

Figure (3) ROC (Receiver operator characteristic curve) to find out the best cut off value of MSBD & detection of sensitivity & specificity value at this point that could predict OV .
Area under the curve = 0.75
X : sensitivity; Y : Specificity

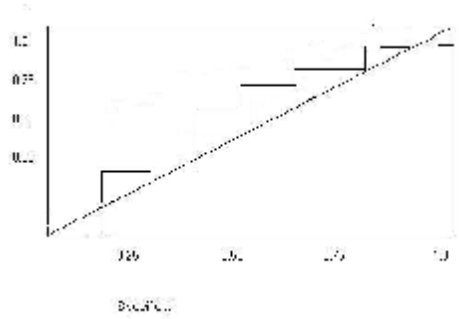

Figure (4) ROC (Receiver operator characteristic curve) to find out the best cut off value of platelet count / spleen ratio & detection of sensitivity & specificity value at this point that could predict OV .
Area under the curve = 0.80
X : sensitivity; Y : Specificity

DISCUSSION

Cirrhosis is the most advanced form of liver disease and variceal hemorrhage is one of its lethal complications. Over half of the patients with cirrhosis will develop varices. The risk of bleeding once OV formed is 20% to 35% within 2 years **(Groszmann et al., 1999).** The reported mortality rate from first episode of variceal bleeding is 17% to 57%. Of those who survive the initial episode of bleeding and who do not receive active treatment, the risk of recurrent bleeding is approximately 66% and usually occurs within 6 months of the initial bleeding episode **(Boyer, 1997 and Zaman, 2003).**

Because cirrhotic patients with large esophageal varices are at a high risk for bleeding, preventive efforts have concentrated on identifying cirrhotic patients with large varices **(Zaman et al., 2001).** In 1997,the American Collage of Gastroenterology (ACG) recommended screening endoscopy for cases with established cirrhosis who were candidates for medical therapy (**Grace, 1997**) . Also, in 1998, the American Association for the study of liver disease (AASLD) recommended screening endoscopy for varices and to be in particular routine in child class B and C patients, but in child class A to be limited to patients with evidence of portal hypertension (thrombocytopenia or large portal vein/collaterals on abdominal imaging) **(Grace, 1998).**

Prophylactic therapy initiated when large varices were discovered on screening endoscopy, had shown a decrease in the incidence of bleeding and an effect on bleeding –related mortality **(Sarin et al, 1999).**

It was estimated that 100 screening endoscopy need to be preformed to prevent 1-2 cases of variceal bleeding (**Boyer, 1997**) Therefore, identification of clinical features that can accurately predict esophageal varices and help identifying patients at greatest risk is important to improve the yield and cost- effectiveness of endoscopic screening (**Zaman, 2003).**

Bleeding occurs in significant proportion of patients with sever PHG which accounts for most nonvariceal bleeding episodes in patients with cirrhosis and portal hypertension. PHG bleeding is a serious complication, which is usually chronic and insidious but occasionally massive and life –threatening **(Perez- Ayuso et al., 1991**).

Overt hemorrhage from the gastric mucosa occurred in 60% of patients with sever PHG with a cumulative risk of bleeding of 75% over a 5 –year follow –up period (**D'Amico et al. 1990).**

In the present study, the parameters linked to portal hypertension (platelet count, portal vein diameter, splenic diameter and platelet count/spleen ratio), were associated with the presence of esophageal varices ,where OV showed significantly ($p<0.05$) positive correlation versus PVD and, MSBD and a significantly ($P<0.05$) inverse correlation versus platelet count and platelet count /splenic diameter ratio. On the other hand there was no statistically significant correlation ($P>0.05$) could be detected between PHG and any of these parameters. Platelet count showed a highly significant statistical inverse correlation with OVgrade which is in agreement with **Thomopulos et al. (2003**) ,who reported that; platelet count was the only common factor found to be significant predictor of both small and large varices.

MSBD showed a significant statistical direct correlation with the presence of OV in the studied cases, which is in agreement with **Chalasani et al., (1999**) who reported that splenomegaly is recognized as one of the diagnostic signs of cirrhosis and portal hypertension.

Correlation between PVD and OV presence showed a significant statistical direct correlation which goes with **Sarwar et al (2004**) who postulated that portal vein diameter more than 11 mm on ultrasonography is independently associated with the presence with OV.

In this study there was a significant statistical inverse correlation between platelet count/ spleen diameter ratio and the presence as well as the grade of OV which is in agreement with **Giannini et al, 2003, and Wolf, 2004**, both reported that the platelet count / spleen diameter ratio has a diagnostic accuracy of 92% as non –invasive parameter in detection of the presence of OV.

In the present study, the cut- off values which were used in diagnosis of OV were as follows : for platelet count was$<100\times10^3/mm^3$with a sensitivity of 78% and specificity of 63% , for MSBD was >145 mm with a sensitivity of 82% and specificity of 60%, for PVD was 13.5mm with sensitivity of 80% and specificity of 55% and for platelet count/spleen diameter ratio was<820 with sensitivity of 85% and specificity of 54% ,these results are comparable to the study **of Giannini et al., 2003** who reported cut off values for diagnosis of OV as follows ; for platelet count was$<112\times10^3$ mm^3, for MSBD was>121 mm, for PVD was > 13 mm, and for platelet count/spleen diameter ratio was<824.

In the studied cases there was no statistically significant correlation could be detected between OV or PHG versus serum albumin which is on the contrary with **Sarwar et al, 2004** who reported that serum albumin less than 2.95 gm/dl is independently associated with OV Presence. As regard WBCs count, there was statistically significant inverse correlation between OV presence and WBCs count, these results are in agreement with **Gue et al., 2004** who reported that leucopenia can be used to stratify

risk for occurrence of OV.

As regard the correlation between Child-Pugh's classification grades and OV grades, there was a statistically significant positive correlation between the grade of OV and the grade of child's classification which was in agreement with the work of **Cales et al., 1990** who postulated that enlargement of OV had been reported to be more common in patients with high initial Child-Pugh score.

In conclusion, Our work suggests that platelet count, MSBD, PVD and platelet count/spleen diameter ratio can be used as simple, commonly available, non invasive and sensitive parameters for prediction of OV in cirrhotic patients that may help in relieve medical, social and economic cost and we recommend further evaluation of these studies on larger scale as well as the trial of other non invasive parameters.

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