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Frequency and characteristic features of portal hypertensive gastropathy in patients with viral cirrhosis.

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ORIGINAL ARTICLE

Frequency and Characteristic Features of Portal Hypertensive Gastropathy in Patients with Viral Cirrhosis

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ABSTRACT

Objective: To determine the frequency and specific characteristic features of portal hypertensive gastropathy (PHG) in cirrhosis due to viral etiology.

Study Design: Cross-sectional descriptive study.

Place and Duration of Study: The Aga Khan University Hospital, Karachi, from June 2006 till June 2008.

Methodology: Patients with hepatitis B and C cirrhosis were included who underwent screening esophago-gastro-duodenoscopy (EGD) for varices. Baveno III consensus statement was used for diagnosing PHG on endoscopy and divided them into two subgroups i.e. mild and severe. Data related to platelet/spleen ratio, MELD score and Child Turcotte Pugh (CTP) score indicating severity of cirrhosis were recorded in all patients. Findings were compared by using independent sample t-test.

Results: Out of 360 patients who underwent screening EGD, 226 (62.8%) were males. Two hundred and eighty one (78%) had hepatitis C while 79 (22%) suffered from hepatitis B related cirrhosis. Three hundred patients (83.3%) had PHG while 71 (24%) had severe PHG. Higher proportion of esophageal varices (89.7%) was present among those who had PHG ($p < 0.001$). On univariate analysis lower platelet counts (117±55 vs. 167±90; $p < 0.001$), increased spleen size (14.1±2.9 cm vs. 12±2.4cm; $p < 0.001$) were found in PHG patients as compared to those without it. Similarly, lower platelet/spleen ratio was noted in patients with severe PHG (916±400 vs. 1477±899; $p < 0.001$). Furthermore, on multivariate analysis CTP score > 8 MELD score > 12 and platelets/spleen ratio < 900 were significantly associated factors with severe PHG.

Conclusion: Frequency of PHG was 83% while severe PHG was seen in 24% cases of viral hepatic cirrhosis. MELD score > 12, CTP score ≥ 8 and platelets/spleen ratio ≤ 900 were significant factors of severe PHG.

Key words: *Viral. Cirrhosis. Portal. Gastropathy. MELD score. Varices.*

INTRODUCTION

Portal hypertension is one of the major complications of chronic liver disease.[1] It develops because of an increase in splanchnic blood flow secondary to vasodilatation within the splanchnic vascular bed; and also because of increased resistance to the passage of blood through the liver.[2]

Amongst the complications of chronic liver disease, portal hypertensive gastropathy (PHG) has emerged as a new entity in the last two decades. It has been described as endoscopic appearance of gastric mucosa, with a characteristic mosaic-like pattern with or without red spots, and is seen in patients with both cirrhotic and non-cirrhotic portal hypertension. These mucosal changes mainly seen in fundus and body of stomach, but can also be noted in the gastric antrum. The prevalence of PHG in cirrhotic patients has been reported to be variable, ranging between 11% and 98%, while the incidence varies from 25% to 50%.[3,4] This difference has been often attributed to the absence of a common classification system, with a subsequent intra and inter-observer variation.[5] The most widely used classification is Baveno III consensus statement,[6] according to it PHG is divided into two subgroups mild and severe. Mild PHG is defined as mosaic like pattern without redness of the areola, while severe PHG consists of mosaic-like pattern superimposed by red signs. Furthermore, the pattern of gastric antral vascular ectasia (GAVE), characterized by aggregates of red spots arranged in a linear pattern or as diffuse lesion, is generally considered a particular pattern of severe PHG.

The severity of PHG however is dynamic, with some patients improving and others deteriorating without any obvious changes noted in liver function.[3] Portal hypertension seems to be key underlying factor in development of PHG with improvement of PHG following shunt procedures reinforcing such an association.[7] However, studies have also reported that the natural history of PHG is also influenced by the severity of liver disease,[8] along with presence and size of gastro-esophageal varices, and previous variceal eradication by endoscopic variceal sclerotherapy or banding.[3]

There are reports to suggest that the esophageal varices (EV) are seen more frequently in patients with advanced cirrhosis based on different factors such as platelet count/spleen diameter ratio, right liver lobe

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diameter/albumin ratio, presence of ascites or thrombocytopenia.[9-11] However, there is insufficient regional and no local data on the frequency, characteristic of PHG and its severity in patients with viral cirrhosis.[12,13]

Therefore, the aim of this study was to determine the frequency and characteristic features of PHG in patients undergoing screening esophago-gastro-duodenoscopy (EGD) for varices due to cirrhosis of viral etiology.

METHODOLOGY

Patients with viral cirrhosis undergoing screening EGD at Aga Khan University Hospital (AKUH) were retrospectively reviewed from June 2006 to June 2008. The diagnosis of cirrhosis was established in all patients with the help of biochemical and ultrasound study of abdomen showing features of cirrhosis with shrunken liver, irregular liver margins, regenerative nodules, splenomegaly and/or dilated portal vein. Out of 360 patients only 79 underwent liver biopsies and were classified with Knodall classification to have stage IV fibrosis.

Patients with prior history of gastrointestinal bleeding secondary to varices, beta blockers use, history of porto-systemic shunt placements, co-existing illnesses or infections influencing the liver and spleen such as lymphoma, leukemia, typhoid and malaria, history of anti-viral treatment currently or in past; or who have been on NSAIDs/steroids in last 4 weeks were excluded.

The data of patients undergoing screening EGD were obtained from Information System Department (ISD) of Endoscopy Unit, AKUH, and a questionnaire was designed. The data included age, gender; etiology of cirrhosis, laboratory parameters [aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, serum albumin, prothrombin time and platelet count]. Presence of hepatitis B surface antigen (HBsAg) and hepatitis C virus (HCV) antibodies by micro enzyme immunoassay (MEIA) were checked as markers of viral hepatitis. All patients underwent an ultrasonography examination of the upper abdomen, during which the diameter of main portal vein and the size of the spleen through the hilum was obtained in the right lateral decubitus position in the coronal plane. Ultrasonographic evidence of splenic varices and ascites was also noted and the platelet count/spleen diameter ratio calculated by using laboratory and ultrasonographic values. The characteristic features studied were Child Turcotte Pugh (CTP), Model for End Stage Liver Disease (MELD) score, platelet count/spleen diameter ratio, bilirubin, albumin, AST, ALT and platelets were studied based on the laboratory and ultrasonological work-up performed within last 6 weeks.

All endoscopies were performed by the endoscopists with at least 5 years of experience, using a GIFQ 160 Gastroscope (Olympus, Tokyo, Japan) in the left lateral position after obtaining a written informed consent from the patient. The esophageal varices were divided into small or large grade (larger than 5 mm in size) according to Baveno III consensus statement.[6] Patients with large esophageal varices were started on propranolol for the primary prophylaxis and dose was titrated with heart rate in follow up clinics. Photo-documentation of endoscopic findings was performed in four standard locations of antrum, cardia, retroflexed position and 2-4 cm above gastro-esophageal junction. For identification of PHG, Baveno III consensus statement was used.[6]

The cut offs of different factors in previously reported studies for assessing the severity of cirrhosis such as platelets counts of < 150,000/cmm, platelet count/spleen diameter ratio ≤ 900, CTP score of ≥ 8 and presence of esophageal varies was used.[9-11] As the level of significance for MELD score is not well defined in literature. It was obtained with the help of receiver operator curve (ROC). The ROC curve had accuracy of 0.82 and the best cut off for MELD score was 12, with a sensitivity of 74% and a specificity of 78% (Figure 1). This study was approved by the Ethics Review Committee (ERC) of AKUH.

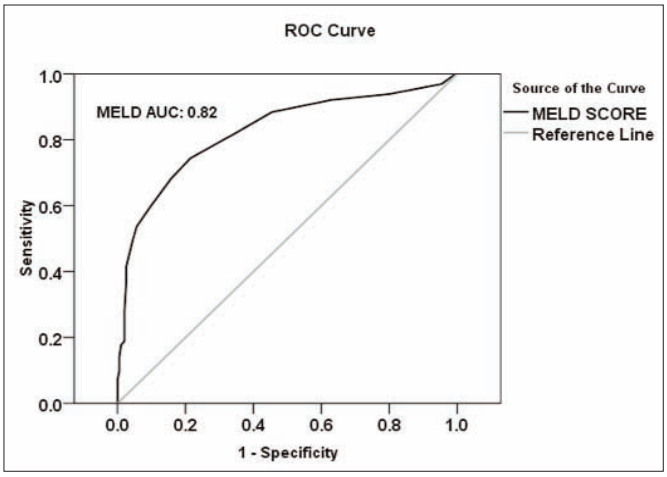

Figure 1: Receiver operating characteristics curve showing the MELD with the best sensitivity and specificity on the basis of the presence of severe portal hypertensive gastropathy. AUC, area under the curve.

Statistical analysis performed using Statistical Package for Social Science SPSS (release 17.0, standard version, copyright © SPSS; 1989-02). Descriptive analysis was performed for demographic, clinical and radiographic features and results were presented as mean ± standard deviation for quantitative variables and number (percentages) for qualitative variables.

Patients with cirrhosis were divided into two groups — those with PHG and without PHG. Chi-square test and Fisher's exact test were used for categorical variables, while independent sample t-test was applied for numerical variables. Receiver-Operating Characteristics (ROC) curve was used to determine the cut-off values of MELD score with the best sensitivity and specificity in discriminating between patients with mild and severe portal gastropathy.

Table I: Demographic, clinical, ultrasonological and endoscopic characteristics among all the study patients (n=360).

Variables	Portal gastropathy (n=300)	No portal gastropathy (n=60)	p-value
Age (years)	48.57 ± 12.47	50.07 ± 12.81	0.39
Gender			
Male	196 (65.3)	30 (50)	0.02
Female	104 (34.7)	30 (50)	
Cause of cirrhosis			
Hepatitis C	229 (76.3)	52 (86.7)	0.07
Hepatitis B	71 (23.7)	8 (13.3)	
Lab parameters			
Albumin g/dl	2.69 ± 0.66	2.99 ± 0.71	0.001
ALT (IU)	59.84 ± 45.68	57.16 ± 36	0.66
AST (IU)	73.54 ± 47.39	65.51 ± 41.75	0.22
Platelets (/cmm)	117.01 ± 55.42	166.77 ± 90.39	< 0.001
Bilirubin (mg/dl)	2.82 ± 3.0	2.0 ± 1.93	0.004
CTP score			
≤ 8	174 (58)	50 (83.3)	< 0.001
> 8	126 (42)	10 (16.7)	
MELD score			
≤ 12	139 (46.3)	57 (95)	< 0.001
> 12	161 (53.7)		
Ultrasound findings			
Portal vein diameter (cm)	1.14 ± 0.23	1.07 ± 0.18	0.02
Spleen size (cm)	14.07 ± 2.94	12.05 ± 2.38	< 0.001
Spleen hilum varices	150 (50)	18 (30)	0.005
Ascites	143 (47.7)	21 (35)	0.07
HCC	25 (8.3)	3 (5)	0.37
Platelet/spleen diameter ratio	916.08 ± 400	1476.83 ± 898.70	< 0.001
> 900	153 (51)	40 (66.7)	0.02
≤ 900	147 (49)	20 (33.3)	
Esophageal varices			
Yes	269 (89.7)	12 (20)	< 0.001
No	31 (10.3)	48 (80)	

AST= Aspartate aminotransferase; ALT=Alanine aminotransferase; CTP score= Child Turcotte Pugh score; MELD score= Model for End Stage Liver Disease score; HCC= Hepatocellular carcinoma.

Univariate analysis of the factors which were correlating the presence and severity of PHG were undertaken. Factors found to be statistically significant in univariate analysis were included in a multivariate logistic regression model. Afterwards, a stepwise selection of significant independent correlates for severity of PHG performed. All p-values were two sided and considered as statistically significant if < 0.05.

RESULTS

A total of 360 patients with viral cirrhosis who underwent screening EGD, were included in this study. The mean age was 49±12 years and there were 226 (62.8%) males. 281 patients (78%) had cirrhosis due to HCV infection, while 79 (22%) had HBV infection. There were 140 (38.9%) patients classified as Child Turcotte Pugh (CTP) class A, 125 (34.7%) and 95 (26.4%) had class B and C cirrhosis respectively.

A total 300 (83%) patients have portal hypertensive gastropathy (PHG) on endoscopic examination of whom 71 (23.6%) had severe PHG. Comparisons of clinical and laboratory parameters have shown statistically significant values of serum total bilirubin of more than 2 mg/dl (p=0.004), serum albumin of less than 3 gm/dl (p=0.001), platelets count of < 150,000 (p-value < 0.001), CTP score > 8 (p < 0.001) and MELD score > 12 (p < 0.001) among patients with PHG as compared to those without portal gastropathy (Table I).

Table II: Univariate logistic regression analysis for the prediction of severe portal hypertensive gastropathy.

	SE	Odd ratio (95% CI)	p-value
Platelets			
> 150,000/cmm	1.0		
≤ 150,000/cmm	0.24	1.78 (1.10-2.88)	0.01
Albumin			
> 3.5 grams/dl	1.0		
≤ 3.5 grams/dl	0.34	2.79 (1.43-5.44)	0.003
Bilirubin			
≤ 3 mg/dl	1.0		
> 3 mg/dl	0.25	1.26 (0.76-2.06)	0.35
PT (control of 12)			
≤ 4 seconds	1.0		
> 4 seconds	0.22	1.73 (1.12-2.67)	0.01
CTP score			
< 8	1.0		
≥ 8	0.26	7.89 (4.73-13.17)	< 0.001
MELD score			
≤ 12	1.0		
> 12	0.34	19.47 (9.85-38.48)	< 0.001
Platelets / spleen ratio			
> 900	1.0		
≤ 900	0.22	3.84 (2.48-5.96)	< 0.001
Esophageal varices			
No	1.0		
Yes	0.39	11.07 (5.13-23.87)	< 0.001

CTP score= Child Turcotte Pugh score; MELD score= Model for End Stage Liver Disease score; PT= Prothrombin time; SE= Standard error.

An increased portal vein diameter of greater than 1 cm (p=0.02), enlarged spleen size of more than 12 cm (p < 0.001) presence of splenic hilum varices (p=0.005) and presence of esophageal varices (p < 0.001) were

significant in patients with PHG as compared to without it (Table I).

On univariate analysis, platelet counts < 150,000/cmm, serum albumin < 3.5 gm/dl, prothrombin time > 4 seconds above control, CTP score > 8, MELD score > 12, platelet/spleen ratio < 900 and presence of esophageal varices were significant factors in patients with severe PHG (Table II).

Using stepwise logistic regression, CTP score > 8, MELD score > 12, platelets/spleen ratio < 900 and presence of EV were found to be independently significant factors in patients with severe PHG (Table III).

The ROC curve had accuracy of 0.82 and the best cut off for MELD score was 12 for the prediction of severe PHG, with a sensitivity of 74% and a specificity of 78% (Figure 1).

Table III: Multivariable logistic regression analysis for prediction of severe portal hypertensive gastropathy.

Variable	SE	p-value
Child score		
< 8	1.0	< 0.001
≥ 8	0.28	
MELD score		
≤ 12	1.0	< 0.001
> 12	0.27	
Platelets / spleen ratio		
> 900	1.0	< 0.001
≤ 900	0.27	
Esophageal varices		
No	1.0	< 0.001
Yes	0.45	

SE= Standard error.

DISCUSSION

This study was aimed to find the characteristic features of PHG in patients with liver cirrhosis secondary to viral etiology. The frequency of PHG in the study was found to be 83% with 24% patients having severe portal hypertensive gastropathy according to Baveno III consensus statement. This high frequency of PHG and its severity is also supported by other studies.[5,17] Current study was focused on patients with viral etiologies and excluded patients with alcohol intake, which are distributed in significant proportion in other studies.[14] By excluding the alcoholics, authors tried to have a homogenous group as the presence and severity of PHG may fluctuate according to the level of alcohol consumption.

Nearly 90% patients in present study with PHG had co-existing esophageal varices. None of these patients had prior variceal obliteration. Furthermore, on univariate and multivariate analysis the presence of esophageal varices was noted to be a predictor of the presence of severe PHG, again suggesting that portal hypertension is a common pathogenic factor in both these conditions. Esophageal varices are known to be a consequence of portal hypertension and a high number of patients with PHG have coexisting esophageal varices. Results from the HALT-C trial showed a total of 40% patients with PHG having varices compared to only 17% in subjects without PHG.[15]

Multivariate analysis identified a CTP score of > 8 and a MELD score of > 12 to be significantly associated with presence and severity of PHG in patients with cirrhosis; both these scores being reflective of severity of liver cirrhosis. In a similar study, Dong *et al.* noted that 68% of their patients with PHG had liver cirrhosis, with 27% of patients with severe PHG being classified as CTP class C and only 7% classified as class A.[13] Similarly, a recently published study by Young *et al*. demonstrated that the MELD score of 11.3±3.5 is a predictor of severe PHG.[6] This too implied an association, albeit controversial, between severity of PHG and severity of liver dysfunction.

Patients with portal hypertension have decreased platelet count and splenomegaly, with the thrombocytopenia occurring secondary to shortened platelet life span and decreased thrombopoeitin production while the enlarged spleen size was due to congestion. In a recent study by Giannini *et al*. it was shown that platelet to spleen ratio could be used as a non-invasive predictor for the presence of esophageal varices in patients with liver cirrhosis.[9] This study found the platelet to spleen ratio as another significant factor for predicting the severity of PHG.

Patients with PHG are at an increased risk of acute as well as chronic gastrointestinal bleeding,[8] although the actual incidence of this bleeding is difficult to quantify and distinguish from that due to esophageal varices. The natural history of PHG is also not very clear, and it is difficult to predict which patients will bleed secondary to PHG and will thus be requiring treatment with beta blockers. The identification of these non-invasive parameters in patients with PHG can be helpful in identifying those with the severe form of PHG. These patients may potentially benefit from medical therapy such as beta blockers without needing to frequently undergo invasive procedures such as endoscopy.

CONCLUSION

Frequency of PHG is high i.e. 83% while its severe form was encountered in 24% patients with viral cirrhosis. A MELD score > 12, CTP score ≥ 8 and spleen/platelets ratio ≤ 900 are helpful in identifying patients with severe PHG. These factors can guide in identifying patients needing early upper GI endoscopy and may benefit from treatment with non-selective beta blockers.

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