

## ***Helicobacter Pylori* Infection in Patients with HCV Related Liver Cirrhosis and Its Association with Portal Hypertensive Gastropathy Severity**

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### **ABSTRACT**

**Aim of the work:** *Helicobacter pylori* infection is a major health problem because about 50% of all humans worldwide are infected with *Helicobacter pylori*. Portal hypertensive gastropathy (PHG), a term used to describe the endoscopic appearance of gastric mucosa with a characteristic mosaic-like pattern with or without red spots is a common finding in patients with portal hypertension. The role of *H. pylori* infection on PHG severity is controversial so we try to prove if there is any role of *H. pylori* infection and severity of PHG. **Patients and methods:** eighty consecutive patients with HCV-related liver cirrhosis were enrolled in the study. Diagnosis of *H. pylori* infection was done by detection of *H. pylori* Ag in the stool by ELISA test. 80 consecutive patients with HCV-related liver cirrhosis were enrolled. Patients and Methods: all patients were subjected to an upper gastrointestinal endoscopy and ELISA test of *H. pylori* Ag in the stool. The diagnosis and the severity of portal hypertensive gastropathy (PHG) were evaluated on doing endoscopy. Child-Pugh and MELD scores were calculated to assess the severity of liver cirrhosis. **Results:** *H. pylori* infection was reported in 46 patients with overall prevalence 57.5%. PHG was found in 57 patients (71.25%); 36 (63.15%) of them had mild and 21 (36.15%) had severe PHG. *H. pylori* was more prevalent among patients with PHG than those without PHG (57.5% vs. 42.5%;  $p < 0.001$ ). No significant relation was found between *H. pylori* infection and severity of liver cirrhosis as regards Child-Pugh score ( $p = 0.383$ ) and MELD score ( $p = 0.666$ ). **Conclusion:** our results showed a significant association between *H. pylori* infection and the occurrence and also the severity of PHG in patients with HCV-related liver cirrhosis. Yet, the severity of liver cirrhosis itself did not correlate with *H. pylori* or the severity of PHG. Thus, eradication of *H. pylori* may be beneficial to ameliorate PHG.

**Keywords:** portal hypertensive gastropathy, *Helicobacter pylori*, liver cirrhosis.

### **INTRODUCTION**

Cirrhosis is a major health problem with high incidence and prevalence worldwide. It is associated with alterations in the gastrointestinal mucosa, with increased risk for peptic ulcer disease<sup>(1)</sup>. Portal hypertensive gastropathy (PHG) is one of the clinically important gastric mucosal lesions because it may cause acute or chronic gastrointestinal blood loss leading to anemia. It is characterized by endoscopic appearance of the gastric mucosa that is classically described as a mosaic-like pattern that resembles snake skin, with or without red spots<sup>(2)</sup>. Infection by *H. pylori* is highly prevalent, especially in low socioeconomic strata of developing countries<sup>(3)</sup>, being responsible for lesions like gastroduodenal erosions and ulcers. In patients with liver cirrhosis, their prevalence is controversial, as well as the existence of associations with PHG<sup>(4-6)</sup>.

### **PATIENTS and METHODS**

Eighty (80) consecutive patients with HCV-related liver cirrhosis attending the Endoscopy Unit of Ain Shams University Hospital were enrolled in the present study. This study was performed in the period between March 2015 and February 2016. An informed consent was obtained from each patient. Any patient had one

or more of the following condition was excluded from the study: patients with primary or secondary hepatic malignancy, history of gastric surgery, liver cirrhosis of any etiology other than HCV, upper GI bleeding or previous endoscopic management for portal hypertension either prophylactic or therapeutic, history of antibiotics intake (up to 1 month) or prior therapy for eradication of *H. pylori* or proton pump inhibitors or H<sub>2</sub> blockers within 4 weeks of endoscopic examination and patients on medical treatment for portal hypertension (e.g. non-selective  $\beta$  blockers, carvedilol). All patients included in this study were subjected to complete medical history taking, full clinical examination, laboratory investigations for evaluation of hepatic state and assure diagnosis of HCV infection, abdominal ultrasound performed for all patients using Toshiba real-time scanner instrument with a 3.5 MHz convex transducer for the assessment of the liver, spleen, portal vein diameter, presence of collaterals and presence or absence of ascites and its degree. The severity of liver disease was assessed using Child-Pugh classification, including total bilirubin, albumin, international normalized ratio (INR) or prothrombin time, hepatic encephalopathy, and ascites, is the most commonly used scoring system for evaluating the

prognosis of liver cirrhosis<sup>(7)</sup>. The Model for End Stage Liver Disease (MELD), which was calculated from serum bilirubin, international normalized ratio of prothrombin time and serum creatinine, offers an objective score that accurately predicts the risk of short-term mortality from chronic liver disease. (8)MELD score =  $3.8 \times \log(\text{serum bilirubin}) + 11.2 \times \log(\text{INR}) + 9.6 \times \log(\text{serum creatinine})$ . *Helicobacter pylori* Ag in the stool was done two days before endoscopic examination using ELISA test. Upper gastrointestinal endoscopy was done for all patients using (Pentax EG-3440 videoscope) to: diagnose esophageal varices and classification using Paquet score<sup>(9)</sup>. Diagnosis and severity of PHG was classified according to the criteria established by the McCormack classification<sup>(10)</sup>.

**The study was done after approval of ethical board of Ain Shams university and an informed written consent was taken from each participant in the study.**

**Statistical analysis of data:** data were fed to the computer and analyzed using IBM SPSS software package 20.0

**RESULTS**

80 patients with HCV related cirrhosis were enrolled in the study. They were 42 males

(52.5%) and 38 females (47.5%); with their age ranged from 38 to 66 years (mean age  $51.96 \pm 7.02$  years). Detection of *H. pylori* infection showed 46 patients (57.5%) were positive and 34 patients (42.5%) were negative. Endoscopic examination showed 57 patients with PHG (71.25%) and 23 without PHG (28.75%). The patients were categorized into two groups. Group with PHG and group without PHG. In-group with PHG 36 patients (63.16%) had mild PHG and 21 patients (36.84%) had sever PHG. Demographic data showed that the age was significantly higher in patients with PHG (P= 0.014). There was no significant difference between the two groups regarding sex (P=0.333)(**Table 1**). In comparison between the two groups regarding radiological investigation, all patients with PHG have splenomegaly (P<0.001), severity of ascites (P<0.001) and portal vein dilatation (P<0.001) was highly significant higher in PHG patients. Regarding endoscopic data comparison between the two groups the presence of esophageal varices was highly significant and more sever in patients with PHG (P<0.001) (**Table 2**). Presence of *H. pylori* infection was highly significant higher in PHG group (79%) versus patients without PHG (4%) and (P<0.001 )(**Table 3**). There was a significant relation between *H. pylori* infection and severity of PHG (P<sub>3</sub>=0.021) (**Table 4**).

**Table 1: comparison between patients with PHG and patients without PHG according to the demographic data.**

	Without PHG (n = 23)		With PHG (Mild/Severe) (n = 57)		Total (n = 80)		P
	No.	%	No.	%	No.	%	
<b>Sex</b>							0.333
Male	10	43.5	32	56.1	42	52.5	
Female	13	56.5	25	43.9	38	47.5	
<b>Age (years)</b>							0.014*
Min. – Max.	38.0 – 66.0		39.0 – 66.0		38.0 – 66.0		
Mean ± SD.	48.96 ± 7.64		53.18 ± 6.44		51.96 ± 7.02		
Median	49.0		54.0		53.0		

**Table 2: comparison between patients with PHG and patients without PHG according to the esophageal varices**

	Without PHG (n = 23)		With PHG (Mild/Severe) (n = 57)		Total (n = 80)		Test of sig.	p
	No.	%	No.	%	No.	%		
<b>Esophageal varices</b>							$\chi^2=57.667$ *	<0.001*
0	20	87.0	2	3.5	22	27.5		
1	2	8.7	18	31.6	20	25.0		
2	1	4.3	22	38.6	23	28.8		
3	0	0.0	15	26.3	15	18.8		
4	0	0.0	0	0.0	0	0.0		

**Table 3: relation between *H. pylori* infection and PHG**

	Without PHG (n = 23)		With PHG (Mild/Severe) (n = 57)		Total (n = 80)		$\chi^2$	P
	No.	%	No.	%	No.	%		
<b>H. Pylori</b>								
Negative	22	95.7	12	21.1	34	42.5	37.319*	<0.001*
Positive	1	4.3	45	78.9	46	57.5		

**Table 4: comparison between the severity PHG and *H. pylori***

	Without PHG (n = 23)		With PHG				Total (n = 80)		P
	No.	%	Mild (n = 36)		Severe (n = 21)		No.	%	
			No.	%	No.	%			
<b>H. pylori</b>									
Negative	22	95.7	11	30.6	1	4.8	34	42.5	<0.001*
Positive	1	4.3	25	69.4	20	95.2	46	57.5	
<b>Sig.bet. Grps</b>	p <sub>1</sub> <0.001*, p <sub>2</sub> <0.001*, p <sub>3</sub> =0.021*								

## DISCUSSION

PHG develops as a consequence of portal hypertension which leads to increase gastric blood flow and congestion of mucosal and submucosal blood vessels which leads to decreased mucous secretion and decreased local mucosal defense and the mucosa becomes susceptible to injurious agents like non steroidal anti inflammatory drugs and *H. pylori* colonization<sup>(11,12)</sup>. In our current study 80 patient with hepatitis C related liver cirrhosis were enrolled to our study. From the demographic point of view, our study showed that no difference between male and female in relation to development of PHG on the other hand the older the patient the more possibility to develop PHG in our study the age of the patients ranges from 38 years to 66 years. **Safwat *et al.***<sup>(13)</sup> in their study documented that there was a significant relation between the age of the cirrhotic patients and the development of PHG with no relation between the sex of the patients and development of PHG. Also **Merli *et al.***<sup>(14)</sup> reported that there was a cumulative incidence of PHG in cirrhotic patient.

In their study, the incidence of PHG between their patients in the first year was 3% in the second year it increase to 10% in third year the incidence become 24%. The conclusion from these studies that the incidence of PHG is higher in older cirrhotic patients. The prevalence of PHG in our study was 71%. **Cormack *et al.***<sup>(15)</sup> reported that prevalence of PHG varies greatly

from 20% to 75% in patients with portal hypertension and varies greatly from about 35% to 80% in patients with cirrhosis. These great variability likely reflects variability in classification criteria, interpretation of endoscopic lesions, study populations, and natural history of PHG<sup>(16)</sup>. In studying the relation of PHG and laboratory investigations, Anemia was higher in patients with PHG. In cases with PHG anemia develop due to blood loss, which is one of PHG presentation clinically. This upper GIT bleeding may be in the acute form or chronic blood loss is more common with PHG and presented as iron deficiency anemia<sup>(17)</sup>. In addition, other factors may contribute in anemia as hypersplenisme, cirrhosis, portal hypertension lead to gastric congestion and decrease iron absorption and superadded *H. Pylori* infection<sup>(18,19)</sup>. We found a significant decline in platelets count in PHG patients and this is in agreement with other studies. **Kim *et al.***<sup>(13)</sup> and **Safwat *et al.***<sup>(20)</sup>. The results of their studies showed that platelets count was lower in PHG patients. That is supporting the result of our study. In addition, laboratory investigations showed significant prolongation of INR in PHG, serum bilirubin was significant higher in PHG and serum albumin was significant lower in PHG. **Fontana *et al.***<sup>(21)</sup> reported that PHG was associated with the histological and biochemical severity of liver disease in patients with HCV and advanced fibrosis and the result of their study showed that in PHG the serum bilirubin was

higher, INR was prolonged and serum albumin was lower. As regard radiological examination (ultrasonography), our study showed that splenic size was significantly larger in PHG patients. **Anegawa et al.** <sup>(10)</sup> reported that PHG may be associated with splenomegaly, and laparoscopic splenectomy may have a beneficial effect on PHG, at least for a short time. Also **Fontana et al.** <sup>(21)</sup> reported that in their study there was a significant relation between splenic size and severity of PHG. **Kim et al.** <sup>(20)</sup> showed that the size of spleen become larger with increase in PHG severity. In the current study, portal vein was significantly dilated in PHG patients in comparison to those without PHG. **Zardi et al.** <sup>(22)</sup> in their study reported that the mean portal vein diameter was  $10.4 \pm 1.67$ mm in cirrhotic patients without PHG and  $11.6 \pm 2.0$ mm in cirrhotic patients with PHG ( $P = 0.0002$ ). Portal vein was more dilated in cirrhotic patients with PHG. In addition, ascites were more significant in PHG patients in comparison with patients without PHG. **Kumar et al.** <sup>(23)</sup> in their study showed a significant relation between PHG and ascites where ascites were more in cirrhotic patients with PHG. As regard, grading of esophageal varices and PHG by endoscopic examination in our current study showed that there was a significant relation between PHG and presence and size of esophageal varices. Esophageal varices were more and larger in PHG patients. This is in accordance with Abbasi et al., 2011 the result of their study showed that the grade of oesophageal varices had significant relation with PHG that was the severity of PHG increased with the grade of esophageal varices, suggesting common pathophysiology of both entities <sup>(24)</sup>. Also, **Primignani et al.** <sup>(25)</sup> showed that PHG was significant related to presence and size of esophagogastric varices and concluded that PHG is common in patients with cirrhosis, and its prevalence parallels the severity of portal hypertension. PHG can progress from mild to severe and vice versa or even disappear completely. On the other hand **Gupta et al.** <sup>(26)</sup> found no significant relation between PHG and esophageal varices alone, but there was a relation to oesophagogastric varices and they concluded that PHG is common in patients with cirrhosis and its frequency increases with the presence of oesophagogastric varices and after sclerotherapy. Also **Bellis et al.** <sup>(27)</sup> found that no significant relation between PHG and severity to esophageal varices and their size. These discrepancies because studies with negative correlation between

PHG and size of esophageal varices were on relatively small number of cases for example **Bellis et al.** <sup>(28)</sup> studied 59 patients in their study used different methods for diagnosis and classification of both PHG and esophageal varices. Splenomegaly, ascites, dilated portal veins and esophageal varices were part of both clinical and radiological manifestation of portal hypertension.

As regard, the relation between PHG and severity of liver disease our present study showed there was a significant correlation between PHG and severity of liver disease monitored by Child-Pugh score. **Merli et al.** <sup>(14)</sup> showed the presence of esophageal varices and the Child-Pugh class B or C were predictive of the incidence of PHG, while only Child-Pugh class B or C was correlated with the progression from mild to severe PHG. In addition, they concluded that the natural history of PHG is significantly affected by the severity of liver disease and severity of PH. Acute bleeding from PHG is rare but may be severe.

Also **Sarin et al.** <sup>(29)</sup> reported that prevalence of PHG in patients with Child-Pugh stage C is higher in comparison to patients with Child-Pugh stage A. **De Lisi et al.** <sup>(30)</sup> reported a significantly higher prevalence of PHG in Child-Pugh stages B or C, as compared to stage A. A minority of studies had negative relation between PHG and Child score. **Primignani et al.** <sup>(25)</sup> reported that the prevalence of severe PHG was lowest in Child-Pugh stage C. In the NIEC study, patients with Child-Pugh stage B had a higher prevalence of PHG than patients with stages A or C <sup>(22)</sup>.

**Fontana et al.** <sup>(21)</sup> reported in their study that there was a relation between PHG and biochemical markers of severity of liver disease (albumin was lower and bilirubin and PT were higher). As regard prognosis of liver disease that calculated by MELD score our study showed significant relation between PHG and MELD score. **Kim et al.** <sup>(20)</sup> reported that there was a significant relation between PHG, MELD score, and concluded that PHG was associated with portal hypertension severity and prognosis in patients with cirrhosis. On the other hand, **Zardi et al.** <sup>(22)</sup> reported that no significant relation between PHG and MELD score. In our current study, there was a significant relation between *H. pylori* infection and the occurrence of PHG where our results showed that *H. pylori* infection was positive in 57.5% in patients with PHG and *H. pylori* infection was negative in 95.7% of patients without PHG with high significant relation  $P <$

0.001). *H. pylori* infection was significant higher in patients with severe PHG (95.2%) in comparison to patients with mild PHG (69.4%). This is in accordance with **Safwat *et al.*** <sup>(25)</sup> who showed that prevalence of *H. pylori* infection was higher in patients with PHG in comparison to patients without PHG (69.2% vs. 42.9%;  $p=0.022$ ) and also *H. pylori* infection was higher in patients with severe PHG (55.6%) in comparison to patients with mild PHG (44.4%) <sup>(13)</sup>.

The conclusion of their study was a significant association between *H. pylori* infection, the occurrence, and the severity of PHG in patients with HCV-related liver cirrhosis. Moreover **Abdul Sattar *et al.*** <sup>(31)</sup> found that the presence of *H. pylori* infection was observed in 31 (44.3%) cirrhotic patients with PHG (cases) compared to 19 (27.1%) cirrhotic patients without PHG (controls). In addition, out of the 31 patients with PHG and *H. pylori* infection, 19 had severe PHG and 12 had mild PHG, while five patients had severe PHG and 34 had mild PHG in the group of *H. pylori* negative patients. They concluded that there is significant association between *H. pylori* infection and PHG in cirrhotic patients that is also related to severity of PHG. Therefore, *H. pylori* need to be eradicated in cirrhotic patients with PHG. On the other hand, there were many studies denying the relation between PHG and *H. Pylori* infection.

**Abbas *et al.*** <sup>(23)</sup> concluded that the presence of *H. pylori* infection does not affect the severity of PHG. There was a decline of virulent *H. pylori* strains and IL-10 levels in patients with advanced PHG.

**Batmanabane *et al.*** <sup>(33)</sup> concluded that Portal hypertensive gastropathy does not provide a favorable environment for the colonization of *H. pylori*. The decline in *H. pylori* positivity with the severity of PHG suggested that this bacterium was unlikely to contribute in the pathogenesis of congestive gastropathy and that hence there might be no need for its routine eradication in patients with PHG. However, the results of this study are doubtful because small number of patients enrolled in the study (37 patients).

This discrepancy in results can be explained by many causes as use of different methods in the diagnosis of *H. pylori* infection, small number of patients enrolled in this study not enough to give significant statistical results, use different score systems for diagnosis and classification of PHG, different etiology of liver cirrhosis in patients enrolled in the studies and finally inter observer variability.

## CONCLUSION

Presence of *H. pylori* infection is related to the presence and severity of PHG, but it is not related to Child Pough or MELD score in HCV related liver cirrhosis.

## RECOMMENDATIONS

We recommend eradication treatment of *H. Pylori* in all patients with PHG in HCV related cirrhosis. Further studies of possible causes of the association between *H. pylori* infection and PHG are recommended.

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