Helicobacter pylori in Egyptian patients with HCV- related liver cirrhosis and portal hypertensive gastropathy: Prevalence and relation to disease severity

Eslam Safwat[1], Hany Aly Hussein[1] and Sarah Adel Hakim[2]

Internal Medicine Department[1], Pathology Department[2], Faculty of Medicine - Ain Shams University, Cairo, Egypt
Hanyaly_79@hotmail.com

Abstract: Background and Aim: *Helicobacter pylori* (*H. pylori*) is a major human pathogen. Its role in the pathogenesis of portal hypertensive gastropathy is debated. The aim of this study was to evaluate the prevalence of this infection in patients with portal hypertension due to HCV-related liver cirrhosis, and its relation with the disease severity. **Patients and Methods**: 80 consecutive patients with HCV-related liver cirrhosis were enrolled. All patients were subjected to an upper gastrointestinal endoscopy and histopathologic testing of *H. pylori*. 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 48 patients with overall prevalence 60%. PHG was found in 52 patients (65%); 28 (53.8%) of them had mild and 24 (46.2%) had severe PHG. *H. pylori* was more prevalent among patients with than those without PHG (69.2% vs. 42.9%; *p*= 0.022). A multivariate logistic regression study showed a significant correlation between H. *pylori* infection and occurrence of PHG as an independent risk factor (OR 4.12, 95% CI: 1.191-14.252; *p*= 0.025). Out of the 36 patients with PHG and *H*. pylori infection, 20 had severe PHG (55.6%) and 16 had mild PHG (44.4%). Yet, no significant relation was found between *H. pylori* infection and severity of liver cirrhosis as regards Child-Pugh score (*p*= 0.56) and MELD score (*p*= 0.787). **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.

[Eslam Safwat, Hany Aly Hussein and Sarah Adel Hakim. ***Helicobacter pylori* in Egyptian patients with HCV-related liver cirrhosis and portal hypertensive gastropathy: Prevalence and relation to disease severity.** *Life Sci J* 2015;12(3):168-173]. (ISSN:1097-8135). http://www.lifesciencesite.com. 22

Keywords: portal hypertensive gastropathy, helicobacter pylori, liver cirrhosis

1.Introduction:

Chronic hepatitis C constitutes a major public health problem, affecting around 200 million people worldwide [1] and predisposes to liver fibrosis and end-stage liver complications [2]. Portal hypertension is responsible for many of the manifestations of liver cirrhosis [3].

Portal hypertensive gastropathy (PHG) is the change in the gastric mucosa of patients with portal hypertension, defined as the presence of mucosal friability and dilated blood vessels in the mucosal surface [4]. Endoscopically, gastric mucosa is classically described as a mosaic-like pattern that resembles snake skin, with or without red spots [5]. Histopathologic features include vascular ectasia of the mucosal and submucosal veins and capillaries [6].

The pathogenesis of PHG is not completely understood and is likely to be complicated. However, evidence suggests that portal hypertension is a key factor, where elevated portal pressure can induce changes of local hemodynamics, thus causing congestion in the stomach. These changes may then activate cytokines and growth factors, such as tumor necrosis factor alpha (TNF-α), which activate endothelial nitric oxide synthase and endothelin 1. Nitric oxide induces hyperdynamic circulation and peroxynitrite overproduction which, together with endothelin overproduction, may cause damage of gastric mucosa. When combined with the characteristics of impaired mucosal defense and healing, these factors may together produce PHG in patients with portal hypertension [7].

Helicobacter pylori (*H. pylori*) is a major etiological factor of peptic ulcer disease; which is frequently encountered in patients with liver cirrhosis [8]. Colonization of the gastric mucosa by *H. pylori* might have an indirect role in PHG as colonization is, at least theoritically, associated with inflammation. *H . pylori* virulence factors induce the production of proinflammatory cytokines such as TNF-α which affect mucosal inflammation [9].

Several investigators have evaluated the effect of *H. pylori* on liver cirrhosis and PHG with controversial results. Some reports have shown a higher seroprevalence and a synergistic effect of *H. pylori* on liver cirrhosis and PHG. However, most studies have not found any correlation between *H. pylori* and PHG [10].

Thus, knowledge of the prevalence of *H. pylori* infection in cirrhotic patients and the study of its

association with PHG could be useful for better understanding of the pathogenesis of PHG.

We performed this study to verify the prevalence of *H. pylori* infection among cirrhotic patients with PHG and to correlate the severity of liver disease and PHG with *H. pylori*.

2.Patients and methods:

A total of eighty (80) consecutive patients with HCV-related liver cirrhosis attending the Endoscopy unit of Ain Shams University hospital were enrolled in the present study. The study was performed in the period between June and December 2014, according to the ethical standards for human experimentation approved by the human reasearch committee of our institution. An informed consent was obtained from each patient.

Patients with hepatic malignancy, with a prior gastric surgery, with peptic ulcer or malignancy found in UGIE, recent acute variceal bleeding (within 2 weeks), patients on beta blockers, nitrates, nonsteroidal anti-inflammatory drugs, proton pump inhibitors; patients on antibiotics (up to 1 month) or a prior *H. pylori* eradication therapy were excluded from the study.

Baseline assessment included a thorough medical history and full clinical examination. A complete panel of laboratory studies, including complete blood count, liver and renal functions were performed for all patients. An abdominal ultrasound (Toshiba real-time scanner instrument with a 3.5 MHz convex transducer) was also done. The diagnosis of liver cirrhosis was based on clinical, biochemichal and radiological findings. HCV antibodies were detected in all patients using Microparticle Enzyme Immunoassay (AxSYM, third generation assay, Abbott Laboratories, IL, USA).

The severity of liver disease was assessed using Child-pugh classification based on patients' clinical and laboratory data (ascites, hepatic encephalopathy, serum albumin and bilirubin, and prothrombin time) and also MELD score. The MELD score was calculated according to original formula proposed by the Mayo clinic group [11], where MELD score = 3.8 × log (serum bilirubin) + 11.2 × log (INR) + 9.6 × log (serum creatinine).

Upper GI endoscopy (UGIE) was performed for all patients (Pentax EG-3440 videoscope) to verify the presence of PHG, to assess its severity and to assess the presence of oesophageal (OV) or fundal varices. Baveno classification was used to assess the severity of PHG [12, 13]. A mild mosaic pattern (mucosa is pink) was given a score of 1, whereas severe mosaic pattern (diffuse erythema of mucosa) was scored as 2. Isolated red marks were scored as 1, whereas confluent red marks were scored as 2. Absence of gastric antral vascular ectasia (GAVE) was scored as 0, whereas the presence of GAVE was scored as 2. PHG was considered to be mild when the total score was less than or equal to 3 and severe if the score was 4 or greater. OV were classified as small (small straight), medium (tortuous occupying less than 1/3 the lumen) , and large (coil shaped occupying more than 1/3 the lumen).

Biopsy specimens were taken from the gastric antrum for histopathologic examination. Paraffin embedded sections were prepared from the specimens. The specimens were routinely dewaxed and taken to water and then incubated in 2% Giemsa solution in distilled water for 30 minutes at room temperature. After rinsing in tap water the sections were quickly dehydrated through ethanol solutions before being cleared with xylene and mounted in DPX (a mixture of distyrene, a plasticizer, dissolved in toluene-xylene). Under light microscopy, curved, bent, pole-like, spiral, and fusiform bacteria were accepted as *H. pylori* (Figure 1, 2)

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (SPSS 15.0.1 for Windows; SPSS Inc.). Quantitative variables are expressed as mean and standard deviation (SD). Qualitative variables are expressed as frequencies and percents. Student t test was used to compare a continuous variable between two study groups. Chi-square and Fisher's exact test were used to examine the relationship between categorical variables. Multivariate logistic regression model was used to detect independent predictors of PHG. P value < 0.05 was considered statistically significant.

3.Results:

A total of eighty (80) adult patients with established liver cirrhosis (clinically, laboratory and radiologically) referred to the endoscopy unit at Ain Shams university hospital were enrolled in the present study. They were 52 males (65%) and 28 females (35%); with their age ranged from 39 to 68 years (mean age 54 ± 7.9 years).

According to Child Pugh classification, 8 patients were classified as Child A (10%), 44 as Child B (55%) and 28 as Child C (35%). *H. pylori* infection was reported in 48 out of 80 patients with overall prevalence 60%. On doing upper GI endoscopy, PHG was found in 52 patients (65%). Out of those 52 patients, 28 had mild PHG (53.8%) and 24 had severe PHG (46.2%).

The mean age of patients with PHG was 55.5 ± 7.8 years compared to 51.1 ± 7.3 years in those without PHG (p= 0.018). *H. pylori* infection was more prevalent among patients with PHG than those without PHG (69.2% vs. 42.9%; p= 0.022). Other clinical

characteristics and endoscopic findings of patients with and without PHG are summarized in table 1.

A multivariate logistic regression study showed a significant correlation between *H. pylori* infection and occurrence of PHG as an independent risk factor (OR 4.12, 95% CI: 1.191-14.252; *p*= 0.025).

More importantly, out of the 36 patients with PHG and *H. pylori* infection, 20 had severe PHG (55.6%) and 16 had mild PHG (44.4%). On the other hand, only 4 patients had severe PHG (25%) and 12 had mild PHG (75%) out of 16 patients who were *H. pylori* negative (*p*= 0.041). (Table 2)

Insignificant relation was found between *H. pylori* infection and severity of liver cirrhosis as regards Child-Pugh score (*p*= 0.56) and MELD score (*p*= 0.787). (Table 3)

Severe PHG (n= 28) was associated with a relatively younger age of patients than mild PHG (50 ± 6.5 vs. 60.1 ± 5.5 years; *p*= 0.0001) and also associated with male gender where all 24 patients with severe PHG were males (*p*= 0.0001). Also, smoking was another factor of severe PHG (*p*= 0.005). Yet, no association between O.V, Child-Pugh or MELD scores and the severity of PHG could be noticed ($p > 0.05$). (Table 4)

Table (1): Clinical and endoscopic characteristics of patients with and without PHG

Patient Characteristics		Patients with PHG (n= 52)	Patients without PHG (n= 28)	*P*-value
Age (years)		55.5 ± 7.8	51.1 ± 7.3	0.018
Gender	Male	32 (61.5)	20 (71.4)	0.376
	Female	20 (38.5)	8 (28.6)	
Child-Pugh score		8.5 ± 1.3	8.7 ± 1.7	0.59
MELD score		18.2 ± 6.1	17.6 ± 4.6	0.468
Oesophageal varices n (%)	No	16 (30.8)	8 (28.6)	0.961
	Small	16 (30.8)	8 (28.6)	
	Medium	8 (15.4)	4 (14.3)	
	Large	12 (23.1)	8 (28.6)	
Patients with *H. pylori* n (%)		36 (69.2)	12 (42.9)	0.022

Table (2): Relation between *H. pylori* infection and the severity of PHG

Severity of PHG	*H. pylori* +ve patients (n= 36)	*H. pylori* –ve patients (n= 16)	*P*-value
Mild PHG n (%)	16 (44.4)	12 (75)	0.041
Severe PHG n (%)	20 (55.6)	4 (25)	

Table (3): Relation between *H . pylori* infection and the severity of liver cirrhosis

Severity of liver disease	*H. pylori* +ve patients (n= 48)	*H. pylori* –ve patients (n= 32)	*P*-value
Child-Pugh score	8.6±1.7	8.5±1	0.787
MELD score	17.1±6.2	19.4±4.4	0.56

Table (4): Comparison between patients with mild and patients with severe PHG

Patient characteristics		Patients with mild PHG (n= 28)	Patients with severe PHG (n= 24)	*P*-value
Age (years)		60.1 ± 5.5	50 ± 6.5	0.0001
Gender	**Male n (%)**	8 (28.57)	24 (100)	0.0001
	Female n (%)	20 (71.43)	0 (0)	
Smoking n (%)		4 (14.29)	12 (50)	0.005
Oesophageal varices n (%)	**No**	8 (28.57)	8 (33.33)	0.803
	Small	8 (28.57)	8 (33.33)	
	Medium	4 (14.29)	4 (16.67)	
	Large	8 (28.57)	4 (16.67)	
Child-Pugh score		8.3 ± 1.4	8.7 ± 1.3	0.315
MELD score		19.7 ± 6.7	16.5 ± 5	0.052

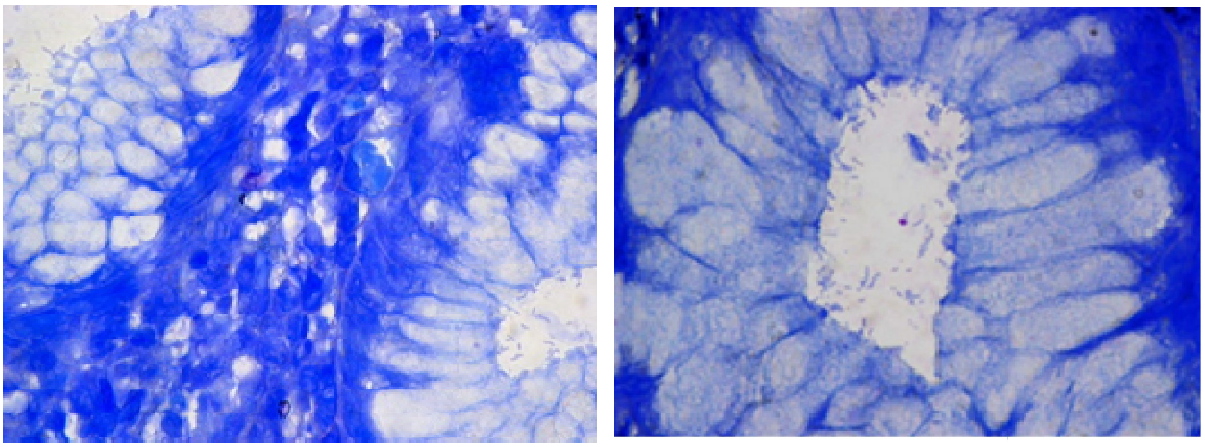

Figure (1): *H. pylori* positive case Gastric Biopsy stained with modified Gimesa showing two gasrtic glands containing the spiral shaped *H. pylori* bacteria (x100 oil imersion).
Figure (2): *H. pylori* positive case a gastric gland stained with modified Gimesa with *H. pylori* staining blue. Some are seen attached to the brush border of the gastric epithelial cell(x100 oil imersion).

4.Discussion:

Portal hypertensive gastropathy is the change in gastric mucosa in patients with portal hypertension, where mucosal friability and dilated blood vessels are present in the mucosal surface [14]. It is reported that about 10% of PHG causes anaemia due to the chronic blood loss, 2.5% of patients experienced acute bleeding, and mortality rate related to acute bleeding reaches 12.5% [15]. Regurgitant blood flow to the stomach due to portal hypertension is consdered as primary cause of PHG, however, the relationship between increased level of portal blood pressure and the severity of PHG is still questionable [16, 17].

The overall prevalence of PHG ranges between 20% and 98% in patients with liver cirrhosis [18]. In our study, the prevalence of PHG was 65%. This discrepancy may be related to patient selection, different etiologies of liver cirrhosis and interobserver variability. There may be a higher prevalence among patients with high Child-Pugh scores, patients with O.V or a history of variceal treatment [15]. In addition, in a cross-sectional descriptive study [19] Child-Pugh score > 8 and MELD score > 12 were significantly associated factors with severe PHG. However, these variables were found to be inconclusive and failed to predict the presence or severity of PHG. In the present study, we could not find any significant relation between Child-Pugh score, MELD score, the presence or the grade of O.V and the occurence or severity of PHG (p> 0.05). These findings correlate with Pan *et al*. [20] who found the development of PHG is less influenced either by the severity of cirrhosis (Child-Pugh grade) and or by the presence or non presence of gastric varices. Furthermore, Abbas *et al*. [21] could not find any correlation of Child-Pugh and MELD scores with the severity of PHG. Of interest, our study was consistent with that of Abbas *et al*. [21] in showing that male gender was more associated with the severity of PHG (p= 0.03 and 0.0001 respectively). In addition, severe PHG was also associated with a relatively younger age of patients (p=0.0001), and those who were smokers (p= 0.005).

The pathogenesis of PHG is still complex, and many controversies exist. Until now, multiple etiologic factors have been illustrated. It is thought to be a vascular disorder, and is associated by changes in splanchnic blood flow. Increased permeability of the gastric mucosa microvessels mediated by endothelin-1, involvement of prostaglandins and overexpression of nitric oxide synthase have been also implicated in mucosal changes [22]. In their study, Arafa *el al*. [23] found that each of *H. pylori* and PHG independently increased inducible nitric oxide synthase (iNOS) in gastric mucosa of cirrhotic patients. However, its role in the development of PHG is still conflicting. In our study, the overall prevalence of *H. pylori* in all patients with liver cirrhosis was 60%, a figure comparable to that of Abbas *et al*. [21] who found a prevalence of 62.1%. Yet, a lower seroprevalence (35.7%) was reported by Sathar *et al*. [22]. This discrepancy could be attributed to the different tools of *H. pylori* diagnosis as they depend on anti-*H. pylori* IgG serology.

Upon investigating the relation between *H. pylori* and PHG in cirrhotic patients, we found a higher prevalence of the infection among patients with rather than those without PHG (69.2 % vs. 42.9 %, p= 0.022), in addtion, a significant association was found between *H. pylori* and PHG as an independent risk factor (OR 4.12, 95% CI: 1.191-14.252; p= 0.025). Similarly, the recent study of Sathar *et al*. [22] showed a significant assocation between *H. pylori* and PHG (OR 2.134, 95% CI: 1.052-4.327; p= 0.034). It has

been reported [24] that *H. pylori* increase obviously in cases with portal hypertension, thus may play a role in development of PHG. On the contrary, other studies suggested that *H. pylori* infection was unlikely to contribute in the pathogenesis of PHG [25, 26]. The socioeconomic status of the studied patients may have an impact on this difference. In addition, it has been postulated that PHG does not provide an adequate environment for *H. pylori* colonization and, therefore, this organism does not add significantly to the occurrence of PHG [27].

Moreover, in the current study, out of the 36 patients with PHG and *H. pylori* infection, 20 (55.6%) had severe PHG, while only 4 (25%) out of 16 *H. pylori* negative patients had severe PHG (p= 0.041), reflecting a significant relation between the infection and severity of PHG. While other studies showed no correlation with PHG severity [20, 21, 28], our results were similar to Sathar *et al*. [22] who noticed a significant relation between *H. pylori* and severity of PHG (p< 0.001). In another study [29], *H. pylori* was supposed to be one of factors important for regulation of gastric mucosal capillary network function and structure i.e. morphometric changes of gastric mucosa.

In view of the association between *H. pylori* and the severity of liver cirrhosis, several investigators have evidenced no relation with the advancement of liver disease [30-32]. Moreover, Kim *et al*. [31] noticed that the prevalence of *H. pylori* infection declines as the Child-Pugh score increases (p< 0.001). Similarly, in our study, no significant correlation was found between *H. pylori* and the degree of severity of liver cirrhosis regarding both Child-Pugh and MELD scores (p> 0.05). On the contrary, El-Masry *et al*. [33] revealed that the prevalence of *H. pylori* infection in HCV-infected patients was increased very significantly (p= 0.003) with increasing MELD and also Child-Pugh score (p= 0.04).

To conclude, our results reflect 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, whether eradication therapy is beneficial or not in patients with PHG has to be explored in the future studies.

References:

1. Lavanchy D. The global burden of hepatitis C. Liver Int. 2009; 29 suppl 1: 74-81.
2. Sebastiani G, Gkouvatsos K, Pantopoulos K. Chronic hepatitis C and liver fibrosis. World J Gastroenterol. 2014; 20(32):11033-53.
3. Al-Busafi SA, McNabb-Baltar J, Farag A, Hilzenrat N. Clinical manifestations of portal hypertension. Int J Hepatol. 2012; 2012:203794. Epub 2012 Sep 17.
4. Chung WJ. Management of portal hypertensive gastropathy and other bleeding. Clin Mol Hepatol. 2014; 20(1):1-5.
5. Thuluvath P, Yoo H. Portal hypertensive gastropathy. Am J Gastroenterol. 2002; 97(12): 2973-8.
6. Cubillas R, Rockey DC. Portal hypertensive gastropathy: a review. Liver Int. 2010; 30(8): 1094-102.
7. Ohta M, Yamaguchi S, Gotoh N, Tomikawa M. Pathogenesis of portal hypertensive gastropathy: a clinical and experimental review. Surgery. 2002; 131(1 Suppl): S165-70.
8. Dore MP, Mura D, Deledda S, Maragkoudakis E, Pironti A, Realdi G. Active peptic ulcer disease in patients with hepatitis C virus-related cirrhosis: The role of *Helicobacter pylori* infection and portal hypertensive gastropathy. Can J Gastroenterol. 2004; 18(8): 521-4.
9. Patel MK, Trombly MI, Kurt-Jones EA. Innate immune responses to *Helicobacter pylori* infection: An overview. Methods Mol Biol. 2012; 921: 205-7.
10. Al Mofleh IA. Does *Helicobacter pylori* affect portal hypertensive gastropathy?. Saudi J Gastroenterol. 2007 Apr-Jun; 13(2): 95-7.
11. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001; 33(2):464-70.
12. De Franchis R. Evolving Consensus in Portal Hypertension Report of the Baveno IV Consensus Workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol. 2005; 43(1): 167-76.
13. Stewart CA, Sanyal AJ. Grading portal gastropathy: Validation of a gastropathy scoring system. Am J Gastroenterol. 2003; 98(8): 1758-65.
14. Chung WJ. Management of portal hypertensive gastropathy and other bleeding. Clin Mol Hepatol. 2014; 20(1): 1-5.
15. Primignani M, Carpinelli L, Preatoni P, Battaglia G, Carta A, Prada A, Cestari R, Angeli P, Gatta A, Rossi A, Spinzi G, De Franchis R. Natural history of portal hypertensive gastropathy in patients with liver cirrhosis. The New Italian Endoscopic Club for the study and treatment of esophageal varices (NIEC). Gastroenterology. 2000; 119(1): 181-7.
16. Ripoll C, Garcia-Tsao G. Management of gastropathy and gastric vascular ectasia in portal

hypertension. Clin Liver Dis. 2010; 14(2): 281-95.
17. Perini RF, Camara PR, Ferraz JG. Pathogenesis of portal hypertensive gastropathy: translating basic research into clinical practice. Nat Clin Pract Gastroenterol Hepatol. 2009; 6(3): 150-8.
18. Thuluvath P, Yoo H, portal hypertensive gastropathy. Am J Gastroenterol. 2002; 97: 2973-8.
19. Ahmed S, Mumtaz K, Ahmed US, Shah HA, Abid S, Hamid S, Jafri W. Frequency and characteristic features of portal hypertensive gastropathy in patients with viral cirrhosis. J Coll Physicians Surg Pak. 2010; 20(11):714-8.
20. Pan WD, Xun RY, Chen YM. Correlations of portal hypertensive gastropathy of hepatitis B cirrhosis with other factors. Hepatobiliary Pancreat Dis Int. 2002; 1(4):527-31.
21. Abbas Z, Yakoob J, Usman MW, Shakir T, Hamid S, Jafri W. Effect of *Helicobacter pylori* and its virulence factors on portal hypertensive gastropathy and interleukin (IL)-8, IL-10, and tumor necrosis factor-alpha levels. Saudi J Gastroenterol. 2014; 20(2): 120-7.
22. Sathar SA, Kunnathuparambil SG, Sreesh S, Narayanan P, Vinayakumar KR. Helicobacter pylori infection in patients with liver cirrhosis: prevalence and association with portal hypertensive gastropathy. Ann Gastroenterol. 2014; 27(1): 48-52.
23. Arafa UA, Fujiwara Y, Higuchi K, Shiba M, Uchida T, Watanabe T, Tominaga K, Oshitani N, Matsumoto T, Arakawa T. No additive effect between Helicobacter pylori infection and portal hypertensive gastropathy on inducible nitric oxide synthase expression in gastric mucosa of cirrhotic patients. Dig Dis Sci. 2003; 48(1): 162-8.
24. Xu HZ, Zhang HW, Jiang QF *et al.* study on the relationship between helicobacter pylori and portal hypertensive gastropathy. Chin J Exp Surg. 1998; 15: 34-5.
25. Balan KK, Jones AT, Roberts NB, Pearson JP, Critchley M, Jenkins SA. The effects of *Helicobacter pylori* colonization on gastric function and the incidence of portal hypertensive gastropathy in patients with cirrhosis of the liver. Am J Gastroenterol. 1996; 91(7): 1400-6.
26. Urso G, Interlandi D, Puglisi M, Abate G, Bertino G, Raciti C, Sciacca C, Bruno M, Panarello A, Di Prima P, La Rosa G. Role of *Helicobacter pylori* in patients with portal hypertensive gastropathy by liver cirrhosis hepatitis C virus-related. Minerva Gastroenterol Dietol. 2006; 52(3): 303-8.
27. Batmanabane V, Kate V, Ananthakrishnan N. Prevalence of *Helicobacter pylori* in patients with portal hypertensive gastropathy-a study from South India. Med Sci Monit. 2004; 10(4):CR133-6.
28. Parikh SS, Desai SB, Prabhu SR, Trivedi MH, Shankaran K, Bhukhanwala FA, Kalro RH, Desai HG. Congestive gastropathy: factors influencing development, endoscopic features, helicobacter pylori infection and microvessel changes. Am J Gastroenterol. 1994; 89(7): 1036-42.
29. Kovaleva OI, Khomeriki SG, Zhukov AG, Koviazina IO, Golovanova EV. Capillary collusion of gastric mucosa in patients with *Helicobacter pylori* gastritis and portal hypertension. Eksp Klin Gastroenterol. 2010; 2: 13-8.
30. Calvet X, Navarro M, Gil M, Mas P, Rivero E, Sanfeliu I, Brullet E, Campo R, Dalmau B, Lafont A. Seroprevalence and epidemiology of *Helicobacter pylori* infection in patients with cirrhosis. J Hepatol. 1997; 26(6):1249-54.
31. Kim DJ, Kim HY, Kim SJ, Hahn TH, Jang MK, Baik GH, Kim JB, Park SH, Lee MS, Park CK. *Helicobacter pylori* infection and peptic ulcer disease in patients with liver cirrhosis. Korean J Intern Med. 2008; 23(1):16-21.
32. Chen CT, Wang TF, Chan CC, Lee FY, Chang FY, Lin HC, Hou MC, Lu RH, Chu CJ, Wang SS, Lee SD. Role of chronic *Helicobacter pylori* infection in hyperdynamic circulation of cirrhotic patients. Hepatogastroenterology. 2002; 49(43):208-12.
33. El-Masry S, El-Shahat M, Badra G, Aboel-Nour MF, Lotfy M. *Helicobacter pylori* and Hepatitis C Virus Coinfection in Egyptian Patients. J Glob Infect Dis. 2010; 2(1):4-9.

3/11/2015