Association between Severity of Liver Disease, Frequency of *Helicobacter pylori* Infection, and Degree of Gastric Lesion in Egyptian Patients with Hepatitis B Virus Infection

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Abstract. The relationship between hepatitis B virus (HBV) infection, severity of liver disease, frequency of *Helicobacter pylori* infection, and degree of gastric lesions was not yet fully investigated in Egyptian patients. The present work was performed on 100 Egyptian patients with HBV from the National Hepatology and Tropical Medicine Institute and 70 healthy volunteers as control group. The participants were subjected to full medical history taking, clinical examination, and laboratory investigations. All patients were positive for HBV surface antigen (HBV sAg), HBV DNA, and negative for hepatitis C virus antibodies. The severity of the liver disease was assessed using Child–Pugh scoring system. Screening of all participants for *H. pylori* Ag in stool was performed. Biopsy specimens were taken from the gastric lesions of *H. pylori*-infected patients for histopathological examination. The mean age of the patients and control group were 34.9 and 33.4 years, respectively. The levels of the liver enzymes were statistically higher in HBV patients than the control group. *Helicobacter pylori* Ag in stool was detected in 45.7% of the control group, and a higher percentage (60%) was detected in the patients group. Chronic gastritis with glandular atrophy and metaplasia was found in 15.6% of patients of Child–Pugh A, 70% of Child–Pugh B, and 100% of Child–Pugh C. It could be concluded that the prognosis of the liver disease significantly influences the severity of the gastric pathology in *H. pylori* infection.

INTRODUCTION

Hepatitis B virus (HBV) infection is a major global health problem with estimated 350–400 million people are chronic HBV surface antigen (sAg) carriers.¹ HBV infection is quite prevalent in Egypt, with 16.6% of blood donors were positive for total anti-HBV core antibodies (Ab) in a cross-sectional study.² While HBV sAg prevalence in the general Egyptian population was reported to be varying from 1.3% to 6.7%³ and a higher prevalence (8–11.7%) was reported in an earlier study.⁴ HBV infection was proven to be the main cause of liver disease with 25–30% of infected patients eventually developing liver cirrhosis.^{5,6} The prevalence of HBV is 25.9% in Egyptian hepatic malignancies.⁷ However, the factors that affect the development of hepatocellular carcinoma in HBV-related cirrhosis are poorly understood. One of the mechanisms of malignant transformation of human cells is chronic infection that leads to chronic inflammation. This is followed by the release of inflammatory mediators, free oxygen radicals, and tumor neovascularization agents. These factors produce local and remote mutagenic effects.⁸ The pathological history of cirrhotic patients includes several gastric complications, such as gastroduodenal erosion, peptic ulcers, upper gastrointestinal hemorrhage⁹, and *Helicobacter pylori* infection.¹⁰

Helicobacter pylori is one of the principle carcinogenic agents that accounts for 5.5% of all cancers. The International Agency for Research on Cancer in 1994 classified *H. pylori* as a type I carcinogenic element.¹¹ Several studies examined *H. pylori* infection and gastric endoscopic lesions in cirrhotic patients. They found *H. pylori* in 60% and 60.7% of the

patients,^{12,13} respectively. *Helicobacter pylori* virulence factors induce the production of proinflammatory cytokines, for example, TNF- α which can mediate inflammation of the gastric mucosa.¹⁴ Several studies investigated the effect of *H. pylori* on liver cirrhosis and portal hypertensive gastropathy (PHG). They detected a high seroprevalence and synergistic effect of *H. pylori* on liver cirrhosis and PHG, suggesting that eradication of *H. pylori* would be beneficial in the treatment of liver cirrhosis.^{15–17} High prevalence of *H. pylori* infection was detected in the Egyptian population. A total of 148 (88%) of clinically healthy pregnant women allowed to receive prenatal care at a Maternal and Child Health Care center in Alexandria, Egypt, were found seropositive for *H. pylori* IgG.¹⁸ *Helicobacter pylori* was detected in 72.38% among 286 of Egyptian school children in a cross-sectional population-based study¹⁹ and in 68% of a group of Egyptian women with primary fibromyalgia.²⁰ Several studies investigated the association between the prevalence of *H. pylori* infection in Egyptian patients and hepatitis C virus (HCV)-related hepatic cirrhosis.^{12,21–23} However, *H. pylori* infection and its effects on gastric mucosa in Egyptians with HBV-related liver cirrhosis have not yet been fully investigated. Therefore, this study was undertaken to be the pioneer reference which determines the prevalence of *H. pylori* infection and the degree of gastric lesions in Egyptian patients with HBV in association with the severity of liver disease.

MATERIALS AND METHODS

Participants. This case control study was conducted on 100 HBV Egyptian patients attending the outpatient clinic at the National Hepatology and Tropical Medicine Institute in Cairo, Egypt. In addition, 70 healthy volunteers were recruited from the blood donor clientele and included as control group. The age of all participants ranged from 20 to 40 years.

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Informed written consent was obtained from all participants before the study, and confidentiality of collected data was guaranteed. The research has been approved from the institutional review board of the National Hepatology and Tropical Medicine Institute and from the Research Ethics Committee, Faculty of Medicine, Cairo University.

All participants subjected to full medical history taking, clinical examination, and laboratory investigations, including

complete blood picture, fasting blood sugar, total bilirubin, direct bilirubin, serum albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamate (GGT), and serum creatinine, were assayed using Beckman CX4 chemistry analyzer (NY) supplied by (Eastern Co. for Eng. & Trade- Giza, Egypt). HBV sAg was detected by ELISA (DiaSorin Kit, Dartford, United Kingdom). Real time polymerase chain reaction was performed for detection

FIGURE 1. Photomicrographs of gastric biopsies of *Helicobacter pylori* positive cases showing: (A, B) The curved spiral-shaped *Helicobacter pylori* bacteria in the lumen of the gastric gland (arrows). (C) Some of them appeared attached to the brush border of the gastric epithelial cells (H). (D) Two reactive lymphoid follicles with germinal centers (arrows). The lamina propria is diffusely infiltrated with dense inflammatory cells (I). (E) Infiltration of the lamina propria by red eosinophils (E) and lymphocytes (L). Atrophy of the gastric glands is seen (short arrows). (F) The epithelial lining of the gastric glands is infiltrated by neutrophils (N) and red eosinophils (E). (G, H) Intestinal metaplasia (arrows) with goblet cells (G) scattered in the gastric glands. (H is higher magnification of G). (A–C: Modified Giemsa stain $\times 600$), (D: Hematoxylin and Eosin (H&E) $\times 200$; E, F: H&E $\times 400$), (G: H&E $\times 200$; H: H&E $\times 400$). This figure appears in color at www.ajtmh.org.

TABLE 1

The mean and standard deviation of the age and sex of the control group (hepatitis B virus (HBV) negative) and the patient group (HBV positive)

	HBV negative (control group) Mean $\pm$ SD (%)	HBV positive (patients group) Mean $\pm$ SD (%)	P value
Age	33.43 $\pm$ 7.64	34.93 $\pm$ 10.69	> 0.05
Sex	44 males (62.8%)	60 males 60%	> 0.05

of HBV DNA (Stratagene, La Jolla, CA). Sera of all participants were screened for anti-HCV Ab by ELISA, using third generation kits (DiaSorin, Crescentino, Italy) according to the manufacturer's instructions.²³ All patients included were strictly positive for HBV sAg, HBV DNA, and negative hepatitis C virus antibodies (HCV Ab). All the involved healthy controls were negative for HBV sAg, HBV DNA, and HCV Ab.

Assessment of the severity of the liver disease. Abdominal ultrasound was performed for all patients. The severity of liver disease was performed using Child-Pugh scoring system.²⁴

Detection of *H. pylori* antigen in stool. All participants were screened for *H. pylori* infection by detecting the presence of *H. pylori* Ag in the stool using a commercial sandwich ELISA assay (*H. pylori* Antigen ELISA Kit, Immundiagnostik, Bensheim, Germany).

All participants were classified according to HBV and *H. pylori* infection into four groups:

1. Group A (HBV negative/*H. pylori* negative)
2. Group B (HBV negative/*H. pylori* positive)
3. Group C (HBV positive/*H. pylori* negative)
4. Group D (HBV positive/*H. pylori* positive)

Histopathology. For histopathological examination, biopsy specimens were taken from the gastric antrum of *H. pylori*-infected HBV patient. Specimens were rapidly fixed in 10% formal saline solution, processed, embedded to obtain paraffin blocks, and cut at 5–6 μ m thickness sections. Sections were subjected to routine Hematoxylin and Eosin stain for identification of gastric lesions. In addition, specimens were stained with modified Giemsa stain for the detection of *H. pylori*. Specimens were incubated in 2% Giemsa solution in distilled water for 30 minutes at room temperature. Then, the sections were quickly dehydrated through ethanol solutions after rinsing in tap water. The sections were cleared with xylene and mounted in distyrene plasticizer xylene (a mixture of distyrene, a plasticizer, dissolved in toluene-xylene).¹² Under light microscope, *H. pylori* appeared as curved, coiled, and spiral bacteria in the lumen of the gastric glands. In some

TABLE 3

Prevalence of *Helicobacter pylori* infection in the control group (hepatitis B virus (HBV) negative) and the patient group (HBV positive)

<i>H. pylori</i> antigens in the stool	HBV negative (control group) N = 70	HBV positive (patients group) N = 100
Positive	32 (45.7%)	60 (60%)
Negative	38 (54.3%)	40 (40%)

cases, they were attached to the brush border of the gastric epithelial cells (Figure 1A–C).

Statistics. Data were statistically described in terms of mean $\pm$ SD, median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was performed using Student *t* test for independent samples. For comparing *H. pylori*, chi-square (χ^2) test was performed. *P* value < 0.05 was considered statistically significant. Analysis of variance (ANOVA) was performed to compare the liver enzymes between the four possibilities of HBV and *H. pylori* infection positivity, followed by *post hoc* analysis using least significant difference (LSD) test to perform pairwise comparison of means of quantitative variable obtained from the four groups. Linear regression analysis models were used to test the association between the liver enzymes and *H. pylori* infection within HBV-infected group. Logistic regression analysis was used to test for the association between Child-Pugh score and *H. pylori* infection. Correlation between Child Pugh score and pathology grade was performed using chi-square (χ^2) test. All statistical calculations were performed using computer program Statistical Package for the Social Science (SPSS Inc., Chicago, IL) release 15 for Microsoft Windows (2006).²⁵

RESULTS

The mean and standard deviation of the age among the control group and the HBV patients group were 33.43 $\pm$ 7.64 and 34.93 $\pm$ 10.69, respectively, with no statistical difference between both groups. Forty-four (62.8%) of the control group and 60 (60%) of the patient group were male with no statistical difference between both groups. Table 1 summarizes the main demographic characteristics of all participants. The results of the total bilirubin, ALT, AST, ALP, and GGT were found to be significantly higher in patients group (Table 2). *Helicobacter pylori* antigen in the stool were detected in 32 (45.7%) of the control group (HBV negative) and in 60 (60%) of the patients group (HBV positive) (Table 3).

Comparison between the levels of the liver enzymes of the four studied groups was performed using a one-way ANOVA

TABLE 2

The mean and standard deviation of the biochemical tests of the control group (hepatitis B virus (HBV) negative) and the patient group (HBV positive)

Biochemical test	HBV negative (control group) Mean $\pm$ SD	HBV positive (patients group) Mean $\pm$ SD	P value
Fasting blood sugar	90.5 $\pm$ 14.32	96 $\pm$ 16.81	> 0.05
Total bilirubin	0.6 $\pm$ 0.3	1.8 $\pm$ 0.6	< 0.05
Alanine aminotransferase	25.8 $\pm$ 4.7	67.4 $\pm$ 12.3	< 0.05
Aspartate aminotransferase	28.6 $\pm$ 8.9	60.6 $\pm$ 19.6	< 0.05
Alkaline phosphatase	56.8 $\pm$ 36.45	197 $\pm$ 54.26	< 0.05
Albumin	3.8 $\pm$ 0.3	3.2 $\pm$ 0.6	> 0.05
Gamma glutamate	36.62 $\pm$ 12.4	71.06 $\pm$ 17.08	< 0.05
Serum creatinine	0.97 $\pm$ 0.136	0.99 $\pm$ 0.127	> 0.05
Prothrombin concentration	72.1% $\pm$ 3.2	68.3% $\pm$ 5	> 0.05

^a *P* < 0.05 is statistically significant compared with the control group.

TABLE 4

Comparison between the liver enzyme levels among the four studied groups using one-way analysis of variance (ANOVA) followed by post hoc analysis using the LSD test

		HBV -ve, <i>Helicobacter pylori</i> -ve	HBV -ve, <i>H. pylori</i> +ve	HBV +ve, <i>H. pylori</i> -ve	HBV +ve, <i>H. pylori</i> +ve	One-way ANOVA	
		Group A	Group B	Group C	Group D	F	P value
Alanine aminotransferase	Mean $\pm$ SD	25.82 $\pm$ 6.85	25.94 $\pm$ 5.58	73.68 $\pm$ 26.18	63.03 $\pm$ 21.16	66.831	0.000
	Range	11–41	17–36	36–120	23–120		
Aspartate aminotransferase	Mean $\pm$ SD	29.89 $\pm$ 8.14	27.03 $\pm$ 4.77	62.00 $\pm$ 22.56	59.70 $\pm$ 28.47	33.230	0.000
	Range	12–58	19–38	40–180	20–180		
Alkaline phosphatase	Mean $\pm$ SD	57.71 $\pm$ 7.72	55.75 $\pm$ 8.78	181.15 $\pm$ 34.00	207.62 $\pm$ 46.57	257.432	0.000
	Range	40–70	40–70	121–280	125–320		
Gamma glutamate	Mean $\pm$ SD	35.95 $\pm$ 10.43	35.53 $\pm$ 10.70	55.97 $\pm$ 19.81	52.68 $\pm$ 20.76	15.928	0.000
	Range	24–59	24–59	15–80	15–105		
Post hoc analysis using LSD test							
Parameters	A vs. B	A vs. C	A vs. D	B vs. C	B vs. D	C vs. D	
ALT	0.979	0.000	0.000	0.000	0.000	0.018	
AST	0.564	0.000	0.000	0.000	0.000	0.586	
ALP	0.803	0.000	0.000	0.000	0.000	0.000	
GGT	0.919	0.000	0.000	0.000	0.000	0.349	

followed by post hoc analysis using the LSD test. It revealed a significant increase in all liver enzymes in groups C and D more than groups A and B. A statistically significant higher level of ALP was detected in group D more than group C. No significant difference was detected between groups A and B (Table 4).

Multiple linear regression with liver enzyme levels was performed to assess the association between the liver prognosis and *H. pylori* infection between groups C and D. It revealed, also, a statistically higher level of ALP in group D more than group C. However, a higher level of ALT was detected in group C more than group D, and no significant difference between both groups regarding AST and GGT was found (Table 5).

According to Child–Pugh score classification, 60 (60%) patients were classified as Child–Pugh A, 32 (32%) as Child–Pugh B, and 8 (8%) as Child–Pugh C (Table 6). *Helicobacter pylori* infection was detected in 45 (75%) patients of Child–Pugh A, in 10 (31.25%) patients of Child–Pugh B, and in 5 (62.5%) patients of Child–Pugh C (Table 7). Logistic regression analysis revealed no effect of *H. pylori* infection on the liver prognosis. However, a significant lower frequency of *H. pylori* infection was detected with poor liver prognosis by Child–Pugh score (Table 8).

Variable pathological changes were found in the gastric mucosa of *H. pylori* positive patients among the three classes of Child–Pugh classification. Chronic gastritis without glandular atrophy or metaplasia was reported in 38 (84.4%) patients of Child–Pugh A, 3 (30%) of Child–Pugh B, and was not found in Child–Pugh C. Reactive lymphoid follicles with

germinal centers indicating marked intensity of the inflammation were found in the gastric mucosa. Dense inflammatory cells diffusely infiltrating the lamina propria (Figure 1D). A significant correlation between the degree of the pathological findings in the gastric mucosa and the prognosis of the liver disease was detected using Child–Pugh score. Chronic gastritis with glandular atrophy and metaplasia was found in 7 (15.6%) patients of Child–Pugh A, in 7 (70%) patients of Child–Pugh B, and in 5 (100%) patients of Child–Pugh C (Table 9). The gastric mucosa was found infiltrated with inflammatory cells, lymphocytes, and red eosinophils with atrophy of the gastric mucosa (Figure 1E). The epithelial lining of the gastric glands is infiltrated by polymorphonuclear leukocytes, neutrophils, and red eosinophils indicating chronic active gastritis (Figure 1F). Intestinal metaplasia with goblet cells was seen scattered in the gastric glands (Figure 1G, H).

DISCUSSION

The present study was conducted to determine the prevalence of *H. pylori* infection and the degree of gastric lesions in Egyptian patients with HBV infection in association with the severity of the liver disease. The patients of our study were young (ranging from 20 to 40 years of age with a mean of 34.93 $\pm$ 10.69) which could be explained by the early exposure to HBV infection during dental procedures or surgical operations. While the volunteers in the control group of our study were also young (the same range as the patients group with a mean of 33.43 $\pm$ 7.64), as this is a common age for blood donation. A total of 60% and 62.8% of the patients and the control groups were males, respectively. These results are in partial agreement with a study conducted on 60 Egyptian HCV positive patients, their age ranged between 40 and 50 years

TABLE 5

Linear regression analysis of hepatitis B virus patients for testing the association between *Helicobacter pylori* infection and the levels of liver enzymes

Predictor	Dependant variable	Unstandardized coefficients		Standardized coefficients β
		B	Standard Error	
<i>H. pylori</i>	ALT	–0.694	5.030	–0.014 (S)
	AST	7.665	5.291	0.145 (NS)
	ALP	4.350	8.938	0.049 (S)
	GGT	–7.070	4.112	–0.172 (NS)

TABLE 6

Child–Pugh classification of hepatitis B virus positive patients (Patients group)

Child–Pugh classification	N = 100
Class A	60 (60%)
Class B	32 (32%)
Class C	8 (8%)

TABLE 7

Correlation between Child–Pugh classification in hepatitis B virus patients and *Helicobacter pylori* infection

Child–Pugh classification	<i>H. pylori</i> positive	<i>H. pylori</i> negative	Total
Class A	45 (75%)	15 (25%)	60
Class B	10 (31.25%)	22 (68.75%)	32
Class C	5 (62.5%)	3 (37.5%)	8
Total	60	40	100

and 75% of them were males.²⁶ In the current study, the differences between the results of the biochemical tests of the control group and the HBV positive patients group were statistically insignificant except for the liver function tests, total bilirubin, ALT, AST, ALP, and GGT, which were found to be significantly higher in the patients group as a result of HBV infection and liver dysfunction.

Helicobacter pylori antigen in the stool was detected, in the present study, in 45.7% of the control group and in a higher percentage (60%) in the patients group. Several studies detected a similar high association between the frequency of *H. pylori* infection and liver cirrhosis.^{27–29} A Chinese study found a higher prevalence (72%) of *H. pylori* in Chinese HBV patients than in the control group (39%).³⁰ However, in the present study, strong association could not be detected between the prognosis of the liver condition and *H. pylori* infection, except in the level of ALP. The significant increase in the level of ALP in HBV patients with *H. pylori* infection (group D) more than HBV patients without *H. pylori* infection (group C) could be explained by the hypothesis that *H. pylori* can affect the integrity of the cell membrane structure of the gall bladder epithelial cells containing ALP. This effect enhances cell disruption and cell damage resulting in ALP enzyme leakage. It could be suggested, from these results, that *H. pylori* can reach the gall bladder and affect the vitality of its epithelium. These findings are in agreement with the results of a cross-sectional study conducted to detect the relationship between *H. pylori* infection and hepatic encephalopathy in cirrhotic patients. The authors detected a high frequency of *H. pylori* infection among patients with hepatic encephalopathy, although there was no significant improvement in the liver parameters and the level of hepatic encephalopathy after *H. pylori* eradication therapy.²⁸ Similarly, another study concluded that there was no correlation between *H. pylori* infection and the clinical course of HCV.²³ By contrast, the results of other studies indicated a strong association between *H. pylori* and chronic hepatitis B infection during HBV progression.^{29,31,32}

In the present study, an association between the severity of the gastric lesion and that of the liver disease according to Child–Pugh classification was recorded. In class A patients, the gastric mucosa showed mainly signs of chronic gastritis,

TABLE 8

Logistic regression analysis for Child–Pugh score for prediction of *Helicobacter pylori* infection

	B	SE	P value	Odds ratio (OR)	95% confidence interval for OR	
					Lower	Upper
Child–Pugh	–0.915	0.339	0.007	0.401	0.206	0.778

whereas in class C patients, glandular atrophy and intestinal metaplasia were detected in 100% of the patients within this group. This could be explained by the fact that hemorrhagic congestion and edema of gastric mucosa because of chronic portal hypertension in HBV patients provide a suitable environment for the colonization of *H. pylori*. In addition, chronic portal hypertension induces the production of high reactive oxygen species resulting from increased nitric oxide synthase expression and disruption of gastric mucosal immunity.³¹

In *H. pylori* infection, the gastric glands were damaged frequently and could not be replaced by the corresponding cells but by proliferated intestinal cells showing intestinal metaplasia, as shown in the present study, found in the gastric biopsies of 70% and 100% of Child–Pugh score B and C, respectively, indicating the significant association between the severity of the gastric lesions on top of *H. pylori* infection and the prognosis of the liver disease in HBV-infected Egyptians.

In conclusion, the present study indicated an association between the frequency of *H. pylori* and HBV infection in Egyptian patients. The prognosis of the liver disease significantly influences the severity of the gastric pathology in *H. pylori* infection. However, the prognosis of the liver condition in HBV patients could not be proved to be affected by *H. pylori* infection. Further studies are recommended to confirm the influence of *H. pylori* infection on the liver condition in HBV patients.

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TABLE 9

Correlation between the degree of gastric pathology and the prognosis of the liver disease

Pathological findings of the gastric mucosa	Child A		Child B		Child C		Chi-square test	
	No.	%	No.	%	No.	%	X ²	P value
Gastritis without glandular atrophy or metaplasia	38	84.4%	3	30.0%	0	0.0%	22.978	0.000
Gastritis with glandular atrophy and metaplasia	7	15.6%	7	70.0%	5	100.0%		

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