Prevalence and Risk Factors of Helicobacter Pylori Recurrence in Egyptian Patients with Liver Cirrhosis

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ABSTRACT

Background: Helicobacter pylori (H. pylori) is a worldwide gastrointestinal infection. It is a common risk factor for peptic ulcer disease (PUD), chronic gastritis, and stomach cancer. In patients with cirrhosis, there is a significant association between H. pylori infection and severity of gastropathy due to portal hypertension, chronic stomach upset, frequent upper gastrointestinal bleeding as well as hepatic encephalopathy.

Objective: To assess the rate and risk factors of recurrence of H. pylori infection in Egyptian patients with liver cirrhosis after successful eradication therapy. **Patients and methods:** This study included 500 liver cirrhosis patients who were tested for H. pylori infection. Patients with positive H. pylori infection received proton pump inhibitors (PPI)-based treatment regimen. Successful eradication therapy was assessed 4-8 weeks and repeated over one year after end of treatment using urea breath test (UBT) and stool antigen test (SAT).

Results: The prevalence of H. pylori infection in cirrhotic patients was 58%. There were significantly higher serum levels of ammonia and C-reactive protein (CRP) in H. pylori positive patients as well as significantly more gastritis in endoscopy findings in comparison with H. pylori-negative patients. H. pylori recurrence after successful eradication therapy was observed in 22.1% patients of H. pylori-positive cirrhotic patients. Multivariate analysis showed that higher serum ammonia level & receiving multiple treatment courses to achieve H. pylori eradication were independent risk factors for H. pylori recurrence in cirrhotic patients.

Conclusion: H. pylori infection is prevalent in liver cirrhosis patients with a significant recurrence rate after eradication therapy. High serum ammonia and the need for multiple treatment courses are risk factors for recurrence.

Keywords: Helicobacter pylori, Liver cirrhosis, Eradication therapy, Hepatitis C, Ammonia level, Bacterial resistance.

INTRODUCTION

H. pylori is a gram-negative, microaerophilic, highly-motile and spiral-shaped bacterium infecting more than 50% of the world population through oro-oral or feco-oral transmission[(1)] . H. pylori infection is the most prevalent risk factor for chronic gastritis, peptic ulcer disease (PUD), gastric carcinoma (which is the second leading cause of cancer-related death worldwide), and mucosal associated lymphoid tissue (MALT) lymphoma. H. pylori is also a probable risk factor for multiple extra-gastric disorders, such as ischemic heart disease, diabetes, iron & vitamin B12 deficiency and idiopathic thrombocytopenic purpura as well as some liver disorders including nonalcoholic fatty liver disease, isolated hypertransaminasemia, and portosystemic encephalopathy[(2, 3)].

H. pylori recurrence is negative detection of H. pylori at 4 weeks after eradication therapy but positive detection at a later time. Despite the awareness of the risks of H. pylori infection & the multiple regimens offered for its eradication, there is still a high risk of H. pylori recurrence after successful eradication therapy with one-year recurrence rate 1-2% in developed countries but 10-70% in developing countries. H. pylori recurrence can occur either by reconolization of the same H. pylori strain (recrudescence) or a new strain (reinfection) with most cases of H. pylori recurrence are due to recrudescence. Many risk factors for H. pylori infection have been reported, including socioeconomic factors, education level, non-compliance to treatment, bacterial resistance & prolonged alcohol intake [(4)].

Cirrhosis caused by chronic hepatitis C virus infection and its complications is one of the major health problems in Egypt. H. pylori infection is a common cause of PUD in cirrhotic patients, and it is also correlated with the severity of portal hypertensive gastropathy (PHG) and frequent upper gastrointestinal bleeding in those patients. However, there are insufficient data in the literature on the rate and risk factors for recurrence of H. pylori infection after successful resection treatment in cirrhotic patients [(5)].

The aim of our study was to assess the rate and risk factors of recurrence of H. pylori infection in Egyptian patients with liver cirrhosis after successful eradication therapy.

PATIENTS AND METHODS

This prospective study was carried on in Gastroenterology and Hepatology Unit, Internal Medicine Department, Zagazig University Hospitals from January 2020 till March 2021. **Inclusion criteria:** included age > 18 years, both sexes, and evidence of liver cirrhosis. **Exclusion criteria:** included pregnant or lactating females, patients with gastric cancer, and history of H. pylori treatment 4 weeks ago or after one year of end of therapy. The study enrolled 500 liver cirrhosis patients who were tested for H. pylori infection. In accordance with American College of

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Gastroenterology (ACG) guidelines 2017, the patients with positive H. pylori infection received proton pump inhibitors (PPI)-based treatment regimen [PPI+ Amoxicillin + Clarithromycin (PAC), PPI+ Amoxicillin + Levofloxacin (PAL) or PPI+ Clarithromycin + Levofloxacin (PCL)] for H. pylori eradication. The confirmation of successful eradication therapy or H. pylori recurrence was done 4-8 weeks after end of treatment course using urea breath test (UBT) and stool antigen test (SAT) [(6)]. Follow up UBT and SAT were performed for patients without recurrence at 3, 6 & 12 months.

Ethical approval:

An approval of the study was obtained from Zagazig University academic and ethical committee. All patients signed an informed consent describing the purpose, possible risks, and benefits of the study.

Statistical analysis: was performed using SPSS software (version 20; SPSS Inc., Chicago, IL, USA). Categorical and continuous parameter differences were expressed using Pearson's chi-square test, Fishers' Exact test and Student t-test respectively. Our results were expressed as numbers (%) and mean ± SD. Univariate and multivariate logistic regression analyses were performed to identify independent risk factors for H. pylori recurrence after successful eradication therapy. The Bonferroni correction for multiple comparisons was used where appropriate. P-values ≤ 0.05 were considered statistically significant.

RESULTS

Table (1): Demographic data of the study groups.

Variables	*H. pylori*-negative *N.* = 210 (42%)	*H. pylori*-positive *N.* = 290 (58%)	P-value
Age (years)	53.4 ± 7.6	52.7 ± 8.6	0.35
Sex (M/F)	131/79	183/107	0.78
BMI (Kg/m^2)	27.8 ± 2.3	28.1 ± 2.8	0.2
Smoking (%)	76 (36.2)	101 (34.8)	0.75
Alcohol intake (%)	3 (1.43)	8 (2.76)	0.32
Education level (%)			
Low	79 (37.6)	118 (40.7)	0.48
Medium	65 (31)	89 (30.7)	0.94
High	66 (31.4)	83 (28.6)	0.49
Socio-economic status (Income) (%)			
≥ 2000 EGP	131 (62.4)	187 (64.5)	0.63
< 2000 EGP	79 (37.6)	103 (35.5)	
Diabetes mellitus (%)	72 (34.3)	98 (33.8)	0.91
Hypertension (%)	21 (10)	33 (11.4)	0.62
Causes of cirrhosis (%)			
HCV	206 (98.1)	287 (98.3)	0.87
HBV	4 (1.9)	5 (1.7)	
Hemoglobin (g/dl)	9.6 ± 0.8	9.5± 1.1	0.26
WBCs (× 10^3/dl)	3.4 ± 0.5	3.3 ± 0.8	0.51
Platelet count (× 10^3/dl)	96.1 ± 9.2	97.4 ± 4.1	0.52
ALT (IU/L)	46 ± 10.2	46.2 ± 10.1	0.83
AST (IU/L)	45.3 ± 2.1	45.7 ± 2.6	0.72
Serum albumin (g/dl)	2.9 ± 0.7	2.85 ± 0.1	0.56
Total Bilirubin (mg/dl)	1.5 ± 0.06	1.6 ± 0.07	0.07
Prothrombin time (sec.)	1.54 ± 0.03	1.56 ± 0.02	0.37
Serum creatinine (mg/dl)	1.09 ± 0.2	1.1 ± 0.2	0.58
Serum ammonia (µmol/l)	103 ± 8.2	115 ± 9.4	**< 0.001***
CRP (ng/ml)	2.4 ± 0.2	2.5 ± 0.1	**< 0.001***
Child–Pugh score	8.9 ± 2.2	8.8 ± 2.4	0.74
MELD score	15.8±3.9	16.2 ± 2.9	0.19
Endoscopic findings (%)			
Esophageal varices	97 (46.2)	129 (44.5)	0.71
Gastric varices	41 (19.5)	62 (21.4)	0.6
PHG	71 (33.8)	117 (40.3)	0.14
Gastritis	144 (69)	222 (77)	**0.04***
PUD	51 (24.3)	81 (27.9)	0.37

This study evaluated 500 liver cirrhosis patients for H. pylori infection. Table (1) showed that 290 cirrhotic patients (58%) tested positive for H. pylori infection, 63% were males and their mean age was 53 years. There were no statistically significant differences between H. pylori-positive & H. pylori-negative cirrhotic patients regarding age, sex, alcohol intake, socio-economic status, education level, underlying cause of liver cirrhosis, Child score, model for end-stage liver disease (MELD) score, esophageal & gastric varices, PHG or PUD. There were significantly higher serum

levels of ammonia and C-reactive protein (CRP) in H. pylori positive patients as well as significantly more gastritis in endoscopy findings in comparison with H. pylori-negative patients.

Table (2): Univariate analysis of risk factors for H. pylori recurrence.

	Cirrhotic patient with H. pylori recurrence (N.= 64)	Cirrhotic patients without H. pylori recurrence (N.= 226)	P-value
Age (years)	51.9 ± 4.1	52.3 ± 5.2	0.57
Alcohol intake (%)	3 (4.7)	5 (2.2)	0.28
Socio-economic status (%) >2000 EGP <2000 EGP	40 (62.5) 24 (37.5)	138 (61.1) 88 (38.9)	0.84
Education level (%) Low High	27 (42.2) 20 (31.3)	91 (40.3) 63 (27.9)	0.79 0.59
Hemoglobin level (gm/dl)	9.1 ± 1.2	9. 2 ± 1.3	0.58
Prothrombin time (sec.)	1.4 ± 0.03	1.3 ± 0.05	0.13
High serum ammonia level (umol/l)	114 ± 5.4	111 ± 9.7	**0.02***
MELD score	15.1 ± 3.2	14.8 ± 3.5	0.54
CRP level (ng/ml)	2.1 ± 0.2	2.1 ±0.4	1
PHG (%)	22 (34.4)	95 (42)	0.27
PUD (%)	17 (26.6)	64 (28.3)	0.79

Table (2) showed that H. pylori recurrence after successful eradication therapy was observed in 64 (22.1%) patients of H. pylori-positive cirrhotic patients. Univariate analysis for risk factors showed that the only probable risk factor for H. Pylori recurrence after successful eradication therapy was higher serum ammonia level in cirrhotic patients with H. pylori recurrence. There was no statistically significant difference between cirrhotic patients with H. pylori recurrence and those without H. pylori recurrence regarding age, alcohol intake, socio-economic status, education level, MELD score and presence of PUD or PHG.

Table (3): Correlation between H. Pylori recurrence & severity of liver cirrhosis.

	Patients with H. pylori recurrence (N. =64)	Patients without H. pylori recurrence (N. =226)	P-value
Compensated liver cirrhosis (Child score < 7)	18 (28%)	72 (32%)	0.54
Decompensated liver cirrhosis (Child score ≥ 7)	46 (72%)	154 (68%)	

Table (3) showed no statistically significant difference between compensated & decompensated liver cirrhosis patients regarding H. pylori recurrence.

Table (4): Multivariate analysis of the study group.

Variant	Odd ratio	95% CI	P-value
Alcohol intake	1.5	0.9-3.1	0.53
High Serum ammonia level	4.2	1.2-14.8	**0.02***
Receiving multiple treatment courses	3.4	1.2-11.3	**0.03***
PHG	2.7	0.7-9.6	0.19

Multivariate analysis revealed that higher serum ammonia level & receiving multiple treatment courses to achieve H. pylori eradication were independent risk factors for H. pylori recurrence in cirrhotic patients after successful eradication therapy as shown in table (4).

DISCUSSION

The prevalence of H. pylori infection in developing countries ranges from 70-90% with a recurrence rate ranging from 10-70% after successful eradication treatment. This high prevalence in developing countries is thought to be due to lower socioeconomic conditions, contaminated food and water, higher cost of eradication treatment and higher non-compliance with treatment [(7)].

In cirrhotic patients, H. pylori infection is implicated in an increased prevalence of upper gastrointestinal bleeding due to more severe PUD and PHG as well as an increased prevalence and severity of systemic portal encephalopathy mainly due to increased ammonia production [(8)].

In our study, we assessed the prevalence and risk factors of H. pylori recurrence in cirrhotic patients after successful eradication therapy. Our results showed that the prevalence of H. pylori infection in patients with liver cirrhosis was 58%. This finding goes in agreement with **Pogorzelska *et al.*** [(9)] who reported H. pylori infection in 61% of patients with liver cirrhosis secondary to HCV infection, while it was 29% in those with alcoholic cirrhosis.

H. pylori-positive cirrhotic patients were mainly males (63%), with a mean age 53 years, and had statistically significant higher serum ammonia levels, serum CRP levels and more gastritis rates in their endoscopic findings. These findings are consistent with those reported by **Abdel-Razik *et al.*** [(10)] and **Leontiadis *et al.*** [(11)].

Abdul Sathar *et al.* [12] reported a strong association between H. pylori infection & PHG where H. pylori infection was present in 44% versus 27% of liver cirrhosis patients without versus with PHG respectively. This association wasn't present in our findings.

Our results revealed that 22% of H. pylori-positive patients showed recurrence after successful eradication therapy. These findings are similar to that recurrence rate reported by **Hong *et al.* [13]** and **Andreev *et al.* [14]** (18% and 20-26% respectively). This recurrence was not correlated with age, sex, alcohol intake, socio-economic status, education level or complication of H. pylori infection (PUD). Also, H. pylori recurrence wasn't correlated with the severity of liver disease according to Child & MELD scores or with presence of PHG.

We found that the independent risk factors associated with H. pylori recurrence in cirrhotic patients after successful eradication therapy were higher serum ammonia level and receiving multiple PPI-based treatment courses to achieve H. pylori eradication. Elevated serum ammonia levels in patients with recurrent H. pylori infection may indicate further gastric and diffuse colonic interference with H. pylori. This is mainly due to the effect of H. pylori urease on protein digestion in the colon. Increased production of ammonia by H. pylori bacteria in cirrhotic patients is implicated in recurrent hepatic encephalopathy in these patients [15]. Increased H. pylori recurrence in patients receiving multiple treatment courses may be a clue for more resistance to antibiotic therapy in our group of patients. This is consistent with the findings of **Silva *et al.* [16]** who reported that recurrence rates of H. Pylori infection is increased with history of previous treatments. This also goes in agreement with **Sachdeva *et al.* [17]** who reported that eradication rates are decreasing over time with increase in antibiotic resistance.

CONCLUSION

H. pylori infection is prevalent in liver cirrhosis patients with a significant recurrence rate after eradication therapy. High serum ammonia & the need for multiple treatment courses are risk factors for recurrence.

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