
Evaluation of Response to Treatment of Helicobacter Pylori Infection in Portal Hypertensive HCV Cirrhotic Patients

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Abstract

Background: *Helicobacter pylori* is an etiology of various gastrointestinal disorders such as chronic gastritis, peptic ulcer, and stomach cancer. **Aim:** The aim was to assess the response to *Helicobacter pylori* treatment in patients with portal hypertensive hepatitis C virus (HCV)

*cirrhosis. **Methods:** two groups; Group A (case group): 52 H. pylori-positive HCV portal hypertensive cirrhotic cases. Group B (control group): 52 H. pylori-positive non-portal hypertensive, non-cirrhotic individuals. Both groups were given levofloxacin-based therapy (Levofloxacin 500 mg / Amoxicillin 1 g bid/ Pantoprazole 40 mg bid) for 2 weeks. The H. pylori stool antigen test was repeated 4 weeks after treatment. **Results:** A statistically significant difference was obtained regarding H. pylori antigen testing before and after treatment in the control group compared to the case group. **Conclusion:** H. pylori infection is associated with a better treatment response in non-cirrhotic, non-portal hypertensive patients compared to those with HCV-cirrhosis and portal hypertension.*

Keywords: *Helicobacter pylori, portal hypertension, HCV-cirrhosis, treatment, Levofloxacin, Pantoprazole.*

Introduction

Warren and Marshall were scientists who identified *Helicobacter pylori* as a Gram-negative bacterium. In developing countries, *H. pylori* is highly prevalent [1,2], that causes peptic ulcer, chronic gastritis, gastric cancer, and mucosal-associated lymphoid tissue lymphoma (MALT). Antimicrobials, proton pump inhibitors, and bismuth-containing compounds comprise the treatment. [3]. The 1st line *H. pylori* treatment is a triple therapy that includes clarithromycin for 14 days, amoxicillin, and PPI or bismuth citrate [4]. The development of antibiotic resistance is a significant issue [5]. In treatment failure, rescue therapy should be tailored to the antibiotic susceptibility [6].

Cirrhosis is due to persistent liver damage, resulting in fibrosis and the loss of the typical architecture with abnormally organized nodules [7]. Causes are viral hepatitis (HBV or HCV) and nonalcoholic fatty liver disease [8]. Portal hypertension is the primary cause of the majority of cirrhosis-related complications [9]. Cirrhosis may be compensated or decompensated, based on clinical and functional manifestations; presence of ascites, hepatic encephalopathy, jaundice [10]. We aimed to assess the efficacy of *H. pylori* treatment in patients with HCV cirrhosis who are portal hypertensive.

Materials and methods

Prospective studies were carried out on a cohort of Egyptian patients, with participants recruited from the outpatient clinics of Alexandria University Hospital, Faculty of Medicine, Egypt. A sample size of 104 is calculated using ClinCalc, with a 1:1 enrollment ratio (52 patients in each group), at a 95% level of significance ($p\text{-value} < 0.05$) and a power of 0.8. Matching of the groups was performed based on age and sex characteristics.

Patients were in two groups:

Group A (cases group): **52** *H. pylori*-positive HCV portal hypertensive cirrhotic.

Group B (control group): **52** *H. pylori*-positive non-portal hypertensive non-cirrhotic healthy individuals.

HCV was assessed by quantifying serum HCV RNA levels using TaqMan 48 automatic fluorescence quantitative polymerase chain reaction (q-PCR) kits on the Roche COBAS AmpliPrep/COBAS TaqMan 48 Analyzer (Roche Diagnostics, Mannheim, Germany); the detection limit was 12 IU/mL. Quantitative *H. pylori* antigen detection in stool was performed using the *ELISA H. pylori* antigen detection kit from DRG International.

Both groups received levofloxacin-based therapy (Levofloxacin 500 mg / Amoxicillin 1 g bid/ Pantoprazole 40 mg bid) for 2 weeks, and *H. pylori* fecal antigen testing was performed 1 month after treatment. An *H. pylori* fecal antigen titer of less than 15 was considered responsive to treatment. Informed consent was obtained from all individuals involved in this work.

Exclusion criteria: All other causes of cirrhosis, like HBV and autoimmune causes.

Results

Patients were allocated in a non-randomized manner based on the inclusion criteria, with sample size calculation based on the response rates of a study examining the correlation between cirrhosis and *H. pylori* treatment.

Group A consisted of 52 patients, with 26 males and 26 females (50:50%), and a mean age of 46.3 ± 14.4 years. Group B comprised 22 males and 30 females (42.3:57.7 %), with a mean age of 41.4 ± 16.9 years. There was no significant difference between the two groups in terms of age and gender.

Group A patients showed statistically significant differences compared to Group B in the presentation of ascites, pallor, lower limb edema, jaundice, and tremors ($p = 0.000, 0.000, 0.000, 0.003, 0.003$, respectively).

Tab 1. **Comparison of clinical findings between the two groups**

		Group A (n=52)		Group B (n=52)		X2	P value
		n	%	n	%	n	
Ascites	Absent	37	71.2%	52	100.0%	17.528	<0.001*
	Present	15	28.8%	0	0.0%		
Lower limb edema	Absent	33	63.5%	52	100.0%	23.247	<0.001*
	Present	19	36.5%	0	0.0%		
Jaundice	Absent	44	84.6%	52	100.0%	8.667	0.003*
	Present	8	15.4%	0	0.0%		
Pallor	Absent	21	40.4%	52	100.0%	44.164	< 0.001*
	Present	31	59.6%	0	0.0%		
Hepatic encephalopathy	Absent	44	84.6%	52	100.0%	8.667	0.003*
	Present	8	15.4%	0	0.0%		
Epigastric pain	Absent	9	17.3%	6	11.5%	0.701	0.402
	Present	43	82.7%	46	88.5%		
Nausea	Absent	21	40.4%	15	28.8%	1.529	0.216
	Present	31	59.6%	37	71.2%		
Vomiting	Absent	35	67.3%	28	53.8%	1.973	0.160
	Present	17	32.7%	24	46.2%		

Data are presented as numbers (%). X2 chi-square *: significant as P value < 0.05.

There was a significant difference between the two groups in terms of CBC, WBCs, platelets, ALT, direct and indirect bilirubin, serum albumin, PT, and INR. Meanwhile, there was no significant difference in AST, Urea, and serum creatinine levels (Table 2).

Tab 2. **Shows the comparison of laboratory investigations between the two groups:**

	Group A Cases (n=52)		Group B Control (n=52)		X2	P value
	Mean	Standard Deviation	Mean	Standard Deviation		
HGB (gm/dl)	10.72	1.20	12.94	1.18	-9.52	(0.001*)
WBCS(WBCs / microlit)	4.65	1.37	6.41	1.88	-5.46	(0.001*)
Platelets(platelets/ microlit)	112.38	47.12	293.81	80.17	-14.06	(0.001*)
AST(U/L)	26.83	12.75	21.67	6.93	2.42	(0.012)
ALT(U/L)	29.40	12.90	20.44	6.54	6.27	(0.001*)
Direct bilirubin (mg/dl)	1.20	1.23	0.18	0.11	7.03	(0.001*)
Total bilirubin(mg/dl)	2.02	1.09	0.89	0.18	8.98	(0.001*)
Serum Albumin(gm/dl)	3.07	0.33	4.38	0.44	-19.14	(0.001*)

PT%	66.21	10.37	94.44	4.14	-20.62	0.001*)
INR	1.33	0.15	0.98	0.05	14.25	(0.001*)
Urea(mg/dl)	26.71	6.54	29.25	7.62	-1.86	0.071
Creatinine(mg/dl)	0.74	0.22	0.73	0.24	0.15	0.671

Data are presented as mean and SD, *X2 chi square *: significant as P value < 0.05. HGB: hemoglobin, WBCs: white blood cells, ALT: alanine transaminase, AST: aspartate transaminase.

The comparison of the independent association by t-test between the two groups revealed a statistically significant difference before the start of therapy ($p = 0.004$), which remained significant after treatment (**Table 3**).

Tab 3. Shows comparison in *H. pylori* testing by detection of fecal antigen before and after treatment for both groups:

	Mean±SD group A	Mean±SD Group B	X2	P value
<i>H. pylori</i> fecal Ag before treatment ,group A	56.10 ±27.79	74.06 ±34.69	2.92	(0.004*)
<i>H. pylori</i> fecal Ag after 1 month of treatment	24.29 ±18.14	15.52 ±13.28	2.81	(0.006)

Data are presented as mean and SD, *X2 chi square *: significant as P value < 0.05.

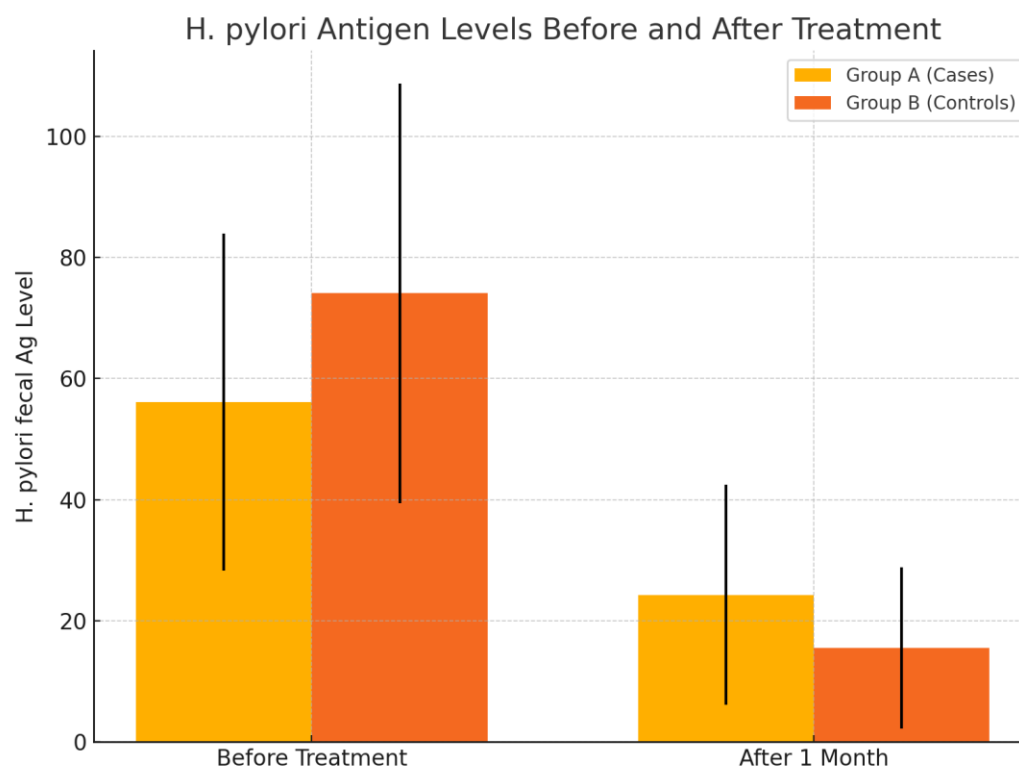


Figure 1. *H. Pylori* fecal antigen levels before and after 1 month of treatment

This bar graph compares the mean *H. pylori* fecal antigen levels in Group A (Cases) and Group B (Controls) before treatment and after one month of treatment.

When comparing the response to treatment in the two groups, a statistically significant difference was obtained regarding the *H. pylori* antigen testing before and after treatment. (35) Individuals were negative after treatment for the control group, and (22) individuals were negative after treatment for the cases group. (Table 4)

Tab 4. Shows the comparison between the two groups regarding *H. pylori* antigen testing before and after therapy:

		Number	Mean	Standard deviation	t	P value
Difference between <i>H. pylori</i> Ag before and after treatment	Group A	52	31.8077	18.85449	-4.891	< 0.001*
	Group B	52	58.5385	34.60390		

Data are presented as mean and SD, *: significant as P value < 0.05.

Based on predictors: CBC(HGB), AST, total and direct bilirubin, creatinine, INR, WBCS, PT%, urea, albumin, platelets, ALT, a regression analysis was performed to correlate predictors to improvements in *H. pylori* Ag after treatment (difference between *H. pylori* Ag before and after

treatment) among both groups, as shown in **Table 5**. The result of this analysis showed a significant difference between the two groups.

Group B: Significant correlation between lab parameters and improvement in *H. pylori* antigen ($R = 0.579$, $P = 0.000$).

Group A: Moderate correlation but not statistically significant ($R = 0.544$, $P = 0.296$).

Table 5. *Linear regression analysis for lab investigation measures and improving H. pylori antigen after treatment:*

	Group B (N=52)				Group A (n=52)			
	Mean	Std. Deviation	R	P value	Mean	Std. Deviation	R	P value
H. pylori Ag	45.17	30.81			31.81	18.85		
HGB(gm/dl)	11.83	1.63			10.72	1.20		
WBCS(WBCs / microlit)	5.53	1.86			4.65	1.37		
platelets(PLT / microlit)	203.09	112.20			112.38	47.12		
AST(U/L)	24.25	10.53			26.83	12.74597		
ALT(U/L)	24.92	11.13			29.40	12.90		
Total bilirubin(mg/dl)	1.45	0.96	0.579	0.000*	2.02	1.09	0.544	0.296
Direct bilirubin(mg/dl)	0.69	1.01			1.20	1.23		
PT%	80.3269	16.21			66.21	10.37		
INR	1.1538	.20712			1.33	0.15		
Serum albumin(gm/dl)	3.7221	.76488			3.06	.33011		
Urea(mg/dl)	27.9808	7.18275			26.71	6.54		
Serum creatinine(mg/dl)	0.7346	0.22930			0.74	0.22		

Data are presented as mean and SD. *: significant as P value < 0.05 . HGB: hemoglobin, BCS: white blood cells, ALT: alanine transaminase, AST: aspartate transaminase.

Discussion

H. pylori's effect on portal hypertension (PHG) and liver cirrhosis remains a topic of debate [11, 12]. Our study was designed to assess *H. pylori* treatment efficacy in HCV cirrhotic cases who suffered from portal hypertension.

The control group had a mean age of 48.19 ± 7.82 years, with 62.5% of the participants being male and 37.5% being female. The mean age of the cases was 47.98 ± 6.74 years, with 68.8% of the participants being male and 31.8% being female, as demonstrated by Alarfaj et al. No significant differences were found between the two groups in terms of sex and age.[13].

Tsai et al. comprised 592 patients, divided into two groups: 136 patients with CLD and 456 patients in the non-CLD group. There was no statistically significant difference between the two groups regarding sex and age, as indicated by the results [14]. These results were consistent with the results of our research.

Furusyo et al. comprised 76 patients with chronic HCV infection, and 228 participants without HCV infection were included. The results indicated that there were no significant differences in sex or age [15]. These results were consistent with the results of our research.

Alarfaj et al. also demonstrated that there were insignificant differences between the cases and the controls in terms of clinical features, platelet count, AST, and ALT [16]. ($p > 0.005$) that did not align with the findings of our investigation.

In comparison to the 158 HCV-non-infected controls with *H. pylori* infection (group B) (57.6% and 15.2%), the 67 HCV-infected patients with *H. pylori* infection (group A) exhibited significantly higher rates of symptoms (77.6% and 34.3%) (all $p < 0.05$), as demonstrated by Furusyo et al. [15] That was in agreement with the results of our research.

Miyaji et al. concluded that *H. pylori* eradication was effectively achieved in patients with chronic hepatic disease. Successful eradication rates of 91.0% for HCV-infected cases and 72.8% for HCV-uninfected controls were demonstrated in the current report [16]. That was in agreement with the results of our study.

The successful eradication rates of *H. pylori* for HCV-infected cases and HCV-uninfected controls were reported by Furusyo et al. to be 91.0% and 72.8%, respectively. Such rates were significantly higher. This could potentially be attributed to the role of liver disease in the metabolism of PPIs. The high eradication rate of *H. pylori* in HCV-infected patients may be attributed to a reduction in PPI metabolism, which may have been induced by HCV infection. Azuma et al. found that the cure rate of *H. pylori* in patients with cirrhosis was 89.3%, which was significantly higher than the 83.5% observed in the non-cirrhotic group. The authors postulated that this was due to reduced

clarithromycin metabolism in patients with liver cirrhosis[15]. That was in agreement with the results of our study.

Alarfaj et al. conducted a study on 25 patients out of 44 patients who tested positive for *H. pylori* (56.8%), who responded to triple therapy with portal hypertension. In contrast, triple therapy was effective in patients without PHG, as evidenced by the fact that 18 out of 22 individuals who tested positive for *H. pylori* (81.8%) responded ($p = 0.045$). In patients with PHG, the severity of PHG improved statistically significantly after *H. pylori* was eradicated using triple therapy ($p = 0.001$) [13].

Tsai et al. PHG severity in PHG patients did not experience statistically significant improvement following the eradication of *H. pylori* through triple therapy [14]. It is crucial to note that *H. pylori* DNA has been detected in human livers and has been associated with CLD and liver cancer. Consequently, it is worthwhile conducting additional in-depth research in this area to gain a deeper understanding of the impact of *H. pylori* infection on CLD patients.

In the Tasi subgroup analysis, it was discovered that a greater number of female patients in the non-CLD group were unable to eradicate *H. pylori* (89.5% vs. 78.5%, $p < 0.001$). The CLD group had a higher percentage of female patients who were unable to eradicate *H. pylori*; however, this difference was not significant in this trial (88.2% vs. 83.8%, $p = 0.458$). The cause has not been fully comprehended to date. In one investigation, the prevalence of metronidazole resistance was higher in females than in males, resulting in lower eradication rates with metronidazole-containing regimens [14].

Our research is subject to some limitations, including a limited number of patients and a brief follow-up period. Further limitations include a lack of alternative methods for confirming *H. pylori*, such as UBT and biopsies, which can be performed during variceal screening.

Consequently, to substantiate the results, it would be necessary to conduct more comprehensive trials with a larger population size and a more extended follow-up period.

Further research is recommended to investigate the relationship between *H. pylori* treatment response and the development of cirrhosis. Our study suggests that for individuals who test positive for *H. pylori*, thorough follow-up is recommended.

Conclusion

Our research revealed that *H. pylori* therapy in cirrhotic patients yielded lower treatment response rates (42%) compared to non-cirrhotic patients (67%).

Footnotes.

Ahmed Fathy (Professor of internal medicine, gastroenterology, and hepatology unit), Mohamed Emara (Professor of gastroenterology, hepatology, and infectious diseases department), and Amany Mohamed (Professor of family medicine and biostatistician) were peer reviewers.

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Ethics approval

Informed consents were obtained from all individuals involved in this work. The Ethics Committee of the Faculty of Medicine at Alexandria University approved the current research in February 2023, with serial number 0305999.

Data and materials availability: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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This work was conducted following the STROBE guidelines.

Authors' contributions:

All authors made substantial contributions to the study's conception, design, data acquisition, analysis, or interpretation; drafting or revising the article; and final approval of the version to be submitted.

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