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ORIGINAL ARTICLE

Evaluation The Prevalence and Impact of *Helicobacter pylori* Infection among Patients with Hepatitis C Virus

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Abstract

Background Recently, we have noticed an increase in stomach disorders in people infected with hepatitis C virus (HCV) for this reason we studied the prevalence and effect of *Helicobacter pylori (H. pylori)* infection in HCV patients in Iraq. Method: Our study included 100 cases of HCV and 100 healthy control group. The necessary clinical and laboratory tests were performed to diagnose HCV and *H. pylori*. Liver enzymes, creatinine bilirubin, IL-6, 8, 17, TNF-α were evaluated according to Kits protocol.

Results *H. pylori* isolated from most HCV patients (61%) while the infection appeared in a lower percentage (31%) among control. Results showed that the most common HCV genotype is genotype 4 with a rate of 43%, followed by 1 and 6 with a rate of 25% and 17%, respectively. In HCV cases, females were most infected with *H. pylori* at a rate of (75%) compared to males (25%). Confection of HCV and *H. pylori* had a higher Meld Score than their non-infected peers ($p = 0.0078$) and Chronic active hepatitis and Child-Pugh score A, B, and C increased by 42%, 43%, 76%, and 78%, respectively, among patients with confection, and these percentages were different from their peers with HCV infection only. Elevated AST and ALT in confection (61.4 and 79.7U/L respectively) compared to HCV patients uninfected by *H. pylori* (22.7 and 47.1 U/L respectively). Moreover, an increase in the concentration of IL-17, TNF-α, and IL-6 in confection (131pg/ml, 99.2 ng/ml, and 79.4 ng/ml, respectively) compared with H.pylori uninfected HCV patients (59.4 pg/ml, 75.6 ng/ml and 58.3ng/ml, respectively).

Conclusion increasing prevalence of *H. pylori* in patients with HCV led to liver ulcers, imbalances in liver enzymes, in addition to immune disorders. A destructive treatment for *H. pylori* may be beneficial for those patients who suffer from chronic HCV.

Keywords: *H. pylori*; HCV, Coinfection; Liver; Interleukin; Stomach

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1 Introduction

Gastric biopsy cases of individuals with persistent gastritis and peptic ulcer infection were identified by Nobel in 1984 as containing *Helicobacter pylori*. The gastric mucosa can become colonised by the Gram-negative winding-formed microbe *Helicobacter pylori*, which can cause gastritis, ulcers, and gastric danger [1, 2]. *H. pylori* infection affects about half of the global population. The prevalence of *H. pylori* illness is high in both developed and developing countries [3]. Financial status and age at infection are the only in-

dependent variables that predict the rate of *H. pylori* infection. Similarly, gastritis develops in everyone infected with *H. pylori* [4]. The carcinogenicity-inducing cytotoxin-related quality A (CagA) and vacuolating cytotoxin quality A (VacA) proteins are released by this bacterial strain. VacA triggers cell death by activating the apoptotic factor Bcl-2 related X protein (Bax), whereas CagA aids in targeting the epithelial cells [5]. After epithelial cells are attacked, growth cell expansion occurs by blocking the movement of the cancer suppressor p53, which prevents apoptosis. Some studies have shown that *H. pylori* infection affects more than only the stomach [6]. For example, De Martel et al. [7] reviewed several studies that looked at the correlation between *H. pylori* infection and biliary tract tumours. The first *H. pylori* cultivated was from a liver biopsy material taken in 2001 from a patient with Wilson's disease-related cirrhosis [8]. Following this, other studies have investigated the role of helicobacter in the development of chronic liver disorders, such as hepatitis and HCC, either alone or in conjunction with other common liver infections, such as hepatitis B virus (HBV) and hepatitis C virus (HCV) [9]. In 1989, the first signs of hepatitis C infection were noticed. There have been over 180 million cases of HCV infection worldwide up to this date. There may be an increase in patient mortality due to chronic hepatitis C (CHC) if it is not well treated, as it can progress to cirrhosis and, ultimately, hepatocellular carcinoma (HCC) [10, 11]. Given the incomplete understanding of the mechanisms behind cirrhosis and HCC, no effective treatments have been developed to date to halt the progression of CHC to these conditions. However, it is recognised that the hepatitis virus load, genotype, and disease duration have important roles in the progression and development of HCC [12, 13].

Although some experts have said that *H. pylori* likely won't contribute to the occurrence of HCV-related health problems, mounting evidence suggests that *H. pylori* could be a risk factor for the development of cirrhosis and HCC in patients with CHC [14]. Our goal in conducting this study was to assess the potential link between *H. pylori* and HCV-related diseases, as the evidence linking this pathogen to chronic hepatitis C (CHC) is still inconclusive and the exact nature of the relationship between *H. pylori* and CHC, as well as the incidence of HCC and cirrhosis, remains unclear [15].

2 Materials and Methods

2.1 Patients and samples collection

This study used a 100-person sample consisting of 100 healthy individuals and 100 patients with HCV. Between February 2022 and March 2023, samples were gathered from several locations in Al-Qadisiyah Governorate, including Al-Diwaniyah Teaching Hospital, Maternity and Children's Teaching Hospital, and outpatient clinics.

Each patient and control group underwent a battery of tests at the research centre, including a full clinical evaluation, an ultrasound of the stomach, and blood tests for total bilirubin, direct bilirubin, total protein, serum albumin, aspartate aminotransferase, alanine aminotransferase, basic phosphatase, high mountain, and serum creatinine. Two methods were used: enzyme-linked immunosorbent assay (ELISA) for hepatitis B surface antigen (HBsAg) and real-time polymerase chain reaction (RT-PCR) for hepatitis C virus RNA (Amplicor PCR; Roche Subatomic Frameworks, Inc., Pleasanton, Calif., USA). Every single patient tested negative for HBV and had a 100% certainty against HCV and HCV RNA. The benchmark group, in contrast, had all traces of HCV and HBV eliminated.

It should be mentioned that we did not include cases of medical complications due to other viruses, cancer patients, or anybody who had received a vaccination of any kind. Each patient group underwent a liver biopsy, following which three pathologists independently evaluated the samples for histopathology and reached a consensus on the grating assessments. The three pathologists who were evaluating the patient failed to pay close attention to the clinical details. Ishak et al. [16] defined the last histological assessment of hepatic cirrhosis. The patients were divided into four groups based on the results of the liver biopsy and stomach ultrasonography. A, B, and C Child-Pugh scores were used to classify these groups, which included chronic active hepatitis (CAH).

After being informed about the nature of the review, all patients agreed to the use of their sera and clinical information for research purposes, in accordance with the current Announcement of Helsinki [17].

2.2 Assessment of severity of liver disease using Child and Meld scores

The severity of liver disease was assessed using the Merge score (a model for end-stage liver disease) in addition to the child Pugh scoring system; the last choice was based on the first recipe suggested by the Mayo Centre groups: The formula for the mean score is as follows: log (creatinine mg/dL) + log (bilirubin mg/dL) + log (1.120) + log (0.643). An online calculator makes determining the Meld score a breeze. Here at https://www.mdcalc.com/calc/78/meld-score-model-end-stage-liver-disease-12-older, you may find the website that we have utilised for our calculations. There were two groups of patients determined by the Meld score: one with a Meld score

of 10 or less, and another with a score of 10 or more [18].

2.3 HCV Genotyping

Using commercially available test kits, we followed the manufacturer's instructions to conduct HCV genotyping, amplification, and nucleic acid extraction. With a 70 µl elution volume, 600 µl of plasma samples were manually extracted for HCV-RNA using the Magrev Viral DNA/RNA Extraction Pack (Anatolia Geneworks, Istanbul, Turkey). In order to depict the HCV genotype, the Anatolia Bosphore HCV Genotyping Unit v3 (Anatolia Tani ve Biyoteknoloji A.S., Istanbul) was used. A responsiveness of 100 IU/ml was obtained by intensifying a location inside the NS5B and using the FAM and HEX channels for fluorescence detection. The test can identify the six most common and main HCV genotypes, which are 1, 2, 3, 4, 5, 6. The Quant Studio DX PCR apparatus was used for intensification.

2.4 Determine *H. pylori* infection

Regular rapid urease tests were conducted using biopsies taken from the stomach mucosa. Watson Bioproducts Inc. of Walkersville, MD tested the patients for serum *H. pylori* antibodies. Gastric biopsy inspiration was used to confirm a dynamic *H. pylori* infection if both tests came out positive. The approach that we had previously described was implemented [19].

2.5 Human enzyme –linked immunosorbent assay kit

We followed the instructions provided by the manufacturer to conduct the experiment and quantitatively determine the levels of IL-6, 8, 17, and TNF-α in serum using ELISA kits manufactured by Cusabio (Germany).

2.6 Statistics

Mean ± standard deviation was used to convey quantitative data. While the Kurskal-Wallis test was used to consider several meetings, the Mann-Whitney U test was used to compare two groups. The chi-square test was used to examine the obvious information, and P values less than 0.05 were considered significantly important. Using the SPSS-19 [20], data was categorised and analysed.

3 Results

The current study included 100 case infected with viral hepatitis C, their ages ranged from 5 to 80 years, with an average age of 36.7 years and a standard deviation of ±12.5 years. Most of the patients were males (52%) and they passed 45 years. Our study also included 100 healthy people who were not previously or currently infected with hepatitis viruses as a control group, their ages ranged from 5 to 81 years, with an average age of 31.4 years, and most of them were males (58%). Also, we did not find statistical differences when comparing the ages and genders of patients with healthy subjects ($p < 0.05$), as shown in Table 1. When investigating for bacterial infection in the studied community, we isolated *H. pylori* from most of the patients (61%), while the infection appeared in a lower percentage (31%) among healthy subjects ($p<0.05$).

Table 1: Demographic properties and *H. Pylori* infection of patients and controls.

Properties	Patients	Control	P value
Age range	5 – 80 year	5-81 year	
Mean	36.7	31.4	0.393
Standard deviation	± 12.5	± 14.9	
Standard error	1.25	1.49	
Age groups	N (%)	N (%)	P value
<15	11 (11%)	15 (15%)	0.511
15-45	29 (29%)	34 (34%)	0.579
>45	60 (60%)	51 (51%)	0.251
Gender	N (%)	N (%)	P value
Male	52 (52%)	58 (58%)	0.408
Female	48 (48%)	42 (42%)	0.410
H. pylori infection	N (%)	N (%)	P value
Positive	61 (61%)	31 (31%)	0.011
Negative	39 (39%)	69 (69%)	0.012
Total number	100	100	

Our results in Table 2 showed that the most common HCV genotype in our society is genotype 4 with a rate of 43%, followed by 1 and 6 with a rate of 25% and 17%, respectively, while the genotype 3 and 5 were the least prevalent with a rate of 4% for each one of them. To determine the relationship of *H. pylori* infection with HCV genotypes, we found that most bacterial infections were associated with genotype 4, followed by genotype 1 and 6, with rates of 49%, 23%, and 18%, respectively. Despite this, the statistical differences ($p<0.05$) in the prevalence of HCV genotype according to the presence of bacteria or not appeared only in the direction of genotype 2 and 4.

In Table 3, females were most infected with *H. pylori* at a rate of (75%) compared to the percentage of infection among males (25%). We also found that the percentage of infection with *H. pylori* increased with age to be the highest percentage (75%) in patients over the age of 45 years. On the other hand, HCV patients infected with the bacteria had a higher Meld Score than their non-infected peers ($p = 0.0078$). Chronic active hepatitis (CAH) and Child-Pugh score A, B, and C increased by 42%, 43%, 76%, and 78%, respectively, among patients infected with *H. pylori*, and these percentages were different from their peers without infection, which led to the emergence of significant differences ($p<0.05$).

To evaluate the patients' liver function, we measured AST, ALT, ALP, and bilirubin, and found elevated AST and ALT in HCV patients infected with *H. pylori* (61.4 and 79.7U/L respectively) compared to HCV patients uninfected by *H. pylori* (22.7 and 47.1 U/L respectively) and healthy controls (5.9 and 8.1 U/L, respectively), while both ALP and bilirubin were elevated in patients with HCV patients without bacterial infections (135.5 U/L and 5.1, respectively) compared with HCV infection with bacterial infections (130 U/L and 3.6 ng/dl, respectively) and healthy controls (47.6 U/L and 0.14 ng/dl, respectively) as shown in Table 4.

On the other hand, we measured some interleukins to evaluate the immune aspect of HCV, especially those infected with *H. pylori*, and we found an increase in the concentration of IL-17, TNF-α, and IL-6 in HVC patients infected with *H. pylori* (131pg/ml, 99.2 ng/ml, and 79.4 ng/ml, respectively). Compared with uninfected HCV patients (59.4 pg/ml, 75.6 ng/ml and 58.3ng/ml, respectively) and healthy controls (23.6 pg/ml, 9.9 ng/ml, and 7.55 ng/ml, respectively), while the concentration of IL-8 was increased in bacterial uninfected HCV patients (224 pg/ml) compared to infected (208 pg/ml) and healthy(11.6 pg/ml).

The results of the Pearson correlation coefficient (r) between the studied indicators in HCV patients infected with *H. pylori* infection showed a linear relationship between all of these indicators, where the value of (r) was positive, which indicates that the occurrence of a disorder in one of the immunological indicators or liver enzymes may be directly or indirectly associated with the effects of other immunological or biochemical indicators, as shown in Table 5.

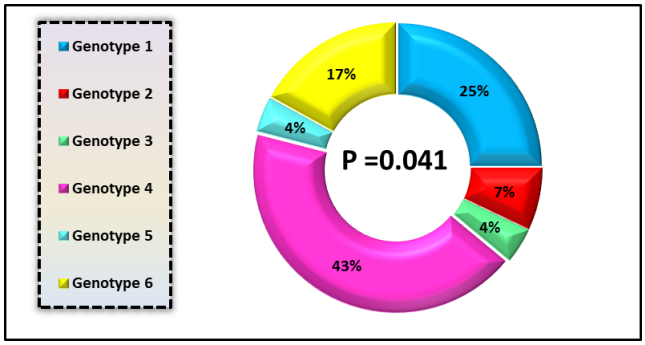

Figure 1: Distribution of studied cases according to HCV genotypes.

Table 2: Distribution of HCV genotypes according to *H. pylori* infection.

HCV genotypes	*H. pylori positive N (%)*	*H. pylori negative N (%)*	P value	Total number
Genotype 1	14 (23%)	11 (28%)	0.314	25 (25%)
Genotype 2	1 (2%)	6 (15%)	0.048	7 (7%)
Genotype 3	3 (5%)	1 (3%)	0.742	4 (4%)
Genotype 4	30 (49%)	13 (33%)	0.043	43 (43%)
Genotype 5	2 (3%)	2 (5%)	0.747	4 (4%)
Genotype 6	11 (18%)	6 (15%)	0.681	17 (17%)
Total number	61	39		100

Table 3: Effects *H. pylori* infection on clinical and demographics of cases.

Parameters	**Positive *H. pylori* (n=61)**	**Negative *H. pylori* (n= 39)**	**P value**
Gender	N (%)	N (%)	
Male	15 (25%)	37 (95%)	0.005
Female	46 (75%)	2 (8%)	0.0001
Age / year	N (%)	N (%)	
>15	4 (7%)	7 (18%)	0.047
15 - 45	11 (18%)	18 (46%)	0.009
>45	46 (75%)	14 (36%)	0.007
Meld score	N (%)	N (%)	
<10	12 (20%)	17 (44%)	0.010
>10	49 (80%)	22 (56%)	0.0078
Child score	N (%)	N (%)	
CAH	10 (42%)	14 (58%)	0.044
A	10 (43%)	13 (57%)	0.042
B	16 (76%)	5 (24%)	0.006
C	25 (78%)	7 (22%)	0.021

Table 4: Evaluation some biochemical and immunological indicators level according to *H. pylori* infection.

Variables	**Mean ± standard deviation**			**X2**	**P value**
	***H. pylori* positive**	***H. pylori* negative**	**Control**		
AST (U/L)	61.4 ± 5.9	22.7 ± 3.8	5.9 ± 1.4	12.63	0.008
ALT (U/L)	79.7 ± 10.2	47.1 ± 7.7	8.1 ± 2.4	15.76	0.005
ALP (U/L)	130 ± 16.6	135.5 ± 15.3	47.6 ± 9.6	4.041	0.035
Bilirubin (ng/dl)	3.6 ± 0.16	5.1± 1.09	0.14 ± 0.11	1.142	0.371
IL- 8 (pg/ml)	208 ± 23.5	224 ± 19.3	11.6 ± 2.7	9.854	0.016
IL- 17 (pg/ml)	313 ± 21.3	159.4 ± 14.6	23.6 ± 7.4	23.69	0.001
TNF-α (ng/ml)	99.2 ± 17.7	75.6 ± 25.3	9.9 ± 7.5	9.186	0.037
IL-6 (ng/ml)	79.4 ± 11.6	58.3 ± 13.7	7.55 ± 4.1	11.33	0.022

Table 5: Pearson correlation coefficient (r) among studied parameters in HCV patients with *H. pylori* infection.

Variables	**IL-8**	**IL-17**	**TNF-α**	**IL-6**
AST	0.6116	0.7147	0.8222	0.4661
ALT	0.5019	0.3155	0.5571	0.3510
ALP	0.3923	0.6331	0.8836	0.4409
Bilirubin	0.9110	0.6462	0.7691	0.2727
IL-8	——	0.4511	0.7091	0.3999
IL-17	0.4511	——	0.8111	0.5392
TNF-α	0.7091	0.8111	——	0.6276
IL-6	0.3999	0.5392	0.6276	——

4 Discussion

Our HCV patients showed a significant rise in H. pylori infection with age and sex, suggesting that half of the world's population is infected. These results are similar to those given by Pellicano et al. [21]. Infection rates of *Helicobacter pylori* vary greatly between communities but tend to rise with age. At age 20, the prevalence drops to 20% in the United States, but it rises to over 50% by age 50 and beyond [22]. Japanese figures show a similar pattern: under 20% at 20 years old, rising sharply to 80% at 40 years old [23]. The highest increased prevalence rate is in Korea, where it reaches 90% in asymptomatic adults over the age of 20 and has previously reached 50% at 5 years old [24].

Patients with liver illness have had their liver tissue tested and shown to have DNA from the *H. pylori* species. This has led to the intriguing hypothesis that these microorganisms may contribute to the development of cirrhosis, hepatocellular carcinoma, chronic viral hepatitis, and hepatic ulcers [25]. Some epidemi-

ological studies have shown that cirrhotic individuals have an extremely high frequency of *H. pylori* [26].

Although hepatitis C virus is highly prevalent in Iraq, with type 4 being the dominant genotype, no conclusive data regarding Iraqi patients has been uncovered, regardless of how widely this data might be accessed.

This study sought to determine if individuals infected with hepatitis C virus also had *H. pylori* infection; the patients had active chronic hepatitis and cirrhosis at varying stages. This bacterial infection was more common in the patient groups compared to the control group, according to the data. Furthermore, there is evidence that *H. pylori* infection rates rise in tandem with Child and Meld scores. Cirrhotic individuals often get stomach and duodenal ulcers in quick succession, which may be explained by the high incidence of *H. pylori* infection, as shown in these studies [21]. Furthermore, it is very probable that Helicobacter spp. are associated with HCC, and Ponzetto et al. [27] proposed that *H. pylori* is involved in the development and progression of cirrhosis, particularly in those infected with HCV.

In coinfection, we observed higher levels of IL-17, TNF-α, and IL-6, while in individuals infected with HCV alone, we discovered an enhanced level of IL-8. The concentrations of these variables in the control group and the patients were significantly different, though. Interleukins, liver enzymes, and bilirubin were also shown to be positively and linearly related in our data. One of the most crucial physiological events in *H. pylori* infection is the start of the stomach mucosal inflammatory response. Hydrochloromyces pylori and its byproducts trigger and include proinflammatory cytokines, specifically IL-17, TNF-α, IL-8, and IL-6. Immunocompetent cells communicate with hematopoietic cells, and immune cells communicate with the neuroendocrine system; nevertheless, pro-inflammatory cytokines are peptide atoms in solution that disrupt these connections [28]. Once the stomach mucosa becomes infected with *H. pylori*, the invading neutrophils and mononuclear cells release a small number of pro-inflammatory cytokines. By focusing on specific receptors on track cells, these cytokines exert their normal effects [29].

Inflammatory cytokines such as interleukins 6, 8, 17 (IL-6, IL-8, IL-17) and TNF-α, as well as the existence of lympho-mono cell penetration and lymphoid follicle development, characterise each provocative cycle of chronic hepatitis [30]. Because they lose their receptors, infections like HCV are only able to produce limited discomfort; this limits the likelihood of interleukin binding to cell receptors. Also, Helicobacters are potent pro-inflammatory cascade inducers; [31,32] infection with these bacteria might cause an abnormally high concentration of lymphocytes and polymorphonuclear cells in the affected tissue.Some species of Helicobacter may be implicated in harming liver parenchyma in vivo because they release a toxin that targets the liver and induces hepatocyte necrosis in cell culture [33]. Next, we will look at the increase of certain interleukins in individuals who are experiencing a concomitant infection. The immune response that follows the virus's entrance into the liver, along with a high concentration of inflammatory interleukins, may damage the stomach tissues through their association with prostaglandins and histamines, allowing the bacteria to easily invade the stomach tissues. This, in turn, may explain why hepatitis C patients have an increased risk of *H. pylori* infection [30, 34]. We have demonstrated that elevated bilirubin and liver enzyme levels may be due to abnormal immune responses; conversely, the vast majority of bacterial and viral components stimulate the immune system in a way that is detrimental to the body, worsening preexisting conditions. There is a lack of data to support the interpretation of our results since there are very few research that evaluate the immune response and its link to liver function.

H. pylori is known to cause HCC by a histidine-rich cytoplasmic protein (hpn), which accounts for almost 2% of the total proteins produced by the bacteria (Liu et al., 32). Hpn is a protein that operates by capturing metal particles within cells; this is important because nickel is known to cause cancer. Molecular targeting of the hpn protein by ubiquitin specific protease 5 (USP5) was recently identified. According to the study, hpn caused cell death and growth inhibition via lowering USP5 expression in HCC cells [32, 33]. Despite growing evidence, clinical trials have failed to establish a link between *H. pylori* and the progression of HCC, so the link remains controversial. According to research by El-Masry et al. [34, 35], the presence of *H. pylori* infection increases the likelihood of HCC, and the risk is more larger when HCV and *H. pylori* are co-infected. One possible way to reduce the risk of getting HCC is to treat curable diseases like *H. pylori* and HCV.

Based on our data, genotype 4 accounts for 43% of HCV infections in our population, followed by genotype 1 at 25% and genotype 6 at 17%; genotypes 3 and 5 had the lowest prevalence rates, at 4% and 4%, respectively. Research throughout Europe shows that there is little variation in the distribution of genotypes throughout the continent's Western, Eastern, and Central regions. When comparing the three regions, genotype 2 was most common in Western European nations (8.9%), but genotype 1 was less variable in Central and Eastern Europe (70% and 68.1%, respectively). Genotype 3 was most prevalent in Western Europe (29%), whereas genotype 4 was spread out

in Central Europe (4.9%) and Eastern Europe (26.6%), respectively [12].

5 Conclusion

Our research showed that having an HCV infection increases the risk of stomach infections caused by *Helicobacter pylori*, which can lead to inflammation and ulcers in the stomach. Our study found that compared to healthy subjects, infected individuals experienced changes in liver enzymes and bilirubin levels, as well as an increase in the immune response through the secretion of immune cells of certain interleukins. These changes were more pronounced in coinfection infections (*H. pylori*-HCV), and they contributed to patients' worsening health status, so it is imperative that therapeutic methods be developed to decrease coinfections.

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Conflict of Interest: No conflicts of interest exist between the authors and the publication of this work.
Ethical consideration: The study received ethical approval from the Continuing Education Unit of the Al-Diwaniyah General Teaching Hospital. After the researcher explained the aim, objectives, and methods of the study, the patients gave their written informed consent during they participated in the study, (No. 151-2022 dated 2/1/2022).

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