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Original article

The Relation between Chronic Viral Hepatitis B Infection and Helicobacter Pylori Infection

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Abstract:

- ***Background***: The relation between H. pylori infection and Viral Hepatitis has been subjected to substantial research in recent years, however, this relationship has not been comprehensively studied in Al Sulaymaniyah. The objective of this study is to Investigate the association between HBV infection and the H. pylori infection.
- ***Method and patient:*** A case-control study using data from 130 participants, from January 2020 to March 2021. Data is divided into two groups, a study group which consists of 65 persons of confirmed hepatitis B infection via PCR, and a control group of 65 persons with confirmed Hepatitis B negative by Hepatitis B surface antigen test, we used stool antigen test to confirm the presence or absence of H. Pylori infection in both groups.
- ***Result:*** 32% of the study group is infected with H. pylori and 15% in the control group have been tested positive for H. pylori infection. The regression analysis results reveal strong evidence that HBV infection increases the likelihood of *H*. pylori infection. This relationship is very robust and consistent even after controlling a vast number of variables as confounding and medical factors.
- ***Conclusions:*** Patients with HBV infection are more vulnerable to H. pylori infection.
- **Keywords:** H. pylori infection, HBV infection, case-control study.

INTRODUCTION

Gastric organisms were first observed more than 100 years ago and their association with gastritis has been recognized since the 1970s. In 1982, Marshall and Warren identified and cultured the gastric bacterium, *Campylobacter pyloridis*, later reclassified as *Helicobacter pylori* (hereafter *H.* pylori) [(1)]. In the case of Hepatitis, this refers to an inflammatory condition of the liver that is commonly caused by a viral infection. However, there are other potential causes of hepatitis such as autoimmune hepatitis or hepatitis that occur as a secondary result of medications, drugs, toxins, and alcohol [(2)]. The relation between *H.* pylori infection and Viral Hepatitis has been subjected to substantial research in recent years; however, this relationship has not been comprehensively studied in Al Sulaymaniyah.

The *H.* pylorus is a spiral-shaped, microaerophilic, gram-negative bacterium measuring approximately 3.5 microns in length and 0.5 microns in width. In vitro, it is a slow-growing organism that can be cultured on blood agar or selective media such as Skirrow's media incubated at 37º C in a 5 percent oxygen atmosphere for three to seven days [(3)]. While the prevalence of *H*. pylori infection is found to be very high in the developing countries - the majority of children are infected before the age of 10 and in adult's peaks at more than 80 percent before age 50 – it is relatively less in developed countries [(4)].

Previous studies indicate that the risk of *H.* pylori infection is related to socioeconomic status and living conditions early in life. Factors such as density of housing, overcrowding, number of siblings, sharing a bed, and lack of running water have all been linked to a higher acquisition rate of *H.* pylori infection and the consumption of salted food appears to increase the possibility of persistent infection with *H.* pylori infection [(5)].

The route by which infection occurs remains unknown, however, some studies demonstrate that *person-to-person* transmission of *H.* pylori via either fecal/oral or oral/oral exposure is the most likely source of infection [(6,7)]. Additionally, contaminated water supplies in developing countries may serve as an environmental source of bacteria, for instance, children who regularly swim in rivers, streams, pools, drink stream water, or eat uncooked vegetables are more likely to be infected [(8)]. Furthermore, the iatrogenic infection has been documented following the use of a variety of inadequately disinfected gastric devices such as endoscopes and their accessories [(9)]. In addition to those suspected of being infected and being tested, gastroenterologists and nurses appear to be at increased risk for acquiring *H.* pylori due to occupational exposure to infected gastric secretions [(10)].

An infected person with *H.* pylori disease can usually be asymptomatic; however, some infected persons may have symptoms including nausea, vomiting, abdominal pain, heartburn, diarrhea, hunger in the early morning, and Halitosis [(11)].

The *H.* pylori infection is associated with many gastrointestinal diseases including peptic ulcers and malignancy such as Gastric adenocarcinoma, and Maltoma [3].

Diagnostic testing for *H.* pylori can be divided into invasive and noninvasive techniques based on the use of upper endoscopy. Endoscopy-based tests, the urea breath test and the stool antigen assay test can be used for active *H.* pylori infection. The choice of test used to diagnose *H.* pylori depends on whether a patient requires an upper endoscopy for evaluation of symptoms or surveillance, and therefore, the endoscopy is not indicated solely to establish *H.* pylori status. The choice of test depends also on other important determinants: the recent use of medications that can suppress the bacterial load of *H.* pylori (e.g., proton pump inhibitor therapy [PPI] and antibiotics), the prevalence of *H.* pylori, the test availability, and the test costs. Before applying *H.* pylori tests, both PPI and bismuth/antibiotic medication use should be stopped within one to two weeks and four weeks before testing, respectively. This is because these medications can decrease the sensitivity of all endoscopy-based tests and non-invasive tests of active *H.* pylori infection including stool antigen and urea breath test [12].

Among patients undergoing upper endoscopy, the choice of test to diagnose *H.* pylori and the type of testing varies depending on the clinical presentation and the endoscopic findings. To be able to conduct proper testing, the following points should be considered [13]:

- ❑ No active peptic ulcer bleeding
- ❑ No recent PPI/bismuth/antibiotic medications use as mentioned earlier and no indication for gastric biopsy: In patients without recent PPI/bismuth/antibiotic medication use and who do not require biopsies of the stomach for histology, the diagnosis of *H.* pylori can be established with a biopsy Rapid urease test.
- ❑ In case of recent PPI/bismuth/antibiotic medications use or indication for gastric biopsy: In patients with visible endoscopic abnormalities (e.g., gastric ulcer, gastropathy), and patients with recent antisecretory/bismuth/antibiotic use, we perform histology to diagnose *H.* pylori. Since recent PPI/bismuth/antibiotic use may diminish the numbers of bacteria detected by histology, we perform a urea breath or stool antigen assay to confirm a negative test result once these medications have been held for an appropriate length of time [14].
- ❑ Prior antibiotic treatment failures: In patients with *H.* pylori that is refractory to two courses of antibiotic therapy, we perform culture and antibiotic sensitivity testing on gastric biopsies to guide treatment.
- ❑ Active peptic ulcer bleeding: In patients with bleeding duodenal or gastric ulcer on upper endoscopy, we perform a gastric mucosal biopsy at the time of the initial endoscopy unless it is impractical or difficult such as with a blood-filled stomach. A negative biopsy result does not exclude *H.* pylori in the setting of an active upper gastrointestinal bleed, and another test (ideally a urea breath test)

should be performed to confirm a negative result [15]. If a gastric mucosal biopsy is not obtained at the time of endoscopy, we perform a urea breath test or stool antigen assay to diagnose *H.* pylori [16].

Regarding Endoscopic-based test types, the following tests are available:

1. Biopsy urease testing: The sensitivity and specificity of biopsy urease testing are approximately 90 and 95 percent, respectively [17].
2. Histology: Gastric biopsies histology can diagnose *H.* pylori infection and associated lesions, for example, atrophic gastritis, intestinal metaplasia, dysplasia, and MALT lymphoma.
3. Bacterial culture and sensitivity testing: Culturing typically is characterized as having a sensitivity greater than 90% and a specificity of 100% when performed under optimal conditions [18].

In patients who do not require endoscopic evaluation, the diagnosis of *H.* pylori should be made with a test for active infection (stool antigen assay or urea breath test). In clinical situations where patients are unable or unwilling to stop PPI therapy one to two weeks before testing, positive test results are true positives; negative results may represent false negatives and should be confirmed with repeat testing after stopping PPI therapy for one to two weeks. The noninvasive tests for the diagnosis of *H. pylori* include urea breath testing (UBT), stool antigen testing, and serology. Of these, UBT and stool antigen assay are tests of active infection. *H.* pylori serology can be positive in patients with an active or prior infection.

Noninvasive based test types include:

1. Urea breath testing (UBT): The sensitivity and specificity of UBT are approximately 88% to 95 % and 95% to 100% [19]. However, false-negative results may be observed in patients who are taking PPIs, bismuth, or antibiotics medications and in the setting of active peptic ulcer bleeding [20].
2. Stool antigen assay (SAT): The first SAT introduced was the polyclonal type and was followed by a monoclonal test. The latter test is better in both testing untreated patients and following up with treated patients [21, 22]. The detection of bacterial antigen indicates an ongoing *H.* pylori infection, and SAT can, therefore, be used to establish the initial diagnosis of *H.* pylori and to confirm eradication [17]. Among the available tests, stool antigen testing is the most cost-effective. The results from the SAT can be affected by the recent use of bismuth compounds, antibiotics, and PPIs medications.
3. Serology: The serological test can be performed via Laboratory-based - An Enzyme-Linked Immunosorbent Assay (ELISA) test - to detect Immunoglobulin G (IgG) antibodies. Although this type of testing is inexpensive and noninvasive, the guidelines recommend that serologic testing should not be used in low prevalence populations, as the low accuracy of serology would result in inappropriate treatment in significant

numbers of patients. This is because this type of testing cannot reliably distinguish between active and past infection [17, 23, 24].

4. Other infrequently invasive- and noninvasive used tests

- ❑ Polymerase chain reaction: Quantitative polymerase chain reaction (PCR) testing on gastric biopsies can be used to detect low bacterial loads. It can also be used to identify specific mutations associated with antimicrobial resistance. However, the use of PCR-based testing is limited by its high cost.
- ❑ 13C-urea assay: A serodiagnostic test using a 13C-urea assay is a noninvasive tool for diagnosis of *H.* pylori infection, but is rarely if ever, used in clinical practice. This test is performed by measuring two serum specimens; the first one is taken before ingestion and the second one 60 minutes after ingestion of a 13C-urea-rich meal. The test has a reported sensitivity of 92% to 100 % and a reported specificity of 96% to 97 % [25].

All patients with evidence of active infection with *H.* pylori should be offered treatment depending on whether there are risk factors for macrolide resistance and the presence of a penicillin allergy [26].

Chronic Viral Hepatitis B (HBV) infection

Hepatitis B Virus (HBV) infection is a global public health problem and according to the World Health Organization (WHO) about 257 million were HBV carriers in the world in 2015, and roughly 887,000 persons died the same year from HBV-related liver disease [28]. Hepatitis B viral infection can be divided into acute or chronic infection depending on the duration of infection and serological markers:

- o Acute Hepatitis B viral infection: The diagnosis of acute HBV infection is based on the detection of hepatitis B surface antigen (HBsAg) and IgM antibody to hepatitis B core antigen (anti-HBc), with elevated alanine aminotransferase (ALT) and with a duration less than 6 months.
- o Chronic viral hepatitis B viral infection: This type is characterized by the persistence of hepatitis B surface antigen (HBsAg) for more than six months.

It is estimated that approximately two billion people worldwide have evidence of past or present infection with hepatitis B virus (HBV), and 257 million individuals are chronic carriers i.e., positive for hepatitis B surface antigen (HBsAg) [28, 29]. In 2013, viral hepatitis, primarily due to HBV and hepatitis C virus, was the seventh leading cause of death worldwide [30]. The prevalence of HBV infection varies depending upon the geographic area, and the wide range in the prevalence is largely related to differences in the age at infection time, which is inversely related to the risk of chronicity. The rate of progression from acute to chronic HBV infection is approximately 90 percent for perinatally acquired infection and in areas of low prevalence,

many of the patients who have chronic HBV were born in areas in which the prevalence is higher [31].

Hepatitis B virus (HBV) is transmitted from patients who are infected to those who are not immune i.e., hepatitis B surface antibody (anti-HBs)-negative. However, the HBV vaccination has significantly reduced the risk of transmission worldwide.

Many patients with chronic HBV are asymptomatic (unless they have decompensated cirrhosis or have extrahepatic manifestations), while others have nonspecific symptoms such as fatigue. Some patients experience exacerbations of the infection which may be asymptomatic, mimic acute hepatitis, or manifest as a hepatic failure.

Physical examination may be normal or there may be stigmata of chronic liver disease like jaundice, splenomegaly, ascites, peripheral edema, and encephalopathy may be present in patients with decompensated cirrhosis. Although the laboratory tests may appear normal, most patients would have a mild to moderate elevation in serum Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT). A progression to cirrhosis is suspected when there is evidence of hypersplenism (decreased white blood cell and platelet counts) or impaired hepatic synthetic function (hypoalbuminemia, prolonged prothrombin time, hyperbilirubinemia).

The extrahepatic manifestations are thought to be mediated by circulating immune complexes. It may be heralded by a serum sickness-like syndrome manifested as fever, skin rashes, arthralgia, and arthritis which usually subside with the onset of jaundice. The two major extrahepatic complications of chronic HBV are polyarteritis nodosa and glomerular disease [33].

Hepatitis B surface antigen (HBsAg) is the serologic hallmark of HBV infection. It can be detected using an Enzyme ImmunoAssay (EIA). The HBsAg appears in serum 1 to 10 weeks after acute exposure to HBV, before the onset of clinical symptoms characteristic for acute hepatitis or elevation of serum alanine aminotransferase (ALT). In patients who subsequently recover, HBsAg usually becomes undetectable after four to six months. The persistence of HBsAg for more than six months implies chronic infection. It is estimated that less than 5 percent of immunocompetent adult patients with genuine acute hepatitis B progress to chronic infection [34]. Among patients with chronic HBV infection, the rate of clearance of HBsAg is found to be approximately 0.5 percent per year [35]. The disappearance of HBsAg is followed by the appearance of a hepatitis B surface antibody (anti-HBs). In most patients, anti-HBs persists for life, thereby conferring long-term immunity from reinfection, however, over time anti-HBs may disappear in some patients, and they may have only isolated hepatitis B core antigen (anti-HBc) IgG.

Chronic HBV infection can be divided into four different phases depending on the level of immune activity, and the type of treatment is based on the phase of the infection [36]. These phases are as follow:

1) Immune-tolerant phase: In this phase, little hepatic inflammation will be observed with normal liver tests despite elevated HBV DNA and positive HBe antigen.
2) Immune-active phase: In the next phase, there will be hepatic inflammation with liver tests, decreased DNA levels of HBV compared to the immune-tolerant phase, the ultimate loss of HBe antigen, and the appearance of HBe antibody.
3) Inactive carrier phase: This phase is characterized by normal liver tests, low HBV DNA levels, and HBe antigen-negative.
4) Reactivation phase: This phase can be recognized when patients have normal or high liver tests, high HBV DNA levels, remain HBe antigen-negative, or revert to HBe antigen-positive.

It is important to note that not all patients go through all 4 phases, and immune clearance and reactivation phases can sometimes be prolonged.

As chronic HBV infection cannot be cured, the goals of treatment are to suppress viral replication, halt the progression of liver disease, and prevent hepatocellular carcinoma. The recommended treatment timing and duration vary by the status of chronic HBV.

1) Immune-tolerant chronic hepatitis B: Most patients in this phase do not need antiviral therapy. However, antiviral therapy should be considered for patients over the age of 40 years that have a normal alanine aminotransferase (ALT) level with elevated HBV DNA (≥ 1,000,000 units/mL) and liver biopsy indicating moderate-to-severe necro-inflammation or fibrosis.
2) Immune-active chronic hepatitis B (HBeAg-negative or HBeAg-positive): In this phase, antiviral therapy is recommended to reduce the risk of liver-associated complications. The preferred drug options for initial therapy include peginterferon and nucleoside/nucleotide analogues (NAs) entecavir and tenofovir. In the case of HBeAg-positive, immune-active chronic hepatitis B with seroconversion to anti-HBe on A nucleoside analog (NA) therapy, discontinuing NA therapy after a period of treatment consolidation should be considered if there is no liver cirrhosis. However, if liver cirrhosis presents, indefinite antiviral therapy should be considered to reduce the risk of potential clinical decompensation and death unless there is a strong indication for treatment discontinuation.
3) Chronic HBV inactive carrier (Normal ALT, HBeAg negative, anti-HBe positive, HBV DNA <10,000 IU/mL and with No inflammation, variable liver fibrosis): This phase of disease does not require treatment.
4) Reactivation Phase (HBeAg negative, anti-HBe positive, HBV DNA >10,000 IU/mL, and Inflammation and fibrosis of liver): In this phase treatment with antiviral therapy should be restarted.

The aim of this study is investigating the association between HBV infection and the likelihood of *H*. pylori infection.

PATIENT and METHOD

This is a case-control study. The data is collected from the Kurdistan Center for Gastroenterology and Hepatology (KCGH) and SHAR teaching hospital in Al Sulaymaniyah at the consultant room of the admission ward. The sample consists of 130 patients over 14 months spanning from January 2020 to March 2021.

We conduct a survey that includes related questions to our study, and all patients were informed about the nature of the study and verbal consent was obtained from each of them. The data were collected randomly through face-to-face interviews over the 14 months with the patients based on a prepared questionnaire list.

The sample of the study is divided into two groups of patients:

- ❑ The first group consists of patients that are chronically infected with hepatitis B virus (study group) and includes all patients who have been diagnosed for at least 1 year with still positive HBsAg.
- ❑ The second group (control group) is randomly selected and includes those who have no known liver disease and tested negative for HBsAg.

To obtain a more accurate result, we restrict the sample by excluding the following:

- ❑ Pregnant women.
- ❑ Patients less than 18 years old.
- ❑ Patients that used protein pump inhibitors (PPIs) in the last two weeks or antibiotics in the last month, before testing for H. pylori infection.

Ethical considerations and official approvals

- ❑ Approval was taken from the scientific council of the Arab Board of Health Specialization in Iraq.
- ❑ Approval was taken from the authority of the Kurdistan Center for Gastroenterology & Hepatology (KCGH) and Shar teaching hospital in Sulaymaniyah.

- ❑ Oral informed consent was taken from each patient who enrolled in this study. Confidentiality was taken into consideration.

Statistical analysis

We applied different identification strategies to conduct this study using our sample of 130 observations. In addition to the twelve variables from the survey mentioned above, we obtained two additional variables that are essential for this study: the results from testing of both stool antigen for *H*. pylori infection and HBsAg for both study and control groups. We start by coding our information obtained from the survey and the test results using the STATA 16 statistic program.

We first conduct descriptive statistics presenting several figures and tables containing the mean and standard deviation of several variables concerning our variable of interest, *H*. pylori infection. Next, we applied *a t*-test to compare the study and the control groups where the only difference between them is whether a participant has or not an HBV infection. Third, we will be calculating and presenting the Odds ratio of this case-control study to further identify whether there is a difference between groups due to HBV infection. The advantage of these statistic tests is providing both *t*-statistics, Chi^2-statistics, and *p*-values allowing us to conclude to evaluate the difference between study- and control groups i.e., the association between *H*. pylori infection and HBV infection.

However, these three identification strategies are, in fact, not sufficient to draw any conclusion on the causal impact of HBV infection on *H*. pylori infection. Therefore, we finally conduct regression analyses to identify and quantify the relation between chronic HBV infection and *H*. pylori infection (the causal relationship). The dependent variable of our regression model (*H*. pylori) is a dummy variable that takes the value 1 if the participant has been tested positive for *H*. pylori infection and takes the value 0 otherwise. Therefore, it is not appropriate to apply the Ordinary Least Squares method (OLS) to estimate the coefficients of the independent variables in the regression models as this method requires a continuous dependent variable. Alternatively, we employ a Poisson regression approach using the maximum likelihood method to estimate our regression models to identify the relation between chronic HBV infection and *H*. pylori infection. For all statistical analyses, a *p*-value of ≤ 0.05 is regarded as statistically significant.

RESULTS

Table 1 below presents an overview of descriptive statistics for both the study and control groups. The study group indicates participants that have been tested positive for HBV infection, and control is a randomly assigned group that has been tested negative for HBV infection. The total sample size consists of 130 participants and is equally distributed among both the study

and control groups. While about 32% of the participants are infected with H. pylori bacterium in the study group (SD 5%), only 15% are infected in the control group (SD 4%). The age of participants range from 19 to 75 years old for the whole sample, and the mean age for the study and control groups is 42.26±15.21 and 39.52±14.70 years old, respectively. The gender seems to be equally distributed in which the study group consists of about 55% males and the control group includes about 52% males.

Table 1 also presents information on other confounding factors such as the residency of participants - whether they live in rural areas or the urban area of Al-Sulaymaniyah - and information on their job status. While all participants in the control group living in the city center, only 40% of the study group lives in the city center (60% lives in rural areas). The share of unemployed participants is higher in the study group, (46%) compared with the control group (38%). Only 12% of the participants in the study group were civil employees, while this category is observed to be higher among the control group (35%). The average duration for HBV infection in study group participants was approximately 5 years. Among all participants that have been diagnosed with HBV infection (study group), only 18% are taking Tenofovir medicine. Further, only 9% have a family history of other members being infected with HBV infection in the study group. Interestingly, we observe that about 52% of the study group participants have been subject to a surgical intervention where the most prevalent is Cesarean Section (C/S) with about 22% while only 15% of the participants in the control group have a history of surgery.

Table 1: General characteristics for study and control groups

	Study group (N=65) (Positive HBV infection)		Control group (N=65) (Negative HBV infection)		
	Numbers	Percentage	Numbers	Percentage	p-value
H. pylori (positive)	21	32	10	15	
Gender (male)	36	55	34	52	0.7
Occupation:					
Military-employee	7	11	3	05	
Civil employee	8	12	23	35	
Free jobs	13	20	14	22	
Unemployed	30	46	25	38	
Residency: Urban area	26	40	65	100	
Rural	39	60	0	0	
Medical factors:					
Hypertension	4	06	5	08	
D.M	1	02	5	08	

Anti-diabetic treatment	3	03	4	06
Tenofovir	12	18	0	00
On medical treatment	18	28	8	12
Past Surgical history:	34	52	10	15
Herniotomy	3	05	1	02
CS	14	22	5	08
Appendectomy	3	05	0	0
Varicocele	2	03	0	0
Family history	6	09	0	0
Social history:				
Smoker	6	09%	8	12%

Note: S.D. denotes the standard deviation of the variable. The total sample size is 130 participants. The study indicates a group that has been tested positive for HBV infection, and control is randomly an assigned group that has been tested negative for HBV infection. Each group consists of 65 participants. The data has been collected for the period from January 2020 to March 2021 from SHAR teaching hospital and Kurdistan Center for Gastroenterology and Hepatology (KCGH).

Figure 1 presents the share of patients who tested positive for H. pylori infection for both the study and control groups. About 16% of the participants that have HBV infection, i.e., the study group, have been tested positive for H. pylori infection. However, considering the control group, the proportion of H. pylori infection seems to be lower relatively with approximately 7.6%. The rest of the patients in our sample (76%) have no H. pylori infection. We can argue that the higher ratio of H. pylori infection observed in the study group could be related to the HBV infection since the only difference between the two groups is whether they are diagnosed positive for HBV infection or not.

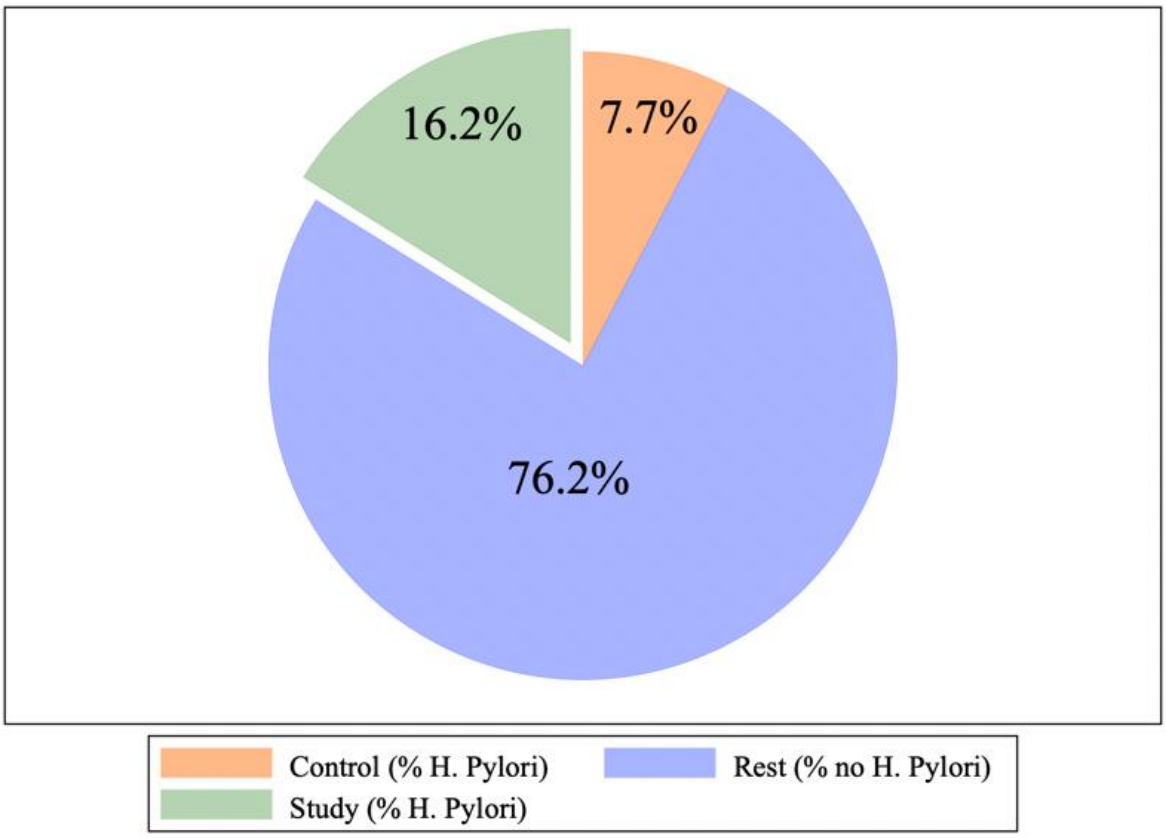


Figure 1: The distribution of patients infected with H. pylori for the whole sample

Note: Study group indicates patients tested positive for H. pylori infection and HBV. The Control group represents randomly assigned participants that have been tested negative for HBV infection.

The mean age of the participant in the study and control groups is about 42 ± 15 and 39 ± 14 years old, respectively. The small difference in mean age between the two groups is in favor of our method conducted in this study because comparing two comparable groups yield more reliable results.

Figure 2 presents the share of patients with H. pylori infection by gender. Considering the whole sample in panel A, 51.61% of H. pylori-infected patients are males and 48.39% are females. Considering the participants that have been tested positive for HBV infection (study group), 52.38% of males are infected with H. pylori and 47.62% of females are infected with H. pylori.

Panel A Panel B

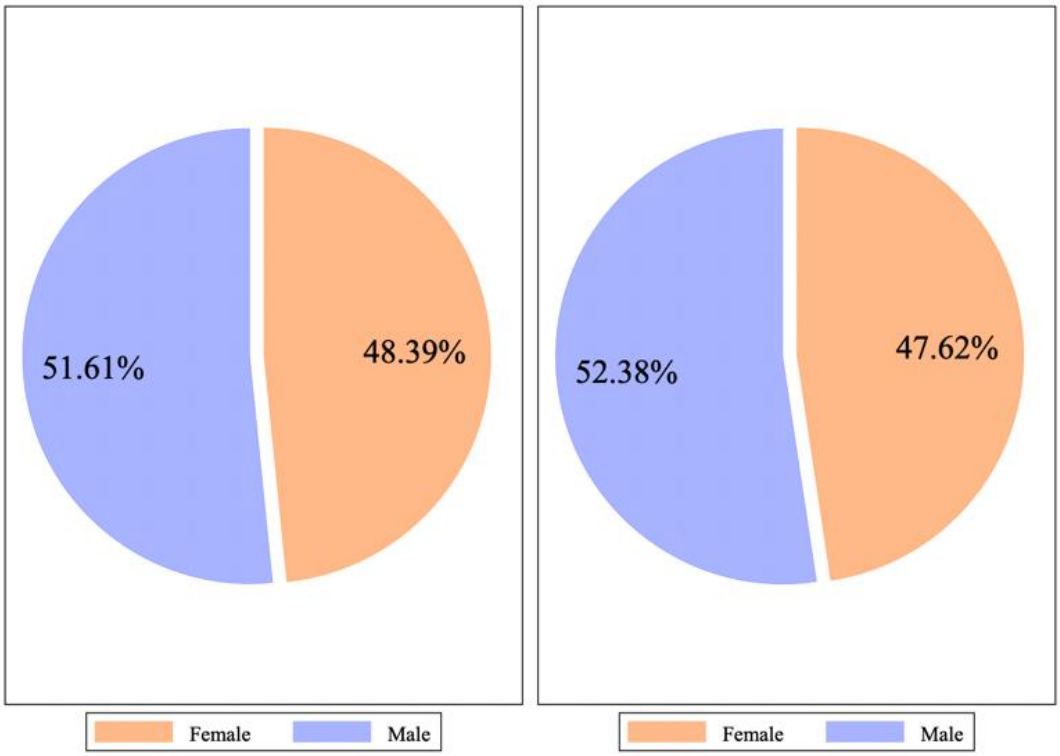
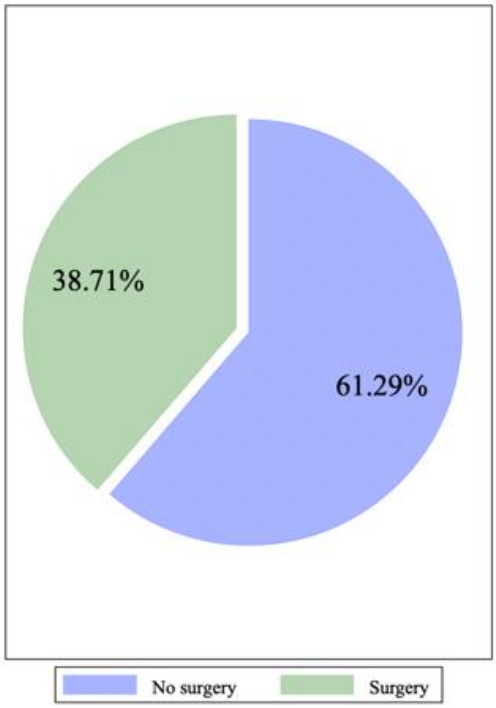


Figure 2: The distribution of patients with H. pylori infection by gender

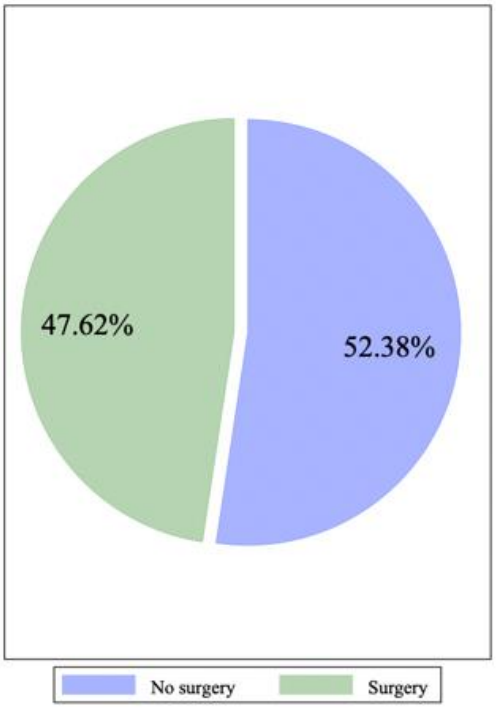
Note: Panel A presents the share of patients who tested positive for H. pylori by gender for both study and control groups (whole sample). Panel B presents the share of patients who tested positive for both H. pylori and HBV infection by gender (study group).

Figure 3 shows the patients that tested positive for H. pylori infection with previous surgical intervention for the whole sample in Panel A. About 39% of all participants have been subject to previous surgery, and about 61% had no surgical intervention. Considering the study group with HBV infection (Panel B), the share of participants with both H. pylori infection and had a surgical intervention is relatively higher (about 48%) compared with the whole sample. Panel C shows that cesarean section is the most prevalent (21.5%) among other types of surgeries. These results from Figure 3.3 may indicate a relation between previous surgical intervention and H. pylori infection prevalence. However, drawing any conclusion based on graphical presentation may be misleading; hence it is early to draw any conclusion regarding the relationship between surgical intervention and H. pylori infection before conducting any tests statistics.

Panel A



Panel B



Panel C

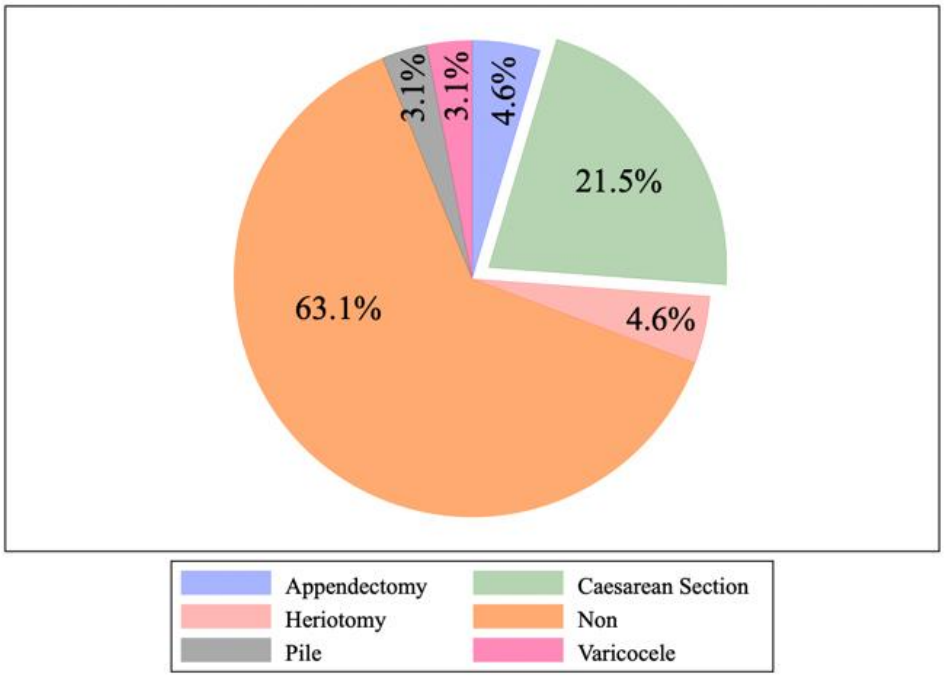


Figure 3: The distribution of H. pylori by surgical intervention

Note: Panel A shows the share of patients infected by H. pylori by surgical intervention for the whole sample (both groups). Panel B shows the share of patients with both H. pylori and HBV infection by surgical intervention (study group). Panel C presents the distribution of surgical intervention by type of surgery of patients with both H. pylori and HBV infection (study group).

T-TEST

This t-test is applied to compare the means of patients that are infected by H. pylori between two groups of patients. The study group includes patients with HBV infection while the control group includes patients that have no HBV infection. This t-test assumes that both samples are randomly assigned and that both groups have equal variance in the population.

Table 2 below shows that the overall mean of patients with H. pylori infection is 0.238, which represents the percentage of H. pylori infection patients in the whole sample (both groups). While the mean of H. pylori infection in the group that has no HBV infection is 0.154, the mean of the study group is 0.323 and the difference in means between both groups is estimated as 0.169 with a standard error equal to 0.0375.

The null hypothesis for this test is that the means are the same for both groups i.e. the difference in means between groups is equal to 0. The t-statistic of the difference in means is 2.292 with 128 degrees of freedom. Further, the p-value for the two-sided t-test is 0.0235, which is less than 0.05) significance level, indicating that the difference in means is statistically significant. Based on this we can with 95% confidence reject the null hypothesis and conclude that there is a difference in means of H. pylori infection between groups due to HBV infection.

Table 2: Two-sample t-test for patients infected with H. pylori infection with HBV infection.

Group	Obs.	Mean	Std. Err.	Std. Dev.	[95%Conf.Interval]		t-statistic	p-value
Study	65	0.3231	0.0585	0.4713	[0.2063	0.4399]		
Control	65	0.1538	0.0451	0.3636	[0.0638	0.2439]		
Combined	130	0.2385	0.0375	0.4278	[0.1642	0.3127]		
Difference		0.1692	0.0738		[0.3153	0.0231]	2 .2921	0.0235

Note: Ho: Difference = 0. Two tail t-test with 128 degrees of freedom. Study and control groups contain information on patients that have Hepatitis B and patients that have not Hepatitis B, respectively.

We also applied the Two-sample t-test to compare means by gender and age concerning H. pylori, presented in Table 3 below. The p-value of 0.77 is greater than the significance level of 5% (0.05) indicating that gender has no relationship with H. pylori infection.

Table 3: Two-sample *t*-test for patients infected with *H*. pylori infection concerning gender (by sex)

Gender	Obs.	Mean	Std. Err.	Std. Dev.	[95%Conf.	Interval]	t statistic	p-value
Female	60	0.25	0.056	0.44	[0.14	0.36]		
Male	70	0.23	0.057	0.42	[0.13	0.33]		
Combined	130	0.24	0.038	0.43	[0.16	0.31]		
Difference		0.02	0.076		[-0.13	0.17]	0.284	0.777

In Table 4 below we applied the t-test for patients infected with H. pylori concerning age. However, the p-value is 0.851 which is greater than the significance level of (0.05) provides evidence that H. pylori infection is not associated with the age of the participants.

Table 4: Two-sample t-test for patients infected with H. pylori infection concerning age (by age)

H. pylori	Obs.	Mean	Std. Err.	Std. Dev.	[95%Conf.	Interval]	t statistic	p-value
Negative	99	41.03	1.47	14.64	[38.11	43.95]		
Positive	31	40.45	2.91	16.19	[34.51	46.39]		
Combined	130	40.89	1.31	14.96	[38.30	43.49]		
Difference		0.58	3.09		[-5.54	6.69]	0.187	0.851

Note: Ho: Difference = 0. Two tail t-test with 128 degrees of freedom.

THE ODDS RATIO

Table 5 shows the results of the odds ratio with the Chi^2 test for the null hypothesis that there is no difference in the odds between the study and control groups, i.e. the odds are equal to 1 (no association between HBV infection and H. pylori infection). Table 5 shows that 21 participants in the study group that have positive HBV infection – have positive H. PYLORI infection and 44 participants are tested negative for H. pylori.

Considering the control group, 10 participants have positive H. pylori infection and 55 of the participants have no H. pylori infection. The total share of H. pylori infections among all

participants in both groups is 24%. The p-value (0.02) from the Chi^2 test is less than 5% (0.05) significance level suggesting that we can reject the null hypothesis. Further, the odds ratio is 2.6 which is greater than 1, indicating that the HBV infection might be a risk factor for the H. pylori infection. The magnitude of the odds ratio – the strength of the association – is above 1 which indicated that the relationship between HBV infection and H. pylori infection is likely causal.

Table 5: The Odd ratio and Chi2 test of the association between HBV and H. pylori infection

	H. pylori (Positive)	H. pylori (Negative)	Total	Share H. pylori (Positive)
Study (Positive HBV)	21	44	65	32%
Control (Negative HBV)	10	55	65	15%
Total	31	99	130	24%
	Point estimate		[95% Conf. Interval]	
Odds ratio	**2.63**		**[1.05**	**6.88]**
Chi^2	5.13			
P-value	0.02			

Note: Chi^2 denotes the Chi-squared test to test the association between HBV and H. pylori infection. Ho: Odds = 1. Study and control groups contain information on patients that have Hepatitis B and patients that have not Hepatitis B, respectively.

POISSON REGRESSION RESULTS

The results from the descriptive statistics, the t-test, and the odds ratio test are not sufficient to provide evidence on the relation between H. pylori infection and HBV infection as the aim of this study is to identify this relationship. We, therefore, conduct a Poisson regression to be able to conclude this relationship.

We first regress the dummy variable H. pylori on the dummy variable that takes the value 1 if the study group - tested positive for HBV infection- and takes the value 0 if the control group. The results present in Table 6 below demonstrate that the coefficient on the variable Group (HBV) is positively significant (p-value < 0.05) indicating that there is a relation between H. pylori and HBV infection. The result can be interpreted as the likelihood of having H. pylori infection higher if a patient tested positive for HBV infection.

Table 6: Poisson regression results without control variables

	Coef.	Robust Std. Err.	Z-statistics	P-value	[95% conf. Interval]
Groups (HBV)	0.74	0.34	2.16	0.03	[0.06 1.41]
Constant	-1.87	0.29	- 6.41	0.00	[-2.44 -1.30]
Observation	130				

Note: The dependent variable is H. pylori infection, which is a dummy that takes the value 1 if the participant tested positive for H. pylori infection and 0 otherwise. Groups (HBV) is a dummy that takes the value 1 if the participant tested positive for HBV infection (study group) and 0 otherwise. We use a 5% significance level, and we use STATA 16 to produce the results. The standard errors reported are robust for heteroskedasticity.

Table 6 above provided evidence on the relation between H. pylori and HBV infection; we include confounding factors in the second regression presented in Table 7 below to check the robustness and the consistency of the coefficient on the Group (HBV). The confounding factors include age, gender, job status, whether the participant is a smoker or not, and the residency of the patients. The coefficients of these variables are, however, non-significant as the p-values are higher than the significance level of 5%. This indicates that, for example, being a man or woman, or living in the city center or the rural area of Al Sulaymaniyah or age has no relation with the likelihood of being infected with H. pylori. These results are not reported, but we reported only the coefficient of the Group (HBV) that is even after controlling for these additional factors is still significant at the 5% level. We notice that the magnitude of the coefficient increases after including these confounding factors (from 0.74 to 1.05).

Table 7: Poisson regression results after controlling for confounding factors.

	Coef.	Robust Std. Err.	Z-statistics	P-value	[95% conf. Interval]
Groups (HBV)	1.05	0.40	2.62	0.01	[0.26 1.84]
Constant	- 2.05	1.00	- 2.04	0.04	[- 4.01 - 0.08]
Observation	130				

Note: The dependent variable is H. pylori infection, which is a dummy that takes the value 1 if the participant tested positive for H. pylori infection and 0 otherwise. Groups (HBV) is a dummy that takes the value 1 if the participant tested positive for HBV infection (study group) and 0 otherwise. The confounding factors include age, gender, job status, whether the participant is a smoker or not, and participant residency. The confounding factors are included in the Poisson regression but not reported in the table. A table of all results can be provided upon request. We use a 5% significance level, and we use STATA 16 to produce the results. The standard errors reported are robust for heteroskedasticity.

In addition to the confounding factors, we lastly include some medical factors to evaluate and check the consistency of the coefficient of the Group (HBV). We reported only the significant

coefficient in Table 8 below. The coefficient of the variable Anti-HTN drugs is positive and significant at a 5% level (p-value 0.00), indicating that a patient with hypertension on a regular medication is less likely to be infected with H. pylori infection.

A growing body of evidence suggests that H. pylori infection is associated with diabetes and may cause insulin resistance. H. pylori-induced gastritis can also potentially affect the secretion of gastric-related hormones and inflammatory cytokines. The coefficient of Diabetes Mellitus (D.M) in Table 8 is positively significant at a 5% level (p-value =0.00) indicating that patients with D.M are more likely to be infected by H. pylori infection. However, being on regular medication (oral hypoglycemic drugs and insulin) decreases the likelihood of H. pylori infection, as shown in Table 8 that the coefficient of the variable D.M medications is negatively significant at a 5% level (p-value =0.00).

The results from Table 8 also provide evidence that among patients with surgical intervention in the participants of our study, Varicocele surgery is negatively associated with H. pylori infection. The viral copies coefficient is positively significant at a 5% level (p-value =0.01), indicating that the higher the Viral copies the higher is the likelihood of H. pylori infection.

Table 8: Poisson regression results after controlling for both confounding and medical factors

	Coef.	Robust Std. Err.	Z-statistics	P-value	[95% conf. Interval]
Groups (HBV)	1.34	0.57	2.35	0.02	[0.22 2.45]
Anti-HTN drugs	-16.25	1.19	-13.58	0.00	[-18.60 -13.90]
D.M	17.36	0.98	17.72	0.00	[15.44 19.28]
D.M medications	-16.33	1.19	-13.76	0.00	[-18.65 -14.00]
Varicocele	-15.75	0.88	-18.00	0.00	[-17.47 -14.04]
Viral copies	9.91e-09	4.02e-09	2.47	0.01	[2.03e-09 1.78e-08]
Constant	-2.11	0.75	-2.80	0.01	[-3.59 -0.63]
Observation	130				

Note: The dependent variable is H. pylori infection, which is a dummy that takes the value 1 if the participant tested positive for H. pylori infection and 0 otherwise. Groups (HBV) is a dummy that takes the value 1 if the participant tested positive for HBV infection (study group) and 0 otherwise. The confounding factors include age, gender, job status, whether the participant is a smoker or not, and participant residency. Additionally, we include medical factors in the regression. Both the medical and the confounding factors are included in the Poisson regression but not reported in the table. A table of all results can be provided upon request. Anti-HTN drugs refer to antihypertensive drugs and D.M medications refer to oral hypoglycemic drugs and insulin. We use a 5% significance level, and we use STATA 16 to produce the results. The standard errors reported are robust for heteroskedasticity.

Considering our variable of interest, Group (HBV), we observe that even after controlling for a vast number of variables, the relation reflected in the significant coefficient is still robust and consistent. The sign of the coefficient is positive in all three regressions (Table 6, 7, and 8), and

the p-value is also less than 0.05. This provides strong evidence allowing us to conclude that HBV infection increases the likelihood of H. pylori infection.

DISCUSSION

The relation between *H.* pylori infection and Viral Hepatitis has been subjected to substantial research in recent years; however, this relationship has not been comprehensively studied in Al Sulaymaniyah. In this study, we applied different identification strategies attempting to conclude the relationship between H. pylori and HBV infection. The total sample size consists of 130 participants and is equally distributed among both the study and control groups. In the study group, 32% of participants are infected with *H.* pylori (SD is approximately 5%), and only 15% of the patients are infected with *H.* pylori in the control group (SD is approximately 4%). The age of participants ranges from 19 to 75 years old for the whole sample, and the average age for the study and control groups were comparable. The gender seems to be equally distributed in which the study group consists of about 55% males and the control group includes about 52% males.

The results indicate that patients that are tested positive for HBV infection have a high probability of being infected by H. pylori. Our finding is following the literature and adds important findings to the existing few studies on the relation between *H.* pylori infection and HBV infection. A similar study was done by Fan et al in 1998. This study concludes that of the 96 patients with hepatitis B, 55 (57.3%) were positive for serum IgG anti-*H.* pylori, significantly greater than in the control group of 104, where 44 (42.3%) were positive ($P < 0.05$) [37].

A study published in 2016 by Wang J et al, showed that *H.* pylori infection may increase the risk of progression of chronic HBV infection among the Chinese population [38].

Patents on regular Anti-HTN drugs are less likely to be infected with *H.* pylori infection, as shown in the results of our study, and the relation between hypertension and H. pylori infection has been subjected to many studies in the last year, for example, a study done by Migneco A et al in 2003, pointed out a significant decrease in blood pressure values, in particular, in diastolic blood pressure values, after *H.* pylori eradication in hypertensive patients [39]. Another study done by Xiong et al in 2020 showed that *H.* pylori infection was positively associated with the prevalence of hypertension [40].

Furthermore, an Egyptian study was done by Mohammed AA et al in 2018 about the association between severity of liver disease, frequency of *H.* pylori Infection, and degree of gastric lesion in patients with HBV infection. This study provided evidence that *H.* pylori antigen in stool was detected in 45.7% of the control group (healthy group), and a higher percentage (60%) was

detected in the patients' group (known case of chronic HBV infection) [41]. In our study there was a significant relationship between H. pylori infection and diabetes, this result is consistent with the literature on the relation between D.M and *H.* pylori done by Kayar et al in 2015 [42].

We have found in our study that the higher the Viral copies the higher is the likelihood of H. pylori infection, this relation has been a subject to some studies previously and our result is consistent with the literature done by Haung et al in 2017 [43].

One potential limitation of this study could be the relatively small sample size. Further research on this topic is recommended to use a larger sample size and include more variables for the patient's medical history and socioeconomic factors.

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There are no conflicts of interest**.**

CONCLUSION

- The mean age of the participant in the study and control groups is about 42 ± 15 and 39 ± 14 years old, respectively.
- The prevalence of H. Pylori infection is about 32% in patients with HBV infection, but it is only 15% in the control group.
- HBV infection increases the likelihood of H. pylori infection.
- Age and gender were not associated with an increase in the incidence of H. pylori infection.

RECOMMENDATIONS

Based on the findings from this study, we suggest that any patients with positive HBV infection are recommended to be tested for *H.* pylori infection.

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