Iraqi Journal of Biotechnology, 2017, Vol. 16, No.1, 1-9

Association of *Helicobacter Pylori* Infection and Gastric Cancer

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Received: August 23, 2016 / **Accepted**: September 25, 2016

Abstract: *Helicobacter pylori* (*H. pylori*) is the most important etiologic factor for gastric cancer. It is one of the most common human pathogens, which colonizes in the mucus layer of the gastric epithelium in more than 50% of the population. The study include 78 samples of gastric cancer in addition to 42 blood samples. The results from 78 gastric cancer samples showed that gastric cancer can occur red at any age, but it increases in older ages and the incidence of *H. pylori* infected positive gastric cancer (HIP-GC) is higher than of *H. pylori* infected negative gastric cancer (HIN-GC). Male is the predominant in both groups and female affected by *H. pylori* more than male and the intestinal type was the predominant type.

Introduction:

Most of cancers arise from genetic instability including chromosomal changes and molecular genetic defects (1,2). Gastric cancer is a a major public health issue as the fourth most common malignancy, and the third most common cause of cancer-related death in both sexes worldwide (3) , partly, because patients are not diagnosed until late-stage cancer is present and a poor prognosis (4).

In Iraq, gastric cancer have low rate (5) and it is the ninth most common cancer (6). Carcinogenesis of stomach progresses through a sequence of preneoplastic lesions that manifest histologically as atrophic gastritis, intestinal metaplasia, and dysplasia, and it is a multistep and multifactorial process (7). Although a number of risk factors such as the infection of *H. pylori*, salt intake, smoking, alcohol, family history, atrophic gastritis, and intestinal metaplasia are well known, they cannot account for all gastric cancers, since gastric carcinogenesis is a multifactorial process. Indeed, a very wide range of factors environmental, genetic and epigenetic affects the risk of developing gastric cancer (8).

Helicobacterpylori (H. pylori) is a Gram negative spiral, microaerophilic bacterium (9). It is a human pathogen that colonizes the stomach's mucosal lining, and it has colonizing and coevolving in the human gut for more than 50,000 years (10) The infection with *H. pylori* is a significant risk factor for the development of gastric carcinoma (11). In 1994 the WHO classified *H .pylori* as a class I carcinogen (12). The infection with *H .pylori* affects more than half of the adult population worldwide (13). *H. pylori* infection is associated with several diseases, mainly, many benign, premalignant, and malignant lesions of the digestive system including chronic gastritis, peptic ulcer, gastric

adenocarcinoma and lymphoma (14, 15).

The constant infection with *H .pylori* causes the development of gastric cancer as a consequence of chronic inflammation of the gastric mucosa (16) .The relationship between *H. pylori* infection and gastric cancer is confirmed by several epidemiologic and clinical studies. More than 90% of gastric cancer patients have current or past *H. pylori* infection (17). *H. pylori* can develops gastric cancer through various mechanisms one of these mechanisms the oxidative stress, *H. pylori* is known to produce reactive oxygen(ROS) and nitrogen species (RNS),causing in DNA damage and mutation in epithelial cells leading to cancer (18) Excessive oxidative stress can damage DNA in gastric epithelial cells, indicating its possible involvement in gastric carcinogenesis(19) . The free radicals, including ROS and reactive nitrogen species, can bind with nucleic acids, converting them into mutated forms that play a role in multistep carcinogenesis (20). Another mechanism to develops gastric cancer is the virulence factor cytotoxin associated gene A (Cag A), The Cag A protein, is an oncoprotein, that can induce malignant neoplasms, which is the major oncogenic factor injected into gastric epithelial cells via bacterial type IV secretion system (T4SS) (21), Cag A interacts with many signaling molecules that are important for the regulation of cell proliferation, scattering, and morphology (22)

Other mechanisms is the induction of AID (Activation-induced cytidine deaminase) expression in human gastric epithelial , *H. pylori* mediate the aberrant AID expression in the epithelial cells of gastric mucosal (20). *H. pylori* strongly induced AID expression in human gastric epithelial cells, through activation of the NF-κB pathway, and induced mutation of p53 (23). It was reported that AID causes mutations in the APC, P53 genes in gastric epithelial cells, relevant to the development of adenocarcinoma (24, 25). AID expression level is decreases after *H. pylori* eradication (26).

The aim of this study was to compare the clinicopathologic characteristics between *H. pylori* negative and positive gastric cancer.

Materials and Methods

Samples Collection

A total of 78 samples of gastric cancer were enrolled in this study included 36 formalin fixed paraffin embedded tissue (FFPE) of gastric cancer patients from Gastroenterology and Hepatology Diseases Center Teaching / Baghdad during, January 2014, to December 2015. In addition to 42 blood samples were collected from patients with gastric cancer, (Patients treated with anti *H .pylori* therapy were excluded).

H . pylori detection:

Gastric cancer FFPE samples were grouped in two subsets according to the presence of *H. Pylori*, FFPE positive for *H. pylori* and FFPE negative for *H . pylori*. The slides of the FFPE blocks were examined by a consultant histopathologist to determine the definite presence of these bacteria. Out of 36 FFPE , 20 samples were positive to *H .pylori* and 16 samples were negative to *H .pylori*. With regard to gastric cancer blood samples, the blood centrifuged (3000 rpm for 3minutes) and the serum immediately examined

by the rapid diagnostic *H. pylori* kit– AMP Rapid Test H .pylori (AMEDA, Austria).

Principle of the test:

The one-step *H.pylori* test device (serum/plasma) is a rapid immune-chromatographic test for qualitative determination of specific IgM and IgG *H .pylori* antibodies in human serum. The test is performed by dispensing the serum sample into the sample well of the test cassette and observing the formation of colored lines. As soon as the sample is positioned at the sample port of the cassette, it is absorbed into the device by capillary effect and flows along the pre-coated membrane.

H .pylori antibodies in the sample combine with the antigen – dye conjugate and are captured by antigen immobilized in the test (**T**) region, as illustrated in (Figure 1).

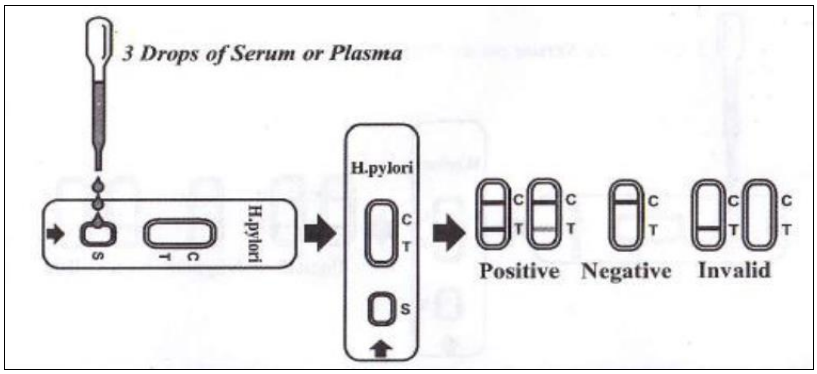

Figure (1): One step *H. pylori* test device (25).

Procedure:

75 µL of the serum was transferred to the sample well (**S**) of the cassette and after 10 minutes the result was interpretated.

Positive (+): Tow colored bands appear on the membrane, one band appears in the control (C) region and another band appears in the in the test (T) region. Appositive result indicates presence of *H .pylori* antibodies, (Figure 2).

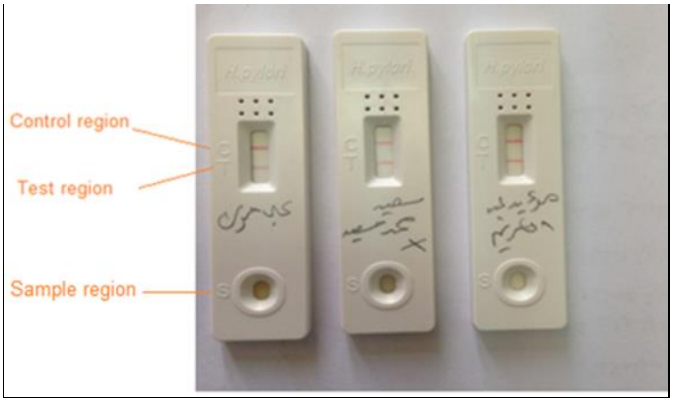

Figure (2): Test cassettes with positive result of 3 samples from patients with gastric cancer.

Negative (-): Only one colored band appears, in the control region (C). No apparent colored band appears in the test (T) region. A negative result indicates that concentration of *H. pylori* antibodies is zero (Figure 3).

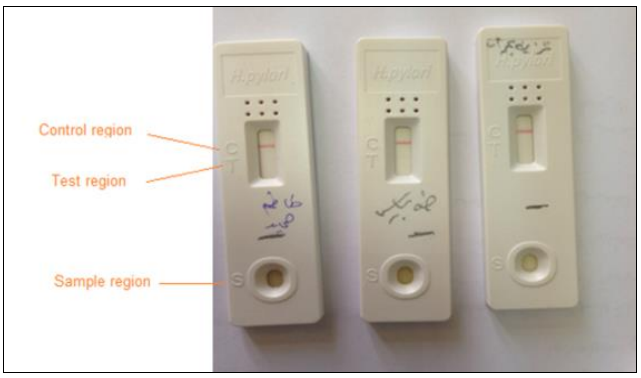

Figure (3): Test cassettes with negative result of 3 samples from patients with gastric cancer

Statistical Analysis

The Statistical Analysis System-SAS (2012) program was used to effect of difference factors in study parameters. Chi-square test was used to significant compare between percentage and least significant difference –LSD test was used to significant compare between means in this study.

Results and Discussion

The total number of GC patients, which enrolled in this study, was 78 samples, 36 of them were FFPE and 42 were blood samples.

The results listed in (Table 1) showed that the incidence of gastric carcinoma was high at ages over 50 years followed by ages between 41 – 50 years.

Patients classified into five groups according to age ,the small number of patients was recorded in two age groups, the 1st age group with 4/78 (5.1%) patients and the 2ed age group 6/87 (7.7%) patients followed by the 3ed age group with 18/78(23.1%) patients while the majority of patients were recorded in the 4th age group 26/78 (33.3%) patients and six th age group 24/78 (30.8%) patients . The mean age for all patients was 55.51 years ranged from 26 - 95 years.

These findings indicate that the incidence of gastric carcinoma can occur at any age, but it increases in older ages. The results of the current study agreed with those obtained by Kelley and Duggan (28) and Nagini (7) .Lim *et al.*,(29) who stated that gastric cancer is considered to be a disease of the aged. Therefore, its incidence expected to rise with the increase of aging population. The frequency of gastric cancer occurrence rising with age can be explained by the accumulation of somatic mutations connected with the occurrence of malignant tumors (30).

Table (1): Distribution of gastric cancer patients according to the ranges of age groups.

Age groups	No. of patients (%)
(21 - 30)	4 (5.1%)
(31 - 40)	6 (7 .7%)
(41 – 50)	18 (23.1%)
(51 – 60)	26 (33.3%)
(over 60)	24 (30.8%)
Chi-square (χ^2)	9.61 **
Total and Percentages	78 (100%)

**** (P<0.01)**

Depending on gender, there was a high percent of male patients in comparison with female patient's percent. The gastric carcinoma incidence was 45/ 78 (57.7%) for male and 33 /78 (42.3%) for female. In a previous Iraqi study by Razak *et al*. (31), they also found that males are affected more than females 90/155 (58%) male and 65/155 (42%) female which is similar to our findings. Environmental or occupation exposures may play a role in such differences between male and female. In addition, men have historically tended to smoke more than women (32), while estrogens may protect women against the development of gastric cancer , delayed menopause and increased fertility may also lower the risk of gastric cancer in women (33,34) .

In the HIP-GC group ,number of males were 25/46(54.3%) ,while the females were 21/46(54.65%) ,the differences was significant .On other hand , in the HIN-GC group, the males were 20/32 (62.50%)and the females were 12/32(37.50%),the difference was highly significant .

Statistically significant differences ($p<0.05$) were seen in the number of male in the HIN-GC group (62.50%) when compared with number of male (54.35%) in the HIP-GC group, in contrast, there is a significant differences ($p<0.05$) in the number of female in the HIP-GC group (45.56%) when compared with the HIN-GC group (37.50%) .

Table (2): Distribution of patients in both groups of gastric cancer according to the gender.

Gender	HIP-GC n=46 (%)	HIN-GC n = 32(%)	p - value	Chi-square (χ^2)
Male	25 (54.35%)	20 (62.50%)	0.493	4.194 *
Female	21 (45.65%)	12 (37.50%)	0.493	4.194 *
Chi-square (χ^2)	4.267 *	9.73 **	---	---

*** (P<0.05)**

These findings were similar with those that obtained by Marrelli *et al*. (35) who found that the ratio of male in the negative group were 61% comparison to 57 % in the positive group , while the ratio of female was 43% in the positive group compared to 39% in the negative group .

These results indicate that the male is the predominant in both groups and

there were differences in the incidence of gastric cancer according to gender between both groups and the female is affected by *H.pylori* more than male.

With regard to *H. pylori* infections, 46 /78 (59%) of patients were HIP-GC which is significantly higher ($p<0.01$) when compared with 32/ 78(41%) that were HIN-GC (Table 3). The numbers of gastric cancer patients with and without *H .pylori* infection in this study were similar to that obtained by Saxena *et al*. (36).

Table (3): Distribution of gastric cancer patients according to *H.pylori* infection.

	HIP-GC	HIN-GC	p - value	Chi-square (χ^2)
No. of patients	46 (59%)	32(41%)	0.0142	6.321 **

**** (P<0.01)**

There are highly significant difference between numbers of patients that have *H .pylori* infection and free of *H .pylori* infection among most ages groups ($P<0.01$) (Table 4). At the 1st age group there were 3 patients in the HIP-GC and 1 patient in the HIN-GC, in the 2ed age group there were 4 patients in the HIP-GC and 2 patients in the HIN-GC, followed by the 3ed age group there were 11 patients in the HIP-GC and 7 patients in the HIN-GC. while the majority of patients were recorded in the 4th age group 16 patients in the HIP-GC and 10 patients in the HIN-GC, and in the six th age group, which is divided equally between both groups equally , 12 patients for each group.

Table (4): Distribution of patients in both groups of gastric cancer according to the ranges of age groups.

Age groups	HIP-GC n=46 (%)	HIN-GC n = 32(%)	p – value	O.R.
(21 - 30)	3 (75%)	1 (25%)	0.0001 **	1.726
(31 - 40)	4 (66.7%)	2 (33.3%)	0.0001 **	1.592
(41 – 50)	11 (61.1%)	7 (38.9%)	0.0039 **	1.238
(51 – 60)	16 (61.5%)	10 (38.5%)	0.0038 **	1.240
(over 60)	12 (50%)	12 (50%)	1.00 NS	0.00
Chi-square (χ^2)	12.05 **	8.92 **	---	---
Total (%)	46 (59%)	32 (41%)	0.0148 **	1.007

**** (P<0.01), NS: Non-significant.**

In the HIP-GC group ,the mean age was 53.85 years and ranged from (38 – 95) years, and in the HIN-GC group ,the mean age was 57.91 years and ranged from (29–79) years . No significant differences noted between the mean ages in both groups.

Gastric cancer patients showed different clinicohistopathological characteristics which involves, type of

gastric cancer (intestinal and diffuse type), and differentiation grade (well, moderate and poor differentiation adenocarcinoma). In all gastric cancer patients , it was found that 71.8% of tumors were intestinal type and low percent 28.2% of diffuse type. The intestinal type was significantly higher (P<0.01) in the HIN-GC group 81.25%) than the HIP-GC group (65.22%) while the diffuse type was highly significant in the HIP-GC group (34.78%) than HIN-GC group (18.75%) (Table 5).

The existence of intestinal type in the negative group, which is to be closely related to chronic *H. pylori* infection, indicate that negative group patients might have a past *H. pylori* infection. As *H. pylori* incidence is gradually decreasing, true rate of *H.pylori* infection including past infection would be higher in the elderly group (29) , since 26/32 (81.25%) of patients in the HIN-GC group have intestinal type were equal or more than 50 years , which make this explanation sensible for such high percent .The results also show that the male is the predominant in the intestinal type in both groups , **t**hese findings agree with Correa and Piazuelo ,(9) ,who stated that the predominant type of gastric cancer is the intestinal and this tumor type shows a male predominance.

Table (5): Characteristics of gastric cancer patients in the *H. pylori* infection and non-infection groups.

Parameters	HIP-GC (n=46)	HIP-GC (n=32)	p - value	Chi-square (χ^2)
Type				
Intestinal	30 (65.22%)	26 (81.25%)	0.0149	6.082 **
Diffuse	16 (34.78%)	6 (18.75%)	0.0149	6.082 **
Chi-square (χ^2)	9.82 **	13.27 **	---	---
Differentiation grad				
Poorly	22 (47.83%)	10 (31.25%)	0.0147	6.009 **
Moderately	19 (41.30%)	15 (46.8%)	0.084	2.163 NS
Well	5 (10.87%)	7 (21.88%)	0.047	5.196 *
Chi-square (χ^2)	9.69 **	8.05 **	---	---

*** (P<0.05), ** (P<0.01), NS: Non-significant.**

With regard to the differentiation grade, in all gastric cancer patients, it was found that (41%) were poor differentiated, with nearly similar percentage (43 .6%) were moderately differentiate, while (15 .4%) were well differentiated in low percent.

In the HIP-GC group,(47.83%) were with poor differentiated, which is significantly higher ($p < 0.01$) than the HIN-GC group (31.25%) ,while the well differentiated in HIN-GC group (21.88%) was significantly higher than the HIP-GC group (10.87%) , and the difference was not statistically significant in the moderately differentiated in both groups (41.30% in the HIP-GC group vs. 46.8% in the HIN-GC group) .

The poorly differentiated was the more frequent ,followed by the moderately differentiated , then the well differentiated in HIP-GC group which is differ than the HIN-GC group in which the more frequent was the moderately differentiated , followed by

the poorly differentiated ,then the well differentiated .

Our finding shows that there were no significant differences between HIP-GC group and HIN-GC group according to the gender, tumor type which is in agreement with Kim *et al* .(37), they also found that there were no significant differences with respect to age, sex and the tumor type observed between the two groups of gastric cancer according to *H. pylori* infection status.

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