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Original Article

Extra-Gastroduodenal Manifestation and *Helicobacter pylori* Infection

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Abstract

Helicobacter pylori (*H. pylori*) which are known as Gram-negative bacteria tend to selectively colonize in the gastric epithelium. The infiltration of neutrophilic and mononuclear cells in the antrum and corpus mucosa is one of the consequences of acute and chronic gastritis colonization with *H. pylori*. This chronic active gastritis is the primary condition related to *H. pylori* colonization, and other *H. pylori*-associated disorders result from this chronic inflammatory process. The present study aimed to assess the relationship between *H. pylori* infection and extra-gastroduodenal manifestations, such as iron deficiency anemia, chronic spontaneous urticarial, diabetes mellitus, and celiac diseases with low ferritin levels. There were 235 subjects aged 3-75 years in the patient's group. The selected eligible patients were subjected to examination by non-invasive methods using stool antigen test and ^{14}C-urea breath test (^{14}C-UBT). The *H. pylori* antigen rapid test cassette (feces) was used for the qualitative detection of *H. pylori* antigens in human feces specimens. In the present study, 183 (71.8%) patients demonstrated positive results for *H. pylori* which had been detected by stool antigen test, out of whom 106 (57.9%) and 77 (42.1%) cases were female and male, respectively. The recorded data pointed out that the rates of Iron deficiency anemia, diabetes mellitus, and celiac diseases were 92(50.3%), 62 (33.9%), and 25 (13.7%), respectively. The findings of the present study revealed that *H.pylori* is more prevalent in females. Moreover, the diagnostic potential of the ^{14}C UBT method was higher and more accurate than the stool antigen assay.

Keywords: Celiac, Diabetes, Gastric manifestation, Gastritis

1. Introduction

Helicobacter pylori (*H. pylori*) which are known as Gram-negative bacteria tend to selectively colonize in the gastric epithelium. These bacteria which are urease, catalase, and oxidase-positive use three to five polar flagella for motility. Moreover, it is well documented that the *H. pylori* host cell signaling pathways are affected by the *H. pylori* virulence factors. It is approved that *H. pylori* have several distinctive features, such as its capability to survive for decades in a highly acidic gastric environment, leading to the inability of the host to remove the infection. The ability of *H. pylori* to resist the highly acidic gastric environment is explained due to the mechanisms of urea metabolization to ammonia by the activity of the urease enzyme. This chemical and enzymatic reaction produces a neutral environment which can preserve the optimum condition for *H. pylori* (1).

The infiltration of neutrophilic and mononuclear cells in the antrum and corpus of stomach mucosa is one of the consequences of acute and chronic gastritis colonization with *H. pylori*. The preliminary

complication of *H. pylori* colonization is known as chronic active gastritis, a chronic inflammatory process, which is the main cause of other *H. pylori*-related disorders (2). It is well documented that several disorders from the outside of the gastrointestinal tract, such as hematologic, metabolic, neurologic cardiopulmonary, and dermatologic disorders, are the consequences of *H. pylori* infection. These are strong pieces of evidence for the so-called extra-gastroduodenal manifestation of *H. pylori* infection (3).

Several mechanisms have been identified that result in iron deficiency anemia (IDA) which is caused by *Helicobacter pylori*. One of the main reasons for IDA would be the active hemorrhage caused by gastritis, peptic ulcer disease, or gastric cancer which leads to an increment in iron loss (4). Some previously conducted studies pointed out that *H. pylori* actively consume iron (5). The role of *H. pylori* in the iron acquisition was reviewed in a study performed by Muhsen et al. (5). It is established that *H. pylori* express some proteins with a key role in iron transport and storage. Nonetheless, the exact underlying molecular mechanisms by which *H. pylori* consume iron have remained unclear (5, 6).

In some previous case studies, it was suggested that *H. pylori* infection may occur concomitantly with diabetes mellitus. Moreover, according to the current knowledge, *H. pylori* leads to gastritis which may consequently affect gut-related hormones (7). The possible reasons for this could be explained as the following: Firstly, an impairment in the cellular and humoral immunity functions caused by diabetes may increase one's susceptibility to *H. pylori* infection. Secondly, diabetes leads to a significant reduction in gastrointestinal tract (GI) movements. Furthermore, the secretion of gastric acid is strongly reduced as a result of diabetes. The reduction of GI movements and gastric acid production brings about a significant increase in the rate of *H. pylori* colonization and infection (8). Thirdly, the consequent changes in glucose metabolism caused by diabetes have a strong influence on the alteration of the gastric mucosa chemical productions. All these alterations lead to the colonization of more bacteria (9-11).

In light of the aforementioned issues, the current study aimed to evaluate the relationship between *H. pylori* infection and extra-gastroduodenal manifestations, such as iron deficiency anemia, chronic spontaneous urticarial, diabetes mellitus, and celiac diseases with low ferritin levels.

2. Materials and Methods

2.1. Patients

This clinical trial study was conducted on 235 patients referring to the gastroenterology clinic of Azadi Teaching Hospital and private Kirkuk clinic in Kirkuk city for upper and lower GI endoscopy and fiberoptic bronchoscopy. Data were collected from November 2019 to February 2021 with clinical symptoms of pain or discomfort in the upper abdomen, nausea, vomiting, loss of appetite, weight loss, black or tarry stool, or red or maroon blood mixed stool. The inclusion criterion was the age range of 3-75 years.

2.2. Samples

The patient's stool was collected in clean, dry, and waterproof containers. The stool assay was performed using *H. pylori* Antigen rapid test cassette.

2.3. *Helicobacter Pylori* Rapid Test (Stool Antigen test)

The *H. pylori* antigen rapid test cassette (feces) was used for the qualitative detection of *H. pylori* antigens in human feces specimens (Linear, Spain catalog No. 5094503).

2.3.1. Principle

The *H. pylori* Antigen rapid test is a qualitative lateral flow immunoassay for the detection of *H. pylori* antigen in human feces specimens. In this test, the membrane is pre-coated with anti-*H. pylori* antibodies on the test line. During testing, the specimen reacts with the particle coated with *H. pylori* antibodies. The mixture migrates upward on the membrane by capillary action to react with anti-*H pylori* antibodies on the membrane and generate a red line. The presence of this

red line in the test region indicates a positive result, while its absence is suggestive of a positive result. To serve as a procedural control, a red line will always appear in the control line region, indicating that a proper volume of specimen has been added and membrane wicking has occurred.

2.3.2. Procedure

1- A sufficient quantity of feces (1-2 ml or 1-2 g) was collected in a clean dry specimen collection container to obtain maximum antigens (if present).

2- Fecal specimen was processed as the following:

-For solid specimens

The cap of the specimen collection tube was unscrewed; thereafter, the specimen collection applicator was randomly stabbed into the fecal specimen in at least three different sites.

-For liquid specimens

The dropper or pipette was held vertically. Fecal specimens were aspirated and then transferred into the specimen collection tube containing the extraction buffer.

3- The pouch was brought to room temperature before opening and prepared to use immediately after the opening of the foil pouch.

4- The specimen collection tube was held upright and the cap was opened onto the specimen collection tube. The specimen collection tube was inverted and transferred two full drops of the extracted specimen to the specimen well of the test cassette, then started the timer.

5- The results were read 10 min after dispensing the specimen.

2.4. Urea Breath Test

Heliprobe system is intended for the diagnosis of *H.pylori* infection in the gastrointestinal tract (stomach, duodenum) using the non-invasive ^{14}C Urea breath test from Kibion AB company, Sweden, catalog No. HPC-001.

2.4.1. Principle

Helicobacter pylori produce urease, an enzyme that catalyzes the hydrolysis of ^{14}C-urea to $^{14}CO_2$ and NH_3. The $^{14}CO_2$ was excreted in exhaled air, while NH_3 and excess ^{14}C-urea were excreted in the urine. Under healthy conditions (absence of *Helicobacter pylori*), ^{14}C-urea was not hydrolyzed and no $^{14}CO_2$ will be present in exhaled air. Therefore, $^{14}CO_2$ was only present in exhaled air during *H.pylori* infection.

2.4.2. Procedure

The patient swallows a HeliCap capsule containing ^{14}C urea (1μCi) and waits 10 min before exhaling into Heliprobe Breath Card, where the reactivity filters adsorb the CO2. The indicator changes color from orange to yellow to indicate when the reactivity filters were saturated and sampling completed.

2.5. Analysis

The analysis principle was based on measuring ß-radiation from $^{14}CO2$ sampled in Heliprobe BreathCard. Radiation was measured, and the result was presented as Heliprobe 0=not infected Heliprobe 1=borderline and Heliprobe 2=infected (Table 1).

Table 1. Cut-off value

		Cut-off value
Heliprob 0	Not infected	$d \leq 25$ counts
Heliprob 1	Borderline	25 counts $< d <$ 50 counts
Heliprob 2	Infected	$d \geq 50$ counts

3. Results

3.1. Distribution of *Helicobacter pylori* Infection According to Age and Gender of Patients

Out of 255 patients, 183 cases demonstrated a positive result for *H. pylori* which was detected by stool antigen test (as a gold standard) as illustrated in figures 1 and 2. The patients were assigned to six groups according to gender and age. The age ranged from 3-75 years with a peak age group of 26-35 years old. The statistical differences between age group and gender were not significant (*P*= 0.927) as depicted in table 2 and figure 3.

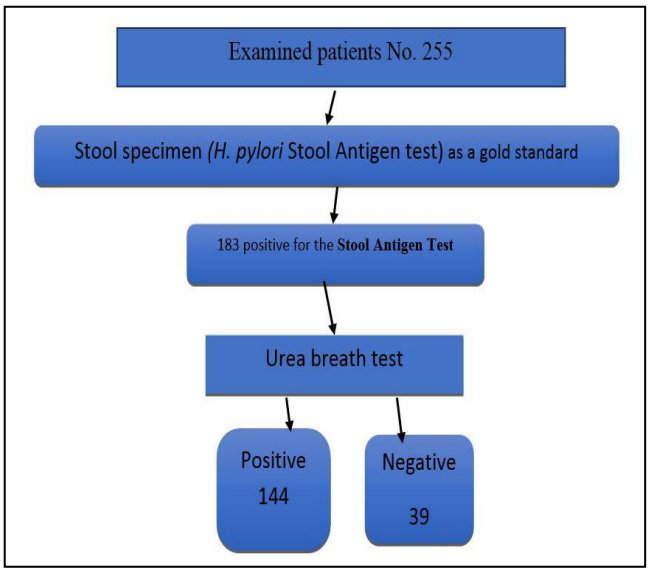

Figure 1. Flow chart of the study with summarized results

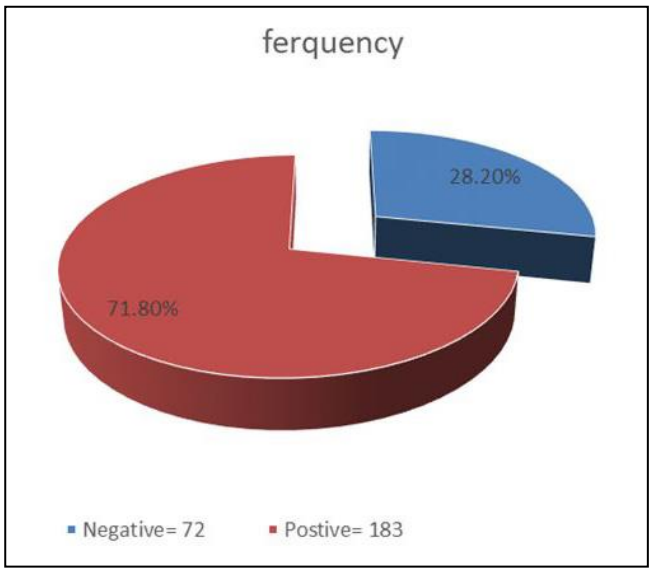

Figure 2. *H. pylori* status of the study patients by using the Stool antigen test as the gold standard

Table 2. Classification by age and gender of patients with *H. pylori* infection

Gender	Frequency of age					
	4-15	**16-25**	**26-35**	**36-45**	**46-55**	**56-75**
Male 77 (42.1%)	3 (1.6%)	12 (6.6%)	23 (12.6%)	23 (12.6%)	9 (4.9%)	7 (3.8%)
Female 106 (57.9%)	7 (3.8%)	25 (13.7%)	33 (18%)	20 (10.9%)	11 (6%)	10 (5.5%)
Total 183 (100%)	10 (5.5%)	37 (20.2%)	56 (30.6%)	43 (23.5%)	20 (10.9%)	17 (9.3%)

Chi-Square = 4.407 *P*-Value = 0.927

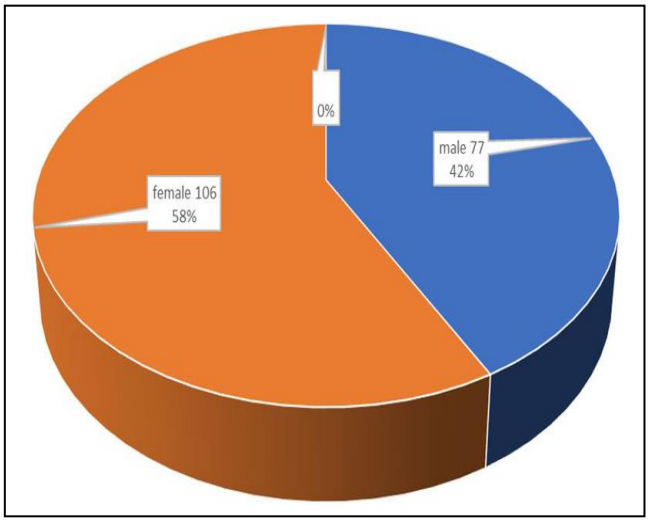

Figure 3. Prevalence of *H. pylori* according to gender

3.2. Gastric Manifestation for *H. Pylori* and Relationship with Extra-Gastroduodenal Manifestation

Data were collected through interviews using a questionnaire that looked at *H. pylori* infection with the clinical indication for endoscopic examination. Moreover, invasive and noninvasive methods were used to detect the *H.pylori* infection. It was observed that the highest incidence was chronic gastritis 66 (36.1%). In addition, it was indicated that extra-gastroduodenal manifestation was associated with *Helicobacter pylori* infection. There was no significant difference between gastric manifestation and extra-gastroduodenal manifestation (*P*=0.990) (Table 3).

3.3. Extra-Gastroduodenal Manifestation

With positive *H. pylori*, stool antigen test (HpSA) was 183 (77.9%). Several accompanying extra-gastroduodenal manifestations were observed and the highest percentage pertained to iron deficiency anemia (50.3%) as presented in figure 4.

3.4. Noninvasive Urea Breath Test and Comparison with A Stool Antigen Test

The urea breath test indicated that 144 (78.7%) cases tested positive for *H. pylori* infection using the stool antigen test. The male showed higher percentage 69 (89.6%) of urea breath test compared with female 75 (70.8%). The relation between gender and UBT was highly significant (*P*=0.002), as displayed in table 4.

Table 3. Association between *H. pylori* infection and the extra-gastroduodenal manifestation

Clinical manifestation	Frequency %	Extra-gastroduodenal manifestation				
		IDA	DM	SI	CD	CVD
Acute gastritis	42 (22.9%)	27	15	18	6	11
Chronic gastritis	66 (36.1%)	33	18	20	9	14
Gastric ulcer	35 (19.1%)	17	13	16	5	8
Duodenal ulcer	27 (14.8%)	11	11	9	5	6
Gastric cancer	13 (7.1%)	4	5	5	-	3
Total Positive (%)	183 (100%)	92 (50.3%)	62 (33.9%)	68 (37.2%)	25 (13.7%)	42 (22.9%)

Chi-Square = 3.608 *P*-Value = 0.990
IDA= Iron deficiency anemia, DM= Diabetes mellitus, SI= Skin infection, CD= Celiac disease, CVD= Cardiovascular diseases

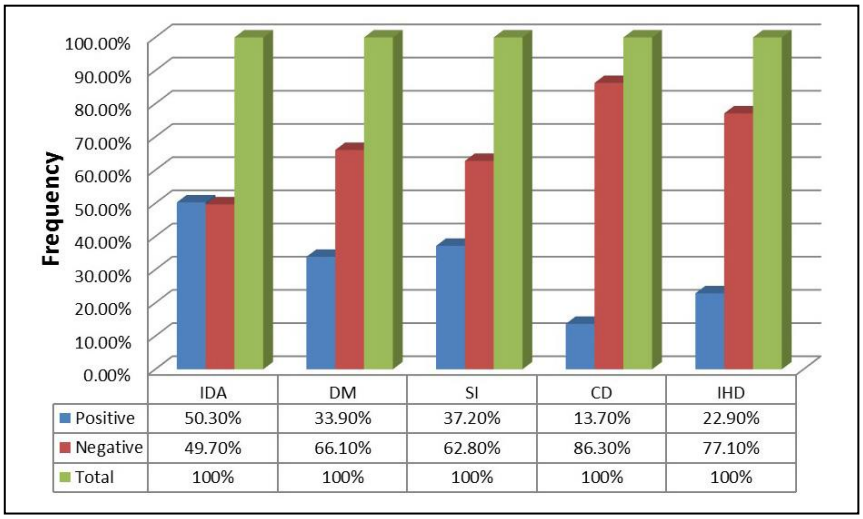

Figure 4. Percentage of extra-gastroduodenal manifestation, using HpSA as the gold standard
IDA= Iron deficiency anemia, DM= Diabetes mellitus, SI= Skin infection, CD= Celiac disease, IHD= Ischemic heart disease

Table 4. Distribution of infection among patients according to gender by using Urea breath test in positive cases by using HpSA as the gold standard

gender	Urea breath test		
	Positive (%)	Negative (%)	Total (%)
Male	69 (89.6%)	8 (10.4%)	77 (100%)
Female	75 (70.8%)	31 (29.2%)	106 (100%)
Total	144 (78.7%)	39 (21.3%)	183 (100%)

Chi-Square = 9.456 *P*-Value = 0.002
HpSA= *H. Pylori* stool antigen test
UBT= Urea breath test

4. Discussion

4.1. Distribution of *Helicobacter Pylori* Infection according to Patients' Age and Gender

The accurate diagnosis and management are vital for facing the *H. pylori* challenge due to its strong association with gastroduodenal diseases and high rate of infectivity, especially in developing countries. Although many diagnostic tests had developed for the detection of *H. pylori*, all have advantages and disadvantages. *Helicobacter pylori* stool antigen test (SAT) is used as a gold standard test for the detection of *H. pylori* infection. As reported by many international studies, it is an accurate and reliable test. The high rates of infections caused by *H. pylori* have been detected in high population densities, low socioeconomic communities, and the prevalence of the bacteria is different between countries (12). The results of the present study indicated that the frequency of identification of *H. pylori* was 71.8% by using SAT as the gold standard. The results were in agreement with those reported by Huwiage, Nami (13) and Thapa, Thapa (14); nonetheless, they were inconsistent with the findings of the studies by Mawlood, Kawther (15) and Bordin, Voynovan (16).

The present study pointed out that the peak incidence of *H. pylori* infection (30.6%) occurred among the age group 26-35 for both genders. Concerning gender, the current study illustrated the highest incidence in females (57.9%). The differences in age and gender distribution were not statistically significant. The same findings were reported by Huwiage, Nami (13) and Alhashimi (17). In their studies, Mawlood, Kawther (15) and Majeed and Khoshnaw (18) reported that the rate of infection was higher among females; moreover, the people over 45 were more infected with this bacterium. Nevertheless, some reports indicated that gender and age were significantly associated with *H. pylori* infection (19). The reason for the gender difference was not known and needs further study (20); however, the present study did not demonstrate such variability.

4.2. Gastric Manifestations and Extra-Gastroduodenal Manifestation

Helicobacter pylori infection results from a complex interplay between bacterial, environmental, and host genetic factors. The spectrum of gastro-duodenal affection mostly passes through asymptomatic infection. Furthermore, the infection evolves into acute and chronic gastritis, and peptic ulcers; moreover, a minority of patients is prone to the most serious sequel gastric cancer. *H. pylori* are classified as a class I carcinogen by the World Health Organization (WHO); therefore, the identification and eradication of the infection are recommended for subgroups of patients as per the current practice guidelines (21). *Helicobacter pylori* infection has remained the most common cause of chronic gastritis (20). In agreement with the studies by Makaju, Dhakal (22), as well as Hagag, Amin (23), the current study illustrated that 36.1% of patients with chronic gastritis infected with *Helicobacter pylori*. This result was higher than those of other studies by Bahadir, Sag (24) and Alsultan (22.5%) Alsultan (25). This discrepancy can be ascribed to the different numbers of patients in these studies.

The list of extra-gastric associations is long and diverse. *H. pylori* have been linked to many metabolic, cardiac, neurological, allergic, ocular, hematological, dermatological, and hepatobiliary diseases. It seems that these associations have been overestimated since the evidence linking *H. pylori* infection to these diseases depends on epidemiological studies (26).

Iron deficiency anemia is highly prevalent in underdeveloped countries, and a few studies have

claimed that *H. pylori* eradication can be used to cure the IDA for which no cause has been identified (27). One of the major causes of IDA during *H. pylori* infection is blood loss due to ulcer bleeding in infected patients. However, *H. pylori*-associated IDA may also occur in patients with intact mucosa, thereby leading to further investigations to better define the pathophysiological mechanisms underlying such association. One of the pathways through which *H. pylori* infection may lead to iron deficiency is affecting iron absorption by enterocytes and its release from macrophages via hepcidin level upregulation and concomitant therapy with non-steroidal anti-inflammatory drugs, including aspirin (28). In this study, IDA was noted in 92 (50.3%) patients with *H. pylori* infection, as compared to results of the studies by Rahat and Kamani (29) (37.5%) and Alboraie, Elhossary (21). It was also suggested that *H. pylori* gastritis can be a common etiological reason for IDA among patients with iron deficiency. A previously conducted study stated that a large proportion of patients with atrophic body gastritis also encounter IDA, out of whom 61% cases were diagnosed with *H. pylori* infection (30). This variation may be attributed to the different prevalence of *H. pylori* in developed and developing countries.

A positive association was detected between *H. pylori* infection and diabetes mellitus in the present study with 33.9%, pointing to a non-significant difference. This result is in agreement with those reported by Chen et al. who demonstrated no significant differences in patients with H. *pylori* infection and diabetes mellitus. Among the hypothesis on how *H. pylori* infection increases the risk of chronic gastritis, it is believed that increased cytokine production leads to the phosphorylation of serine residues from the insulin receptor substrate, whose linkage with insulin receptors turns deficient (31). In contrast, Tawfeeq, Amin (32) demonstrated that the prevalence of *H. pylori* infection is higher in patients with high HbA1c levels, while the rate of *H. pylori* infection is lower in patients with low levels of HbA1c. A meta-analysis of case-control studies found a significant association between *H. pylori* and diabetes mellitus, and the authors acknowledged a significant heterogenicity (33). Moreover, according to Al-Awadhi, Bahaj (34), the prevalence of *H. pylori* was 49% in diabetic patients. Therefore, the association between *H. pylori* infection and diabetes mellitus remains inconclusive.

In the current study, 33.9% of patients with dermatological diseases were infected with *H. pylori*, and no significant differences were detected between *H. pylori* infection and dermatological diseases. The aforementioned findings are in accordance with those reported by Majeed and Khoshnaw (18), Alfahaad (35), and Dennis, Mavura (36) who explained that Chronic Urticaria (CU) occurs mostly in adults.

The current study demonstrated that the prevalence of *H. pylori* in celiac disease was 13.7%. Agin, Batun (37), (38) determined the prevalence rates of *H. pylori* to be 30.7% and 27.5%, respectively. In their meta-analysis of 26 studies, Amlashi, Norouzi (39) revealed a significant and negative association between *H. pylori* colonization and cardiovascular diseases (CVDs). The present study demonstrated that 22.9% of patients who tested positive for *H. pylori* infection had CDVs. These findings disagreed with Aldhalmi, Aldabbagh (40) who reported Aldhalmi, Aldabbagh (40) that H. pylori positivity was 67% in patients with CVDs, pointing to a significant association between the prevalence of *H. pylori* and CVDs. Epidemiological research indicated that *H. pylori* infection may be a new risk factor for CVDs, and a higher prevalence of hypertension in patients with *H. pylori* infection may be ascribed to the factors specific to *H. pylori* that also play a role in CVDs (41). These discrepancies in the ratio can be attributed to differences in the number of patients.

4.3. Urea Breath Test

The present study used a ^{14}C urea breath test and *H. pylori* stool antigen. This study aimed to assess the most accurate method for the diagnosis of *H. pylori*, compared to the gold standard SAT. In addition, these

methods were used to evaluate the success of *H. pylori* eradication after the use of an appropriate regime by gastroenterologists. These results pointed out that the ^{14}C urea breath test outperformed the *H. pylori* stool antigen for diagnosis. The ^{14}C urea breath test was more sensitive and accurate than *H. pylori* stool antigen testing. The accuracy of the ^{14}C urea breath test was 78.7% and it was highly associated with gender, being more positive with the male gender (89.6%). However, the detected prevalence rate in this study was much higher than that reported by Altamimi, Alsharkhat (42) from Jordan using the UBT method (14.6%). This discrepancy may be due to the differences in the studied population or the age of participants.

Regarding gender differences, a study for adult patients in occupied Palestine by Eisdorfer, Shalev (43) proved quantitative differences between men and women. They also found that environmental or host-related factors might affect the quantitative value of UBT. This study reported that the ^{14}C urea breath test outperformed SAT for the diagnosis of *H. pylori*. In agreement with the current research, Eisdorfer, Shalev (43) compared *H. pylori* diagnosis methods and concluded that the sensitivity, positive predictive, negative predictive values, and accuracy of UBT were higher than those of SAT.

Authors' Contribution

Study concept and design: K. O. M. A.
Acquisition of data: K. O. M. A.
Analysis and interpretation of data: S. S. A. H.
Drafting of the manuscript: S. S. A. H.
Critical revision of the manuscript for important intellectual content: Y. I. S.
Statistical analysis: S. S. A. H.
Administrative, technical, and material support: Y. I. S.

Ethics

Ethical approval for the study was obtained from the Northern Technical University, Kirkuk Technical Institute, Kirkuk, Iraq Ethics and Law Committee and the Local Research Ethics Committees.

Conflict of Interest

The authors declare that they have no conflict of interest.

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