ORIGINAL ARTICLE

Diagnosis of Helicobacter Pylori Infection by Invasive and Non-Invasive Methods: A comparative study

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ABSTRACT

Background: More than 50% of the adult population all over the world are infected with H. pylori. H. pylori infection is a significant reason for chronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue (MAL) lymphoma, and gastric carcinoma. Diagnosis can be achieved by invasive (endoscopic-based) and non-invasive (urea breath test, H. pylori stool antigen test and IgG antibodies) methods. Objective: Comparison between different methods for diagnosis of H. pylori infection. Methodology: This study included 118 patients attending Gastrointestinal Endoscopy Unit at Zagaiz University Hospitals. Samples included biopsies, stool, and blood. Biopsies were assessed by Polymerase Chain Reaction (PCR) through amplification of ureC (glmM) gene and rapid urease test (RUT). Stool samples were processed for analysis by stool antigen test (SAT) ELISA kit. H. pylori IgG antibodies were detected by Helicobacter pylori IgG ELISA kit. Results: The percentages of positive cases of all tests used were as follows; RUT (67.8%), PCR (50%), RUT and PCR (gold standard) (5.7%), SAT (57.6%), IgG antibodies (51.69%) and combined SAT with IgG antibodies (36.4%). The sensitivities and specificities were as follows; RUT (100%, 59%), PCR (100%, 92.18%), SAT (77.77%, 59.3%), IgG antibodies (50%, 46.87%) and combined stool antigen test with IgG antibodies (42.59%, 68.7%). Conclusion: Invasive tests were more accurate than non-invasive tests for diagnosis of H. pylori-infected patients. Non-invasive test may be used for follow up after treatment of H. pylori infection. Combination of SAT with anti-H. pylori IgG antibodies improves the specificity and the accuracy as compared to anti-H. pylori IgG antibodies alone but improves the specificity only when compared to SAT alone.

INTRODUCTION

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Helicobacter pylori (H. pylori) is a gram-negative microaerophilic spiral bacterium, which colonize the gastric mucosa of approximately 50% of the human population in the world. A minority of the infected population suffer from chronic gastritis and peptic ulcer disease (PUD), and some even progress to gastric carcinoma (GC) and gastric mucosa-associated lymphoid tissue lymphoma 1. Hence, since 1994, the World Health Organization has classified it as class I carcinogen that the eradication of H. pylori can reduce the risk of gastric cancer 2. The most probable mode of transmission is person-to-person spread but oral-oral and fecal-oral transmissions have also been reported 3.

Different virulence factors that play a role in the pathogenesis of the disease such as urease enzyme, flagella, cytotoxin-associated gene A (CagA), vacuolating cytotoxin A (VacA), and induced by contact with epithelium (IceA) gene have been described 4.

Accurate diagnosis of H. pylori infection involves the combined knowledge, effort and research of laboratories, gastroenterologists and pathologists 5. Diagnostic tests are usually divided into invasive (endoscopic-based) and noninvasive methods. Invasive diagnostic tests include endoscopic image, histology, rapid urease test, culture, and molecular methods. Non-invasive diagnostic tests included urea breath test, stool antigen test, serological, and molecular examinations 6. No single test can be relied upon to diagnose H. pylori infection, and a combination of two tests is more optimal 7. 

PCR is the accurate method that is used for detecting the H. pylori DNA by using several gene targets such as urease operon genes, cag A and Hsp60. Although PCR could be performed even with a traces of bacterial DNA, it is mainly considered as an invasive method that needs biopsy 7. Several commercially available ELISA kits have been used for detection of H. pylori infection, which differs in target antigens and antibody preparations 89.
The aim of this study was to comparatively evaluate invasive (RUT and PCR) and non-invasive (stool antigen test and H. pylori IgG antibodies) methods for diagnosis of infection.

**METHODOLOGY**

**Study design:**
This study was conducted at Gastrointestinal Endoscopy Unit at Zagazig University Hospitals, Immunology Research and Molecular Biology laboratories at Microbiology and Immunology Department and Scientific and Medical Research Center of Zagazig University, Faculty of Medicine, Zagazig University during 2016 - 2017.

**Subjects:**
Representative samples were drawn by systematic random sample from 118 subjects (61 females and 57 males) attending gastrointestinal endoscopy unit at Zagazig University Hospitals. They were informed about the nature and the purpose of the study and written informed consents were taken. Subjects who had received antimicrobial therapy, H2-receptor blockers, proton-pump inhibitors and non-steroidal anti-inflammatory drugs 30 days prior to endoscopy were excluded from the study.

Two biopsy specimens were collected from the antrum and/or fundus of the stomach; one was reserved for RUT, and the other one for PCR. Biopsies for PCR were preserved at -80°C for further DNA extraction. Stool specimens and serum samples from these patients were collected and kept on -20°C until used.

**Diagnosis of H. pylori infection:**

**a. Invasive methods**
• **Rapid Urease Test:** RUT was done by using commercial paper RUT according to the manufacturer’s protocol (HelicotecUT® Plus; Catalog No. HUP01, Strong Biotech Corporation, Taiwan). The biopsy specimen was transferred onto the test paper with the applicator included in the test kit. Color changes were observed within one hour.

• **PCR:** DNA was extracted from biopsies using the Genomic DNA purification system according to the manufacturer's instructions (QIAamp® DNA Mini kit; catalog No 51304, QIAGEN, Germany) and stored at -20°C until analysis. A sequence of 294 bp in the ureC (glmM) gene was amplified by PCR (Maxime PCR Premix Kit (i-Tag), catalog No 25025, iNTRON BIOTECHNOLOGY. Korea). Primer pair used for ureC amplification had the nucleotide sequence as follows: forward primer is:
5'- AA GCTTTTAGGTTAGGGGT TT-3';
and reverse primer is:
5'-AAGCTTACTTTCTAACA TAGGC-3'.
The amplification was carried out in a thermal cycler (Verit® 96-Well Thermal Cycler, Applied Biosystems, Singapore) according to the following program: an initial denaturation step at 95°C for 10 min, followed by 35 cycles of denaturation at 95°C for 30 s, annealing at 55°C for 1 min, and a final extension step at 72°C for 5 min. Amplified PCR products were resolved by agarose gel electrophoresis (5 V/60 min) using 1.5% agarose in Tris Acetate-EDTA (TAE) buffer containing 0.5 ug/mL of ethidium bromide. Molecular size ladder of 100 bp (Roche, Lewes, East Sussex) was used to determine the size of the bands. The gel was viewed and photographed over the U.V. transilluminator at 320 nm.

**b. Non-Invasive methods**
• **Stool antigen test:** The H. pylori stool antigen level of the study subjects was measured by sandwich ELISA according to the manufacturer’s protocol (HELICOBACTER PYLORI STOOL ANTIGEN (HpSA) Enzyme Immune Assay test kit; catalog No 10224, Chemux Bioscience, USA). Diluted fecal samples were dispensed into the appropriate wells and incubated for 30 minutes at room temperature. Sample wells were washed to remove unbound samples. Enzyme conjugate was dispensed to each well and incubated for 30 minutes at room temperature. Unbound enzyme conjugate was washed. TMB chromogenic substrate were dispensed to each well and incubated for 15 minutes at room temperature. Stop solution was added to stop the reaction. The optical density of each well was determined within 30 min, using ELISA reader (Stat Fax® 303 Plus) set to 450 nm. A standard curve was constructed by plotting the O.D. 450 nm on the Y-axis against the concentration of calibrator ng/ml on the X-axis with an order polynomial trendlines.

• **H.pylori IgG antibody detection:** Five ml blood was taken from patients and transferred to the laboratory. The sera were separated and kept until the day of testing at -20°C. The serum level of H.pylori IgG antibody of the study subjects was measured by sandwich ELISA according to the manufacturer’s protocol (Helicobacter pylori IgG ELISA; catalog No HP013G, Calbiotech, USA). The optical density of each well was determined within 15 min, using ELISA reader (Stat Fax® 303 Plus) set to 450 nm. Cut-off value was calculated as follows: calibrator O.D × calibrator factor. Antibody index of each determination was calculated by dividing the O.D. value of each sample by cut-off value.

**Statistical analysis:**
Data were collected and coded, and all analyses were performed using Statistical Package for the Social Sciences software (SPSS version 20, Inc., Chicago, IL, USA.). Data were entered as variables, represented by tables and graphs. Sensitivities, specificities, predictive
values and accuracy of the biopsy-based and the ELISA-based diagnostic assays were calculated for all 118 patients in relation to the gold standard. Agreement between the results of the \textit{H. pylori} tests was evaluated by calculating the Cohen’s kappa coefficient.

A Chi-square test and Fisher’s exact test were used to assess the association amongst the genotypes and between specific genotypes and upper gastrointestinal diseases. Mann-Whitney \textit{U} test and \textit{t}- test were used for calculation of mean difference between different groups. All analyses were 2-tailed. Results were considered statistically significant when \textit{p} (probability) values were equal to or less than 0.05 at confidence interval (CI) 95%.

**RESULTS**

**Diagnosis of \textit{H.pylori} infection**

**Invasive methods**

RUT results were detected within a few minutes up to 1 hour. If the test paper changes color to pink or red, the test of \textit{H.pylori} is positive. If it remains yellow in color then the test is negative. Positive PCR results were visualized on agarose gel as a band at with 294 bp in size (Fig.1). Combination of endoscopic-based techniques (RUT and PCR) were considered the gold standard for determination of the specificity and sensitivity of each test. Patients were infected with \textit{H. pylori} if those two tests were positive.

There were 54 positive cases of combined RUT and PCR, 36 males (63.2%) and 18 females (29.5%). Meanwhile, there were 80 positive cases of RUT, 46 males (80.7%) and 34 females (55.7%). Fifty-nine cases were positive by PCR, 36 out of them were male patients (63.15%), and 23 were female patients (37.7%) (Table.1).

There was statistical significant association between the gender of studied patients and the number of positive cases of RUT, PCR and combined RUT with PCR (gold standard), (\textit{P}≤0.05) (Table.1). Meanwhile, there was no statistical significant association between different age groups of the studied patients and positive cases of RUT, PCR and combined RUT with PCR (gold standard), (\textit{P}>0.05) (Table.2).

**Table 1: Positive invasive tests as regards the gender of the studied patients.**

<table>
<thead>
<tr>
<th>Test</th>
<th>Gender</th>
<th>\textit{fisher’s exact test} =\chi^2</th>
<th>\textit{p}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Rapid urease test</td>
<td>34 (55.7%)</td>
<td>46 (80.7%)</td>
<td>8.41</td>
</tr>
<tr>
<td>PCR</td>
<td>23 (37.7%)</td>
<td>36 (63.2%)</td>
<td>7.63</td>
</tr>
<tr>
<td>(RUT+PCR)</td>
<td>18 (29.5%)</td>
<td>36 (63.2%)</td>
<td>13.44</td>
</tr>
</tbody>
</table>

\textit{n= number, RUT=rapid urease test, PCR=polymerase chain reaction, P of fisher’s exact test, * = P≤0.05.}

![Fig. 1: PCR products for \textit{H. pylori} with glmM (ure C) gene based primers. The product size is 294 bp. Lane 1and 11 are ladders. Lane 2-10 and 12-19 are patients’ biopsy samples.](image-url)
Table 2: Positive invasive tests as regards the age groups of the studied patients.

<table>
<thead>
<tr>
<th>Test</th>
<th>Age 19-&lt;34y (n=32)</th>
<th>Age 34-&lt;49y (n=37)</th>
<th>Age 49-&lt;64y (n=45)</th>
<th>Age ≥64 y (n=4)</th>
<th>fisher’s exact test =χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid urease test</td>
<td>22 68.7%</td>
<td>28 62.2%</td>
<td>31 68.9%</td>
<td>4 100.0%</td>
<td>2.47</td>
<td>0.48</td>
</tr>
<tr>
<td>PCR</td>
<td>16 50.0%</td>
<td>20 54.1%</td>
<td>21 46.7%</td>
<td>2 50.0%</td>
<td>0.44</td>
<td>0.93</td>
</tr>
<tr>
<td>(RUT+PCR)</td>
<td>14 43.8%</td>
<td>17 45.9%</td>
<td>21 46.7%</td>
<td>2 50.0%</td>
<td>0.09</td>
<td>0.99</td>
</tr>
</tbody>
</table>

n= number, RUT=rapid urease test, PCR=polymerase chain reaction, P of fisher’s exact test

Non-invasive methods

The levels of *H.pylori* antigen in stool and IgG antibodies in serum were measured by sandwich ELISA technique. The mean value of *H.pylori* antigen of male patients was (18.96±8.71 ng/ml). On the other hand, the mean value of *H.pylori* antigen of female patients was (15.63±8.66 ng/ml). There was statistically significant difference in the mean value of *H.pylori* antigen in male patients when compared to female patients, (P≤0.05).

Meanwhile, the mean value of *H.pylori* IgG antibody of male patients was (1.64 ±1.68). On the other hand, the mean value of *H.pylori* IgG antibody of female patients was (1.16±1.41). There was no statistically significant difference in the mean value of *H. pylori* IgG antibody in male patients when compared to female patients, (P>0.05).

The positive cases of non-invasive tests were as follows; 86 (57.6%) for stool antigen test (Fig.2), 61 (51.69%) for *H.pylori* IgG antibody (Fig.3) and 43 (36.4%) for combined *H.pylori* stool antigen test and IgG antibody.

![Fig.2: Bar chart shows the distribution of the studied subjects (male & female) as regard *H.pylori* stool antigen](image)

![Fig.3: Bar chart shows the distribution of the studied subjects (male & female) as regard *H.pylori* IgG antibodies](image)
There was no statistical significant association between the gender of studied patients and positive cases of stool antigen test and IgG antibodies, \((P>0.05)\). On the other hand, there was statistical significant association between the gender of studied patients and the combination of \(H. pylori\) stool antigen and IgG antibodies, \((P\leq 0.05)\) (Table 3). Interestingly, there was statistical significant relation between positive cases of IgG antibodies and different age groups, \((P\leq 0.05)\) (Table 4).

Sensitivities, specificities, predictive values and accuracy of biopsy based methods (RUT and PCR) as well as ELISA based tests (stool antigen test and IgG antibodies) were calculated for all 118 patients in relation to the gold standard and are presented in (Table 5).

**Agreement between different tests used for diagnosis of \(H. pylori\) infection**

There was high statistical significant good agreement between the gold standard and (PCR, RUT, \(H. pylori\) stool antigen test and combination of \(H. pylori\) stool antigen test and IgG antibodies), \((P\leq 0.05)\). However, there was no statistical significant agreement between RUT with PCR (gold standard) and \(H. pylori\) IgG antibodies, \((P>0.05)\) as shown in (Table 6).

### Table 3: Positive non-invasive tests as regards the gender of the studied patients.

<table>
<thead>
<tr>
<th>Test</th>
<th>Gender</th>
<th>Fisher's exact test = ( \chi^2 )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female n %</td>
<td>Male n %</td>
<td></td>
</tr>
<tr>
<td>Stool antigen test</td>
<td>31 (50.8%)</td>
<td>37 (64.9%)</td>
<td>2.39</td>
</tr>
<tr>
<td>Anti (H. pylori) IgG antibodies</td>
<td>28 (45.9%)</td>
<td>33 (57.9%)</td>
<td>1.69</td>
</tr>
<tr>
<td>Anti (H. pylori) IgG antibodies</td>
<td>17 (27.86%)</td>
<td>26 (45.6%)</td>
<td>4.00</td>
</tr>
</tbody>
</table>

\( n = \) number, \( P \) of fisher’s exact test, \(* = P \leq 0.05\)

### Table 4: Positive non-invasive tests as regards the age groups of the studied patients.

<table>
<thead>
<tr>
<th>Test</th>
<th>Age 19-&lt;34y (n=32)</th>
<th>Age 34-&lt;49y (n=37)</th>
<th>Age 49-&lt;64y (n=45)</th>
<th>Age (\geq 64) y (n=4)</th>
<th>Fisher’s exact test = ( \chi^2 )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No %</td>
<td>No %</td>
<td>No %</td>
<td>No %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stool antigen test</td>
<td>20 62.5%</td>
<td>20 54.1%</td>
<td>26 57.8%</td>
<td>2 50.0%</td>
<td>0.6</td>
<td>0.89</td>
</tr>
<tr>
<td>Anti (H. pylori) IgG antibodies</td>
<td>15 46.9%</td>
<td>26 70.3%</td>
<td>20 44.4%</td>
<td>0 0.0%</td>
<td>10.6</td>
<td>0.01*</td>
</tr>
<tr>
<td>(Stool antigen test + Anti (H. pylori) IgG antibodies)</td>
<td>13 40.6%</td>
<td>14 37.8%</td>
<td>16 35.6%</td>
<td>0 0.0%</td>
<td>2.58</td>
<td>0.46</td>
</tr>
</tbody>
</table>

\( n = \) number, \( P \) of fisher’s exact test, \(* = P \leq 0.05\)

### Table 5: Validity of invasive and non-invasive tests for diagnosis of \(H.pylori\) infection in relation to gold standard (RUT+PCR).

<table>
<thead>
<tr>
<th>Validity</th>
<th>Invasive tests</th>
<th>Non-invasive test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RUT</td>
<td>PCR</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>100%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Specificity</td>
<td>59.37%</td>
<td>92.18%</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>67.5%</td>
<td>91.52%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>77.96%</td>
<td>95.76%</td>
</tr>
</tbody>
</table>
Table 6: Agreement between different measures used to diagnose *H. pylori* infection.

<table>
<thead>
<tr>
<th>Diagnosis of <em>H. pylori</em> infection</th>
<th>RUT and PCR (Gold standard)</th>
<th>PCR</th>
<th>RUT</th>
<th><em>H. pylori</em> stool antigen test</th>
<th><em>H. pylori</em> IgG antibodies</th>
<th><em>H. pylori</em> Stool antigen test and IgG antibodies</th>
<th>Kappa test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Negative</td>
<td>54</td>
<td>45.8</td>
<td>59</td>
<td>50.0</td>
<td>80</td>
<td>67.8</td>
<td>68</td>
<td>57.6</td>
</tr>
<tr>
<td></td>
<td>64</td>
<td>54.2</td>
<td>59</td>
<td>50.0</td>
<td>38</td>
<td>32.2</td>
<td>50</td>
<td>42.4</td>
</tr>
<tr>
<td></td>
<td>50</td>
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<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

N=number, %=percentage, p of Cohen’s kappa coefficient, * = P<0.05.

P1 agreement between gold standard and PCR.
P2 agreement between gold standard and RUT.
P3 agreement between gold standard and *H. pylori* stool antigen.
P4 agreement between gold standard and *H. pylori* IgG antibodies.
P5 agreement between gold standard and combination of *H. pylori* stool antigen test and anti IgG antibodies.

**DISCUSSION**

Various diagnostic methods are developed to detect *H. pylori* infection and that divided into two groups of invasive and noninvasive methods according to the necessity of endoscopic biopsy. This study was designed to evaluate different methods for diagnosis of *H. pylori* infection. Some studies considered that the gold standard for diagnosis of *H. pylori* infection is the combination of two positive invasive tests. On the other hand, other studies considered one invasive test as the gold standard for detection of *H. pylori* infection and to verify *H. pylori* eradication after treatment. The present study used the combination of both invasive tests (RUT and PCR) as a gold standard for diagnosis of *H. pylori* infection.

In our study, RUT and PCR presented the highest sensitivities (100%) but PCR was more specific than RUT (92.18% and 59.37%, respectively). Consistently, Jalalypour and his colleagues reported similar results. This may be attributed to several factors, which affect the results of RUT including the biopsy condition as well as the type of disease. The accuracy of RUT is dependent on site, number, size and bacterial density of biopsy specimen. PCR is more accurate due to the need for limited quantity of bacteria which enables PCR to recognize infection when other tests are negative due to low bacterial density. It allows detection of specific genes relevant to pathogenesis and specific mutations associated with antimicrobial resistance in addition to detection of the microorganism. On the contrary, other studies reported that the sensitivity and specificity of RUT were higher than PCR.

The present study reported that the sensitivity and the specificity of *H. pylori* stool antigen test were 77.77% and 59.37% respectively. Consistently, Pourakbari and his colleagues reported high sensitivity and low specificity of stool antigen test (87.8% and 75% respectively). Low specificity of stool antigen test can be explained by several mechanisms including the occurrence of transient *H. pylori* infection (spontaneous clearance of the infection) which has been reported as a common phenomenon in children. On the contrary, Khalifehgholi and his colleagues reported lower sensitivity (73.9%) and higher specificity (86.7%). This could be attributed to different types of kits used. The accuracy of the test might change from lot to lot and intertest variability has already been reported by. Differences in the antigens and the stool condition may affect the accuracy of stool antigen test.

This study revealed that anti-*H. pylori* IgG antibodies showed the lowest sensitivity (50%) and specificity (46.87%). Khalifehgholi and his colleagues were in agreement with our results as regard the specificity (55.6%), but the sensitivity was (91.3%). On the other hand, Red´een and his colleagues reported that the sensitivity was (99%) and the specificity was (82%).

Most of the published data measured the validity of *H. pylori* stool antigen test or anti-*H. pylori* IgG antibodies only, but the present study combined both tests to elevate the validity measures. This study revealed that the specificity, positive predictive value, negative predictive value and accuracy has been increased by this combination when compared to anti-*H. pylori* IgG antibodies alone. As regards the stool antigen...
test, only specificity was elevated by this combination. Therefore, for both non-invasive methods analyzed, we think that the combination of them is more accurate for diagnosis of *H. pylori* infection.

Based on the results provided by this study, the accuracy of the tests for *H. pylori* diagnosis can be arranged in order as follows; PCR (95.76%), RUT (77.96%), stool antigen test (67.79%), combined *H. pylori* stool antigen test with IgG antibodies (56.77%) and finally anti-*H. pylori* IgG antibodies (48.3%). In the same context, several studies have reported nearly similar results with slight change in the arrangement.

Considering the agreement between different tests, the present study found high statistical significant agreement between PCR with RUT (gold standard) and RUT (0.91), PCR (0.572), stool antigen test (0.364) and combined *H. pylori* stool antigen test with IgG antibodies (0.608). On the other hand, there was no statistical significant agreement between anti-*H. pylori* IgG antibodies and PCR with RUT (gold standard) (0.031). Asrat and his colleagues reported better agreement between PCR, RUT, stool antigen test and the gold standard (1, 0.94, and 0.92, respectively). Furthermore, there was a difference between our results and those reported by Redéen and his colleagues who revealed good agreement between anti-*H. pylori* IgG antibodies and RUT (0.77).

**CONCLUSION**

Invasive tests were more accurate than non-invasive tests in diagnosis of *H. pylori* infection. Stool antigen test may be used for follow up after eradication therapy. Combination of stool antigen with anti-*H. pylori* IgG antibodies improves the specificity, positive predictive value and accuracy rather than using anti-*H. pylori* IgG antibodies or stool antigen test alone for diagnosis of *H. pylori* infection.

**REFERENCES**