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Diagnostic performance of the rapid urease test versus histopathology for diagnosing *Helicobacter pylori*: A prospective study in Saudi Arabia

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ABSTRACT

Background: *Helicobacter pylori* (*H. pylori*) can be quickly identified using a rapid urease test (RUT)/campylobacter-like organism (CLO) test, although its accuracy is often not comparable to histopathology. Therefore, this study aimed to examine the utility of the CLO test in routine endoscopy procedures.

Methods: This prospective study enrolled 100 patients undergoing upper gastrointestinal endoscopy. Gastric biopsies were used for CLO and histopathological examination of tissue. The CLO test's sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated, with histopathology as the reference standard.

Results: The CLO test demonstrated a sensitivity of 32.5%, a specificity of 70.0%, a PPV of 81.25%, and an NPV of 20.59%. The overall accuracy was 40%. In patients with recent proton pump inhibitor or antibiotic use, the sensitivity and specificity of the CLO test were 85.71% and 100%, respectively.

Conclusion: The CLO test's moderate capability in diagnosing *H. pylori* was observed, primarily due to its high PPV; however, its sensitivity is limited. When the CLO test result is negative, it may not detect all infections. Therefore, histopathology or additional tests should be considered. Further research is needed to understand the impact of medication use on test accuracy.

Keywords: *helicobacter pylori*, rapid urease test, CLO test, histopathology, gastric biopsy, diagnostic accuracy, Saudi Arabia

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram-negative, microaerophilic bacterium infecting the gastric mucosa, a main etiological factor in the onset of gastritis, some types of gastric cancer, and peptic ulcers. The infection is known to increase the risk of acquiring some types of gastric cancer, which is the second most common cause of cancer-related death worldwide. Although the mechanism of *H. pylori* transmission is still uncertain, most researchers hypothesize that *H. pylori* can spread through several pathways, such as the gastro-oral, fecal-oral, and oral-oral routes [1]. However, *H. pylori* infection is found in about half of the world's population [1, 2]. A Vietnamese study reported that the prevalence of H. pylori infection in children with gastroenteritis is very high and observed that children who live in a family where there is a history of H. pylori infection were nine times more likely to have H. pylori infection [3].

Furthermore, *H. pylori* infection is considered significant because it is very common, and the World Health Organization classified it as a 'class I carcinogen' due to its strong association with causing gastric cancer [4]. A study on a large population of patients in Saudi Arabia illustrated a substantially higher prevalence (82.53%) of patients with a history of *H. Pylori*, with an infection rate of *H. Pylori* in patients undergoing gastric biopsy at 37%, peaking in middle age and declining in older individuals [5]. Based on epidemiological studies, gastric cancer driven by *H. pylori* infection is a significant problem, as evidenced by a recent analysis showing that infected individuals have a significantly higher risk of developing this disease. The primary location of this spiral-shaped bacterium is in gastric mucosa, where it has been linked to chronic gastritis, peptic ulcer disease, and sgastric cancer [6]. Evidence suggests that eradicating *H. pylori* promptly helps prevent gastric cancer, making it crucial to be aware of and detect the bacteria early [7].

H. pylori infection is diagnosed using various methods, from invasive to non-invasive, each with pros and cons [8, 9]. In the case of invasive tests, endoscopic biopsy samples are required, along with histopathological examination, rapid urease test (RUT), and culture, among the available tests. Historically, histopathology has been viewed as the most useful for diagnosis due to its high sensitivity and specificity; however, RUT is now preferred more often because it is straightforward, speedy, and relatively inexpensive [10]. This test leverages the fact that *H. pylori* produces a substantial amount of urease, which breaks down urea into ammonia,

thereby altering the pH indicator to a visible color [11]. Several companies produce RUT kits, introducing new designs to expedite test results and enhance accuracy. It was described as a new type of test for urease, which enables faster and more accurate detection of infection, requiring much less waiting time [12]. However, RUT results may be influenced by several factors, including the number of bacteria present, recent use of certain medications, and errors in sample collection. Notably, the use of proton pump inhibitors (PPIs) can decrease the growth, structure, and urease activity of *H. pylori*, potentially leading to an incorrect result [13]. This condition highlights the importance of accurate patient preparation and the proper interpretation of healthcare tests.

It has been noted that there is a shortage of information on the effectiveness of various screening methods in detecting *H. pylori* infection in Saudi Arabia. The resistance to screening was apparent, and there is a requirement to dispel screening myths among the Saudi population by conducting health education programs [14]. A previous study in [15] investigated the differences between *H. pylori* stool antigen and campylobacter-like organism (CLO) tests (a type of RUT) in a Saudi group with dyspepsia. However, further coverage of present diagnostics is limited. In 2019, it was explored different methods of diagnosing diseases in Saudi kids and stressed that unique algorithms are needed for Saudi children [16]. The accuracy of tests for *H. pylori* varies significantly across different populations and hospitals. Research in [17] demonstrated that the accuracy of diagnostic tests varies significantly in an Alaska native population, underscoring the need for confirming specific testing methods in diverse populations.

Though *H. pylori* strain diagnostic tests are available in the Saudi healthcare system, it is crucial to identify the most effective test for this infection among the population. It is essential to consider sensitivity and specificity, as well as cost, test availability, the time required to obtain results, and patient compliance when evaluating the performance of a diagnostic test. Hence, this study focuses on comparing the ability of the RUT to detect *H. pylori* based on its histopathological findings in a Saudi Arabian population. The study aimed to evaluate the accuracy, predictive values, and agreement of two standard invasive diagnostic methods to inform better guidance on testing for *H. pylori* infection, especially in Saudi population . The findings of this study will inform the development of cost-effective diagnostic methods and may also guide the formation of new local guidelines for addressing *H. pylori*-related illnesses.

METHODS

Study Design and Setting

A prospective study was conducted at a tertiary care center in the Eastern Province of Saudi Arabia from January 2024 to December 2024. The study aimed to compare the diagnostic performance of the RUT (CLO test) and histopathological examination in detecting *H. pylori* infection.

Inclusion Criteria

This study included 100 adult patients aged 16 years or older who underwent diagnostic upper gastrointestinal endoscopy for dyspepsia, epigastric pain, or other upper gastrointestinal symptoms. Patients were eligible for the study if they had not received *H. pylori* eradication therapy within the past 12 months. Informed consent was obtained from all participants.

Exclusion Criteria

Patients were excluded if they had received antibiotics, PPIs, or bismuth-containing compounds within two weeks before endoscopy, had a history of gastric surgery, or were known to have a malignancy or a bleeding disorder.

Biopsy Sampling and CLO Test

A detailed endoscopic examination was performed, and several biopsies were taken for histological examination according to the Sydney system protocol, which involves placing five biopsies in the same container. The biopsy samples were sent for tissue processing with the final preparation of hematoxylin-eosin (H&E) and Warthin-Starry silver stains. Further, these samples were evaluated and diagnosed based on the Sydney classification. Pathologists were blinded to CLO results. Besides, two additional biopsies were obtained adjacent to the prior sites using separate biopsy forceps for the CLO test. The CLO test results were read 24 hours later to evaluate the *H. pylori* status.

Histopathological Examination

Biopsy specimens for histopathological examination were fixed in 10% buffered formalin, embedded in paraffin, and sectioned at a thickness of five. All sections were stained with H&E and modified Giemsa stain to enhance the visualization of *H. pylori*. Additionally, Warthin-Starry silver stain was used in cases where H&E and Giemsa results were equivocal. Two experienced pathologists, blinded to the CLO test results and clinical information, independently performed the histopathological assessment. Any discrepancies between the two pathologists were resolved by consensus or through consultation with a third independent pathologist.

Statistical Analysis

Data analysis was performed using SPSS version 29.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as frequencies, percentages, means, and standard deviations as appropriate. The diagnostic performance of the CLO test was evaluated by calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-), and overall accuracy. A 95% confidence interval (CI) was calculated for each measurement.

Ethical Considerations

This study was approved by the Institutional Review Board (IRB approval number: IRB-2021-01-419, dated 10/11/2021) and conducted following the principles of the Declaration of Helsinki. All patients provided written informed consent before participating in the study. Besides, this study maintained the confidentiality of the patient data.

RESULTS

The patients' mean age and standard deviation were 44.7 ± 15.6 years, ranging from 16 to 76 years. Most patients (27%; n = 27) were found to be in the 51-60 age group, while 22% (n = 22) were aged between 31 and 40. The patient population

Table 1. Demographic and clinical characteristics of study participants (N = 100)

Characteristics		F	P (%)
Age M ± SD (min, max)	44.7 ± 15.6 (16, 76)		
Age	≤ 20	8	8
	21 to 30	13	13
	31 to 40	22	22
	41 to 50	15	15
	51 to 60	27	27
	> 60	15	15
Gender	Male	48	48
	Female	52	52
Prior use of PPI or antibiotics in the last 4 weeks	Yes	20	20
	No	80	80
RUT (CLO test)	*H. pylori* negative	68	68
	*H. pylor*i positive	32	32
Histopathology	*H. pylori* negative	60	60
	H. pylori positive	40	40

Note. F: Frequency; P: Percentage; M: Mean; & SD: Standard deviation

Table 2. Distribution of study variable by prior use of PPI or antibiotics

Factors	Prior use of PPI or antibiotics in the last 4 weeks	
	Yes (n = 20)	No (n = 80)
Gender		
Male	13 (65%)	35 (44%)
Female	7 (35%)	45 (56%)
Age (in years)		
M ± SD	45.45 ± 16.41	44.54 ± 15.47
RUT (CLO test)		
Positive	7 (35%)	25 (31%)
Negative	13 (65%)	55 (69%)
Histopathology		
Positive	6 (30%)	34 (42.5%)
Negative	14 (70%)	46 (57.5%)

Note. M: Mean & SD: Standard deviation

consisted of 52% females and 48% males. Only 20% (n = 20) of the patients had taken PPIs or antibiotics within the past 4 weeks. Overall, the results of the RUT (CLO test) showed that 32% of patients tested positive (n = 32), while 68% of patients were negative (n = 68). Upon histopathological examination, pathologists found *H. pylori* infection in 40% of patients (n = 40), while 60% (n = 60) showed no evidence of disease (**Table 1**).

Table 2 presents the distribution of patients across variables related to prior use of PPIs or antibiotics. Despite the larger number of males in the group receiving recent medication, gender did not significantly influence test results within the different subgroups. The mean age in both groups was nearly the same (45.5 ± 16.4 and 44.5 ± 15.5 years, respectively).

For the 20 patients who used PPIs or antibiotics before testing, the CLO test showed 92.86% NPV, 85.71% sensitivity, 100% specificity, and 100% PPV. In contrast, the sensitivity and specificity of those who did not use PPIs or antibiotics were 80.0% and 74.55%, respectively. The proportion positive in this group was 58.82% for PPV and 89.13% for NPV. These observations were lower compared to those who had used PPIs or antibiotics in the last four weeks (**Table 3**).

A general description of the test results for the RUT (CLO test) is provided in **Table 4**, using histopathology as a reference. As the reference standard was histopathology, the CLO test had a True positive of 32.5% and a True negative of

Table 3. Diagnostic performance of RUT (CLO test) compared to histopathology based on prior use of PPI or antibiotics

Test	Prior use of PPI or antibiotics in the last 4 weeks	
	Yes (n = 20)	No (n = 80)
Sensitivity (95% CI)	85.71% (42.13-99.65)	80% (59.30-93.17)
Specificity (95% CI)	100% (75.29-100)	74.55% (61-85.33)
PPV (95% CI)	100%	58.82% (46.60-70.05)
NPV (95% CI)	92.86% (67.93-98.76)	89.13% (78.67-94.80)

Table 4. Overall diagnostic performance characteristics of the RUT (CLO test) compared to histopathology

Statistic	Value	95% CI
True positive	32.50%	22.45-43.89
True negative	70.00%	45.72-88.11
LR+	1.08	0.52-2.27
LR-	0.96	0.70-1.33
Disease prevalence	80.00%	70.82-87.33
PPV	81.25%	67.40-90.08
NPV	20.59%	15.78-26.40
Accuracy	40.00%	30.33-50.28

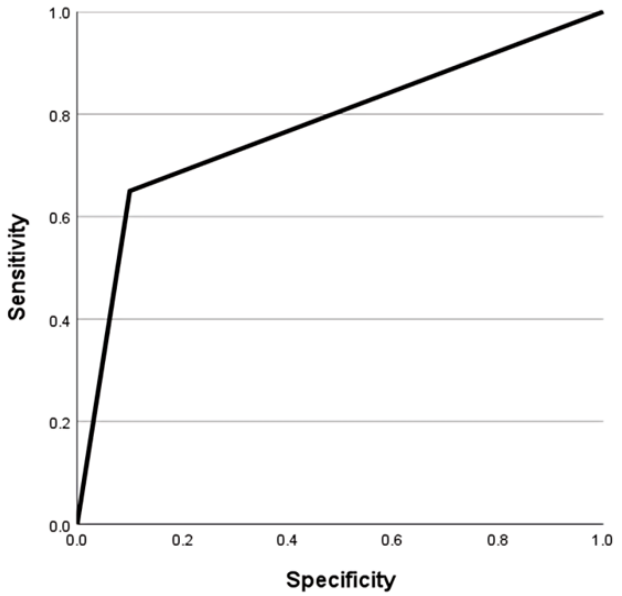

Figure 1. ROC curve between patients with an *H. pylori* infection and those without (Source: Author's own elaboration)

70.0%. The PPV for the diagnostic test was 81.25%, while the NPV was 20.59%. The accuracy for all diagnostic tests was 40.0% (95% CI: 30.33%-50.28%). The score for an LR+ was 1.08 (95% CI: 0.52-2.27). When the result was negative, the likelihood ratio was 0.96 (95% CI: 0.70-1.33). The results showed that 80% of patients had the disease (95% CI: 70.82%-87.33%).

The receiver operating characteristic (ROC) curve analysis with an area under the curve (AUC) of 0.775 (CI: 0.674-0.876) demonstrates that the CLO test has a good discriminatory capacity compared to histopathology, which is the gold standard for identifying *H. pylori*. The CLO test shows a 77.5% accuracy in differentiating between patients with an *H. pylori* infection and those without. The diagnostic value of the CLO test is good but not exceptional (**Figure 1**).

DISCUSSION

The study investigated the performance of the CLO test in detecting *H. pylori* infections compared to histopathology in a tertiary care hospital in Saudi Arabia. The results highlighted the effectiveness of diagnostic tests used by ordinary clinicians.

Demographic Characteristics and Clinical Conditions

The wide age range and mean age suggest a diverse participant pool, helping to generalize findings across age groups. This age distribution in the region aligns with previous studies, which show an increased prevalence of *H. pylori* in the region with significantly more frequency in adults, especially in middle-aged adults in the area [14, 18, 19]. *H. pylori* was positive in 40% of the histopathology samples, matching what is generally reported in Eastern Saudi Arabia, with a prevalence of 35 to 46 percent [20]. Further, most participants (80%) did not use PPIs or antibiotics in the last 4 weeks before participation. This is crucial for ensuring that the study results are not influenced by recent medication use that could affect *H. pylori* detection. Research demonstrates that *H. pylori* infection will be significantly lower with reported antibiotic usage. Therefore, in studies, information on prior antibiotic usage should always be considered when evaluating the prevalence and risk factors of *H. pylori* infection [21, 22].

Effect of Previous Medications

Although this study excluded patients who had used PPIs and antibiotics for at least two weeks before endoscopy, 20% of included patients had used these medications in the previous four weeks. Further, the study observed that more males (65%) had a history of PPIs or antibiotic exposure than females (35%), which suggests males may have better medication adherence. Alternatively, females constituted a greater proportion of nonusers (56%). This suggests potential gender-related differences in drug exposure, highlighting the challenges of preparing patients for *H. pylori* testing, as explained in [23]. The findings also discuss how PPIs may alter bacterial presence, potentially affecting histopathological findings. Further, the observations also highlight how PPIs may alter bacterial presence, potentially affecting histopathological findings [24]. Thus, the results confirm how prior exposure to PPIs or antibiotics may influence the detection of *H. Pylori* by histopathology and rapid tests. Therefore, prior exposure is liked with lower histopathology positivity, which suggests potential masking by such drugs. It highlights the importance of drug history in the study and diagnosis of *H. Pylori*.

Variations in Diagnostic Results Regarding Patient's Drug History

We also observed that prior medication use impacts the sensitivity and specificity of the CLO test in detecting *H. pylori*. Those who had recently taken PPIs or antibiotics had higher sensitivity (85.71% vs. 80.00%) and specificity (100% vs. 74.55%) than patients who had not taken either drug. These findings underscore the importance of considering prior medication history when interpreting test results for *H. pylori*. PPIs and antibiotics impact the density of bacteria, influencing the sensitivity and specificity of CLO tests. Various other studies [25, 26] have similarly reported compromised diagnostic performance depending on acid suppression therapy, thus underlining the importance of logical test interpretation. However, in contrast to this observation, another finding suggests that people recently treated with medication do worse on tests [27]. Having only twenty people in the medication group may account for the improvement in accuracy, or it may also be that the 2-4 weeks of medications reduced the bacteria without eliminating them, so unclear results were less likely to occur.

Total Performance of the CLO Test

The study outcomes reported that the CLO test performs only moderately well compared to histopathology. Although the predictive value for positive cases is solid, the low value for negative cases suggests that many true negatives may be unidentified. The results from this study were less accurate than what is typically found in research from other countries [28]. However, the NPV (20.59%) is relatively low, meaning that a negative test does not reliably exclude infection, necessitating further confirmatory testing. Additionally, the likelihood ratios show that the test is not very helpful since it has a negative (0.96) and favorable (1.08) ratio closer to 1. The results suggest that using the CLO test alone is ineffective in diagnosing the Saudi population definitively. Further, the low NPV suggests that histopathology remains essential for definitive *H. pylori* diagnosis, particularly in clinical scenarios where infection suppression by PPIs is a concern, aligning with the findings in [25].

ROC Analysis

The diagnostic accuracy observed by the study (**Figure 1**) aligns with other studies [25, 29], which discuss CLO test reliability and how prior medication exposure affects bacterial activity, thus influencing ROC curve results. ROC curve analysis stated that the predictive capability is better than average but imperfect (AUC = 0.775; CI: 0.674-0.876). This outcome is consistent with previous research, which finds that AUC for RUTs tends to fall between 0.70 and 0.85 [30]. Further, the curve proves that the CLO test should not be considered a substitute for histopathology, though it has good diagnostic significance. Such findings are vital in making clinical decisions about diagnosing *H. pylori* in Saudi Arabia. Because the connection between CLO and histology is not very close, a combination of both tests could be considered, mainly when either drug history is missing or if the test results clash with the symptoms seen [31].

CONCLUSION

This study measured the ability of RUT and histopathology to identify *H. pylori* infection in a hospital in Saudi Arabia. It was observed that positive CLO could accurately diagnose active *H. Pylori* infection; however, its overall accuracy of 40% and NPV of 20.59% are not as good as those found in histopathology. The findings of the ROC analysis (AUC = 0.775) showed that the CLO test is effective at distinguishing between individuals, but it is not the most powerful test. Furthermore, patients who have used PPI or antibiotics within a few weeks showed better test performance, which deserves further investigation with a larger sample size. Since these diagnostic methods often agree less than many expect, using a single method might easily overlook some diagnoses, particularly false negatives in the CLO test. Based on these findings, it is recommended that healthcare providers detect *H. pylori* infection by combining

RUT with microscopic examination of tissue samples, particularly in regions where the infection is prevalent, such as Saudi Arabia. Further research on larger groups of subjects is needed to validate these results and determine how medication used affects test performance. All patients should receive the same preparation guidelines to help ensure the accuracy of the diagnostic tests.

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Ethical statement: The author stated that the study was approved by the Institutional Review Board on 10 November 2021 with approval number IRB-2021-01-419 and conducted following the principles of the Declaration of Helsinki. Written informed consents were obtained from the participants.

AI statement: The author stated that no generative AI or AI-based tools were used in any part of the study, including data analysis, writing, or editing.

Declaration of interest: No conflict of interest is declared by the author.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the author.

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