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A novel rapid and accurate method for detecting *Helicobacter Pylori*: the modified antigen test

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Abstract. – OBJECTIVE: We aim to assess the diagnostic accuracy of the gastric biopsy *Helicobacter pylori (H. pylori)* antigen stool test as a novel method for detecting *H. pylori*, comparing this test with the histopathological evaluation of *H. pylori* and *H. pylori* antigen stool test as the reference standards.

PATIENTS AND METHODS: The study involves patients who are scheduled for an upper gastrointestinal endoscopy. Gastric biopsies were endoscopically obtained from all patients, and *H. pylori* antigen stool tests were performed for all patients. Results from the gastric biopsies that were studied using the *H. pylori* antigen stool test in terms of the novel method were obtained and recorded. The inter-rater agreement between the *H. pylori* tests in determining positive and negative results was investigated using Fleiss' and Cohen's kappa tests. The capacity of applied tests in predicting the presence of *H. pylori* was analyzed using a receiver operating characteristic (ROC) curve analysis.

RESULTS: A total of 55 patients were studied (32 females and 23 males). The strongest coherence was obtained between the gastric biopsy test and histopathological evaluation with a kappa value of 0.664 in Cohen's kappa analysis of overall coherence between tests. The most accurate sensitivity and specificity values were obtained for the gastric biopsy test and histopathological evaluation crosstabulation for both overall comparisons at 90.5% sensitivity and 79.4% specificity.

CONCLUSIONS: With this new, rapid, and easy-to-apply method, patients' endoscopies and gastric biopsies looking for the presence of *H. pylori* would be determined with more sensitive and more specific accuracy rates than current antigen stool tests, and *H. pylori* can be eradicated immediately without waiting for the histopathological evaluation period.

Key Words:

Helicobacter pylori, H. pylori antigen stool test, Immunochromatographic *H. pylori* test, *H. pylori* diagnosis, Endoscopic *H. pylori* test.

Introduction

Helicobacter pylori (*H. pylori*) screening tests are frequently used in gastroenterology for detecting *H. pylori*-related diseases and morbidities. *H. pylori* eradication therapy and the control of related diseases can be more effective and successful with methods that are more effective, easier to apply, faster, and more reliable than existing tests. Peptic ulcer disease, chronic gastritis, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma are some of the diseases related to *H. pylori*[1-3].

Diagnostic tests for *H. pylori* can be divided into the upper gastrointestinal system (GIS) endoscopy-mediated (i.e., invasive, gastric biopsy), and non-invasive techniques. Examples of non-endoscopic tests include the urea breath test and the stool antigen test for active *H. pylori* infection. In addition, an urease test can be performed on the gastric specimen taken during the endoscopic examination; the sensitivity and specificity are approximately 90% and 95%, respectively[2]. Gastric biopsies can diagnose *H. pylori* infection and associated lesions (e.g., atrophic gastritis, intestinal metaplasia, dysplasia, and MALT lymphoma). Even as stated in the guidelines, H. pylori eradication is the first-line treatment for localized stage gastric MALT lymphoma[4]. The sensitivity and specificity of histopathological diagnosis of *H. pylori* infections are 95% and 98%, respectively. Detecting the presence of the bacterial antigen indicates an ongoing *H. pylori* infection. Thus, the stool antigen test can be used both to initially diagnose *H. pylori* and to confirm eradication[2]. Among the available tests, the antigen stool test is the most cost-effective in regions with a low to the moderate prevalence of *H. pylori*[5]. Rapid monoclonal immunochromatographic antigen (Ag) stool tests have high specificity but limited

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acceptability due to their low sensitivity (96% specificity while only 50% sensitivity)[6]. Commercially, rapid PCR stool tests are also available[7]. Serology-based tests are not valid for diagnosing an active *H. pylori* infection, as *H. pylori* antibodies may show positive results for years after eradication[8].

The use of proton pump inhibitors (PPI) within one to two weeks and of bismuth/antibiotics within four weeks after the test may reduce the sensitivity of all endoscopy-based as well as non-invasive tests (i.e., antigen stool and urea breath test) for active *H. pylori* infection[9]. Patients should be advised to stop PPI therapy one to two weeks before the test. If possible, testing should be performed at least four weeks after completing the bismuth/antibiotic therapy.

In the present trial, we study and evaluate the monoclonal immunochromatographic *H. pylori* antigen stool test to detect the presence of *H. pylori* in gastric biopsies sampled during an upper GIS endoscopic examination. We aim to assess the diagnostic accuracy of the gastric biopsy *H. pylori* antigen test as a novel method for detecting *H. pylori* compared to the histopathological evaluation of *H. pylori* and the *H. pylori* antigen stool test as the reference standards.

Patients and Methods

Written informed consent was obtained from all patients included in the study. Outpatients who were admitted to the Gastroenterology Endoscopy Unit were included in the study after obtaining approval from the Ethics Committee (registered as 2019/2012). This is a single-center, prospective data collection and method comparison study performed between January and December 2020.

Patients

Adult patients who plan to undergo endoscopic examination and gastric biopsy due to dyspeptic complaints and gastroesophageal reflux-related symptoms as well as complications screening, epigastric pain, epigastric burning, postprandial fullness, weight loss, early satiation, and suspicion of malignancy were included in the study. Gastric biopsies were endoscopically obtained from all patients, and *H. pylori* antigen stool tests were performed for all patients. Both patients using and those not using proton pump inhibitors (PPIs) as well as patients whose *H. pylori* have and have not been eradicated were included in the study. Patients with gastrointestinal bleeding were excluded.

Data Collection

The endoscopy indications, endoscopic diagnoses, PPI status, history of *H. pylori* eradication, and *H. pylori* antigen stool test results from all patients were recorded. Histopathological evaluations of gastric biopsies were recorded for *H. pylori* status, atrophy, and intestinal metaplasia for all patients. Results from the gastric biopsies studied with *H. pylori* antigen stool test in terms of the novel method were obtained and recorded. Double-blind evaluations were made for both the histopathological examinations and stool antigen tests.

Procedure

A minimum of two biopsy samples from the gastric antrum (greater and lesser curvature, 3 cm proximal to the pyloric region) and two from the middle of the gastric body were collected for histopathological evaluation during the upper endoscopic examination; an additional four samples (two antrum and two corpus) were collected for the H. pylori antigen stool test kit. Gastric samples were physically homogenized in saline to obtain an adequate soluble sample and then dropped into the opening of the rapid immunochromatographic *H. pylori* antigen stool test kit (Laboquick, Helicobacter Pylori Ag Test, LHAG.01, Izmir, Turkey). Stool tests were performed with the same rapid immunochromatographic *H. pylori* antigen stool test kit. Results were recorded as positive or negative for the presence of *H. pylori*.

Tissue Homogenization

Tissue homogenization was carried out using the materials available in our unit as follows; after the outer metal sheath of a biliary lithotripter was cut to a length of approximately 12 cm, a metal wire was placed inside its lumen to provide both an oblique axis and stiffness. Thus, a slightly curved metal grinder with a distal crown shape was obtained. The metal tip was attached to a drill and used to break up the tissue. Physical homogenization was carried out at 2,900 rpm for at least 3 minutes in 2 ml of saline. The physical homogenization equipment is illustrated in Figure 1.

Statistical Analysis

Statistical analyses were performed with the software IBM Statistics SPSS (ver. 25) and MedCalc Statistics (ver. 19). The variables were inves-

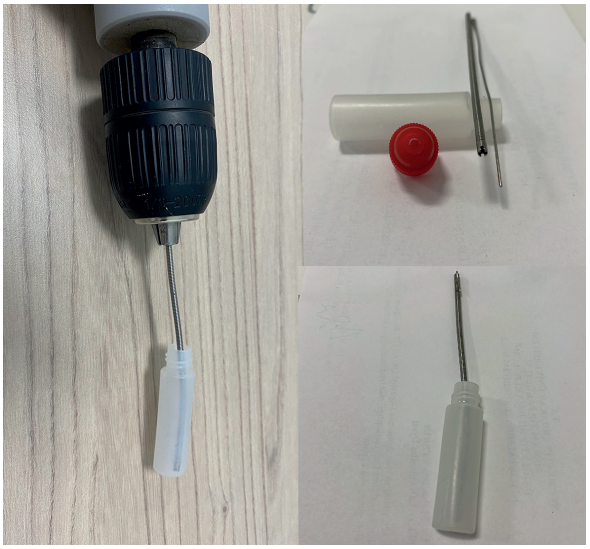

Figure 1. Equipment used for physical tissue homogenization.

tigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk's tests) to determine whether or not the data are normally distributed. The inter-rater agreement between the *H. pylori* tests in determining the positive and negative results was investigated using Fleiss' and Cohen's kappa tests. The capacity of applied tests in predicting the presence of *H. pylori* was analyzed using the receiver operating characteristics (ROC) curve analysis. When a significant cut-off value was observed, the sensitivity, specificity, positive and negative predictive values were presented. While evaluating the area under the curve, a 5% type-I error level was used to accept a statistically significant predictive value of the test variables. A *p*-value of less than 0.05 was considered to show a statistically significant result for all analyses.

Results

A total of 55 patients have been studied (32 females and 23 males). While the females have a median age of 42.5 years (R = 27 to 52.75), the males have a median age of 34 (R = 23 to 45). Previous *H. pylori* eradication had occurred in 26 (47.3%) of the patients; 39 (70.9%) patients were on PPI while testing. The antigen stool tests were positive in 16 (29.1%) patients. Histopathological evaluation revealed a number of positive *H. pylori* results in 21 (38.2%) patients. Gastric biopsy test was positive in 26 (47.3%) patients. Histopathological evaluation revealed atrophy only in 1 (1.8%) patient and intestinal metaplasia in 4 (7.3%). Characteristics of the tests, clinics, and gastric samples are summarized in Table I.

Endoscopies indicated dyspepsia for 31 (56.4%) patients, epigastric pain for 14 (25.5%), pyrosis for 7 (12.7%), celiac disease for 2 (3.6%), and esophagitis for 1 (1.8%). Endoscopic diagnoses revealed gastritis for 34 patients (61.8%), esophagitis for 8 (14.5%), duodenal ulcers for 5 (9.1%), gastric ulcers for 2 (3.6%), nodular gastropathies for 2 (3.6%), normal for 2 (3.6%), both gastric and duodenal ulcers for 1 (1.8%), and atrophic gastritis for 1 (1.8%).

We obtained 81.25% sensitivity and 66.67% specificity in the ROC curve analysis of the gastric biopsy tests adjusted for positive stool antigen tests (Figure 2). Similarly, the ROC curve analysis for the gastric biopsy test adjusted for histopathological evaluation positivity showed 90.48% sensitivity and 79.41% specificity (Figure 3). The

Table I. Characteristics of tests, clinics, and gastric samples.

	Positive	**Negative**
Gastric Biopsy Test	26 (47.3%)	29 (52.7%)
Stool Test	16 (29.1%)	29 (70.9%)
Histopathological H. pylori Status	21 (38.2%)	34 (61.8%)
	Yes	**No**
PPI Status	39 (70.9%)	16 (29.1%)
H. pylori Eradication	26 (47.3%)	29 (52.7%)
Atrophy	1 (1.8%)	54 (98.2%)
Intestinal Metaplasia	4 (7.3%)	51 (92.7%)

H. pylori = H*elicobacter pylori*, Ag = Antigen, PPI = Proton pump inhibitor.

Table II. Cohen's kappa analysis of overall coherence between tests.

	Kappa	Spearman Correlation	*p*
Fleiss' kappa analysis	0.455	NA	< 0.001
H. pylori gastric Bx test *vs. H. pylori* stool test	0.405	0.436	0.001
H. pylori stool test *vs*. Pathology *H. pylori*	0.308	0.314	0.021
H. pylori gastric Bx test *vs.* Pathology *H. pylori*	0.664	0.676	< 0.001

NA = Not applicable, *H. pylori* = *Helicobacter pylori*, Bx = Biopsy.

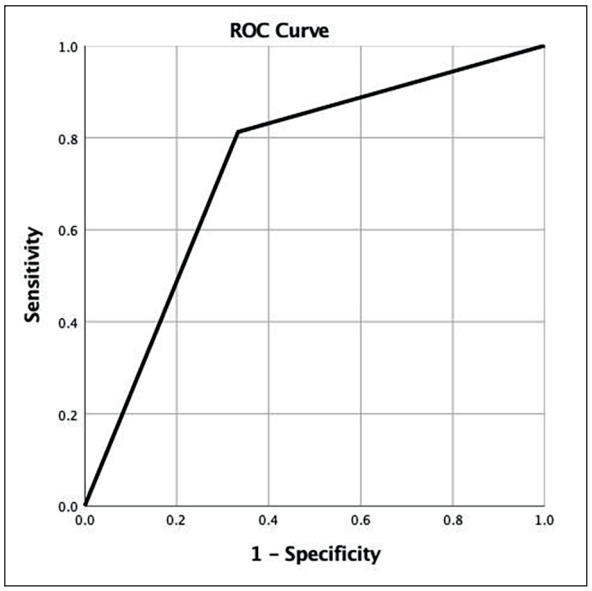

Figure 2. ROC curve of gastric biopsy test adjusted for stool test positivity. Area under the ROC curve (AUC) = 0.740, $p < 0.001$, Youden index J = 0.479, Sensitivity = 81.25%, Specificity = 66.67%.

ROC curve analysis of stool tests adjusted for histopathological evaluation positivity had 47.62% sensitivity and 82.35% specificity (Figure 4).

The strongest coherence was obtained between the gastric biopsy test and the histopathological evaluation, with a Kappa value of 0.664 in Cohen's kappa analysis of overall coherence between tests (Table II). Cohen's kappa analysis for the coherence of tests according to PPI status and non-eradicated *H. pylori* showed the strongest coherence between the gastric biopsy test and histopathological evaluation, with a kappa value of 0.875 in patients not using PPI, 0.581 in patients using PPI, 0.792 in patients with uneradicated *H. pylori*, and 0.473 in patients with eradicated *H. pylori* (Tables III and IV). Coherence between the gastric biopsy test and antigen stool test was strongest in patients with eradicated H. pylori, with a Kappa value of 0.570 (Table IV).

Diagnostic comparisons of tests in terms of positivity with crosstabulations are detailed in Tables V and VI. The most accurate sensitivity and specificity values were obtained in the crosstabulation of the gastric biopsy test and histopathological evaluations for both overall and PPI status comparisons with 90.5% sensitivity and 79.4% specificity for overall comparisons, 100% sensitivity and 89.9% specificity for non-usage of PPI, and 85.7% sensitivity and 76% specificity for PPI users (Table V). In addition, the cross-tabulations for the gastric biopsy test and the histopathological evaluation for patients with uneradicated *H. pylori* had an 85.7% sensitivity and 93.3% specificity, while having a 75% sensitivity and 83.3% specificity for patients whose *H. pylori* had been eradicated (Table VI).

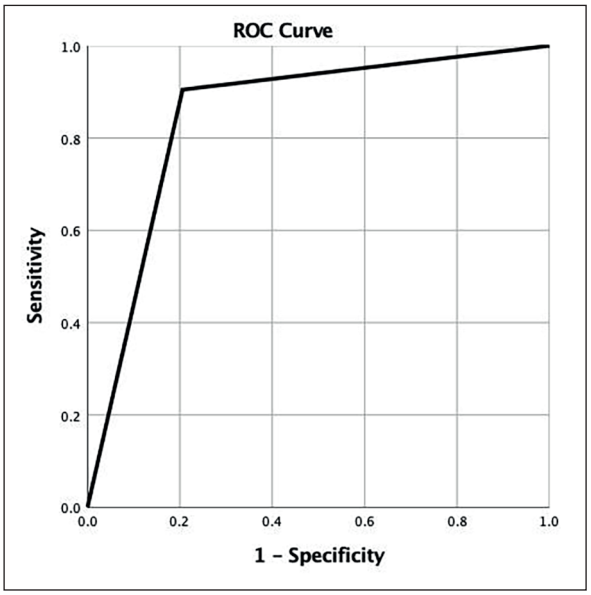

Figure 3. ROC curve of the gastric biopsy test adjusted for histopathological evaluation positivity. Area under the ROC curve (AUC) = 0.849, $p < 0.001$, Youden index J = 0.699, Sensitivity = 90.48%, Specificity = 79.41%.

Table III. Cohen's kappa analysis for the coherence of tests according to PPI status.

Tested without PPI	Kappa	Spearman Correlation	p
Fleiss' kappa analysis	0.743	NA	< 0.001
H. pylori gastric Bx test *vs. H. pylori* stool test	0.625	0.674	0.007
H. pylori stool test *vs*. Pathology *H. pylori*	0.738	0.764	0.002
H. pylori gastric Bx test *vs*. Pathology *H. pylori*	0.875	0.882	< 0.001
Tested with PPI	**Kappa**	**Spearman Correlation**	**p**
Fleiss' kappa analysis	0.338	NA	< 0.001
H. pylori gastric Bx test *vs. H. pylori* stool test	0.310	0.334	0.001
H. pylori stool test *vs*. Pathology *H. pylori*	0.123	0.125	0.43
H. pylori gastric Bx test *vs*. Pathology *H. pylori*	0.581	0.594	< 0.001

NA = Not applicable, *H. pylori* = *Helicobacter pylori*, PPI = Proton pump inhibitor, Bx = Biopsy

Discussion

When assuming *H. pylori* positivity in the histopathological evaluation of gastric tissue as a reference, high sensitivity and specificity values were obtained as well as high PPV and NPV values when applying the antigen stool test that is frequently used for noninvasive diagnosis of *H. pylori* to gastric biopsy samples of individuals being examined endoscopically. In fact, higher values were obtained in non-PPI cases when using this method. Similarly, higher values were obtained in cases where *H. pylori* had not yet been eradicated. The strongest coherence was between the gastric biopsy test and histopathological evaluation of *H. pylori* in gastric biopsies (K = 0.664, $p < 0.001$).

In our study, the dominant symptom was dyspepsia as an indication for endoscopy, while the second most common indication was epigastric pain. Since both indications are the most common symptoms in *H. pylori*-related admissions, the current study gives the impression of an appropriate patient population to study for diagnosing *H. pylori*.

The fact that the patients are taking PPI before or during the diagnostic tests is a negative situation in terms of obtaining an accurate *H. pylori* diagnosis and increases the probability of obtaining a false negative[9]. Even in patients not receiving PPI therapy, histopathological evaluation may show interobserver variability due to the variable distribution and heterogeneous localization of *H. pylori*[10,11]. In our study, 39 (70.9%) patients were on PPI while testing. Additionally, 26 (47.3%) patients had a previous history of *H. pylori* eradication. Therefore, considering both negative conditions, the success rates of the tests, including the new method we study, are expected to be low; however, despite this situation, accurate and acceptable results were obtained with the *H. pylori* antigen stool test in gastric biopsies.

Considering the positivity rates of *H. pylori* in all three tests, the highest positivity rate was found

Table IV. Cohen's Kappa analysis for the coherence of tests according to *H. pylori* eradication.

Tested in *H. pylori* eradicated	Kappa	Spearman Correlation	p
Fleiss' kappa analysis	0.445	NA	< 0.001
H. pylori gastric Bx test *vs. H. pylori* stool test	0.570	0.590	0.003
H. pylori stool test *vs.* Pathology *H. pylori*	0.283	0.285	0.14
H. pylori gastric Bx test *vs*. Pathology *H. pylori*	0.473	0.505	0.01
Tested in *H. pylori* uneradicated	**Kappa**	**Spearman Correlation**	**p**
Fleiss' kappa analysis	0.445	NA	< 0.001
H. pylori gastric Bx test *vs. H. pylori* stool test	0.270	0.305	0.101
H. pylori stool test *vs.* Pathology *H. pylori*	0.319	0.350	0.060
H. pylori gastric Bx test *vs.* Pathology *H. pylori*	0.792	0.794	< 0.001

NA = Not applicable, *H. pylori* = *Helicobacter pylori*, PPI = Proton pump inhibitor, Bx = Biopsy

Table V. Diagnostic comparisons of tests in terms of positivity for overall and PPI status: Crosstabulations.

Overall comparisons	Sensitivity	Specificity	PPV	NPV
H. pylori gastric Bx test *vs*. Pathology *H. pylori*	90.5%	79.4%	73.1%	93.1%
H. pylori gastric Bx test *vs*. *H. pylori* stool test	81.3%	66.7%	50%	89.7%
H. pylori stool test *vs.* Pathology *H. pylori*	47.6%	82.4%	62.5%	71.8%
Comparisons for PPI off	**Sensitivity**	**Specificity**	**PPV**	**NPV**
H. pylori gastric Bx test *vs*. Pathology *H. pylori*	100%	89.9%	87.5%	100%
H. pylori gastric Bx test *vs*. *H. pylori* stool test	100%	72.7%	62.5%	100%
H. pylori stool test *vs.* Pathology *H. pylori*	71.4%	100%	100%	81.8%
Comparisons for PPI on	**Sensitivity**	**Specificity**	**PPV**	**NPV**
H. pylori gastric Bx test *vs*. Pathology *H. pylori*	85.7%	76%	66.7%	90.5%
H. pylori gastric Bx test *vs*. *H. pylori* stool test	72.7%	64.3%	44.4%	85.7%
H. pylori stool test *vs.* Pathology *H. pylori*	35.7%	76%	45.5%	67.9%

PPV = Positive predictive value, NPV = Negative predictive value, *H. pylori* = *Helicobacter pylori*, PPI = Proton pump inhibitor, Bx = Biopsy.

in the *H. pylori* antigen stool test applied in gastric biopsies for 26 (47.3%) patients. We think that false negatives can be detected in the histopathological evaluation of gastric biopsies due to the heterogeneous distribution of *H. pylori*, but higher positivity could be detected with the gastric biopsy *H. pylori* antigen test since homogenized gastric samples will provide antigenic contamination and provide a positive result in either case.

To evaluate both the antigen stool test and the gastric biopsy test in terms of efficacy and safety, we determined the histopathological evaluation as the most reliable reference available. When comparing both test methods with histopathological evaluations, the gastric biopsy test had a stronger coherence according to the antigen stool test (K = 0.664, $p < 0.001$). In addition, the gastric biopsy test adjusted for histopathological evaluation positivity has a significantly higher specificity (79%) and sensitivity (90.5%) than the antigen stool test. The most accurate sensitivity (100%) and specificity (89.9%) values were found in the tests performed on patients not using PPI (K = 0.875, $p < 0.001$). Similarly, the highest accuracy was found in patients whose H. pylori had not yet been eradicated (K = 0.792, $p < 0.001$).

Although ELISA-based tests have the lowest cost-effectiveness ratios, stool antigen tests provide increased accuracy at modest incremental costs[5]. The commercial antigen stool tests used in our study are very economical and cost-effective, as well as being easily available.

As Kelly et al[12] stated, *H. pylori* can be isolated from feces obtained from adults. This explains why the fecal-oral infectious transmission of *H. pylori* is feasible and at the same time *H. pylori* antigen stool can be detected. Therefore, the diluted antigen spilled into the intestinal tract is more difficult and less likely to detect compared to detecting it directly in the gastric mucosa, which is the source of the antigen. Therefore, it is more likely and easier to detect *H. pylori* antigen in homogenized gastric biopsy samples.

Wu et al[13] reported no statistically significant

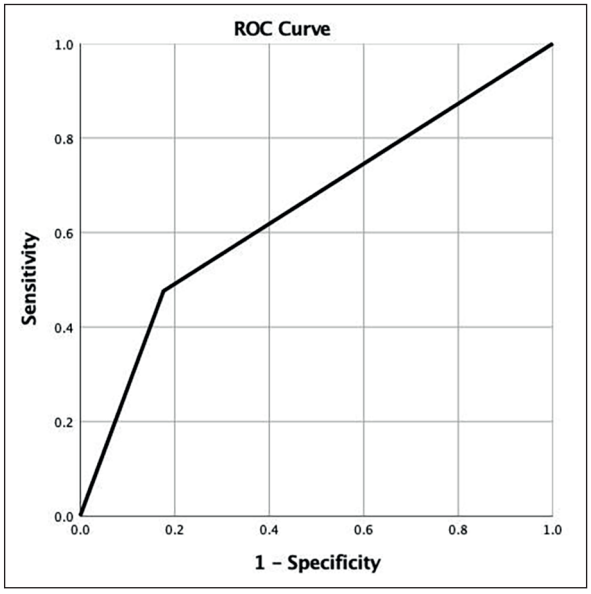

Figure 4. ROC curve of stool test adjusted for histopathological evaluation positivity. Area under the ROC curve (AUC) = 0.650, $p = 0.021$, Youden index J = 0.299, Sensitivity = 47.62%, Specificity = 82.35%.

Table VI. Diagnostic comparisons of tests in terms of positivity for *H. pylori* eradication status: Crosstabulation.

Comparisons for *H. pylori* not eradicated	Sensitivity	Specificity	PPV	NPV
H. pylori gastric Bx test *vs.* Pathology *H. pylori*	85.7%	93.3%	92.3%	87.5%
H. pylori gastric Bx test *vs. H. pylori* stool test	55%	77.8%	84.6%	43.8%
H. pylori stool test *vs.* Pathology *H. pylori*	85.7%	46.7%	60%	77.8%
Comparisons for *H. pylori* eradicated	**Sensitivity**	**Specificity**	**PPV**	**NPV**
H. pylori gastric Bx test *vs*. Pathology *H. pylori*	75%	83.3%	93.8%	50%
H. pylori gastric Bx test *vs*. *H. pylori* stool test	78.9%	85.7%	93.8%	60%
H. pylori stool test *vs.* Pathology *H. pylori*	80%	50%	84.2%	42.9%

PPV = Positive predictive value, NPV = Negative predictive value, *H. pylori = Helicobacter pylori*, Bx = Biopsy.

differences between stool enzyme immunoassay and immunochromatographic methods for detecting *H. pylori* antigens, stating them to be rapid, simple, and accurate in-clinic tests for diagnosing *H. pylori*. Based on this, similar test results will be obtained in all stool antigen tests except for stool-based PCR tests. In this case, the test and method become more applicable and accessible.

While the acid suppression by PPI shifts *H. pylori* toward the corpus and fundus mucosa with an increasing but still low colonization gradient, the antrum is cleared of *H. pylori* in up to 40% to 80% of patients using PPI[14]. Similarly, according to the study from Attumi et al[15] supporting this concept, low antigen loads in the stool due to low gastric *H. pylori* density is the most common cause of false-negative tests. Our method yielded more accurate and reliable results than the stool antigen test, even in 70.9% of the patients who use PPI ($K = 0.581$, $p < 0.001$ compared to $K = 0.123$, $p = 0.43$). According to this inference, *H. pylori* positivity may also be detected by using our method with the least false-negative rates even in patients using PPI.

Today, endoscopic examination is available in many health centers and gastroenterology units and is the preferred examination method for most patients. If no contraindication occurs during the endoscopic examination, gastric biopsies are sampled from almost all patients, and histopathological *H. pylori* positivity in the biopsy samples is evaluated. Since histopathological evaluations are mostly reported within days, this may cause delays and sometimes even incomplete *H. pylori* eradication treatments. Therefore, a test that is both as reliable as the histopathological evaluation and as rapid as the stool antigen test will fill this gap. This new method that our study proposes, precisely meets these criteria.

Technically, the method is easy to implement and more cost-effective than histopathological examination. A gastric biopsy test does not impose an additional burden in terms of procedure time and complications. Furthermore, immediate results can be obtained following the endoscopic procedure. The most crucial and superior aspect of the method is that it has higher PPV and NPV values compared to the antigen stool test, as well as better rates for positive case detection compared to the histopathological evaluation. Another advantage of this method is that high PPV and NPV values can be obtained even in patients using PPI or whose H. pylori have been eradicated.

As a disadvantage, this method cannot be applied in patients with no endoscopic indication; they are not clinically suitable for the procedure, or the biopsy is contraindicated. In some units, the method cannot be used even when endoscopic examination is impossible; however, in today's conditions, this case is extremely rare. The tissue homogenization process may be a problem in practice for some centers, but can be handled very economically and easily with the technique we have described. The antigen stool test kit we performed in our study is standard and does not have any additional features or superiority. Therefore, this method can provide similar results with almost any kit available.

Conclusions

With this new, rapid, and easy-to-apply method, the presence of *H. pylori* can be determined in patients undergoing endoscopies and gastric biopsies with more sensitivity and more specificity compared to current antigen stool tests, and *H. pylori* can be eradicated immediately without waiting histopathological evaluation period. Studies with different stool antigen tests in larger patient populations will increase the accuracy and reliability of this novel method.

Ethics Committee Approval

Necmettin Erbakan University, Meram School of Medicine Ethics Committee – registered as 2019/2012.

Informed Consent

Patients' written consents were obtained from themselves.

Author Contributions

Concept-1; Design-1; Supervision-1; Resources-None; Materials-1, 2; Data Collection and/or Processing-1, 2; Analysis and/or Interpretation-1; Literature Search-1, 2; Writing Manuscript-1; Critical Review-1, 2; Other-None.

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Compliance with Ethical Standards

This study was not supported by any funding. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Consent for publication was obtained for every individual person's data included in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

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