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Diagnostic Validity of a Serological Test with the Current Infection Marker in Thai Adults before and after *Helicobacter pylori* Eradication Therapy

Setthachai Piwchan[1], Kittipoom Tossapornpong[2], Suppana Chuensakul[1], Ekawee Sripariwuth[1]

[1]Division of Gastroenterology, Department of Medicine, Faculty of Medicine, Naresuan University, [2]Department of Medicine, Faculty of Medicine, Naresuan University, Phitsanulok, Thailand

Helicobacter pylori infection poses significant health risks, such as gastric adenocarcinoma, necessitating accurate diagnosis and effective treatment in primary care. This study evaluated the diagnostic efficacy of the serological current infection marker (CIM) test in identifying current *H. pylori* infection. The CIM test samples from 159 participants undergoing gastroscopy were collected, and *H. pylori*-positive outpatients received triple therapy based on histology or rapid urease test results. Following treatment, 45 patients underwent a ^{13}C-urea breath test and the CIM test for eradication assessment. For pre-eradication, the CIM test demonstrated 89.6% sensitivity, 95.7% specificity, 93.8% positive predictive value, 92.6% negative predictive value, and 93.1% accuracy. Following post-eradication, the CIM test exhibited sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 71.4%, 92.1%, 62.5%, 94.6%, and 88.9%, respectively, using the ^{13}C-urea breath test as the reference standard. The CIM test showcased commendable diagnostic performance, emphasizing its efficacy in both pre- and post-eradication scenarios. Notably, the accuracy, non-invasiveness, user-friendliness, and cost-effectiveness of the CIM test advocate for its recommendation as a preferred diagnostic tool in primary care settings for *H. pylori* infection detection.

Key Words *Helicobacter pylori*, Diagnosis, Ambulatory care, Serological test, Primary health care

INTRODUCTION

Helicobacter pylori is a Gram-negative microaerobic curved bacillus that colonizes the human stomach by producing urease enzymes, which effectively neutralize the acidic environment. This colonization process has been linked to the development of various gastroduodenal diseases [1]. The global prevalence of *H. pylori* infection exceeds 50% among adults, with significant regional and socioeconomic variations. Southeast Asian countries, in particular, exhibit a prevalence range of 35% to 75%, with South Korea having the highest prevalence [2]. In a comprehensive study conducted in Thailand in 2015, the overall prevalence of *H. pylori* infection was approximately 46%, as determined by the presence of serum anti-CagA antibodies [3].

The infection caused by *H. pylori* can result in a wide range of diseases, including asymptomatic cases, *H. pylori*-associated dyspepsia, chronic gastritis, peptic ulcers, mucosa-associated lymphoid tissue lymphoma, and notably, gastric adenocarcinoma [4-7]. Recognizing the profound implications of this bacterium, the World Health Organization (WHO) designated *H. pylori* as a Class I human carcinogen (definite carcinogen) in 1994, based on compelling epidemiological evidence [8]. Gastric cancer, according to the latest data from Global Cancer Observatory 2020, is the fourth most prevalent cancer worldwide and ranks as the fourth leading cause of cancer-related mortality. In Thailand, specifically, the estimated incidence of gastric cancer is two cases per 100,000 person-years. Alarmingly, the 5-year survival rate remains below 10% [9]. Recognizing the urgency of the matter, the WHO published an The International Agency for Research on Cancer monograph in 2014, emphasizing the eradication of *H. pylori* as a preventive strategy against gastric cancer. Consequently, accurate diagnosis and effective treatment of *H. pylori* infections assume critical importance within the primary medical field.

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Correspondence to Ekawee Sripariwuth, E-mail: ekawesri@gmail.com, https://orcid.org/0000-0003-2924-1337

The diagnostic modalities for *H. pylori* infection can be categorized into invasive and non-invasive approaches. Invasive methods, such as the rapid urease test, histology, and culture, rely on biopsies obtained through gastroscopy. In contrast, non-invasive approaches, including antibody-based tests, stool antigen tests, and urea breath tests (UBT), are more patient-friendly [10]. Among the non-invasive tests, the ^{13}C-UBT is widely accepted, but it is costly and requires skilled technicians for accurate interpretation. The stool antigen test is also reliable; however, it can be challenging to perform and may be limited in patients currently using antibiotics or proton pump inhibitors (PPIs). Serum anti-*H. pylori* antibody detection is useful for large-scale epidemiological studies, as it remains accurate regardless of peptic ulcer bleeding, gastric atrophy, or the use of PPIs and antibiotics. However, most tests cannot differentiate between current and past infections [10,11]. Consequently, there is a need for user-friendly, non-invasive, rapid, cost-effective, and reliable *H. pylori*-specific antibody-based tests.

The Assure® *H. pylori* rapid test with a current infection marker (CIM) or CIM test is an indirect solid-phase immunochromatographic assay designed to detect active *H. pylori* infections. It achieves this by identifying IgG antibodies produced during an ongoing *H. pylori* infection present in the serum or plasma. Recent studies have validated the efficacy of this test, affirming its suitability for accurately diagnosing active *H. pylori* infections [12-17]. Notably, this test holds promise for implementation in primary care settings. However, the available data regarding its validity, especially after eradication of infection, in Thailand and Southeast Asian countries is sparse. Therefore, our study aimed to evaluate the CIM test's diagnostic efficacy for *H. pylori* infection pre-eradication therapy and conduct a pilot study to assess its performance post-eradication therapy.

MATERIALS AND METHODS

Subject selection

In the present study, consecutive patients who underwent diagnostic gastroscopy due to conditions such as dyspepsia, iron deficiency anemia, or upper gastrointestinal bleeding were recruited from January 2022 to June 2022 at Naresuan University Hospital, Phitsanulok, Thailand. Patients with a history of stomach resection, prior *H. pylori* therapy, recent use of antibiotics or anti-secretory drugs within the last 4 weeks were excluded from the study.

All participants gave written informed consents. The study protocol was approved by the ethics committee of the Institutional Review Board of Naresuan University (IRB No. P3-0121/2564).

Detection of anti-IgG antibodies of current *H. pylori* infection (CIM test)

The Assure® *H. pylori* rapid test or the serological test with CIM test, an indirect solid-phase immunochromatographic assay, provided by MP Biomedicals Germany GmbH (MP Diagnostics) is a highly conserved *H. pylori* specific secret protein produced by recombinant DNA technology. With the presence of anti-CIM IgG antibody, active *H. pylori* infection is highly predictive.

The test relies on the upward migration of the sample from the well, resulting in the creation of antibody–antigen complexes on the membrane with immobilized *H. pylori* antigens, signaling the presence of *H. pylori*-specific IgG antibodies. These complexes are then identified using antihuman IgG antibodies linked to colloidal gold. The test is structured with three bands: a control line incorporating protein A, serving as a confirmation of proper sample addition, and the CIM band, highlighting a recently discovered *H. pylori*-specific recombinant protein as an indicator of an existing infection.

The assay was conducted following the instructions provided by the manufacturer. A single drop of capillary or whole blood sample was placed on the designated test area, and chase buffer was added. After a 15-minute incubation period, the results were assessed. The presence of the "A" band served as a control line. If both bands at positions "B" and "C" were visible, it indicated a current *H. pylori* infection. Conversely, the presence of only the band at position "C" suggested a past infection (refer to Fig. 1 and 2). An investigator, blinded to the participants' *H. pylori* infection status and endoscopic findings, analyzed and recorded all the samples.

Definition of current *H. pylori* infection (standard reference)

In all patients, endoscopy accompanied by histological examination (body and antrum) and rapid urease test was conducted and utilized as the gold standard for evaluating current *H. pylori* infection before initiating eradication therapy. During the endoscopy, two gastric biopsies were obtained from both the antrum and the body of the stomach (four biopsies in total). Positive results on either histology (hematoxylin and eosin staining) or rapid urease tests were indicative of an *H. pylori* infection. Other pathological reports, including atrophic gastritis, intestinal metaplasia, and carcinoma were also provided. Additionally, for secondary analysis, the ^{13}C-urea breath test (^{13}C-UBT) was performed as the reference standard to assess the successful treatment of *H. pylori* infection. Briefly, exhaled breath samples were gathered prior to and 30 minutes after administering 75 mg of ^{13}C-urea, dissolved in distilled water from the Thai Otsuka Co., Ltd., Thailand. The [$^{13}CO_2$]/[$^{12}CO_2$] ratio (d$^{13}CO_2$/mL) was quantified using a continuous flow isotope ratio mass spectrometer. A positive indication of *H. pylori* infection was determined by a delta over baseline value surpassing 2.6%.

Eradication therapy and evaluation

Patients diagnosed with active *H. pylori* infections were subjected to a 14-day triple therapy regimen consisting of

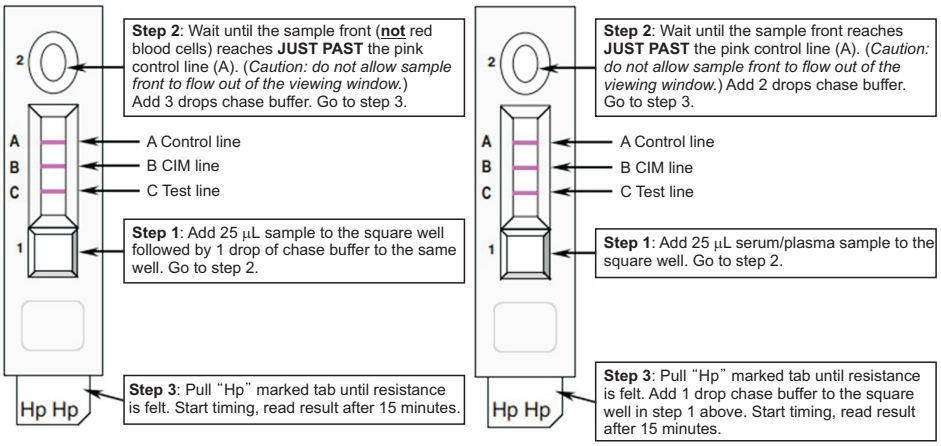

Figure 1. Assay procedure for whole blood or serum/plasma samples. CIM, current infection marker.

Figure 2. Interpretation of results (positive A + B + C: active infection, positive A + C: past infection).

omeprazole 20 mg, amoxicillin 1,000 mg, and clarithromycin 500 mg, administered twice daily. To determine the success of eradication, the ^{13}C-UBT was conducted at least 4 weeks after completing the treatment.

Statistical analysis

To determine the sample size for our study, we employed the case-control analog method described by Dhand and Khatkar [18] for estimating a single proportion using Statulator, an online sample size calculator [19]. We considered the efficacy of The Assure® *H. pylori* rapid test kit in diagnosing *H. pylori* infection in Thai children, which demonstrated a sensitivity of 96% and a specificity of 95% [20]. In order to achieve a confidence level of 95% and a precision or margin of error of 5%, our study required a minimum of 60 samples from the *H. pylori*-positive group, calculated from sensitivity value, and 73 samples from the *H. pylori*-negative group, calculated from specificity value.

Continuous data with normal distributions were represented using means and standard deviations. On the other hand, continuous data with non-normal distributions were presented as medians and interquartile ranges. Categorical data were displayed as frequencies and percentages. When comparing two continuous variables against the control group, an appropriate statistical test was used, such as a two-sample independent *t*-test or Wilcoxon rank-sum (Mann–Whitney) test. Categorical variables were compared using Fisher's exact test. The efficacy of the ASSURE® *H. pylori* rapid test was assessed by comparing it with the standard method for diagnosing *H. pylori* infection before and after eradication. This assessment included measures such as sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and overall accuracy.

RESULTS

Patient characteristics

A total of 159 patients were prospectively enrolled in this study. Among them, 67 individuals exhibited an active *H. pylori* infection, as confirmed by positive hematoxylin and eosin staining in gastric tissues and/or rapid urease testing. Within the cohort of 159 patients, the *H. pylori*-positive group comprised 41 out of 67 participants (61.2%) who were male, whereas the *H. pylori*-negative group consisted of 40 out of 92 participants (43.5%) who were male. The mean age for patients in the *H. pylori*-positive group was 62.5 ± 13.2 years, while in the *H. pylori*-negative group, it was 63.8 ± 14.8 years. The primary indications for undergoing gastroscopy and *H. pylori* testing were dyspepsia (56%), iron deficiency anemia (28%), and upper gastrointestinal hemorrhage (16%). Notably, the distribution of baseline underlying diseases was comparable between the two groups. Based on the pathological reports, non-specific gastritis was the most prevalent (90%). Out of 159 patients, 8 had intestinal metaplasia, and 5 were diagnosed with gastric adenocarcinoma. All cases of intestinal metaplasia were of the complete non-extensive type with antral predominance. For detailed information regarding the endoscopic and histological findings (Table 1).

Table 1. Patients' characteristics and endoscopic findings

Characteristics	*H. pylori* infection (n = 67)	*H. pylori* non-infection (n = 92)	*P*-value
Male	41 (61.2)	40 (43.5)	0.037
Age (yr)	62.5 ± 13.2	63.8 ± 14.8	0.558
Type 2 diabetes	14 (20.9)	22 (23.9)	0.848
Hypertension	24 (35.8)	45 (48.9)	0.144
Dyslipidemia	17 (25.4)	33 (35.9)	0.225
Kidney disease	8 (11.9)	9 (9.8)	0.795
Ischemic stroke	9 (13.4)	10 (10.9)	0.627
Ischemic heart disease	0 (0)	9 (9.8)	0.011
Indication for gastroscopy			0.316
Dyspepsia	33 (49.3)	56 (60.9)	
Upper gastrointestinal bleeding	12 (17.9)	14 (15.2)	
Iron deficiency anemia	22 (32.8)	22 (23.9)	
Endoscopic findings			0.003
Gastro-duodenitis	40 (59.7)	70 (76.1)	
Peptic ulcer	26 (38.8)	15 (16.3)	
Esophageal varices/portal hypertensive gastropathy	0 (0)	3 (3.3)	
Carcinoma	1 (1.5)	4 (4.3)	
Histologic findings			0.358
Non-specific gastritis	60/66 (90.9)	73/80 (91.3)	
Intestinal metaplasia	5/66 (7.6)	3/80 (3.7)	
Adenocarcinoma	1/66 (1.5)	4/80 (5.0)	

Values are presented as number (%) or mean ± standard deviation.

Table 2. Comparison of the current infection marker test with histology and rapid urease test

Reference standard (histology and/or rapid urease test)	Current infection marker	
	Positive	Negative
Positive	60	7
Negative	4	88
Total	64	95

Performance of the CIM test before eradication therapy

Among 159 patients who underwent upper endoscopy, a total of 67 individuals were diagnosed with active *H. pylori* infection. The observed prevalence of *H. pylori* infection was determined to be 42.1% (95% CI, 34.4%-50.2%). Within this group, consisting of 67 patients who tested positive for *H. pylori* based on histology and/or rapid urease test, 60 individuals yielded positive results in the CIM test, which is recognized as an indicator of current infection. In contrast, within the *H. pylori*-negative group comprising 92 patients, only 4 individuals demonstrated positive CIM test results, while reference tests confirmed negative outcomes (Table 2).

The performance of the CIM test in detecting the current disease was evaluated using sensitivity, specificity, positive predictive value, negative predictive value, and accuracy measures. The CIM test demonstrated a sensitivity of 89.6%, specificity of 95.7%, positive predictive value of 93.8%, and negative predictive value of 92.6%. The corresponding accuracy of the CIM test was determined to be 93.1% (95% CI, 87.9%-96.5%) (Table 3).

Performance of the CIM test after eradication therapy

During the post-eradication period, a subset of 22 patients (out of the initial 67 patients who received triple therapy) were lost to follow-up, resulting in a remaining sample of 45 patients for analysis. The ^{13}C-UBT was scheduled for these 45 individuals to confirm the success of *H. pylori* eradication. Among the participants, a total of 37 patients demonstrated successful elimination of the bacteria, leading to an overall eradication rate of 82.2%. The average duration of follow-up for these patients was 6.1 ± 1.7 weeks. Detailed findings comparing the reference test and the CIM test can be found in Table 4. Notably, it is important to highlight that the CIM test displayed a notable false positive rate, particularly when the reference test was conducted within 4 weeks after treatment [12].

Regarding the performance evaluation of the CIM test in confirming *H. pylori* eradication, key metrics were determined. The sensitivity, specificity, positive predictive value, and negative predictive value were calculated to be 71.4%, 92.1%, 62.5%, and 94.6% respectively. Furthermore, the accuracy of the CIM test was reported as 88.9% (95% CI, 76.9%-96.5%) (Table 3).

DISCUSSION

Several diagnostic tools have been developed to identify active *H. pylori* infection. The biopsy-based tests, histology, and rapid urease test are considered the gold standard for diagnosing current infections, despite their invasive nature.

Table 3. Performance of the current infection marker test before and after eradication therapy

CIM test	Performance				
	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio
Before eradication therapy	89.6 (79.7-95.7)	95.7 (89.2-98.8)	93.8 (84.8-98.3)	92.6 (85.4-97.0)	20.60 (7.87-53.90)
After eradication therapy	71.4 (29.0-96.3)	92.1 (78.6-98.3)	62.5 (24.5-91.5)	94.6 (81.8-99.3)	9.05 (2.77-29.53)

Values are presented as percentage (95% CI). CIM test, current infection marker test.

Table 4. Comparison of the current infection marker test with the ^{13}C-urea breath test

Reference standard (^{13}C-urea breath test)	Current infection marker	
	Positive	Negative
Positive	5	2
Negative	3	35
Total	8	37

However, noninvasive methods such as the ^{13}C-UBT, stool antigen test, and serological test have gained wide acceptance due to their accuracy, cost-effectiveness, and ease of use. It's worth noting that these noninvasive methods can yield false-negative results in cases involving antibiotic or PPI usage or active bleeding peptic ulcers. In a previous systematic review consisting of 101 studies, the ^{13}C-UBT demonstrated superior performance compared to stool antigen tests and serology, with sensitivities of 94%, 83%, and 84% respectively [21]. The serological test, commonly employed in epidemiological studies, detects anti-IgG antibodies related to *H. pylori* infection but cannot differentiate between current and previous infections.

The Assure® *H. pylori* rapid test with a CIM test has been developed specifically to detect ongoing *H. pylori* infections. This test identifies anti-IgG antibodies produced as a response to active *H. pylori* infection in serum or plasma. Various studies have been conducted to evaluate the diagnostic performance of the CIM test, yielding diverse accuracies dependent on population characteristics, geographic data, methodologies employed, and the reference standard test. For instance, a study from China involving 221 patients reported satisfactory performance of the CIM test, with a sensitivity and specificity of 93% and 90% respectively, when compared to the gold standard ^{13}C-UBT [12]. Similarly, a study from Hong Kong comprising 78 individuals diagnosed with positive *H. pylori* infection using biopsy-based tools showed promising results for the CIM test, with a sensitivity of 94% and specificity of 90% [13]. In contrast, a recent study from Vietnam reported less favorable outcomes with a sensitivity of 89% and a specificity of 75%, potentially due to the use of a non-gold standard test, positive CIM test, rapid urease test, or PCR test for diagnosing *H. pylori* infection [16]. In Thailand, a study involving 82 children compared biopsy and rapid urease test results, and the CIM test exhibited a promising sensitivity and specificity of 96% and 94.6% respectively, attributed to a robust immune response against infection in children [20]. However, data from Thai adults in this context are still limited.

The present study aimed to validate the diagnostic accuracy of the CIM test in 159 Thai adults with indications for gastroscopy, including uninvestigated dyspepsia, iron deficiency anemia, or upper gastrointestinal bleeding. The gold standard reference for this study was any positive histology and/or rapid urease test. The cohort consisted of 69 *H. pylori* positive patients and 92 *H. pylori* negative patients. Our study yielded results that aligned with the aforementioned studies, with a sensitivity, specificity, positive predictive value, and negative predictive value of 89.6% (95% CI, 79.7%-95.7%), 95.7% (95% CI, 89.2%-98.8%), 93.8% (95% CI, 84.8%-98.3%), and 92.6% (95% CI, 85.4%-97.0%) respectively, along with an accuracy of 93.1%. Notably, we analyzed the diagnostic performance in the post-eradication period. Considering that *H. pylori* IgG antibodies can persist for 6 to 12 months after therapy, serological tests during this period may struggle to differentiate between active and past infectious states [22]. Notably, prior research did not explore anti-CIM antibodies. In a recent study involving 115 patients in post-eradication follow-up, the CIM test demonstrated a sensitivity of 50% to 66.7%, specificity of 66.7% to 84.6%, positive predictive value of 25% to 50%, negative predictive value of 85.7% to 91.7%, and an accuracy of 63.6% to 81.3% at 4 to 12 weeks follow-up [12]. These results indicate that the CIM test could be a viable option for confirming successful eradication. Our study revealed acceptable validity with a test precision accuracy of 88.9% (95% CI, 76.9%-96.5%). The mean follow-up duration was 6.1 ± 1.7 weeks. It is important to highlight that the CIM test exhibited false-positive results when performed as early as six weeks after eradication treatment. These findings contrast with the previously mentioned recommendation not to conduct the serological test 6 to 12 months after the conclusion of anti-*H. pylori* therapies [22]. Nevertheless, the long-term efficacy of eradication may be impeded by recurrent infection if we perform the test at 6 months post-eradication. In light of our findings, we suggest that the CIM test could be a potentially effective tool for confirming *H. pylori* eradication.

To the best of our knowledge, this is the first study to assess the diagnostic accuracy of CIM testing before and after eradication therapy in Southeast Asian adults individuals. Our study focused on the practical performance of the test in

various clinical settings, including dyspepsia, iron deficiency anemia, and upper gastrointestinal bleeding, which require gastroscopic evaluation for *H. pylori* infection. The strength of our study lies in using the gold standard or most accurate tests as the reference, employing any positive histology and/or rapid urease test for pre-treatment evaluation and the ^{13}C-UBT for post-treatment evaluation. However, our study has some limitations. Firstly, it was conducted in a specific area of a tertiary care University hospital in Thailand, which may limit the generalizability of the results to a national context. Nevertheless, the prevalence of *H. pylori* infection observed in this study was approximately 42%, similar to that reported in a previous nationwide cohort study in Thailand [3]. Hence, the diagnostic accuracy of the test is not significantly affected. Furthermore, our study's sample size met the required threshold based on the aforementioned statistical analysis. Secondly, the number of patients lost to follow-up in the post-eradication period raised some concerns. This dropout rate resulted in a post-treatment analysis involving only 45 individuals. Therefore, caution should be exercised due to the small sample size and imprecise range of the 95% CI when interpreting the test results.

In summary, the CIM test exhibits promising diagnostic performance for active *H. pylori* infection, especially in limited settings, considering its accuracy, acceptance, availability, and cost-effectiveness—making it preferable for primary care, particularly in the pre-treatment period. However, in suspected cases with negative CIM test results, the use of tissue-based tools alongside gastroscopy remains valuable. Caution is essential in the post-eradication period due to relatively imprecise test performance data. If the CIM test produces a positive result, follow-up with a ^{13}C-UBT is advisable to confirm persistent infection, considering the potential for false positives from lingering anti-IgG *H. pylori* antibodies. Conversely, a change from positive to negative post-treatment may indicate successful infection treatment. Nevertheless, additional large sample size-based and longitudinal studies are required to evaluate CIM test performance in the post-eradication phase and determine the persistence of specific anti-CIM antibodies before its application in clinical practice.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

ORCID

Setthachai Piwchan, https://orcid.org/0000-0003-2101-9002
Kittipoom Tossapornpong, https://orcid.org/0009-0007-3938-5728
Suppana Chuensakul, https://orcid.org/0000-0003-1833-3738
Ekawee Sripariwuth, https://orcid.org/0000-0003-2924-1337

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