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# Developing Operational Definitions Related to *Helicobacter pylori* Eradication Therapy

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## ABSTRACT



**Background:** The lack of well-established operational definitions is a major limitation of *Helicobacter pylori* eradication studies that use secondary databases. We aimed to develop and validate operational definitions related to *H. pylori* eradication therapy.

**Methods:** Operational definitions were developed by analyzing a nationwide *H. pylori* eradication registry and validated using real-world data from hospital medical records. The primary endpoint was the sensitivity of the operational definitions in identifying individuals who received *H. pylori* eradication therapy. The secondary endpoint was the sensitivity and specificity of the operational definition in identifying successful *H. pylori* eradication therapy.

**Results:** *H. pylori* eradication therapy was defined as a prescription for one of the following combinations: 1) proton pump inhibitor (PPI) + amoxicillin + clarithromycin, 2) PPI + amoxicillin + metronidazole, 3) PPI + metronidazole + tetracycline, 4) PPI + amoxicillin + levofloxacin, 5) PPI + amoxicillin + moxifloxacin, or 6) PPI + amoxicillin + rifabutin. In the validation set, the sensitivity of the operational definition for identifying individuals who received *H. pylori* eradication therapy was 99.7% and 99.8% for the first- and second-line therapies, respectively. Operational definition to determine success or failure of the *H. pylori* eradication therapy was developed based on a confirmatory test and the prescription of rescue therapy. The sensitivity and specificity of the operational definition for predicting successful eradication were 97.6% and 91.4%, respectively, in first-line therapy and 98.6% and 54.8%, respectively, in second-line therapy.

**Conclusion:** We developed and validated operational definitions related to *H. pylori* eradication therapy. These definitions will help researchers perform various *H. pylori* eradication-related studies using secondary databases.

**Keywords:** *Helicobacter pylori*; Eradication; Operational Definition

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The authors have no potential conflicts of interest to disclose.

**Author Contributions**

Conceptualization: Lee J, Kim JG. Data curation: Park CH, Yang HJ, Kim JS, Kim BJ, Choi SI, Seo SI. Formal analysis: Park CH, Jung SY, Lee JW, Lee J. Investigation: Park CH, Jung SY. Methodology: Park CH, Jung SY, Lee JW, Lee J. Project administration: Kim JG. Supervision: Kim JG. Validation: Park CH, Jung SY, Lee JW. Visualization: Park CH. Writing - original draft: Park CH, Jung SY. Writing - review & editing: Park CH, Jung SY, Lee JW, Yang HJ, Kim JS, Kim BJ, Choi SI, Seo SI, Lee J, Kim JG.

**INTRODUCTION**

Approximately 50% of the global population is infected with *Helicobacter pylori*,<sup>1</sup> which causes various gastrointestinal diseases including peptic ulcer disease and gastric cancer.<sup>2,3</sup> Recently, *H. pylori* infection has been associated with several diseases, including hematologic, cardiovascular, and neurological diseases, in addition to gastrointestinal diseases.<sup>4,5</sup> To determine the impact of *H. pylori* eradication therapy on these diseases, population-based studies utilizing large-scale, nationwide, secondary databases have been performed.<sup>6-8</sup> The National Health Information Database of the Korean National Health Insurance Service (NHIS), which is a mandatory health insurance system that covers the entire Korean population, is one such database.<sup>9</sup> It has an extensive dataset of 1.3 trillion records, which includes sociodemographic status, diagnoses, operations, and prescriptions.<sup>6,9,10</sup> It also includes follow-up data, spanning approximately 20 years.<sup>6,11</sup> Studies utilizing secondary databases may help clinicians better understand the clinical characteristics and treatment outcomes of rare diseases (e.g., metachronous lesions after gastric cancer treatment). Furthermore, they may help analyze diseases requiring long-term follow-up (e.g., the risk of gastric cancer in the general population). However, these studies may be limited by the lack of well-established operational definitions. In most studies, *H. pylori* eradication was defined arbitrarily without validation.<sup>6-8</sup> Moreover, the success or failure of *H. pylori* eradication therapy could not be determined because such results were unavailable in the secondary databases.<sup>6-8</sup> Because post-eradication persistence of *H. pylori* infection is an important confounding variable in *H. pylori*-related diseases, it is difficult to draw conclusions without knowing the outcome of the eradication therapy. Therefore, a definitive conclusion could not be reached by exploring the secondary databases alone.

To facilitate the use of secondary databases in studies and help reach a more definitive conclusion, we developed an operational definition of *H. pylori* eradication therapy. We also developed and validated operational definitions for predicting successful or failed treatment based on the prescriptions of eradication confirmatory tests and rescue therapy. These operational definitions will help researchers better analyze and interpret data from secondary databases.

**METHODS****Study participants**

Two databases of patients who underwent *H. pylori* eradication therapy were used in this study. One was a nationwide registry (development set), which prospectively enrolled patients who received *H. pylori* eradication therapy between 2010 and 2015 at 34 hospitals in South Korea.<sup>12</sup> The other database was a real-world dataset (validation set) of patients who received *H. pylori* eradication therapy between 2018 and 2019 from four university-affiliated hospitals in South Korea (Chung-Ang University Hospital, Incheon St. Mary's Hospital, Kangbuk Samsung Hospital, and Hanyang University Guri Hospital). The *H. pylori* eradication regimen (i.e., active ingredients of medications) and type and results of the confirmatory test for *H. pylori* eradication were reviewed.

**Measurements and study endpoints**

The operational definition of *H. pylori* eradication therapy was developed based on the major regimens used in the nationwide registry and the current guidelines in Korea.<sup>13</sup> The intervals between the first- and second-line therapies and the second- and third-line therapies were

evaluated to identify duplicate prescriptions or early changes in medications for any reason (loss of medications or adverse events). The interval between the prescription of eradication therapy and confirmatory test was also analyzed to ensure the validity of the confirmatory tests. The operational definition of success (or failure) of the eradication therapy was developed based on the presence of a confirmatory test or rescue therapy, the interval between eradication therapy and the confirmatory test, and that between the confirmatory test and rescue therapy initiation.

The primary endpoint was the sensitivity of the operational definition in identifying individuals who received *H. pylori* eradication therapy. The secondary endpoint was the sensitivity and specificity of the operational definition of a successful eradication therapy.

### Statistical analysis

Descriptive statistics, including the number of participants and their proportions, were used to present the results. All statistical analyses were conducted using R (version 4.0.4; R Foundation for Statistical Computing, Vienna, Austria).

### Ethics statement

This study was approved by the Institutional Review Board of study institutes and the requirement for informed consent was waived (Chung-Ang University Hospital, IRB No. 2110-014-19388; Incheon St. Mary's Hospital, IRB No. OC21RIDIO106; Kangbuk Samsung Hospital, IRB No. KBSMC 2021-09-026; Hanyang University Guri Hospital, IRB No. GURI 2021-09-009).

## RESULTS

### Identifying individuals who received *H. pylori* eradication therapy

We obtained and reviewed data of 6,740 and 1,572 patients, who received *H. pylori* eradication therapy, from the nationwide registry (development set) and real-world hospital medical records (validation set), respectively. The major *H. pylori* eradication regimens utilized included conventional, metronidazole-based, levofloxacin-based, or rifabutin-based triple therapy and bismuth-based or non-bismuth (sequential or concomitant) quadruple therapy (Table 1). Based on this, *H. pylori* eradication therapy was defined as a prescription for one of the following combinations: 1) proton pump inhibitor (PPI) + amoxicillin + clarithromycin; 2) PPI + amoxicillin + metronidazole; 3) PPI + metronidazole + tetracycline; 4) PPI + amoxicillin + levofloxacin; 5) PPI + amoxicillin + moxifloxacin; and 6) PPI + amoxicillin + rifabutin (Table 2). All the major regimens were screened for these combinations. Using the operational definition of *H. pylori* eradication therapy, 98.6% and 99.7% of the patients who received first-line *H. pylori* eradication therapy were identified in the development and validation sets, respectively (Table 3). Additionally, 92.4% and 99.8% of the patients who received second-line *H. pylori* eradication therapy were identified in the development and validation sets, respectively.

### Treatment duration, interval, and confirmatory tests

The durations of the first-, second-, and third-line eradication therapies are shown in Supplementary Fig. 1. *H. pylori* eradication therapies were typically administered for 7–14 days. Fig. 1 shows the treatment intervals between the *H. pylori* eradication therapies, which was  $\geq 28$  days in > 99% of patients. Only a few patients had a treatment interval of < 28 days, where the initial treatment was stopped early owing to adverse events; thereafter, rescue therapy was administered. The confirmatory test was employed in 98.6% and 87.0% of the

**Table 1.** *H. pylori* eradication regimens included in the study

Variables	Prospective, nationwide registry (development set)	Real-world data from hospital medical records (validation set)
<b>First-line <i>H. pylori</i> eradication regimen</b>		
Number of participants	6,740	1,572
Conventional triple therapy (PPI + amoxicillin + clarithromycin)	6,191 (91.9)	1,544 (98.2)
Bismuth-based quadruple therapy (PPI + bismuth + tetracycline + metronidazole)	146 (2.2)	19 (1.2)
Sequential or concomitant therapy (PPI + amoxicillin + clarithromycin + metronidazole)	204 (3.0)	1 (0.1)
Metronidazole-based triple therapy (PPI + amoxicillin + metronidazole)	75 (1.1)	2 (0.1)
Levofloxacin-based triple therapy (PPI + amoxicillin + levofloxacin)	5 (0.1)	1 (0.1)
Others	119 (1.8)	5 (0.3)
<b>Second-line <i>H. pylori</i> eradication regimen</b>		
Number of participants	1,157	440
Conventional triple therapy (PPI + amoxicillin + clarithromycin)	20 (1.7)	2 (0.5)
Bismuth-based quadruple therapy (PPI + bismuth + tetracycline + metronidazole)	961 (83.1)	434 (98.6)
Metronidazole-based triple therapy (PPI + amoxicillin + metronidazole)	2 (0.2)	1 (0.2)
Levofloxacin-based triple therapy (PPI + amoxicillin + levofloxacin)	4 (0.3)	2 (0.5)
Others	170 (14.7)	1 (0.2)
<b>Third-line <i>H. pylori</i> eradication regimen</b>		
Number of participants	58	23
Bismuth-based quadruple therapy (PPI + bismuth + tetracycline + metronidazole)	6 (10.3)	1 (4.3)
Levofloxacin-based triple therapy (PPI + amoxicillin + levofloxacin)	31 (53.4)	19 (82.6)
Rifabutin-based triple therapy (PPI + amoxicillin + rifabutin)	3 (5.2)	3 (13.0)
Others	18 (31.0)	0 (0.0)

Values are presented as number (%).

PPI = proton pump inhibitor.

patients in the development and validation sets, respectively (**Supplementary Table 1**). In most patients, a confirmatory test was performed 21 days to six months after the initiation of *H. pylori* eradication therapy (**Fig. 2**). Based on these findings, we defined confirmatory tests as the prescription of the confirmatory tests during the following periods: 1) between 21 days from the initiation of the eradication therapy and the date of rescue therapy, and 2) between 21 days to six months from the initiation of eradication therapy (both criteria should be met) (**Table 2**).

### Determining the success or failure of *H. pylori* eradication therapy

Subsequently, we tested and validated the diagnostic performance of the operational definition in determining the success or failure of *H. pylori* eradication therapy (**Table 4**). In the development set, the sensitivity and specificity of the operational definition for predicting successful eradication were 95.3% and 72.1%, respectively, for first-line therapy and 95.4% and 33.6%, respectively, for second-line therapy. In the validation set, the sensitivity and specificity were 97.6% and 91.4%, respectively, for first-line therapy and 98.6% and 54.8%, respectively, for second-line therapy.

Additionally, the criteria for *H. pylori* reinfection was set as the success of the initial eradication therapy followed by the administration of additional therapy one year after the initial confirmatory test (**Table 2**). However, the operational definition of reinfection could not be validated in this study because no participant with reinfection of *H. pylori* was identified in the validation set.

**Table 2.** Operational definition of *H. pylori* eradication therapy and its consequences

Measurement	Operational definition
<i>H. pylori</i> eradication therapy	
First-line therapy	The first prescription of one of the therapy combinations (see ‘medication combinations for <i>H. pylori</i> eradication therapy’ <sup>a</sup> category).
Date of the first-line therapy	Initiation of the first-line therapy.
Second-line therapy	The first prescription of one of the therapy combinations (see ‘medication combinations for <i>H. pylori</i> eradication therapy’ <sup>a</sup> category) 28 days after the initiation of the first-line therapy.
Date of the second-line therapy	Initiation of the second-line therapy.
Third-line therapy	The first prescription of one of the therapy combinations (see ‘medication combinations for <i>H. pylori</i> eradication therapy’ <sup>a</sup> category) 28 days after the initiation of the second-line therapy.
Date of the third-line therapy	Initiation of the third-line therapy.
Confirmatory test for <i>H. pylori</i> eradication	
Confirmatory test for the first-line therapy	Prescription of one of the confirmatory tests (see ‘type of confirmatory test’ <sup>b</sup> category) that was performed during the following periods (both criteria should be met): 1) Between 21 days from the initiation of the first-line therapy and the date of the second-line therapy. 2) Between 21 days to 6 months from the initiation of the first-line therapy. When multiple prescriptions met the criteria, the earliest one was regarded as the confirmatory test for the first-line therapy.
Date of confirmatory test for the first-line therapy	The date of prescription of a confirmatory test for the first-line therapy.
Confirmatory test for the second-line therapy	Prescription of one of the confirmatory tests (see ‘type of confirmatory test’ <sup>b</sup> category) that was performed during the following periods (both criteria should be met): 1) Between 21 days from the initiation of the second-line therapy and the date of the third-line therapy. 2) Between 21 days to 6 months from the initiation of the second-line therapy. When multiple prescriptions met the criteria, the earliest one was regarded as the confirmatory test for the second-line therapy.
Date of confirmatory test for the second-line therapy	The date of prescription of a confirmatory test for the second-line therapy.
Confirmatory test for the third-line therapy	Prescription of one of the confirmatory tests (see ‘type of confirmatory test’ <sup>b</sup> category) that was performed between 21 days to 6 months from the initiation of the third-line therapy. When multiple prescriptions met the criteria, the earliest one was regarded as the confirmatory test for the third-line therapy.
Date of confirmatory test for the third-line therapy	The date of prescription of a confirmatory test for the third-line therapy.
Success of <i>H. pylori</i> eradication therapy	
Success of the first-line therapy	Presence of a confirmatory test for the first-line therapy, with no second-line therapy within 1 year from the confirmatory test for the first-line therapy.
Failure of the first-line therapy	Presence of a confirmatory test for the first-line therapy, and the presence of a second-line therapy within 1 year from the confirmatory test for the first-line therapy.
Unknown result of the eradication therapy	No confirmatory test for the first-line therapy.
Success of the second-line therapy	Presence of a confirmatory test for the second-line therapy, with no third-line therapy within 1 year from the confirmatory test for the second-line therapy.
Failure of the second-line therapy	Presence of a confirmatory test for the second-line therapy, and the presence of a third-line therapy within 1 year from the confirmatory test for the second-line therapy.
Unknown result of the second-line therapy	No confirmatory test for the second-line therapy.
<i>H. pylori</i> reinfection	
Reinfection after first-line therapy	Success of the first-line therapy, and presence of the second-line therapy after 1 year from the confirmatory test for the first-line therapy.
Reinfection after second-line therapy	Success of the second-line therapy, and presence of the third-line therapy after 1 year from the confirmatory test for the second-line therapy.

PPI = proton pump inhibitor.

<sup>a</sup>Medication combinations for *H. pylori* eradication therapy: 1) PPI + amoxicillin + clarithromycin, 2) PPI + amoxicillin + metronidazole, 3) PPI + metronidazole + tetracycline, 4) PPI + amoxicillin + levofloxacin, 5) PPI + amoxicillin + moxifloxacin, 6) PPI + amoxicillin + rifabutin.

<sup>b</sup>Type of confirmatory test: 1) Urea breath test, 2) Rapid urease test, 3) Giemsa stain, 4) Polymerase chain reaction for *H. pylori*, 5) Upper gastrointestinal endoscopy + pathological examination.

### Sensitivity analysis

We evaluated the *H. pylori* eradication regimen, sensitivity of the operational definition for identifying individuals who received eradication therapy, and performance of the operational definition in determining the success or failure of eradication therapy according to the hospital in the validation set (**Supplementary Tables 2-4**). Although the sample size of each hospital was small, the major results were similar to the overall results in the validation set.

**Table 3.** Sensitivity of the operational definition for identifying individuals who received *H. pylori* eradication therapy

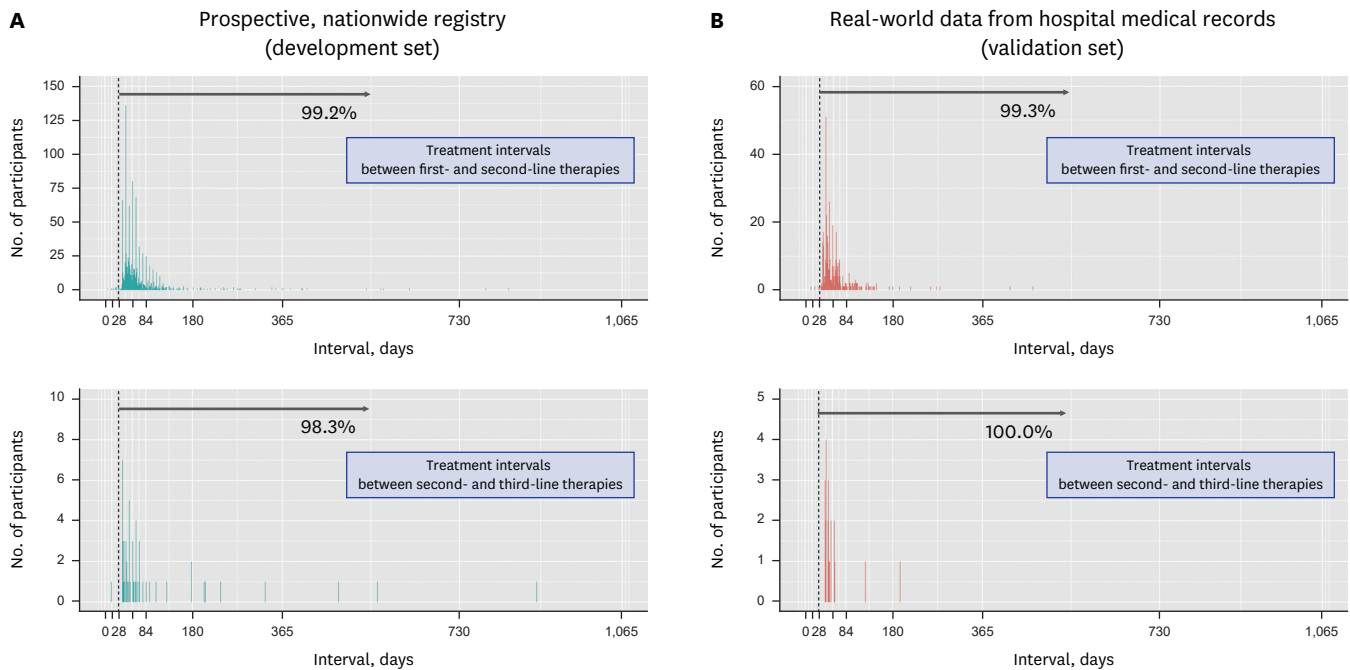
Variables	Prospective, nationwide registry (development set)	Real-world data from hospital medical records (validation set)
<b>First-line therapy</b>		
Number of participants	6,740	1,572
Within the operational definition (sensitivity)	6,649 (98.6)	1,567 (99.7)
Beyond the operational definition (minor regimens)	91 (1.4)	5 (0.3)
PPI + amoxicillin	6 (0.1)	1 (0.1)
PPI + clarithromycin	20 (0.3)	0 (0.0)
PPI + metronidazole	1 (0.01)	0 (0.0)
PPI + clarithromycin + metronidazole	58 (0.9)	0 (0.0)
PPI + levofloxacin + clarithromycin	1 (0.01)	0 (0.0)
PPI + levofloxacin + metronidazole	2 (0.03)	0 (0.0)
PPI + moxifloxacin + clarithromycin	0 (0.0)	3 (0.2)
PPI + moxifloxacin + metronidazole	0 (0.0)	1 (0.1)
PPI + moxifloxacin + rifabutin	1 (0.01)	0 (0.0)
PPI + bismuth + metronidazole	1 (0.01)	0 (0.0)
PPI + bismuth + amoxicillin + doxycycline	1 (0.01)	0 (0.0)
<b>Second-line therapy</b>		
Number of participants	1,157	440
Within the operational definition (sensitivity)	1,069 (92.4)	439 (99.8)
Beyond the operational definition (minor regimens)	88 (7.6)	1 (0.2)
PPI + tetracycline	1 (0.1)	0 (0.0)
PPI + metronidazole	3 (0.3)	0 (0.0)
PPI + amoxicillin + rifampicin	0 (0.0)	1 (0.2)
PPI + clarithromycin + metronidazole	1 (0.1)	0 (0.0)
PPI + metronidazole + doxycycline	1 (0.1)	0 (0.0)
PPI + levofloxacin + metronidazole	2 (0.2)	0 (0.0)
PPI + moxifloxacin + metronidazole	1 (0.1)	0 (0.0)
PPI + moxifloxacin + rifabutin	20 (1.7)	0 (0.0)
PPI + metronidazole + tetracycline + rifaximin	1 (0.1)	0 (0.0)
PPI + moxifloxacin + tetracycline + rifabutin	1 (0.1)	0 (0.0)
PPI + bismuth + amoxicillin	1 (0.1)	0 (0.0)
PPI + bismuth + metronidazole	2 (0.2)	0 (0.0)
PPI + bismuth + tetracycline	3 (0.3)	0 (0.0)
PPI + bismuth + clarithromycin + metronidazole	1 (0.1)	0 (0.0)
PPI + bismuth + moxifloxacin + metronidazole	2 (0.2)	0 (0.0)
PPI + bismuth + moxifloxacin + tetracycline	2 (0.2)	0 (0.0)
PPI + bismuth + metronidazole + doxycycline	42 (3.6)	0 (0.0)
Bismuth + amoxicillin + metronidazole	4 (0.3)	0 (0.0)
<b>Third-line therapy</b>		
Number of participants	58	23
Within the operational definition (sensitivity)	54 (93.1)	23 (100.0)
Beyond the operational definition (minor regimens)	4 (6.9)	0 (0.0)
PPI + amoxicillin	1 (1.7)	0 (0.0)
PPI + moxifloxacin	1 (1.7)	0 (0.0)
PPI + moxifloxacin + clarithromycin	1 (1.7)	0 (0.0)
PPI + bismuth + levofloxacin + tetracycline	1 (1.7)	0 (0.0)

Values are presented as number (%).

PPI = proton pump inhibitor.

## DISCUSSION

This is the first study to assess the operational definition of *H. pylori* eradication therapy. We developed an operational definition based on the major regimens utilized in the prospective nationwide registry established in 2010–2015. Minor regimens, including dual therapy (e.g., PPI + amoxicillin, PPI + clarithromycin, or PPI + metronidazole) and quinolone-containing clarithromycin-based therapy (e.g., PPI + levofloxacin + clarithromycin or PPI + moxifloxacin + clarithromycin), were excluded from the operational definition. Dual therapy is not popular

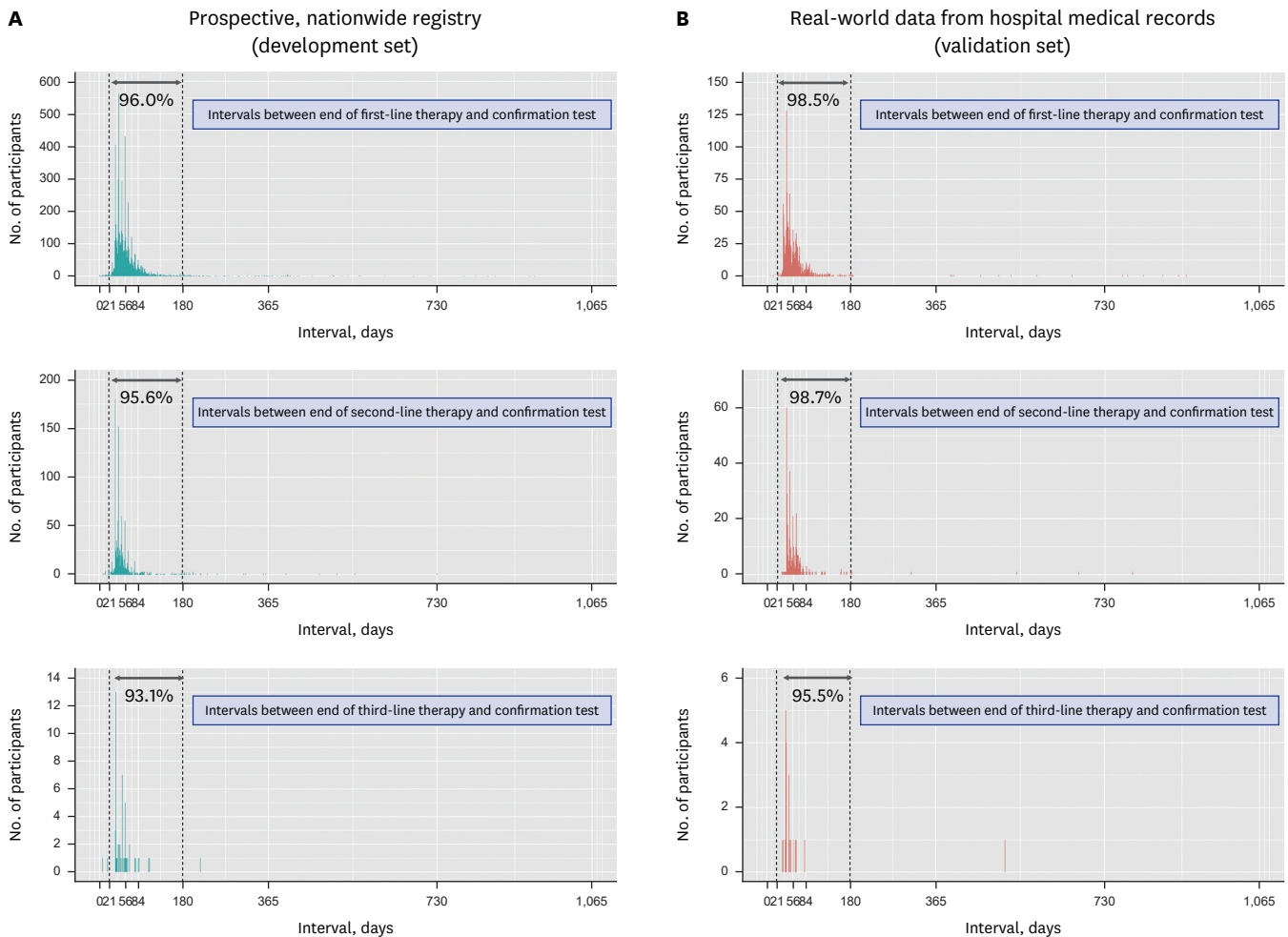


**Fig. 1.** Treatment intervals between *H. pylori* eradication therapies in the nationwide registry (**A**) and real-world data from hospital medical records (**B**). Gray arrows and percentages indicate the proportion of patients with treatment intervals  $\geq 28$  days.

in Korea because of its low eradication rate.<sup>14,15</sup> Quinolone-based therapies are not favored, except for third-line treatment (e.g., PPI + amoxicillin + quinolone), because it is also used to treat tuberculosis in Korea, which is highly prevalent. Although some regimens were not included in the operational definition, its sensitivity to detect *H. pylori* eradication therapy was high, even in the validation set. This finding suggests that most regimens used in real-world settings can be predicted. The high sensitivity may be attributed to the dissemination of common guidelines and the fact that antibiotics not covered by the NHIS were infrequently prescribed in the real world. All regimens recommended in the Korean guidelines, including triple, sequential, concomitant, and bismuth-based quadruple therapies, were included in the operational definition.<sup>13</sup>

In the present study, second- or third-line therapies was defined as the prescription of one of the *H. pylori* eradication regimens 28 days after the previous eradication therapy. The time interval of 28 days was selected to exclude duplicate prescriptions for lost medications or early changes in the eradication regimen. In our analysis, approximately 99% of the participants received rescue therapy 28 days after their initial therapy. Given that the performance of confirmatory tests for *H. pylori* eradication and issuance of rescue therapy prescriptions typically occur at least 3–4 weeks after treatment, the operational definition was clinically relevant and reliable.

We also set the time interval between eradication therapy and the confirmatory test as 21 days to six months, because most participants obtained a confirmatory test during this time period. Although very few participants were subjected to confirmatory tests six months after the treatment, an interval of more than six months was not considered valid as the minimum follow-up duration was six months. The time interval was limited to six months because it may be difficult to distinguish between treatment failure and reinfection if tests are conducted after a long time.



**Fig. 2.** Intervals between completion of the *H. pylori* eradication therapy and performance of the eradication confirmatory test in the prospective, nationwide registry (**A**) and real-world data from hospital medical records (**B**). Gray arrows and percentages indicate the proportion of patients who underwent testing for confirmation of *H. pylori* eradication 21 days to 6 months after initiation of eradication therapy.

Finally, we developed an operational definition to determine success or failure of the *H. pylori* eradication therapy based on a confirmatory test and the prescription of rescue therapy. In the validation set, the sensitivity and specificity for determining successful *H. pylori* eradication with first-line treatment were sufficiently high. Thus, the results of the first-line *H. pylori* eradication therapy could be determined without knowing the exact results of the confirmatory test in the secondary databases. However, the specificity for determining successful *H. pylori* eradication therapy after second-line treatment was relatively low. This is because administration of third-line therapy is uncommon in the real-world setting. The operational definition may mistakenly classify individuals in whom second-line therapy failed and who were not administered third-line therapy as having received successful second-line therapy. Therefore, caution should be exercised when interpreting the results of the second-line therapy.

Although our study is the first to develop and validate an operational definition of *H. pylori* eradication therapy, it has several limitations. First, the operational definition was developed in Korea considering the local clinical settings and preferences, including the major eradication regimens. If the operational definition is applied to other countries or regions, the preferred *H. pylori* eradication regimens of that country/region should be considered.



**Table 4.** Performance of the operational definition in determining successful or failed *H. pylori* eradication therapy

<i>H. pylori</i> eradication therapy based on the operational definition	Based on the confirmatory test			
	Success	Failure	Unknown	Total
Prospective, nationwide registry (development set)				
First-line therapy				
Success	4,897 (95.3)	344 (22.8)	0 (0.0)	5,241 (78.8)
Failure	0 (0.0)	1,085 (72.1)	0 (0.0)	1,085 (16.3)
Unknown	244 (4.8)	77 (5.1)	2 (100.0)	323 (4.9)
Total	5,141 (100.0)	1,506 (100.0)	2 (100.0)	6,649 (100.0)
Second-line therapy				
Success	896 (95.4)	75 (58.6)	0 (0.0)	971 (90.8)
Failure	0 (0.0)	43 (33.6)	0 (0.0)	43 (4.0)
Unknown	43 (4.6)	10 (7.8)	2 (100.0)	55 (5.1)
Total	939 (100.0)	128 (100.0)	2 (100.0)	1,069 (100.0)
Real-world data from hospital medical records (validation set)				
First-line therapy				
Success	867 (97.6)	39 (8.2)	0 (0.0)	906 (57.8)
Failure	0 (0.0)	433 (91.4)	0 (0.0)	433 (27.6)
Unknown	21 (2.4)	2 (0.4)	205 (100.0)	228 (14.6)
Total	888 (100.0)	474 (100.0)	205 (100.0)	1,567 (100.0)
Second-line therapy				
Success	341 (98.6)	19 (45.2)	0 (0.0)	360 (82.0)
Failure	0 (0.0)	23 (54.8)	0 (0.0)	23 (5.2)
Unknown	5 (1.4)	0 (0.0)	51 (100.0)	56 (12.8)
Total	346 (100.0)	42 (100.0)	51 (100.0)	439 (100.0)

Values are presented as number (%).

Participants treated with an *H. pylori* eradication regimen that met the operational definition criteria were included in this analysis.

Second, the institutions included in the development and validation sets overlapped, indicating that the development and validation sets may depend on each other. However, the institutions included in the validation set accounted for only a small proportion of the nationwide registry, and the study periods for the development and validation sets were distinctly separated. Moreover, the impact of the bias caused by interdependency between the development and validation sets may have been minimal. Third, the operational definition of *H. pylori* reinfection was not validated because of the lack of participants with reinfection in the validation set. Fourth, we did not include potassium-competitive acid blockers (P-CABs) in our operational definitions. Although tegoprazan, a P-CAB, has been approved for *H. pylori* eradication therapy in Korea in 2021, our study included only patients who received *H. pylori* eradication therapy in 2019 or before. We plan to extend our operational definitions to include patients who received P-CAB-based *H. pylori* eradication therapy. Although the operational definition for reinfection seems to be clinically relevant, long-term follow-up data are required to validate them. Fifth, unknown treatment results could not be ignored in the validation set, as some patients could have been lost to follow-up or may not have undergone confirmatory tests in real-world practice. Operational definitions do not provide information on the success of eradication therapy in such patients. Finally, the practical use of operational definitions in secondary databases, such as the NHIS claim database, was not tested. We plan to apply the operational definition to perform various subsequent clinical studies. A modified version of the operational definition may be derived for subsequent studies.

Despite these limitations, our study provides valid and applicable operational definitions that can be used for *H. pylori*-related studies utilizing a secondary database. Using prescriptions of major *H. pylori* eradication regimens, we developed an operational definition for identifying individuals who received *H. pylori* eradication therapy. Additionally, the operational definition of a successful or failed eradication therapy was based on the presence of a confirmatory

test and rescue therapy prescription. Our operational definitions may be useful for various studies that utilize secondary databases.

## SUPPLEMENTARY MATERIALS

### Supplementary Table 1

Adherence to confirmatory tests after *H. pylori* eradication therapy

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### Supplementary Table 2

*H. pylori* eradication regimens according to the hospital in the validation set

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### Supplementary Table 3

Sensitivity of the operational definition for identifying individuals who received *H. pylori* eradication therapy according to the hospital in the validation set

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### Supplementary Table 4

Performance of the operational definition in determining the success or failure of *H. pylori* eradication therapy according to the hospital in the validation set

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### Supplementary Fig. 1

Duration of the first-, second-, and third-line *H. pylori* eradication therapies in the prospective, nationwide registry (A) and real-world data from hospital medical records (B).

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