Annals of Clinical Microbiology www.acm.or.kr

Original article

Prevalence of *Helicobacter pylori* infection and clarithromycin resistance rate from 2015 to 2018 using the laboratory information system of the Seegene Medical Foundation in Korea: a repeated cross-sectional study

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Abstract

Background: Numerous studies have examined the prevalence of *Helicobacter pylori* infection and clarithromycin (CLA) resistance rate of *H. pylori*. However, in South Korea, there is a lack of research analyzing specimens from local clinics and hospitals using molecular methods. This study aimed to assess the prevalence of *H. pylori* infection and CLA resistance across sex and age groups, as well as to explore regional variations in CLA resistance and its characteristics.

Methods: Data from a laboratory information system from 2015 to 2018 were retrospectively analyzed to determine the prevalence of *H. pylori* infection and CLA resistance rate. The 23S ribosomal RNA genes of *H. pylori* were analyzed using a dual priming oligonucleotide-based multiplex polymerase chain reaction method.

Results: The overall prevalence of *H. pylori* infection was 50.5%(12,000/23,773), with a significantly higher prevalence among males (53.5%) than females (47.0%). The CLA resistance rate was 28.3%, with a significantly higher rate among females (34.9%) than males (23.8%). Age group analysis revealed that the highest prevalence of *H. pylori* infection was among individuals in their 40s, whereas the highest CLA resistance rate was observed among those in their 60s. The CLA resistance rate exhibited an upward trend and varied among patients based on their place of residence, and A2143G mutation was the most prevalent across all regions.

Conclusion: The prevalence of *H. pylori* infection and CLA resistance rate in Korea remain high and vary according to sex, age, and region. To effectively eradicate *H. pylori,* it is crucial to periodically monitor regional CLA resistance patterns and conduct CLA susceptibility testing before prescription.

Keywords: *Helicobacter pylori,* clarithromycin, resistance, 23S ribosomal RNA, Korea

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OPEN ACCESS

pISSN : 2288-0585
eISSN : 2288-6850

Ann Clin Microbiol 2024 March, 27(1): 4
https://doi.org/10.5145/ACM.2024.27.1.4

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Received: February 23, 2024
Revised: March 15, 2024
Accepted: March 19, 2024

Introduction

Background

Helicobacter pylori, identified by Marshall and Warren in 1982, is a pathogen recognized by the World Health Organization as one of the 12 antibiotic-resistant priority pathogens affecting humans [1,2]. While the global prevalence of *H. pylori* infection decreased from 50%–55% to 43% from 2014 to 2020 [3,4], the prevalence in Korea was reported to be over 50% in 2017-2018 [5].

H. pylori has been implicated in various diseases, including chronic atrophic gastritis, peptic ulcer, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer. The eradication of *H. pylori* has been shown to reduce the incidence of gastric cancer [6]. Clarithromycin (CLA), a macrolide antibiotic, is a bacteriostatic agent widely used as the primary antibiotic for *H. pylori* eradication in both standard triple and combination therapies. Its efficacy is attributed to features such as low minimal inhibitory concentration, minimal effect on gastric acidity, and favorable mucosal diffusion [7,8].

Unfortunately, the extensive use of CLA has led to an increase in global CLA resistance rates, which vary among patient groups according to sex, age, disease, and geographic location [9]. Consequently, several international guidelines advise against using the triple therapy regimen in areas where the CLA resistance rate exceeds 15% [10,11].

Culture-based CLA susceptibility testing (phenotypic testing method) is considered the gold standard for selecting appropriate *H. pylori* eradication regimens; however, its limitations, such as difficulty culturing the organism and slow growth, have led to the adoption of tailored therapies using molecular methods such as polymerase chain reaction (PCR) in clinical practice [12].

Since the World Health Organization identified CLA-resistant *H. pylori* as a high priority for antibiotic research and development in 2017, significant research efforts have been directed towards this pathogen [2]. A systematic review and meta-analysis conducted across 54 countries using the culture-based method from 1990 to 2021 revealed a global CLA resistance rate of 27.53%, with a recent uptrend [13].

Previous studies in Korea have explored the CLA resistance rate for *H. pylori* eradication and its associated characteristics. However, most national-scale studies were based on the phenotypic testing method, and those employing the genotypic testing method have been typically limited to single institutions with small sample sizes [5,14-20].

Objectives

This study aimed to investigate the prevalence of *H. pylori* infection and the CLA resistance rate within the 23S ribosomal RNA (rRNA) genes, stratified by sex and age, using gastric specimens obtained from local clinics and hospitals across South Korea. The dual priming oligonucleotide-based PCR (DPO-PCR) method, a culture-independent approach, was used for this purpose. Additionally, we investigated the regional and temporal variations in CLA resistance rates and analyzed mutation patterns within the 23S rRNA genes of *H. pylori*.

Methods

Ethics statement

This study was approved by the Institutional Review Board of Seegene Medical Foundation (IRB No. SMF-IRB-2019-03).

Study design

It is a repeated cross-sectional study. It was described according to STROBE statement (https://www.strobe-statement.org/).

Setting

Laboratory results were obtained using the laboratory information system of the Seegene Medical Foundation, Seoul, Korea.

Participants

This retrospective study included data from Korean patients who visited 138 local clinics and hospitals between January 2015 and December 2018 for molecular testing of *H. pylori* and CLA resistance at Seegene Medical Foundation.

Variables

Presence of *H.pylori* and its resistance to clarithromycin were outcome variables.

Data sources and measurement

Gastric biopsy specimens comprising at least one sample from the antrum or body of the stomach were used. Prior to analysis, all data were anonymized, and records lacking age or sex information were excluded. Genomic DNA was extracted from gastric biopsy samples using the QIAamp DNA Mini Kit (Qiagen), according to the manufacturer's instructions. The Seeplex® ClaR-*Hp* ACE detection kit (Seegene) was used for DPO-PCR, as per the manufacturer's instructions. The initial incubation step was performed at 94°C for 15 min, followed by 40 amplification cycles in a SeeAmp thermal cycler (Seegene), with the following parameters: 94°C for 30 s, 65°C for 30 s, and 72°C for 1 min. The final extension step was performed at 72°C for 10 min. The PCR products were visualized under UV light after 2% agarose gel electrophoresis stained with ethidium bromide. A 621-bp band indicated wild-type *H. pylori*, whereas bands at 475 bp and 194 bp signified A2142G and A2143G mutations, respectively.

Bias

There was no selection bias because all target samples were included.

Study size

Sample size estimation was not required because all target materials were selected.

Statistical methods

Categorical variables were assessed using the chi-squared test. Additionally, P_{trend} values were tested over one year. All statistical analyses were performed using SPSS Statistics for Windows (version 26.0; IBM Corp.). A P value < 0.05 was considered statistically significant.

Results

Participants

This study included 23,773 patients, comprising 12,740 males (age range: 14–96 years; mean age: 52.1 years) and 11,033 females (age range: 12–89 years; mean age: 52.8 years).

Prevalence of *H. pylori* infection

Table 1 illustrates the prevalence of *H. pylori* infection according to sex and age. The overall prevalence determined by DPO-PCR was 50.5% (12,000/23,773), with a higher rate among males at 53.5% (6,811/12,740) than among females at 47.0% (5,189/11,033) (P < 0.001). The prevalence sharply increased from the under-30-year age group to the 40-year-old group, peaking in the latter and then gradually declining in the 70-and-older age group.

Table 1. Prevalence of *Helicobacter pylori* infection across sex and age groups between 2015 and 2018

Characteristics	*H. pylori*-positive samples (n = 12,000)	*H. pylori*-negative samples (n = 11,773)	Total	*P*-value
Sex				< 0.001
Male	6,811 (53.5)	5,929 (46.5)	12,740	
Female	5,189 (47.0)	5,844 (53.0)	11,033	
Age, years				< 0.001
< 30	306 (37.4)	513 (62.6)	819	
30–39	1,139 (48.4)	1,215 (51.6)	2,354	
40–49	3,349 (55.8)	2,655 (44.2)	6,004	
50–59	3,730 (52.2)	3,409 (47.8)	7,139	
60–69	2,376 (47.4)	2,633 (52.6)	5,009	
≥ 70	1,100 (44.9)	1,348 (55.1)	2,448	

Values are presented as n (%) or n.

Clarithromycin resistance rates of *H. pylori*

Table 2 presents the sex- and age-stratified CLA resistance rates of *H. pylori*. Of the 12,000 *H. pylori*-positive specimens, 3,436 (28.6%) were resistant to CLA. Resistance rates were higher in females (34.9%; 1,812/5,189) than in males (23.8%; 1,624/6,811) across all age groups except the under-30-year age group (*P*

Table 2. Clarithromycin resistance rate of *Helicobacter pylori* according to sex and age between 2015 and 2018

Age, years	N	Males			Females			*P*-value
		R	S	N	R	S	N	
< 30	306	44 (25.4)	129 (74.6)	173	29 (21.8)	104 (78.2)	133	0.460
30–39	1,139	170 (24.6)	521 (75.4)	691	152 (33.9)	296 (66.1)	448	< 0.001
40–49	3,349	419 (20.7)	1,601 (79.3)	2,020	436 (32.8)	893 (67.2)	1,329	< 0.001
50–59	3,730	458 (22.1)	1,610 (77.9)	2,068	582 (35.0)	1,080 (65.0)	1,662	< 0.001
60–69	2,376	383 (29.3)	923 (70.7)	1,306	426 (39.8)	644 (60.2)	1,070	< 0.001
≥ 70	1,100	150 (27.1)	403 (72.9)	553	187 (34.2)	360 (65.8)	547	< 0.001
Total	12,000	1,624 (23.8)	5,187 (76.2)	6,811	1,812 (34.9)	3,377 (65.1)	5,189	< 0.001

Values are presented as n (%) or n.
Abbreviations: N, number; R, resistant; S, susceptible.

< 0.001). Notably, the 60–69-year-old group showed the highest resistance rates in both sexes. Among males, the CLA resistance rate decreased from 52.9% in 2015 to 44.8% in 2017, with the lowest in 2017, followed by an increase to 47.0% in 2018. Conversely, among females, the CLA resistance rate increased from 47.1% in 2015 to a peak of 55.2% in 2017, before decreasing in 2018 (data not shown).

Table 3 shows the CLA resistance rates of *H. pylori* in various geographic regions. There was a significant increase in the CLA resistance rate, from 24.3% in 2015 to 30.3% in 2017 ($P < 0.05$), followed by a decrease to 28.3% in 2018. Throughout the study period, CLA resistance rates were 29.4%, 29.0%, 19.3%, 28.6%, 29.7%, and 27.4% in Gyeonggi, Seoul, Kangwon, Chungcheong, Cholla, and Kyungsang, respectively. Notably, the Kangwon region exhibited a significantly divergent resistance rate compared with the other regions ($P < 0.05$). In the Gyeonggi region, the CLA resistance rate progressively increased from 20.8% in 2015 to 31.6% in 2018. Conversely, the Chungcheong and Cholla regions witnessed an increase from 2015 to 2016, peaking at 31.5% and 37.0% in 2016, before declining in 2018. The CLA resistance rate in Chungcheong was similar to the overall rate, while Gangwon and Kyungsang had lower rates, and the remaining regions had higher rates than the overall CLA resistance rate.

Table 3. Clarithromycin resistance rate of *Helicobacter pylori* according to the geographic region between 2015 and 2018

Year	Gyeonggi		Seoul		Kangwon		Chungcheong		Cholla		Kyungsang		Total	
	R	S	R	S	R	S	R	S	R	S	R	S	R	S
2015*	20.8	79.2	27.5	72.5	26.9	73.1	31.3	68.7	34.7	65.3	19.9	80.1	24.3	75.7
2016*	23.9	76.1	27.9	72.1	22.6	77.4	31.5	68.5	37.0	63.0	30.1	69.9	28.5	71.5
2017*	31.1	68.9	29.9	70.1	17.4	82.6	26.5	73.5	32.9	67.1	34.9	65.1	30.3	69.7
2018	31.6	68.4	28.9	71.1	17.6	82.4	24.9	75.1	27.4	72.6	20.9	79.1	28.3	71.7
Total	29.4	70.6	29.0	71.0	19.3	80.7	28.6	71.4	29.7	70.3	27.4	72.6	28.6	71.4

Values are presented as percentage (%).
*$P_{trend} = 0.005$.
Abbreviations: R, resistant; S, susceptible.

Table 4 outlines the CLA resistance rate of *H. pylori* in relation to the 23S rRNA gene mutation type. Of the *H. pylori* specimens exhibiting CLA resistance, 3,436 (28.6%) had either A2142G or A2143G point mutations or both. Specifically, 200 (1.7%) samples had A2142G mutations, 3,149 (26.2%) had A2143G mutations, and 87 (0.7%) had both mutations. These 87 specimens with A2142G and A2143G mutations

Table 4. Clarithromycin resistance rate of *Helicobacter pylori* according to the 23S rRNA genotype between 2015 and 2018

Year	N	Wild-type	Mutation type			
			A2142G only	A2143G only	A2142G + A2143G	Total
2015	1,051	796 (75.7)	14 (1.3)	228 (21.7)	13 (1.2)	255 (24.3)
2016	2,614	1,868 (71.5)	47 (1.8)	683 (26.1)	16 (0.6)	746 (28.5)
2017	3,861	2,693 (69.7)	67 (1.7)	1,075 (27.8)	26 (0.7)	1,168 (30.3)
2018	4,474	3,207 (71.7)	72 (1.6)	1,163 (26.0)	32 (0.7)	1,267 (28.3)
Total	12,000	8,564 (71.4)	200 (1.7)	3,149 (26.2)	87 (0.7)	3,436 (28.6)

Values are presented as n (%) or n.
Abbreviation: N, number.

were diagnosed as gastritis (n = 72), gastric ulcer (n = 13), or gastric polyp/adenoma (n = 2) (data not shown). During the study period, A2143G mutations were observed approximately 15.7 times more frequently than A2142G mutations.

Table 5 shows the CLA resistance rate of *H. pylori* in relation to the 23S rRNA genotype and the frequency in each regional area. In all regions, A2143G mutation was the most frequently observed, followed by A2142G mutation and double-point mutation (A2142G and A2143G) in that order. Double-point mutations were not detected in the Gangwon region. Remarkably, A2143G mutation exceeded 20% in all regions except Gangwon (16.6%).

Table 5. Clarithromycin resistance rate of *Helicobacter pylori* according to the 23S rRNA genotype and frequency for each regional area between 2015 and 2018

Regional areas	N	Wild-type	Mutation type			
			A2142G only	A2143G only	A2142G + A2143G	Total
Gyeonggi	2,280	1,610 (70.6)	42 (1.8)	604 (26.5)	24 (1.1)	670 (29.4)
Seoul	5,623	3,991 (71.0)	91 (1.6)	1,504 (26.7)	37 (0.7)	1,632 (29.0)
Kangwon	290	234 (80.7)	8 (2.8)	48 (16.6)	0 (0.0)	56 (19.3)
Chungcheong	1,025	732 (71.4)	13 (1.3)	273 (26.6)	7 (0.7)	293 (28.6)
Cholla	975	685 (70.3)	19 (1.9)	266 (27.3)	5 (0.5)	290 (29.7)
Kyungsang	1,807	1,312 (72.6)	27 (1.5)	454 (25.1)	14 (0.8)	495 (27.4)
Total	12,000	8,564 (71.4)	200 (1.7)	3,149 (26.2)	87 (0.7)	3,436 (28.6)

Values are presented as n (%) or n.
Abbreviation: N, number.

Discussion

Key results

During the study period, we observed an overall *H. pylori* infection prevalence of 50.5%. The CLA resistance rate was 28.3%, with a significantly higher rate among females (34.9%) than males (23.8%). The most prevalent mutation in the 23S rRNA genes was A2143G (26.2%), followed by A2142G (1.7%), and double-point mutations (A2142G and A2143G, 0.7%).

Interpretation/comparison with previous studies

The *H. pylori* infection prevalence of this study is consistent with a recent multicenter nationwide report indicating a prevalence of 51.0% in the Korean population between 2015 and 2016 [21]. Given the enhanced sensitivity of the PCR method compared with the enzyme-linked immunosorbent assay, we infer a decline in *H. pylori* infection prevalence, mirroring the global trend, likely due to improvements in socioeconomic conditions and hygiene practices [1].

Although most studies have reported no significant difference in the prevalence of *H. pylori* infection between men and women, our study showed higher positivity rate for *H. pylori* infection in men (53.5%) than in women (47.0%), which is comparable to the results of a recent Korean study [22]. This may partially explain why *H. pylori*-associated diseases are more common in Korean men [22]. Notably, the peak age range for *H. pylori* infection in our study shifted downward (in the 40s age group) relative to that reported in previous Korean studies; for example, a 2011 study involving 19,272 individuals reported the highest prevalence in the 60s age group, and a 2015-2016 study of 4,920 individuals reported it in the 50s age group [21,22]. This shift may reflect increased cumulative exposure to antibiotics or proton pump inhibitors among older age groups [22], warranting further investigation. Although the prevalence of *H. pylori* infection exceeded 70% in less developed regions, in contrast to less than 40% in more developed areas [23], the prevalence in our study, excluding those in their 30s (37.4%), remained high and did not reach the levels observed in more developed regions.

In this study, the CLA resistance rate determined by DPO-PCR was 28.6%, which is within the 15.8%–38.7% range reported by previous Korean studies conducted at single institutions using the same method [14-20].

Consistent with numerous studies, our findings indicate a significantly higher CLA resistance rate among females than males ($P < 0.001$) [24-28]. This study revealed that the CLA resistance rate exceeded 20% across all age groups for both sexes, with the highest rates observed in the 60s age group (29.3% in males and 39.8% in females). This trend may be linked to the increased cumulative exposure to CLA, particularly because of its frequent use in the treatment of respiratory and urinary tract infections [28].

A recent study by Kocsmár et al. in central Hungary indicated that the primary resistance to CLA, which showed no significant difference between sexes, was predominantly due to the transmission of resistant bacteria (98.7%) rather than spontaneous mutations (1.3%) [25]. The study also found an age-related predominance of CLA resistance among females, particularly in secondary (macrolide-exposed) infections, which were mainly associated with the prior use of macrolides for non-eradication purposes, such as the treatment of gynecological or urinary infections [25]. These findings suggest that the observed age-dependent predominance of CLA resistance among females in our study could be partially attributed to the higher consumption of macrolides among females for non-eradication treatments [25,28].

Our comprehensive study revealed regional disparities in CLA resistance rates across South Korea. Throughout the study period, the CLA resistance rates exceeded 25% in most regions, including Cholla (29.7%), Gyeonggi (29.4%), Seoul (29.0%), Chungcheong (28.6%), and Kyungsang (27.4%), and only

the Kangwon region showed the rate below this threshold at 19.3%. Lee et al.[5] also reported that the CLA resistance rates in Cholla and Gyeonggi were higher than those in other regions. The observed regional differences in the CLA resistance rates might be due to comparatively high consumption of CLA in regions like Cholla and Gyeonggi, suggesting that CLA antibiotic consumption vary by region [29].

Historical data from university hospitals on symptomatic patients, analyzed using the DPO-PCR method, indicated a CLA resistance rate of 16.7% in Seoul in 2008, 20.0% in Gyeonggi from 2011 to 2012, 26.0% in Jeju from 2011 to 2012, 22.2% in Kyungsang from 2011 to 2013, 23.0% in Chungcheong from 2011 to 2015, and a peak of 38.7% in Gyeonggi from 2015 to 2016 [14-20]. Although these figures stem from single-institution studies conducted in various regions, they collectively suggest an upward trend in CLA resistance rates from 2008 to 2016. In our study, the CLA resistance rate continued to increase from 2015 to 2017 before showing a decline in 2018. Ongoing surveillance is essential to determine whether this trend persists and is critical for selecting the most effective antibiotics to enhance the eradication rate of *H. pylori*.

A previous prospective study by Lee et al.[5], encompassing 15 centers across six geographic regions of Korea from 2017 to 2018, reported a CLA resistance rate of 17.8%, which was notably lower than our findings (an average of 27.0% from 2017 to 2018). This discrepancy may be attributed to several factors. First, Lee et al. determined the prevalence of phenotypic resistance to CLA using the culture-based method, whereas our study assessed genotypic resistance using the PCR-based method [5]. This is in line with the findings of de Francesco et al. indicating that the genotypic testing tends to yield higher resistance rates than that of phenotypic testing because it can also detect hetero-resistant isolates that are only identifiable by PCR [30]. Second, the difference may stem from distinct patient group characteristics in the two studies. Our study investigated data from patients visiting local clinics and hospitals but lacked clinical information, whereas the study by Lee et al. (targeting a small number of patient specimens, n = 590) included data from patients visiting university hospitals; the patients had no history of *H. pylori* eradication therapy and were of higher socioeconomic status and more likely to have comorbidities. Further investigations are warranted to elucidate the variation in CLA resistance rates based on the clinical information, such as whether the patients visited university hospitals or local clinics and hospitals.

The mechanisms underlying the CLA resistance of *H. pylori* are linked to point mutations in the 23S rRNA gene, multidrug efflux pump systems, and certain outer membrane proteins [31]. In the Western and high-income countries, most CLA resistance is associated with point mutations in the peptidyl transferase region of the V domain of the 23S rRNA gene [32]. Primary point mutations linked to CLA resistance include A2142G, A2143G (adenine-to-guanine transition at position 2142 or 2143), A2142C (adenine-to-cytosine transversion at position 2142), and A2115G (adenine-to-guanine transition at position 2115) [7].

The most prevalent mutation in the 23S rRNA genes, A2143G (26.2%), followed by A2142G (1.7%) and double-point mutations (A2142G and A2143G, 0.7%), are consistent with prior Korean and Western studies [14-20,33,34]. In contrast, a study conducted in northern Peru identified A2142G as the predominant mutation (46.9%), followed by double-point mutation (28.6%), and A2143G mutation (4.1%) [35]. Furthermore, an Iranian study reported regional differences in dominant mutations within the same country [36]. However, our findings indicate that A2143G mutations were the most common and double-point

mutation were the least common across all regions throughout the study period. Despite the lower prevalence of A2142G than A2143G, both mutations were associated with the CLA resistance [34]. The presence of mixed *H. pylori* infections with both susceptible and resistant strains, as seen in double-point mutations, may reduce the efficacy of *H. pylori* eradication efforts. Therefore, caution is advised when using CLA for *H. pylori* eradication [17].

The strengths of our study are the large sample size (23,773 eligible subjects) and its national scope, which allowed us to determine the prevalence and CLA resistance rates of *H. pylori* across Korea using PCR, which is known to be a more sensitive method than the conventional phenotypic methods. Our findings provide a comprehensive representation of all regions and serve as valuable baseline data for formulating *H. pylori* eradication policies and achieving satisfactory eradication rates in Korea.

Limitations

One of these is our inability to discern whether CLA resistance was primary or secondary, owing to the lack of the patients' prior CLA treatment history. According to Kocsmár et al., most cases are caused by secondary resistance. Additionally, although most samples were requested by health check-up examination codes and accurate clinical information could not be confirmed, considering that the tests for CLA resistance of *H. pylori* were performed, it is believed that most patients had symptoms of gastritis. Finally, our testing method did not detect A2142C or other mutations because DPO-PCR was specifically designed to identify only two point mutations (A2142G and A2143G). Although A2142C and other mutations constitute a minor percentage of CLA-resistant *H. pylori* infections, it may still be important to consider the rates of these mutations in Korea. However, DPO-PCR remains a practical method for detecting *H. pylori* infection and determining CLA susceptibility.

Conclusion

The prevalence of *H. pylori* infection was 50.5%, and the rate of CLA resistance was 28.3%. Notably, these rates vary according to sex and age. An increasing trend in CLA resistance was observed from 2015 to 2017, with regional differences. The most frequent mutation was A2143G. Our findings underscore the importance of periodically monitoring CLA resistance patterns regionally and conducting CLA susceptibility testing before prescription to ensure the successful eradication of *H. pylori*.

Conflicts of interest

No potential conflicts of interest relevant to this article were reported.

Funding

This work was supported by the Research Fund (2021) of the *Helicobacter* Study Group of the Korean Society of Clinical Microbiology.

Data availability

The datasets generated during the current study are available from the corresponding author upon request.

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