Original Article

Rate and predictive factors of *Helicobacter pylori* recurrence: Analysis of a screening cohort

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Abstract

Background/Aim: The aim of the study was to identify the recurrence rate of *Helicobacter pylori* after successful eradication in an endemic area and investigate baseline and clinical factors related to the recurrence.

Patients and Methods: *H. pylori* infected patients from a screening cohort of National Cancer Center between 2007 and 2012 were enrolled in the study. A total of 647 patients who were confirmed to be successfully eradicated were annually followed by screening endoscopy and rapid urease test. Median follow-up interval was 42 months. Annual recurrence rate of *H. pylori* was identified. Demographics, clinical factors, and endoscopic findings were compared between *H. pylori* recurrence group and persistently eradicated group (control group).

Results: *H. pylori* recurrence was observed in 21 (3.25%) patients. Its annual recurrence rate was 0.91% (1.1% in males and 0.59% in females). Mean age was higher in the recurrence group than that in the control group (55.9 vs 50.7, $P = 0.006$). Median follow-up was shorter in the recurrence group than that in the control group (34 vs. 42.5 months, $P = 0.031$). In multivariate analysis, OR for *H. pylori* recurrence was 1.08 per each increase in age ($P = 0.012$). Adjusted ORs for *H. pylori* recurrence were 0.20 (95% CI: 0.06–0.69) and 0.25 (95% CI: 0.08–0.76) in age groups of 50–59 years and less than 50 years, respectively, compared to the group aged 60 years or older.

Conclusion: *H. pylori* recurrence rate in Korea is very low after successful eradication. Advanced age is at increased risk for *H. pylori* recurrence. Thus, *H. pylori* treatment for patients who are under 60 years of age is more effective, leading to maintenance of successful eradication status.

Keywords: Eradication, *Helicobacter pylori*, recurrence

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INTRODUCTION

Helicobacter pylori (H. pylori) is known as a risk factor for gastric cancer. It was classified as a type I carcinogen by the International Agency for Research on Cancer (IARC) in 1994.[1] Long-term *H. pylori* infection can lead to premalignant histological changes such as atrophic gastritis and intestinal metaplasia.[2] Although the incidence of gastric cancer has decreased substantially in the Western world, it is still the fourth most common cancer and the second leading cause of mortality due to cancers

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worldwide.[3] South Korea has the highest incidence rate of gastric cancer.[3] Nationwide biennial gastric cancer screening for individuals aged 40 years or older has been conducted in South Korea since 1999.[4] Recently, there has been an increased concern about early eradication of *H. pylori* to prevent gastric cancer.[5] *H. pylori* infection is also a risk factor for peptic ulcer diseases (PUD) and gastric MALT lymphoma. The updated American College of Gastroenterology (ACG) guideline strongly recommends *H. pylori* eradication for patients with PUD, a history of PUD, low-grade gastric MALT lymphoma, or a history of endoscopic resection of early gastric cancer.[6] The success rate of eradication therapy in South Korea has been reported to be around 80% recently.[7,8] However, a negative result on follow-up test after *H. pylori* treatment does not guarantee subsequent persistent eradication status in the future. To prevent progression of premalignant histological changes and recurrent peptic ulcer diseases, it is important to maintain *H. pylori* eradication status after successful treatment.

After successful eradication, *H. pylori* may be detected again. This is usually considered a recurrence. However, recurrence refers to the recrudescence of the original strain of *H. pylori* that remains suppressed and undetectable, whereas reinfection refers to infection by a new strain of *H. pylori*.[9] Reported rate of annual recurrence, sometimes including reinfection, ranges from 2.0% to 9.1% in Korean studies.[10-14] The rate of recurrence generally varies depending on the country, race, research period, research method, and so on. Reviewing recurrence rate can help us assess the relevance of treatment and predict future development of *H. pylori*-related diseases. Due to socioeconomic development and improved hygiene in South Korea, the prevalence of *H. pylori* infection has gradually decreased, although it is still over 50%.[15] Types of eradication regimens and bacterial resistance may also affect the recurrence rate. Along with these various changes, the recurrence rate of *H. pylori* in South Korea is also changing. The aim of this study was to determine the recurrence rate of *H. pylori* after successful eradication in an endemic area and to identify baseline and clinical factors related to the recurrence.

PATIENTS AND METHODS

Study design and patients

Consecutive persons who participated in the voluntary health screening program at National Cancer Center, South Korea, between January 2007 and December 2012 were considered. The National Cancer Center has established a screening cohort for health checkups since 2001. Inclusion criteria were: screening cohort participants who provided informed consent screening cohort, those who underwent annual gastric cancer screening with upper endoscopy and *H. pylori* test, and those who were suitable as study subjects based on appropriate physical examination and questionnaire. Among 10,651 persons who met the inclusion criteria, 5,216 case persons had positive *H. pylori* test results during the study period, and 1,755 persons received anti-*H. pylori* treatment. Among them, 1,476 cases for which *H. pylori* eradication was successful were eligible for the study [Figure 1]. Of them, 531 subjects were excluded as they did not undergo annual follow-up endoscopy after successful eradication. We additionally excluded subjects because of the following reasons: follow-up endoscopy with interval less than 12 months (n = 166), those who did not undergo *H. pylori* test on follow-up endoscopy (n = 114), and those who were diagnosed with primary or metastatic gastric cancer (n = 18). Finally, 647 subjects were included in the analysis. Information relating to patients' endoscopic findings and their baseline characteristics was obtained via questionnaires and review of medical records. This study was approved by the Institutional Review Board of the National Cancer Center (NCCNCS13739).

Endoscopy and *H. pylori* eradication

All participants underwent esophagogastroduodenoscopy (GIF-H260, Olympus Optical Co., Ltd, Tokyo, Japan) after fasting overnight. Pharyngeal anesthesia with 4% xylocaine

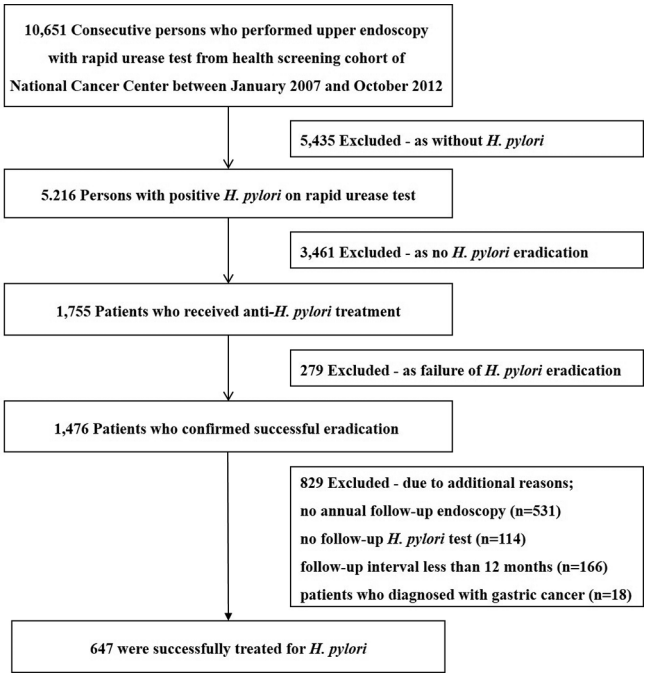

Figure 1: Study flow of screening cohort. We selected 647 subjects who were successfully treated for *H. pylori*

spray was routinely performed and intravenous midazolam was administered for conscious sedation. During each endoscopic examination, a rapid urease test (Pronto Dry; Medical Instruments, Solothurn, Switzerland) was routinely performed via a specimen obtained from the greater curvature of the corpus. *H. pylori*-positive subjects, who were clinically indicated for *H. pylori* eradication or according to patients' desire, received a 7-day triple therapy with omeprazole 20 mg twice daily, amoxicillin 1000 mg twice daily, and clarithromycin 500 mg twice daily as the first-line anti-*H. pylori* treatment. Quadruple regimen was provided as a second line therapy for patients who were considered as having triple therapy failure. Assessment of successful *H. pylori* treatment was performed at least 4–5 weeks after the end of the eradication treatment, using a histological examination, a rapid urease test, or a C^{13} urea breath test. Patients were instructed not to take antacids during the period. Those with all negative results from available tests were regarded as successfully eradicated persons. *H. pylori* recurrence was defined when *H. pylori* infection was confirmed in a rapid urease test on follow-up screening endoscopy performed at intervals of 12 months or more after a confirmed successful *H. pylori* eradiation. The period was defined as follow-up interval. For subjects who did not have a recurrence, follow-up interval was calculated as the period from the time of successful eradication to the last follow-up endoscopy within the study period.

Statistical analysis

Annual recurrence rate of *H. pylori* in the study population was calculated by dividing the total number of re-infected subjects by the total number of patient year observed (%), and Kaplan–Meier survival analysis was performed. Baseline characteristics and clinical findings were compared between subjects with *H. pylori* recurrence ("case group") and those who showed persistently successful eradication status ("control group"). Pearson's Chi-square test or Fisher's exact test was used to compare categorical variables (sex, regimen of eradication, smoking and drinking status, comorbidity, medication history, and endoscopic findings) whereas independent sample *t*-test or Mann–Whitney U-test was used to compare continuous variables (age, follow-up period, and anthropometric indices). Multivariate logistic regression analyses using odds ratios (ORs) and 95% confidence intervals (CIs) were performed considering significant factors with *P* values less than 0.05 in the univariate analysis and possible confounding factors. All *P* values are two-sided. Statistical significance was considered when *P* value was less than 0.05. SPSS Statistics 19.0 (IBM, Armonk, NY, USA) was used for all statistical analyses.

RESULTS

Baseline demographic data

The mean age of the study population was 50.9 ± 8.5 years, and 62% were male. Median follow-up interval was 42 months (range: 12-98 months). *H. pylori* recurrence was observed in 21 (3.25%) of 647 enrolled subjects, whereas the remaining 626 subjects showed persistent eradication status. Annual recurrence rate was 0.91% (1.1% in males and 0.59% in females). Kaplan–Meier survival curve was shown in Figure 2. Results of comparison of baseline demographics and clinical findings between patients with *H. pylori* recurrence and those with persistent eradication are shown in Table 1. Mean age was significantly higher in *H. pylori* recurrence group than that in the control group (55.9 vs 50.7 years, $P = 0.006$). Median follow-up was significantly lower in *H. pylori* recurrence group (34 months, range: 16–71 months) than that in control group (42.5 months, range: 12–98 months) ($P = 0.031$). Among the study population, 88 (13.6%) subjects received second line therapy. The number of subjects receiving second line therapy was not significantly different between the recurrence group and the control group. There was no significant difference in anthropometric indices, smoking status, drinking status, comorbidity, medication history, or endoscopic findings between the two groups.

Clinical features related to *H. pylori* recurrence

We performed univariate and multivariate logistic regression analyses [Table 2]. The model included age, sex, follow-up month, type of regimens, smoking status, drinking status, history of cancer, atrophic gastritis and height. Adjusted OR for *H. pylori* recurrence was 1.08 per each increase in age ($P = 0.012$). Follow-up duration was significantly different in univariate analysis. However, it did not show significant difference between the two groups in

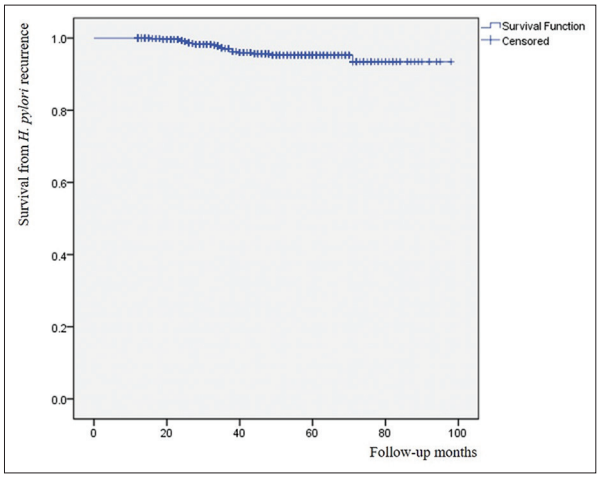

Figure 2: Kaplan–Meier survival curve for *H. pylori* recurrence

Table 1: Characteristics of the study population

Variables	Total (*n*=647)	Control group (*n*=626)	Recurrence group (*n*=21)	*P*
Age, mean±SD	50.9±8.5	50.7±8.5	55.9±8.4	0.006
Male sex, *n* (%)	401 (62.0)	385 (61.5)	16 (76.2)	0.173
Follow-up (mo), mean±SD	42.7±19.2	43.0±19.3	33.6±11.9	0.002
Second line regimen, *n* (%)	88 (13.6)	86 (13.7)	2 (9.5)	0.755
Height (cm), mean±SD	165.6±8.1	165.5±8.0	168.1±8.5	0.139
Weight (kg), mean±SD	66.6±11.3	66.5±11.2	70.0±14.1	0.172
Current smoking, *n* (%)	169 (26.1)	164 (26.2)	5 (23.8)	0.806
Current drinking, *n* (%)	427 (66.0)	412 (65.8)	15 (71.4)	0.593
Hypertension, *n* (%)	115 (17.8)	111 (17.7)	4 (19.0)	0.777
Diabetes, *n* (%)	38 (5.9)	37 (5.9)	1 (4.8)	0.999
Dyslipidemia, *n* (%)	66 (10.2)	64 (10.2)	2 (9.5)	0.999
Cancer, *n* (%)	30 (4.6)	28 (4.5)	2 (9.5)	0.254
Heart disease, *n* (%)	31 (4.8)	30 (4.8)	1 (4.8)	0.999
Aspirin, *n* (%)	59 (9.1)	57 (9.1)	2 (9.5)	0.999
NSAID, *n* (%)	4 (0.6)	4 (0.6)	0 (0)	0.999
Atrophic gastritis, *n* (%)	264 (40.8)	254 (40.6)	10 (47.6)	0.518
Intestinal metaplasia, *n* (%)	83 (12.8)	80 (12.8)	3 (14.3)	0.743
Peptic ulcer, *n* (%)	71 (11.0)	69 (11.0)	2 (9.5)	0.999

SD: Standard deviation

Table 2: Odds ratios for *H. pylori* recurrence in regression model

Variables	Crude OR	95% CI	*P*	Adjusted OR	95% CI	*P*
Age*	1.07	1.02-1.13	0.006	1.08	1.02-1.14	0.012
Male sex	2.00	0.72-5.54	0.181	0.98	0.20-4.92	0.981
Follow-up (mo)*	0.97	0.95-0.99	0.031	0.98	0.95-1.00	0.085
Second regimen	0.66	0.15-2.89	0.582	0.53	0.11-2.49	0.418
Current smoking	0.88	0.32-2.44	0.807	0.89	0.30-2.65	0.830
Current drinking	1.30	0.50-3.40	0.594	1.19	0.39-3.64	0.762
Cancer	2.25	0.50-10.13	0.292	2.23	0.43-11.51	0.337
Atrophic gastritis	1.33	0.56-3.18	0.520	1.20	0.46-3.14	0.710
Height (cm)*	1.04	0.99-1.10	0.141	1.06	0.97-1.15	0.213

CI, confidence interval; OR, odds ratio.*Included as continuous variables

the multivariate analysis (adjusted OR: 0.98, $P = 0.085$). Other variables showed no significance in multivariate logistic regression analysis either. Next, we performed multivariate regression analysis with age as a categorical variable (<50, 50–59 and ≥60 years). Adjusted ORs for *H. pylori* recurrence were 0.20 (95% CI: 0.06–0.69) and 0.25 (95% CI: 0.08–0.76) for age group of 50–59 years and age group of less than 50 years ($P = 0.011$ and $P = 0.014$, respectively) compared to age group of ≥60 years.

DISCUSSION

Some meta-analyses have reported that the global recurrence rate of *H. pylori* is approximately 2.8% to 4.3% per person-year.[16,17] Our finding showed an annual recurrence rate of 0.91%, which was much lower than results reported in recent Korean studies.[11-13,18] The low recurrence rate of our study could be due to some plausible reasons. It is known that the recurrence rate is high in areas with high prevalence of *H. pylori*.[19,20] Therefore, our low recurrence could be due to a gradually decreasing trend of *H. pylori* prevalence in Korea recently.[15] A recent meta-analysis showed that the recurrence rate of *H. pylori* is inversely correlated with national health development index (HDI).[16] HDI is a composite index measuring average achievement in three basic dimensions of human development: (i) life expectance at birth; (ii) mean and expected years of schooling; and (iii) gross national income per capita.[16] Therefore, another reason for the low recurrence rate might be associated with an increasing HDI in South Korea. Because recrudescence rather than reinfection is likely to be responsible for most cases of recurrence,[20] public interest in *H. pylori* eradication and increase in compliance might have contributed to the decreased recurrence rate in South Korea. Lastly, our study targeted a health screening population. This might lead to outcomes different from previous studies that targeted patients who visited outpatient clinics.

As mentioned earlier, chronic *H. pylori* infection can induce premalignant histological changes. Recent researches have highlighted the global burden of noncardiac gastric cancer attributable to chronic *H. pylori* infection.[21,22] It is known that *H. pylori* treatment can improve gastric histology including mucosal inflammation and atrophic change.[23,24] Therefore, early treatment of *H. pylori* and persistence of treated condition might be important for the prevention

of gastric cancer. In addition, recurrence of peptic ulcers is significantly lower in successfully eradicated patients.[25,26] In a recent randomized trial, no ulcer recurred in patients who maintained persistent *H. pylori* eradication for one year while the rate of ulcer recurrence after *H. pylori* eradication in ulcer patients was 6.7% to 25.7%.[27] To maintain *H. pylori* eradicated status, it is necessary to know which patients are more likely to have recurrence. In previous studies, underdeveloped country, male gender, low education level, low income, high number of family members, and the presence of peptic ulcer have been found to be risk factors related to *H. pylori* recurrence.[11,28-30]

The present study found that increasing age was an independent risk factor for *H. pylori* recurrence, consistent with a recent study,[31] but inconsistent with others.[32-34] There are a few possibilities to consider in terms of the positive association between advanced age and recurrence rate. First, severe atrophic and metaplastic changes due to increasing age can lead to false negative result on follow-up test after *H. pylori* eradication. Frequent use of proton pump inhibitors also can affect the result of *H. pylori* test. In addition, decreasing compliance due to lack of concern in *H. pylori* eradication and increasing resistance of *H. pylori* to eradication according to advanced age might be possible causes. Recurrence rates are known to be high in young children or adults with intellectual disability in some previous studies.[35-37] This may represent the importance of compliance in terms of maintaining successful eradication status. Lastly, elderly people tend to lack the idea of hygiene and maintain traditional eating habits in Korea. They could be vulnerable to *H. pylori* recurrence compared to younger people.

This is a relatively large-scale cohort study performed in an endemic area of *H. pylori*. Because study subjects were enrolled from a screening cohort of participants who underwent regular follow-up endoscopy and routine urea breath test, results of *H. pylori* tests and follow-up intervals were strongly reliable. Moreover, we identified various clinical conditions including social history, anthropometrics, comorbidity, medication history, and endoscopic findings of cohort subjects. Thus, it could minimize possible confounders. In addition, we performed a follow-up test at least 4–5 weeks after the end of *H. pylori* eradication. Moreover, patients were instructed not to take any antacids during the period from the end of the treatment until the follow-up test of *H. pylori*. This might have increased the accuracy of follow-up tests. Nevertheless, this study had several limitations. First, this was a single-center study of a tertiary cancer center. Therefore, we cannot exclude the possibility of selection bias which could affect *H. pylori* recurrence rate. Multicenter studies to determine whether geographic location is associated with *H. pylori* recurrence rate will help identify the overall recurrence rate of the general population. Second, enrolled subjects voluntarily participated in screening endoscopy. These subjects may have had higher health concerns and better health behaviors or economic status compared to the general population. Third, we did not have data related to self-administration of proton pump inhibitors or antibiotics that could affect *H. pylori* results and underestimate the recurrence rate. Further observations are required to confirm persistent eradication status. Fourth, some patients with recurrence could potentially have had a false negative *H. pylori* test, meaning an eradication failure rather than a recurrence. In addition, patients without recurrence during the study period might be positive in subsequent follow-up, especially in those with short-term intervals. However, because annual follow-up was done and median follow-up period was relatively long, the probability of false negatives can be neglected. Fifth, we routinely performed rapid urease test on screening endoscopy after successful *H. pylori* eradication, some of which may be false negative. However, the sensitivity and specificity of the rapid urease test performed at the greater curvature of the corpus were as high as 96% and 100%, respectively, in our institute.[38] Finally, recrudescence and reinfection could not be clearly distinguished in our study.

CONCLUSION

Annual *H. pylori* recurrence rate is 0.91% in South Korea. Advanced age is at increased risk for *H. pylori* recurrence, and *H. pylori* treatment for patients under 60 years of age was more effective to maintain successful eradication status. In addition, our study implies that additional follow-up tests are required after a confirmation of successful *H. pylori* eradication, especially for elderly patients.

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Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Humans, Schistosomes, liver flukes and *Helicobacter pylori*. IARC Monogr Eval Carcinog Risks Hum 1994;61:1-241.
2. Kuipers EJ, Uyterlinde AM, Pena AS, Roosendaal R, Pals G, Nelis GF, *et al.* Long-term sequelae of *Helicobacter pylori* gastritis. Lancet 1995;345:1525-8.
3. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
4. Hahm MI, Choi KS, Park EC, Kwak MS, Lee HY, Hwang SS. Personal background and cognitive factors as predictors of the intention to

be screened for stomach cancer. Cancer Epidemiol Biomarkers Prev 2008;17:2473-9.
5. Nam JH, Choi IJ, Kook MC, Lee JY, Cho SJ, Nam SY, *et al.* OLGA and OLGIM stage distribution according to age and *Helicobacter pylori* status in the Korean population. Helicobacter 2014;19:81-9.
6. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of *Helicobacter pylori* Infection. Am J Gastroenterol 2017;112:212-39.
7. Kim BJ, Kim HS, Song HJ, Chung IK, Kim GH, Kim BW, *et al.* Online registry for Nationwide Database of Current Trend of *Helicobacter pylori* Eradication in Korea: Interim Analysis. J Korean Med Sci 2016;31:1246-53.
8. Park JS, Park JE, Oh BS, Yoon BW, Kim HK, Lee JW, *et al.* Trend in the eradication rates of *helicobacter pylori* infection over the last 10 years in West Gyeonggi-do, Korea: A single center experience. Korean J Gastroenterol 2017;70:232-8.
9. Pellicano R, Ribaldone DG, Fagoonee S, Astegiano M, Saracco GM, Megraud F. A 2016 panorama of *Helicobacter pylori* infection: Key messages for clinicians. Panminerva Med 2016;58:304-17.
10. Lee JH, Kim N, Chung JI, Kang KP, Lee SH, Park YS, *et al.* Long-term follow up of *Helicobacter pylori* IgG serology after eradication and reinfection rate of H. pylori in South Korea. Helicobacter 2008;13:288-94.
11. Kim MS, Kim N, Kim SE, Jo HJ, Shin CM, Lee SH, *et al.* Long-term follow-up *Helicobacter pylori* reinfection rate and its associated factors in Korea. Helicobacter 2013;18:135-42.
12. Kim SY, Hyun JJ, Jung SW, Koo JS, Yim HJ, Lee SW. *Helicobacter pylori* recurrence after first- and second-line eradication therapy in Korea: The problem of recrudescence or reinfection. Helicobacter 2014;19:202-6.
13. Ryu KH, Yi SY, Na YJ, Baik SJ, Yoon SJ, Jung HS, *et al.* Reinfection rate and endoscopic changes after successful eradication of *Helicobacter pylori*. World J Gastroenterol 2010;16:251-5.
14. Cheon JH, Kim N, Lee DH, Kim JM, Kim JS, Jung HC, *et al.* Long-term outcomes after *Helicobacter pylori* eradication with second-line, bismuth-containing quadruple therapy in Korea. Eur J Gastroenterol Hepatol 2006;18:515-9.
15. Lim SH, Kwon JW, Kim N, Kim GH, Kang JM, Park MJ, *et al.* Prevalence and risk factors of *Helicobacter pylori* infection in Korea: Nationwide multicenter study over 13 years. BMC Gastroenterol 2013;13:104.
16. Yan TL, Hu QD, Zhang Q, Li YM, Liang TB. National rates of *Helicobacter pylori* recurrence are significantly and inversely correlated with human development index. Aliment Pharmacol Ther 2013;37:963-8.
17. Hu Y, Wan JH, Li XY, Zhu Y, Graham DY, Lu NH. Systematic review with meta-analysis: The global recurrence rate of *Helicobacter pylori*. Aliment Pharmacol Ther 2017;46:773-9.
18. Kim MS, Kim N, Kim SE, Jo HJ, Shin CM, Park YS, *et al.* Long-term follow up *Helicobacter Pylori* reinfection rate after second-line treatment: Bismuth-containing quadruple therapy versus moxifloxacin-based triple therapy. BMC Gastroenterol 2013;13:138.
19. Parsonnet J. What is the *Helicobacter pylori* global reinfection rate? Can J Gastroenterol 2003;17(Suppl B):46-8.
20. Gisbert JP. The recurrence of *Helicobacter pylori* infection: Incidence and variables influencing it. A critical review. Am J Gastroenterol 2005;100:2083-99.
21. Plummer M, Franceschi S, Vignat J, Forman D, de Martel C. Global burden of gastric cancer attributable to *Helicobacter pylori*. Int J Cancer 2015;136:487-90.
22. Leja M, Axon A, Brenner H. Epidemiology of *Helicobacter pylori* infection. Helicobacter 2016;21(Suppl 1):3-7.
23. Ito M, Haruma K, Kamada T, Mihara M, Kim S, Kitadai Y, *et al.* *Helicobacter pylori* eradication therapy improves atrophic gastritis and intestinal metaplasia: A 5-year prospective study of patients with atrophic gastritis. Aliment Pharmacol Ther 2002;16:1449-56.
24. Lu B, Chen MT, Fan YH, Liu Y, Meng LN. Effects of *Helicobacter pylori* eradication on atrophic gastritis and intestinal metaplasia: A 3-year follow-up study. World J Gastroenterol 2005;11:6518-20.
25. Wheeldon TU, Hoang TT, Phung DC, Bjorkman A, Granstrom M, Sorberg M. Long-term follow-up of *Helicobacter pylori* eradication therapy in Vietnam: Reinfection and clinical outcome. Aliment Pharmacol Ther 2005;21:1047-53.
26. Rollan A, Giancaspero R, Fuster F, Acevedo C, Figueroa C, Hola K, *et al.* The long-term reinfection rate and the course of duodenal ulcer disease after eradication of *Helicobacter pylori* in a developing country. Am J Gastroenterol 2000;95:50-6.
27. Das R, Sureshkumar S, Sreenath GS, Kate V. Sequential versus concomitant therapy for eradication of *Helicobacter Pylori* in patients with perforated duodenal ulcer: A randomized trial. Saudi J Gastroenterol 2016;22:309-15.
28. McMahon BJ, Bruce MG, Hennessy TW, Bruden DL, Sacco F, Peters H, *et al.* Reinfection after successful eradication of *Helicobacter pylori*: A 2-year prospective study in Alaska Natives. Aliment Pharmacol Ther 2006;23:1215-23.
29. Bruce MG, Bruden DL, Morris JM, Reasonover AL, Sacco F, Hurlburt D, *et al.* Reinfection after successful eradication of *Helicobacter pylori* in three different populations in Alaska. Epidemiol Infect 2015;143:1236-46.
30. Salih BA. *Helicobacter pylori* infection in developing countries: The burden for how long? Saudi J Gastroenterol 2009;15:201-7.
31. Vilaichone RK, Wongcha Um A, Chotivitayatarakorn P. Low re-infection rate of *helicobacter pylori* after successful eradication in Thailand: A 2 years study. Asian Pac J Cancer Prev 2017;18:695-7.
32. Soto G, Bautista CT, Roth DE, Gilman RH, Velapatino B, Ogura M, *et al.* Helicobacter pylori reinfection is common in Peruvian adults after antibiotic eradication therapy. J Infect Dis 2003;188:1263-75.
33. Gomez Rodriguez BJ, Rojas Feria M, Garcia Montes MJ, Romero Castro R, Hergueta Delgado P, Pellicer Bautista FJ, *et al.* Incidence and factors influencing on *Helicobacter pylori* infection recurrence. Rev Esp Enferm Dig 2004;96:620-7.
34. Gisbert JP, Arata IG, Boixeda D, Barba M, Canton R, Plaza AG, *et al.* Role of partner's infection in reinfection after *Helicobacter pylori* eradication. Eur J Gastroenterol Hepatol 2002;14:865-71.
35. Nguyen TV, Bengtsson C, Nguyen GK, Yin L, Hoang TT, Phung DC, *et al.* Age as risk factor for *Helicobacter pylori* recurrence in children in Vietnam. Helicobacter 2012;17:452-7.
36. Sivapalasingam S, Rajasingham A, Macy JT, Friedman CR, Hoekstra RM, Ayers T, *et al.* Recurrence of *Helicobacter pylori* infection in Bolivian children and adults after a population-based "screen and treat" strategy. Helicobacter 2014;19:343-8.
37. Wallace RA, Schluter PJ, Webb PM. Recurrence of *Helicobacter pylori* infection in adults with intellectual disability. Intern Med J 2004;34:131-3.
38. Kim CG, Choi IJ, Lee JY, Cho SJ, Nam BH, Kook MC, *et al.* Biopsy site for detecting *Helicobacter pylori* infection in patients with gastric cancer. J Gastroenterol Hepatol 2009;24:469-74.