

Clinical background factors affecting outcomes of *Helicobacter pylori* eradication therapy in primary care

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Abstract

Objective: Few studies have reported the influence of clinical background factors on the outcome of *Helicobacter pylori* eradication therapy in primary care practice. We aimed to determine which clinical background factors influence the outcome of eradication therapy in a primary care setting.

Methods: This was a retrospective study of patients who received *H pylori* eradication therapy at Higashiohmi City Gamo Medical Center, Shiga, Japan, from January 2012 to December 2015. We investigated clinical background factors associated with success, failure, and self-interruption of *H pylori* eradication therapy: patients' age, gender, first- or second-line treatment, reasons for receiving gastroenterological endoscopic examination, method of drug administration, and attending physicians' age and their specialties.

Results: There were 369 patients (208 females, 161 male), with a mean age of 59 years (range 30-88 years). The middle-aged group (50-69 years) was associated with successful eradication therapy compared with the young group (30-49 years). The elderly group (>70 years) was associated with eradication therapy failure compared with the middle-aged group. The young group was associated with self-interruption of eradication therapy. There was a marginally significant association between male patients and self-interruption. Older attending physicians (>50 years) were also associated with failure compared with younger physicians. There was no difference in outcome of eradication therapy between generalists and gastroenterology specialists.

Conclusion: We have identified clinical factors associated with success, failure, and self-interruption of *H pylori* eradication therapy in a primary care setting.

KEYWORDS

eradication therapy, generalist, *Helicobacter pylori*, patient age, physician age, primary care

1 | INTRODUCTION

Helicobacter pylori infection has attracted attention for its relationship with gastric cancer as well as other upper gastroenterological diseases.^{1,2} Even though eradication therapy causes adverse drug reactions among 4% of patients,³ it can prevent infection from progressing to gastric mucosal atrophy, thereby reducing early-stage gastric cancer.^{4,5} A population-based study has revealed that delays in eradication therapy after peptic ulcer diagnosis increase the risk of recurrent ulcer in a time-dependent manner.⁶ *Helicobacter pylori* eradication therapy can be beneficial in patients with other specific diseases, such as idiopathic thrombocytopenic purpura,⁷ mucosa-associated lymphoid tissue lymphoma,⁸ and iron-deficiency anemia.⁹ Recent studies have also addressed the association between *H pylori* infection and type 2 diabetes mellitus,¹⁰ Parkinson's disease,¹¹ and coronary artery disease.^{12,13} For these reasons, eradication therapy should be recommended/enforced for all patients with *H pylori* infection, for the purpose of preventive medicine.

Helicobacter pylori eradication rates for first-line therapy have clearly decreased in Japan because of increasing clarithromycin (CAM) resistance, which is estimated at 30% among all infected patients.¹⁴⁻¹⁶ To achieve adequate eradication therapy against CAM-resistant *H pylori*, pretreatment testing for CAM sensitivity is recommended.^{17,18} However, routine CAM sensitivity testing for all patients with *H pylori* infection would be difficult because of high clinical costs. Probiotic therapy is reported to improve the efficacy and tolerability of eradication therapy; however, this remains controversial.¹⁹⁻²² Drug adherence and smoking cessation guidance contribute to improvement in the *H pylori* eradication rate without increasing the cost.²³⁻²⁸ However, external evaluation of these methods is difficult.

In daily practice in primary care, physicians assess which clinical background factors affect health outcome of patients, as well as which specific treatments are successful. *Helicobacter pylori* eradication therapy is now an important routine practice among gastroenterological specialists as well as general physicians. However, to our knowledge, few studies have reported the clinical background factors that influence the outcome of eradication therapy in primary care practice. We aimed to establish which clinical background factors contributed to the improvement of clinical outcomes and eradication rate in patients with *H pylori* infection in a primary care setting.

2 | MATERIALS AND METHODS

2.1 | Study design, setting, and participants

We conducted a retrospective study to review medical records of 369 patients who received *H pylori* eradication therapy at Higashiohmi City Gamo Medical Center, Shiga, Japan, from January 2012 to December 2015. The hospital usually provides primary health care with 19 beds in a rural region. Seven physicians including three generalists and four gastroenterology specialists were working at this hospital during the

study period. The study was approved by the Ethics Board of Jichi Medical University, Tochigi, Japan (approved on December 2017; approval acceptance No. 17-089).

2.2 | Measurements

We investigated patients' background factors associated with three clinical outcomes of *H pylori* eradication therapy: (a) success, (b) failure, and (c) self-interruption. We determined successful or unsuccessful outcomes by the result of urea breath test after eradication therapy. The self-interruption patients were defined as those who never received any subsequent examinations to determine the outcome of eradication therapy. Patients' background factors included age, gender, treatment status, reasons for receiving gastroenterological endoscopic examination, method of drug administration, and attending physicians' age and their specialties. We divided age group into three categories: 30-49, 50-69, and ≥ 70 years, which were defined as young, middle-aged, and elderly groups, respectively. Treatment status was defined by first-line or second-line *H pylori* eradication. Reasons for endoscopic examination were classified by whether patients had any symptoms, resulting in three categories: (a) symptomatic complaints, (b) regular checkup, and (c) referral checkup from other facilities. Symptoms included epigastralgia, indigestion, heartburn, nausea, difficulty swallowing, and melena. Regular checkup included examination requests from regularly attending patients themselves. Referral checkup included referrals from other medical or governmental facilities for advanced examination of any abnormal findings. Drug administration methods were dichotomized into packed or nonpacked formulations. Attending physicians' factors were categorized by age (<50 or ≥ 50 years) and their specialties (gastroenterologist or generalist).

2.3 | Statistical analysis

All analyses were performed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA). Descriptive statistics of the participants were mean \pm SD for age, and proportion for all other variables. We conducted logistic regression analyses to determine factors associated with each of the three clinical outcomes. Using univariate analysis, crude odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for all factors. Adjusted ORs (95% CIs) were then obtained, adjusting for all variables. We applied the minimum ORs for each factor as references (ORs = 1) so that the results could be interpreted clearly.

3 | RESULTS

3.1 | Basic characteristics of the study participants

Basic characteristics of all 369 participants are shown in Table 1. Mean age of all patients was 59 ± 12 (range 30-88) years, and mean age of men and women was 58 ± 13 (30-83) and 60 ± 11 (31-88) years, respectively. The percentages of patients by age group 30-49, 50-69,

TABLE 1 Basic characteristic of all 369 participants

	All patients (N = 369) (%)	Success (n = 292) (%)	Failure (n = 55) (%)	Self-interruption (n = 22) (%)
Age (mean ± SD), y	59 ± 12	60 ± 11	57 ± 15	48 ± 13
30-49: Young aged	87 (24)	56 (19)	16 (29)	15 (68)
50-69: Middle aged	207 (56)	178 (61)	23 (42)	6 (27)
≥70: Elderly	75 (20)	58 (20)	16 (29)	1 (5)
Gender				
Male	161 (44)	123 (42)	24 (44)	14 (64)
Female	208 (56)	169 (58)	31 (56)	8 (36)
Treatments				
First-line	320 (87)	252 (86)	50 (91)	18 (82)
Second-line	49 (13)	40 (14)	5 (9)	4 (18)
Reasons for endoscopic examination				
Symptomatic complaints	56 (15)	41 (14)	8 (15)	7 (32)
Asymptomatic reasons (n = 313) ^a				
Regular checkup	174 (56)	143 (57)	27 (57)	4 (27)
Referral checkup	139 (44)	108 (43)	20 (43)	11 (73)
Medication				
Pack formulation	305 (83)	239 (82)	49 (89)	17 (77)
Nonpack formulation	64 (17)	53 (18)	6 (11)	5 (23)
Attending physicians' Factor				
Age				
<50	253 (69)	207 (71)	29 (53)	17 (77)
≥50	116 (31)	85 (29)	26 (47)	5 (23)
Specialty				
Gastroenterologist	278 (75)	217 (74)	46 (84)	15 (68)
Generalist	91 (25)	75 (26)	9 (16)	7 (32)

SD, standard deviation.

^aExcluding patients who received endoscopic examination with any symptoms.

and ≥ 70 years were 24%, 56%, and 20%, respectively. Fifty-six percent of patients were female, and 87% received first-line therapy. Fifteen percent of patients received endoscopic examination for any symptomatic complaints. Packed formulation drugs were prescribed for 83% patients. With regard to the attending physicians, 69% were aged < 50 years, and 75% were gastroenterological specialists.

All patients were treated by proton pump inhibitor (PPI) with CAM and amoxicillin, or PPI with amoxicillin and metronidazole. None used vonoprazan. The eradication rate was 79% for first-line therapy and 82% for second-line therapy. Successful eradication rates by age group were 64%, 86%, and 77% for 30-49, 50-69, and ≥ 70 years, respectively. The rates for men and women were 76% and 81%, respectively. Compared with older patients, younger patients had a higher proportion of those with any symptomatic complaints, resulting in detection of *H pylori* infection and administration of eradication therapy. In contrast, older patients, especially middle-aged patients, had a higher proportion of those who received endoscopic examination for medical checkup.

3.2 | Factors associated with clinical outcomes

Factors associated with successful outcome of eradication therapy are shown in Table 2. The middle-aged group was associated with successful eradication therapy in univariate logistic regression analysis (crude OR = 3.4; 95% CI = 1.8-6.8), compared with the young group. This association was also significant in multivariate analysis after adjusting for all the factors (adjusted OR = 3.5; 95% CI = 1.8-6.8).

Table 3 shows factors associated with failure of eradication therapy. The elderly group was associated with failure in both univariate (crude OR = 2.2, 95% CI = 1.1-4.4) and multivariate (adjusted OR = 2.2, 95% CI = 1.1-4.7) logistic regression analyses, compared with a reference middle-aged group. Older attending physicians (>50 years) were also associated with failure in both univariate (crude OR = 2.2, 95% CI = 1.2-4.0) and multivariate (adjusted OR = 2.2, 95% CI = 1.2-4.0) analyses, compared with younger physicians.

TABLE 2 Factors associated with successful eradication therapy (n = 292)

	Crude OR (95% CI)	Adjusted ^a OR (95% CI)
Age (mean ± SD), y		
30-49: Young aged	1 (Reference)	1 (Reference)
50-69: Middle aged	3.4 (1.9-6.1)	3.5 (1.8-6.8)
≥70: Elderly	1.9 (0.94-3.8)	1.9 (0.85-4.2)
Gender		
Male	1 (Reference)	1 (Reference)
Female	1.3 (0.81-2.2)	1.2 (0.71-2.0)
Treatments		
First-line	1 (Reference)	1 (Reference)
Second-line	1.2 (0.56-2.6)	1.4 (0.62-3.3)
Reasons for endoscopic examination		
Symptomatic complaints	1 (Reference)	1 (Reference)
Regular checkup	1.7 (0.83-3.4)	1.1 (0.45-2.5)
Referral checkup	1.3 (0.62-2.6)	0.82 (0.37-1.8)
Medication		
Pack formulation	1 (Reference)	1 (Reference)
Nonpack formulation	1.3 (0.66-2.7)	1.1 (0.49-2.5)
Attending physicians' Factor		
Age		
<50	1.6 (0.98-2.8)	1.7 (0.95-2.9)
≥50	1 (Reference)	1 (Reference)
Specialty		
Gastroenterologist	1 (Reference)	1 (Reference)
Generalist	1.3 (0.72-2.4)	1.3 (0.64-2.6)

CI, confidence interval; OR, odds ratio; SD, standard deviation.

^aAdjusted for all variables.

Table 4 shows factors associated with self-interruption of eradication therapy. The young group was associated with self-interruption outcome in both univariate (crude OR = 15, 95% CI = 2.0-120) and multivariate (adjusted OR = 11, 95% CI = 1.2-89) logistic regression analyses, compared with older groups. Although symptomatic patients were associated with the self-interruption outcome in univariate analysis (crude OR = 6.1, 95% CI = 1.7-22), the association was not significant after adjusting in multivariate analysis. There was a marginally significant association between male patients and self-interruption.

The specialty of the attending physicians had no significant associations with all three outcomes of *H pylori* eradication therapy.

4 | DISCUSSION

Our results indicated that the middle-aged group compared with other age groups was significantly associated with successful

TABLE 3 Factors associated eradication therapy failure (n = 55)

	Crude OR (95% CI)	Adjusted ^a OR (95% CI)
Age (mean ± SD), y		
30-49: Young aged	1.8 (0.90-3.6)	2.1 (0.97-4.7)
50-69: Middle aged	1 (Reference)	1 (Reference)
≥70: Elderly	2.2 (1.1-4.4)	2.2 (1.1-4.7)
Gender		
Male	1 (0.56-1.8)	0.9 (0.49-1.6)
Female	1 (Reference)	1 (Reference)
Treatments		
First-line	1.6 (0.62-4.3)	1.9 (0.69-5.4)
Second-line	1 (Reference)	1 (Reference)
Reasons for endoscopic examination		
Symptomatic complaints	1 (Reference)	1 (Reference)
Regular checkup	1.1 (0.47-2.6)	1.3 (0.45-3.5)
Referral checkup	1 (0.42-2.4)	1.4 (0.52-3.6)
Medication		
Pack formulation	1.9 (0.76-4.5)	1.2 (0.43-3.1)
Nonpack formulation	1 (Reference)	1 (Reference)
Attending physicians' factor		
Age		
<50	1 (Reference)	1 (Reference)
≥50	2.2 (1.2-4.0)	2.2 (1.2-4.0)
Specialty		
Gastroenterologist	1.8 (0.85-3.9)	1.5 (0.63-3.4)
Generalist	1 (Reference)	1 (Reference)

CI, confidence interval; OR, odds ratio; SD, standard deviation.

^aAdjusted for all variables.

eradication therapy even after adjusting for other factors. Middle-aged patients may have been more motivated than other-aged patients because they received eradication therapy via recommendation from their health checkup results more often than other-aged patients did. Additionally, middle-aged patients are usually less likely to forget to take their medication compared with older patients. This is supported by previous studies that have reported that "forgetting to take the drug" was one of the factors involved in treatment failure.²⁶ This supports our finding that patients aged >70 years were associated with failure of eradication therapy even after adjusting for other factors.

Our study indicated that failure of eradication therapy was affected by attending physicians' factors as well as patients' factors. Our results showed that older attending physicians (>50 years) were associated with failure. Tsugawa et al²⁹ investigated the association between 30-day mortality rates and healthcare costs in acute care hospitals, and found that mortality rates were higher among older physicians, which is similar to our results. We did not assess the length of time spent explaining the eradication therapy and the drug

TABLE 4 Factors associated with self-interruption of the eradication therapy (n = 22)

	Crude OR (95% CI)	Adjusted ^a OR (95% CI)
Age (mean ± SD), y		
30-49: Young aged	15 (2.0-120)	11 (1.2-89)
50-69: Middle aged	2.2 (0.26-19)	2.1 (0.24-18)
≥70: Elderly	1 (Reference)	1 (Reference)
Gender		
Male	2.4 (0.97-5.8)	2.4 (0.92-6.1)
Female	1 (Reference)	1 (Reference)
Treatments		
First-line	1 (Reference)	1 (Reference)
Second-line	1.5 (0.48-4.6)	1.4 (0.39-5.2)
Reasons for endoscopic examination		
Symptomatic complaints	6.1 (1.7-22)	2.4 (0.55-10)
Regular checkup	1 (Reference)	1 (Reference)
Referral checkup	3.7 (1.1-12)	2.3 (0.65-7.9)
Medication		
Pack formulation	1 (Reference)	1 (Reference)
Nonpack formulation	1.4 (0.51-4.0)	0.94 (0.27-3.3)
Attending physicians' Factor		
Age		
<50	1.6 (0.58-4.4)	1.6 (0.53-4.8)
≥50	1 (Reference)	1 (Reference)
Specialty		
Gastroenterologist	1 (Reference)	1 (Reference)
Generalist	1.5 (0.58-3.7)	0.97 (0.32-2.9)

CI, confidence interval; OR, odds ratio; SD, standard deviation.

^aAdjusted for all variables.

regimen. Given that patients prefer experienced physicians with a long career path, older physicians may have less time for each patient, resulting in insufficient explanation of eradication therapy, which may adversely affect outcome.

Our results indicated that elderly patients aged >70 years were at high risk for *H pylori* eradication therapy failure compared with other-aged patients. Elderly patients generally have many medications prescribed, often suffer from cognitive decline, and frequently have physical limitations, which would affect their medication compliance and possibly result in unsuccessful outcome of therapies.³⁰ Nevertheless, Mamori et al³¹ previously investigated the general risk factors that affected outcome of eradication therapy in Japanese patients, and found that the success rate in patients aged >70 years were over 90%, which was higher than those in younger-aged groups. This report was contrary to our findings. Our study included patients aged >70 years more than those in the previous study, which might lead to the opposite results. Older attending physicians

(>50 years) might be mostly assigned to elderly patients in our study, which could confound the results. Study setting might influence the results; our study was conducted in a small hospital located in a rural region. Further study is required to assess whether the differences would occur related to patients' characteristics as well as study settings, using a large-scale dataset.

Physicians would like to avoid self-interruption of *H pylori* eradication therapy by patients because of the increased chance of *H pylori* acquiring resistance to other antibiotics. Our results showed that self-interruption was common in young patients who did not attend regular hospital visits for other underlying diseases. The need for regular hospital visits for other underlying diseases generally increases with age; therefore, regular visiting might reduce self-interruption of eradication therapy in older patients. In patients with more serious underlying diseases, such as tuberculosis or human immunodeficiency virus (HIV) infection, regular hospital visits would result in more successful treatment outcome. Conversely, those who do not have regular hospital visits are associated with a high risk of self-interruption, resulting in treatment failure.³²⁻³⁴ It has also been shown that younger age is a risk factor for unsuccessful clinical outcomes among HIV patients.³⁵ Our study found that young patients usually visited the hospital with symptoms such as epigastralgia. Young patients might have self-interrupted eradication therapy because their symptoms ceased shortly after taking PPIs, which resulted in an unsuccessful outcome.

Aggressive intervention that aims to increase compliance in younger patients could improve the successful outcome of eradication therapy. Eidan et al²³ reported that regular counseling and follow-up of patients were effective in eradication therapy. Other studies have also reported that human interventions have played a major role in successful eradication, such as enhanced compliance programs,³⁶ and other regular counseling for treatment.²³ Especially among younger patients, *H pylori* eradication therapy should aim to increase compliance with careful follow-up and aggressive intervention.

In 1996, Hirth et al³⁷ compared the outcomes of *H pylori* eradication therapy between generalists and gastroenterologists. They concluded that eradication therapy was not provided appropriately by generalists compared with gastroenterologists at that time.³⁷ However, >20 years have passed since then, and eradication therapy is now an important routine practice even among generalists.³⁸ In our study, no difference was found between generalists and gastroenterologists in the outcome of eradication therapy. Given that patients' compliance affects the results of eradication therapy, generalists could achieve comparable or better outcomes than gastroenterological specialists. Another previous study reported that medical specialists and generalists served different primary care roles for different populations, and found that generalists saw younger patients most often for new problems, compared with specialists.³⁹ Generalists may influence younger patients to refrain from self-interruption of eradication therapy more often than gastroenterologists do.

Our study had four major limitations. The primary limitation was the small sample size with a limited number of attending

physicians, which could have caused beta errors in the statistical analyses. Furthermore, the study was conducted in a small medical institution that mainly acts as a primary healthcare provider in a rural area in Japan, which may have distorted the validity of the results. The number of physicians who prescribed the eradication therapy was small and had a gender bias (all male); that is, the results might have been affected by selection bias. In addition, the results may have been influenced by unknown confounding factors. A larger sample with more patients and physicians is needed for more accurate investigation. Second, the study could have assessed other factors that were previously reported to affect outcome of eradication therapy, such as smoking, alcohol use, and use of combined probiotics.^{19–21,28} These factors could not be controlled because we conducted a retrospective review of the patients' medical records. Third, drug adherence was insufficiently assessed because we could not establish whether they had forgotten to take the drugs. Based on these limitations, a prospective study is required to strengthen our results.

Finally, self-interruption would be rather included in unsuccessful outcome in *H pylori* eradication therapy. However, self-interruption patients included both those could hardly manage their medication by themselves and those could not help quitting the therapy because of severe side effects. For this reason, we defined self-interruption as an independent outcome. On the other hand, success and failure are opposite each other; therefore, either might be enough to show the results. Nevertheless, we show both so that they could be interpreted clearly. A reciprocal relationship was just found in odds ratio of all the relevant factors between successful and unsuccessful outcomes, and the significant factors were consistent. Although there was a marginally significant association between successful outcome and older attending physicians (>50 years), this might be influenced by a small study sample. Our result would be valid, but this is a limitation of the study.

5 | CONCLUSIONS

This study revealed clinical background factors associated with successful and unsuccessful outcome of *H pylori* eradication therapy in a primary care setting. Middle-aged patients (50–69 years) had the most successful eradication therapy compared with other age groups. Failure was associated with elderly patients (≥70 years) and older attending physicians (≥50 years). Self-interruption was common in young patients. No difference was found between generalists and gastroenterological specialists for outcome of eradication therapy. In primary care practice, generalists may play an important role in prevention of self-interruption of *H pylori* eradication therapy among young patients, as well as failure among elderly patients.

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CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

AUTHORS' CONTRIBUTIONS

NY, KK, and MA contributed to study concept and design; NY, KK, MA, TN, TY, and KM involved in acquisition of data; NY, RA, TS, and YN contributed to analysis and interpretation of data; NY, RA, YN, YM, and KK involved in manuscript preparation; all authors have approved the manuscript for submission.

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