

Long-term effects and benefits of *Helicobacter pylori* eradication on the gastric mucosa in older individuals

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Abstract

Background: The current international consensus report indicated that all *Helicobacter pylori* (*H. pylori*)-positive patients should be treated. This study aimed to evaluate the long-term effects and benefits of *H. pylori* eradication on the gastric mucosa in the elderly population.

Methods: We performed a retrospective cohort study with 311 individuals aged ≥ 60 years, including 83 with persistent *H. pylori* infection (persistent group), 128 with successful *H. pylori* eradication (eradicated group), and 100 without *H. pylori* infection (control group). The results of endoscopy and mucosal histology were investigated at baseline and followed up for 5 and 10 years.

Results: In the 5 to 10-year follow-up, there was a significant difference in the atrophy score among the three groups ($P < 0.001$); however, no significant difference was observed in the intestinal metaplasia (IM) score ($P > 0.05$). There was no significant difference in the cumulative incidence of gastric neoplastic lesion (GNL) between the eradicated and persistent groups during the 5 to 10-year follow-up period ($P > 0.05$). The baseline IM score of patients with GNL was significantly higher than that of those without GNL in the eradicated and control groups ($P < 0.05$). In all patients with GNL, the mean interval time between baseline and diagnosis of GNL was more than 6 years. The severity of baseline mucosal IM (odds ratio: OR 3.092, 95% confidence interval [CI]: 1.690–5.655, $P < 0.001$) and *H. pylori* infection (OR: 2.413, 95%CI: 1.019–5.712, $P = 0.045$) significantly increased the risk for GNL.

Conclusions: Older patients with a life expectancy of less than 5 to 10 years, especially those with moderate to severe gastric mucosal IM, may not benefit from the eradication of *H. pylori* to prevent gastric cancer.

Keywords: Atrophy, elderly, *Helicobacter pylori*, intestinal metaplasia, life expectancy

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INTRODUCTION


With an aging population, increasing attention has been paid to the prevention and treatment of cancer. As a promoter of gastric carcinogenesis, the World Health

Organization has categorized *Helicobacter pylori* (*H. pylori*) as a class I carcinogen for gastric cancer in 1994.^[1] *H. pylori* infection is considered a global public health problem. Older individuals aged over 60 years have the highest

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infection rate,^[2] and the infection rate of *H. pylori* in the older population in Shanghai, China, is as high as 72.4%.^[3]

Given the risk of *H. pylori* infection, the current international consensus report indicated that all *H. pylori*-positive patients should be treated.^[1,4,5] In areas with a high incidence of gastric cancer, especially in high-risk individuals, the “test and treat” strategy for *H. pylori* infection is recommended. *H. pylori* gastritis is an infectious disease.^[1,4] Still, there is no upper age limit for *H. pylori* eradication therapy. The older population, especially senior patients (aged ≥ 80 years), have a higher number of comorbidities, usage of medications, prevalence of atrophy and intestinal metaplasia (IM) (89% and 82%, respectively), or a combination of these factors.^[6] In addition, because of the positive correlation between life expectancy and incidence of cancer,^[7] the previous literature and international consensus reported that age alone is not sufficient to determine the appropriateness of screening and treatment. In particular, individuals who have a life expectancy of less than 5 years will not benefit from cancer screening.^[8] Thus, the potential benefits of *H. pylori* eradication in older patients for the prevention of

gastric cancer may be reduced. However, it remains unclear whether *H. pylori* eradication therapy should be carried out in older patients.^[9] At present, there is no consensus on the treatment of *H. pylori* infection in older adults, and only a few studies reported the impact of eradication treatment in older individuals.^[2,10] Hence, this study aimed to evaluate the long-term effects and benefits of *H. pylori* eradication on the gastric mucosa in older individuals.

SUBJECTS AND METHODS

Study patients

From January 2007 to December 2009, as a result of a screening program for early detection of gastric cancer in the elderly aged ≥ 60 years, 3,671 individuals who underwent esophagogastroduodenoscopy (EGD) due to digestive diseases or routine health screening examinations were registered in Huadong Hospital Affiliated to Fudan University. Of these patients, 3,028 were investigated for their *H. pylori* status, and 1,636 were confirmed to have an active *H. pylori* infection (baseline investigation). These patients were informed about the increased risk of GC associated with *H. pylori* and about the need to undergo

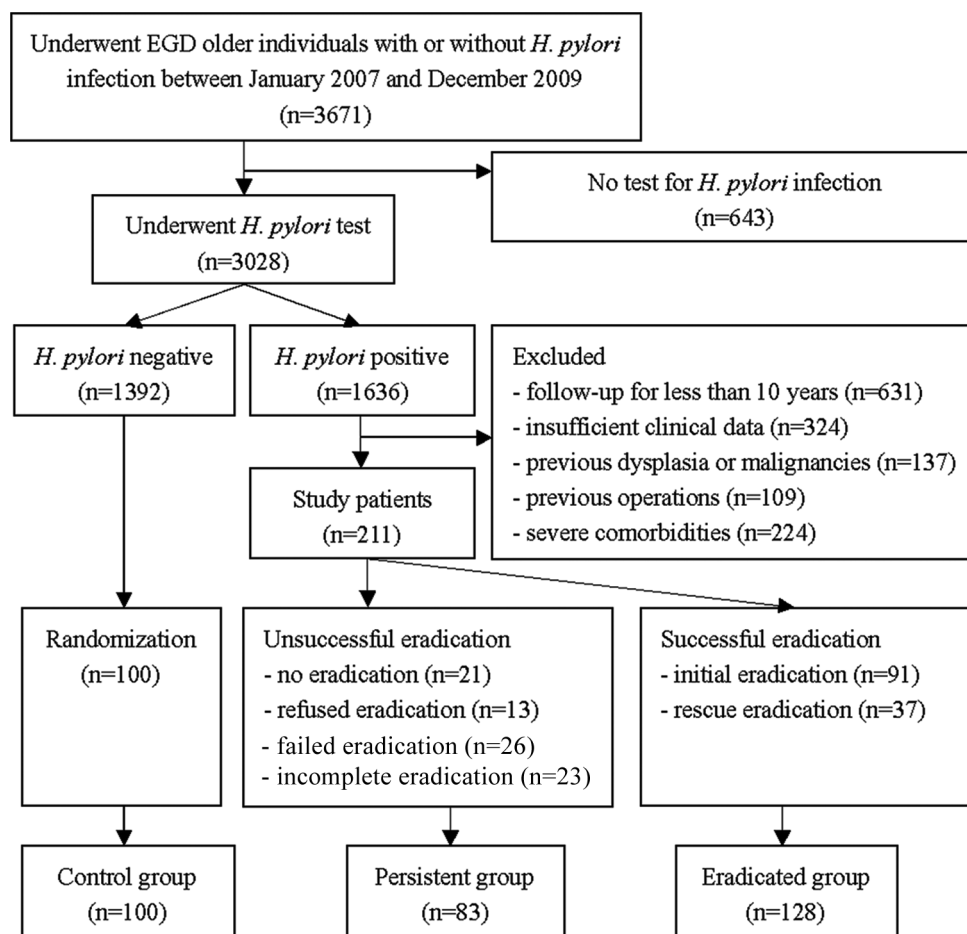


Figure 1: Flow of study patients. EGD: oesophagogastroduodenoscopy; *H. pylori*: *Helicobacter pylori*

regular endoscopic histological follow-up investigations, at intervals not exceeding 3 years. The following inclusion criteria were used to enroll these individuals within the screening program: 1. age over 60 years, 2. long-term follow-up data on results of the ^{13}C -urea breath test, EGD, and pathological examination, 3. a follow-up period of at least 10 years. Exclusion criteria included patients with 1. severe comorbidities (such as heart, lung, and other organic diseases); 2. prior dysplasia of the gastric mucosa and malignancies, or who underwent surgery, radiation, and chemical treatment; 3. cognitive behavior abnormalities who were unable to communicate and cooperate with related examinations; 4. follow-up loss. Therefore, 211 *H. pylori*-positive patients were enrolled in this study. All of them were divided into two groups according to *H. pylori* infection status, diagnosis, and treatment history: 1. persistent group ($n = 83$ patients), with 21 having *H. pylori* infection without treatment, 13 who refused treatment, 26 who experienced treatment failure, and 23 who had incomplete eradication; and 2. eradicated group ($n = 128$), with 91 who received initial treatment for eradication and 37 with remedial treatment for eradication, and with none of the patients experiencing reinfection. A total of 100 older subjects with no history of *H. pylori* infection were randomly selected as the control group in the same period [Figure 1]. General demographic and medical history data were obtained by reviewing outpatient and inpatient medical records, as well as through a telephone interview. This study was designed as a retrospective cohort study. The Ethics Committee of Huadong Hospital Affiliated with Fudan University approved this study (number: 2017K039), and all participants provided written informed consent.

EGD and pathological examination

According to mucosal manifestations, two pieces of mucosal

tissues were obtained from the gastric antrum (from the lesser curvature of the antrum within 2 to 3 cm of the pylorus) and one piece of mucosal tissue from the gastric body (from the greater curvature of the middle of the gastric body). Samples were fixed, embedded, sectioned, and stained by modified Giemsa for mucosal histological examination and *H. pylori* diagnosis. The results of EGD and mucosal histology in 311 patients were investigated at baseline and followed up for 5 and 10 years. Pathological analysis was performed by an experienced pathologist who was blinded to the clinical information. Histopathological changes (inflammation, activity, atrophy, and IM), based on the visual analog scale of the updated Sydney System, were graded (none = 0, mild = 1, moderate = 2, and severe = 3).^[11] The mean scores of the above two sites of each individual were recorded. Follow-up endoscopic examinations were performed to identify any gastric neoplastic lesion (GNL). A GNL was defined as a new adenocarcinoma, adenoma with dysplasia, or dysplasia without endoscopic lesions.

Detection of *H. pylori* infection

H. pylori infection was diagnosed when the ^{13}C -UBT, rapid urease test, or histologic examination result was positive. When the ^{13}C -UBT result was negative, a diagnosis of no *H. pylori* infection was established.^[5]

Statistical analysis

Statistical analysis was performed using SPSS version 22.0. The measurement data are expressed as mean \pm SD and analyzed using Student's *t*-test, one-way analysis of variance, or Wilcoxon's rank-sum test. Categorical data were analyzed using the Chi-square test or Fisher's exact test. The cumulative incidence of GNL was calculated using the Kaplan–Meier method, and the values among

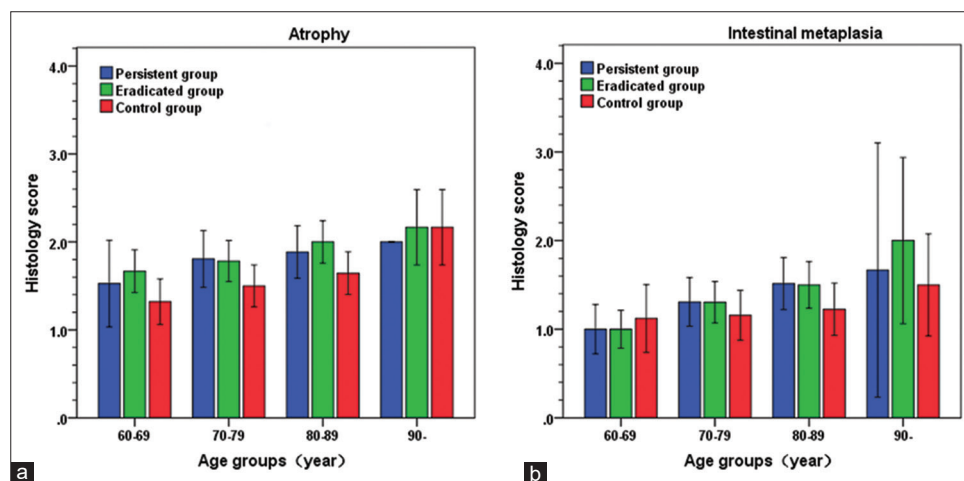


Figure 2: Relationship between age and the histopathological score of gastric mucosa in all groups. (a) Atrophy scores; (b) Intestinal metaplasia scores

Table 1: Baseline characteristics of all groups

	Persistent group (n=83)	Eradicated group (n=128)	Control group (n=100)	Statistic	P
Median age (y)	76.82±8.419	75.52±8.655	75.12±8.790	F=0.946	0.389
Sex (M: F)	51:32	75:53	53:47	$\chi^2=1.420$	0.492
Follow-up time (y)	11.28±1.079	11.06±1.070	11.01±1.115	F=1.506	0.223

y: years; M: male; F: female

Table 2: Kaplan-Meier survival analysis for the cumulative incidence of GNL in all groups

	Cumulative proportion incidence (n of cumulative events) at the time (y)									
	1	2	3	4	5	6	7	8	9	10
Persistent group (n=83)	0% (0)	1.2% (1)	1.2% (1)	3.6% (3)	4.8% (4)	4.8% (4)	6.0% (5)	10.8% (9)	12.0% (10)	13.3% (11)
Eradicated group (n=128)	0% (0)	0% (0)	0.8% (1)	0.8% (1)	1.6% (2)	3.9% (5)	3.9% (5)	6.2% (8)	6.2% (8)	7.8% (10)
Control group (n=100)	0% (0)	0% (0)	1.0% (1)	1.0% (1)	1.0% (1)	2.0% (2)	2.0% (2)	3.0% (3)	4.0% (4)	5.0% (5)

GNL: gastric neoplastic lesion; n: number; y: years.

the groups were compared using the log-rank test. Risk factors of GNL were examined by multivariate analysis using the logistic regression model. *P* values < 0.05 were considered significant.

RESULTS

General information

A total of 311 older patients were enrolled in the study. Patients were aged 60 to 90 years, of whom 121 (38.9%) were senior patients (aged ≥80 years). At baseline and all follow-up investigations no cases of loss of visit and death occurred. There was no significant difference in the distribution of age, sex, and follow-up time among the three groups (*P* > 0.05) [Table 1].

Age, sex, and gastric mucosa histopathological score

At baseline, mild-to-moderate gastric mucosal lesions were detected in the patients in all age groups. It was also noted that the scores of gastric mucosal atrophy and IM increased with age. The IM scores in the eradicated group and the atrophy scores in the control group were significantly

increased in all age groups ($\chi^2 = 11.999$, *P* = 0.007; $\chi^2 = 8.303$, *P* = 0.04, respectively). At baseline, the scores of gastric mucosa atrophy and IM in the three groups were not correlated with sex (data not shown), and the differences were not statistically significant (*P* > 0.05) [Figure 2].

Follow-up time and gastric mucosa histopathological score

At baseline, the scores of gastric mucosal atrophy and IM in the persistent group were similar to those in the eradicated group (*Z* = -0.448, *P* = 0.654; *Z* = -0.384, *P* = 0.701). These scores were higher than those in the control group (*Z* = -2.172, *P* = 0.030; *Z* = -3.466, *P* = 0.001). In the 5-year follow-up, the atrophy and IM scores in the eradicated group decreased by 0.183 points (*Z* = -2.669, *P* = 0.008) and 0.013 points (*Z* = -0.033, *P* = 0.974), respectively, compared with those at baseline. Moreover, there was a more significant improvement in atrophy scores compared with IM scores in the eradicated group (*Z* = -6.895, *P* < 0.001). There was a statistically significant difference in the atrophy score among the three groups ($\chi^2 = 16.768$, *P* < 0.001), but no significant

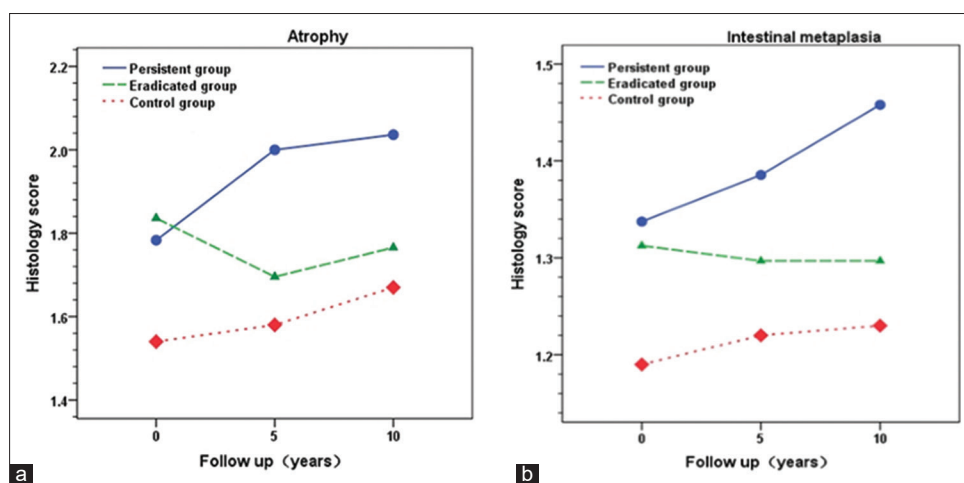


Figure 3: Relationship between the follow-up time and histopathological score of gastric mucosa in all groups. (a) Atrophy scores; (b) Intestinal metaplasia scores

Table 3: Comparison of clinicopathological features between individuals with and without GNL in all groups

	Persistent group		P	Eradicated group		P	Control group		P
	GNL negative (n=72)	GNL positive (n=11)		GNL negative (n=118)	GNL positive (n=10)		GNL negative (n=95)	GNL positive (n=5)	
Median age (y)	76.97±8.53	75.82±7.91	0.676	75.63±8.70	74.30±8.39	0.710	75.10±8.88	75.50±7.79	0.649
Sex (M: F)	44:28	7:4	0.873	79:39	6:4	0.922	60:35	4:1	0.848
Median interval (y)	/	6.64±2.50	/	/	7.00±2.21	/	/	7.67±2.25	/
Baseline gastric mucosa									
Atrophy	1.82±0.87	1.833±0.90	0.994	1.80±0.91	1.890±0.74	0.781	1.521±0.66	1.83±0.98	0.487
IM	1.319±0.78	1.45±0.52	0.611	1.246±0.77	2.10±0.56	0.001	1.149±0.84	2.00±0.00	0.009

GNL: gastric neoplastic lesion; y: years; M: male; F: female; IM: intestinal metaplasia.

difference in the IM score ($\chi^2 = 3.070$, $P = 0.215$). In the 10-year follow-up, the atrophy score of the three groups was higher than that in the 5-year follow-up, the difference among the three groups was statistically significant ($\chi^2 = 15.401$, $P < 0.001$). The IM score was not significantly different among the three groups ($\chi^2 = 5.320$, $P = 0.070$). The atrophy and IM scores of the three groups were compared with their respective scores at baseline, and the differences were not statistically significant ($P > 0.05$) [Figure 3].

Cumulative incidence of GNL

At the 5-year follow-up, four patients (4.82%) in the persistent group, two (1.56%) in the eradicated group, and one (1%) in the control group developed GNL. At the 10-year follow-up, 11 patients (13.25%) in the persistent group, 10 (7.81%) in the eradicated group, and 5 (5%) in the control group developed GNL. There was no significant difference in the cumulative incidence of GNL among the three groups ($\chi^2 = 4.190$, $P = 0.123$) [Figure 4, Table 2].

Clinicopathological features of patients with GNL

Among the three groups, the baseline gastric mucosal atrophy score of the patients with GNL was slightly higher than those without ($P > 0.05$). The baseline IM score of patients with GNL was significantly higher than those without ($P < 0.05$) (except for the persistent group). In contrast, the average severity of IM of patients with GNL was moderate or high. In all patients with GNL, the median interval time between baseline and diagnosis of GNL was more than 6 years; there was no significant difference among the three subgroups with GNL ($F = 0.375$, $P = 0.691$). No significant difference was observed in other clinical characteristics, including age and sex, between the patients with and without GNL in each group ($P > 0.05$) [Table 3].

Table 4: Results of multivariate logistic regression analysis of risk factors for GNL

Risk factors	β	Wald	OR	95%CI	P
Baseline mucosal IM	1.129	13.425	3.092	1.690-5.655	<0.001
<i>H. pylori</i> infection	0.881	4.013	2.413	1.019-5.712	0.045

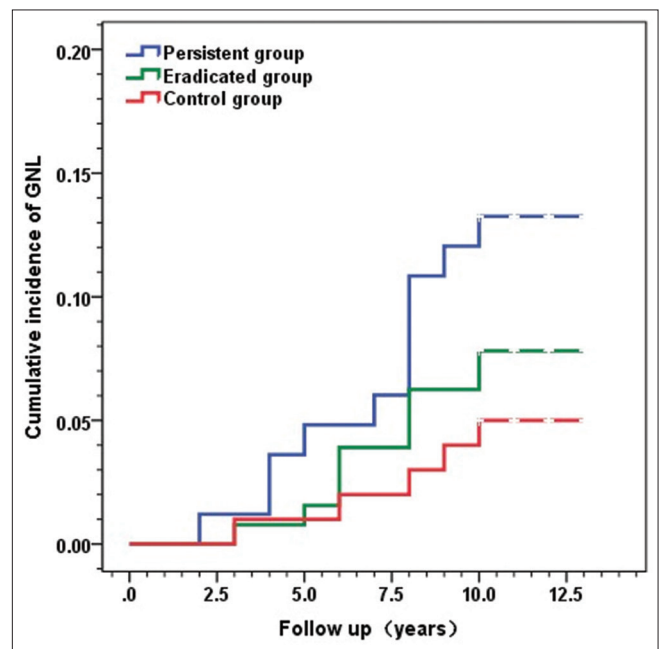
β : coefficient; OR: odds ratio; CI: confidence interval; IM: intestinal metaplasia; *H. pylori*: *Helicobacter pylori*.

Factors related to GNL

A multivariate logistic regression model was used to analyze the risk factors for GNL, including age, sex, follow-up time, the severity of baseline mucosal atrophy, and IM. Results showed that the severity of baseline mucosal IM (odds ratio [OR]: 3.092, 95% confidence interval [CI]: 1.690–5.655, $P < 0.001$) and *H. pylori* infection (OR: 2.413, 95% CI: 1.019–5.712, $P = 0.045$) significantly increased the risk for GNL, but it had no correlation with age, sex, follow-up time, and the severity of baseline mucosal atrophy ($P > 0.05$) [Table 4].

DISCUSSION

In older individuals, *H. pylori* infection is mostly acquired during childhood,^[12] and the proportion of people with normal gastric mucosa decreases (approximately 50%) with age.^[13] Our investigation showed that over 10 years, older patients generally develop mild-to-moderate gastric mucosal lesions and higher atrophy and IM scores

**Figure 4: Kaplan–Meier analysis of the cumulative incidence of GNL in all groups. GNL: gastric neoplastic lesion**

compared with younger patients, even in the control group; these differences were found to be regardless of sex. This trend is not only related to *H. pylori* infection but also shows that the extent of gastric mucosal aging and atrophy varies and is age-dependent.^[13,14] This conclusion is slightly different from the results of previous Japanese studies. Asaka showed that *H. pylori* infection, rather than aging itself, caused atrophic gastritis and IM.^[15] However, in *H. pylori*-positive individuals, both atrophy and IM were aggravated by aging.^[16]

The benefit of *H. pylori* eradication may be related to the length of the follow-up period.^[17] A 12-year randomized controlled study in high-risk areas showed that *H. pylori* eradication had a significant effect on the repair of precancerous gastric lesions, which was cumulative and enhanced over time.^[18] Our results showed that the severity of atrophy and IM gradually increased in the persistent *H. pylori* infection group during the disease, whereas it decreased in the eradicated group. At the 5-year follow-up, the reduction in atrophy was more evident than that of IM, showing the expected curative effect and indicating that eradication of *H. pylori* in older patients may have more benefit in individuals with atrophy at baseline than in those with IM within a short period (<5 years). This finding is consistent with the results of Mera.^[19] However, long-term (≥5–10 years) efficacy showed no cumulative improvement effect on atrophy. On the contrary, the severity of atrophy gradually increased, especially in the control group, and the severity of atrophy and IM also showed a slow upward trend. This phenomenon indicates that with the prolonged course of the disease, even without *H. pylori* infection, the risk of bile reflux, and exposure to environmental factors (drugs, food, and tobacco) as well as the socioeconomic status will also significantly increase in older patients, which can lead to further chronic injury of the gastric mucosa, lamina propria glandular atrophy, and IM.^[20,21]

In this study, improvement in the IM score in the eradication group was relatively gradual during the follow-up period, which confirmed that the recovery of IM is a long-term process.^[18] The eradication of *H. pylori* can at least prevent further development of IM; because its molecular regulatory mechanism may be different from atrophy, the change in IM after eradication of *H. pylori* may not be related to the latter.^[22]

According to a previous study,^[23] in addition to *H. pylori* infection (*HR* = 3.9), the severity of basic gastric mucosal atrophy (*HR* = 3.9) is also a primary contributor to the risk of gastric cancer. We have similar findings in the

baseline gastric mucosal survey of patients with GNL. In the eradicated group, even if the effect of *H. pylori* was eliminated, the risk for GNL in patients with moderate or severe gastric mucosal IM at baseline remained significantly higher than that in patients with mild or insufficient IM at baseline. The above characteristics were also noted in the control group but not in the persistent group. Therefore, the preventive effect of *H. pylori* eradication on gastric cancer depends on the severity of baseline gastric mucosal lesions. When *H. pylori* eradication can no longer prevent the development of gastric cancer, the precancerous state (such as moderate or severe mucosal IM) may represent the point of irreversibility.^[1,24] IM is the most common precancerous lesion, but most patients with IM will not develop gastric cancer, which is closely related to the subtypes of IM rather than *H. pylori* infection eradication.^[19] Therefore, older patients who experienced moderate and severe IM of the gastric mucosa may not benefit from the eradication of *H. pylori* to prevent gastric cancer.

Studies have shown that the spontaneous clearance rate of *H. pylori* is higher in older individuals than in younger adults.^[1,25] Kawaguchi demonstrated that among older patients aged over 85 years, the severity score of IM in the gastric mucosa was significantly higher in *H. pylori*-negative patients than in those who were positive.^[20] This suggests that IM may promote clearance of *H. pylori* infection in older individuals. Gastric mucosa with severe atrophy and intestinal mucosa is not conducive to *H. pylori* colonization.^[6] As a result, there is a possibility for older patients with *H. pylori* infection to avoid treatment for it.

The benefits of *H. pylori* eradication differ among patients, especially in older individuals. A 10-year follow-up study in Japan found that a lower incidence of gastric cancer after *H. pylori* eradication was negatively correlated with age.^[26] Furthermore, a recent retrospective study from Hong Kong,^[27] China, showed that *H. pylori* eradication in populations aged over 60 years could also be beneficial. Still, the effect of reducing the incidence of gastric cancer would not be apparent until 10 years after eradication. As a result, some studies have proposed that conventional cancer screening and treatment have no real net benefit to individuals with a limited life span.^[8,28] In 2014, gastric cancer incidence in men peaked at the age of 80 to 84 years in China, whereas in women, it peaked at the age of >85 years.^[29] The average life expectancy was 76.34 years (men, 73.64 years; women, 79.43 years) at the same time.^[7] In the current study, there was no significant difference in the cumulative incidence of GNL between the eradicated and persistent groups during the 5 to 10-year follow-up period. Meanwhile, the median

interval time between baseline and diagnosis of GNL in all groups was more than 6 years. Therefore, we believe that the eradication of *H. pylori* in older individuals does not show apparent primary prevention advantages and maximum curative effect within the expected limited time (5–10 years), compared with the non-eradication of *H. pylori*. It is necessary to carefully evaluate the benefit–risk ratio of the eradication of *H. pylori* in older patients, and individualized treatment should be carried out based on comprehensive factors, such as life expectancy and comorbidity.

The results of this study confirmed that the severity of baseline gastric mucosal IM and *H. pylori* infection were closely related to GNL. As a primary preventive measure to reduce the risk of gastric cancer, the eradication of *H. pylori* cannot eliminate the risk of gastric cancer in patients with gastric mucosa IM. Therefore, it is necessary to carry out secondary preventive measures according to the basic gastric mucosal status of older individuals.^[30] However, for older patients whose life expectancy is less than 5 to 10 years, especially those who have moderate or severe IM of the gastric mucosa, eradication of *H. pylori* is not recommended. In these cases, other corresponding treatments can be given, as appropriate, and attention should be paid to the infectivity of *H. pylori*.^[6] Therefore, for older patients with *H. pylori* infection, the “endoscopy and treat” strategy may be more appropriate instead of the *H. pylori* “test and treat” strategy.^[10]

This study had some limitations. First, this study was a single-center retrospective cohort study without a non-elderly control group, which may be biased by selection. Second, due to the multifocal distribution of gastric precancerous lesions, there may be sampling errors, and no stratified studies have been conducted on the lesion site (antrum, corpus of the stomach), IM subtype, environmental factors (drugs, tobacco), *H. pylori* infection course, and treatment frequency. Third, the 10-year follow-up may not be sufficient to fully analyze the long-term results.

In conclusion, it is necessary to eradicate *H. pylori* in older patients to improve or delay gastric precancerous lesions and prevent gastric cancer. However, even if *H. pylori* is eradicated, the baseline status of the gastric mucosa in older adults affects the progression of such precancerous lesions. Older patients with a life expectancy of less than 5 to 10 years, especially those with moderate-to-severe gastric mucosal IM, may not benefit from the eradication of *H. pylori* infection. In future studies, a larger number of patients need to be followed up for a longer time to confirm our conclusion.

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Conflicts of interest

There are no conflicts of interest.

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