

Helicobacter pylori Infection Combined with OLGA and OLGIM Staging Systems for Risk Assessment of Gastric Cancer: A Retrospective Study in Eastern China

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Purpose: *Helicobacter pylori* (*H. pylori*) infection is a high-risk factor for gastric cancer (GC). The main aim of this study was to evaluate the effect of *H. pylori* on gastritis staging systems and the value of *H. pylori* combined with gastritis staging systems in predicting GC risk.

Patients and Methods: This study enrolled 609 patients with gastric atrophy (GA) and 527 patients with gastric intestinal metaplasia (GIM), who were graded by the OLGA and OLGIM staging systems, respectively. Each individual underwent serum pepsinogen (PG) test, *H. pylori* detection and questionnaire investigation. We did a real-world retrospective follow-up survey for them in April 2022.

Results: Compared with *H. pylori*-negative patients, *H. pylori*-positive patients had higher serum PGs/gastrin-17 (G-17) levels and lower PGR levels, regardless of OLGA/OLGIM stages I–II or III–IV. Furthermore, eight patients with atrophic gastritis who progressed to GC were previously in OLGA stages III–IV and OLGIM stages II–IV. The average duration of this process was 2.19 ± 1.03 years. Logistic regression analysis indicated that PGI and *H. pylori* infection were independent risk factors of individuals with OLGA stages III–IV. Age and PGR were independent risk factors of patients with OLGIM stages III–IV. PGI and PGR had good clinical diagnostic values for OLGA stages III–IV and OLGIM stages III–IV, respectively.

Conclusion: Patients with OLGA/OLGIM stages III–IV should undergo endoscopic surveillance regardless of *H. pylori* infection. *H. pylori*-positive patients with OLGIM stage II also have a high risk of GC. *H. pylori* combined with PGI and PGR is helpful to evaluate the severity of chronic gastritis.

Keywords: atrophy, metaplasia, *Helicobacter pylori*, gastric cancer, risk factors

Introduction

Gastric cancer (GC) is the fifth most common cancer and the third most common cause of cancer death in the world.¹ Its risk factors include *H. pylori* infection, age, smoking, alcohol consumption, family susceptibility and poor dietary habits.^{1,2} GC is often diagnosed at an advanced stage and its mortality rate is high.³ Therefore, early detection and treatment are the keys to reducing the mortality of GC.⁴

Gastric atrophy (GA) and gastric intestinal metaplasia (GIM) are important risk factors for intestinal-type gastric cancer.^{5,6} Therefore, endoscopic surveillance of them is conducive to early detection of GC.⁷ Operative link on gastritis assessment (OLGA) is a visual analog grading using the biopsy sampling protocol and the Houston updated Sydney system recommendation.⁸ Atrophy staging is the result of combining the degree of atrophy scored on histology with the

morphology of atrophy as determined by biopsy mapping.⁹ For patients with GIM, the operative link on gastric intestinal metaplasia assessment (OLGIM) is a tool for risk stratification.¹⁰ Multiple studies found that patients with OLGA stages III–IV have a high risk of developing GC.^{11,12} According to the findings of the European Society for Gastrointestinal Endoscopy, endoscopic surveillance is recommended for patients with OLGIM III–IV.¹³ However, China has an enormous population and the living habits of different regions vary greatly. Therefore, the incidence of gastric cancer varies in different regions of China, and large-scale follow-up studies are still lacking.

Serum pepsinogen (PG) and gastrin-17 (G-17) produced by gastric-associated cells could reflect the state of the gastric mucosa to a certain extent.^{14–16} *H. pylori* was classified as a group I carcinogen of GC by the International Agency of the World Health Organization in 1994.¹⁷ *Helicobacter pylori* is a gram-negative motile bacterium that causes acute and chronic gastrointestinal and extragastrintestinal infections in humans.¹⁸ It takes a long time for gastritis to develop into GC, so the secondary prevention of GC is worth exploring.^{19,20} However, the lack of standardization of treatment in most patients with gastritis in China makes it difficult to perform regular endoscopic surveillance. Therefore, exploring the relationship among *H. pylori*, serum PGs levels, and the severity of gastritis would be more meaningful for predicting the risk of GC. The aim of this study was to analyze the effect of *H. pylori* on OLGA/OLGIM staging and to validate the appropriate timing of endoscopic surveillance in high-risk groups.

Materials and Methods

Patients Selection

This cross-sectional study was carried out at the First Affiliated Hospital of University of Science and Technology of China from April 2015 to April 2020, including physical examination centers and outpatient populations in Anhui Province, eastern China. All patients had no renal dysfunction. Inclusion criteria: patients (age > 18 years old) with gastroscopic biopsy. The exclusion criteria: patients with a history of tumor or gastric surgery; missing results; pathological results were non-atrophic gastritis; lost to follow-up. It is worth mentioning that there were 10 patients with atrophic gastritis combined with autoimmune diseases. Therefore, they were not included in the analysis. The case-selection flow chart has been presented in Figure 1.

Endoscopy and Histology

Based on the Sydney system, five pathology samples were taken: two from the gastric body; one from the mucosa of the incisura, and two from the antral mucosa. The tissues were processed in the same pathology laboratory. Patients with gastric atrophy were staged I–IV by the OLGA staging system from the combination of “antrum score” and “corpus score” (no atrophy = 0%, score = 0; mild atrophy = 1–30%, score = 1; moderate atrophy = 31–60%, score = 2; and severe atrophy ≥60%, score = 3).^{21,22} OLGIM staging adopted the same scoring system based on the severity and morphology of GIM.¹⁰ Stages III–IV were defined as high-risk stages for both of them. All tissue sections were read by two senior pathologists.

Serum Pepsinogen Test, *H. Pylori* Detection and Questionnaire Survey

Each patient collected 5 mL of venous blood at 8:00 am and submitted it for inspection within 30 minutes. The levels of serum PGs (PGI, serum pepsinogen I; PGII, serum pepsinogen II) and G-17 were analyzed by ELISA (BioHit, Helsinki, Finland) and PGR (PGI and PGII ratio) was calculated. All patients were informed to stop taking PPI (proton pump inhibitor) for two weeks before the *H. pylori* detection. After that, we tested the levels of serum PGs/G-17. Each individual was given a 13C-urea or 14C-urea breath test on the same day as the endoscopy. Furthermore, they all received a detailed questionnaire investigation, including age, gender, height and weight, smoking, alcohol consumption, and family history of gastrointestinal tumors.

Statistical Analysis

Pearson's *X* test was conducted to analyze the categorical variables. Significant differences in age and BMI among groups were assessed by analysis of variance (ANOVA) or *t*-test. Two-sample rank-sum test and multi-sample rank-sum test were used to analyze skewed data. Univariate and multivariate logistic regression models were used to analyze the high-risk factors

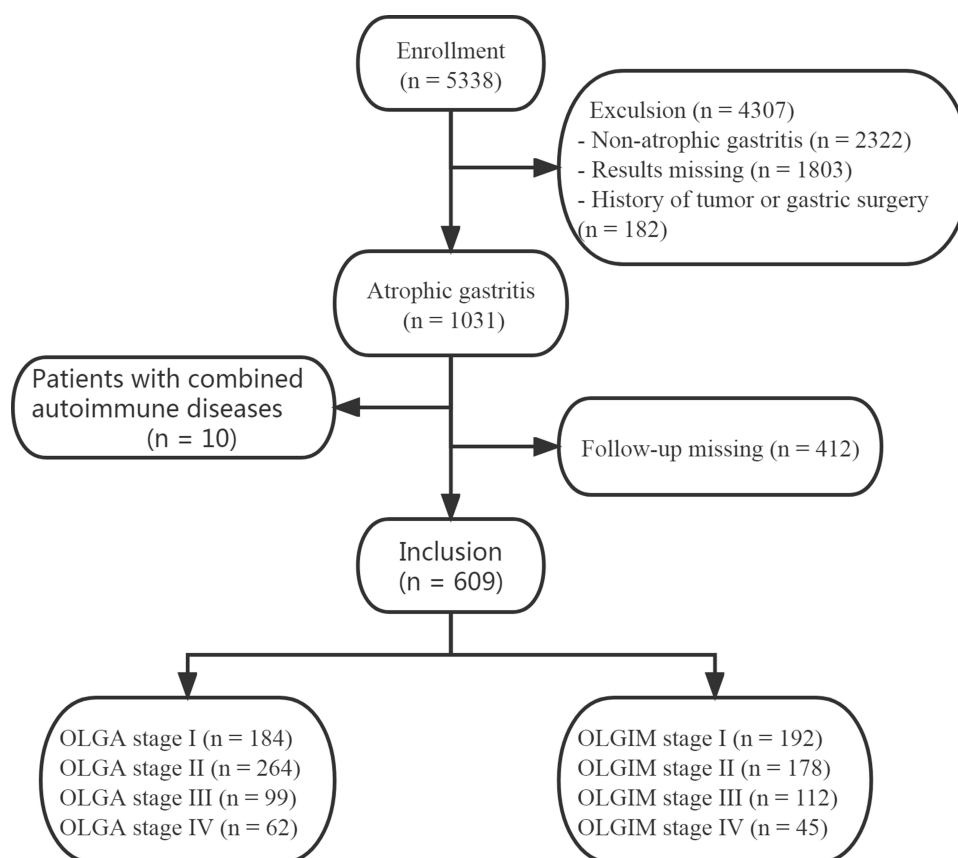


Figure 1 A flow chart for screening the study subjects was established.

of OLGA stages III–IV and OLGIM stages III–IV. The optimal index was selected by the ROC curve to reflect the clinical diagnostic value of high-risk groups. Data analysis was performed using SPSS 25.0 software. We conducted a retrospective follow-up of gastritis patients in April 2022 and summarized the characteristics of patients with GC. Two-sided p -value < 0.05 was considered statistically significant.

Results

Baseline Data of the Study Subjects

609 atrophic patients had a mean age of 51.13 (SD = 9.95) years, of whom 359 were male and 250 were female. According to OLGA stage, 184 patients (30.21%), 264 patients (43.35%), 99 patients (16.26%) and 62 patients (10.18%) were in stage I–IV, respectively. There were 527 patients had atrophy combined with intestinal metaplasia, including 283 males and 244 females. Their mean age was 50.83 (SD = 9.95) years. According to OLGIM stage, 192 patients (36.43%), 178 patients (33.78%), 112 patients (21.25%) and 45 patients (8.54%) were in stage I–IV, respectively. Meanwhile, the rate of *H. pylori* infection was 42.53% in GA patients and 38.90% in GIM patients (Table 1).

Serum PGs in OLGA/OLGIM Stage

There was a statistical difference in serum PGI, PGR, G-17, family history rate (all $p < 0.001$) and *H. pylori* infection rate ($p = 0.002$) in OLGA staging. As OLGA stage increased, PGI and PGR levels decreased, while *H. pylori* infection rate increased. The G-17 level and family history ratio were the highest in OLGA stage IV. Meanwhile, there were significant differences in serum PGI ($p = 0.001$), PGR, PGII, G-17, *H. pylori* infection rate (all $p < 0.001$) and family history ratio ($p = 0.008$) in OLGIM staging. Besides, the mean age of patients with OLGIM III–IV was older than patients with OLGIM I–II ($p = 0.003$) (Table 2).

Table 1 Baseline Characteristics of Patients with Atrophic Gastritis in This Study

	GA (n = 609)		GIM (n = 527)	
Age, years, mean (SD)	51.13 (9.95)		50.83 (9.95)	
BMI, kg/m ² , mean (SD)	24.28 (2.92)		24.06 (3.27)	
Gender, Male, n (%)	359 (58.95)		283 (53.70)	
Smoking, n (%)	253 (41.54)		225 (42.69)	
Alcohol consumption, n (%)	262 (43.02)		239 (45.35)	
Family history, n (%)	60 (9.85)		58 (11.01)	
<i>H. pylori</i> infection, n (%)	259 (42.53)		205 (38.90)	
	OLGA stage I, n (%)	184 (30.21)	OLGIM stage I, n (%)	192 (36.43)
	OLGA stage II, n (%)	264 (43.35)	OLGIM stage II, n (%)	178 (33.78)
	OLGA stage III, n (%)	99 (16.26)	OLGIM stage III, n (%)	112 (21.25)
	OLGA stage IV, n (%)	62 (10.18)	OLGIM stage IV, n (%)	45 (8.54)

Abbreviations: GA, gastric atrophy; GIM, gastric intestinal metaplasia; BMI, body mass index; SD, standard deviation; OLGA, operative link on gastritis assessment; OLGIM, operative link on gastric intestinal metaplasia assessment.

Serum PGs in OLGA/OLGIM I-II and III-IV

Combined with the status of *H. pylori* infection, we further found that the levels of PGI was lower in *H. pylori*-positive patients with OLGA III–IV. For *H. pylori*-negative patients with GA, the levels of PGI ($p < 0.001$) was lower in the high-risk stages. Besides, *H. pylori*-positive patients and *H. pylori*-negative patients were analyzed separately. Lower levels of PGI/PGR and higher levels of PGII/G-17 were observed in OLGIM stages III–IV compared to OLGIM stages I–II in this study. Regardless of OLGA/OLGIM stages I–II or III–IV, *H. pylori*-positive patients had higher PGI, PGII, G-17 levels, and lower PGR levels compared to *H. pylori*-negative patients (Table 3).

Risk Factors for OLGA/OLGIM Stages III-IV

We performed risk factors analysis for OLGA/OLGIM stages III–IV (Tables 4 and 5). Univariate logistic regression results showed that PGI, PGR, G-17, *H. pylori* infection, and family history were significantly associated with OLGA stages III–IV. Multivariate logistic regression results suggested PGI ($p = 0.001$) and *H. pylori* infection ($p < 0.001$) were independent risk factors of OLGA stages III–IV. Independent risk factors for OLGIM stages III–IV were age ($p = 0.027$) and PGR ($p < 0.001$).

Follow-Up Results

Eight patients with atrophic gastritis who progressed to GC were observed in this study which spanned 4.5 ± 1.87 years (Table 6). Miraculously, they were all male, with an average age of 66.50 (SD = 8.94) years. In addition, eight patients were previously in OLGA stages III–IV and OLGIM stages II–III, and three of the OLGIM stage II patients were *H. pylori*-positive, but they failed anti-*H. pylori* therapy. Meanwhile, we found that five patients had smoked, four patients had drunk, and two patients had a family history of gastrointestinal tumors. Besides, the average time of progression to GC was 2.19 ± 1.03 years.

ROC Curves

We analyzed the diagnostic value of PGI for OLGA stages III–IV according to *H. pylori* status. We found that the area under the curve (AUC) was 0.789 (95% CI: 0.730–0.850, $p < 0.001$), the optimal cut-off value was 115.23, the sensitivity was 82.8% and the specificity was 66.9% for *H. pylori*-positive patients with GA. For all patients with GIM, the AUC was 0.801 (95% CI: 0.761–0.842, $p < 0.001$), the best cut-off value was 9.93, the sensitivity was 82.8% and the specificity was 68.1% (Figure 2).

Table 2 Serum PGs/G-17 Levels and Population Characteristics in OLGA/OLGIM Stage

	OLGA					OLGIM				
	Stage I (n = 184)	Stage II (n = 264)	Stage III (n = 99)	Stage IV (n = 62)	p-value	Stage I (n = 192)	Stage II (n = 178)	Stage III (n = 112)	Stage IV (n = 45)	p-value
PGI, µg/L	120.59	101.72	100.02	58.70	< 0.001	103.42	101.15	89.50	71.12	0.001
Median (IQR)	(83.78–168.36)	(78.03–130.07)	(76.40–110.15)	(46.18–72.31)		(81.46–134.43)	(75.56–128.03)	(63.87–127.26)	(54.85–107.52)	
PGII, µg/L	11.50	9.56	9.92	9.93	0.060	7.58	9.84	12.29	14.15	< 0.001
Median (IQR)	(6.67–21.33)	(6.49–15.83)	(6.45–14.73)	(6.09–14.76)		(5.32–11.77)	(6.67–17.17)	(7.10–20.43)	(9.62–20.62)	
PGR,	10.53	10.60	9.43	6.26	< 0.001	13.70	10.13	7.65	4.61	< 0.001
Median (IQR)	(7.65–13.48)	(7.10–14.01)	(6.67–14.16)	(4.02–10.71)		(10.58–16.29)	(7.09–12.59)	(5.90–9.85)	(2.66–6.36)	
G-17, pmol/L	3.01	2.48	2.33	4.75	< 0.001	2.08	3.10	3.10	8.28	< 0.001
Median (IQR)	(1.34–7.70)	(1.33–6.56)	(1.29–5.89)	(2.54–29.24)		(1.16–5.13)	(1.33–6.46)	(1.69–10.33)	(3.61–36.38)	
Age, years, mean (SD)	51.41 (9.48)	51.10 (9.99)	50.32 (9.15)	52.52 (11.67)	0.369	49.63 (9.03)	49.96 (10.09)	53.52 (10.70)	52.60 (10.01)	0.003
BMI, kg/m ² , mean (SD)	24.56 (2.95)	24.18(3.03)	24.27 (2.98)	23.95 (3.26)	0.469	24.26 (3.15)	23.89 (3.41)	24.13 (3.31)	23.62 (3.36)	0.595
<i>H. pylori</i> infection, n (%)	68 (36.96)	104(39.40)	48 (48.48)	39 (62.90)	0.002	50 (26.04)	71 (39.89)	52 (46.43)	32 (71.11)	< 0.001
Smoking, n (%)	80 (43.48)	105 (39.78)	45 (45.45)	23 (37.10)	0.625	83 (43.23)	78 (43.82)	52 (46.43)	12 (26.67)	0.140
Alcohol consumption, n (%)	83 (45.11)	108 (40.91)	44 (44.44)	27 (43.55)	0.826	85 (44.27)	85 (47.75)	55 (49.11)	14 (31.11)	0.185
Family history, n (%)	16 (8.70)	18 (6.82)	7 (7.07)	19 (30.65)	< 0.001	16 (8.33)	14 (7.87)	18 (16.07)	10 (22.22)	0.008
Gender, Male, n (%)	122 (66.30)	143 (54.17)	61 (61.61)	33 (53.23)	0.052	109 (56.77)	91 (51.12)	65 (58.04)	18 (40.00)	0.142

Abbreviations: PGI, serum pepsinogen I; PGII, serum pepsinogen II; PGR, pepsinogen I and II ratio; G-17, gastrin-17; BMI, body mass index; SD, standard deviation; IQR, interquartile range.

Table 3 Serum PGs/G-17 in OLGA/OLGIM Stages I–II and III–IV

		OLGA				OLGIM			
		PGI, µg/L Median (IQR)	PGII, µg/L Median (IQR)	PGR, Median (IQR)	G-17, pmol/L Median (IQR)	PGI, µg/L Median (IQR)	PGII, µg/L Median (IQR)	PGR, Median (IQR)	G-17, pmol/L Median (IQR)
<i>H. pylori</i> -Positive	Stages I–II	136.09 (107.43–164.03)	19.81 (12.68–24.38)	7.08 (5.60–9.43)	6.81 (4.28–14.06)	114.52 (99.52–153.44)	14.74 (11.26–22.52)	7.96 (5.91–12.77)	6.02 (3.18–10.01)
	Stages III–IV	89.00 (70.85–111.90)	13.41 (9.08–18.81)	6.69 (5.08–8.90)	5.13 (2.48–11.31)	108.98 (67.23–141.50)	17.80 (13.84–24.72)	5.68 (4.46–6.66)	6.48 (4.14–19.02)
	<i>p</i> -value	<0.001	<0.001	0.252	0.075	0.018	0.015	<0.001	0.030
<i>H. pylori</i> -Negative	Stages I–II	90.12 (73.67–121.54)	7.29 (5.66–10.46)	12.7 (10.27–14.83)	1.70 (1.08–3.26)	90.36 (71.42–118.56)	6.92 (5.02–9.46)	13.20 (11.11–15.95)	1.61(1.08–3.22)
	Stages III–IV	74.92 (54.23–111.66)	6.55 (4.85–9.96)	11.28 (7.40–15.78)	1.71 (1.20–4.03)	70.70 (59.13–93.19)	7.55 (6.02–11.74)	9.00 (6.94–11.10)	2.10(1.30–6.66)
	<i>p</i> -value	<0.001	0.132	0.009	0.308	<0.001	0.006	<0.001	0.008
Stages I–II	<i>H. pylori</i> -negative	90.12 (90.12–73.67)	7.29 (5.66–10.46)	12.70 (10.27–14.83)	1.70 (1.08–3.26)	90.36 (71.42–118.56)	6.92 (5.02–9.46)	13.20 (11.11–15.95)	1.61(1.08–3.22)
	<i>H. pylori</i> -positive	136.09 (107.43–164.03)	19.81 (12.68–24.38)	7.08 (5.60–9.43)	6.81 (4.28–14.06)	114.52 (99.25–153.44)	14.74 (11.26–22.52)	7.96 (5.91–10.01)	6.02(3.18–10.01)
	<i>p</i> -value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Stages III–IV	<i>H. pylori</i> -negative	74.92 (54.23–101.95)	6.55 (4.85–9.96)	11.28 (7.40–15.78)	1.71 (1.20–4.03)	70.70 (59.13–93.19)	7.55 (6.02–11.74)	9.00 (6.94–11.10)	2.10(1.30–6.66)
	<i>H. pylori</i> -positive	89.00 (70.85–111.90)	13.41 (9.08–28.88)	6.69 (5.08–8.90)	5.13 (2.48–11.31)	108.98 (67.23–141.50)	17.80 (13.84–24.72)	5.68 (4.46–6.66)	6.48(4.14–19.02)
	<i>p</i> -value	0.002	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Abbreviations: PGI, serum pepsinogen I; PGII, serum pepsinogen II; PGR, pepsinogen I and II ratio; IQR, interquartile range; G-17, gastrin-17.

Table 4 Univariate Logistic Regression Analysis of Risk Factors for Patients with OLGA/OLGIM III–IV

Risk factors	OLGA I–II VS OLGA III–IV				OLGIM I–II VS OLGIM III–IV			
	OLGA I–II (n = 448)	OLGA III–IV (n = 161)	p-value	OR (95% CI)	OLGIM I–II (n = 370)	OLGIM III–IV (n = 157)	p-value	OR (95% CI)
Gender, Male, n (%)	265 (59.15)	94 (58.39)	0.865	0.969 (0.672–1.397)	200 (54.05)	83 (52.87)	0.803	0.953 (0.658–1.386)
Age, years, mean (SD)	51.33 (9.78)	51.10 (10.30)	0.798	0.998 (0.980–1.016)	49.79 (9.58)	53.29 (10.39)	<0.001	1.036 (1.017–1.057)
BMI, kg/m ² , mean (SD)	24.32 (2.92)	24.16 (2.90)	0.545	0.981 (0.922–1.044)	24.09 (3.27)	23.97 (3.28)	0.712	0.989 (0.934–1.048)
Smoking, n (%)	185 (41.29)	68 (42.24)	0.835	1.039 (0.722–1.497)	161 (43.51)	64 (40.76)	0.560	0.893 (0.612–1.305)
Alcohol consumption, n (%)	191 (42.63)	71 (44.10)	0.747	1.061 (0.738–1.526)	170 (45.95)	69 (43.95)	0.674	0.922 (0.634–1.343)
Family history, n (%)	34 (7.59)	26 (16.15)	0.002	2.345 (1.358–4.050)	30 (8.11)	28 (17.83)	0.001	2.460 (1.414–4.279)
<i>H. pylori</i> infection, n (%)	172 (38.39)	87 (54.04)	0.001	1.887 (1.311–2.714)	121 (32.70)	84 (53.50)	<0.001	2.368 (1.617–3.468)
PGI, µg/L Median (IQR)	107.05 (79.49–141.21)	79.53 (64.36–107.90)	<0.001	0.986 (0.981–0.990)	101.97 (78.42–132.98)	85.31 (62.33–122.29)	0.019	0.995 (0.992–0.999)
PGII, µg/L Median (IQR)	10.35 (6.57–17.80)	9.92 (6.45–14.73)	0.283	0.989 (0.970–1.009)	8.50 (6.01–13.04)	13.84 (7.68–20.81)	<0.001	1.055 (1.034–1.076)
PGR, Median (IQR)	10.58 (7.34–17.02)	8.01 (5.86–12.64)	<0.001	0.925 (0.888–0.964)	11.89 (8.73–14.87)	6.67 (4.98–9.13)	<0.001	0.739 (0.695–0.787)
G-17, pmol/L Median (IQR)	2.85 (1.33–7.05)	3.06 (1.54–9.52)	0.040	1.015 (1.001–1.029)	2.37 (1.28–5.89)	4.32 (2.06–14.38)	<0.001	1.062 (1.040–1.085)

Abbreviations: PGI, serum pepsinogen I; PGII, serum pepsinogen II; PGR, pepsinogen I and II ratio; G-17, gastrin-17; BMI, body mass index; SD, standard deviation; IQR, interquartile range.

Table 5 Multivariate Logistic Regression Analysis of Risk Factors for Patients with OLGA/OLGIM III–IV

Risk Factors	OLGA stages III–IV		OLGIM Stages III–IV	
	p-value	OR (95% CI)	p-value	OR (95% CI)
Age	-	-	0.027	1.026 (1.003–1.050)
PGI	0.001	0.982 (0.976–0.988)	0.238	0.994 (0.985–1.004)
PGII	-	-	0.825	1.007 (0.948–1.070)
PGR	0.399	0.977 (0.925–1.031)	<0.001	0.726 (0.641–0.824)
G-17	0.605	0.995 (0.978–1.013)	0.402	1.011 (0.985–1.037)
<i>H. pylori</i> infection	<0.001	2.916 (1.796–4.736)	0.059	0.572 (0.320–1.021)
Family history	0.166	1.536 (0.837–2.821)	0.126	1.704 (0.861–3.372)

Abbreviations: PGI, serum pepsinogen I; PGII, serum pepsinogen II; PGR, pepsinogen I and II ratio; G-17, gastrin-17.

Discussion

Chronic atrophic gastritis is a precancerous stage of GC. Most studies showed that severe atrophy and intestinal metaplasia are the risk factors of GC.^{9,23,24} Asia has a large population and the results of studies are variable. Most findings indicate that patients with OLGA or OLGIM III–IV have a higher risk of gastric cancer and that these patients could benefit from endoscopic surveillance.^{24–26} Serum PGs combined with *H. pylori* antibody (named ABC method) has been proposed as a predictive method for patients with GC.²⁷ A multicenter study in China developed score-based prediction rules including variables such as age, sex, PG I/II ratio, G-17 concentration, anti-*H. pylori* IgG status, and consumption of pickled and fried foods for secondary prevention of GC.⁴ The 13C-urea/14C-urea breath test was chosen in our study, which reflected the current infection of *H. pylori*. We explored the relationship between the current infection of *H. pylori* and serum PGs in OLGA/OLGIM staging systems. This may provide us with a more accurate risk assessment method for GC. All *H. pylori*-positive patients are required to receive *H. pylori* eradication therapy. In this study, endoscopic biopsy was not performed on patients with mild lesions. However, there were few large-scale follow-up studies in China, which is why we followed up patients with definite atrophic gastritis to verify the risk stage of GC.

Rugge et al conducted a follow-up study of 93 patients for more than 12 years and found that PGR was significantly negatively correlated with OLGA staging.¹¹ In another study, serum PGI was negatively correlated with OLGA staging, and PGR was negatively correlated with OLGIM staging.²⁵ Our study proposed that serum PGI, PGR, and G-17 were associated with OLGA staging, whereas serum PGs, PGR, and G-17 were related to OLGIM staging (Table 2). These results are generally consistent with the findings of previous studies, which demonstrates that serum-related indicators can reflect the severity of GA and GIM. In addition, *H. pylori* infection and age were found to be independent risk factors of gland atrophy or gastric intestinal metaplasia in most studies.^{28–30} In the results, the mean age of OLGIM III–IV patients was older than that of OLGIM I–II patients, but there was no statistical difference in age between OLGA stages. The study also observed that as the OLGA/OLGIM stage increased, the *H. pylori* infection rate increased. Furthermore, early studies presented that *H. pylori* infection resulted in increased serum pepsinogen levels.³¹ Higher levels of PGI, PGII, G-17 and lower level of PGR in *H. pylori*-positive patients were observed in our study compared to *H. pylori*-negative patients, regardless of OLGA stages I–II or III–IV. The same finding was also shown in patients with gastric intestinal metaplasia (Table 3). Therefore, serum PGs should be differentiated according to different *H. pylori* status to assess the severity of gastritis.

The majority of researches considered that one of two staging systems (OLGA or OLGIM staging) was recommended as a reference for endoscopic surveillance of severe chronic gastritis.^{32–34} In the staging of gastritis, intestinal metaplasia instead of atrophy significantly improved the interobserver agreement, and their correlation in gastritis severity remained pronounced.¹⁰ Simultaneous description of the OLGA and OLGIM staging systems may be more accurate than separate descriptions. Therefore, we focused on the OLGA/OLGIM stages III–IV. According to our retrospective follow-up results, eight patients who progressed to GC were in OLGA stages III–IV and OLGIM stages II–III previously. We noticed that three OLGIM stage II patients were *H. pylori*-positive, and their anti-*H. pylori* treatment failed. These results

Table 6 Characteristics of Eight Patients with GC

Gender	Age (y)	<i>H. Pylori</i> Infection	Treatment of <i>H. Pylori</i>	OLAG Stage	OLGIM Stage	The Lesion Location	The Lesion Type	Follow-up Time	Smoking	Alcohol Consumption	Family History
Male	69	Positive	Failed	III	II	Corpus	HGIN	1.5 years	N	N	N
Male	65	Negative	-	III	III	Antrum	HGIN	1 year	Y	Y	N
Male	68	Negative	-	IV	III	Corpus	Adenocarcinom	3 years	Y	Y	N
Male	55	Negative	-	III	II	Corpus	HGIN	2.5 years	Y	N	Y
Male	58	Positive	Failed	III	II	Antrum	HGIN	4 years	Y	N	N
Male	83	Negative	-	III	III	Antrum	HGIN	2.5 years	N	Y	N
Male	73	Positive	Failed	III	II	Antrum	HGIN	2 years	N	N	Y
Male	61	Positive	Failed	III	III	Corpus	Adenocarcinoma	1 year	Y	Y	N

Notes: Y, patient with a history of smoking, patient with a history of alcohol consumption, patient with family history of gastrointestinal tumors. N, patient without a history of smoking, patient without a history of alcohol consumption, patient without family history of gastrointestinal tumors.

Abbreviation: HGIN, high grade intraepithelial neoplasia.

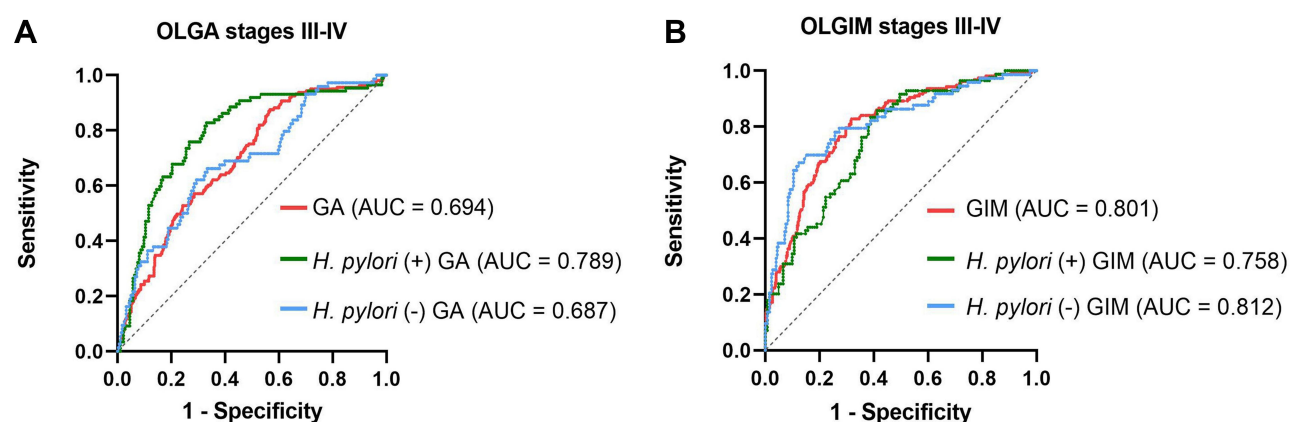


Figure 2 (A) ROC curves of PGI for the diagnosis of OLGA stages III–IV of atrophic gastritis (the green line is patients with *H. pylori*-positive; the blue line is patients with *H. pylori*-negative; the red line is all patients with GA). (B) ROC curves of PGR for the diagnosis of OLGIM stages III–IV of atrophic gastritis (the green line is patients with *H. pylori*-positive; the blue line is patients with *H. pylori*-negative; the red line is all patients with GIM).

Abbreviation: AUC, area under the curve.

indicate that patients with OLGIM stage II are worthy of note as well, especially in terms of those who are *H. pylori*-positive and their anti-*H. pylori* treatment failed. Persistent *H. pylori* infection may accelerate disease progression. Microbial-host interactions depend on environmental changes in microbial virulence gene expression. Detection of *H. pylori* virulence gene expression in gastric biopsy specimens can help predict disease outcomes.³⁵ In addition, gastric cancer is the result of multiple factors. In this regard, a larger scale and more rigorous experimental design are needed. Besides, the incidence of GC in men was twice as high as in women from a study.³ All patients in this follow-up outcome were male. A prospective, longitudinal, multicenter study conducted in Singapore found that patients with OLGIM III–IV and OLGIM II benefit from repeat endoscopic surveillance at 2 and 4–5 years, respectively.²⁴ Previously, only OLGIM stages III–IV were used as being the priority endoscopic surveillance stages,^{23,36} and re-biopsy within 3 years was recommended.¹³ Our study showed that the average duration of progression to GC was 2.19 ± 1.03 years. This result sparked our interest in exploring the risk factors of OLGA stages III–IV and OLGIM stages III–IV. Patients with OLGIM II are also worthy of further study.

According to a survey in the United States, there were many risk factors of GC, including *H. pylori* infection, smoking, low socioeconomic status, and high-salt diet.² Therefore, these factors may be associated with severe gastritis. The results demonstrated that serum PGI and *H. pylori* infection were independent risk factors for OLGA stage III–IV, whereas age and PGR were independent risk factors for OLGIM stage III–IV. A study has shown that smoking is strongly associated with the development of GC, and after 10 years of smoking cessation, the risk of smokers suffering from GC could be reduced to the same as that of patients who never smoked.³⁷ However, in the multiple logistic regression analysis of our study, age and smoking history had no statistical difference in OLGA III–IV, while age had statistical difference in OLGIM III–IV. The majority of patients participating in this study were middle-aged, making for statistically no differences. In addition, the family history ratio was highest at OLGA stage IV and increased with increasing OLGIM stage. There was statistically significant difference in the family history ratio between OLGIM stage I–II and OLGIM stages III–IV. Meanwhile, serum PG cut-off points derived from previous studies were considered as potential predictors of gastric cancer development, specifically $\text{PGI} \leq 70 \text{ ng/mL}$, and $\text{PGI: PGII serum ratio} \leq 3.0$.^{38,39} Figure 2 presented that PGI was of great significance for patients with OLGA III–IV and PGR was more sensitive to patients with OLGIM III–IV. Therefore, we plotted ROC curves for different *H. pylori* status, which performed well in terms of sensitivity or specificity. Many studies based on high risk patients of GC have reported high sensitivity ($> 90\%$) and high specificity ($> 75\%$) of serum PGs.^{40,41} So we believe that the results may be more ideal by balancing gender, age and other factors. Particularly, these data indicated that *H. pylori* combined with serum PGs could reflect the severity of gastritis. Real-world follow-up results are more instructive for a multifactorial confounding reality.

The study also had some limitations. Some positive results were lost during real-world retrospective follow-up. Besides, lifestyle and special age groups at both ends (<18 and >85 years old) were not considered. Furthermore, our study only included patients living in eastern China, without extensive regional representation. Finally, the sample size was limited and more multicenter studies are needed to validate our findings.

To conclude, serum PGs were significantly correlated with severity of gastritis. According to the results of our follow-up, it could be seen that patients who progressed to GC were in OLGA stages III–IV and OLGIM stages II–III previously. Therefore, endoscopic surveillance should be performed for patients with OLGA stages III–IV or OLGIM stages III–IV. *H. pylori*-positive patients with OLGIM stage II also have a high risk of GC. Finally, *H. pylori* combined with PGI and PGR was helpful to evaluate the severity of GA and GIM.

Abbreviations

H. pylori, *Helicobacter pylori*; GC, gastric cancer; GA, gastric atrophy; GIM, gastric intestinal metaplasia; OLGA, operative link on gastritis assessment; OLGIM, operative link on gastric intestinal metaplasia assessment; PGs, serum pepsinogens; G-17, gastrin-17; PGI, serum pepsinogen I; PGII, serum pepsinogen II; PGR, pepsinogen I and II ratio; PPI, proton pump inhibitor.

Data Sharing Statement

The primary contributions in this study are presented in the article. Contact the corresponding author directly for further inquiries.

Ethical Statement

The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This study was reviewed and approved by the Medical Research Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China (No. 2022-RE-052). Each patient signed written informed consent.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Disclosure

The authors declare that there is no conflict of interest.

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