Established nomogram based on clinicopathological characteristics, lifestyle, and comorbidities risk factors for metachronous recurrence in curative endoscopic submucosal dissection

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Abstract

Background: Metachronous gastric cancer (MGC) has gained increasing attention due to the preservation of the stomach during endoscopic resection for early gastric cancer (EGC).
Objectives: This study aims to investigate the risk factors associated with MGC in the postoperative surveillance of endoscopic submucosal dissection (ESD).
Design: A retrospective case-control study.
Methods: The retrospective study was conducted between January 1, 2014, and June 30, 2020, at the Affiliated Drum Tower Hospital of Nanjing University Medical School.
Results: Several independent risk factors for developing MGC were identified as smoking history (hazard ratio (HR) 2.39, 95% confidence interval (CI) 1.25–4.58), metabolic dysfunction-associated steatotic liver disease (MASLD; HR 2.44, 95% CI 1.23–4.87), cerebrovascular disease (CD; HR 2.55, 95% CI 1.09–5.99), multiple lesions (HR 2.06, 95% CI 1.17–3.63), *Helicobacter pylori* infection status (eradicated vs negative: HR 1.42, 95% CI 0.60–3.39; persistent vs negative: HR 5.47, 95% CI 2.13–14.03), and atrophic gastritis (AG; moderate vs mild: HR 4.44, 95% CI 1.36–14.53; severe vs mild: HR 7.30, 95% CI 2.11–25.22). The established nomogram based on these risk factors demonstrated high accuracy both in the training and test sets, with concordance indexes of 0.787, 0.762, and 0.845 for the training set, and 0.764, 0.824, and 0.788 for the test set at 2, 3, and 5years, respectively.
Conclusion: The risk factors for developing MGC after curative ESD for EGC were identified as smoking history, MASLD, CD, multiple lesions, *H. pylori* infection status, and AG. To reduce the risk of MGC, a healthy lifestyle, regular *H. pylori* testing, and annual endoscopic screening are recommended.

Plain language summary

Risk factors for MGC in curative EGC

Identified risk factors for developing MGC after curative ESD for EGC include smoking history, metabolic dysfunction-associated steatotic liver disease, cerebrovascular disease, multiple lesions, *Helicobacter pylori* infection status, and atrophic gastritis. To mitigate the risk of MGC, it is recommended to adopt a healthy lifestyle, undergo regular *H. pylori* testing, and participate in annual endoscopic screenings.

Keywords: comorbidities, endoscopic submucosal dissection, lifestyle, metachronous gastric cancer, risk factors

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Introduction

Globally, the number of new cancer cases has risen by 26.3% from 18.7 million in 2010 to 23.6 million in 2019. Among all cancers, stomach cancer has the fourth-highest incidence and the third-highest mortality rate.[1] Early gastric cancer (EGC) is a lesion that is defined as the mucosa or submucosa, regardless of whether there is regional lymph node metastasis and endoscopic treatment is considered the first-line option for EGC.[2,3] Endoscopic resection (ER) is currently recognized as the standard and minimally invasive treatment for EGC. However, various forms of cancer recurrence, such as local and metachronous recurrence have raised endoscopists' concerns. The incidence of synchronous and metachronous neoplasms in gastric cancer (GC) after endoscopic submucosal dissection (ESD) was 2.7%–12.9% and 2.5%–4.5%.[4,5] The cumulative incidence of metachronous gastric cancer (MGC) in 5-, 7-, and 10-year were 9.5%, 13.1%, and 22.7%, respectively.[6] Thus, exploring the independent risk factors for MGC and scheduling routine follow-up and surveillance is important.

Prior studies have indicated that males, age >70, *Helicobacter pylori* infection, smoking, differentiated type, serum pepsinogen levels, and severe atrophic gastritis (AG) were risk factors for MGC after ESD.[6–12] Some studies suggested that comorbidities such as metabolic dysfunction-associated steatotic liver disease (MASLD; relative risk (RR) 2.3, 95% confidence interval (CI) 1.3–4.1), type 2 diabetes mellitus (hazard ratio (HR) 1.11, 95% CI 1.04–1.20), and Parkinson disease (HR 1.59, 95% CI 1.30–1.94) have been linked to a higher risk of GC.[13–16] Previous studies have indicated a strong positive association between hypertension, stroke, and GC from 21 countries over a 20-year period.[17] In Korea, obesity was associated with EGC (odds ratio (OR) 1.657; 95% CI 1.086–2.528; $p = 0.019$) in men and was related to gastric dysplasia (OR 2.086; 95% CI 1.011–4.302; $p = 0.047$) in women.[18] Whether these comorbidities play a role in the development of MGC after ESD in EGC patients is not clear. It is necessary to explore the risk factors of MGC and develop corresponding follow-up strategies for high-risk stratification of MGC.

In this study, we attempted to investigate the risk factors of MGC after curative ESD of EGC focusing on clinicopathological characteristics, lifestyles, and comorbidities.

Materials and methods

Study design and population

The retrospective case-control study was conducted at the Affiliated Drum Tower Hospital of Nanjing University Medical School, a tertiary-care hospital with a large, well-established Digestive Endoscopy Treatment Center. From January 2014 to June 2020, a total of 2039 patients with EGC or neoplasm were treated with ESD. Patients were required to meet certain criteria for inclusion: (1) underwent curative ESD; (2) with *H. pylori* infection information. Exclusion criteria consisted of (1) loss to follow-up; (2) follow-up period less than 12 months after ESD; (3) history of GC with gastrectomy; (4) scheduled for surgery within a year; (5) multiple EGCs with at least one non-curative resection. The curative resection of EGC was assessed based on the Japanese GC treatment guidelines.[19]

Verbal informed consent was obtained from each enrolled patient, and the requirement for written informed consent was waived due to the retrospective nature of the study. The study protocol was approved by the Human Ethics Review Committees of Nanjing Drum Tower Hospital (The approval number: 2024-395-01). This study followed the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[20]

Variables

Demographics and clinical characteristics such as age, gender, comorbidities, and *H. pylori* infection status were collected. Endoscopic and histologic features of the lesions were evaluated by two experienced gastrointestinal endoscopists and two experienced pathologists according to the WHO classification of GC.[21] Pack-year of cigarette smoking ⩾26.7 was defined as smoking history. Alcoholic behavior ⩾2 times/week was defined as a drinking history.[22] Lesion characteristics included size, location, pathological type, depth, differentiation, and AG. Histologically, differentiated type tumors included papillary adenocarcinoma (pap) and well- to moderately differentiated tubular adenocarcinoma (tub1 and tub2), while undifferentiated type tumors consisted of poorly differentiated adenocarcinoma (por), mucinous adenocarcinoma (muc), and signet-ring cell carcinoma (sig).[23] The degree of gastric mucosa atrophy was classified into three

grades: mild (C0–C1), moderate (C2–C3), and severe (O1–O3) according to the Kimura-Takemoto classification.[24,25] Medication use—including metformin, aspirin, statins, and proton pump inhibitors—along with certain genetic and epigenetic markers, obesity, and dietary factors, was not included in the analysis.

Helicobacter pylori *infection*

Helicobacter pylori was tested using the rapid urease test, urea breath test, and histological analysis. Patients were considered *H. pylori*-positive if they tested positive in any one of the tests. The patients were categorized into three groups based on their *H. pylori* infection status: (1) negative group without active *H. pylori* infection at the time of resection and before based on medical history and endoscopic performance; (2) eradicated group with successful *H. pylori* eradication before or after ESD; (3) persistent group with positive *H. pylori* infection failed or no *H. pylori* eradication. *Helicobacter pylori* infection was assessed about 4–6 weeks after the eradication therapy using the urea breath test.

Comorbidities

The diagnoses of MASLD, cerebrovascular disease (CD), cardiovascular disease, diabetes, and hypertension were confirmed and validated with the International Classification of Diseases, Tenth Revision, and Clinical Modification. Diagnosis of MASLD, without other causes of chronic liver diseases, was based on ultrasonography or computed tomography at routine preoperative examination by experienced radiologists. Cardiovascular and CDs were defined as the composite of cardiovascular diseases (including angina pectoris, myocardial infarction, coronary artery diseases, cardiovascular procedures, and heart failure) and CDs (ischemic stroke, hemorrhagic stroke, and transient ischemic attack).[26]

Follow-up after initial ESD and primary outcomes

After the initial ESD procedure, follow-up endoscopic examinations were performed in the first 3, 6, and 12 months, and annually thereafter to detect metachronous or synchronous lesions. MGC was defined as a secondary carcinoma occurring in areas other than the site of the primary lesion at least 1 year after curative ESD.[27] The histological examination of specimens obtained from biopsy, ER, or gastrectomy provided confirmation of MGC. The follow-up period was determined as the duration between the initial ESD and the last endoscopic examination or the histologically confirmed occurrence of MGC.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (for parametrically distributed data) or median (interquartile range; for nonparametrically distributed data). Statistical comparisons for continuous variables were performed using t tests or Mann–Whitney U tests. Any selective predictors that had missing data exceeding 15% were excluded. Categorical data were analyzed using the Pearson Chi-squared test or Fisher's exact test. Univariable and multivariable Cox regression analyses were conducted to identify independent risk factors for MGC. Covariates with clinical or statistical significance ($p < 0.1$) in univariable analysis were included in the multivariable analysis. The cumulative probabilities of developing MGC were calculated using the Kaplan–Meier method and compared using the log-rank test. Discrimination and calibration of the nomogram were evaluated using time-dependent receiver operating characteristic curves and calibration plots. All statistical tests were two-sided, and $p < 0.05$ were considered statistically significant. All statistical analyses were conducted with SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics in ESD patients

This retrospective study included 1358 subjects, as depicted in Figure 1. During a median follow-up time of 39 months, the rates of metachronous recurrence were 4.1% (8/196), 5.2% (55/1061), and 25.7% (26/101) for the negative, eradicated, and persistent groups, respectively. In addition, the cumulative incidence of MGC at 2, 3, and 5 years in our population was 3.1%, 4.9%, and 10.7%, respectively. Table 1 presents the clinicopathological characteristics of the population, with a median age of 64 years (range 57–70) and a male-to-female ratio of 7:3 (961 men and 397

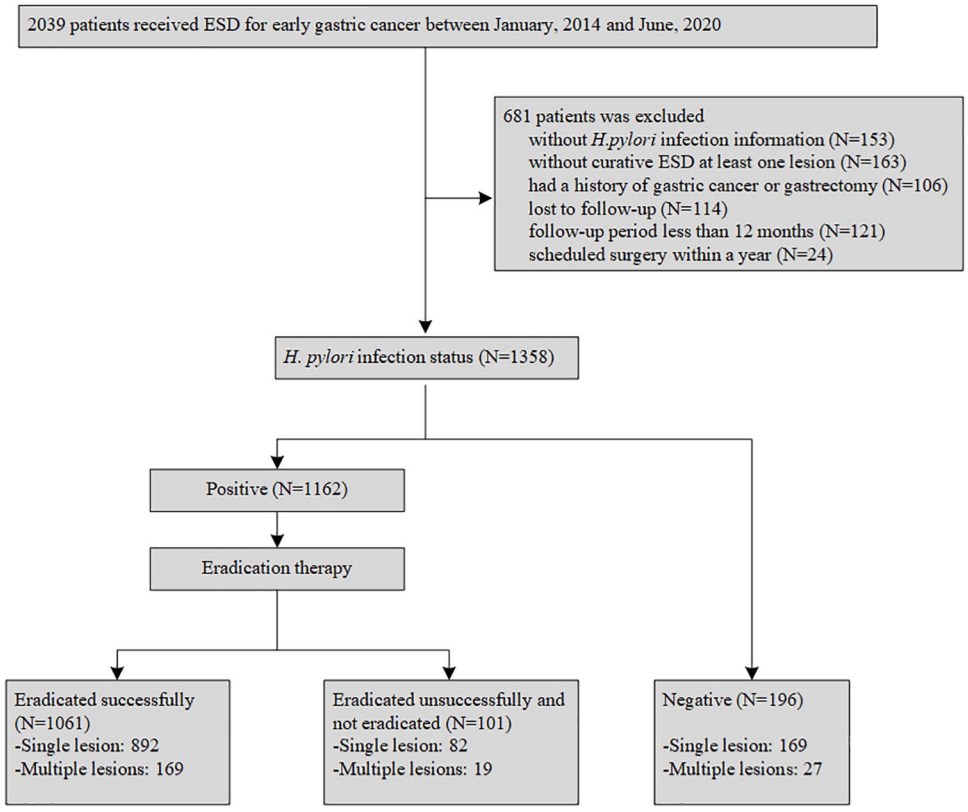

Figure 1. Outcomes of curative endoscopic submucosal dissection for early gastric cancer: study flowchart of the enrolled patients.

women). The incidence of MASLD in our population was 9.6% and the prevalence of diabetes was 8.8%. The data were randomly divided into a 7:3 ratio, with a training set of 950 subjects and a test set of 408 subjects, used for risk factor analysis, model establishment, and validation, respectively.

Risk factors for the development of MGC after curative ESD

Univariate Cox analysis was performed to examine the demographics and clinical characteristics contributing to the development of MGC (as shown in Table 2). The results indicated that male gender ($p = 0.018$), history of smoking ($p < 0.001$) or drinking ($p = 0.022$), comorbidities, including hypertension ($p = 0.023$), MASLD ($p < 0.001$), CD ($p < 0.001$), kidney disease ($p < 0.001$), and persistent *H. pylori* infection ($p < 0.001$) were significant risk factors for MGC development. As for endoscopic features, the presence of multiple lesions ($p < 0.001$) and AG ($p < 0.001$) showed significant differences between the non-MGC and MGC groups. Multivariate Cox regression analysis identified several risk factors associated with MGC development, including smoking history (HR 2.39, 95% CI 1.25–4.58), MASLD (HR 2.44, 95% CI 1.23–4.87), CD (HR 2.55, 95% CI 1.09–5.99), multiple lesions (HR 2.06, 95% CI 1.17–3.63), *H. pylori* infection status (eradicated vs negative: HR 1.42, 95% CI 0.60–3.39; persistent vs negative: HR 5.47, 95% CI 2.13–14.03), and AG (moderate vs mild: HR 4.44, 95% CI 1.36–14.53; severe vs mild: HR 7.30, 95% CI 2.11–25.22). These results are illustrated in Table 2.

Development and validation of the nomogram for predicting MGC occurrence

A nomogram (Figure 2) was developed using the training set by assigning weighted scores to each independent variable obtained from the multivariable Cox regression model (Table 2). This nomogram calculated the likelihood of developing MGC at 2, 3, and 5 years after curative ESD. The c-indexes, indicating predictive accuracy,

Table 1. The baseline and clinicopathological characteristics.

Characteristics	ALL	Training set	Test set	*p*
	N **= 1358**	***N*** **= 950**	***N*** **= 408**	
Age, years	64 (57–70)	64 (57–70)	64 (58–70)	0.391
Sex				0.534
Male	961 (70.8%)	667 (70.2%)	294 (72.1%)	
Female	397 (29.2%)	283 (29.8%)	114 (27.9%)	
Smoking history	502 (37.0%)	346 (36.4%)	156 (38.2%)	0.566
Drinking history	416 (30.6%)	291 (30.6%)	125 (30.6%)	1.000
Tumor family	276 (20.3%)	194 (20.4%)	82 (20.1%)	0.951
Hypertension	360 (26.5%)	258 (27.2%)	102 (25.0%)	0.442
Diabetes	119 (8.8%)	89 (9.4%)	30 (7.4%)	0.272
MASLD	130 (9.6%)	87 (9.2%)	43 (10.5%)	0.489
Cardiovascular disease	73 (5.4%)	53 (5.6%)	20 (4.9%)	0.707
CD	60 (4.4%)	42 (4.4%)	18 (4.4%)	1.000
Kidney disease	54 (4.0%)	38 (4.0%)	16 (3.9%)	1.000
Respiratory disease	48 (3.5%)	36 (3.8%)	12 (2.9%)	0.538
Helicobacter pylori status				0.061
Negative	196 (14.4%)	151 (15.9%)	45 (11.0%)	
Eradicated	1061 (78.1%)	731 (76.9%)	330 (80.9%)	
Persistent	101 (7.4%)	68 (7.2%)	33 (8.1%)	
Tumor size, cm				0.966
<2	805 (59.3%)	564 (59.4%)	241 (59.1%)	
$\geqslant 2$	553 (40.7%)	386 (40.6%)	167 (40.9%)	
Location				0.414
Upper	576 (42.4%)	401 (42.2%)	175 (42.9%)	
Medium	340 (25.0%)	247 (26.0%)	93 (22.8%)	
Lower	442 (32.5%)	302 (31.8%)	140 (34.3%)	
Multiple lesions	215 (15.8%)	146 (15.4%)	69 (16.9%)	0.527
Gross appearance				0.043
Protruding	443 (32.6%)	291 (30.6%)	152 (37.3%)	
Flatted	367 (27.0%)	259 (27.3%)	108 (26.5%)	
Depressed	548 (40.4%)	400 (42.1%)	148 (36.3%)	

(Continued)

Table 1. (Continued)

Characteristics	ALL	Training set	Test set	*p*
	N **= 1358**	***N*** **= 950**	***N*** **= 408**	
Depth of invasion				0.995
Mucosa	1040 (76.6%)	727 (76.5%)	313 (76.7%)	
Submucosa	318 (23.4%)	223 (23.5%)	95 (23.3%)	
Differentiation				0.243
D-type	1182 (87.0%)	834 (87.8%)	348 (85.3%)	
UD-type	176 (13.0%)	116 (12.2%)	60 (14.7%)	
Ulceration	105 (7.7%)	71 (7.5%)	34 (8.33%)	0.665
AG				0.891
Mild (C0, C1)	300 (22.1%)	213 (22.4%)	87 (21.3%)	
Moderate (C2, C3)	739 (54.4%)	516 (54.3%)	223 (54.7%)	
Severe (O1, O2, O3)	319 (23.5%)	221 (23.3%)	98 (24.0%)	
Gastritis cystic profunda	220 (16.2%)	147 (15.5%)	73 (17.9%)	0.304

C, closed; O, open.

were 0.787 (95% CI 0.701–0.874), 0.762 (95% CI 0.683–0.841), and 0.845 (95% CI 0.786–0.904) for the training set at 2, 3, and 5 years, respectively (Figure 3(a)). The c-indexes for the test set were 0.764 (95% CI 0.628–0.900), 0.824 (95% CI 0.721–0.927), and 0.788 (95% CI 0.662–0.914; Figure 3(b)). The accuracy of the nomogram was validated by a strong correlation between the predicted and observed probabilities, as illustrated in the calibration plot (Figure 3(c) and (d)). In both the training and test sets, the *p*-values for the Hosmer–Lemeshow (H–L) tests were 0.92 and 0.36, respectively, indicating no significant difference between the predicted and actual values.

MASLD and CD combined with AG for the occurrence of MGC

The cumulative incidence of MGC was analyzed for five risk factors, demonstrating statistical significance ($p < 0.001$) in sFigures 1 and 2 (in the Supplemental Material), and Figure 4. The Kaplan–Meier method revealed a higher occurrence of MGC in the MASLD and CD groups with severe AG ($p < 0.001$; Figure 4(a)–(d)). sFigure 3 (in the Supplemental Material) showed MGC development in different *H. pylori* status and AG groups, with a shorter time interval observed in the groups with persistent *H. pylori* infection and AG of O3.

The incidence of MGC was 5.83, 18.55, and 34.82 per 1000 person-year in mild (C0, C1), moderate (C2, C3), and severe (O1, O2, O3) mucosal atrophy groups, respectively (Table 3). The MASLD group exhibited higher incidence rates of MGC at 13.71, 51.11, and 80.00 per 1000 person-years in different subgroups compared to the non-MASLD group. Similarly, the CD group also had higher incidence rates of MGC. Additional information regarding the incidence of MGC in the groups of smoking, different *H. pylori* infection status, and number of lesions can be found in sTables 1–3 (in the Supplemental Material).

Discussion

Previous studies have shown that ER carries a higher risk of developing MGC (HR 6.72, 95% CI, 2.00–22.58) compared to gastrectomy.[28]

Table 2. Univariate and multivariate Cox analyses associated with the occurrence of MGC after curative ESD.

Characteristics	Non-MGC	MGC	Univariate analysis		Multivariate analysis	
	N = 885	*N* = 65	HR (95% CI)	*p*	HR (95% CI)	*p*
Age, years	64 (57–70)	65 (60–69)	1.02 (0.99–1.05)	0.146		
Gender				0.018		
Male	612 (69.2%)	55 (84.6%)	Ref.			
Female	273 (30.8%)	10 (15.4%)	0.45 (0.23–0.89)			
Smoking history	307 (34.7%)	39 (60.0%)	2.69 (1.64–4.42)	<0.001	2.39 (1.25–4.58)	0.009
Drinking history	262 (29.6%)	29 (44.6%)	1.76 (1.08–2.86)	0.022		
Tumor family	178 (20.1%)	16 (24.6%)	1.27 (0.72–2.24)	0.404		
Hypertension	233 (26.4%)	25 (38.5%)	1.77 (1.08–2.93)	0.023		
Diabetes	80 (9.0%)	9 (13.8%)	1.68 (0.83–3.40)	0.145		
MASLD	72 (8.1%)	15 (23.1%)	3.71 (2.08–6.63)	<0.001	2.44 (1.23–4.87)	0.011
Cardiovascular disease	50 (5.7%)	3 (4.6%)	0.88 (0.28–2.81)	0.828		
CD	34 (3.8%)	8 (12.3%)	3.46 (1.65–7.26)	<0.001	2.55 (1.09–5.99)	0.031
Kidney disease	30 (3.4%)	8 (12.3%)	3.97 (1.89–8.33)	<0.001		
Respiratory disease	36 (4.1%)	0 (0.0%)	–	0.119		
Helicobacter pylori status				<0.001		
Negative	145 (16.4%)	6 (9.2%)	Ref.			
Eradicated	689 (77.9%)	42 (64.6%)	1.49 (0.63–3.51)		1.42 (0.60–3.39)	0.424
Persistent	51 (5.8%)	17 (26.2%)	6.76 (2.66–17.2)		5.47 (2.13–14.03)	<0.001
Tumor size, cm				0.868		
<2	527 (59.5%)	37 (56.9%)	Ref.			
⩾2	358 (40.5%)	28 (43.1%)	0.96 (0.59–1.57)			
Location				0.852		
Upper	371 (41.9%)	30 (46.2%)	Ref.			
Medium	231 (26.1%)	16 (24.6%)	1.16 (0.63–2.13)			
Lower	283 (32.0%)	19 (29.2%)	0.97 (0.54–1.72)			
Multiple lesions	124 (14.0%)	22 (33.8%)	3.24 (1.93–5.42)	<0.001	2.06 (1.17–3.63)	0.012
Gross appearance				0.035		
Protruding	272 (30.7%)	19 (29.2%)	Ref.			
Flatted	234 (26.4%)	25 (38.5%)	1.80 (0.99–3.27)			
Depressed	379 (42.8%)	21 (32.3%)	0.89 (0.48–1.67)			

(Continued)

Table 2. (Continued)

Characteristics	Non-MGC	MGC	Univariate analysis		Multivariate analysis	
	N = 885	*N* = 65	HR (95% CI)	*p*	HR (95% CI)	*p*
Depth of invasion				0.477		
Mucosa	682 (77.1%)	45 (69.2%)	Ref.			
Submucosa	203 (22.9%)	20 (30.8%)	1.21 (0.71–2.06)			
Differentiation				0.141		
Differentiated type	774 (87.5%)	60 (92.3%)	Ref.			
Undifferentiated type	111 (12.5%)	5 (7.7%)	0.51 (0.20–1.27)			
Ulceration	67 (7.57%)	4 (6.2%)	0.67 (0.25–1.86)	0.443		
AG				<0.001		
Mild (C0, C1)	210 (23.7%)	3 (4.6%)	Ref.		Ref.	
Moderate (C2, C3)	476 (53.8%)	40 (61.5%)	6.47 (2.00–20.9)		4.44 (1.36–14.53)	0.014
Severe (O1, O2, O3)	199 (22.5%)	22 (33.8%)	11.5 (3.43–38.6)		7.30 (2.11–25.22)	0.002
Gastritis cystic profunda	133 (15.0%)	14 (21.5%)	1.64 (0.91–2.97)	0.097		

AG, atrophic gastritis; C, closed; CD, cerebrovascular disease; CI, confidence interval; ESD, endoscopic submucosal dissection; HR, hazard ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; MGC, metachronous gastric cancer; O, open.

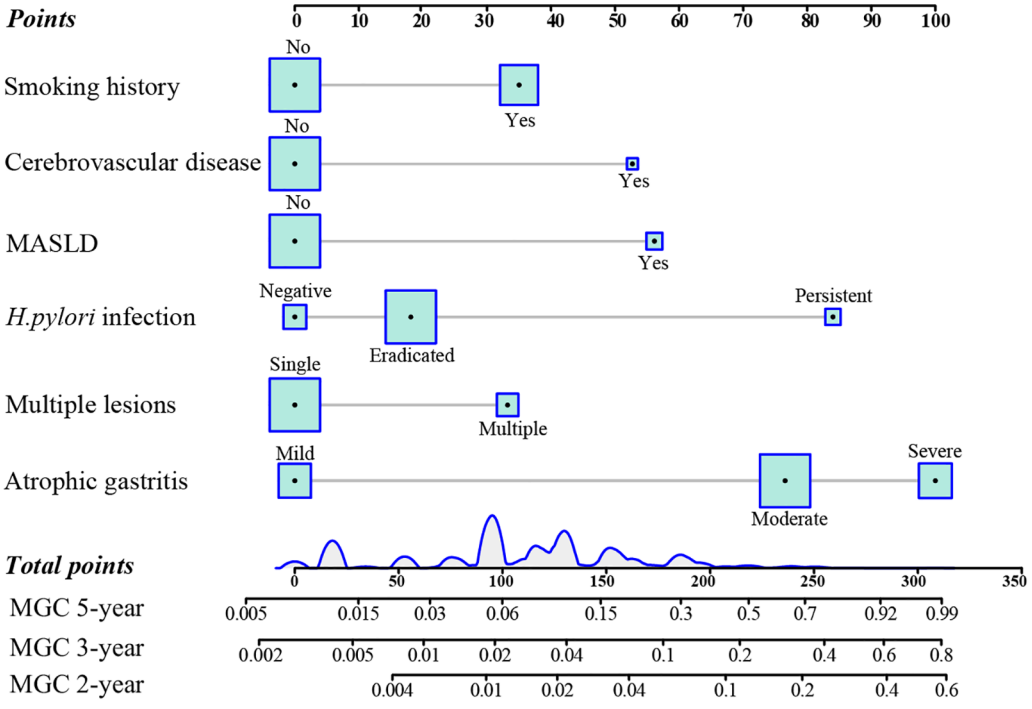

Figure 2. The nomogram for calculating the likelihood of occurrence of MGC after curative ESD.
ESD, endoscopic submucosal dissection; MASLD, metabolic dysfunction-associated steatotic liver disease; MGC, metachronous gastric cancer.

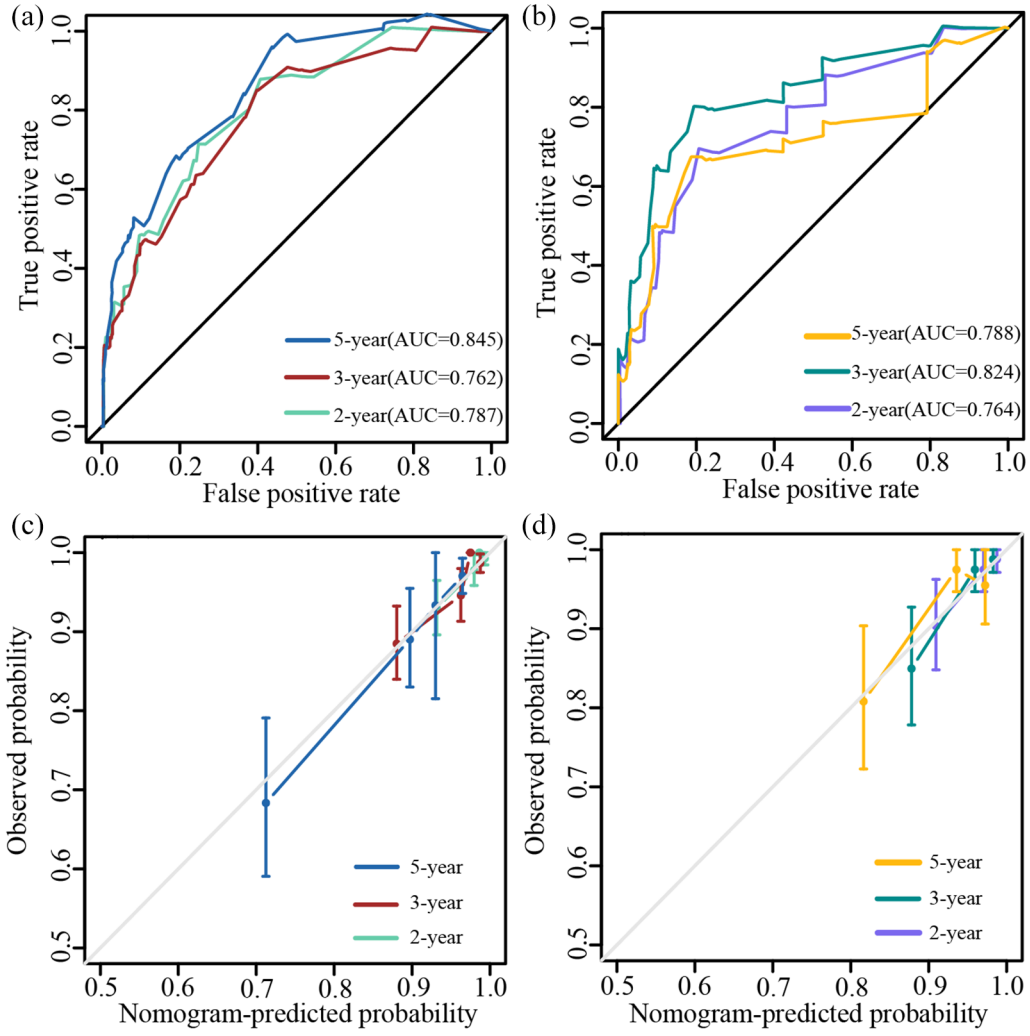

Figure 3. The training set and the test set in the nomogram model. (a, b) Receiver operating characteristic curves at different time points for the training set (a) and the test set (b). (c, d) Calibration plot at different time points for the training set (c) and the test set (d).

Metachronous recurrence rates were significantly lower in the negative (4.1%) and eradicated (5.2%) groups compared to the persistent group (25.7%) during a median follow-up of 39 months. Our study identified several independent risk factors for MGC, including smoking history, MASLD, CD, and *H. pylori* infection. This provides a new method for risk stratification of MGC after curative ESD.

Consistent with previous research, current smoking was associated with a higher risk of MGC (HR 1.5–2.1, $p < 0.05$).[10,29,30] Our study found that both ex-smokers and active smokers had an increased risk of MGC compared to never smokers (HR 2.39, 95% CI 1.25–4.58, $p = 0.009$). The association between *H. pylori* infection and MGC development is widely discussed, with conflicting findings regarding the effect of *H. pylori* eradication on preventing MGC. The trial at the National Cancer Center in South Korea reported a reduced cumulative incidence of MGC in the eradicated group during a median follow-up of 5.9 years.[31] However, other studies have conflicting results. Choi et al.[32] reported that *H. pylori* eradication after ER in a prospective trial did not reduce MGC incidence during a median follow-up of 3 years.[27] In our study, the incidence of MGC in the eradicated group was similar to the negative group but lower than the persistent group (persistent vs negative: HR 5.47, 95% CI 2.13–14.03). A meta-analysis indicated that patients with

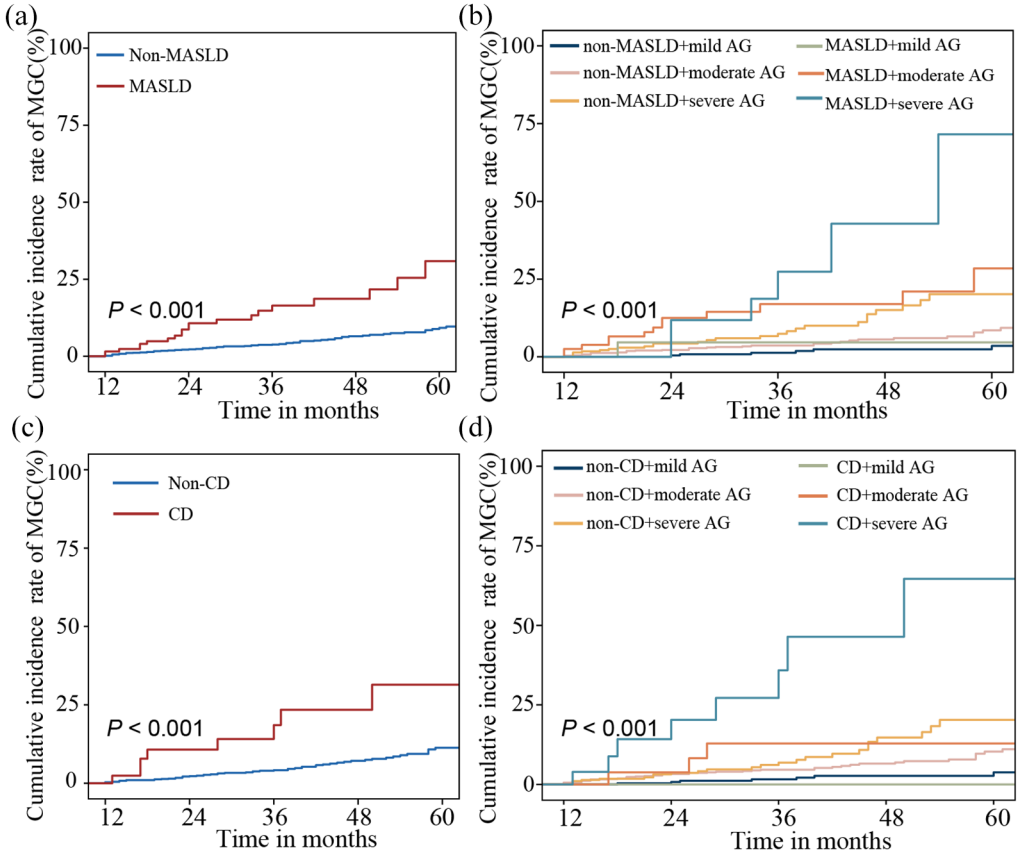

Figure 4. The cumulative incidence of MGC after curative ESD between different MASLD groups (a) or MASLD combined with different AG groups (b), CD (c), or CD combined with different AG groups (d).
AG, atrophic gastritis; CD, cerebrovascular disease; ESD, endoscopic submucosal dissection; MASLD, non-alcoholic fatty liver disease; MGC, metachronous gastric cancer.

severe endoscopic atrophy who underwent ER for early gastric neoplasms have a pooled RR of 1.96 (95% CI 1.39–2.75) for developing MGC.[33,34] Therefore, *H. pylori* eradication before the progression of gastric mucosal atrophy may be beneficial.

The epidemiological evidence supported that excess adiposity and metabolic syndrome have been associated with an increased risk of gastrointestinal cancers.[35,36] Of 1840 patients who underwent upper endoscopies, MASLD was found in 35.7% of GC patients, which was higher than the average in the Turkish population.[37,38] MASLD has also been associated with an increased risk of metachronous colorectal neoplasia in both men (adjusted HR (aHR) 1.17, 95% CI 1.06–1.29) and women (aHR 1.63, 95% CI 1.27–2.07).[39] In our study, the occurrence of MGC in the MASLD and CD groups was not significant among the different *H. pylori* groups (Table 3), for the number of subgroups was too small to reach a definitive conclusion. However, the association was stronger between MASLD (HR 2.44, 95% CI 1.23–4.87, $p < 0.001$), CD (HR 2.55, 95% CI 1.09–5.99), and MGC, but further investigation is needed. Multiple lesions (HR 2.06, 95% CI 1.17–3.63) were also identified as a risk factor for MGC, consistent with previous studies.[6,40–42]

While various studies have explored the risk factors of MGC, only a few nomograms have been established for predicting MGC. The FAMISH score, which includes six clinical predictors—male sex, corpus intestinal metaplasia, positive family history of GC, older age, synchronous gastric lesions, and persistent *H. pylori* infection—was useful in identifying patients at low to intermediate risk for MGC recurrence.[43,44] Other predictive factors, such as a tumor-positive lateral margin and a lateral safety margin of less than 5 mm, were also associated with an increased risk

Table 3. MGC occurrence among different MASLD or CD groups with different AG (Cox regression analysis).

Comorbidities		Number of MGC (%)		Incidence of MGC (per 1000 person-year)
Overall ($n = 1358$)				
C0 and C1 ($n = 300$)		7 (2.33)		5.83
C2 and C3 ($n = 739$)		49 (6.63)		18.55
O1, O2, and O3 ($n = 319$)		33 (10.34)		34.82
	Pairwise comparisons		*p*-Value	
	C0 and C1 vs O1, O2, and O3		<0.001	
	C2 and C3 vs O1, O2, and O3		0.002	
	C0 and C1 vs C2 and C3		0.003	
non-MASLD ($n = 1228$)				
C0 and C1 ($n = 278$)		6 (2.16)		5.33
C2 and C3 ($n = 659$)		36 (5.46)		15.08
O1, O2, and O3 ($n = 291$)		27 (9.28)		30.93
	Pairwise comparisons		*p*-Value	
	C0 and C1 vs O1, O2, and O3		<0.001	
	C2 and C3 vs O1, O2, and O3		0.002	
	C0 and C1 vs C2 and C3		0.013	
MASLD ($n = 130$)				
C0 and C1 ($n = 22$)		1 (4.55)		13.71
C2 and C3 ($n = 80$)		13 (16.25)		51.11
O1, O2, and O3 ($n = 28$)		6 (21.43)		80.00
	Pairwise comparisons		*p*-Value	
	C0 and C1 vs O1, O2, and O3		0.097	
	C2 and C3 vs O1, O2, and O3		0.312	
	C0 and C1 vs C2 and C3		0.214	
non-CD ($n = 1298$)				
C0 and C1 ($n = 293$)		7 (2.39)		5.98
C2 and C3 ($n = 712$)		46 (6.46)		18.10
O1, O2, and O3 ($n = 293$)		25 (8.53)		28.49
	Pairwise comparisons		*p*-Value	
	C0 and C1 vs O1, O2, and O3		<0.001	

(Continued)

Table 3. (Continued)

Comorbidities		Number of MGC (%)	Incidence of MGC (per 1000 person-year)
	C2 and C3 vs O1, O2, and O3	0.033	
	C0 and C1 vs C2 and C3	0.004	
CD ($n = 60$)			
C0 and C1 ($n = 7$)		0 (0)	–
C2 and C3 ($n = 27$)		3 (11.11)	29.83
O1, O2, and O3 ($n = 26$)		8 (30.77)	113.61
	Pairwise comparisons	*p*-Value	
	C0 and C1 vs O1, O2, and O3	–	
	C2 and C3 vs O1, O2, and O3	0.056	
	C0 and C1 vs C2 and C3	–	

AG, atrophic gastritis; C, closed; CD, cerebrovascular disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MGC, metachronous gastric cancer; O, open.

of MGC recurrence.[45] In our study, we developed a nomogram that integrates demographics, comorbidities, *H. pylori* infection status, and endoscopic and histologic features to identify the risk factors for MGC. Unlike previous studies that separated the risk factors,[6–9,12] our nomogram integrated these risk factors to provide an individualized prediction, thus capturing the heterogeneity among patients. Based on the six risk factors of smoking history, MASLD, CD, multiple lesions, *H. pylori* infection, and AG, we plotted a nomogram and evaluated the predictive accuracy, which seemed useful and meaningful in predicting the likelihood of MGC after curative ESD. Several variables such as drinkers and differentiation did not notably demonstrate predictive ability in our cohort, potentially due to the influence of these institution-dependent variables. The nomogram demonstrated good discrimination and calibration, with higher c-index values and improved predictive accuracy compared to previous models (c-index of 0.72).[46] Based on the predicted risk, endoscopic surveillance is recommended every 4 years for scores $\leqslant$55. For scores between 55 and 165, surveillance every 2 years is advised, while annual endoscopic surveillance is recommended for sum scores $\geqslant$165. The user-friendly graphical interface of the nomogram may facilitate its use in clinical decision-making and guide follow-up strategies for patients after ESD. The nomogram could be widely used if it is verified in the prospective cohort studies and multicenter validation studies.

However, our study has some limitations. First, the study population was collected at a single tertiary referral center and was performed retrospectively. Second, while the study population was large, the distribution of patients with different *H. pylori* status was uneven. Third, not all patients underwent annual endoscopic follow-ups, and there was a time lag between the actual MGC occurrence and the medical records. Otherwise, the follow-up retrospective review of previous imaging was not considered in the definition of MGC, which could lead to an overestimation of the actual occurrence of MGC. Fourth, some important genetic and epigenetic markers that had shown promise in the prediction of MGC were not detected in our population.[47,48] Fifth, the evaluation of metachronous recurrence for 5-, 7-, and 10-year was inadequate due to the median duration of follow-up being 39 months. Therefore, more frequent and longer endoscopic and imaging surveillance for MGC should be performed. Thus, further large-scale cohort studies with

longer follow-ups are necessary to evaluate the risk factors for MGC after curative ESD.

Conclusion

The nomogram we developed, incorporating smoking history, MASLD, CD, multiple lesions, *H. pylori* status, and AG as independent risk factors, shows good discrimination and calibration. It could be used to calculate individualized probabilities of MGC and guide surveillance strategies. The clinical utility of this predictive nomogram should be tested in prospective randomized controlled trials in the future.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were approved by the Human Ethics Review Committees of the Nanjing Drum Tower Hospital (the approval number: 2024-395-01). This research was retrospective and the data on patients were anonymous. Verbal informed consent was obtained from each patient and the requirement for informed consent was waived by the Ethics Committee.

Consent for publication

All the data were anonymous and patient images were not reported in our study. Verbal informed consent for publication was obtained from each patient or guardian.

Author contributions

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Supplemental material

Supplemental material for this article is available online.

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Appendix

Abbreviations

AG	atrophic gastritis
C	closed
CD	cerebrovascular disease
EGC	early gastric cancer
ER	endoscopic resection
ESD	endoscopic submucosal dissection
GC	gastric cancer
HR	hazard ratio
MASLD	metabolic dysfunction-associated steatotic liver disease
MGC	metachronous gastric cancer
O	open