Gut and Liver
https://doi.org/10.5009/gnl220060
pISSN 1976-2283 eISSN 2005-1212

Original Article

A Prediction Model Based on the Risk Factors Associated with Pathological Upgrading in Patients with Early-Stage Gastric Neoplasms Diagnosed by Endoscopic Forceps Biopsy

Yu Han Zhao[1], Yu Zheng[2], Jie Sha[3], Hong Jin Hua[4], Ke Dong Li[4], Yu Lu[1], Yi Ni Dang[1], and Guo Xin Zhang[1]

Departments of [1]Gastroenterology and [2]Rehabilitation Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, [3]Department of Gastroenterology, Jingjiang People's Hospital, Jingjiang, and [4]Department of Pathology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Article Info

Received February 12, 2022
Revised April 25, 2022
Accepted May, 13, 2022
Published online September 2, 2022

Corresponding Author

Guo Xin Zhang
ORCID https://orcid.org/0000-0002-7103-3630
E-mail guoxinz@njmu.edu.cn

Yi Ni Dang
ORCID https://orcid.org/0000-0001-6449-516X
E-mail yeani_hi@126.com

Yu Han Zhao and Yu Zheng contributed equally to this work as first authors.

Background/Aims: The discrepancies between the diagnosis of preoperative endoscopic forceps biopsy (EFB) and endoscopic submucosal dissection (ESD) in patients with early gastric neoplasm (EGN) exist objectively. Among them, pathological upgrading directly influences the accuracy and appropriateness of clinical decisions. The aims of this study were to investigate the risk factors for the discrepancies, with a particular focus on pathological upgrading and to establish a prediction model for estimating the risk of pathological upgrading after EFB.

Methods: We retrospectively collected the records of 978 patients who underwent ESD from December 1, 2017 to July 31, 2021 and who had a final histopathology determination of EGN. A nomogram to predict the risk of pathological upgrading was constructed after analyzing subgroup differences among the 901 lesions enrolled.

Results: The ratio of pathological upgrading was 510 of 953 (53.5%). Clinical, laboratorial and endoscopic characteristics were analyzed using univariable and binary multivariable logistic regression analyses. A nomogram was constructed by including age, history of chronic atrophic gastritis, symptoms of digestive system, blood high density lipoprotein concentration, macroscopic type, pathological diagnosis of EFB, uneven surface, remarkable redness, and lesion size. The C-statistics were 0.804 (95% confidence interval, 0.774 to 0.834) and 0.748 (95% confidence interval, 0.664 to 0.832) in the training and validation set, respectively. We also built an online webserver based on the proposed nomogram for convenient clinical use.

Conclusions: The clinical value of identifying the preoperative diagnosis of EGN lesions is limited when using EFB separately. We have developed a nomogram that can predict the probability of pathological upgrading with good calibration and discrimination value. **(Gut Liver 2023;17:78-91)**

Key Words: Early gastric neoplasm; Pathological upgrading; Prediction model; Endoscopic forceps biopsy; Endoscopic submucosal dissection

INTRODUCTION

Early gastric neoplasm (EGN) is a group including low grade intraepithelial neoplasia (LGIN), high grade intraepithelial neoplasia (HGIN), and early gastric carcinoma (EGC).[1-4] LGIN and HGIN, for which the differences lie in the degree of cellular or structural heterogeneity, are ascribed as dysplasia and classified as precursor lesions. In current guidelines, endoscopic submucosal dissection (ESD) is preferred for EGN to prevent the deterioration of EGC to progressive gastric cancer, which has the following advantages: minimally invasive, faster recovery, higher curative ratio, and preservation of gastric function.[5-8] Advanced endoscopic instruments, such as chromoendoscopy, high-definition white-light endoscopy, narrow-band imaging, are not yet widely applied and not easily mastered, and conventional white-light endoscopy in combination with endoscopic forceps biopsy (EFB) is under routine

practice in the clinical context.

EFB is an important tool for the histopathological diagnosis of EGN. With multiple EFB, the diagnostic efficiency would be improved to some extent based on literature review and our clinical experience.[9,10] However, further biopsies were not able to increase positive diagnosis cumulative rates, and may increase workload and medical cost, and may lead to trauma, bleeding, or perforation.[11,12] On the other hand, the pathological outcomes of EFB and ESD are often inconsistent. These discrepancies could be divided into downgrading and upgrading. It has been reported that the overall rate of discrepancy between EFB and ESD ranges from 20.1% to 76.3%,[10,11] with 16.3% to 44.9% pathological upgrading ultimately.[7-9,12-16] In addition, the pathological upgrading group showed a significant tendency of submucosal invasion and lymphovascular/perineural invasion, which would lead to endoscopic noncurative resection and suboptimal prognostic results.[17,18] Therefore, the question in front of us is how to classify patients with increased risk of pathological upgrading upon EFB. Indeed, it may be attributed to the experience of the endoscopist, but also highly associated with morphological features or biological characteristics of the lesion itself. Hitherto the risk factors associated with pathological upgrading remain unclear and the lack of a visual assessment model in clinical practice has led to insignificant improvements in diagnostic compliance.[16]

Considering the above concerns, this retrospective study was designed: (1) to investigate the risk factors of histological discrepancies between EFB and ESD, with a particular focus in pathological upgrading, and (2) to establish a prediction model in estimating the risk of pathological upgrading upon EFB.

MATERIALS AND METHODS

1. Study design and settings

This is a retrospective single-center cohort study to explore the risk factors for pathological upgrading between EFB and ESD in patients with EGN. The secondary outcome was to construct a nomogram to show the predictive efficacy of detected risk factors on pathological upgrading. This clinical study consisted of two stages. The first stage (training set) retrospectively identified patients diagnosed with EGN according to EFB or ESD in the First Affiliated

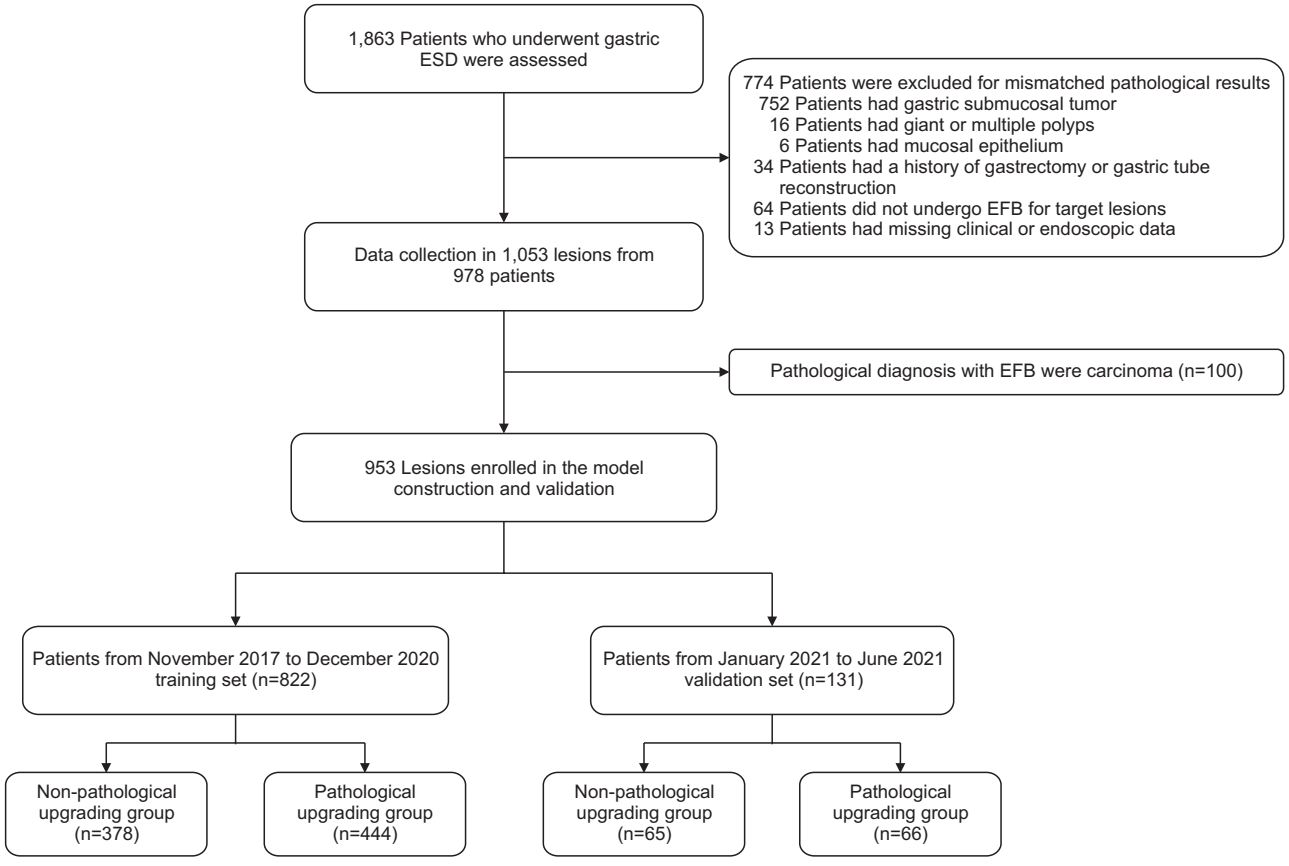

Fig. 1. Flowchart of the study. The "n" in parentheses represents lesions.
ESD, endoscopic submucosal dissection; EFB, endoscopic forceps biopsy.

Hospital of Nanjing Medical University from December 2017 to December 2020. The second stage (validation set) included patients from January 2021 to July 2021. The detailed procedure of the study is shown in Fig. 1. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the First Affiliated Hospital of Nanjing Medical University (IRB number: 2021-SR-227). It has been previously registered in Chinese Clinical Trial Registry (ChiCTR2100048088). Informed consent was waived due to the nature of the study design.

2. Study population

From December 2017 to July 2021, a total of 1,863 patients underwent gastric ESD. Indications followed the Japanese gastric cancer treatment guidelines 2018 (5th edition).[6] Endoscopic refinement is recommended for suspected lesions, with endoscopic interventions if necessary.[19,20] The target population were diagnosed with EGN according to EFB or ESD. Initially, 774 patients were excluded because of pathological diagnosis of ESD was inconsistent with the purpose of this study. After further data collection, patients were excluded if: (1) with a history of gastrectomy or gastric tube reconstruction; (2) did not undergo EFB for target lesions; or (3) with no clinical or endoscopic data. After excluding lesions of which pathological diagnosis with EFB were carcinoma, the lesions were divided into two groups (training set and validation set). Training set was analyzed to develop the nomogram model to predict the risk of pathological upgrading. The validation set was used to further external validate the predictive model. Lesions that presented as pathological consistency or pathological downgrading were assigned into the non-pathological upgrading group.

3. Pathological diagnostic criteria

Collection of biopsies before ESD were conducted in our center and the pathological diagnosis was confirmed by at least two experienced pathologists. However, according to the routine clinical practice, part of EFB may be conducted prior to the patients' admission to our center, therefore repeating endoscopic procedures would be performed for non-neoplastic pathology or questionable discrepancies between the pathologic results obtained at our institu-

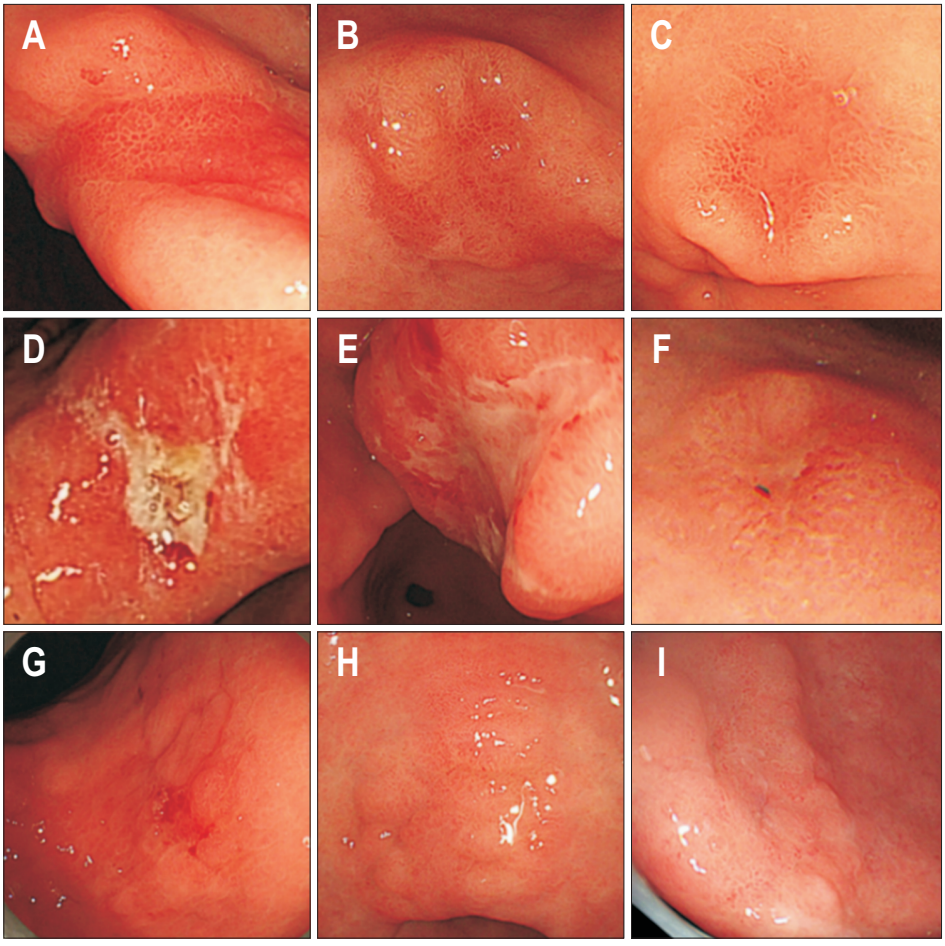

Fig. 2. Illustrations of the endoscopic features. (A-C) Lesions with remarkable redness. (D-F) Lesions with ulceration or scaring. (G-I) Lesions with an uneven surface.

tion and at the referring hospital.[14] The gastroenterologist would evaluate lesions for the indication of ESD based on pathological and endoscopic records. The ESD consent form was signed on the patient's own wishes. In fact, even though additional surgeries may be required due to exceeding ESD indications, the majority of target patients in our institution chose to undergo ESD first, based on the advantages of ESD, even though additional surgeries may be required due to exceeding ESD indications,[17,18,21] which ensured us screening up sufficient study population.

In this study, we followed the World Health Organization pathological diagnostic criteria in digestive system.[1] We enrolled patients with different pathological outcomes (e.g., acute inflammation, chronic gastric atrophy, gastric intestinal metaplasia, LGIN, HGIN, and intramucosal carcinoma) and prespecified principles to define pathological upgrading and non-upgrading according to EFB and ESD examinations. For instance, if one patient showed LGIN during EFB while the pathological grade was reported as HGIN or carcinoma following ESD, this was identified as pathological upgrading. On the other hand, if one patient showed lower or consistent pathological grade after ESD as compared to that from EFB, they were finally assigned as non-pathological upgrading.[14,22]

4. Data collection

Demographic (e.g., age, sex, and body mass index) and clinical data (e.g., *Helicobacter pylori* infection status, medical history, and comorbidity), and EFB information were collected during patients' admission before ESD according to their medical records. Endoscopic data (e.g., location, macroscopic type, and lesion size) were collected during ESD and pathological information of ESD specimens were collected according to pathological reports. In case of multiple lesions, one patient was treated as two cases and distinguished with their pathological characteristics.

Individual medical history and digestive comorbidity was defined positive as written down in medical records or outpatient documents. Symptoms of digestive system were considered as existing if the following words appeared in the records: abdominal pain, nausea, vomiting, dyspepsia, eructation, heartburn, loss of appetite, weight loss.

Ulceration or ulcer scar was considered positive after excluding those caused by the biopsy.[23] Remarkable redness was defined as discoloration on the mucosal surface of the lesion compared to the surrounding mucosa, and uneven surface was defined as the presence of irregularly raised or nodular mucosa.[24,25] Fig. 2 shows the following endoscopic features in sequence: remarkable redness, ulceration or scar and uneven surface.

5. Statistical analysis

All of the following statistical analyses were performed with SPSS 23.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as means and standard deviations or medians with interquartile ranges. Categorical variables were demonstrated as numbers and percentages. Differences between groups were assessed using the chi-square test, the Student t-test, or the Mann-Whitney test in the univariate analysis, as appropriate. Variables detected with $p<0.05$ in the univariate logistic regression were further included in the multivariate logistic regression analysis to determine the variables that were independent influencing factors of pathological upgrading.

A predictive nomogram was constructed, based on the variables selected with the multivariate logistic regression analysis and by using the package of rms in R software (rms in R version 4.0.4, R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/). The model was validated internally in the training set and externally in the validation set. A calibration plot with bootstrapping (1,000 replications) was used to illustrate the association between the actual probability and the predicted probability. In addition, five training models were constructed to compare the robustness of each model. The performance of the prediction model was evaluated using the area under the curve (AUC) in receiver operating characteristic analysis. Decision curve analysis was used to explain the utility of benefits in clinical use.

RESULTS

1. Clinical characteristics

We retrospectively collected data for 1,053 lesions from 978 patients who underwent ESD for EGN. The comparison of diagnosis between the original EFB and the final ESD is summarized in Table 1. The predominant pathological upgrading involved upgrading from LGIN to HGIN or carcinoma (n=178) and upgrading from HGIN to carcinoma (n=270). After excluding lesions of which pathological diagnosis with EFB were carcinoma, 822 lesions were enrolled into the training and 131 were enrolled into validation sets. Clinical and endoscopic characteristics are summarized in Tables 2 and 3. Lesions (54.0%, 444/822) showed higher-grade disease after ESD in the training set (LGIN from non-neoplasia, HGIN or carcinoma from LGIN or non-neoplasia, or carcinoma from HGIN).

2. Baseline characteristics

As shown in Table 4, statistical differences were detected in those with history of smoking, drinking, chronic

Table 1. Comparison of Pathological Diagnosis by Initial Biopsy and Final Endoscopic Resection

Pathologic diagnosis with EFB	Pathologic diagnosis with ESD				
	Non-neoplasia	LGIN	HGIN	Carcinoma	Total No. (%)
Non-neoplasia	15†	42*	11*	10*	78 (7.4)
LGIN	11†	293†	108*	70*	482 (45.8)
HGIN	1†	29†	93†	270*	393 (37.3)
Carcinoma	0†	5†	4†	91†	100 (9.5)
Total No. (%)	27 (2.6)	369 (35.0)	216 (20.5)	441 (41.9)	1,053

EFB, endoscopic forceps biopsy; ESD, endoscopic submucosal dissection; LGIN, low grade intraepithelial neoplasia; HGIN, high grade intraepithelial neoplasia.
*Pathological upgrading; †Non-pathological upgrading.

Table 2. Clinical Characteristics of the Training and Validation Sets

Characteristics	Training set (n=822)	Validation set (n=131)
Age, yr	63 (55–69)	63 (57–70)
Male sex	592 (72.0)	103 (78.6)
Body mass index, kg/m^2	23.8±3.3	24.1±2.9
Helicobacter pylori infection		
Negative	289 (35.1)	45 (36.4)
Previous eradicated or infected	533 (64.9)	86 (65.6)
Symptoms of digestive system	599 (72.9)	56 (42.7)
Smoking	198 (24.1)	44 (33.6)
Drinking	78 (20.6)	24 (18.3)
Comorbidity		
History of CAG	466 (56.7)	61 (46.6)
History of peptic ulcer	137 (16.7)	13 (9.9)
Medical history		
Hypertension	258 (31.4)	58 (44.3)
Diabetes	74 (9.0)	14 (10.7)
Coronary heart disease	33 (4.0)	3 (2.3)
History of cholecystectomy	58 (7.1)	19 (14.5)
History of malignancy	80 (9.7)	4 (3.1)
Family history of malignancy	133 (16.2)	12 (9.2)
Laboratory examination		
CEA, ng/mL	3.4±4.6	2.8±4.4
CA19-9, U/mL	12.7±28.2	12.8±8.0
CA724, U/mL	3.9±8.3	4.0±5.0
HDL, mmol/L	1.2±0.3	1.1±0.3
LDL, mmol/L	2.9±0.7	2.8±0.6
Albumin, g/L	39.9±3.9	39.0±3.0
Calcium, mmol/L	2.3±0.1	2.3±0.1

Data are presented as median (range), number (%), or mean±SD.
CAG, chronic atrophic gastritis; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CA724, carbohydrate antigen 724; HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 3. Endoscopic Characteristics of the Training and Validation Sets

Characteristics	Training set (n=822)	Validation set (n=131)
Locations of lesions		
Upper third	241 (29.3)	40 (30.5)
Middle third	93 (11.3)	21 (16.0)
Lower third	488 (59.4)	70 (53.4)
Macroscopic type of lesions		
Elevated	405 (49.3)	55 (42.0)
Flat	197 (24.0)	26 (19.8)
Depressed	220 (26.8)	50 (38.2)
Pathologic diagnosis of EFB		
Non-neoplasia	74 (9.0)	4 (3.1)
LGIN	413 (50.2)	69 (52.7)
HGIN	335 (40.8)	58 (44.3)
Pathologic diagnosis of ESD		
Non-neoplasia	27 (3.3)	
LGIN	314 (38.2)	50 (38.2)
HGIN	179 (21.8)	33 (252)
Carcinoma	302 (36.7)	48 (36.8)
Pathologic upgrading		
Yes	444 (54.0)	66 (50.4)
No	378 (46.0)	65 (49.6)
Multiple lesions	52 (13.8)	24 (18.3)
Endoscopic features		
Ulceration or scar	167 (20.3)	39 (29.8)
Uneven surface	364 (44.3)	64 (48.9)
Remarkable redness	531 (64.6)	88 (67.2)
Lesion size		
≤2 cm	581 (70.7)	78 (59.5)
>2 cm	241 (29.3)	53 (40.5)
Procedure time, min	60 (45–90)	60 (45–90)
Depth of invasion		
M	763 (92.8)	126 (96.2)
SM1	29 (3.5)	1 (0.8)
SM2	30 (3.6)	4 (3.1)

Data are presented as number (%) or median (range).
EFB, endoscopic forceps biopsy; LGIN, low grade intraepithelial neoplasm; HGIN, high grade intraepithelial neoplasm; ESD, endoscopic submucosal dissection; M, intraepithelial and/or the deepest infiltration depth is within the mucosal lamina propria; SM1, the infiltration depth >500 μm from the muscularis mucosae; SM2, the infiltration depth >500 μm from the muscularis mucosae.

atrophic gastritis (CAG), and symptoms of digestive system. History of CAG was less commonly detected in the pathological upgrading group than in the non-pathological upgrading group (50.2% vs 60.9%, p<0.001). The rate of *H. pylori* infection was more than 60% in both groups.

The contradistinction of endoscopic characteristics is presented in Table 5. Pathological upgrading more frequently occurred in lower third (51.1%), followed by upper third (36.5%) and middle third (12.4%) in the upgrading

Table 4. Clinical Characteristics of Lesions with or without Pathological Upgrading

Characteristics	Non-pathological upgrading group (n=378)	Pathological upgrading group (n=444)	p-value*
Age, yr	63 (55–69)	65 (58–70)	<0.001
Male sex	250 (66.1)	342 (77.0)	0.001
Body mass index, kg/m^2	23.6±3.1	23.9±3.4	0.082
Helicobacter pylori infection			0.680
Negative	131 (34.7)	160 (36.0)	
Previous eradicated or infected	247 (65.3)	284 (64.0)	
Symptoms of digestive system	260 (68.8)	339 (76.4)	0.015
Smoking	105 (27.8)	159 (35.8)	0.014
Drinking	78 (20.6)	120 (27.0)	0.033
Comorbidity			
History of CAG	243 (64.3)	223 (50.2)	<0.001
History of peptic ulcer	71 (15.4)	82 (18.5)	0.224
Medical history			
Hypertension	104 (27.5)	154 (34.7)	0.073
Diabetes	30 (7.9)	44 (9.9)	0.270
Coronary heart disease	11 (2.9)	22 (5.0)	0.269
History of cholecystectomy	22 (5.8)	36 (8.1)	0.236
History of malignancy	35 (9.3)	45 (10.1)	0.531
Family history of malignancy	61 (16.1)	72 (16.2)	0.700
Laboratory examination			
CEA, ng/mL	3.3±4.5	3.5±4.4	0.398
CA19-9, U/mL	12.4±30.5	13.1±26.2	0.734
CA724, U/mL	4.0±9.7	3.8±6.9	0.682
HDL, mmol/L	1.2±0.3	1.1±0.2	0.015
LDL, mmol/L	2.9±0.7	2.9±0.7	0.099
Albumin, g/L	40.2±3.6	39.7±4.2	0.056
Calcium, mmol/L	2.3±0.1	2.2±0.1	0.004

Data are presented as median (range), number (%), or mean±SD.
CAG, chronic atrophic gastritis; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CA724, carbohydrate antigen 724; HDL, high density lipoprotein; LDL, low density lipoprotein.
*p-value was derived from the chi-square test, Student t-test, or Mann-Whitney test.

group. The predominant macroscopic type in both groups was elevated pattern, with a gradual tendency of depressed pattern in the pathological upgrading group. The endoscopic ulceration, uneven surface, remarkable redness was found to account for 26.8%, 56.1%, and 75.4% in cases of pathological upgrading, accordingly.

3. Analysis of risk predictors

Multivariate analysis (logistic regression analysis) was further performed to analyze the variables that were statistically significant in univariate analysis. Ultimately, a total of nine variables which pertained to clinical, laboratorial, endoscopic characteristics separately were enrolled to build the clinical prediction model. As revealed in Table 6, history of CAG (odds ratio [OR], 0.59; 95% confidence interval [CI], 0.42 to 0.84; p=0.003), blood high density lipoprotein (HDL) concentration (OR, 0.46; 95% CI, 0.24 to 0.86; p<0.016) were protective predictors. Age, symptoms of digestive system, macroscopic type of lesions, pathologic diagnosis of EFB, remarkable redness were risk factors, while uneven surface (OR, 2.35; 95% CI, 1.66 to 3.32; p<0.001), lesion size >2 cm (OR, 2.20; 95% CI, 1.50 to 3.22; p<0.001) were independent risk predictors.

4. Dynamic nomogram construction and validation

We developed a nomogram to predict the risk of pathological upgrading in patients with EGN (Fig. 3). For instance, a 65-year-old patient, with a previous history of CAG, without symptoms of digestive system, and blood HDL concentration of 1.0 mmol/L, was found to have an elevated lesion with remarkable redness and uneven surface, and less than 2 cm in diameter at endoscopy. If the EFB pathology was HGIN, the incidence of pathological upgrading would be 65.1% (95% CI, 0.522 to 0.761). The online version of our nomogram software is accessible at https://zyh-njmu.shinyapps.io/Dynamic_nomogram/.

We performed validation by using the bootstrap method with 1,000 repetitions to display the calibration of the nomogram (Fig. 4A and B). Accuracy of the nomogram was examined with AUC. The C-statistics for our nomogram model was 0.804 (95% CI, 0.774 to 0.834) and 0.748 (95% CI, 0.664 to 0.832) in the training and validation set, respectively (Fig. 4C and D).

To assess the predictive ability of our nomogram, sev-

Table 5. Endoscopic Characteristics and Posttreatment Evaluation of the Lesions with or without Pathological Upgrading

Characteristics	Non-pathological upgrading group (n=378)	Pathological upgrading group (n=444)	p-value*
Locations of lesions			<0.001
Upper third	79 (20.9)	162 (36.5)	
Middle third	38 (10.1)	55 (12.4)	
Lower third	261 (69.0)	227 (51.1)	
Macroscopic type of lesions			<0.001
Elevated	206 (54.5)	199 (44.8)	
Flat	106 (28.0)	91 (20.5)	
Depressed	66 (17.5)	154 (34.7)	
Pathologic diagnosis of EFB			<0.001
Non-neoplasia	16 (3.5)	58 (13.1)	
LGIN	261 (56.7)	152 (34.2)	
HGIN	101 (22.0)	234 (52.7)	
Multiple lesions	52 (13.8)	68 (15.3)	0.528
Endoscopic features			
Ulceration or scar	48 (12.7)	119 (26.8)	<0.001
Uneven surface	115 (30.4)	249 (56.1)	<0.001
Remarkable redness	197 (52.1)	334 (75.4)	<0.001
Lesion size			<0.001
≤2 cm	306 (81.0)	275 (61.9)	
>2 cm	72 (19.0)	169 (38.1)	
Procedure time, min	60 (45–90)	60 (45–100)	<0.001
Depth of invasion			<0.001
M	378 (95.0)	385 (86.7)	
SM1	-	29 (6.5)	
SM2	-	27 (6.8)	

Data are presented as number (%) or median (range).
EFB, endoscopic forceps biopsy; LGIN, low grade intraepithelial neoplasm; HGIN, high grade intraepithelial neoplasm; M, intraepithelial and/or the deepest infiltration depth is within the mucosal lamina propria; SM1, the infiltration depth >500 μm from the muscularis mucosae; SM2, the infiltration depth >500 μm from the muscularis mucosae.
*p-value was derived from chi-square test or Mann-Whitney test.

Table 6. Univariate and Multivariate Regression Analyses of the Predictors Associated with Pathological Upgrading According to the Analyzed Variables

Factor	Univariate logistic analysis		Multivariate logistic analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.05 (1.03–1.06)	<0.001	1.04 (1.03–1.06)	<0.001
Sex (ref. male)	0.60 (0.44–0.82)	0.001		
Smoking (ref. no)	1.38 (1.02–1.87)	0.036		
Drinking (ref. no)	1.39 (1.03–1.89)	0.034		
Comorbidity: CAG (ref. no)	0.47 (0.35–0.63)	<0.001	0.47 (0.33–0.68)	<0.001
Symptoms of digestive system (ref. no)	1.44 (1.05–1.97)	0.025	1.60 (1.08–2.36)	0.019
Laboratory examination: HDL	0.34 (0.20–0.58)	<0.001	0.44 (0.24–0.81)	0.008
Laboratory examination: calcium	0.09 (0.02–0.37)	0.001		
Locations of lesions (ref. upper third)	1.00			
Middle third	0.71 (0.43–1.18)	0.187		
Lower third	0.40 (0.29–0.56)	0.001		
Macroscopic type of lesions (ref. elevated)	1.00		1.00	
Flat	0.84 (0.60–1.19)	0.331	0.74 (0.48–1.13)	0.164
Depressed	2.25 (1.68–3.20)	<0.001	1.63 (1.13–2.32)	0.045
Pathological diagnosis of EFB (ref. non-neoplasia)	1.00		1.00	
LGIN	0.01 (0.01–0.08)	<0.001	0.01 (0.01–0.06)	<0.001
HGIN	0.04 (0.01–0.30)	0.002	0.02 (0.01–0.13)	<0.001
Endoscopic features: ulceration or scar (ref. no)	2.63 (1.79–3.84)	<0.001		
Endoscopic features: uneven surface (ref. no)	2.69 (2.01–3.60)	<0.001	2.24 (1.58–3.19)	<0.001
Endoscopic features: remarkable redness (ref. no)	2.95 (2.19–3.99)	<0.001	2.26 (1.57–3.27)	<0.001
Lesion size (ref. ≤2 cm)	2.47 (1.78–3.41)	<0.001	2.20 (1.49–3.24)	<0.001

OR, odds ratio; CI, confidence interval; ref., reference group; CAG, chronic atrophic gastritis; HDL, high density lipoprotein; EFB, endoscopic forceps biopsy; LGIN, low grade intraepithelial neoplasm; HGIN, high grade intraepithelial neoplasm.

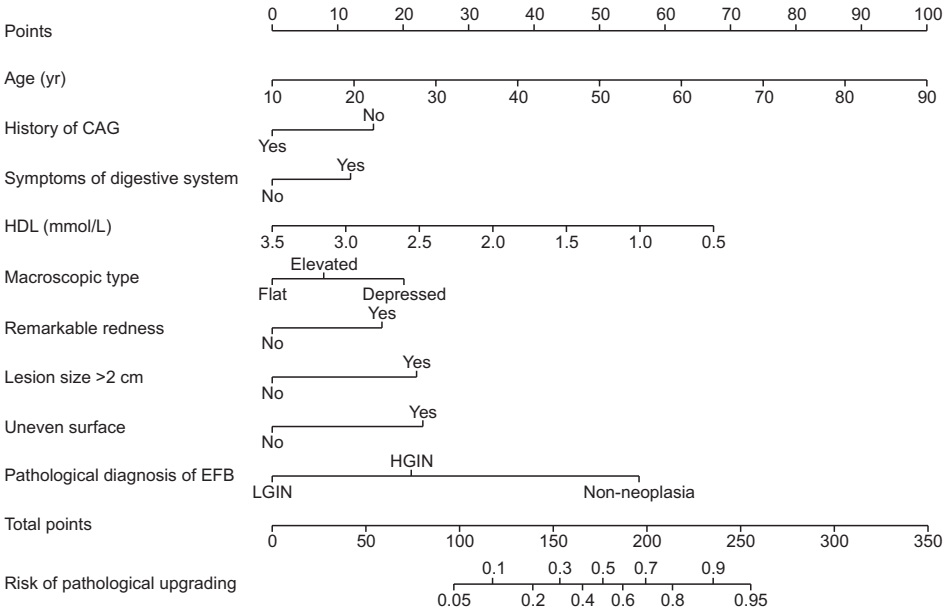

Fig. 3. Illustration of the prediction nomogram model based on clinical, laboratorial, endoscopic characteristics.
CAG, chronic atrophic gastritis; HDL, high density lipoprotein; EFB, endoscopic forceps biopsy; LGIN, low grade intraepithelial neoplasm; HGIN, high grade intraepithelial neoplasm.

eral training schemes (namely training models 1 to 5) were constructed (Fig. 5). Afterwards, we performed internal validation and AUC computation for training models 1 to 5 and EFB, and the calibration plot and C-statistics for each model were shown in Figs 6 and 7, respectively.

DISCUSSION

EFB and ESD are used for diagnosis of EGN. However, EFB is not able to show histology of the entire lesion, which may lead to discrepancy between histological diagnosis of EFB and resected specimen. Therefore, it is urgently needed to establish a clinical predictive tool to identify the risk of pathological upgrading. Nomogram is a visualization prediction tool that can incorporate different variables affecting outcomes.[26] We developed a nomogram for pathological upgrading in patients received EFB before ESD which showed a steady accuracy in evaluating the risk of pathological upgrading.

In the current study, rate of pathological upgrading was 44.9%. It was similar to the results of previous studies.[15,27-31] Sixty-nine point nine percent of HGIN in EFB were diagnosed as EGC in our study, which was comparable to reported results.[30,32,33] It has been found that pathological upgrading was positively correlated with longer operation time and deeper submucosal invasion. In addition, the depth of invasion was verified in predicting the risk of nodal metastasis in EGCs.[17,34,35]

In agreement with reported data, our study demonstrated that the depressed pattern, nodular surface, surface redness, lesion size >2 cm, and location in the upper third of the stomach were risk factors in pathological upgrading.[23,36,37] EGCs located in the lower third of the stomach, especially in the antrum, might be detected easily, but for those in the upper third, detection may be difficult due to denser mucosal folds, thinner stomach, and limited endoscopic visual fields.[36]

Ideally, one would incline to have a validated noninvasive biomarker to predict cancer risk. However, no positive values of traditional tumor markers in predicting pathological upgrading have been observed in our study. We found that associations between pathological upgrading and metabolic features such as body mass index, hypertension, and dyslipidemia were not significant except for HDL. A 2015 meta-analysis, which summarized studies associating apolipoprotein E gene and cancer, demonstrated that reduced circulating HDL might be a potentially causal risk factor for the development of overall cancer in Asians.[38] As studies from several other centers have shown, the decreased HDL level was related to increased risk of gastric cancer and advanced disease stage.[39-42] One possible explanation is that HDL may promote cancer development by generating reactive oxygen species, increasing hormone production and availability (e.g., insulin-like growth factor, insulin, and adipokines), and forming an energy rich environment. This imbalance of hormones, the redox system, and energy availability plays a role in epithelium transition.[43,44]

It was interesting to note that our study showed significant statistical differences in both univariate and multivariate analyses for history of CAG and symptoms of digestive system between groups. The intestinal type of gastric cancer typically follows the Correa precancerous cascade of changes initiated by a non-self-limiting inflammation, of

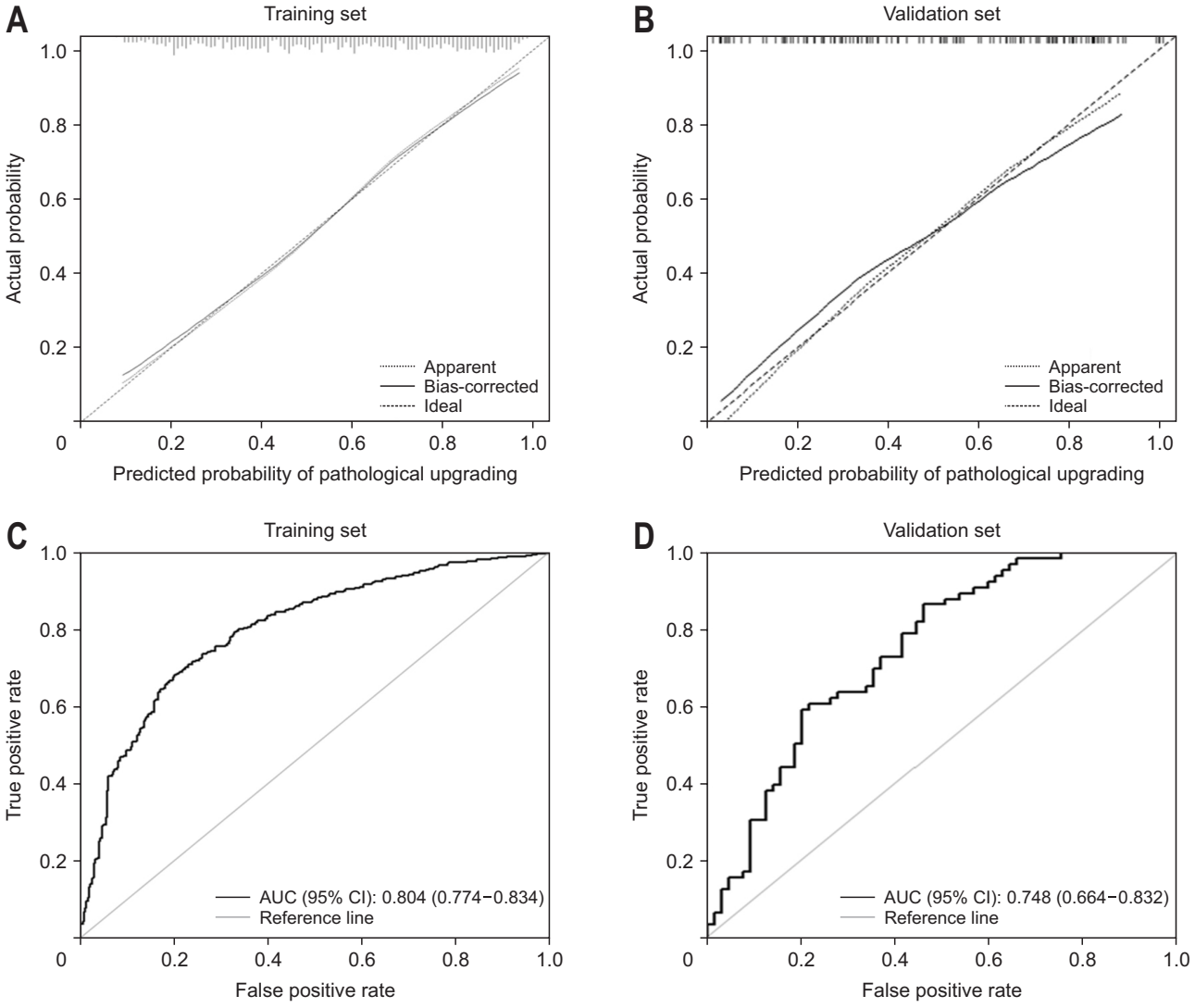

Fig. 4. Calibration and diagnostic ability of the nomogram. Calibration curves by using bootstrapping (1,000 repetitions) in the training set (A) and validation set (B). The receiver operating characteristic curve in the training set (C) and validation set (D).
AUC, area under the curve; CI, confidence interval.

which CAG represents the relatively early stage.[45] With the upgrading of gastric carcinogenesis, non-specific conditions such as gastritis and ulceration may appear.[46,47] Poor prognosis from gastric cancer is mainly due to late presentation. Alarm symptoms of EGN include abdominal or epigastric pain or discomfort, nausea and vomiting, etc.[48,49] EGN is usually asymptomatic. Therefore, referral guidelines have been developed to encourage early detection.[50,51] Normally, endoscopists would be more careful with symptomatic patients during endoscopy.[52,53] We assumed that patients who had CAG or suffered from digestive symptoms may be concerned about their digestive system health and would go through endoscopic checks.[52,54] Therefore, the history of CAG and symptoms of digestive system seem to be protective factors.

Here, we reported predictors for pathological upgrading, also we established a nomogram in a visualized pattern. Another strength of our study was that our predictors included clinical, laboratorial and endoscopic features, and its performance was verified in the comparison with other training models (Figs 7 and 8). The nomogram yielded the highest AUC demonstrating the best discrimination in estimating the risk of pathological upgrading in patients with EGN. The final decision curve analysis showed that as long as setting the threshold probability of patients or clinicians beyond 10% (i.e., if no intervention was provided for patient with pathological upgrading was considered probably inappropriate), screening strategies based on our nomogram's pathological upgrading risk estimates resulted in superior net benefit than screen-none or screen-all strategies

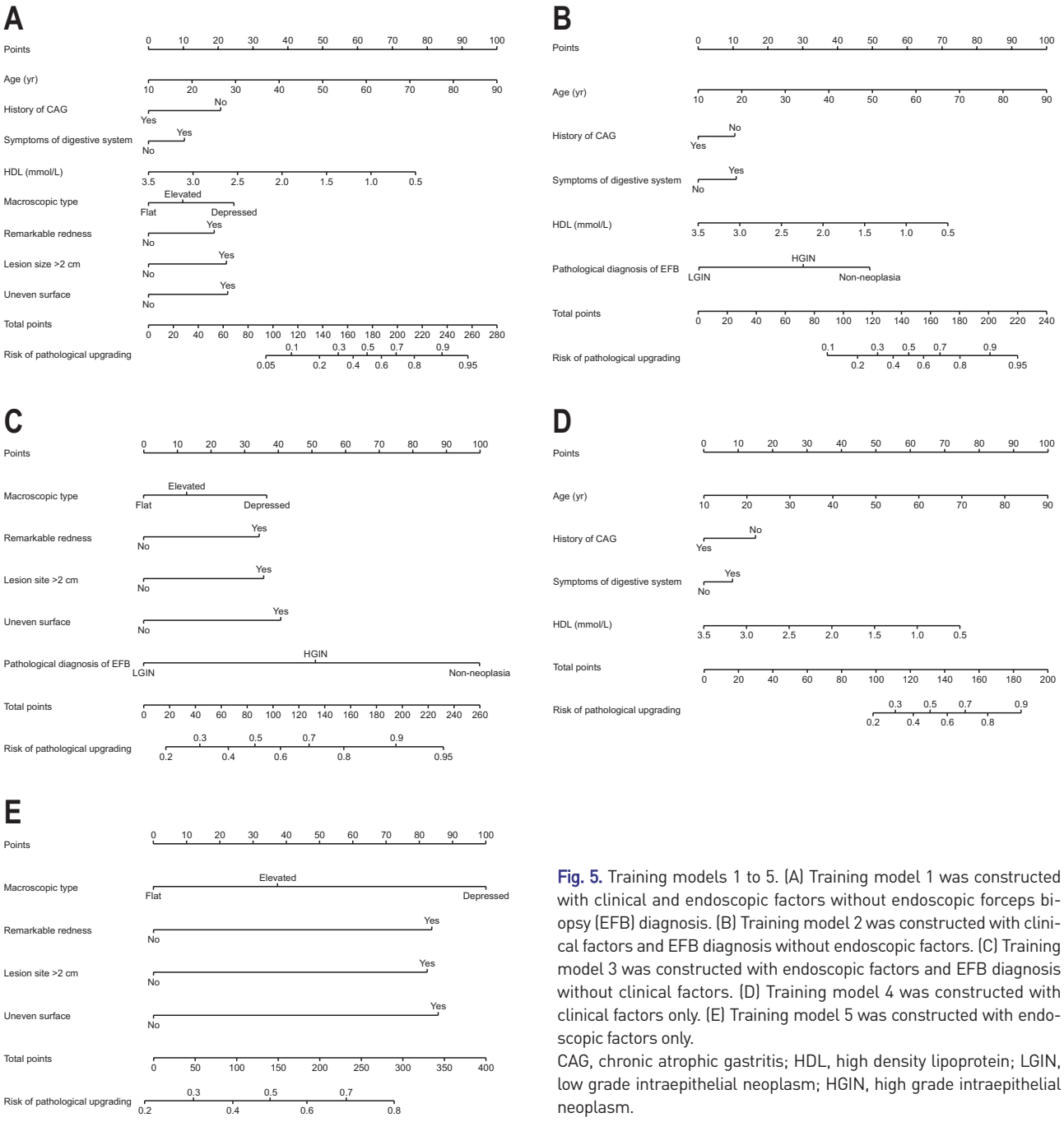

Fig. 5. Training models 1 to 5. (A) Training model 1 was constructed with clinical and endoscopic factors without endoscopic forceps biopsy (EFB) diagnosis. (B) Training model 2 was constructed with clinical factors and EFB diagnosis without endoscopic factors. (C) Training model 3 was constructed with endoscopic factors and EFB diagnosis without clinical factors. (D) Training model 4 was constructed with clinical factors only. (E) Training model 5 was constructed with endoscopic factors only.
CAG, chronic atrophic gastritis; HDL, high density lipoprotein; LGIN, low grade intraepithelial neoplasm; HGIN, high grade intraepithelial neoplasm.

(Fig. 7). When we set the threshold up to 40% or higher, the predictive effect of nomogram was still better than that of any training model. For practical application, we recommended explaining the upgrading risk predicted by nomogram to patients based on EFB findings. For EFB diagnosis of HGIN, intervention of ESD is necessary regardless of upgrading.[6,55] For LGIN or non-neoplasia, a predicting value >50% indicates a greater risk of misdiagnosis, and secondary examination or immediate endoscopic intervention would be recommended.

This study has some limitations. First of all, this was a retrospective cohort study, in which data were mainly obtained by reviewing medical records or endoscopic results from a single center. Thus, it may restrict application to a wider population. Second, the operational differences between primary examiner at the local clinic and the procedural endoscopic resection operator, as well as the impact of random/guided biopsies, number of biopsies, could not be evaluated.[4,56] Several studies have reported that white-light endoscopy combined with narrow-band imaging is superior to white-light endoscopy alone in identifying patients with gastric intestinal metaplasia and dysplasia.[57,58]

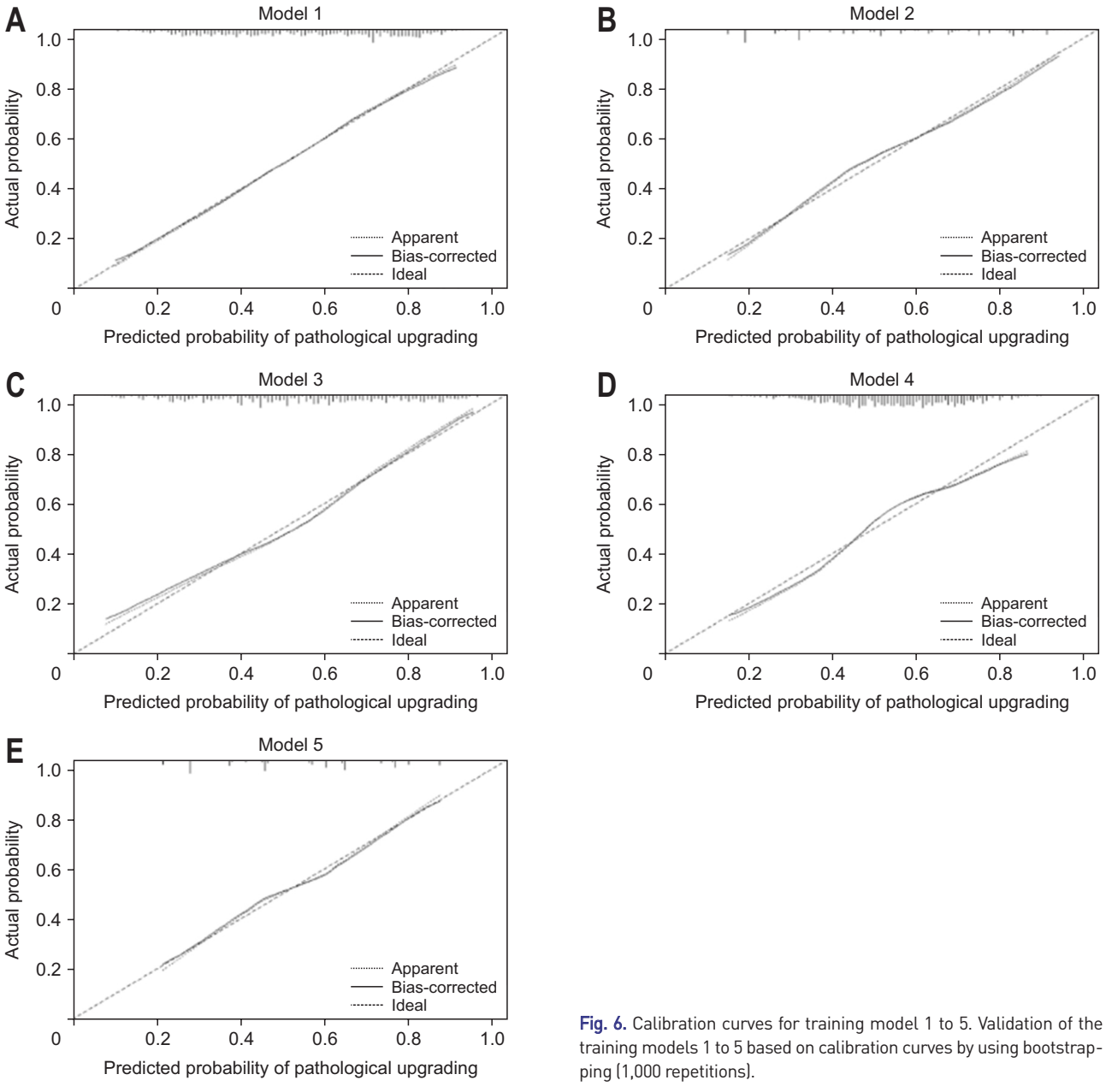

Fig. 6. Calibration curves for training model 1 to 5. Validation of the training models 1 to 5 based on calibration curves by using bootstrapping (1,000 repetitions).

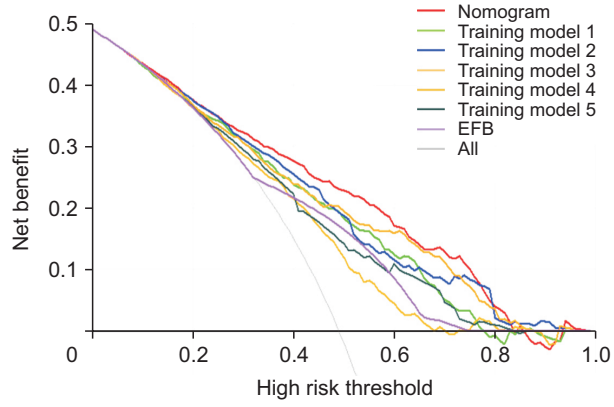

Fig. 7. Decision curve analysis for the nomogram, training models 1 to 5, and endoscopic forceps biopsy (EFB).

In fact, there were still many medical institutions in which virtual chromoendoscopy and high-definition processors and screens were not routinely available. Here, we enrolled no endoscopic features other than from white-light endoscopy.

In conclusion, pathological upgrading in EGN is common with specific clinical, laboratorial and endoscopic characteristics. Based on the above identified risk factors, a nomogram was developed to objectively and accurately predict individualized pathological upgrading risk of patients with EGN before ESD.

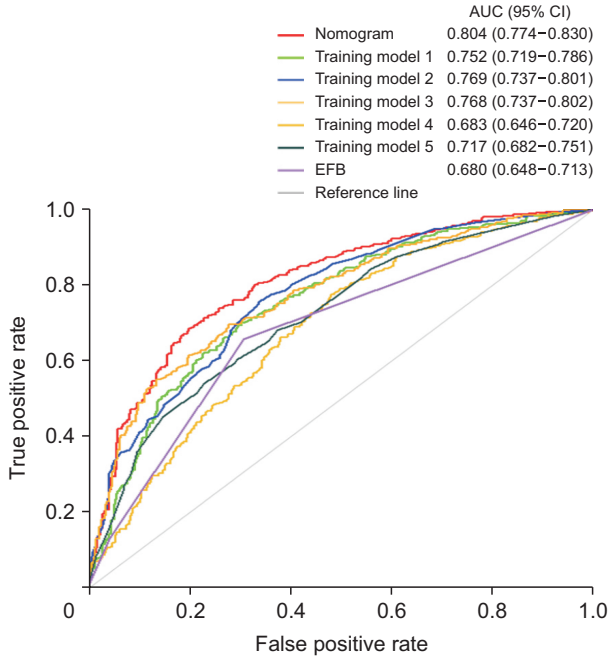

Fig. 8. Receiver operating characteristic analysis for the nomogram, training model 1 to 5, and EFB.
AUC, area under the curve; CI, confidence interval; EFB, endoscopic forceps biopsy.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This study was supported by the Jiangsu Municipal Science and Technology Bureau (No. BE2020784), the National Natural Science Foundation of China (No. 82000529), and the Natural Science Foundation of Jiangsu Province (No. SBK 2020042595). The funding body had no role in the study design, data collection, analysis, and interpretation of data.

The authors appreciate the study participants and the inestimable support from the research center. The authors are grateful for support of the medical and research staff of this study.

AUTHOR CONTRIBUTIONS

Study concept and design: Y.H.Z., Y.N.D., G.X.Z. Data acquisition: Y.H.Z., Y.L., J.S. Pathological support: H.J.H., K.D.L. Data analysis and interpretation: Y.H.Z. Drafting of the manuscript: Y.H.Z., J.S. Critical revision of the manuscript for important intellectual content: Y.Z. Statistical analysis: Y.H.Z., Y.Z. Obtained funding: Y.N.D., G.X.Z. Study supervision: Y.N.D., G.X.Z. Approval of final manuscript: all authors.

ORCID

Yu Han Zhao https://orcid.org/0000-0003-2788-5964
Yu Zheng https://orcid.org/0000-0001-5529-0306
Jie Sha https://orcid.org/0000-0002-2705-467X
Hong Jin Hua https://orcid.org/0000-0001-5320-1509
Ke Dong Li https://orcid.org/0000-0002-5019-518X
Yu Lu https://orcid.org/0000-0003-1072-9156
Yi Ni Dang https://orcid.org/0000-0001-6449-516X
Guo Xin Zhang https://orcid.org/0000-0002-7103-3630

REFERENCES

1. Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology 2020;76:182-188.
2. Huang D, Zhu XZ, Sheng WQ. 2019 updates of the WHO classification of the digestive system tumors, part: epithelial neoplasms in gastrointestinal tract. Zhonghua Bing Li Xue Za Zhi 2020;49:209-213.
3. Schlemper RJ, Riddell RH, Kato Y, et al. The Vienna classification of gastrointestinal epithelial neoplasia. Gut 2000;47:251-255.
4. Marcos P, Brito-Gonçalves G, Libânio D, et al. Endoscopic grading of gastric intestinal metaplasia on risk assessment for early gastric neoplasia: can we replace histology assessment also in the West? Gut 2020;69:1762-1768.
5. Ono H, Yao K, Fujishiro M, et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. Dig Endosc 2016;28:3-15.
6. Ono H, Yao K, Fujishiro M, et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer (second edition). Dig Endosc 2021;33:4-20.
7. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2015;47:829-854.
8. Shichijo S, Uedo N, Kanesaka T, et al. Long-term outcomes after endoscopic submucosal dissection for differentiated-type early gastric cancer that fulfilled expanded indication criteria: a prospective cohort study. J Gastroenterol Hepatol 2021;36:664-670.
9. Kwack WG, Ho WJ, Kim JH, et al. Understanding the di-

agnostic yield of current endoscopic biopsy for gastric neoplasm: a prospective single-center analysis based on tumor characteristics stratified by biopsy number and site. Medicine (Baltimore) 2016;95:e4196.
10. Lal N, Bhasin DK, Malik AK, Gupta NM, Singh K, Mehta SK. Optimal number of biopsy specimens in the diagnosis of carcinoma of the oesophagus. Gut 1992;33:724-726.
11. Choi Y, Choi HS, Jeon WK, et al. Optimal number of endoscopic biopsies in diagnosis of advanced gastric and colorectal cancer. J Korean Med Sci 2012;27:36-39.
12. Graham DY, Schwartz JT, Cain GD, Gyorkey F. Prospective evaluation of biopsy number in the diagnosis of esophageal and gastric carcinoma. Gastroenterology 1982;82:228-231.
13. Dekker W, Tytgat GN. Diagnostic accuracy of fiberendoscopy in the detection of upper intestinal malignancy: a follow-up analysis. Gastroenterology 1977;73(4 Pt 1):710-714.
14. Kim YJ, Park JC, Kim JH, et al. Histologic diagnosis based on forceps biopsy is not adequate for determining endoscopic treatment of gastric adenomatous lesions. Endoscopy 2010;42:620-626.
15. Xu G, Zhang W, Lv Y, et al. Risk factors for under-diagnosis of gastric intraepithelial neoplasia and early gastric carcinoma in endoscopic forceps biopsy in comparison with endoscopic submucosal dissection in Chinese patients. Surg Endosc 2016;30:2716-2722.
16. Soh JS, Lim H, Kang HS, Kim JH, Kim KC. Does the discrepancy in histologic differentiation between a forceps biopsy and an endoscopic specimen necessitate additional surgery in early gastric cancer? World J Gastrointest Oncol 2017;9:319-326.
17. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer 2021;24:1-21.
18. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer 2017;20:1-19.
19. Beijing Society of Digestive Endodcopology. Expert consensus on standard diagnosis and treatment of low grade intraepithelial neoplasm. Chin J Gastrointest Endosc 2019;6:49-56.
20. National Clinical Research Center for Digestive Disease. Chinese consensus on management of gastric epithelial precancerous conditions and lesions (2020). Chin J Dig 2020;40:731-741.
21. Yamada Y, Boku N, Mizusawa J, et al. Docetaxel plus cisplatin and S-1 versus cisplatin and S-1 in patients with advanced gastric cancer (JCOG1013): an open-label, phase 3, randomised controlled trial. Lancet Gastroenterol Hepatol 2019;4:501-510.
22. Choi CW, Kim HW, Shin DH, et al. The risk factors for discrepancy after endoscopic submucosal dissection of gastric category 3 lesion (low grade dysplasia). Dig Dis Sci 2014;59:421-427.
23. Yabuuchi Y, Takizawa K, Kakushima N, et al. Discrepancy between endoscopic and pathological ulcerative findings in clinical intramucosal early gastric cancer. Gastric Cancer 2021;24:691-700.
24. Maekawa A, Kato M, Nakamura T, et al. Incidence of gastric adenocarcinoma among lesions diagnosed as low-grade adenoma/dysplasia on endoscopic biopsy: a multicenter, prospective, observational study. Dig Endosc 2018;30:228-235.
25. Nam HS, Choi CW, Kim SJ, et al. Endoscopic predictive factors associated with local recurrence after gastric endoscopic submucosal dissection. Scand J Gastroenterol 2018;53:1000-1007.
26. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. Lancet Oncol 2015;16:e173-e180.
27. Hwang JW, Bae YS, Kang MS, et al. Predicting pre- and post-resectional histologic discrepancies in gastric low-grade dysplasia: a comparison of white-light and magnifying endoscopy. J Gastroenterol Hepatol 2016;31:394-402.
28. Cho SJ, Choi IJ, Kim CG, et al. Risk of high-grade dysplasia or carcinoma in gastric biopsy-proven low-grade dysplasia: an analysis using the Vienna classification. Endoscopy 2011;43:465-471.
29. Kang DH, Choi CW, Kim HW, et al. Predictors of upstage diagnosis after endoscopic resection of gastric low-grade dysplasia. Surg Endosc 2018;32:2732-2738.
30. Jeon JW, Kim SJ, Jang JY, et al. Clinical outcomes of endoscopic resection for low-grade dysplasia and high-grade dysplasia on gastric pretreatment biopsy: Korea ESD Study Group. Gut Liver 2021;15:225-231.
31. Kim JM, Sohn JH, Cho MY, et al. Inter-observer reproducibility in the pathologic diagnosis of gastric intraepithelial neoplasia and early carcinoma in endoscopic submucosal dissection specimens: a multi-center study. Cancer Res Treat 2019;51:1568-1577.
32. de Vries AC, van Grieken NC, Looman CW, et al. Gastric cancer risk in patients with premalignant gastric lesions: a nationwide cohort study in the Netherlands. Gastroenterology 2008;134:945-952.
33. Kato M, Nishida T, Tsutsui S, et al. Endoscopic submucosal dissection as a treatment for gastric noninvasive neoplasia: a multicenter study by Osaka University ESD Study Group. J Gastroenterol 2011;46:325-331.
34. Kang HJ, Kim DH, Jeon TY, et al. Lymph node metastasis from intestinal-type early gastric cancer: experience in a single institution and reassessment of the extended criteria for endoscopic submucosal dissection. Gastrointest Endosc 2010;72:508-515.
35. Kim Y, Yoon HJ, Kim JH, et al. Effect of histologic differenc-

es between biopsy and final resection on treatment outcomes in early gastric cancer. Surg Endosc 2020;34:5046-5054.
36. Ryu DG, Choi CW, Kang DH, et al. Clinical outcomes of endoscopic submucosa dissection for high-grade dysplasia from endoscopic forceps biopsy. Gastric Cancer 2017;20:671-678.
37. Takao M, Kakushima N, Takizawa K, et al. Discrepancies in histologic diagnoses of early gastric cancer between biopsy and endoscopic mucosal resection specimens. Gastric Cancer 2012;15:91-96.
38. Yang C, Tian G, Mi J, et al. Causal relevance of circulating high-density lipoprotein cholesterol with cancer: a Mendelian randomization meta-analysis. Sci Rep 2015;5:9495.
39. Nam SY, Park BJ, Nam JH, Kook MC. Effect of Helicobacter pylori eradication and high-density lipoprotein on the risk of de novo gastric cancer development. Gastrointest Endosc 2019;90:448-456.
40. Kim EH, Lee H, Chung H, et al. Impact of metabolic syndrome on oncologic outcome after radical gastrectomy for gastric cancer. Clin Res Hepatol Gastroenterol 2014;38:372-378.
41. Li F, Du H, Li S, Liu J. The association between metabolic syndrome and gastric cancer in Chinese. Front Oncol 2018;8:326.
42. Gerig R, Ernst B, Wilms B, Thurnheer M, Schultes B. Gastric Helicobacter pylori infection is associated with adverse metabolic traits in severely obese subjects. Obesity (Silver Spring) 2013;21:535-537.
43. Castro JP, Grune T, Speckmann B. The two faces of reactive oxygen species (ROS) in adipocyte function and dysfunction. Biol Chem 2016;397:709-724.
44. Braun S, Bitton-Worms K, LeRoith D. The link between the metabolic syndrome and cancer. Int J Biol Sci 2011;7:1003-1015.
45. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process: First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. Cancer Res 1992;52:6735-6740.
46. Wang FH, Shen L, Li J, et al. The Chinese Society of Clinical Oncology (CSCO): clinical guidelines for the diagnosis and treatment of gastric cancer. Cancer Commun (Lond) 2019;39:10.
47. Watari J, Chen N, Amenta PS, et al. Helicobacter pylori associated chronic gastritis, clinical syndromes, precancerous lesions, and pathogenesis of gastric cancer development. World J Gastroenterol 2014;20:5461-5473.
48. Crisan A, Badulescu F, Badulescu A, Simionescu C, Andrei I, Cimpeanu R. Clinical, histological and prognosis correlations in diagnosis and treatment of gastric cancer. Curr Health Sci J 2016;42:238-256.
49. Gallo A, Cha C. Updates on esophageal and gastric cancers. World J Gastroenterol 2006;12:3237-3242.
50. National Institute for Health and Care Excellence (NICE). Suspected cancer: recognition and referral. London: NICE, 2015.
51. Spahos T, Hindmarsh A, Cameron E, et al. Endoscopy waiting times and impact of the two week wait scheme on diagnosis and outcome of upper gastrointestinal cancer. Postgrad Med J 2005;81:728-730.
52. Banks M, Graham D, Jansen M, et al. British Society of Gastroenterology guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma. Gut 2019;68:1545-1575.
53. Machlowska J, Baj J, Sitarz M, Maciejewski R, Sitarz R. Gastric cancer: epidemiology, risk factors, classification, genomic characteristics and treatment strategies. Int J Mol Sci 2020;21:4012.
54. Kim GH, Liang PS, Bang SJ, Hwang JH. Screening and surveillance for gastric cancer in the United States: is it needed? Gastrointest Endosc 2016;84:18-28.
55. Pimentel-Nunes P, Libânio D, Marcos-Pinto R, et al. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. Endoscopy 2019;51:365-388.
56. Kitagawa Y, Hara T, Ikebe D, et al. Magnified endoscopic observation of small depressed gastric lesions using linked color imaging with indigo carmine dye. Endoscopy 2018;50:142-147.
57. Buxbaum JL, Hormozdi D, Dinis-Ribeiro M, et al. Narrow-band imaging versus white light versus mapping biopsy for gastric intestinal metaplasia: a prospective blinded trial. Gastrointest Endosc 2017;86:857-865.
58. Pimentel-Nunes P, Libânio D, Lage J, et al. A multicenter prospective study of the real-time use of narrow-band imaging in the diagnosis of premalignant gastric conditions and lesions. Endoscopy 2016;48:723-730.