Neoplasia 56 (2024) 101030

Contents lists available at ScienceDirect

Neoplasia

journal homepage: www.elsevier.com/locate/neo

Original Research

A new, simplified endoscopic scoring system for predicting clinical outcome in gastric low-grade intraepithelial neoplasia: the "e-cout system"

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ARTICLE INFO

Keywords:
Gastric low-grade intraepithelial neoplasia
Clinical prognosis prediction
Scoring system
Two-Stage study

ABSTRACT

Background and Objectives: The clinical outcomes of gastric low-grade intraepithelial neoplasia (LGIN) exhibit significant diversity, and the current reliance on endoscopic biopsy for diagnosis poses limitations in devising appropriate treatment strategies for this disease. This study aims to establish a prognostic prediction scoring system (e-Cout system) for gastric LGIN, offering a theoretical foundation for solving this clinical challenge.
Methods: Retrospectively selecting 1013 cases meeting the inclusion and exclusion criteria from over 300,000 cases of upper gastrointestinal endoscopy performed at the Digestive Endoscopy Center of our hospital between 2000 and 2022, the cohort included 484 cases as development cohort and 529 cases for validation. Employing relevant statistical analysis, we used development cohort data to establish the e-Cout system for gastric LGIN, and further used validation cohort data to for internal validation.
Results: In the developmental stage, based on accordant regression coefficients, we assigned point values to six risk factors for poor prognosis: 4 points for microvessel (MV) distortion, 3 points for MV thickening, 2 points for ulcer, and 1 point each for lesion size $>$ 2cm, disease duration $>$ 1 year, and hyperemia and redness on the lesion surface. Patients were then categorized into four risk levels: low risk (0-1 point), medium risk (2-3), high risk (4-6), and very high risk ($\geq$7). During the validation stage, significant differences in the three different outcomes of gastric LGIN were observed across all risk levels. The probability of reversal and progression showed a significant decrease and increase, respectively, with escalating of risk levels, and these differences were statistically significant ($P <$ 0.001).
Conclusions: The proposed e-Cout system holds promise in aiding clinicians to predict the probability and risk levels of different clinical outcomes in patients with gastric LGIN. This system is expected to provide an improved foundation and guidance for the selection of clinical strategies for this disease.

Introduction

The continuous evolution of digestive endoscopic diagnostic and therapeutic techniques, coupled with the widespread adoption of endoscopic screening, has led to a rise in the number of diagnosed cases of gastric low-grade intraepithelial neoplasia (LGIN) [1]. Different from high-grade intraepithelial neoplasia (HGIN), consensus among clinicians and scholars on the optimal clinical management strategies for gastric LGIN remains elusive, and unified opinions have yet to be established [2–4].

Guided by the World Health Organization (WHO) and Vienna Classification guidelines [5–7], clinical management strategies for gastric LGIN primarily encompass regular follow-up and proactive endoscopic intervention [8,9]. The former involves endoscopic biopsy follow-up, while the latter includes endoscopic resection and damage therapies [10–14]. However, these recommendations lack specificity regarding the timing of follow-up or treatment, and they do not prescribe detailed endoscopic treatment methods. This limitation is attributed to the varied clinical outcomes of gastric LGIN and the constraints associated with predominantly relying on endoscopic biopsy for clinical diagnosis

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https://doi.org/10.1016/j.neo.2024.101030
Received 9 May 2024; Received in revised form 8 July 2024; Accepted 8 July 2024
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[15–19]. Although recent studies have explored the clinical management of gastric LGIN [20,21], the absence of quantitative criteria for predicting its prognosis remains a notable gap. This deficiency is a primary source of challenges in clinical decision-making, leaving a significant void in research in this domain.

Therefore, our study endeavors to address this gap by conducting a retrospective analysis of extensive clinical samples. Our aim is to build a preliminary prediction scoring system (e-Cout system) for the clinical prognosis of gastric LGIN. As it is a clinical outcome prediction system established based on endoscopy-related factors, we chose three representative words, endoscopic, clinical and outcome, to name this scoring system. This effort seeks to furnish a relatively objective, practical, and reliable theoretical foundation, facilitating informed decisions in the selection of clinical diagnosis and treatment strategies for this disease.

Materials and methods

Patients

In this retrospective analysis, we examined over 300,000 accessible upper gastrointestinal endoscopy cases conducted at our digestive endoscopy center between August 1, 2000, and February 1, 2022. Initially, 6484 cases of gastric LGIN were screened out after endoscopic biopsy and confirmed by pathology. From these cases, we selected a development cohort comprising 484 patients with complete clinical and pathological data. These patients underwent magnification endoscopic (ME) combined with narrow band imaging (NBI) screening and eventually received either endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), based on relevant inclusion and exclusion criteria. Concurrently, a validation cohort was established, consisting of 529 patients who exclusively received endoscopic follow-up. This group was followed for more than 3 years, or a duration less than 3 years if progression to HGIN occurred under the same screening conditions. Both the development and validation cohorts were incorporated into this study (Fig. 1). All enrolled patients had signed written informed consent for either endoscopy or endoscopic surgery (EMR or ESD).

Inclusion and exclusion criteria

The inclusion criteria were defined as follows: (1) age ≥18 years old; (2) patients in the development cohort pathologically confirmed as gastric LGIN through ME combined with NBI screening, following WHO/Vienna evaluation criteria [5–7]. Subsequently, these patients underwent either EMR or ESD (informed consent for treatment needs to be signed). Postoperative pathological results included findings of inflammation, LGIN, or HGIN; (3) patients in the validation cohort were pathologically confirmed as gastric LGIN through ME combined with NBI screening according to WHO/Vienna evaluation criteria [5–7], and subsequently, received no endoscopic therapy. They completed annual endoscopic follow-up for more than 3 years, or progressed to HGIN with specific duration recorded; (4) adequate and clear endoscopic images of the biopsy of the lesion area during the follow-up of cases in the verification cohort, allowing for confirmation through before-and-after comparison; and (5) available of other clinical data.

The exclusion criteria were stipulated as follows: (1) patients screened by ME combined with NBI according to WHO/Vienna evaluation criteria [5–7], with pathological findings limited to inflammation, or where HGIN and cancer could not be definitively ruled out; (2) patients identified as gastric LGIN by the criteria in (1), but underwent endoscopic treatments other than EMR or ESD, such as radiofrequency ablation (RFA), argon plasma coagulation (APC), etc.; (3) pathological confirmation of cancer in patients receiving EMR or ESD; (4) patients with less than 3 years of follow-up or who failed to adhere to at least annual follow-ups, based on gastric LGIN not progressing to HGIN; (5) unavailability or poor quality of endoscopic images from biopsies of the lesion area in follow-up patients, hindering confirmation of the biopsy of the original lesion site; and (6) incomplete or missing other clinical data.

Clinical data

The clinical data encompassing both cohorts primarily consisted of general information and endoscopy-related details. General data included the outpatient ID, age, gender, smoking history, contact information, chief complaint, time of receiving endoscopic treatment and/or review, disease duration, history of prior relevant examinations, and

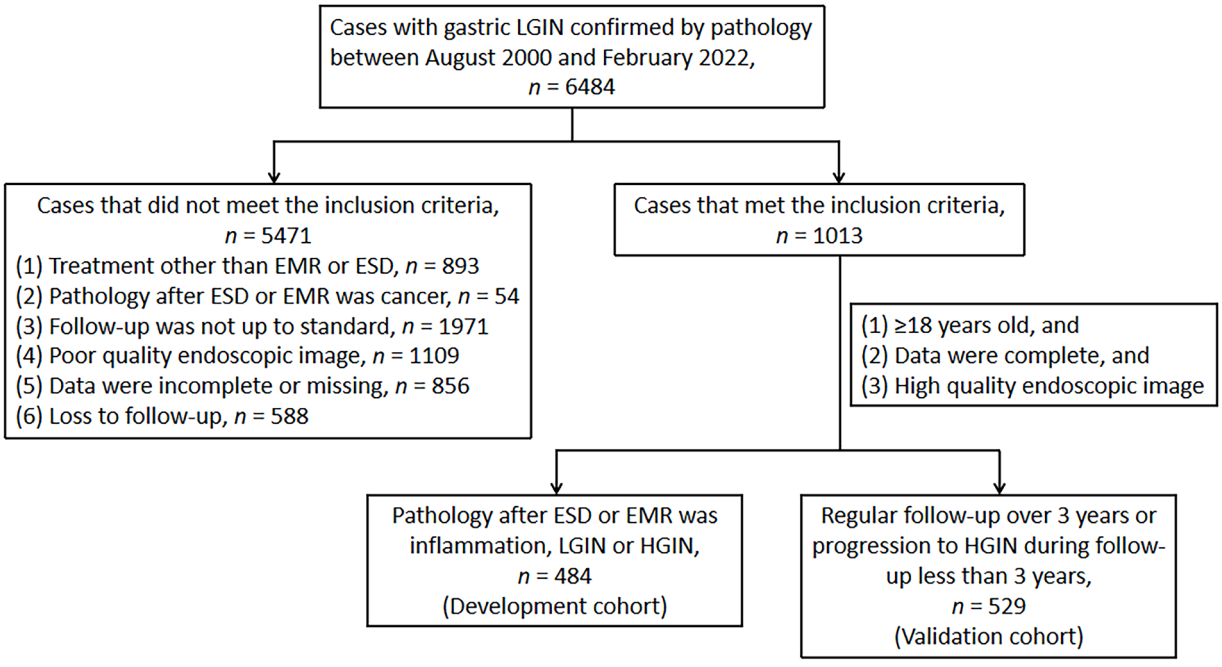


Fig. 1. Flowchart of patients enrollment. LGIN: low-grade intraepithelial neoplasia; HGIN: high-grade intraepithelial neoplasia; EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection.

pathology reports. On the other hand, endoscopy-related data comprised details such as the lesion's location, size, surface morphology [22], color, presence of erosion, ulceration, nodular changes, as well as the coexistence of atrophic gastritis, intestinal metaplasia, and helicobacter pylori (Hp) infection. Furthermore, data used by ME combined with NBI to observe the presence of lesions boundaries and the condition of surface microvessels (MV), including thickness and distortion, were systematically collected. Among them, MV thickening means that the diameter of MV observed under ME combine with NBI is more than 1.5 times that of the surrounding reference vessel, and MV distortion refers to the appearance of a group of bent or twisted blood vessels. For the validation cohort, specific attention was given to recording the duration within which cases progressed to HGIN during the 3-year follow-up period.

It is worth mentioning that more than 1000 cases included in the study were observed by magnifying endoscopy to fully obtain relevant information, such as the MV mentioned above. All endoscopic images were interpreted by two experienced endoscopists (Dr. Linghu and Dr. Chai). At the same time, the pathological results of all cases were reinterpreted by two experienced pathologists, and if they were different from the original pathological results, the final confirmation was made by another pathologist with higher seniority. Through the above study design, we hope to improve the intra-observer reliability and inter-observer reliability as much as possible.

Two-Stage study

This study unfolded in two distinct stages. The initial stage involved the formulation of a scoring system aimed at predicting the prognosis of gastric LGIN and categorizing the possibility of various clinical outcome associated with gastric LGIN. The subsequent stage encompassed the internal verification of the scoring system.

During the first stage, we collected potential risk factors distinguishing intraepithelial neoplasia from normal gastric mucosa to establish the e-Cout system. This phase primarily focused on data derived from patients with gastric LGIN who underwent either EMR or ESD, yielding complete postoperative pathologic results, constituting the developmental cohort. Drawing insights from numerous preceding researches on the clinical outcomes of gastric LGIN, we identified and summarized 17 factors as potential risk factors [23-30]. These factors included patient age, sex and smoking history, lesion location, size, and surface morphology, disease duration, and the presence of features such as congestive redness, nodular changes, erosion, and ulcers. Furthermore, factors such as atrophic gastritis, intestinal metaplasia, Hp infection, and lesions with clear boundaries, surface MV thickening, or distortion under ME combined with NBI were also integrated. In addition, in this study, LGIN progression was defined as its evolution into HGIN, LGIN reversal was defined as its transformation into inflammation, and LGIN maintenance signified the persistent stability of LGIN, neither progressing nor reversing.

First, we conducted univariate and multivariate logistic regression analyses on patients diagnosed with gastric intraepithelial neoplasia to identify the risk factors affecting its occurrence. Second, the risk factors identified through multivariate regression analysis were assigned weight scores proportional to the value of the β regression coefficient (rounded to the nearest whole number). We then calculated the sum of the risk factor scores, establishing a risk score for each case in the development cohort. Following this, we calculated the respective proportions of the three outcomes in each score and conducted a multifactor chi-square analysis to examine potential differences in both the overall score distribution and inter-group distribution among the three outcomes. Finally, drawing upon previous research experience in scoring system development and in alignment with practical clinical requirements [31,32], we divided the calculated risk score into three or four risk levels - namely, low risk, medium risk, high risk, or low risk, medium risk, high risk, and very high risk. The Cochran-Armitage trend test was used to detect whether there was a significant trend in the probability of disease progression or reversal with an increase in the risk level.

To internally validate the effectiveness of the constructed e-Cout system, we selected the validation cohort. We guaranteed biopsy conduction at the original lesion site through meticulous comparative analysis of images before and after the procedure, subsequently determining the nature of the lesion based on the biopsy pathological results. These results were critically examined to validate the reliability and accuracy of the constructed scoring system. In the validation cohort, patients were categorized according to the risk levels established in the first stage. For internal validation analysis, Kaplan-Meier method was used to describe the progression and reversal of gastric LGIN. And the log-rank test was used to assess the differences in progression and reversal among the various risk levels. In addition, Cox proportional hazard regression analysis was conducted to evaluate the effectiveness of the e-Cout system in predicting the progression and reversal of gastric LGIN, providing the calculation of hazard ratio. Finally, the Cochran-Armitage trend test was reapplied to detect whether the probability of disease progression and reversal showed a significant trend with an increase in risk level.

Statistical analysis

Excel (Microsoft USA) software was used to record the original recorded data, and SPSS statistical software (SPSS Statistics for Windows, version 26.0; IBM, Armonk, USA) and R software (version 4.1.2, R Foundation for Statistical Computing, Vienna, Austria) were used for data analysis. Counting data are described by frequency and percentage, while measurement data are expressed as mean value ± standard deviation or median with range. Chi-square test or Fisher test were used to compare the counting data between groups, whereas T-test, one-way ANOVA, or rank sum test were used for measurement data based on the normal distribution conformity of the data, respectively. For both development and validation cohorts, the predictive accuracy of the scoring system was assessed by calculating the C statistic. Moreover, calibration of the model was evaluated using the calibration-in-the-large and calibration slope. $P < 0.05$ was considered statistically significant. It should be noted that factors with $P < 0.10$ in univariate logistic regression analysis are considered for inclusion in multivariate logistic regression analysis.

Results

Clinical characteristics of the two cohorts

Within the 484 cases in developmental cohort, 117 cases exhibited inflammation, 274 cases were diagnosed with LGIN, and 93 cases manifested as HGIN. Correspondingly, among the 529 cases in the validation cohort, 215, 237, and 77 cases were of these three types of lesions, respectively. The baseline characteristics and a comparison of cases between the two cohorts are detailed in Table 1. We counted and compared the 17 factors mentioned in the research method, and the difference between them was not statistically significant. ($P > 0.05$)

Establishment of the scoring system (the first stage)

In the univariate logistics regression analysis, a total of nine factors (lesion size, disease course, smoking history, hyperemia and redness on lesion surface, nodular change, ulcer, Hp infection, MV thickening, and MV distortion) showed $P < 0.10$ thus included in the multivariate analysis. Subsequent multivariate logistics regression analysis showed that six factors, including lesion size, disease course, hyperemia and redness on lesion surface, ulcers, MV thickening, and MV distortion, were independent risk factors affecting prognosis (Table 2).

To calculate the risk score, each independent risk factor was assigned

Table 1
Comparison of baseline features between patients in the development cohort and the validation cohort.

	Development cohort (n = 484)	Validation cohort (n = 529)	*P* value
Age, mean ± SD (y)	56.2 ± 17.5	55.6 ± 17.3	0.639
Sex, n (%)			0.774
Male	317 (65.5)	351 (66.4)	
Female	167 (34.5)	178 (33.6)	
Location, n (%)			0.974
Gastric fundus	15 (3.1)	17 (3.2)	
Gastric body	53 (11.0)	60 (11.3)	
Gastric angle - antrum	416 (85.9)	452 (85.4)	
Smoking, n (%)			0.493
Yes	72 (14.9)	87 (16.4)	
No	412 (85.1)	442 (83.6)	
Size, n (%)			0.507
< 2 cm	195 (40.3)	224 (42.3)	
≥ 2 cm	289 (59.7)	305 (57.7)	
Course of disease, n (%)			0.569
< 1 year	221 (45.7)	251 (47.4)	
≥ 1 year	263 (54.3)	278 (52.6)	
Surface morphology, n (%)			0.414
0-I	166 (34.3)	169 (31.9)	
0-II	267 (55.2)	291 (55.0)	
0-III	51 (10.5)	69 (13.0)	
Congestive redness, n (%)			0.763
Yes	144 (29.8)	162 (30.6)	
No	340 (70.2)	367 (69.4)	
Nodular change, n (%)			0.640
Yes	99 (20.5)	102 (19.3)	
No	385 (79.5)	427 (80.7)	
Erosion, n (%)			0.906
Yes	126 (26.0)	136 (25.7)	
No	358 (74.0)	393 (74.3)	
Ulcer, n (%)			1.000
Yes	43 (8.9)	47 (8.9)	
No	441 (91.1)	482 (91.1)	
Atrophic gastritis, n (%)			0.629
Yes	168 (34.7)	176 (33.3)	
No	316 (65.3)	353 (66.7)	
Intestinal metaplasia, n (%)			0.485
Yes	57 (11.8)	70 (13.2)	
No	427 (88.2)	459 (86.8)	
Hp infection, n (%)			0.225
Yes	82 (16.9)	75 (14.2)	
No	402 (83.1)	454 (85.8)	
Boundary, n (%)			0.128
Yes	123 (25.4)	113 (21.4)	
No	361 (74.6)	416 (78.6)	
MV thickening, n (%)			0.952
Yes	38 (7.9)	41 (7.8)	
No	446 (92.1)	488 (92.2)	
MV distortion, n (%)			0.118
Yes	93 (19.2)	82 (15.5)	
No	391 (80.8)	447 (84.5)	

SD: standard deviation; Hp: helicobacter pylori; MV: microvessels.
Course of disease refers to the time interval between the first endoscopic diagnosis of LGIN and the evaluation of the score. Surface morphology refers to the Paris classification.

a score proportional to the β regression coefficient. Employing the linear transformation of the corresponding β regression coefficients, we divided the coefficients for each factor by 0.661 (the lowest β value corresponding to the risk factor of hyperemia and redness on the lesion surface) and rounded to the nearest whole number. The results showed that lesion size > 2cm, disease duration > 1 year, and hyperemia and redness on the lesion surface were 1 point, ulcer was 2 points, MV thickening was 3 points, and MV distortion was 4 points (Table 3). By summing the scores corresponding to the above risk factors, the total risk score for each case in the developmental cohort was calculated on a scale ranging from 0 to 12. Subsequently, the respective proportions of the three outcomes for cases under each score were calculated. The results showed statistical differences in both the overall score distribution and inter-group distribution of each outcome ($P < 0.001$) (Table 4). Finally, we divided the predictive e-Cout system into four risk levels according to the difference in the risk of LGIN progression, maintenance, and reversal under each score: low risk (0-1), medium risk (2-3), high risk (4-6), and very high risk (≥7). The results showed that from low risk to very high risk, the probability of LGIN reversal was 44.5 %, 17.6 %, 3.0 % and 0; the probability of maintenance was 49.7 %, 64.8 %, 64.3 % and 25.9 %; and the probability of progression was 5.8 %, 17.6 %, 32.7 % and 74.1 %, respectively (Table 5). The Cochran-Armitage trend test confirmed that with an increase of risk level, the probability of reversal decreased significantly, while the probability of progress increased significantly ($P < 0.001$). The predictive accuracy of the risk score and risk classification for the reversal and progression of LGIN, as measured by the C statistic, was 0.76 (95 % confidence interval (CI), 0.65–0.87) and 0.74 (95 % CI, 0.66–0.82), respectively.

Internal validation of the scoring system (the second stage)

According to the gastric LGIN endoscopic clinical outcome prediction scoring system (e-Cout system) constructed in the first stage, the respective proportions of the three outcomes under each score in the verification cohort were shown in Table 6. Both the overall score distribution and inter-group distribution of each outcome demonstrated statistical differences ($P < 0.001$). Within the validation cohort, 42.0 %, 33.6 %, 18.3 %, and 6.1 % of cases were classified into low, medium, high, and very high risk levels, respectively (Table 7). Importantly, this distribution exhibited no statistically significant difference when compared to the risk level distribution in the development cohort (42.0 %, 33.6 %, 18.3 %, 6.1 % vs 39.4 %, 34.1 %, 20.9 %, 5.6 %, $p = 0.723$). Figs. 2 and 3 illustrated the results derived from the Kaplan-Meier method, effectively describing the progression and reversal of LGIN. The log-rank test corroborated significant difference in the progression and reversal of lesions among risk levels ($P < 0.001$). Moreover, Cox proportional hazard regression analysis was used to evaluate the results of the predictive scoring system in predicting the progression and reversal of LGIN, as shown in Table 8, revealing statistically significant differences in the observed trend of change ($P < 0.001$). Finally, the predictive accuracy of the risk score and risk classification for the reversal and progression of LGIN, as measured by the C statistic, was 0.74 (95 % CI, 0.66–0.83) and 0.73 (95 % CI, 0.67–0.80), respectively. Figs. 4 and 5 showed the calibration curves for the assessment of calibration using calibration-in-the-large and calibration slope.

Discussion

In recent years, there has been a surge in clinical studies aiming to enhance the diagnostic accuracy of LGIN, with the ultimate goal of accurate predicting the prognosis of lesions. For example, the fine screening mode of ME combined with NBI, blue laser magnifying endoscopy, confocal laser endoscopy, chromoendoscopy and virtual chromoscopy, have shown active explorations and attempts to improve the accuracy of diagnosis and prognosis prediction of LGIN [33–39]. However, the collective findings from these explorations and research have not yet culminated in a unified conclusion or a relatively objective, quantifiable evaluation system or prediction model. Therefore, the longstanding challenge of accurately predicting the clinical prognosis of gastric LGIN remains unresolved to date.

Therefore, our comprehensive cohort study endeavors to fill this crucial gap by introducing a novel, simplified, and quantifiable prognostic scoring system, encompassing 6 key risk factors for predicting

Table 2
Univariate and multifactorial logistic regression analysis of risk factors in development cohort.

	Inflammatory group (n=117)	Intraepithelial neoplasia group (n=367)	Univariate logistic regression analysis			Multifactorial logistic regression analysis		
			OR	95 % CI	*P* value	OR	95 % CI	*P* value
Age, mean ± SD (y)	56.06 ± 17.75	56.20 ± 17.44	1.00	0.99-1.01	0.939			
Sex, n (%)			1.26	0.82-1.93	0.302			
Male	72 (61.5)	245 (66.8)						
Female	45 (38.5)	122 (33.2)						
Location, n (%)			1.05	0.67-1.65	0.826			
Gastric fundus	4 (3.4)	11 (3.0)						
Gastric body	13 (11.1)	40 (10.9)						
Gastric angle - antrum	100 (85.5)	316 (86.1)						
Smoking, n (%)			0.52	0.26-1.03	0.059	0.48	0.23-1.00	0.051
Yes	11 (9.4)	61 (16.6)						
No	106 (90.6)	306 (83.4)						
Size, n (%)			2.75	1.79-4.22	< 0.001	2.57	1.6-4.13	< 0.001
< 2 cm	69 (59.0)	126 (34.3)						
≥ 2 cm	48 (41.0)	241 (65.7)						
Course of disease, n (%)			2.58	1.68-3.96	< 0.001	2.43	1.5-3.94	< 0.001
< 1 year	74 (63.2)	147 (40.1)						
≥ 1 year	43 (36.8)	220 (59.9)						
Surface morphology, n (%)			0.92	0.66-1.29	0.635			
0-I	29 (24.8)	137 (37.3)						
0-II	84 (71.8)	183 (49.9)						
0-III	4 (3.4)	47 (12.8)						
Congestive redness, n (%)			1.77	1.08-2.89	0.024	1.94	1.11-3.36	0.019
Yes	25 (21.4)	119 (32.4)						
No	92 (78.6)	248 (67.6)						
Nodular change, n (%)			1.84	1.03-3.3	0.039	1.61	0.85-3.07	0.145
Yes	16 (13.7)	83 (22.6)						
No	101 (86.3)	284 (77.4)						
Erosion, n (%)			1.03	0.64-1.65	0.912			
Yes	30 (25.6)	96 (26.2)						
No	87 (74.4)	271 (73.8)						
Ulcer, n (%)			4.65	1.41-15.31	0.012	4.2	1.2-14.7	0.025
Yes	3 (2.6)	40 (10.9)						
No	114 (97.4)	327 (89.1)						
Atrophic gastritis, n (%)			1.20	0.77-1.87	0.421			
Yes	37 (31.6)	131 (35.7)						
No	80 (68.4)	236 (64.3)						
Intestinal metaplasia, n (%)			0.98	0.51-1.86	0.942			
Yes	14 (12.0)	43 (11.7)						
No	103 (88.0)	324 (88.3)						
Hp infection, n (%)			2.31	1.18-4.53	0.015	1.84	0.89-3.83	0.101
Yes	11 (9.4)	71 (19.3)						
No	106 (90.6)	296 (80.7)						
Boundary, n (%)			1.34	0.81-2.21	0.249			
Yes	25 (21.4)	98 (26.7)						
No	92 (78.6)	269 (73.3)						
MV thickening, n (%)			6.25	1.48-26.36	0.013	6.02	1.3-27.94	0.022
Yes	2 (1.7)	36 (9.8)						
No	115 (98.3)	331 (90.2)						
MV distortion, n (%)			12.35	3.83-39.79	< 0.001	10.61	3.2-35.12	< 0.001
Yes	3 (2.6)	90 (24.5)						
No	114 (97.4)	277 (75.5)						

OR: odds ratio; CI: confi dence interval.

clinical outcomes in endoscopic lesions diagnosed as gastric LGIN. Through an extensive literature search, we have confirmed that quantitative prognostic scoring system (e-Cout system) we developed is the first of its kind for gastric LGIN. This pioneering system incorporates multiple factors, providing specific scores and risk stratification, making it an innovative contribution to the field. Moreover, the study is underpinned by robust data from both the development cohort and the validation cohort, ensuring the statistical power required for meaningful research outcomes. In addition, we conducted an array of detailed statistical analyses, employing SPSS statistical software and R software. This rigorous approach ensured that our results are not only genuine and reliable but also compelling in their implications.

The e-Cout system developed in this study offers several advantages. First of all, during the stage of incorporating variables into singlevariate logistics regression analysis, we conducted an extensive review of previous studies, inclusively considering all factors that could impact the prognosis of the disease to reduce errors [23–30]. Furthermore, since all the cases in the development cohort had clear pathological results after endoscopic resection, we were able to conduct additional screening and validation of some factors with subjective judgment components. For example, we confirmed MV thickening and MV distortion may exert important effects on the prognosis through careful comparison of preoperative magnifying endoscopic images. Subsequently, the statistical results affirm that the latter two factors are independent risk factors affecting the prognosis of gastric LGIN, occupying a high proportion. Therefore, such analysis enhances the realism and objective of the constructed predictive scoring system.

It is crucial to highlight that Hp infection, which has been closely related to the occurrence of gastric cancer in previous literature reports [27]. In our univariate analysis, Hp infection was suggested as a potential risk factor, however, it was eventually excluded as an independent risk factor in the final multivariate analysis. Upon reviewing the

Table 3
Multifactor logistic regression analysis and scoring system of risk factors in the development cohort.

	Inflammatory group (n=117)	Intraepithelial neoplasia group (n=367)	OR	95 % CI	*P* value	β regression coefficient	Points[a]
Size, n (%)							
≥ 2cm	48 (41.0)	241 (65.7)	2.75	1.79-4.22	< 0.001	0.944	1
< 2cm	69 (59.0)	126 (34.3)	1	Reference			
Course of disease, n (%)							
≥ 1 year	43 (36.8)	220 (59.9)	2.58	1.68-3.96	< 0.001	0.889	1
< 1 year	74 (63.2)	147 (40.1)	1	Reference			
Congestive redness, n (%)							
Yes	25 (21.4)	119 (32.4)	1.77	1.08-2.89	0.024	0.661	1
No	92 (78.6)	248 (67.6)	1	Reference			
Ulcer, n (%)							
Yes	3 (2.6)	40 (10.9)	4.65	1.41-15.31	0.012	1.435	2
No	114 (97.4)	327 (89.1)	1	Reference			
MV thickening, n (%)							
Yes	2 (1.7)	36 (9.8)	6.25	1.48-26.36	0.013	1.795	3
No	115 (98.3)	331 (90.2)	1	Reference			
MV distortion, n (%)							
Yes	3 (2.6)	90 (24.5)	12.35	3.83-39.79	< 0.001	2.361	4
No	114 (97.4)	277 (75.5)	1	Reference			

[a] The assignment of points to risk factors was based on a linear transformation of the corresponding β regression coefficient. The coefficient of each variable was divided by 0.661 (the lowest β value, corresponding to congestive redness) and rounded to the nearest integer.

Table 4
The distribution of each risk score and each disease outcome in the developmental cohort.

Total points	Cases	Inflammation (%)	LGIN (%)	HGIN (%)
0	47	25 (53.2)	21 (44.7)	1 (2.1)
1	144	60 (41.7)	74 (51.4)	10 (6.9)
2	117	23 (19.7)	73 (62.4)	21 (17.9)
3	48	6 (12.5)	34 (70.8)	8 (16.7)
4	19	1 (5.3)	12 (63.1)	6 (31.6)
5	39	0 (0)	27 (69.2)	12 (30.8)
6	43	2 (4.6)	26 (60.5)	15 (34.9)
7	12	0 (0)	5 (41.7)	7 (58.3)
8	6	0 (0)	2 (33.3)	4 (66.7)
9	5	0 (0)	0 (0)	5 (100)
10	4	0 (0)	0 (0)	4 (100)
11	0	——	——	——
12	0	——	——	——

LGIN:low-grade intraepithelial neoplasia; HGIN: high-grade intraepithelial neoplasia.

Table 5
The endoscopic scoring system for predicting clinical outcome of gastric LGIN (e-Cout system).

Risk level	Total points	Cases	Inflammation (%)	LGIN (%)	HGIN (%)
Low	0-1	191	85 (44.5)	95 (49.7)	11 (5.8)
Medium	2-3	165	29 (17.6)	107 (64.8)	29 (17.6)
High	4-6	101	3 (3.0)	65 (64.3)	33 (32.7)
Very high	≥7	27	0 (0)	7 (25.9)	20 (74.1)

data, it became apparent that our determination on whether a patient was infected with Hp largely relied on the pathological results of endoscopic biopsy. However, it is well-established that the C-urea breath test and serologic detection were commonly used for clinical detection of Hp infection. Due to the retrospective nature of our study, data records for these examination were absent in some patients. This limitation might have led to a reduction in the actual data related to Hp infection, potentially narrowing the discernible difference between non-Hp infected individuals and those with Hp infection. Similar to Hp infection, factors such as a history of drinking, a preference for pickled and fried foods, and a family history of tumors, including smoking history in this study, have been suggested as potential risk factors for the prognosis of gastric LGIN in some literatures [40]. However, due to the

Table 6
The distribution of each risk score and each disease outcome in the validation cohort.

Total points	Cases	Inflammation (%)	LGIN (%)	HGIN (%)
0	64	41 (64.1)	22 (34.4)	1 (1.6)
1	158	94 (59.5)	59 (37.3)	5 (3.2)
2	125	56 (44.8)	54 (43.2)	15 (12.0)
3	53	14 (26.4)	29 (54.7)	10 (18.9)
4	31	4 (12.9)	20 (64.5)	7 (22.6)
5	47	4 (8.5)	30 (63.8)	13 (27.7)
6	19	2 (10.5)	13 (68.4)	4 (21.1)
7	18	0 (0)	8 (44.4)	10 (55.6)
8	6	0 (0)	1 (16.7)	5 (83.3)
9	5	0 (0)	1 (20.0)	4 (80.0)
10	2	0 (0)	0 (0)	2 (100)
11	1	0 (0)	0 (0)	1 (100)
12	0	——	——	——

Table 7
The distribution of each disease outcome at each risk level in the validation cohort.

Risk level	Total points	Cases	Inflammation (%)	LGIN (%)	HGIN (%)
Low	0-1	222	135 (60.8)	81 (36.5)	6 (2.7)
Medium	2-3	178	70 (39.3)	83 (46.6)	25 (14.0)
High	4-6	97	10 (10.3)	63 (64.9)	24 (24.7)
Very high	≥7	32	0 (0)	10 (31.2)	22 (68.8)

inherent limitations of the retrospective study, coupled with the extensive time span of some cases and potential patients' recall bias, significant missing data exist in this aspect, warranting further discussion and investigation. Clarifying the relationship between these factors and the prognosis of gastric LGIN necessitates future prospective studies to enhance understanding and provide more conclusive insights.

On the other hand, clinically, reversal of LGIN to inflammation can be observed when Hp infection is eradicated. As mentioned above, there is also a lack of information on whether Hp infection has been eradicated in our study. If the Hp infection is eradicated before patients receive ESD or EMR, there may be a phenomenon in which the postoperative pathological outcome is inflammation. In addition, some patients may have only a small amount of LGIN and have been completely removed by the preoperative biopsy, so their postoperative pathology is also inflammation. In both our development and validation cohort, a certain proportion of LGIN patients reversed to inflammation, which may be related

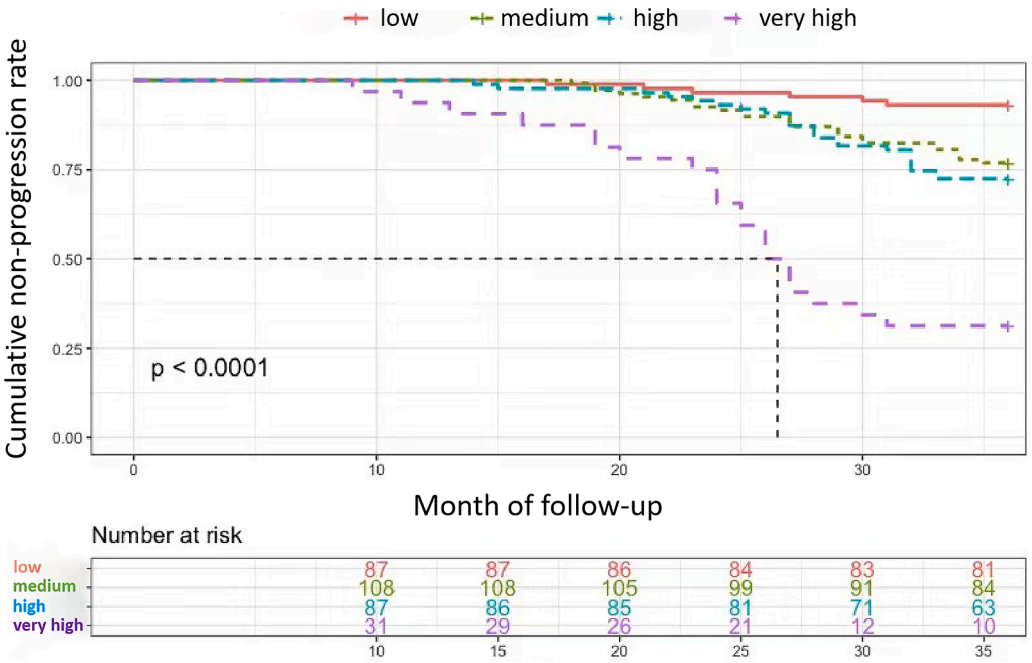


Fig. 2. The rate of non-progression of LGIN at different risk levels in the validation cohort. The non-progression differed among four risk groups in the validation cohort ($P<0.001$).

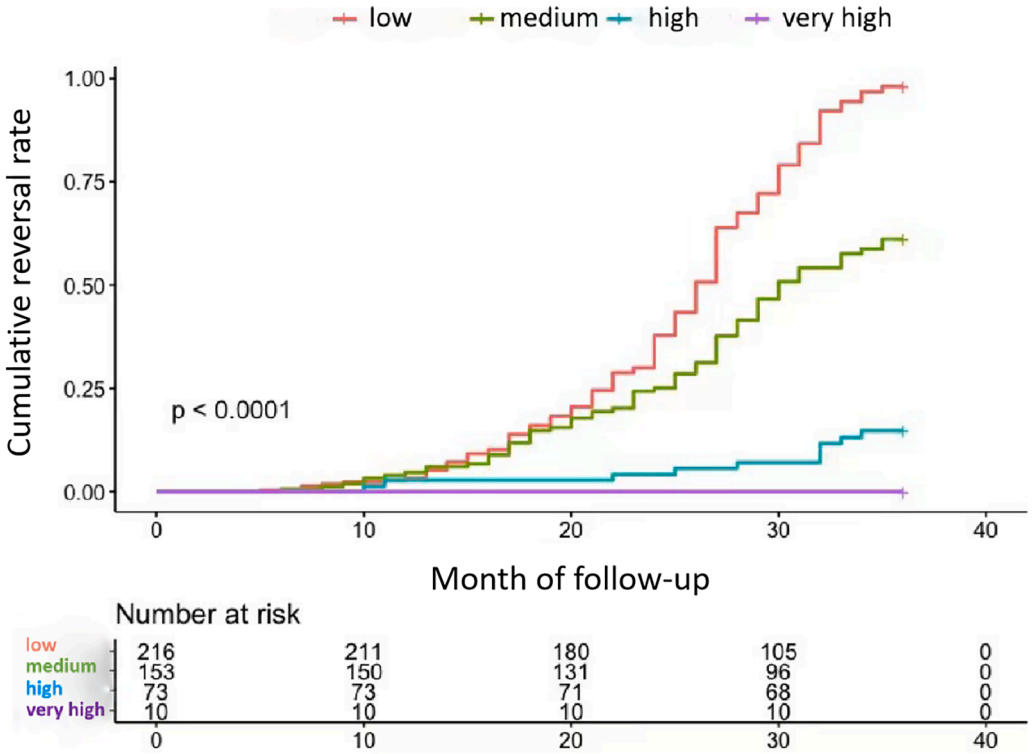


Fig. 3. The rate of reversal of LGIN at different risk levels in the validation cohort. The reversal differed among four risk groups in the validation cohort ($P<0.001$).

to the above reasons. This is also consistent with similar research reports [15–19].

Secondly, the e-Cout system was constructed based on readily ascertainable clinical and endoscopic features, effectively predicting the trajectory of different clinical outcomes in gastric LGIN through risk level classification. The reversal rate of LGIN exhibited a declining trend with increasing risk levels, with the reversal rate standing at 44.5 % in the low risk level. Correspondingly, the progression rate of LGIN increased proportionally with escalating risk levels, reaching a notable 74.1 % at the very high-risk level. The results of the multi-factor Chi-square test revealed significant differences in the overall score distribution and inter-group distribution of the three disease outcomes. Meanwhile, the Cochran-Armitage trend test further indicated that the progression and reversal of the disease were also significantly different. Additionally, the c-index of both the development and validation stage reached above 0.7, and the calibration curve of the validation stage also

Table 8
The COX proportional hazard regression analysis of LGIN progression and reversal in the validation cohort.

Risk level	LGIN progression			LGIN reversal		
	HR	95 % CI	*P* value	HR	95 % CI	*P* value
Low	1	Reference		1	Reference	
Medium	3.628	1.488-8.845	< 0.001	0.633	0.474-0.846	< 0.001
High	4.389	1.794-10.738	< 0.001	0.148	0.078-0.282	< 0.001
Very high	17.969	7.258-44.486	< 0.001	6.500E-08	0.000-inf	< 0.001

HR: hazards ratio.

showed a good fit. Therefore, this straightforward and practical e-Cout system can make relatively accurate predictions of the reversal and progression of LGIN, which exhibits potential promising clinical applicability.

Third, the e-Cout system can offer clinical guidance for follow-up treatment strategies. In the low-risk level, the consensus choice for both clinicians and patients would be regular, albeit not overly frequent, follow-up rather than opting for endoscopic therapy. Conversely, in the very high-risk level of patients, endoscopic therapy, especially endoscopic resection therapy (such as EMR or ESD), may be strongly recommended over endoscopic damage therapy (such as RFA or APC). Meanwhile, for high-risk patients, simple follow-up is no longer suitable, and consideration should be given to endoscopic treatment. Endoscopic damage therapy could be considered, with endoscopic resection therapy serving as a supplementary option or a direct choice due to the close to 1/3 progression rate. Finally, for intermediate-risk patients, relatively aggressive treatment at this stage is understandable, considering the progression rate of 17.6 % and a maintenance rate exceeding 60 %, which should not be underestimated. Due to the high proportion of LGIN in this risk level, endoscopic damage therapy is one of the recommended treatment methods. However, if patients opt for endoscopic follow-up, an appropriate increase in the frequency of follow-up should be recommended, such as once every 3 to 6 months, to closely monitor the possible progression of LGIN. In general, the e-Cout system elucidates specific independent risk factors and quantifies risk probabilities, which diverges from past judgments primarily reliant on clinicians' own experience, fostering greater clinical applicability and potential to serve as a reference for future clinical decision-making in the field of gastric LGIN diagnosis and treatment.

There are some limitations in our study. First, it is imperative to acknowledge the retrospective nature of our investigation. In an effort to reduce recall bias, we judiciously excluded data and cases with large portion of missing values or doubtful authenticity, but this approach may introduce selection bias, potentially influencing our results. Second, this study is confined to a single-center, implying potential constraints on its representativeness. Third, based on the huge volume of data, we had to choose several endoscopists and pathologists for image interpretation and pathological analysis. Although they all have abundant clinical experience, the intra-observer and inter-observer reliability is still not perfect. Finally, the e-Cout system constructed in this study still lacks robust external validation. As a proactive measure, future endeavors should involve multi-center, prospective studies to execute comprehensive external verification, address the identified limitations, and refine the scoring system.

In conclusion, leveraging insights from 17 potential clinical and endoscopic risk factors, this study established a prognostic scoring system (e-Cout system) for gastric LGIN through statistical analysis and calculation. The e-Cout system holds promise in assisting clinicians to predict the probability and risk level of different clinical outcomes in patients with gastric LGIN, thus serving as a valuable reference for devising follow-up diagnosis and treatment strategies. However, its full potential hinges on further multi-center, prospective studies for external validation and subsequent refinement, thereby enhancing its clinical applicability and ensuring maximal benefit for a broader spectrum of patients.

Source of funding

This work was supported by the National Key Research and Development Program of China (No. 2022YFC2503600) and Chinese PLA General Hospital Young Independent Innovation Science Fund

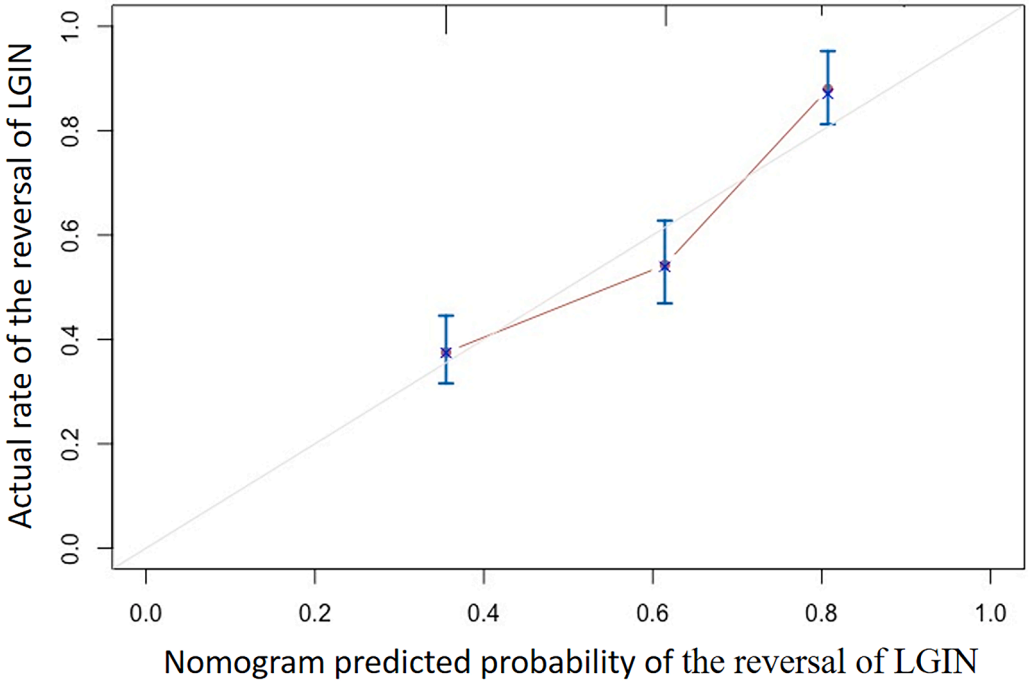


Fig. 4. The calibration curve for the assessment of calibration of predicting the reversal of LGIN.

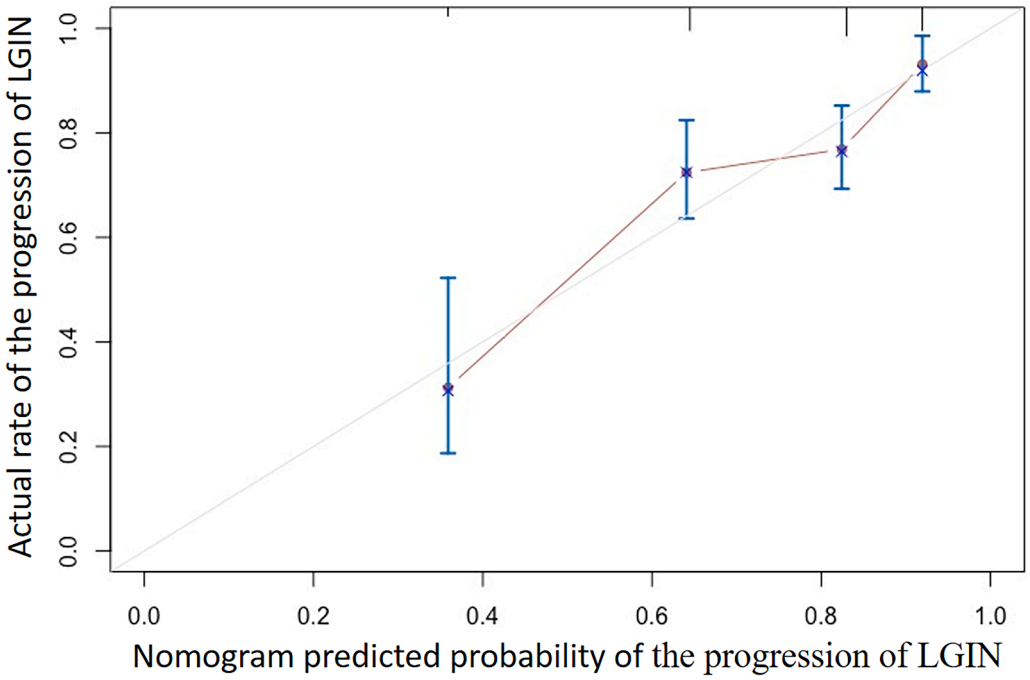


Fig. 5. The calibration curve for the assessment of calibration of predicting the progression of LGIN.

(No.22QNFC028).

Ethics approval and consent to participate

The study proposal was reviewed and approved by the Ethics Committee of the Chinese PLA General Hospital. All patients gave written informed consent after explaining the risks and benefits of the procedure or examination.

CRediT authorship contribution statement

Nanjun Wang: Writing – original draft, Methodology, Investigation. **Xiaotong Niu:** Writing – original draft, Methodology, Investigation. **Longsong Li:** Writing – original draft, Methodology, Investigation. **Jing Tang:** Supervision, Project administration. **Yawei Bi:** Supervision, Project administration. **Shengzhen Liu:** Supervision, Project administration. **Ke Han:** Software, Conceptualization. **Yaxuan Cheng:** Software, Conceptualization. **Zhaobei Cai:** Software, Conceptualization. **Ningli Chai:** Writing – review & editing, Validation. **Enqiang Linghu:** Writing – review & editing, Validation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data obtained or analyzed during this work are included within the article.

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