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Prediction of post-ESD esophageal stricture by a nomogram and risk factor analysis of ineffective oral steroids prophylaxis

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Abstract

Background and aims Several risk models for esophageal stricture after endoscopic submucosal dissection have been developed. However, some of them did not include the use of steroids in the risk analysis. Glucocorticoid sensitivity mediated by glucocorticoid receptor expression has not been discussed in this condition.

Methods Clinical and endoscopic characteristics were included in the logistic regression model to establish a nomogram for stenosis prediction. The score for each risk factor was estimated. Risk factors of ineffective oral steroid prophylaxis were analyzed and glucocorticoid receptor expressions were detected by immunohistochemistry.

Results Three hundred fourteen patients of endoscopic submucosal dissection for esophageal superficial neoplasms were included to develop the nomogram. The circumferential range(≤ 3/4, 3/4–1 or the whole circumference), longitudinal diameter reached 4 cm (yes or not) and lesion location (the cervical and upper thoracic part, the middle thoracic part or the lower thoracic part) consisted of the nomogram. Patients have a high risk of esophageal stricture if they have a total point greater than 36. In the simplified risk score model, the corresponding cutoff score was 1. 92 patients with oral steroid prophylaxis were separately analyzed and the circumferential mucosal defect involving 7/8 or more was an independent risk factor of ineffective prevention (OR 12.2, 95%CI 5.27–28.11). The expression of glucocorticoid receptor β was higher in the stricture group ($p = 0.042$ for AOD; $p = 0.016$ for the scoring system).

Conclusions We established a nomogram for esophageal stricture prediction. Depending on the characteristics of lesions, it is possible to estimate the risk of stricture under routine post-ESD treatments (no steroids or oral steroids). Alternative treatments should be considered if the risk is extremely high, especially for patients with mucosal defects involving 7/8 or more of circumference in which oral steroid treatment tends to be ineffective. The higher glucocorticoid receptor β may indicate potential glucocorticoid resistance.

Keywords Esophageal stricture after ESD, Glucocorticoid receptor, Inverse probability of treatment weighting, Risk model

Introduction

Esophageal cancer ranks seventh in terms of incidence (604,000 new cases) and sixth in mortality overall (544,000 deaths) in 2020 while Eastern Asia exhibits the highest regional incidence rates with a large burden in China [1]. Superficial esophageal neoplasms (SENs) are being diagnosed increasingly frequently and endoscopic submucosal resection (ESD) is widely used as a

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therapeutic method for SENs providing excellent oncologic outcomes. However, esophageal stricture, as one of the major complications of esophageal ESD, severely impairs patients' quality of life.

Recent guidelines strongly recommend steroid management in patients with mucosal defects involving 3/4 or more of the circumference to prevent stenosis after ESD [2]. Six studies have developed risk-scoring models for post-ESD esophageal stricture prediction [3–8]. However, some of them did not include the use of steroids (local injection or oral administration) in the risk analysis [3, 4, 8]. Therefore, the efficacy of risk ratings may be insufficient because it was not clarified whether the high risk predicted by these models should be treated by prophylactic steroids or surgery.

Risk factors of esophageal stricture under prophylactic steroids treatment were also explored by a few studies [9–12]. It helped to determine which patients are suitable for steroid therapy or for whom surgical treatment is recommended. But most of them are focused on local triamcinolone injection and the sample size of patients with oral prednisolone is relatively small.

Glucocorticoid sensitivity is a new perspective that has not been explored in the post-ESD esophageal stricture formation until now. Glucocorticoids exert their action via intracellular glucocorticoid receptors (GRs) and GR has two isoforms; while GRα is the predominant isoform, capable of binding to specific glucocorticoid response element (GRE) DNA sequences and inducing gene transcription, GRβ does not bind glucocorticoids and is transcriptionally inactive as a candidate for a dominant negative inhibitor of GRα activity, which may participate in defining the sensitivity of target tissues to glucocorticoids [13–16].

Here, we developed a nomogram based on the patients with ESD for esophageal superficial neoplasms, and the use of steroids was enrolled in the analysis. Meanwhile, the predictors of ineffective steroid prophylaxis were analyzed to aid in clinical decision-making. The association of GR expression and glucocorticoid response was explored in several pairs of patients.

Methods

Patients

There was a retrospective study in a single center in China. 314 consecutive patients with 400 SENs resected by ESD were enrolled between January 2014 and March 2023. Among them, 92 patients with 136 lesions received prophylactic oral prednisolone treatment. The larger lesion in patients with multiple lesions was considered the target lesion. The ethics committee of Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology approved our protocol (TJ-IRB20230451). Details that might disclose the identity of the patients had been omitted.

ESD procedure and postoperative management

A complete description of the ESD procedure has been reported [10]. For patients with mucosal defects affecting 3/4 or more of the circumference, oral prednisolone was routinely started at 30 mg per day on the third day after ESD, tapered gradually, and then discontinued 8 weeks later. Some of them received oral prednisolone plus polyglycolic acid (PGA) shielding. PGA sheets were delivered through the scope with forceps by multiple patches to cover the entire circumference of the esophagus [17].

Repeat endoscopy at 1,6 and 12 months after ESD was recommended. The presence of stricture was confirmed when a standard 9.2-mm diameter upper gastrointestinal endoscope could not be passed through the treatment site. Patients with a complaint of dysphagia received an endoscopic evaluation at any time. Endoscopic balloon dilation (EBD) was performed in necessity. The refractory esophageal stricture was diagnosed as the result of an inability to successfully remediate the anatomic problem to a diameter of 14 mm over 5 sessions of EBD at 2-week intervals [18].

Data collection

Patient characteristics, lesion characteristics, and prophylactic treatment were collected to demonstrate the predictors associated with esophageal stricture formation. Patient characteristics comprised gender, age, and history of chemoradiotherapy. Lesion characteristics included location, longitudinal diameter, lesion number, ESD scar, macroscopic appearance, histological invasion depth, muscular layer injury, and circumference range. The circumferential range was measured as the proportion of the esophageal circumference that was removed, based on its division into 12 equal parts when the esophageal lumen was spread to its maximum width using full insufflation. It was measured by the endoscopist and represented as percentages. Prophylactic treatment consisted of oral steroids and PGA sheets.

In the cases with oral steroids, after risk factors were identified, pathological specimens were matched by them and the expression of GRs was detected by immunohistochemistry. Sections were randomized, blinded, and then graded respectively. A five-point scale of 0 = no staining to 4 = maximal staining was used to quantify the expression of GRα [16]. A four-point scoring system was used for GRβ staining: 0 = no detectable expression to 3 = widespread and strong expression [19]. In addition, the average optical density (AOD) value (integrated optical density/area) of the immunoreactive terminals in the tissue was measured to determine the variance of GR expression [20–23]. Both

scoring methods were used in five visions from each section, and detections of GRα and GRβ were based on the same part of each section. The average was determined to be the final result for each specimen. Comparisons were using the the student's t-test.

Statistical analyses

Potential predictors were analyzed using univariate analysis first, and the variables with $P<0.05$ were included in the multivariate analysis. Then, covariates with $P<0.05$ were identified as independent impactors and enrolled in the logistic regression model. Risk factors and their effects on stricture formation were evaluated by calculating the odds ratio (OR) and the 95% confidence interval (CI). Then, a nomogram was established based on the multivariate logistic regression model. Internal validation was estimated by the concordance index (C-index) and calibration curves (1000 bootstrap resamples). The reliability of the model was evaluated using the Hosmer–Lemeshow test for goodness-of-fit. Total points were derived based on the variables and converted to the predicted probability. Receiver operating characteristic (ROC) curve analysis was used to calculate the optimal cutoff values that maximized the Youden index.

For easier clinical use, a simplified scoring model was derived to calculate the probabilities of esophageal strictures. Each risk factor score was weighted based on the beta coefficient received from the earlier multivariate logistic regression analysis. The predictive probability of different total scores was calculated. The validity of the model was assessed by estimating the area under the receiver operating characteristic (ROC) curve using c-statistics.

In the analysis of patients with prophylactic steroids, the ROC curve and Youden index were used to determine the optimal cutoff value of circumferential mucosal defect extent. The inverse probability of treatment weighting (IPTW) technique based on propensity scores was used to reduce selection bias by creating a "pseudo-population" in the study. We adjusted for the confounding factors by using the estimated propensity scores to assign weights to the data.

The statistical analyses were performed using R 4.5.3 and IBM SPSS software, version 27.0 for Windows (IBM Corporation, Armonk, NY, USA). All of the statistical tests were two-sided, and a value of $p<0.05$ was considered statistically significant.

Results

Clinical characteristics of all cases received esophageal ESD for SENs

Three hundred fourteen patients with 400 lesions received esophageal ESD of SENs. 370 lesions achieved en-bloc resection (92.5%). 54 patients developed esophageal stenosis including 16 patients without prophylactic treatment, 28 with oral prednisolone, and 10 with oral steroid plus PGA shielding. The stenosis rate was 17.2%. Univariate analysis was performed and the result was shown in Table 1. Variables with $P<0.05$ were enrolled into the multivariate analysis including location, longitudinal diameter, circumferential range, and prophylactic treatment. Multivariate analysis showed that lesion in the cervical and upper thoracic part (OR 5.717, 95%CI 2.169-15.067), longitudinal diameter reached 4 cm (OR 3.075, 95CI% 1.270-7.446), and circumferential range (>3/4-<1: OR 5.338, 95%CI 2.234-12.759; whole circumference: OR 38.664, 95%CI 11.507-129.914) were independent risk factors of post-ESD esophageal stricture formation. Prophylactic treatment did not show significant protective or negative effects in the multivariate analysis (Table 1). The final formula for predicting post-ESD esophageal stricture was:

$$\mathrm{Logit(P)} = -3.195 + 0.793X_1 + 1.783X_2 + 1.653X_3 + 3.562X_4 + 0.900X_5$$

In the formula, P indicated the predicted esophageal stricture probability, X indicated the variables that were included in the model (X_1 to X_5 represented the lower thoracic part, the cervical or upper thoracic part, circumferential range > 3/4, the whole circumference, and longitudinal ≥ 4 cm, respectively). X was assigned 1 when the patient was consistent with the variable; otherwise, X was assigned 0.

Identification and validation of the novel nomogram

A nomogram was visualized based on the multivariate logistic regression analysis (Fig. 1). The C-index was 0.826 (95%CI 0.757–0.894, $p<0.001$), thus reflecting the good accuracy and discrimination ability of the nomogram. The calibration curves also indicated good consistency between the actual observation and the nomogram prediction of esophageal stenosis (Figure S1). The Hosmer–Lemeshow Chi-square was 1.526 ($p>0.822$) indicating good reliability. The cutoff score that maximized the Youden index (0.525) was a total of 36 points, with a sensitivity of 74.1% and a specificity of 78.5%. The probability of the cutoff point was 12.6%. A risk stratification was derived as the low-risk group (total point of 0–36) and the high-risk group (total point of 36–175). Total points and corresponding stricture risk are shown in Fig. 1. Using this risk stratification system, all subjects were accurately differentiated($p<0.001$) with esophageal stricture rates of 6.4% (14/218) and 41.6% (40/96), respectively.

For easier clinical use, a risk score model was established. By rounding the score to the nearest integer of the absolute beta coefficient value, we assigned 1 point to the location in the lower thoracic part and the longitudinal diameter reached 4 cm, 2 points to the location

Table 1 Univariate and multivariate analysis in 314 cases of endoscopic submucosal dissection for esophageal superficial neoplasms

		No-stenosis ($n=260$) (%)	Stenosis ($n=54$) (%)	Univariate analysis			Multivariate analysis		
				OR	95%CI	*P* value	OR	95%CI	*P* value
Patient characteristics	Gender			1.114	0.581–2.138	**0.745**			
	female	78(30.0)	15(27.8)						
	male	182(70.0)	39(72.2)						
	Age (mean ± SD)	62.5 ± 7.97	62.7 ± 6.49	1.005	0.967–1.044	**0.798**			
	Previous chemoradiotherapy			9.962	0.887–111.899	**0.063**			
	no	259(99.6)	52(96.3)						
	yes	1(0.4)	2(3.7)						
Lesion characteristics	Location					**0.007***			**0.002***
	middle thoracic part(> 24- ≤ 32 cm)	192(73.8)	29(53.7)	1.00			1.00		
	lower thoracic part(> 32 cm)	47(18.1)	14(25.9)	1.972	0.967–4.024	0.062	2.072	0.865–4.962	0.102
	cervical and upper thoracic part(≤ 24 cm)	21(8.1)	11(20.4)	3.468	1.516–7.933	0.003	5.717	2.169–15.067	< 0.001
	Longitudinal diameter (cm) (mean ± SD)	3.7 ± 1.58	5.3 ± 2.80	1.479	1.249–1.752	**< 0.001***			
	Longitudinal diameter ≥ 4 cm					**< 0.001***			**0.013***
	no	120(46.2)	9(16.7)	1.00			1.00		
	yes	140(53.8)	45(83.3)	4.286	2.012–9.128		3.075	1.270–7.446	
	Lesion number					**0.066**			
	single	216(83.1)	39(72.2)	1.00					
	multiple	44(16.9)	15(27.8)	1.888	0.958–3.719				
	ESD scar					**0.557**			
	no	254(97.7)	52(96.3)	1.00					
	yes	6(2.3)	2(3.7)	1.628	0.320–8.292				
	Macroscopic appearance					**0.332**			
	flat	227(87.3)	51(94.4)	1.00					
	protruded	26(10.0)	2(3.7)	3.039	0.700–13.184	0.138			
	depressed	7(2.7)	1(1.9)	0.000	0.000	0.999			
	Circumferential range					**< 0.001***			**< 0.001***
	≤ 3/4	236(90.8)	24(44.4)	1.00			1.00		
	> 3/4- < 1	20(7.7)	13(24.1)	6.392	2.830–14.437	< 0.001	5.338	2.234–12.759	< 0.001
	1	4(1.5)	17(31.5)	41.792	13.005–134.294	< 0.001	38.664	11.507–129.914	< 0.001
	Histological invasion depth					**0.052**			
	EP/LPM	186(71.5)	32(59.3)	1.00					
	MM/SM1	62(23.8)	15(27.8)	1.406	0.714–2.768	0.324			
	SM2	12(4.7)	7(12.9)	3.391	1.241–9.261	0.017			
	Muscular layer injury					**0.366**			
	no	224(86.2)	49(90.7)	1.00					
	yes	36(13.8)	5(9.3)	0.635	0.237–1.700				
Prophylactic treatment						**< 0.001***			**0.123**
	no	206(79.2)	16(29.6)	1.00					
	Oral steroids	44(16.9)	28(51.9)	8.011	4.003–16.032	< 0.001			0.074
	Oral steroids + PGA sheet	10(3.9)	10(18.5)	14.306	5.085–40.242	< 0.001			0.811

SD standard deviation, *OR* odds ratio, *CI* confidence interval, *ESD* endoscopic submucosal dissection, *EP* epithelium, *LPM* lamina propria mucosa, *MM* muscularis mucosa, *SM1* submucosal invasion < 200um, *SM2* submucosal invasion ≥ 200um, *PGA* polyglycolic acid , * indicates *P* value<0.05

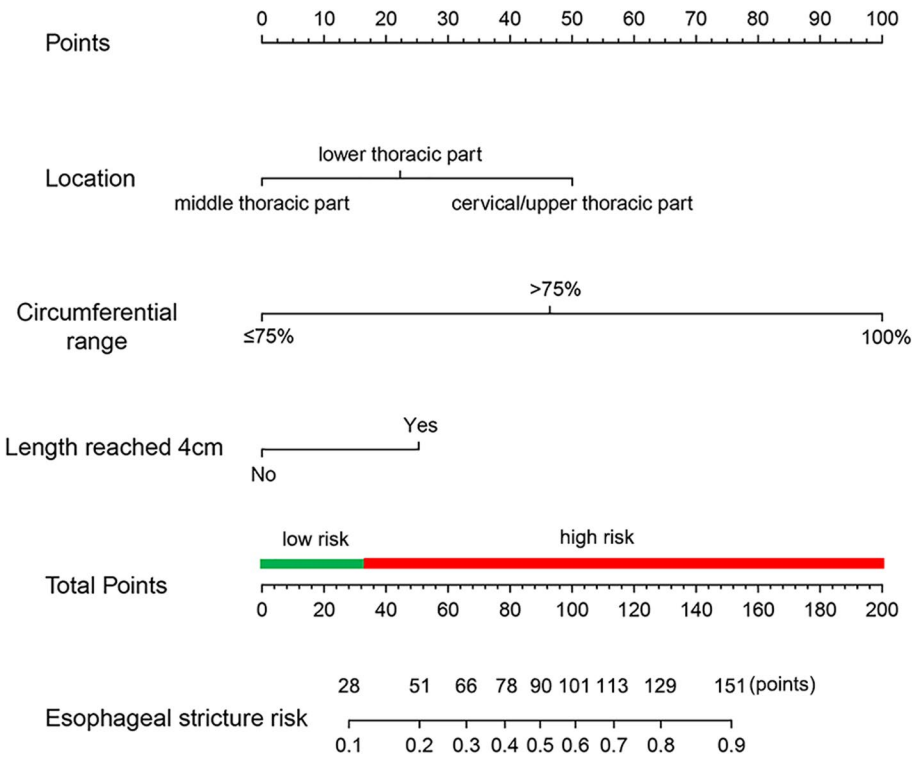

Fig. 1 Nomogram for the individualized prediction of esophageal stricture after endoscopic submucosal dissection

in the cervical and upper thoracic part, and circumferential range of > 3/4—< 1, 4 points to whole circumferential range(Table 2). The area under the curve (AUC) of this model was 0.819 (95%CI 0.749–0.890, $p < 0.001$), close to the C-index of the nomogram. Similarly, the cutoff value was identified in the risk model with the low risk of score 0–1 and the high risk of 2–7. The estimated probability of the total point was calculated in Table 3.

Clinical characteristics of patients with prophylactic oral prednisolone

Among the 314 patients of esophageal SENs ESD, 92 patients with 136 lesions received the oral prednisolone treatment. Consequently, 127 lesions achieved en-bloc resection (93.4%).

Fifty-four patients were found no stricture in the endoscopic evaluation at 8 weeks after ESD. During the subsequent follow-up, they do not complain of difficulty with swallowing. 38 patients (41.3%) were confirmed post-ESD esophageal stricture with ineffective prophylactic oral prednisolone. 12 of them received EBD (6 to 21 sessions with an average of 14.1 sessions) and were diagnosed with refractory esophageal stricture. 26 patients were confirmed esophageal stricture through endoscopy and 20 of them received EBD (1 to 5 sessions with an average of 2.5 sessions). Of the patients who had a circumferential mucosal defect ($n = 20$), 16 of them got stricture (80.0%).

Table 2 Development of the risk score model to predict esophageal stricture after ESD

Risk factor	Categories	β	B	Score
Location	middle thoracic part(> 24- ≤ 32 cm)(reference)	-	0.793	0
	lower thoracic part(> 32 cm)	0.793		1
	cervical and upper thoracic part(≤ 24 cm)	1.783		2
Circumferential range	≤ 3/4(reference)	-	0.793	0
	> 3/4- < 1	1.653		2
	1	3.562		4
Longitudinal diameter ≥ 4 cm	no(reference)	-	0.793	0
	yes	0.900		1

ESD endoscopic submucosal dissection

Table 3 Estimate risk of the risk score model

Point total	Estimate of risk	Stenosis rate
0	0.039	Low risk (14/218,6.4%)
1	0.083	
2	0.167	High risk (40/96,41.6%)
3	0.307	
4	0.494	
5	0.684	
6	0.827	
7	0.913	

The predictive factor of stricture formation under prophylactic steroids

Between the two groups with polarized treatment outcomes, other factors were similar except for the extent of the circumferential range (%) (OR1.091, 95%CI 1.043–1.141) (Table 4). Using the ROC curve analysis, the cutoff value for the circumferential range was 87.5% (7/8) with a sensitivity of 68.4% and a specificity of 74.1% according to the maximized Youden index of 0.425. The AUC value was 0.743 (95%CI 0.636–0.849, $p < 0.001$).

Using this cutoff value, we determined that the frequency of esophageal stricture formation in the patients given oral prednisolone increased if the circumferential mucosal defect involved 7/8 or more (26/40, 65.0% vs 12/52, 23.1%, $p < 0.001$).

Logistic regression analysis determined the circumferential mucosal defect reached 7/8 or more as an independent risk factor (OR 6.190, 95%CI 2.478–15.465) (Table 5). For IPTW, the inverse propensity score was applied as weights for patients with circumferential mucosal defect involving 7/8 or more, and the inverse of 1 minus the propensity score was applied for patients without it. 9 variables were used to generate a propensity score including location, previous chemoradiotherapy, longitudinal diameter, lesion number, ESD scar, macroscopic appearance, invasion depth, muscular layer injury, and PGA shielding. The propensity score model was well calibrated (Hosmer–Lemeshow test: $P = 0.204$) and showed good discrimination between the groups (c-statistics = 0.769, 95% CI 0.672–0.865, $p < 0.001$).

After adjusting the model using the IPTW method, we determined the odds ratio of esophageal stricture formation in patients with circumferential mucosal defect involving 7/8 or more (OR 12.170, 95%CI 5.265–28.106) (Table 5). Moreover, the average EBD session in the ≥7/8 group was larger than the <7/8 group (0.69 ± 0.41 vs 4.57 ± 1.00, $p = 0.001$) (Table S1).

Immunohistochemistry staining of glucocorticoid receptors

After clarifying the risk factors of esophageal stricture under oral prednisolone, 8 pairs of patients were matched based on whether the circumferential mucosal defect was ≥7/8 and if the longitudinal diameter was ≥5 cm [24].

Immunohistochemistry revealed that GRα staining was widely positive in the epithelium, lamina propria, and muscularis mucosa. In contrast, GRβ staining was scant in the epithelium (Figure S2). For GRα, the expression level was similar in the two groups ($p = 0.701$ for AOD; $p = 0.230$ for the scoring system). For GRβ, the expression level was higher in the stricture group ($p = 0.042$ for AOD; $p = 0.016$ for the scoring system) (Table 6; Table S2).

Discussion

Esophageal stricture is one of the most common complications of esophageal large-area ESD. Several studies have identified the risk factors of post-ESD esophageal stenosis and established a nomogram for clinical prediction. However, some of them did not include the use of prophylactic steroids in the analysis [3, 4, 8], the others showed that steroid treatment was not a protective factor in the risk model [5–7]. Thus, whether the predicted high risk can be reduced or resolved through prophylactic steroids is unclear. We developed a nomogram based on the retrospective data and similar to previous reports, the circumferential range, longitudinal diameter, and lesion location were included in the risk model. Meanwhile, our study enrolled the use of oral steroids in the risk factor analysis and came to a consistent conclusion that oral prednisolone is not an independent protective factor for post-ESD esophageal stenosis.

However, the conclusion can be biased and the effect of steroids should not be denied because the steroid treatment is only applied in patients with mucosal defects involving 3/4 or more, which is primarily a high-risk population of esophageal stenosis. Consequently, the high risk indicates that under the use of oral steroids, there is still a risk of stricture formation.

To help better clinical decisions, it is necessary to determine the predictor of stricture formation after prophylactic oral steroids. We enrolled all patients with prophylactic oral steroids and using the ROC curve, a mucosal defect involving 7/8 or more of the entire esophageal circumference was determined as an independent risk factor for stricture formation. It remains an independent risk factor through the IPTW method to adjust the baseline confounding bias without reducing

Table 4 Univariate and multivariate analysis in 92 cases with prophylactic oral steroids

		No-stenosis (*n* = 54) (%)	Stenosis (*n* = 38) (%)	Univariate analysis			Multivariate analysis		
				OR	95%CI	*P* value	OR	95%CI	*P* value
Patient characteristics	Gender			0.931	0.392–2.208	**0.870**			
	female	19(35.2)	14(36.8)						
	male	35(64.8)	24(63.2)						
	Age (mean ± SD)	63.7 ± 8.85	63.0 ± 6.64	0.988	0.938–1.041	**0.648**			
	Previous chemoradiotherapy			2.944	0.257–33.697	**0.385**			
	no	53(98.1)	36(94.7)						
	yes	1(1.9)	2(5.3)						
Lesion characteristics	Location					**0.200**			
	middle thoracic part(> 24- ≤ 32 cm)	37(68.5)	20(52.6)	1.00					
	lower thoracic part(> 32 cm)	13(24.1)	11(28.9)	1.565	0.593–4.129	0.365			
	cervical and upper thoracic part(≤ 24 cm)	4(7.4)	7(18.5)	3.237	0.845–12.408	0.087			
	Longitudinal diameter (cm)(mean ± SD)	5.2 ± 1.77	5.8 ± 3.14	1.102	0.923–1.315	**0.282**			
	Lesion number			0.607	0.245–1.507	**0.282**			
	single	34(63.0)	28(73.7)						
	multiple	20(37.0)	10(26.3)						
	ESD scar			1.444	0.194–10.732	**0.719**			
	no	52(96.3)	36(94.7)						
	yes	2(3.7)	2(5.3)						
	Macroscopic appearance					**0.080**			
	flat	39(72.2)	35(92.1)	1.00					
	protruded	13(24.1)	2(5.3)	5.833	1.229–27.679	0.026			
	depressed	2(3.7)	1(2.6)	3.250	0.193–54.777	0.413			
	Circumferential range (%) mean ± SD)	80.5 ± 9.72	90.1 ± 11.11	1.091	1.043–1.141	**< 0.001***	1.091	1.043–1.141	**< 0.001***
	Histological invasion depth					**0.583**			
	EP/LPM	36(66.7)	22(57.9)	1.00					
	MM/SM1	14(25.9)	11(28.9)	1.286	0.497–3.329	0.605			
	SM2	4(7.4)	5(13.2)	2.045	0.496–8.443	0.323			
	Muscular layer injury			0.576	0.139–2.385	**0.446**			
	no	47(87.0)	35(92.1)						
	yes	7(13.0)	3(7.9)						
Prophylactic treatment				2.037	0.748–5.547	**0.164**			
	Oral prednisolone	44(81.5)	28(73.7)						
	Polyglycolic acid sheets plus oral steroids	10(18.5)	10(26.3)						

SD standard deviation, *OR* odds ratio, *CI* confidence interval, *ESD* endoscopic submucosal dissection, *EP* epithelium, *LPM* lamina propria mucosa, *MM* muscularis mucosa, *SM1* submucosal invasion < 200um, *SM2* submucosal invasion ≥ 200um, * indicates *P* value <0.05

the sample size. Patients with mucosal defects involving 7/8 or more of the circumference showed a higher stenosis rate (65.0% vs 23.1%) and more EBD sessions (4.6 vs 0.7). Similarly, OlamotoK et.al reported that in patients with local triamcinolone injection, the rate of esophageal stricture (71.4%) was highest in cases involving mucosal defects that covered more than 7/8 of the circumference [25]. Therefore, if the pre-operative assessment predicts a high risk according to the risk model with the addition of a circumferential range of the mucosal defect covering 7/8 or more, surgery could be considered as an alternative.

Table 5 Multiple and IPTW logistic odds ratio of stricture formation associated with circumferential mucosal defect (cutoff value:87.5%)

Stenosis risk	OR	95%CI	*P* value
Multivariate analysis before IPTW-adjusted	6.190	2.478–15.465	< 0.001*
Multivariate analysis after IPTW-adjusted	12.170	5.265–28.106	< 0.001*

IPTW inverse probability of treatment weighting, *OR* odds ratio, *CI* confidence interval, * indicates *P* value <0.05

Table 6 GRs expression in pathological specimens from 8 pairs of patients

Patient ID	Pairs	Gender	Age	Circumferential mucosal defect	Longitudinal diameter (cm)	Location	GRα		GRβ		Stricture or not	*P* value for GRα		*P* value for GRβ	
							AOD (mean)	Score(mean)	AOD (mean)	Score(mean)		AOD	Score	AOD	Score
4	1	male	78	0.833	5	middle thoracic part	0.170583	2.8	0.326282	1	No	0.701	0.230	0.042	0.016
19	1	male	65	0.75	5	cervical part	0.126821	1.2	0.304878	0.4	Yes				
26	2	male	70	0.75	4	lower thoracic part	0.155337	2.2	0.324803	0.8	No				
88	2	male	61	0.75	3.8	middle thoracic part	0.166155	2.2	0.316771	0.6	Yes				
25	3	male	54	0.75	5.5	middle thoracic part	0.190039	3	0.327075	0.8	No				
20	3	female	53	0.833	5.5	upper thoracic part	0.160925	2.4	0.357775	2	Yes				
21	4	male	55	0.833	4	middle thoracic part	0.138581	2	0.317828	0.8	No				
23	4	female	64	0.75	4.5	middle thoracic part	0.193384	2.8	0.363089	1.8	Yes				
22	5	male	73	0.917	5	middle thoracic part	0.133434	1.8	0.346390	1.2	No				
6	5	male	67	1	5	lower thoracic part	0.148980	2	0.338651	1.4	Yes				
24	6	female	58	1	7	middle thoracic part	0.193607	3	0.309153	0.4	No				
18	6	male	66	1	7	lower thoracic part	0.156426	2	0.365951	2	Yes				
1	7	male	70	0.917	6	middle thoracic part	0.134460	1.8	0.299872	0	No				
2	7	male	54	0.917	7	middle thoracic part	0.128541	1.4	0.345325	1.6	Yes				
89	8	male	68	0.917	5	middle thoracic part	0.159869	2	0.323628	1	No				
11	8	male	60	1	6	lower thoracic part	0.159246	2	0.345216	2	Yes				

GR glucocorticoid receptor, *AOD* average optical density

Specifically, we showed a stenosis rate of 50% (10/20) in patients with a mucosal defect involving 7/8 or more and less than the entire circumference. For the patients with circumferential mucosal defect, the incidence rate was 80% (16/20) after oral prednisolone treatment. The effect of oral steroids seems better than local steroid injection since T.Kadota et.al reported stenosis rates of 56.0% and 100% respectively in the two groups [26]. The steroid injection followed by oral steroids may be a better choice as they reported stricture rates of 20% (2/10) and 71% (10/14) in the two groups. Moreover, the higher oral dose of prednisolone (50 mg/d) was applied in a small sample size with a stenosis rate of 0% (0/14) including 3 patients with 7/8 or more circumferential mucosal defect [27]. Further investigation of prevention was warranted in the patients with poor effects of steroid treatment, especially the entire circumferential defect.

Primarily, the normal mucosa should be preserved as much as possible, and circumferential resection should be avoided. Besides, we tried another perspective to explain the stricture formation following the use of oral steroids. D.Rutkowski et. al reported that steroid-responsive patients had increased GRα expression at baseline compared with non-responders in keloid disease [16]. In contrast, GRβ overexpression was reported as a commonly proposed mechanism for steroid resistance in severe asthma [13, 14]. Mitsunori Honda et. al found that the positive rate of GRβ mRNA detected in peripheral blood mononuclear cells significantly increased in patients with glucocorticoid-resistant ulcerative colitis [15]. Consistently, we revealed that GRβ showed a higher expression level in the specimens from patients with stricture formation than the other group, suggesting that insensitivity to glucocorticoids may potentially contribute to the failure of prophylactic steroid treatment.

It reminds us that the primary sensitivity or resistance to glucocorticoid should be considered when dealing with extensive lesion endoscopic resections. If patients are resistant or not sensitive to steroids, extensive ESD should be cautious to avoid refractory stenosis and its negative impact on patient quality of life.

The limitations of this study are as follows: First, it is a retrospective single-center study and the model lacked external validation. The generalizability to other locations was limited. Second, the cutoff value (circumferential range involving 7/8 or more) needs to be examined in larger cohorts. Third, due to the study design and the limitation of specimen acquisition, the association between expression of GRs and esophageal stricture formation was investigated in only 8 pairs of patients. To enhance the reliability of the conclusion, we employed two scoring systems to assess the expression of GRs. The association between GR expression and stricture formation should be evaluated in larger sample sizes. Additionally, the predictive value of the expression level of GRs should be examined in prospective cohorts, in which the expression level could be detected in fresh tissues using quantitative approaches, such as immunoblot and polymerase chain reaction. Meanwhile, it is better to detect the expression in biopsy specimens before the ESD is performed to aid in clinical decision-making.

In conclusion, we established a nomogram for esophageal stricture prediction. Depending on the characteristics of lesions, it is possible to estimate the risk of stricture under routine post-ESD treatments (no steroids or oral steroids). Alternative treatments should be considered if the risk is extremely high, especially for patients with mucosal defects involving 7/8 or more of circumference in which oral steroid treatment tends to be ineffective. The higher glucocorticoid receptor β may indicate potential glucocorticoid resistance, possibly participating in the ineffective treatment.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-024-03448-9.

Supplementary Material 1.

Supplementary Material 2: Figure S1. The calibration curve for the test accuracy of the nomogram.

Supplementary Material 3: Figure S2. Typical examples (x200 magnification) of different expression levels in the specimens graded according to the GR score system. GRα: (A) score 1, (B) score 2, (C) score 3. GRβ: (D) score 0, (E) score 1, (F) score 2. GR: glucocorticoid receptor.

Supplementary Material 4.

Supplementary Material 5.

Supplementary Material 6.

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Authors' contributions
Xinxia Feng, Panpan Lu, Qiang Ding, and Mei Liu contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Miaoxin Zhang, Wei Tian, Jin Ma, and Ninghui Zhao. The first draft of the manuscript was written by Miaoxin Zhang and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Ethical considerations: The ethics committee of Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology approved our protocol (TJ-IRB20230451). Details that might disclose the identity of the patients had been omitted.
The informed consent was waived by the ethics committee.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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