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Risk-Scoring System for Prediction of Non-Curative Endoscopic Submucosal Dissection Requiring Additional Gastrectomy in Patients with Early Gastric Cancer

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ABSTRACT

Purpose: When patients with early gastric cancer (EGC) undergo non-curative endoscopic submucosal dissection requiring gastrectomy (NC-ESD-RG), additional medical resources and expenses are required for surgery. To reduce this burden, predictive model for NC-ESD-RG is required.

Materials and Methods: Data from 2,997 patients undergoing ESD for 3,127 forceps biopsy-proven differentiated-type EGCs (2,345 and 782 in training and validation sets, respectively) were reviewed. Using the training set, the logistic stepwise regression analysis determined the independent predictors of NC-ESD-RG (NC-ESD other than cases with lateral resection margin involvement or piecemeal resection as the only non-curative factor). Using these predictors, a risk-scoring system for predicting NC-ESD-RG was developed. Performance of the predictive model was examined internally with the validation set.

Results: Rate of NC-ESD-RG was 17.3%. Independent pre-ESD predictors for NC-ESD-RG included moderately differentiated or papillary EGC, large tumor size, proximal tumor location, lesion at greater curvature, elevated or depressed morphology, and presence of ulcers. A risk-score was assigned to each predictor of NC-ESD-RG. The area under the receiver operating characteristic curve for predicting NC-ESD-RG was 0.672 in both training and validation sets. A risk-score of 5 points was the optimal cut-off value for predicting NC-ESD-RG, and the overall accuracy was 72.7%. As the total risk score increased, the predicted risk for NC-ESD-RG increased from 3.8% to 72.6%.

Conclusions: We developed and validated a risk-scoring system for predicting NC-ESD-RG based on pre-ESD variables. Our risk-scoring system can facilitate informed consent and decision-making for preoperative treatment selection between ESD and surgery in patients with EGC.

Keywords: Endoscopic mucosal resection; Gastrectomy; Stomach neoplasms

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INTRODUCTION

Endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) is non-curative in 15%–20% of cases, and patients typically require additional endoscopic treatment or radical gastrectomy [1-4]. To reduce the rate of non-curative ESD and avoid using additional medical resources and increasing total costs, a preoperative predictive model for non-curative ESD is required [5-8].

Several previous studies have investigated the predictive factors of non-curative ESD for EGC [5-11]. Large tumor size, proximal tumor location, and presence of ulcer were identified as independent predictors of non-curative ESD in most previous studies. However, these studies had an important limitation in that they regarded non-curative ESD as a single entity, regardless of the risk of lymph node (LN) metastasis. Non-curative ESD can be classified into 2 groups according to the risk of LN metastasis and additional treatment required [12]. When lateral resection margin involvement or piecemeal resection is the only causative factor for non-curative ESD, the risk of LN metastasis is negligible and patients can be cured with additional endoscopic treatment alone, without the need for radical gastrectomy [4,12-14]. For these patients, predicting non-curative ESD before the procedure would be of less importance, as curative treatment can still be achieved with endoscopic treatment alone, and pre-ESD prediction of non-curative resection would have little effect on how a treatment strategy is chosen. However, previous studies on the predictive factors for non-curative ESD included these patients in the analysis and did not focus on patients requiring additional gastrectomy [5-11]. When patients undergo non-curative ESD for other causative factors such as deep submucosal or lymphovascular invasion, additional radical gastrectomy with LN dissection is definitely indicated after endoscopic treatment due to the risk of LN metastasis [1-3,12,15]. As treatment strategies need to be changed and additional medical resources are required for surgery, identifying predictive factors for non-curative ESD requiring gastrectomy is of great importance. In addition, it can help in the decision-making for preoperative treatment selection between ESD and surgery in patients with EGC. To date, however, few studies have evaluated the predictive factors for non-curative ESD requiring additional gastrectomy.

The present study aimed to identify the predictive factors for non-curative ESD requiring additional gastrectomy based on pre-ESD variables in patients with EGC. Using these factors, we developed and validated a risk-scoring system to predict non-curative ESD requiring additional gastrectomy.

MATERIALS AND METHODS

Patients
Between January 2009 and December 2016, 3,023 patients with 3,153 forceps biopsy-proven differentiated-type EGC underwent their first ESD at Samsung Medical Center. Pre-ESD forceps biopsy-based diagnoses of differentiated-type EGCs included well-differentiated or moderately differentiated EGCs, papillary EGCs, and extremely well-differentiated adenocarcinomas (EWDAs) [12,16]. Among these patients, 25 subjects with 25 EGCs arising in the remnant stomach and one with one EGC in the reconstructed gastric tube after esophagectomy were excluded from the study population. Finally, 2,997 patients with 3,127 biopsy-proven differentiated-type EGCs treated with ESD were included in the analysis. ESD procedures and histopathological evaluations of ESD specimens in our institution have been

described in detail elsewhere [17,18]. Pre-ESD clinicopathologic data, including endoscopic tumor size, endoscopic tumor morphology based on major gross appearance, and forceps biopsy-based diagnoses were obtained through a retrospective review of medical records from the intranet resources of Samsung Medical Center. Because this study was based on a retrospective analysis of existing administrative and clinical data, the Institutional Review Board of Samsung Medical Center waived the requirement for informed patient consent and approved the study protocol (approval number: 2018-08-143). All research was conducted in accordance with the guidelines of the Declaration of Helsinki.

Definitions

ESD was defined as curative when all the following criteria were fulfilled [12]: a differentiated-type EGC was resected en bloc, and both lateral and vertical resection margins were negative with no lymphovascular invasion. In addition, one of the following criteria needed to be fulfilled: 1) tumor size ≤2 cm, mucosal cancer, no ulcer in the tumor; 2) tumor size >2 cm, mucosal cancer, no ulcer in the tumor; 3) tumor size ≤3 cm, mucosal cancer, ulcer in the tumor; or 4) tumor size ≤ 3 cm, SM1 cancer (submucosal invasion depth <500 μm from the muscularis mucosa layer). Non-curative ESD was defined when any of the above curative resection criteria were not met. Non-curative ESD requiring gastrectomy was defined as non-curative ESD without meeting the following criteria: 1) lateral resection margin involvement as the only non-curative factor or 2) piecemeal resection as the only non-curative factor [12].

Papillary adenocarcinoma was defined as a tumor with papillary structures composed of epithelial projections with a central fibrovascular core as a scaffold [19-22]. Gastric EWDA was diagnosed when branching tubules formed interconnecting and anastomosis structures, forming the shapes of the letters W, H, Y, or X under low-power view, and lacked overt back-to-back arrangements of glands [16,23-25]. Histological heterogeneity was defined as the presence of a differentiated-type cancer with a component of undifferentiated-type cancer (signet ring cell carcinoma or poorly differentiated adenocarcinoma) [12,26,27].

Statistical analysis

The primary endpoint was non-curative ESD requiring gastrectomy. The entire dataset was randomly partitioned into a ratio of 3:1 for training and validation. There were no missing data. Using the training set (n=2,345), we identified predictive factors for each endpoint in 2 steps. First, univariate logistic regression was used to investigate whether any pre-ESD clinicopathologic factors correlated with each endpoint. Factors with P-values <0.2 in the univariate analysis were considered in a multivariate logistic stepwise regression analysis (significance criteria of 0.05 for entry and 0.05 for stay) to identify significant predictors for each endpoint. We further developed a beta-coefficient-based risk-scoring system using identified predictors for non-curative ESD requiring gastrectomy. A score was assigned to each predictive factor for non-curative ESD requiring gastrectomy by dividing its beta coefficient by the smallest value among the coefficients of all identified factors. For simplicity, the scores were rounded to the nearest integer. The total score was calculated as the sum of the scores for all factors.

The predicted probability of non-curative ESD requiring gastrectomy was estimated based on the total score in a logistic regression equation [exp (−3.239 + 0.421 × total score)/1 + exp (−3.239 + 0.421 × total score)]. The optimal cut-off for the total score was determined by evaluating the performance criteria, including the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value, for each possible cut-off value. We

used Youden's index method [Youden's index = sensitivity + specificity − 1 = 2 × (balanced accuracy) − 1] to select the optimal cut-off value [28].

For the scoring-based prediction, the apparent validation was conducted in the training set using the Hosmer-Lemeshow goodness-of-fit chi-square test and the area under the receiver-operating characteristics (ROC) curve to confirm good calibration and assess the predictability, respectively. Finally, we internally validated the scoring-based prediction model by computing the area under the curve in the validation set (n=782). All analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

RESULTS

Predictive factors for non-curative ESD requiring gastrectomy

The total study population included 3,127 forceps biopsy-proven differentiated-type EGCs treated with ESD. The rate of non-curative ESD requiring gastrectomy was 17.3%. **Table 1** summarizes the clinicopathological characteristics of EGC lesions with non-curative ESD requiring gastrectomy.

In the total study population, non-curative ESD requiring gastrectomy was associated with forceps biopsy-based diagnoses, endoscopic tumor size, axial location, circumferential location, endoscopic tumor morphology, and histologic heterogeneity (**Table 1**). The univariate analysis results in the training set that included the 2,345 EGCs were the same as those of the total study population (**Table 2**).

Table 2 shows the results of the multivariate logistic stepwise regression analysis that was performed to determine the independent pre-ESD predictors for non-curative ESD requiring gastrectomy in the training set. In this analysis, moderately differentiated EGC, papillary adenocarcinoma, large tumor size (>2 cm), proximal tumor location, tumor location at the greater curvature, elevated or depressed macroscopic morphology, and presence of ulcer were identified as independent predictors for non-curative ESD requiring gastrectomy. Forceps biopsy-based diagnosis of papillary adenocarcinoma and presence of ulcer showed the highest odds ratios of 9.492 and 3.689, respectively.

Derivation and validation of the risk-scoring system for non-curative ESD requiring gastrectomy

A risk score was assigned to each pre-ESD predictive factor for non-curative ESD requiring gastrectomy, as shown in **Table 3**. The final total score ranges from 0 to 10. As the total risk score increased, the predicted risk for non-curative ESD requiring gastrectomy increased from 3.8% to 72.6% (**Fig. 1**). The area under the ROC curve of the risk-scoring system derived from the training set was 0.672 (95% confidence interval [CI], 0.644–0.700) (**Fig. 2**). Our predictive model showed good calibration in the Hosmer–Lemeshow goodness-of-fit test (P=0.966). When the fitted model derived from the training set was applied to the validation set that included 782 EGCs, the area under the ROC curve was 0.672 (95% CI, 0.626–0.719), which indicated that our risk-scoring system had a good discriminatory performance (**Fig. 2**).

Optimal threshold of the risk-scoring system

Based on Youden's index method, a risk score of 5 points was the optimal cut-off value for predicting non-curative ESD requiring gastrectomy in our risk-scoring system. When the risk

Table 1. Pre-operative characteristics of early gastric cancer lesions with and without NC-ESD-RG in 3,127 forceps biopsy-proven differentiated-type early gastric cancers

Variables	NC-ESD-RG (n=543)	Curative ESD or non-curative ESD requiring additional endoscopic treatment (n=2,584)[†]	P-value
Age (yr)*			0.119
Mean ± SD	64.0±9.9	63.4±9.8	
Median (range)	65 (35–89)	64 (22–93)	
Sex (%)*			0.688
Male	420 (77.3)	2,019 (78.1)	
Female	123 (22.7)	565 (21.9)	
Pathology on forceps biopsy (%)			<0.001
Well-differentiated	101 (18.6)	858 (33.2)	
Moderately differentiated	420 (77.3)	1,676 (64.9)	
Papillary adenocarcinoma	15 (7.0)	9 (0.3)	
EWDA	7 (1.3)	41 (1.6)	
Size on endoscopy (%)			<0.001
≤2 cm	434 (79.9)	2,333 (90.3)	
>2 cm	109 (20.1)	251 (9.7)	
Axial location (%)			<0.001
Antrum/Angle	323 (59.5)	1,900 (73.5)	
Low body/Mid-body	131 (24.1)	482 (18.7)	
High body/Fundus/Cardia	89 (16.4)	202 (7.8)	
Circumferential location (%)			0.027
Lesser curvature	208 (38.3)	1,164 (45.0)	
Anterior wall	88 (16.2)	404 (15.6)	
Posterior wall	116 (21.4)	487 (18.8)	
Greater curvature	131 (24.1)	529 (20.5)	
Macroscopic morphology (%)			<0.001
Flat	35 (6.4)	255 (9.9)	
Elevated	318 (58.6)	1,246 (48.2)	
Depressed	190 (35.0)	1,083 (41.9)	
Ulcer (%)			0.067
Absent	536 (98.7)	2,571 (99.5)	
Present	7 (1.3)	13 (0.5)	
Histologic heterogeneity (%)			<0.001
Absent	527 (97.1)	2,562 (99.1)	
Present	16 (2.9)	22 (0.9)	
Number of lesions (%)			0.528
Single	509 (93.7)	2,372 (91.8)	
Multiple	34 (6.3)	212 (8.2)	

NC-ESD-RG = non-curative endoscopic submucosal dissection requiring gastrectomy; ESD = endoscopic submucosal dissection; SD = standard deviation; EWDA = extremely well-differentiated intestinal-type adenocarcinoma.
*A total of 511 patients undergoing non-curative ESD requiring additional gastrectomy and 2,486 patients undergoing curative ESD or non-curative ESD requiring additional endoscopic treatment were included. [†]Seven patients showed both lateral resection margin involvement and piecemeal resection.

score was <5 and ≥5, non-curative ESD requiring gastrectomy was found in 12.4% (216/1,735) and 30.5% (186/610) of cases, respectively. Using a cut-off value of 5 points, the sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of the risk-scoring system were 46.3%, 78.2%, 30.5%, 87.6%, and 72.7%, respectively.

DISCUSSION

Previous studies on the predictive factors for non-curative ESD for EGC were limited in that they regarded non-curative ESD as a single entity regardless of the risk of LN metastasis and types of additional treatment required. Previous studies included patients with a negligible risk of LN metastasis and could be cured with additional endoscopic treatment alone, without the need for radical gastrectomy [4,12-14]. Therefore, predictive models for non-

Table 2. Predictive factors for non-curative endoscopic submucosal dissection requiring gastrectomy identified in the training set (n = 2,345)

Variables	Univariate OR (95% CI)	P-value	Multivariate OR (95% CI)	P-value
Age (yr)	1.008 (0.997–1.019)	0.172		
Sex		0.828		
Male	Ref			
Female	0.972 (0.750–1.259)			
Pathology on forceps biopsy		<0.001		
Well-differentiated	Ref		Ref	
Moderately differentiated	2.197 (1.670–2.892)		2.365 (1.785–3.134)	<0.001
Papillary adenocarcinoma	12.696 (4.687–34.393)		9.492 (3.378–26.670)	<0.001
EWDA	1.720 (0.694–4.265)		1.898 (0.739–4.875)	0.183
Size on endoscopy		<0.001		
≤2 cm	Ref		Ref	
>2 cm	2.167 (1.616–2.904)		2.136 (1.576–2.894)	<0.001
Axial location		<0.001		
Antrum/angle	Ref		Ref	
Low-body/mid-body	1.532 (1.178–1.993)		1.635 (1.246–2.147)	<0.001
High body/fundus/cardia	2.588 (1.879–3.564)		2.727 (1.937–3.842)	<0.001
Circumferential location		0.028		
Lesser curvature	Ref		Ref	
Anterior wall	1.292 (0.939–1.777)		1.271 (0.913–1.769)	0.155
Posterior wall	1.259 (0.937–1.692)		1.056 (0.773–1.444)	0.731
Greater curvature	1.508 (1.144–1.989)		1.572 (1.181–2.092)	0.002
Macroscopic morphology		<0.001		
Flat	Ref		Ref	
Elevated	2.108 (1.348–3.296)		2.446 (1.538–3.890)	<0.001
Depressed	1.464 (0.925–2.317)		1.733 (1.076–2.790)	0.024
Ulcer		0.106		
Absent	Ref		Ref	
Present	2.435 (0.828–7.161)		3.689 (1.197–11.371)	0.023
Histologic heterogeneity		0.030		
Absent	Ref			
Present	2.449 (1.092–5.492)			
Number of lesions	0.770 (0.535–1.110)	0.161		

OR = odds ratio; CI = confidence interval; EWDA = extremely well-differentiated intestinal-type adenocarcinoma.

curative ESD derived from previous studies might be inappropriate as a decision-making tool for preoperative treatment selection between ESD and surgery in patients with EGC. To provide a practical tool for preoperative treatment selection in patients with EGC, we
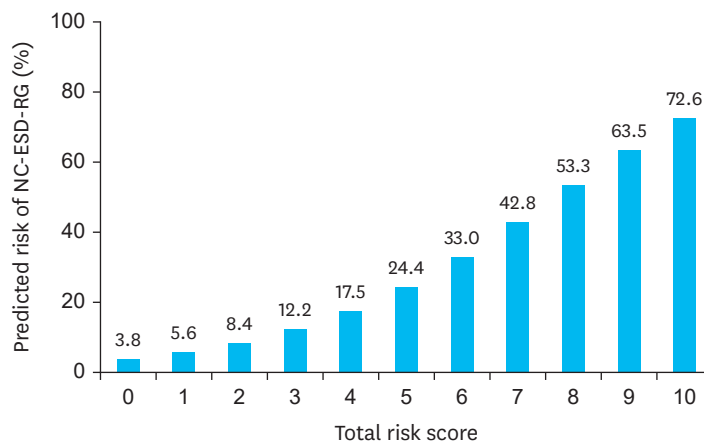
Fig. 1. Predicted risk for NC-ESD-RG according to the total risk score.
NC-ESD-RG = non-curative endoscopic submucosal dissection requiring gastrectomy.

Table 3. Derivation of the risk-scoring system for non-curative endoscopic submucosal dissection requiring gastrectomy

Variables	Multivariate odds ratio (95% CI)	Beta	Standard error	Scores	P-value
Pathology on forceps biopsy					
Well-differentiated	Ref			0	
Moderately differentiated	2.365 (1.785–3.134)	0.861	0.144	2	<0.001
Papillary adenocarcinoma	9.492 (3.378–26.670)	2.250	0.527	5	<0.001
EWDA	1.898 (0.739–4.875)	0.641	0.481	0	0.183
Size on endoscopy					
≤2 cm	Ref			0	
>2 cm	2.136 (1.576–2.894)	0.759	0.155	2	<0.001
Axial location					
Antrum/angle	Ref			0	
Low-body/mid-body	1.635 (1.246–2.147)	0.492	0.139	1	<0.001
High body/fundus/cardia	2.727 (1.937–3.842)	1.003	0.175	2	<0.001
Circumferential location					
Lesser curvature	Ref			0	
Anterior wall	1.271 (0.913–1.769)	0.240	0.169	0	0.155
Posterior wall	1.056 (0.773–1.444)	0.055	0.160	0	0.731
Greater curvature	1.572 (1.181–2.092)	0.452	0.146	1	0.002
Macroscopic morphology					
Flat	Ref			0	
Elevated	2.446 (1.538–3.890)	0.895	0.237	2	<0.001
Depressed	1.733 (1.076–2.790)	0.550	0.243	1	0.024
Ulcer					
Absent	Ref			0	
Present	3.689 (1.197–11.371)	1.305	0.574	3	0.023

CI = confidence interval; EWDA = extremely well-differentiated intestinal-type adenocarcinoma.

focused on patients undergoing non-curative ESD requiring gastrectomy. To the best of our knowledge, this is the first study to develop a risk-scoring system for predicting non-curative ESD requiring gastrectomy based on pre-ESD variables.

In the present study, forceps biopsy-based diagnosis of papillary adenocarcinoma showed the highest odds ratio when identifying predictors of non-curative ESD requiring gastrectomy. Previous studies based on surgical specimens reported that papillary EGC has higher lymphovascular and submucosal invasion rates than other subtypes of EGC [19,20,29].
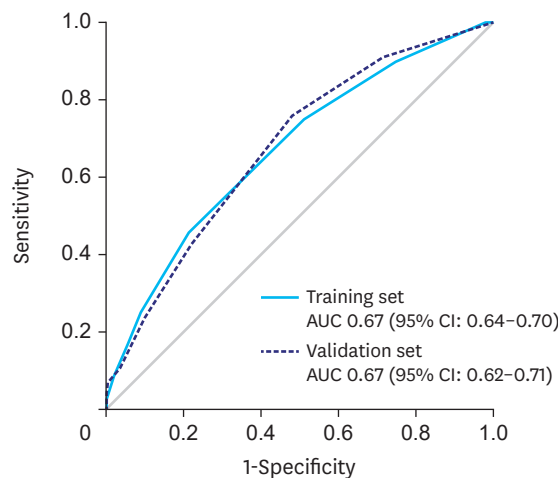
Fig. 2. Receiver-operating characteristic curve of the risk-scoring system for predicting non-curative endoscopic submucosal dissection requiring gastrectomy.
AUC = area under the curve; CI = confidence interval.

Consistent with these findings, the curative ESD rate for papillary EGC was below 50% in recent studies, including ours [22,30]. Forceps biopsy-based diagnosis of moderately differentiated adenocarcinoma was also identified as a histologic predictor of non-curative ESD requiring gastrectomy. This might be explained by higher lymphovascular and deep submucosal invasion rates in moderately differentiated versus well-differentiated EGC, as reported in previous studies [29]. The present study yielded consistent results.

In this study, proximal tumor location and tumor location at the greater curvature were identified as predictors of non-curative ESD requiring gastrectomy. Previous studies also reported that tumor location at the mid or upper third of the stomach was a predictive factor for non-curative ESD [5-11]. As reported in a previous study, EGCs at a proximal tumor location might have higher lymphovascular and deep submucosal invasion rates than those at the antrum or angle [31]. This might be partially explained by the difficulty of early detection of tumors that are located at the mid or upper third of the stomach; this is because EGC can be hidden between gastric folds, especially when they are located at the greater curvature. In addition, Yamagiwa et al. [32] argued that gastric cancers in the greater curvature might grow faster than those in other areas.

In the present study, elevated or depressed macroscopic morphology and presence of ulcer were identified as predictors of non-curative ESD requiring gastrectomy. Previous studies reported that lesions with elevated or depressed morphology and lesions with ulcers were associated with a higher risk of lymphovascular infiltration and deep submucosal invasion compared to flat lesions or lesions without ulcers [6,29,33,34]. As lymphovascular and deep submucosal invasion are established risk factors for LN metastasis, these findings justify the use of elevated or depressed macroscopic morphology and presence of ulcer as predictors of non-curative ESD requiring additional gastrectomy.

Compared to pure differentiated-type EGCs, differentiated-type EGCs with histological heterogeneity have more aggressive clinicopathologic features, such as frequent lymphovascular and submucosal invasion [27,35-37]. Consistent with these findings, our group reported that curative ESD was achieved in only 53.8% of differentiated-type EGCs with histological heterogeneity [27]. In addition, Horiuchi et al. [9] found that histological heterogeneity was a significant risk factor for non-curative ESD. Their study was limited in that the diagnosis of histological heterogeneity was based on the final pathology of an ESD specimen instead of a forceps biopsy specimen taken before the procedure. In the present study, the rates of histologic heterogeneity were 1.2% (38/3,127) and 11.8% (370/3,127), respectively, using forceps biopsy specimens and final ESD specimens. In our previous study that was based on ESD specimens, differentiated-type EGCs with histological heterogeneity accounted for 10.7% of all differentiated-type EGC cases treated with ESD [27]. This low detection rate of histological heterogeneity in forceps biopsy specimens and the close association of histological heterogeneity with moderately differentiated histology might limit the value of histological heterogeneity as a significant predictor of non-curative ESD requiring gastrectomy in the present study [27,37].

The strengths of this study include the large sample size and use of detailed endoscopic and pathologic variables such as forceps biopsy-based diagnoses of papillary adenocarcinoma and histologic heterogeneity. Using these strong points, we could overcome the limitations of previous studies that considered non-curative ESD as a single entity regardless of the risk of LN metastasis. In addition, we developed and validated a risk-scoring system for predicting

non-curative ESD requiring gastrectomy based on pre-ESD variables that is intuitive and easy to use in clinical practice. This risk-scoring system may facilitate accurate preoperative treatment selection between ESD and surgery in patients with EGC. Considering the invasiveness and decreased quality of life after gastrectomy, however, we acknowledge that diagnostic ESD for EGC may play be required, as opposed to using a prediction model. Fujiya et al. [38] reported that approximately 30% of differentiated-type EGCs preoperatively diagnosed as submucosal cancer met the curative resection criteria of ESD if the endoscopic tumor size was 30 mm or less. This result suggests the potential role of diagnostic ESD in selected cases of submucosal EGC. In the present study, our predictive model showed limited sensitivity and a positive predictive value, and non-curative ESD requiring gastrectomy was found only in 30.5% of patients with a risk score ≥5, which again suggested the potential role of diagnostic ESD. With this system, however, patients with EGC can be advised of the risk of needing additional gastrectomy after ESD. As shown in **Fig. 1**, the predicted risk for non-curative ESD requiring gastrectomy increased from 3.8% to 72.6% as the total risk score increased. In our risk-scoring system, patients with risk scores of 9 and 10 had predicted risks of 63.5% and 72.6%, respectively, for non-curative ESD requiring gastrectomy. This information on the individually estimated risk of non-curative ESD requiring gastrectomy can be critical when obtaining informed consent, as patients with EGC usually want to know the actual risk of additional surgery after ESD in order to make a reasonable decision between ESD and surgery.

This study had several limitations. First, it was a retrospective study conducted at a single tertiary referral center. Second, as only internal validation was performed, external validation is required to verify the efficacy of our risk-scoring system. Third, as our risk-scoring system was based on pre-ESD variables, lymphovascular invasion, a well-known risk factor for LN metastasis, could not be incorporated into the system as a variable, which might limit the accuracy of this prediction model.

In summary, we identified the predictive factors for non-curative ESD requiring additional gastrectomy based on pre-ESD variables in patients with EGC. Using these factors, we developed and validated a risk-scoring system for predicting non-curative ESD requiring gastrectomy. With this system, patients with EGC can be advised of the risk of needing additional gastrectomy after ESD, which is critical for informed consent. For physicians, our risk-scoring system can help in decision-making for preoperative treatment selection between ESD and surgery in patients with EGC, especially when their risk scores are high.

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