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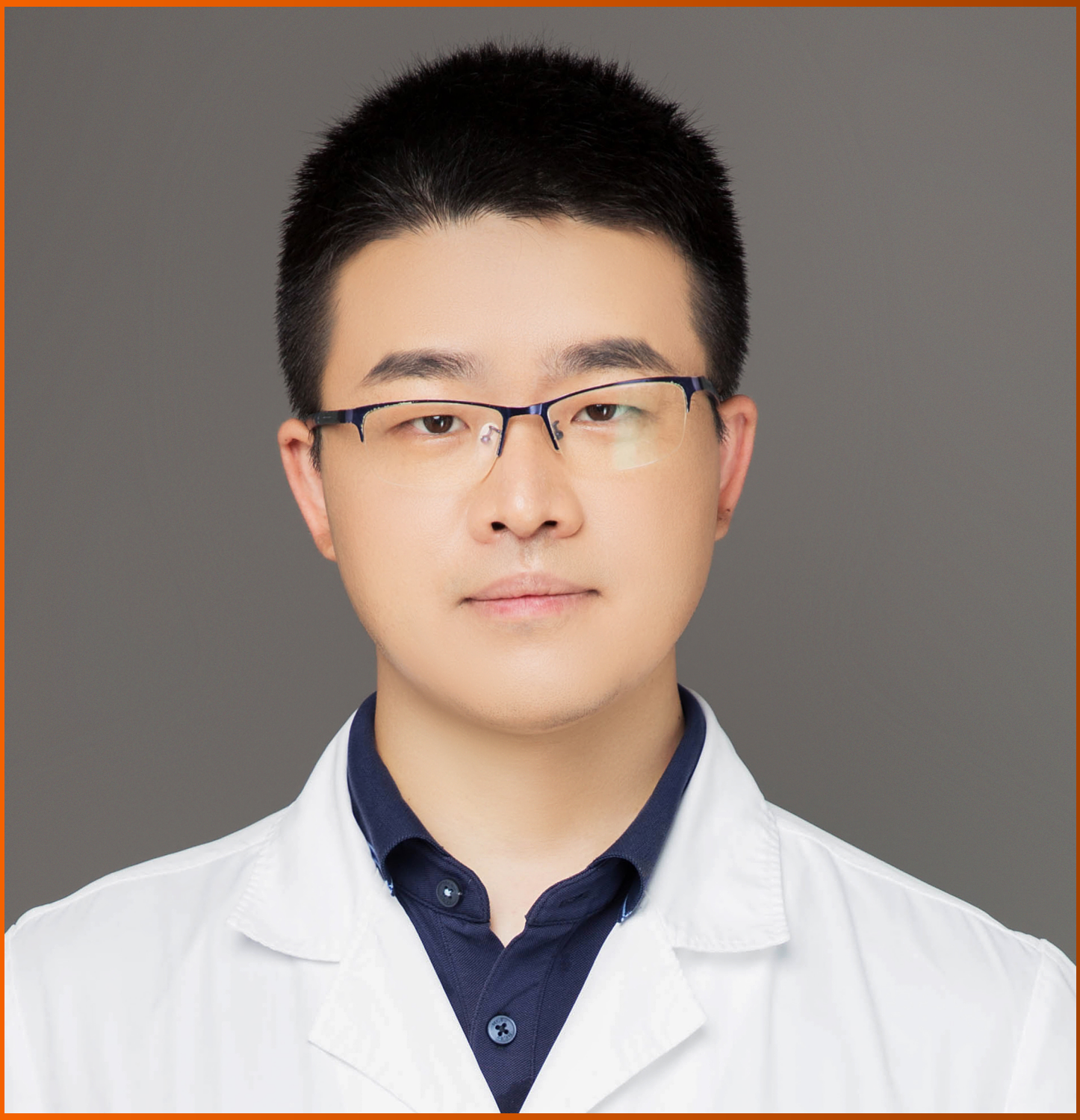

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ORIGINAL ARTICLE

Retrospective Study

# Predictors of stricture after endoscopic submucosal dissection of the esophagus and steroids application

Qing-Xia Wang, Yuan Ding, Qi-Liu Qian, Yin-Nan Zhu, Rui-Hua Shi

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## Abstract

### *BACKGROUND*

Endoscopic submucosal dissection (ESD) is a reliable method to resect early esophageal cancer. Esophageal stricture is one of the major complications after ESD of the esophagus. Steroid prophylaxis for esophageal strictures, particularly local injection of triamcinolone acetonide (TA), is a relatively effective method to prevent esophageal strictures. However, even with steroid prophylaxis, stenosis still occurs in up to 45% of patients. Predicting the risk of stenosis formation after local TA injection would enable additional interventions in risky patients.

### *AIM*

To identify the predictors of esophageal strictures after steroids application.

### *METHODS*

Patients who underwent esophageal ESD and steroid prophylaxis and who were comprehensively assessed for lesion- and ESD-related factors at Southeast University Affiliated Zhongda Hospital between February 2018 and March 2023 were included in the study. The univariate and multivariate regression analyses were conducted to identify the predictors of stricture among patients undergoing steroid prophylaxis.

### *RESULTS*

A total of 120 patients were included in the analysis. In the oral prednisone and oral prednisone combined with local tretinoin injection groups, the stenosis rates were 44/53 (83.0%) and 56/67 (83.6%), respectively. Among them, univariate analysis showed that the lesion circumference ($P$ = 0.01) and submucosal injection solution ($P$ = 0.04) showed significant correlation with the risk of stenosis formation. Logistic regression analyses were then performed using predictors that were significant in the univariate analyses and combined with known predictors from previous reports, such as additional chemoradiotherapy and tumor location.

We identified a lesion circumference < 5/6 (OR = 0.19; $P$ = 0.02) and submucosal injection of sodium hyaluronate (OR = 0.15; $P$ = 0.03) as independent predictors of on esophageal stricture formation.

***CONCLUSION***

Steroid prophylaxis effectively prevents stenosis. Moreover, the lesion circumference and submucosal injection of sodium hyaluronate were independent predictors of esophageal strictures. Additional interventions should be considered in high-risk patients.

**Key Words:** Endoscopic submucosal dissection; Esophageal stricture; Oral steroids; Triamcinolone acetonide; Predictors



**Core Tip:** Steroid administration can help prevent post-esophageal endoscopic submucosal dissection (ESD) stricture. This study was clarified the risk factors of stricture even with steroid administration. Although steroids were administered to prevent esophageal strictures after ESD, the lesion circumference and submucosal injection of sodium hyaluronate remained independent predictors of esophageal stricture formation. Among them, submucosal injection of sodium hyaluronate was the first influential factor that may be a guide for clinical prevention.

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## INTRODUCTION

Esophageal cancer is the seventh most common type of cancer worldwide and the sixth leading cause of cancer deaths[1]. Endoscopic submucosal dissection (ESD) is a reliable method for early esophageal cancer resection[2,3]. Although ESD offers overall tumor resection, more accurate histological diagnosis, and reduced risk of local recurrence[2], it is associated with postoperative esophageal stenosis[4]. Some studies have reported a high risk of postoperative strictures with ESD resections of > 3/4 of the circumferential diameter, especially for total circumferential resections, wherein esophageal stricture rates reach 100%[5-7]. Patients with esophageal strictures after ESD usually require multiple endoscopic balloon dilatations or probe strip dilatation for symptomatic relief, which degrades the quality of life and increases healthcare costs[8,9]. As a result, researchers have developed various methods, such as mechanical devices, tissue engineering, and autologous tissues, to prevent stricture formation in the esophagus following ESD[10-12]. Among these methods, steroid prophylaxis for esophageal strictures, particularly local injection of triamcinolone acetonide (TA), is a relatively effective method for preventing esophageal strictures[13-15]. However, even after local TA injection, stenosis occurs in up to 45% of patients undergoing noncircumferential resection[13,16]. Therefore, predicting the risk of stenosis formation after local TA injection would help guide additional interventions in risky patients. Nevertheless, few studies identified the predictors of stenosis formation after local TA injection. Thus, the aim of this retrospective study was to identify the predictors of esophageal stricture after steroid application and to evaluate the efficacy of steroids prophylaxis in preventing post-ESD esophageal stenosis.

## MATERIALS AND METHODS

### *Patients*

Patients with superficial esophageal cancers who underwent ESD and received steroid prophylaxis immediately after ESD at Southeast University Affiliated Zhongda Hospital between February 2018 and March 2023 were included in this study (Figure 1). The inclusion criteria were as follows: (1) Patients with superficial esophageal carcinoma that was an indication for ESD; (2) Patients with mucosal defects ≥ 3/4 of the circumferential esophageal lumen following ESD; (3) Patients with histologically confirmed high-grade squamous intraepithelial neoplasia or squamous cell carcinoma after ESD; and (4) Patients who were receiving oral steroids or/and local injection of TA immediately after ESD. The exclusion criteria were as follows: (1) Preoperative pathology suggestive of poorly differentiated or undifferentiated carcinoma; (2) History of esophageal surgery and radiotherapy; (3) Additional surgical treatment or radiofrequency ablation required after ESD; (4) Inability to follow up for more than six months; and (5) The long-term use of glucocorticoids. This study was approved by the Southeast University Affiliated Zhongda Hospital Ethics Committee approval (2018ZDSYLL018-P01), and all patients were informed and signed an informed consent form.

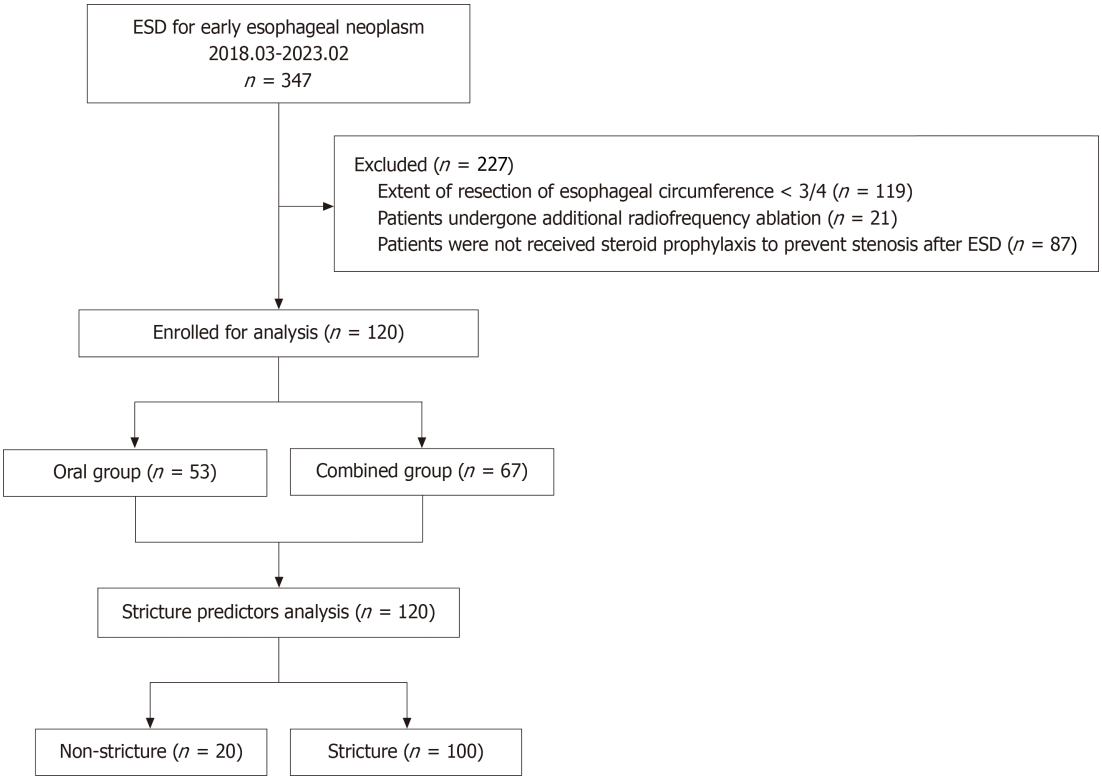


**Figure 1 Flow diagram of the study.** ESD: Endoscopic submucosal dissection.

### *ESD procedure*

All procedures were performed by experienced endoscopists at our center who had been practicing for at least five years and performed more than 100 ESD esophageal procedures prior to this study. All surgeries were performed under general anesthesia with tracheal intubation. A tip-covered knife (IT knife, KD-611 L; Olympus), tip-uncovered knife (Dual knife KD-650 Q, Olympus), hook knife (KD-620 LR, Olympus), or hybrid knife (Erbe Elektromedizin GmbH) was used for ESD. Intraoperative bleeding was treated using an electrocoagulation (FD-410 LR, Olympus). Single-channel endoscopes with hoods (GIFQ 260, GIF-Q260 J, Olympus) were used for endoscopy, and an endoscopic electrosurgical generator ESG-100 (Olympus) was used for ESD procedures. A 3% lugol solution was used to clarify the margins of the lesion, and a needle or double knife was used to mark 2 mm outside the margins of the target lesion. Two submucosal injections were used: Primarily epinephrine glycerol solution and diluted indigo carmine or melphalan, and diluted hyaluronic acid was used when submucosal fibrosis was encountered. The electrocoagulation modes were Endo Cut I, forced coagulation, or rapid coagulation mode. The endoscopist then retreated the scope after spraying fibrin glue on wounds based on experience.

### *Treatment strategy to prevent postESD strictures*

In the oral group, 8-week oral prednisone therapy was initiated as follows: Oral prednisone acetate 30 mg/d was started on the third day after ESD, reduced to 25 mg/d after week 2, 20 mg/d after week 2, 15 mg/d after week 1, 10 mg/d after week 1, 5 mg/d after week 1, and then finally discontinued in the ninth week. In the oral combined with local injection group, 80 mg of tretinoin was injected into the residual submucosal layer of the lesion in multiple spots during ESD, taking care to avoid injecting into the muscular layer of the mucosa, and the 8 week oral prednisone therapy (same as the oral group) was initiated on the third day after the surgery. Proton pump inhibitors were routinely administered orally after ESD in both the groups.

### *Follow-up and outcomes*

Gastroscopy was performed 3 months after ESD, and endoscopic dilatation of the exploratory strip was performed at any time when the patient developed dysphagia. The follow-up period lasted until March, 2023. The outcome data included (1) relevant predictors, such as age, gender, body mass index, smoking habits, lesion characteristics (tumor location, longitudinal length of the lesion, macroscopic type, tumor invasion depth, histopathologic diagnosis), additional chemoradiotherapy (CRT), type of endo-knife, procedure time, electrosurgical unit modes, type of submucosal injection solution, *en bloc* resection, and fibrin glue; and (2) stenosis rate. Stenosis was defined as a stricture with a diameter of < 9.8 mm through which a standard endoscope (GIF H 260, Olympus) could not pass (Figure 2). *En bloc* resection was defined as the removal of the lesion as a single specimen.

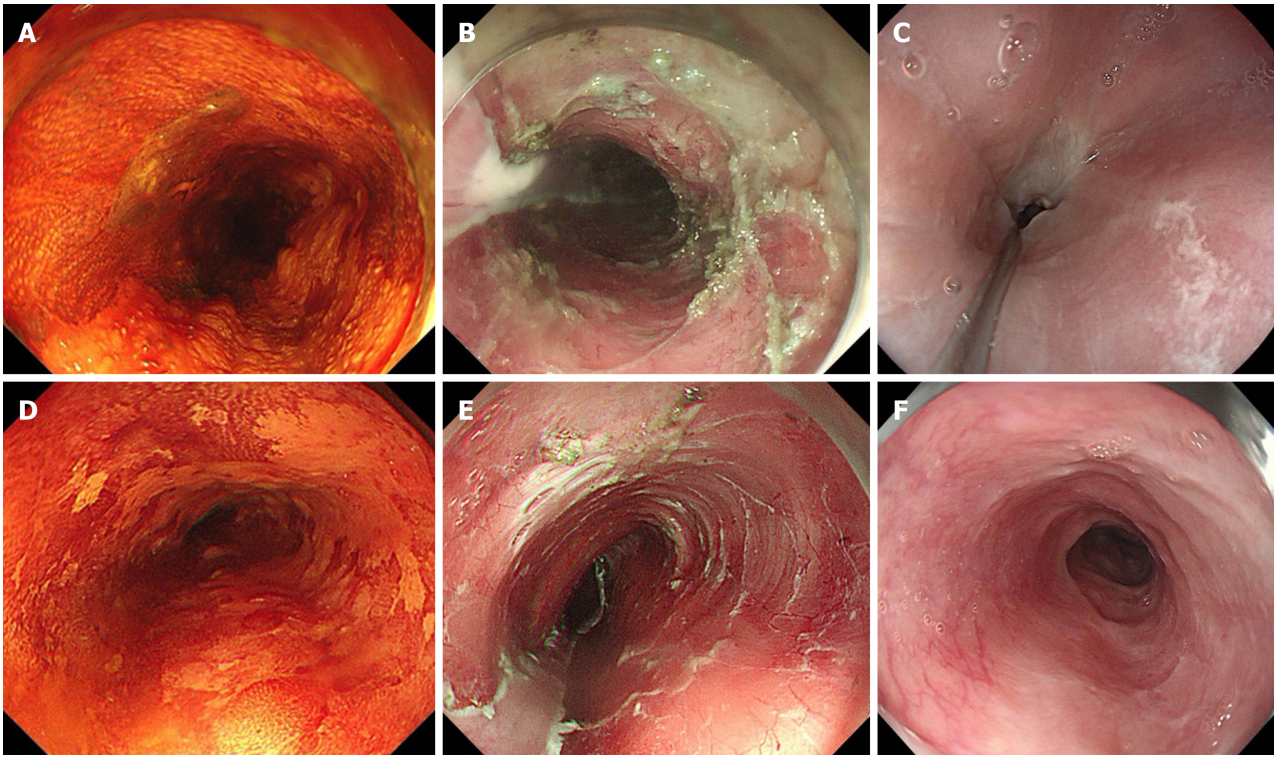


**Figure 2 Endoscopic image.** A: Lugol's chromoendoscopy showed lesion located at 18-24 cm of the incisors; B: The mucosal defect after endoscopic submucosal dissection (ESD) involved 4/5$^{th}$ of the esophageal circumference and the longitudinal length of defect was 65 mm. The patient took no prophylactic measures; C: Stricture developed after one month located at 20 cm of the incisors. The patient underwent a total of three exploratory strip dilatations after esophageal stricture; D: Lugol's chromoendoscopy showed lesion located at 28-35 cm of the incisors; E: The mucosal defect after ESD involved 4/5$^{th}$ of the esophageal circumference and the longitudinal length of defect was 55 mm. This patient took prophylactic measures to prevent postoperative stenosis with local multipoint injections of triamcinolone acetonide and oral prednisone; F: No stricture developed after seven months. The standard diagnostic endoscope (9.8 mm in diameter) could pass through the ESD wound scar smoothly.

### *Statistical analysis*

Categorical variables are presented as counts and percentages. Continuous and normally distributed variables are presented as mean ± SD. The $\chi^2$ test was performed to compare categorical variables, and t-test was used to compare continuous variables. Univariate and multivariate regression analyses were conducted to identify the predictors of stricture among patients undergoing steroid prophylaxis. A $P$ value < 0.05 was considered statistically significant. Statistical analysis was performed by using JMP Pro software version 16.0 (SAS Institute, Inc, Cary, NC, United States).

## RESULTS

### *Patient flow and characteristics*

Patient characteristics are presented in Table 1. From February 2018 to March 2023, 120 patients with a mean age of 67.02 ± 0.70 years were included in this study. Overall, 84 (70.0%) patients were male, and 60 (50.0%) lesions were in the mid-thoracic esophagus. There were 53 and 67 patients in the oral steroids and oral steroids combined with the topical injection of TA groups, respectively. There were no statistically significant differences between two groups of patients in the baseline data.

### *Stricture rate*

The stricture rate was 44/53 (83.0%) in the oral steroids group, and 56/67 (83.6%) in the oral steroids combined with local injection group. There was no statistically significant difference between the groups ($\chi^2$ = 0.01, $P$ = 0.93).

### *Potential factors associated with esophageal strictures after ESD with steroids prophylaxis*

Stenosis-influencing factors were analyzed in 120 patients who received glucocorticoids for stenosis prophylaxis, either oral prednisone or oral prednisone combined with local tretinoin injection. Among them, univariate analysis showed that lesion circumference ($P$ = 0.01) and submucosal injection solution ($P$ = 0.04) showed significant correlation with the risk of stenosis formation. Logistic regression analyses were then performed using predictors that were significant in the univariate analyses and combined with known predictors from previous reports, such as additional CRT and tumor location [16-18]. Lesion circumference < 5/6 (OR = 0.19; $P$ = 0.02) and submucosal injection of sodium hyaluronate (OR = 0.15; $P$ = 0.03) were independent factors for esophageal stricture formation. Stricture rates stratified according to predictors are

**Table 1 Demographics and characteristics of patients included in the study**

| Variables | Oral group (*n* = 53) | Combined group (*n* = 67) | *F*/$\chi^2$ | *P* value |
|---|---|---|---|---|
| Age (years, mean ± SD) | 67.70 ± 1.06 | 66.49 ± 0.94 | 0.73 | 0.40 |
| BMI (kg/m$^2$, mean ± SD) | 22.87 ± 0.43 | 22.77 ± 0.38 | 0.03 | 0.86 |
| Gender (male, %) | 33 (62.3) | 51 (76.1) | 2.71 | 0.10 |
| Smoke (%) | 13 (24.5) | 15 (22.4) | 0.08 | 0.78 |
| Macroscopic type [*n* (%)] | | | 2.08 | 0.35 |
| 0-IIa | 11 (20.7) | 9 (13.4) | | |
| 0-IIb | 32 (60.4) | 39 (58.2) | | |
| 0-IIc | 10 (18.9) | 19 (28.4) | | |
| Histopathologic diagnosis [*n* (%)] | | | 2.08 | 0.35 |
| High-grade intraepithelial neoplasia | 25 (47.2) | 26 (38.8) | | |
| Esophageal squamous cell carcinoma | 28 (52.8) | 41 (61.2) | | |
| Lesion circumference [*n* (%)] | | | 2.66 | 0.10 |
| < 5/6 and ≥ 3/4 | 37 (69.8) | 37 (55.2) | | |
| ≥ 5/6 | 16 (30.2) | 30 (44.8) | | |
| Length of lesion (mm, mean ± SD) | 61.36 ± 2.91 | 60.55 ± 2.59 | 0.04 | 0.84 |
| Depth of invasion [*n* (%)] | | | 1.04 | 0.60 |
| M1/M2 | 40 (75.5) | 49 (73.1) | | |
| M3/SM1 | 8 (15.1) | 14 (20.9) | | |
| SM2 | 5 (9.4) | 4 (6.0) | | |
| Additional chemoradiotherapy [*n* (%)] | 7 (13.2) | 10 (14.9) | 0.22 | 0.90 |
| Tumor location [*n* (%)] | | | 0.07 | 0.78 |
| Cervical and upper thoracic esophagus | 13 (24.5) | 13 (19.4) | | |
| Middle thoracic esophagus | 24 (45.3) | 36 (53.7) | | |
| Lower thoracic esophagus | 16 (30.2) | 18 (26.9) | | |

M1: Intraepithelial; M2: Lamina propria; M3: Muscularis mucosae; SM1: < 200 μm from the muscularis mucosae; SM2: ≥ 200 μm from the muscularis mucosae.

shown in Table 2.

### *Complications*

Three patients in the oral prednisone group developed wound bleeding and vomited blood, which improved after endoscopic hemostatic treatment. One patient in the combined group developed postoperative lung infection, which was not perforated by endoscopy, as it was caused by mis-aspiration; following antibiotic treatment the patient's condition was relieved. No other patients experienced adverse events related to ESD, glucocorticoid, endoscopic dilatation.

## DISCUSSION

ESD is the preferred method to treat early esophageal cancer[3] because it offers a high lesion resection rate, which enhances postsurgical pathological diagnosis. Compared with surgery, ESD resulted in fewer injuries and was correlated with faster postoperative recovery. However, ESDs that resect more than 3/4 of the esophageal mucosa are often prone to postoperative esophageal stenosis, and the stricture rate can be as high as 80%-100%[7]. As a result, many researchers have studied various ways to treat esophageal strictures, but each treatment has some limitations. Self-expanding coated metal stents and biodegradable stents can help prevent postoperative esophageal strictures; however, esophageal stents are associated with the risks of bleeding, perforation, and migration[19]. In addition, some scholars have successfully transplanted autologous tissues to prevent esophageal stenosis; however, the safety and efficacy of these procedures need to be verified in more clinical studies[10,20]. Although the effectiveness of oral steroids is well recognized, steroids may

**Table 2 Univariate and multivariate logistic regression analyses of predictors of post-esophageal endoscopic submucosal dissection stricture formation**

| Characteristics | Univariate analysis | | | Multivariate analysis | |
|---|---|---|---|---|---|
| | Non-stricture (*n* = 20) | Stricture (*n* = 100) | *P* value | OR (95%CI) | *P* value |
| Age (year) | 66.70 ± 10.41 | 67.09 ± 7.09 | 0.84 | - | - |
| Gender [*n* (%)] | | | 0.12 | | |
| Male | 11 (55.0) | 129 (70.5) | | | |
| Female | 9 (45.0) | 54 (29.5) | | | |
| BMI | 22.81 ± 3.72 | 22.82 ± 2.97 | 0.99 | - | - |
| Smoke [*n* (%)] | | | 0.31 | | |
| Yes | 3 (15.0) | 25 (25.0) | | - | - |
| No | 17 (85.0) | 75 (75.0) | | - | - |
| Histopathologic diagnosis [*n* (%)] | | | 0.21 | | |
| High-grade intraepithelial neoplasia | 6 (30.0) | 45 (45.0) | | - | - |
| Esophageal squamous cell carcinoma | 14 (70.0) | 55 (55.0) | | - | - |
| Additional chemoradiotherapy [*n* (%)] | | | 0.54 | | |
| Yes | 2 (10.0) | 15 (15.0) | | 2.12 (0.41-11.10) | 0.37 |
| No | 18 (90.0) | 85 (85.0) | | Reference | - |
| Tumor location [*n* (%)] | | | 0.51 | | |
| Cervical and upper thoracic esophagus | 6 (30.0) | 20 (20.0) | | Reference | |
| Middle thoracic esophagus | 10 (50.0) | 50 (50.0) | | 1.77 (0.49-6.41) | 0.38 |
| Lower thoracic esophagus | 4 (20.0) | 30 (30.0) | | 3.06 (0.64-14.53) | 0.16 |
| Macroscopic type [*n* (%)] | | | 0.89 | | |
| 0-IIa | 4 (20.0) | 16 (16.0) | | - | - |
| 0-IIb | 11 (55.0) | 60 (60.0) | | - | - |
| 0-IIc | 5 (25.0) | 24 (24.0) | | - | - |
| Clinical depth of invasion [*n* (%)] | | | 0.79 | | |
| Epithelium/lamina propria | 16 (80.0) | 73 (73.0) | | - | - |
| MM/SM1 | 3 (15.0) | 19 (19.0) | | - | - |
| SM2 | 1 (5.0) | 8 (8.0) | | - | - |
| Procedure time (minute) | 105.00 ± 62.56 | 81.53 ± 5.46 | 0.08 | - | - |
| Endo-knife [*n* (%)] | | | 0.17 | | |
| Hook knife | 2 (10.0) | 7 (7.0) | | - | - |
| IT/Dual knife | 18 (90.0) | 84 (84.0) | | - | - |
| Hybrid knife | 0 (0.0) | 9 (9.0) | | - | - |
| Electrosurgical unit modes [*n* (%)] | | | 0.64 | | |
| Swift coagulation | 2 (10.0) | 10 (10.0) | | - | - |
| Forced coagulation | 15 (75.0) | 82 (82.0) | | - | - |
| Endocut | 3 (15.0) | 8 (8.0) | | - | - |
| Submucosal injection solution [*n* (%)] | | | 0.04 | | |
| Sodium hyaluronate | 4 (20.0) | 5 (5.0) | | 0.15 (0.03-0.82) | 0.03 |
| Other | 16 (80.0) | 95 (95.0) | | Reference | |
| Steroids group [*n* (%)] | | | 0.93 | | |

| | | | | | |
|---|---|---|---|---|---|
| Oral steroids | 9 (45.0) | 44 (44.0) | | Reference | |
| Combined group | 11 (55.0) | 56 (56.0) | | 0.60 (0.20-1.82) | 0.37 |
| Longitudinal length of the resected lesion (mm) | 63.60 ± 21.77 | 60.37 ± 21.03 | 0.53 | - | - |
| Circumferential range [*n* (%)] | | | 0.01 | | |
| < 5/6 and ≥ 3/4 | 17 (85.0) | 57 (57.0) | | 0.19 (0.05-0.74) | 0.02 |
| ≥ 5/6 | 3 (15.0) | 43 (43.0) | | Reference | |
| *En bloc* resection [*n* (%)] | | | 0.91 | | |
| Yes | 17 (85.0) | 84 (84.0) | | - | - |
| No | 3 (15.0) | 16 (16.0) | | - | - |
| Fibrin glue [*n* (%)] | | | 0.12 | | |
| Yes | 9 (45.0) | 64 (64.0) | | - | - |
| No | 11 (55.0) | 36 (36.0) | | - | - |

95%CI: 95% confidence interval; OR: Odds ratio; BMI: Body mass index.

cause systemic adverse effects such as osteoporosis, immunosuppression, diabetes, peptic ulcers and infections[15,21]. Yamaguchi *et al*[22] first explored the effectiveness of oral prednisone in preventing esophageal strictures after ESD, and the stricture rate was only 5.3%, which was more effective than local injection. Sato *et al*[23] found that oral steroids alone were not effective in preventing post-ESD strictures with circumferential mucosal resection. It has even been shown that stenosis still occurs in patients undergoing steroid prophylaxis and total circumferential resection of the esophagus[13]. In our study, the stenosis rate in the oral steroids alone group was 83%. Moreover, among patients who underwent circumferential or near circumferential resection, the stenosis rate was 92.5%. Stenosis did not occur in all cases, suggesting that oral steroids can prevent stenosis.

The injection of TA has also achieved good results; however, but local injection may injure the muscularis propria and cause delayed perforation, limiting its widespread use[13]. The local injections of steroids also have limited effectiveness in circumferential resection[24]. Previously, Chu *et al*[25] combined oral and local steroid injections to investigate their effectiveness in preventing post-ESD strictures, and the rate of strictures decreased to 14.7% (5/34) in the combined group compared to the control (52.8%, 19/36). In our study, the stenosis rate was 56/67 (83.6%) in the combined group. These differences may be because Chu *et al*[25] included fewer patients and those with lesions resected ≥ 2/3 of the circumference of the lesion, whereas the present study included patients with lesions resected ≥ 3/4 of the circumference of the lesion. However, the difference between the oral and combined groups was not statistically significant ($P$ = 0.93). A possible complication of local injection of steroids is perforation. Yamashina reported a case of delayed perforation after local injection of TA, probably due to injury to the lamina propria of the esophagus[26]. In addition, oral steroids may cause osteoporosis, immunosuppression, diabetes, peptic ulcers and infections[15,21]. In our study, the cumulative oral prednisone dose was 1120 mg over an eight-week period; no adverse effects associated with oral prednisone were recorded. However, Waljee *et al*[27] found that the short-term use of steroids increased the risk of adverse events over a three-year period. Therefore, the timing and dosage of oral steroids after esophageal ESD remains controversial and requires further study.

Steroids nevertheless help prevent stenosis; therefore, there is a need to identify the factors that influence the occurrence of stenosis after steroid prophylaxis. Previous studies have shown that spread of the circumference of a resected lesion to seven-eighths or five-sixths of its circumference is a precursor to stenosis formation[16,28]. This is consistent with the present study, where lesion circumference ≥ 5/6 was an independent predictor for the development of esophageal stricture. Wang *et al*[29] identified longitudinal length of the resected lesion > 70 mm as an independent risk factor for esophageal stricture after ESD. The larger the resection lesion, the longer the lesion healing time and higher the likelihood of esophageal stricture. Previous studies have shown that lesions in the cervical esophagus are the predictors of strictures after endoscopic resection and that strictures in the cervical esophagus are also refractory to dilatation therapy[18,30]. Miyake *et al*[18] also found that a history of CRT is a predictor of post-ESD stricture. Interestingly, our study did not show a statistically significant difference in lesion location among the stenosis predictors, which is inconsistent with previous studies. This may be due to a small sample size of only 10 patients with cervical and upper thoracic esophageal lesions in our study. Furthermore, our study suggests that the submucosal injection of sodium hyaluronate is an independent protective factor against stenosis. This may be because sodium hyaluronate can better elevate lesions, providing an adequate safety margin between the mucosal and muscular layers[31] that lowers the risk of hemorrhage and perforation associated with ESD. A previous study evaluated the utility and safety of sodium hyaluronate for ESD of esophageal lesions; only five patients (5/107, 4.7%) developed post-ESD stenosis that required dilatation[32]. It has also been shown that there is no significant difference in performance between sodium hyaluronate and previous sodium alginate injection materials and sodium hyaluronate can be safely used for ESD[33].

There are some limitations to this study. First, this was a single-center, retrospective study with possible analytical and selection bias. Second, each patient's treatment was individualized and based on the principle of shared decision-making

without a standard protocol, which is another limitation of this retrospective study.

## CONCLUSION

In conclusion, oral prednisone or oral prednisone combined with local TA injection can effectively prevent esophageal stenosis. This study clarified the risk factors for stricture even after steroid administration. Post-ESD esophageal strictures were more likely to occur in patients with a circumference of the resected lesion ≥ 5/6 and in patients with endoscopic submucosal injection solution without sodium hyaluronate. This study will inform future clinical experimental studies to develop more effective methods for treating and preventing esophageal stenosis.

## FOOTNOTES

**Author contributions:** Wang QX design the study and write the report; Ding Y, Qian QL and Zhu YN collect, analyze, and interpret the data; Shi RH provide guidance on thesis design; all authors agree to submit for publication.

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**Informed consent statement:** All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

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