Int J Clin Exp Med 2018;11(12):13736-13742
www.ijcem.com /ISSN:1940-5901/IJCEM0076263

*Original Article*

# Risk factors of infection after endoscopic submucosal dissection of esophageal mucosal lesions

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Received September 26, 2017; Accepted September 5, 2018; Epub December 15, 2018; Published December 30, 2018

**Abstract:** Aims: This study aims to analyze risk factors of infection after the endoscopic submucosal dissection (ESD) of esophageal mucosal lesions within 24 hours from the procedures, and formulate an antibiotic treatment plan. Methods: A total of 153 patients with esophageal mucosal lesions undergoing ESD in our hospital were enrolled from January 2010 to August 2016. Patients with fever (body temperature ≥38.0°C), elevated white blood cell (WBC) count (>$10\times10^9$), and/or elevated C-reactive protein level (CRP) (>0.8 mg/L) within 24 hours from the procedures were regarded as the case group. The patients, lesions and procedure characteristics were retrospectively analyzed for risk factors of post-ESD infection. Results: The rate of post-ESD infection was 16.3% (25/153). The univariate analysis suggests that there are significant differences in the maximum diameters of the resected specimens ($P$ = 0.005), the proportion of circumferential extension ($P$<0.001), operating time ($P$ = 0.001), and exposure of the muscular layer ($P$<0.001). The multivariate analysis reveal that the proportion of circumferential extension >3/4 ($P$ = 0.028, OR: 5.391, 95% CI: 1.200-24.214) and exposure of the muscular layer ($P$ = 0.005, OR: 7.776, 95% CI: 1.834-32.973) are independent risk factors for post-ESD infection. Conclusion: Exposure of the muscular layer and the proportion of circumferential extension >3/4 are reliable risk factors for post-ESD infection. Antibiotic therapy is recommended for its treatment.

**Keywords:** Endoscopic submucosal dissection, esophagus, postoperative bacteremia, antibiotic

## Introduction

Endoscopic submucosal dissection (ESD) is an important treatment option with a perfect *en bloc* and $R_0$ resection rate and low complication rate for superficial esophageal carcinoma (SEC) [1, 2]. The main complications of the ESD procedure for esophageal mucosal lesions are postoperative stricture, hemorrhage and perforation [3-5]. The prevention and management of these frequent complications have been thoroughly and comprehensively studied [4, 6]. However, few studies have focused on other less frequent but important complications, such as aspiration pneumonia, mediastinal emphysema, transient bacteremia and the general use of antibiotics in patients without perforation before and/or after esophageal ESD. Recently, the use of antibiotics before and/or after ESD highly depends on the diagnostic criteria of institutions. In our endoscopy center, some patients experienced fever and increased levels of CRP and/or WBC count after ESD of the esophagus. Hence, the present study aimed to analyze the main risk factors for post-ESD infection within 24 hours from the procedures, and verified the need for prophylactic antibiotics.

## Materials and methods

### *Patients*

A total of 155 cases underwent ESD for the treatment of esophageal mucosal lesions from January 2010 to August 2016 at the Endoscopic Center of PLA General Hospital. The clinical, endoscopic and pathological data of those patients were retrospectively analyzed. Inclusion criteria: (1) patients with normal body temperature, C-reactive protein (CRP) levels and white blood cell (WBC) count before the surgery; (2) patients who underwent the ESD procedures through the same endoscopist (L.Z.S.).

Exclusion criteria: (1) patients with a history of autoimmune or inflammatory disorders, hepatitis or liver disease, tumor or cancer, or infectious complications after surgery; (2) patients who received antibiotics within one week before the procedure, and the indications for the antibiotic prophylaxis was determined according to the American Society for Gastrointestinal Endoscopy (ASGE) published on 2003 [7]; (3) patients whose procedures were terminated due to sever adhesion. A written informed consent was obtained from all participants prior to undergoing the ESD. Patients with a body temperature ≥38°C and elevated WBC count and/or CRP were identified as the case group. The remaining patients who had a negative clinical parameter or only had fever or elevated WBC count and/or CRP were identified as the control group.

*ESD procedure*

All ESD procedures were performed by an endoscopist (L.Z.S.), who had more than five years of experience and performed 600 cases of ESD. Standard single channel GIF Q260J gastroscopes (Olympus, Optical Co. Ltd, Tokyo, Japan) with the additional water delivery feature were used. A short, transparent cap (Olympus, Japan) was attached to the tip of the gastroscope to provide a constant endoscopic view. The Erbotom ICC 200 or the VIO 200 D (Erbe, Germany) was used as the high-frequency electrosurgical unit. The lesions were located by the narrow band imaging (NBI) magnification, and 2.5% Lugol solution staining performed to ensure a clear margin. At 0.3-0.5 cm from the margin of the lesion, thermal coagulation markers were made around the lesion at 0.5-cm intervals. Following the submucosal injection of a solution (glycerol and fructose solution mixed with epinephrine at a ratio of 1:100,000), the submucosal injection was applied along the margin of the lesion to uplift the mucosa. The solution was repeatedly injected during the dissection, when necessary. An incision was made at approximately 0.5 cm away from the markers to cut the layers from the mucosa to the submucosa. The dissection was performed along the submucosa, and continued until the mucosa of the lesion was completely dissected using a Dual knife or IT-2 knife (forced co 40 w). Bleeding during ESD was managed by electric coagulation, and exposed vessels on the artificial ulcers were also coagulated using hemostatic forceps to prevent delayed bleeding after the dissection of the submucosa.

*Pathological evaluation*

Complete resection was defined as a resection with tumor-free lateral and basal margins. The resected specimens were fixed and measured. Histopathological evaluations were performed by a pathologist after ESD. The pathology diagnostic criteria were based on the World Health Organization (WHO) criteria [8]. The depth of the tumor invasion was also based on the WHO criteria [1]: M1 = tumors located in the epithelial lining; M2 = tumors that infiltrated into the lamina propria; M3 = tumors that invaded into the muscularis mucosa; SM1 = tumors that infiltrated into the submucosa to a depth of <1/3.

*Clinical factors*

Blood routine examination was obtained before and after the ESD procedure. Patients who had fever (body temperature ≥38.0°C) and elevated WBC count (>$10\times10^9$) and/or elevated CRP levels (>0.8) [9] within 24 hours from the procedures were regarded as the case group. Delayed bleeding was clinically relevant when there was a decrease in hemoglobin level of ≥2 g/dl, which is an evidence of the requirement for overt bleeding and endoscopic intervention [10]. The proportion of circumferential extension of the mucosal defect after ESD was classified into three groups: under one-half (<1/2), one-half to three-quarters (1/2-3/4), and over three-quarters and complete circumference (>3/4). The size of the resected specimen was measured as the greatest diameter after ESD. Total procedure time was defined as that required for the entire procedure, from the marking of the lesion to finishing the hemostasis. The tumor location was categorized into three groups, based on the Japanese classification of gastric carcinoma [11]. History of pulmonary disease was identified through preoperative chest radiography or computed tomography (CT) scans.

*Statistical analysis*

Fisher's exact test and chi-squared test were used to compare the categorical variables.

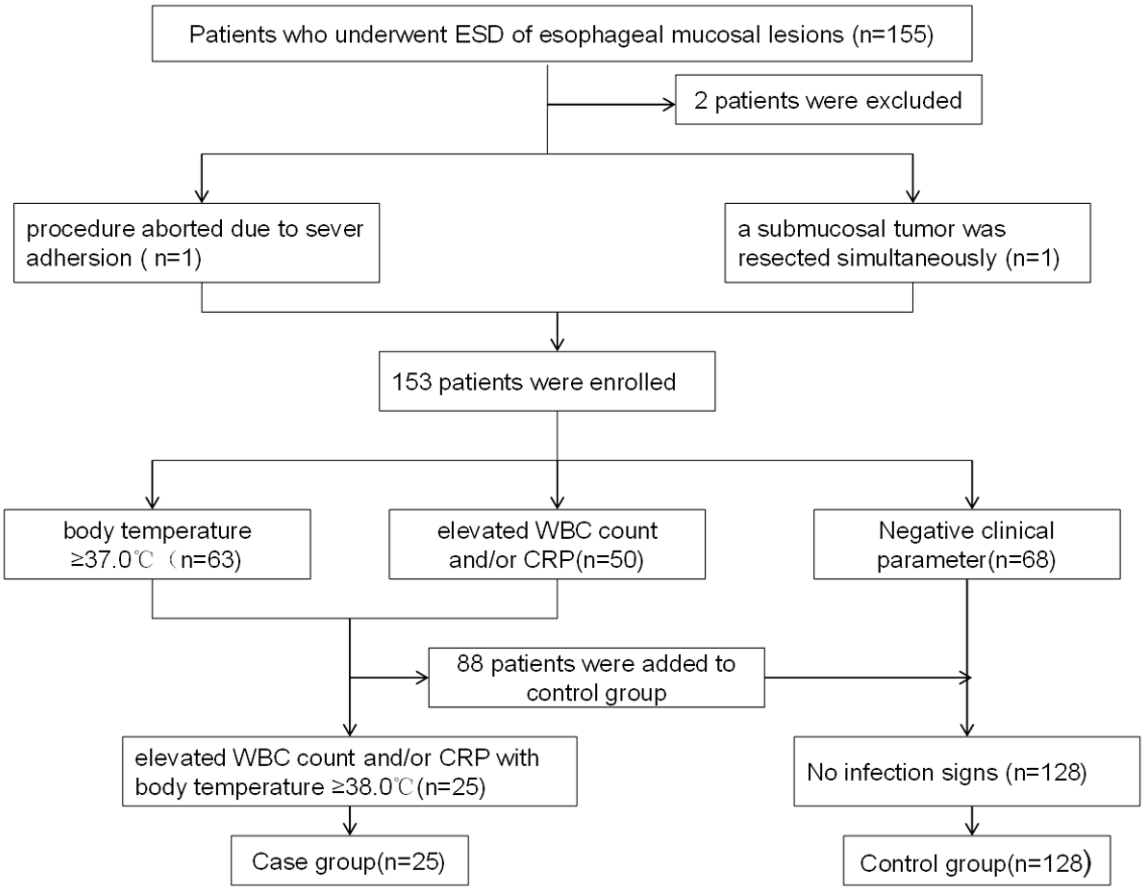


**Figure 1.** The clinical course of patients with ESD for esophageal mucosal lesions. WBC: white blood cell; CRP: C-reactive protein level; ESD: endoscopic submucosal dissection.

Student's *t*-test was used for continuous variables, and the results were presented as mean ± standard deviation (SD). After the univariate analysis, variables that were found to be potentially predictive of the outcome variable ($P< 0.05$) were included in the multivariate logistic regression models. A *P*-value of <0.05 was considered statistically significant. The associations between variables and postoperative bacteremia risk factors were examined using multivariate logistic regression models. Statistical analyses were performed using IBM SPSS Statistics 19.0.

## Results

*General data*

A total of 155 patients with esophageal mucosal lesions undergoing ESD met the inclusion criteria, but only 153 patients were enrolled in the present study. One patient was excluded due to an aborted procedure, while another patient was excluded due to the simultaneous resection of a submucous tumor (**Figure 1**). Among these 153 patients, 109 are male (71.2%) patients, and the male-to-female ratio was 2.5:1.0. The mean age of these patients was 61 ± 8.2 years old (range: 30-80 years old), and high body temperature (>37°C) after ESD was observed in 41.2% (63/153) of these patients. Furthermore, elevated WBC count and/or CRP were observed in 32.7% (50/153) of these patients. However, merely 25 (16.3%) patients had a body temperature ≥38°C with an elevated WBC count and/or CRP (**Figure 1**). In addition, the corresponding mean age was 60.2 ± 6.7 years old (range: 49-76 years old).

*Predictive factors for post-ESD bacteremia*

The rate of post-ESD fever and blood change was 16.3%. The predictive factors for this complication were further analyzed by comparing these between the case group ($n$ = 25) and control group ($n$ = 128) (**Table 1**).

**Table 1.** Baseline characteristics of the study population

| | Infection group | No infection group | Chi-square | t | *P* value |
|---|---|---|---|---|---|
| Patient characteristics | | | | | |
| Number, n (%) | 25 (16.3) | 128 (83.7) | | | |
| Gender, male/female, n | 15/10 | 94/34 | 1.843 | | 0.175 |
| Age, y (mean±SD) | 60.2±6.7 | 61.1±8.5 | | -0.503 | 0.616 |
| Smoke, n (%) | 8 (32) | 60 (46.9) | 1.874 | | 0.171 |
| Pulmonary disease, n (%) | 9 (36) | 30 (23.4) | 1.738 | | 0.187 |
| Delayed hemorrhage, n (%) | 3 (12) | 5 (3.9) | 2.765 | | 0.123 |
| Mediastinal emphysema, n (%) | 1 (4) | 1 (0.8) | 1.680 | | 0.301 |
| Lesion characteristics | | | | | |
| Location, n(%) | | | 4.091 | | 0.129 |
| Upper esophagus | 3 (12) | 5 (3.9) | | | |
| Middle esophagus | 16 (64) | 73 (57) | | | |
| Lower esophagus | 6 (24) | 50 (39.1) | | | |
| Maximum diameter of the resected specimen, n (%) | | | 10.749 | | 0.005 |
| ≤1.0 cm | 0 (0) | 2 (1.6) | | | |
| 1.1-3.0 cm | 7 (28) | 79 (61.7) | | | |
| >3.0 cm | 18 (72) | 47 (36.7) | | | |
| Proportion of circumferential Extension, n (%) | | | 17.725 | | <0.001 |
| <1/2 | 4 (16) | 64 (50) | | | |
| 1/2-3/4 | 9 (36) | 46 (35.9) | | | |
| >3/4 | 12 (48) | 18 (14.1) | | | |
| Depth of invasion, n (%) | | | 3.136 | | 0.371 |
| M1 | 18 (72) | 91 (71.1) | | | |
| M2 | 3 (12) | 12 (9.4) | | | |
| M3 | 4 (16) | 13 (10.2) | | | |
| ≥SM1 | 0 (0) | 12 (9.4) | | | |
| Procedure characteristics | | | | | |
| Total procedure time, (mean ± SD), minute | 110.5±97.6 | 66.8±48.4 | | 3.389 | 0.001 |
| Exposure of the muscular layer, n (%) | 6 (24) | 5 (3.9) | 12.656 | | <0.001 |
| Perforation, n (%) | 1 (4) | 0 (0) | 5.154 | | 0.163 |
| Insertion of esophageal stent, n (%) | 0 (0) | 3 (2.3) | 0.598 | | 1.000 |

M1: Intramucosal cancer; M2: Lamina propria; M3: Muscularis mucosa; SM1: Shallow submucosal layer.

There is no significant difference in factors between these two groups, such as gender, age, history of smoking and pulmonary disease, complications of delayed bleeding, perforation, mediastinal emphysema, lesion location, depth of invasion, and insertion of an esophageal stent ($P>0.05$). However, the maximum diameter of the resected specimen, the proportion of circumferential extension, total procedure time, and exposure of the muscular layer were statistically different ($P<0.05$, **Table 1**). Gender, age, maximum diameter of the resected specimen, the proportion of circumferential extension, total procedure time, and exposure of the muscular layer were included in the multivariate analysis. The logistic regression identified that the proportion of circumferential extension >3/4 ($P = 0.028$, OR: 5.391, 95% CI: 1.200-24.214) and exposure of the muscular layer ($P = 0.005$, OR: 7.776, 95% CI: 1.834-32.973) were independent risk factors for postoperative fever and blood changes (**Table 2**).

## Discussion

The ESD technique is presently widely accepted and performed for patients with superficial esophageal carcinoma [12-14]. Many studies have focused on the common risks of ESD, including perforation, bleeding, aspiration pneu-

**Table 2.** Results of the multivariate logistic regression analysis

| | *P* value | OR | β | 95% CI |
|---|---|---|---|---|
| Gender | 0.218 | 0.510 | -0.673 | 0.175-1.489 |
| Age | 0.990 | 1.000 | 0.000 | 0.943-1.060 |
| Total procedure time | 0.717 | 1.001 | 0.001 | 0.994-1.009 |
| Maximum diameter of the resected specimen | | | | |
| ≤1.0 cm | 0.243 | - | - | - |
| 1.1-3.0 cm | 1.000 | >10 | 17.583 | 0.000 |
| >3.0 cm | 0.999 | >10 | 18.591 | 0.000 |
| Proportion of circumferential extension | | | | |
| <1/2 | 4.832 | - | - | - |
| 1/2-3/4 | 0.162 | 2.671 | 0.983 | 0.675-10.574 |
| >3/4 | 0.028 | 5.391 | 1.685 | 1.200-24.214 |
| Exposure of the muscular layer | 0.005 | 7.776 | 2.051 | 1.834-32.973 |

OR: odds ratio; CI: confidence interval; β: beta value.

monia and technical difficulties [3-5, 15]. However, there is a lack of studies focusing on less frequent risks such as bacteremia. Bacteremia could be caused by the bacterial translocation of endogenous microbial flora through the injured mucosa into the bloodstream during the endoscopy procedure [16]. This infectious complications have been reported to be infrequent and transient in both EMR and ESD of the stomach and colon [17-19]. The main incidence of bacteremia related to esophageal ESD is 1% (95% CI: 0-5%) [20]. The incidence related to gastroscopy with or without biopsy is 4.4% (0-8%) [21]. In addition, the incidence related to therapeutic colon procedures is 6.3% [22]. Although these studies revealed that ESD-related bacteremia is uncommon and not a lethal adverse event, it might lengthen the hospitalization period and require additional tests, including routine blood test, blood cultures, and CT. Furthermore, in practice, the use of antibiotics is common after esophageal ESD, which is performed according to the patient's disease characteristics and operation conditions, such as perforation and hemorrhage. However, the timing of this application is decided by the clinical experience of an operator, who may lack a consensus [20]. Therefore, it is important to find possible risk factors for post-ESD infectious adverse events, and identify the timing of prophylactic antibiotic administration, in order to prevent bacteremia and reduce additional pain and medical costs.

In the present study, bacteremia may be correlated with fever and blood change in patients treated with ESD of the esophagus. The results of the one-dimensional factor analysis indicated that the maximum diameter of the resected specimen, the proportion of circumferential extension, total procedure time, and exposure of the muscular layer were associated with fever and blood change after ESD. However, the results of the multivariate regression analysis revealed that only the proportion of circumferential extension >3/4 and exposure of the muscular layer were risk factors for post-ESD fever and blood change. Hence, prophylactic antibiotics may reduce local inflammation and systemic infection after esophageal ESD.

The mechanism of endoscopy-related infectious complication is correlated to the following reasons. First, during the operation procedure, repeated submucosal injections might directly inoculate bacteria from the mucosa or deeper trauma into the blood through a contaminated needle [17, 20]. Hence, a longer procedure time would lead to more times of injection, and mucosal injuries cause high incidence rates of fever and blood change. Second, the extensive exposure of the muscular layer after esophageal ESD results in the direct contact with bacteria and digestive juices [17-20]. Hence, the proportion of circumferential extension >3/4 and the greater size of the exposed wound would cause the high incidence rates of infectious complication. Therefore, the rational use of antibiotic prophylaxis during esophageal ESD could reduce the risk of iatrogenic infectious adverse events.

According to the literature, fever with increased levels of CRP and WBC are usually suggestive

for Gram-negative bacteremia (GNB) [23]. The frequency of bacteremia associated with an endoscopic procedure may probably influence the risk of some infectious complications, such as endocarditis [24]. However, the identification of the isolated pathogen, including an antibiogram, is available at least 24 hours after the samples for blood cultures are performed. The main aim of the present study was to analyze any risk factors for fever and blood change within 24 hours from the procedures, in order to verify the need for prophylactic antibiotics. Early recognition of even the first minor signs of infection in case of a beginning bacteremia could thereby help to identify patients who are more likely infected, and this could be used as a guide in the treatment of antibiotics.

In conclusion, the administration of prophylactic antibiotics during esophageal ESD, which has high risks such as exposure of the muscular layer and the proportion of circumferential extension >3/4, might reduce the risk of fever and blood change. In order to confirm this conclusion, more multicenter large-scale studies should be carried out in the future.

## Disclosure of conflict of interest

None.

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