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Original Article

Risk factors of fever after endoscopic submucosal dissection of gastrointestinal tumors

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Abstract: *Aim:* This study aims to identify the risk factors of fever after endoscopic submucosal dissection (ESD) of gastrointestinal tumors and the value of the highest body temperature within 24 hours (T_{max}) after ESD to predict postoperative complications of ESD. *Material/Methods:* A retrospective study was performed on 100 patients of ESD in our hospital from December 2012 to December 2015. Two patients were excluded for not meeting the inclusion criteria. Based on whether the patients had postoperative fever (T ≥ 38.0°C), they were divided into two groups. *Results:* Between fever group (n = 33) and no fever group (n = 65), there was no significant difference in basic characteristics, gross type, postoperative hospital stay and cost. The operation time was longer in fever group than no fever group (respectively, 124 min vs 86 min, P < 0.05). The mean resected specimen size was larger in fever group than no fever group [respectively, 4.0 cm (range 1.2-10.0 cm) vs 1.9 cm, (range 1.0-6.5 cm), P < 0.05]. The complication rate was higher in fever group than no fever group (respectively, 39.4% vs 4.6%, P < 0.05). The multivariate logistic regression suggested that the resected specimen size (OR = 1.797, 95% CI = 1.174-2.750, P < 0.05) was an independent risk factor for fever after ESD. The AUC of T_{max} after ESD for postoperative complications of ESD was 0.845. *Conclusions:* The ESD resected specimen size (≥ 2.70 cm) is an independent risk factor of fever after ESD. T_{max} (≥ 38.0°C) after ESD could be a predictor of postoperative complications of ESD.

Keywords: Endoscopic submucosal dissection, fever, gastrointestinal tumors

Introduction

Gastrointestinal malignant tumor is one of the most common malignant tumors in the world. Early detection and early treatment are critical to the treatment for gastrointestinal malignant tumors. With the continuous development of endoscopic technology, endoscopic therapy has become an effective treatment for early gastrointestinal malignant tumors. Endoscopic therapy mainly includes endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Compared with the EMR, ESD is accompanied with a higher risk of complications [1-4].

ESD is available to treat not only large lesions but also ulcer lesions and undifferentiated tumors. ESD has gradually become a mainstream treatment method for early gastrointestinal tumors in globe [5-8]. The postoperative complications of ESD mainly included bleeding, perforation, pneumonia and so on. Previous studies reported that in Gastric ESD, the rate of perforation ranged from 1.2% to 9.7%, the rate of postoperative bleeding varied from 0.1% to 15.6% and the incidence rate of pneumonia was 0.6%-14.4% [9-11]. One study reported that in Esophageal ESD the perforation rate was 5.2% (3.3%-7.9%), the postoperative bleeding rate was close to 0, the incidence rate of pneumonia was 1.6% (0.7%-3.5%) and the incidence rate of esophageal stenosis was 7.1% (4.9%-10.2%) [12]. Another study reported that the perforation rate of colorectal ESD was 4.7% (1.4%-8.2%) and the postoperative bleeding rate was 1.5% (0.5%-9.5%) [13]. ESD complication rates were associated not only with operator's techniques, experience and endoscopic equipment conditions but also with patient characteristics such as the age, the size of the lesion, the lesion location and so on [14-17].

Fever is one of the most common clinical manifestations in patients after surgery [18]. Fever is supposed to be caused by the release of inflammatory cytokines and self-limited under some circumstances. [19, 20]. Clinical fever often indicated infection and a previous study had shown that the sensitivity and specificity of postoperative fever to indicate infection was 37% and 80%, respectively [21]. Fever is also a common clinical manifestation after ESD. Previous studies reported that the rate of fever after ESD ranged from 2.1% to 46.7% [22, 23]. However, few studies had focused on the fever after ESD. And the studies on the risk factors of fever after ESD were even scarcer [23]. To the best of our knowledge, the relationship between ESD postoperative fever and complications including pneumonia and perforation still lacks a sufficient study. Therefore, in this study we investigated the risk factors of postoperative fever in patients after ESD. In addition, we analyzed the relationship between postoperative fever and complications of ESD and accessed the predictive value of T_{max}, the highest body temperature within 24 hours after ESD, for the postoperative complications of ESD.

Material and methods

Ethical issues

This study was reviewed and approved by the Institutional Review Board (IRB) of the Second Affiliated Hospital of Zhejiang University School of Medicine. After the approval of the IRB, we used the patient identification numbers to collect and analyze the clinical records. The personal information was anonymous and de-identified prior to analysis.

Patients

This was a retrospective study. Between December 2012 and December 2015, ESD was performed for 100 patients with gastrointestinal tumors by the same experienced expert at the Second Affiliated Hospital, School of Medicine, Zhejiang University, China. The inclusion criteria were as follows: 1) patients who were treated with ESD, 2) postoperative hospital stay length more than 24 hours. The exclusion criteria were as follows: 1) body temperature ≥ 38.0°C within 24 h before ESD, 2) patients who didn't measure body temperature. A total of 98 patients were enrolled according to the inclusion and exclusion criteria.

ESD procedure

ESD was used to remove all lesions. A circumferential incision was made using an insulation-tipped (IT) electrosurgical knife and/or a DualKnife (KD-650), and the submucosal layer was dissected using an IT knife and/or a DualKnife. Whenever active bleeding was observed during ESD, hemostasis was dealt with titanium clips or hemostatic forceps. Ulcer dimensions were estimated by measuring the maximal diameters of the resected specimen.

Definition

Fever was defined as an ear temperature ≥ 38°C, evaluated by a medical care-giver. CT scan was decided by the physician according to patients' situation. Delayed bleeding, which was defined as hematemesis or melena within 30 postoperative days, was usually treated with emergency endoscopy. Pneumonia was diagnosed based on a chest radiography finding or computed tomography scan with the presence of new or progressive infiltrates, consolidation, or pleural effusion in patients who had no evidence of pneumonia on chest radiography or CT scan before ESD.

Perforation was defined as direct endoscopic observation of mesenteric fat or the presence of free air on an abdominal radiography or computed tomography scan. En bloc resection was defined as the lesion being resected in one piece. Curative resection was defined as follows: 1) lateral and vertical margins negative for the lesion, and 2) no venous or lymphatic invasion by microscopic tissue examination.

Statistical analysis

All statistical analyses were conducted with SPSS 20.0. Values were expressed as the number (percentage) of patients or the median (range). Differences in categorical variables between groups were examined by the χ^2 test or by Fisher's exact test when required. The nonparametric Mann-Whitney U test was used for the comparison of continuous variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a logistic analysis for the risks of fever after ESD, and receiver operating characteristic (ROC) analysis was used to detect cut-off points for T_{max} after ESD for postoperative complications. A $P < 0.05$ was considered statistically significant.

Table 1. Characteristic information between fever group and no fever group after ESD

	Fever (n = 33)	No fever (n = 65)	P
Age (ys)	61 (41-85)	63 (43-86)	0.804
Sex (M:F)	18:15	41:24	0.415
BMI (kg/m^2)	23.03 (15.43-28.12)	23.38 (16.02-31.63)	0.937
Hypertension	7 (21.2%)	20 (30.8%)	0.317
Diabetes mellitus	3 (9.1%)	4 (6.2%)	0.906
Smoking	9 (27.3%)	23 (35.4%)	0.418
Drinking	13 (39.4%)	25 (38.5%)	0.929
Postion (esophagus:gastric:colon)	12:14:7	8:52:5	0.001
Specimen size (cm)	4.0 (1.2-10.0)	1.9 (1.0-6.5)	< 0.001
En bloc resection	30 (90.1%)	64 (98.5%)	0.213
Curative resection	28 (84.8%)	54 (83.1%)	0.823
Operation time (min)	124 (35-390)	86 (36-260)	0.004
Gross type (I:II)	6:27	16:49	0.471
T_{max} (°C)	38.3 (37.3-39.8)	37.3 (36.0-38.1)	< 0.001
Fasting time (d)	2 (1-11)	2 (2-8)	0.008
Follow-up time (m)	15 (2-39)	12 (1-38)	0.184
Complications	13 (39.4%)	3 (4.6%)	< 0.001
Intraoperative perforation	1 (3.0%)	0	0.337*
Delay bleeding	1 (3.0%)	1 (1.5%)	1*
Delay perforation	2 (6.1%)	0	0.111*
Pneumonia	10 (30.3%)	1 (1.5%)	< 0.001
Esophageal stenosis	2 (6.1%)	1 (1.5%)	0.543
Antibiotic using	26 (78.8%)	18 (27.7%)	< 0.001
Postoperative hospital stay	6 (2-27)	6 (2-12)	0.661
Hospital cost	16396 (11936-123606)	15775 (6531-32080)	0.060

T_{max}: the highest body temperature within 24 hours; *: Fisher test.

Results

Characteristics of the ESD patients with or without fever

During December 2013 to December 2015, a total of 100 ESD patients were identified, of whom 2 patients did not meet the inclusion criteria. A total of 98 patients were included in the study.

According to whether patients had fever after ESD, we divide patients into two groups. The patients' basic characteristics were provided in **Table 1**. There was no significant difference between the two groups on age, gender, BMI, history of hypertension, diabetes, smoking and alcohol (P > 0.05). There was a significant difference on the incidence rates of fever among different positions (P < 0.05), with that of esophagus, gastric and colon to be 60%, 21.2% and 58.3%, respectively. The postoperative fever rate of gastric ESD was lower than that of esophageal and colorectal ESD (respectively, 21.2% vs 59.4%, P < 0.05). The operation time of fever group was 124 min (35-390 min), significantly longer than that of no fever group [86 min (36-260 min), (P < 0.05)]; The specimen size in fever group [4.0 cm (1.2-10.0 cm)] was significantly larger than that of no fever group [1.9 cm (1.0-6.5 cm), (P < 0.05)]; Antibiotics using rate in fever group (78.8%) was significantly higher than that in no fever group (27.7%, P < 0.05). Considering the complications, the incidence rate of pneumonia in fever group was higher than that in no fever group (P < 0.05). There was no significant difference with respect to intraoperative perforation, delayed hemorrhage and delayed perforation between the two groups (P > 0.05). About 30.3% (10/33) patients with fever had pneumonia. The fever rate was significantly higher in patients with pneumonia [90.9% (10/11)] than without pneumonia [26.4% (23/87)] (P < 0.05). The duration

Table 2. Logistic analyze for the risks of fever after ESD

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Age (ys)	1.000	0.960-1.041	0.989	0.998	0.950-1.050	0.950
Specimen size (cm)	1.996	1.429-2.807	< 0.001	1.797	1.174-2.750	0.007
Opertation time (min)	1.009	1.003-1.016	0.003	1.005	0.996-1.014	0.280
Gastric	1.000			1.000		
Esophagus	5.571	1.908-16.271	0.002	0.111	0.025-0.498	0.004
Colon	5.200	1.431-18.900	0.012	0.442	0.082-2.374	0.341

Table 3. Logistic analyze for the risks of fever after ESD without pneumonia

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Age (ys)	1.109	0.972-1.068	0.435	1.005	0.951-1.063	0.858
Specimen size (cm)	1.802	1.260-2.577	0.001	1.725	1.118-2.660	0.019
Opertation time (min)	1.009	1.003-1.006	0.004	1.004	0.995-1.013	0.355
Gastric	1.000			1.000		
Esophagus	2.122	0.543-8.293	0.279	2.131	0.479-9.487	0.321
Colon	3.714	0.941-14.659	0.530	6.917	1.375-34.803	0.019

Table 4. Spearman analysis between fever and complications

	Correlation coefficient	P
Pneumonia	0.431	< 0.001
Delay perforation	0.203	0.045
Delay bleeding	0.050	0.616
Esophageal stenosis	0.124	0.224

Table 5. Spearman analysis between T_{max} and complications

	Correlation coefficient	P
Pneumonia	0.439	< 0.001
Delay perforation	0.236	0.019
Delay bleeding	0.111	0.276
Esophageal stenosis	0.092	0.366

T_{max}: the highest body temperature within 24 hours.

of fever was 1 day in 75.8% (25/33) patients. After ESD, patients were followed up for 14 months (1-39 months). 1 case was found with vestigital, and 1 case was found with heterochrony relapse.

Logistic analyze for the risks of fever after ESD

In patients after ESD, we performed a logistic regression to analyze the risk factors of postoperative fever, as was shown in **Table 2**. We found that age was not a risk factor for fever (OR = 1.000, 95% CI = 0.960-0.989, P > 0.05) while specimen size (OR = 1.996, 95% CI = 1.429-2.807, P < 0.05) and operation time (OR = 1.009, 95% CI = 1.003-101.6, P < 0.05) were the risk factors of fever after ESD. By multivariate logistic regression, we found that the specimen size (OR = 1.797, 95% CI = 1.174-2.750, P < 0.05) was an independent risk factor for postoperative fever while the operation time was not (OR = 1.005, 95% CI = 0.996-1.014, P < 0.05). Meanwhile, the postoperative fever rate varied among different operation positions. The fever rate was significantly higher in patients with pneumonia than without pneumonia [90.9% (10/11) vs 26.4% (23/87), P < 0.05]. A subgroup analysis to identify the risk factors in patients without pneumonia was conducted **Table 3**. The multivariate regression analysis found that the specimen size (OR = 1.725, 95% CI = 1.118-2.660, P < 0.05) was an independent risk factor for postoperative fever while operation time was not (OR = 1.004, 95% CI = 0.995-1.013, P < 0.05).

Relationship between ESD complications and fever or T_{max}

By Spearman analysis, we found that both pneumonia (r = 0.431, P < 0.05) and delayed

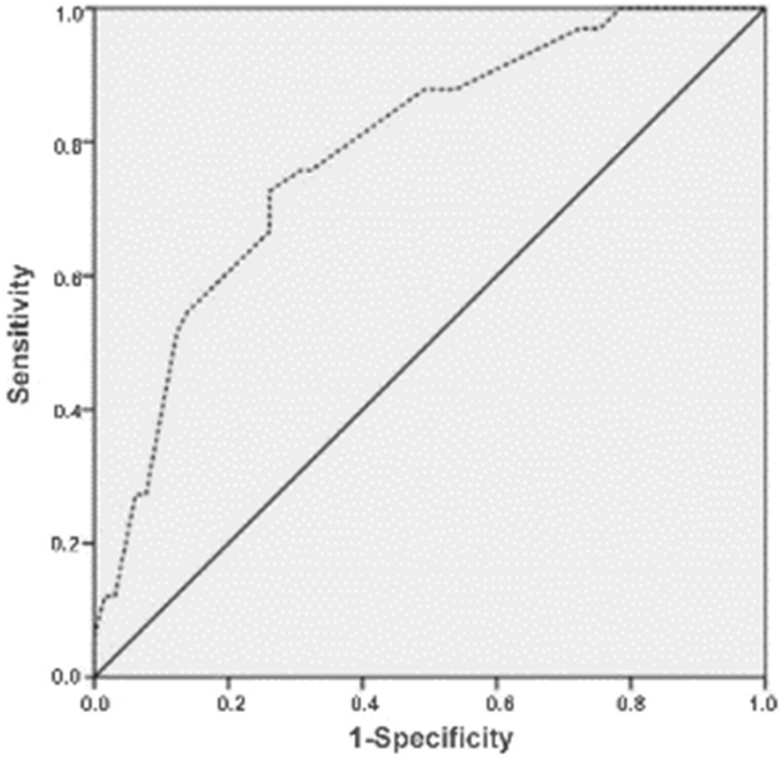

Figure 1. Specimen size for fever after ESD by ROC curve, AUC = 0.786.

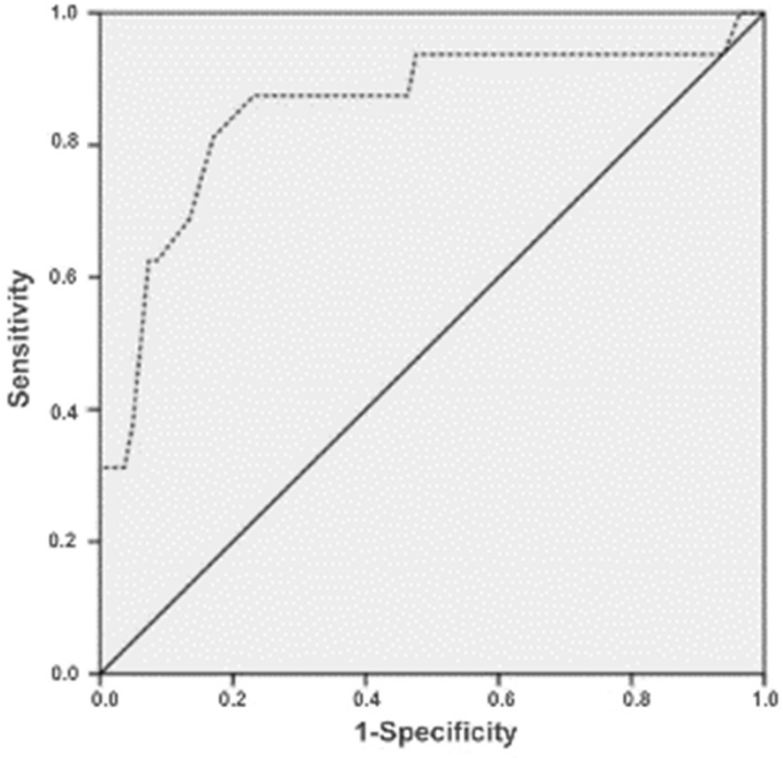

Figure 2. T_{max} after ESD for postoperative complications of ESD by ROC curve, AUC = 0.845, T_{max}: the highest body temperature within 24 hours.

perforation (r = 0.203, P < 0.05) were significantly associated with postoperative fever while esophageal stenosis (r = 0.124, P > 0.05) and delayed bleeding were not significantly related (r = 0.050, P > 0.05) in **Table 4**. As the fever occurred within 24 hours after ESD in 97% (32/33) patients, we analyzed the correlation between T_{max} and complications. Results are shown in **Table 5**. We could find that both pneumonia (r = 0.439, P < 0.05) and delayed perforation (r = 0.236, P < 0.05) were significantly correlated with T_{max} while neither esophageal stenosis (r = 0.092, P > 0.05) nor delayed bleeding (r = 0.111, P > 0.05) was significantly related with T_{max}.

The diagnostic values of specimen size for fever and T_{max} for ESD complications

The ROC curve analysis of specimen size for ESD postoperative fever was shown in **Figure 1** with the AUC = 0.786. Setting the cutoff value of 2.70 cm, the sensitivity was 72.7% and the specificity was 73.8%. In **Table 5**, we could find that T_{max} was associated with postoperative complications. By multivariate logistic regression, we found that T_{max} was an independent risk factor for complications (OR = 7.042, 95% CI 1.968-25.204. P < 0.05). The ROC curve analysis of T_{max} for postoperative complications was provided in **Figure 2** and **Table 6**. In **Table 6**, we found that the

Table 6. T_{max} after ESD for postoperative complications by ROC curve

	AUC	P	95% CI	Cutoff	Sensitivity	Specificity
Gastrointestinal	0.845	< 0.001	0.716-0.974	37.95	86.7%	75.9%
Gastric	0.907	0.018	0.810-1.000	37.95	100.0%	82.5%
Esophagus and colon	0.752	0.019	0.568-0.937	38.05	86.3%	70.0%

T_{max}: the highest body temperature within 24 hours.

sensitivity and specificity was 86.7% and 75.9%, respectively, in gastrointestinal ESD patients with the cutoff value of 37.95°C. In gastric ESD patients, the sensitivity and specificity was 100% and 82.5% with the cutoff value of 37.95°C, respectively. In esophageal and colorectal ESD patients the sensitivity and specificity was 86.3% and 70% with the cutoff value of 38.05°C, respectively.

Discussion

ESD is now acknowledged to be the first choice for the treatment of early gastrointestinal tumors. Inevitably, there exist some complications during or after ESD [24]. Although fever is the most common clinical manifestation after ESD, few studies reported the ESD postoperative fever and its influence in detail. In the present study, the incidence rate of fever after ESD was 33.7% (33/98). According to the multivariate logistic regression analysis, the specimen size (≥ 2.70 cm) was an independent risk factor of fever after ESD. Previous studies had also indicated that the specimen size was an independent risk factor of fever after ESD [23]. Ulcer formation was one of the complications after ESD. Different from common gastrointestinal ulcer, ESD postoperative ulcer was formed in a short period of time and ulcer infiltration was deeper. Therefore, we consider the big scar formation and healing which led to inflammatory reaction were the main reasons for fever. Meanwhile, fever may be caused by ESD or by the removal of tumor, the humoral immunity can be changed and can cause subfebrile fever [25, 26]. Large specimen sizes had been repeatedly proved to a risk factor for bleeding and perforation. The studies between specimen size and postoperative fever of ESD were scarce and this study was a good supplement in this field.

In the present study, 30.3% (10/33) patients with fever were eventually diagnosed with pneumonia and pneumonia was significantly associated with fever (r = 0.431, P < 0.05). In subgroup analysis we found that specimen size (OR = 1.725, 95% CI 1.118-2.660, P < 0.05) was still an independent risk factor of fever in no pneumonia group. Besides pneumonia, there were other factors related to the fever after ESD.

In this study, the incidence rates of fever varied among lesion positions which was 60.0% (12/20), 21.2% (14/66) and 58.3% (7/12) for esophageal, gastric and colon, respectively. The incidence rates of postoperative fever in esophagus and colon ESD patients were significantly higher than that in gastric ESD patients (P < 0.05). We considered the higher rate of fever in esophageal ESD may be due to the lesion close to the trachea, which might cause pneumonia and fever. With respect to colon ESD, we considered there was a higher risk of infection in colon and the electro coagulation process may cause serosal inflammation [27, 28]. According to previous studies the use of antibiotics could reduce the rates of fever after colorectal ESD [29]. About postoperative infection, although we didn't have blood culture and urine culture of ESD postoperative fever patients, but according to the previous studies, the fever within 48 hours often not be caused by infection and previous studies showed the risk of bacteria disease was very low after gastric and colorectal ESD [23, 30].

In this study, we found that the antibiotic using had a close correlation with fever. Although the use of antibiotics can reduce the incidence rate of postoperative fever after ESD, there was no guideline suggesting the routine use of antibiotics after ESD. According to the latest guidelines for gastrointestinal endoscopy operation, antibiotics were not needed to prevent fever and pneumonia after endoscopic operation [31, 32]. In the previous study of 101 esophageal ESD patients, the blood culture test showed that the postoperative infection rate was 1% in esophageal ESD, which suggested prophylactic antibiotics was unnecessary [33]. However, more researches were needed to clarify wheth-

er prophylactic use of antibiotics was necessary and whether it could reduce the rate of postoperative pneumonia and fever.

In this study, we found that specimen size (≥ 2.70 cm) could be a predictive factor of fever after ESD with the sensitivity and specificity to 72.7% and 73.8% by ROC curve analysis, respectively. We suggested that patients with a large specimen size should be careful of postoperative fever. In this study, we found that fever after ESD had no significant influence on the postoperative hospital stay and cost ($P > 0.05$). We thought the reason may be due to the antibiotics using and good care which enhanced the recovery from fever. Patients with fever had a significantly longer fasting time than those without fever ($P < 0.05$), which could decrease the patients' satisfaction. Therefore how to reduce the fever rate after ESD was still important.

In clinical practice, fever is not only the clinical manifestation of many diseases, but also could indicate a lot of diseases. In the previous study and found that aspect emphysema patients, the temperature was higher than that of the normal group, suggesting that temperature could be predictive factor of clinical complications [34]. In the present study the multivariate logistic regression analysis suggested that T_{max} after ESD (OR = 7.042, 95% CI = 1.968-25.204, $P < 0.05$) was an independent risk factor of complications. The ROC curve analysis indicated that T_{max} after ESD ($T \geq 37.95°C$) could predict postoperative complications of gastrointestinal ESD with the sensitivity and specificity of 86.7% and 75.9%, respectively. Therefore, for patients with fever after ESD, on the one hand, we should try our best to avoid the occurrence, on the other hand, we should pay enough attention to patients whose $T_{max} \geq 38.0°C$.

There were many limitations in this retrospective study. The ESD operations were done by a single senior director in our research center which excluded the impact of surgeon experience and level of interference. Still the study was small with only 98 patients included. Whether to do a CT scan was decided by doctors and not every patient after ESD had a CT scan, which could result in the miss diagnosis of pneumonia. This study found the relationship between postoperative fever and the use of antibiotics but whether antibiotics could reduce postoperative fever rate could not be proved in the present study. In this study not every fever patient had a blood culture and the correlation between infection and fever needed a further exploration. In the study we didn't have the accurate electric coagulation time, so whether electric coagulation time was a risk factor of fever still needed to be studied. Considering the different effects of anesthetic drugs on postoperative pneumonia which was one of the main causes of fever, the relationship between anesthesia and fever should be further studied [35].

The ESD resected specimen size is an independent risk factor for fever after ESD. Patients need to be paid more attention in case of postoperative fever when the resected specimen size was larger than 2.70 cm. T_{max} after ESD can be a predictor of postoperative complications of ESD. Physicians should pay more attention to patients whose $T_{max} \geq 38.0°C$ after ESD.

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Disclosure of conflict of interest

None.

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