

# Risk factors for pyrexia after endoscopic submucosal dissection of gastric lesions

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## Abstract



**Background and study aims:** Endoscopic submucosal dissection (ESD) is widely used in the resection of gastric tumors en bloc, however, complications such as pyrexia frequently occur following the procedure. The study aim was to elucidate the incidence, clinical characteristics, and risk factors of post-ESD pyrexia.

**Patients and methods:** We conducted a retrospective cohort study of 471 consecutive patients with 485 gastric lesions resected by ESD between December 2005 and 2010. Pyrexia was defined as body temperature above 37.5 °C, regardless of its duration.

Blood tests and chest radiography were performed three times before and after ESD. Chest

and abdominal computed tomography (CT) was taken on postoperative day 1.

**Results:** Post-ESD pyrexia developed in 117 patients (24.8%), including 40 patients with pneumonia as shown by computed tomography. The pyrexia was resolved in all the patients after 1 day (median; range, 1–36 days). A multivariate analysis identified age ( $P=0.0029$ ) and resection diameter ( $P=0.0009$ ) as risk factors for pyrexia in patients without pneumonia, and operation time ( $P=0.0025$ ) as a risk factor for pyrexia in patients with pneumonia.

**Conclusion:** The patient would be at risk for post-ESD pyrexia if a large ESD is performed in the elderly. The longer operation time would raise the risk for pneumonia-associated fever.

## Introduction



Endoscopic submucosal dissection (ESD) is a widely accepted modality that enables *en bloc* resection and more accurate histopathological assessment of gastric lesions than conventional techniques [1–4]. Furthermore, the recent development of advanced ESD devices has expanded the indication of gastric ESD to lesions with ulcerations or undifferentiated carcinoma [1,4–11]. However, the gastric ESD used for these additional indications is more extensive and deeper than previous ESD procedures, thereby requiring the endoscopist to be more highly skilled, and is associated with a higher risk of complications than endoscopic mucosal resection (EMR) [1–3,12–14].

Many studies have reported complications arising from ESD, including bleeding, pneumonia, perforation, and peritonitis [1–4,8,9,12–19]. However, no report has described in detail the complication of pyrexia, which commonly occurs after ESD. Nonetheless, the incidence of pyrexia as reported by several previous studies suggests that the risk factors for post-ESD pyrexia should be ex-

amined. In particular, one previous study reported that pyrexia (defined as a body temperature above 37.5 °C) occurred at an incidence of >6% after gastric ESD [20]. Meanwhile, at our institution, we observed post-ESD pyrexia in 19.5% of patients [21]. Within this context, the clinical significance and treatment requirements for pyrexia after gastric ESD remain unclear because this pathophysiological condition is related to many other complications such as pneumonia.

In this study, we investigated the characteristics and risk factors of pyrexia after gastric ESD. We further analyzed its association with other complications, particularly pneumonia found on chest computed tomography (CT) 1 day after ESD and transmural air leaks.

## Patients and methods



### Patients

This was a retrospective cohort study. Between December 2005 and December 2010, ESD was performed for 485 gastric lesions in 471 consecu-

## License terms



tive patients at Gifu University Hospital, Japan. The study protocol was approved by the ethics committee for clinical research at our institution. All patients provided written informed consent before ESD.

The indications for ESD with curative intent were clinically diagnosed adenoma or intramucosal cancer and fulfillment of the criteria of the Japanese Gastric Cancer Treatment Guidelines 2010 [22] as follows: 1) differentiated cancer up to 20 mm in size with no ulceration, as with the criteria of the guidelines; 2) differentiated cancer of > 20 mm in size with no ulceration; 3) differentiated cancer of up to 30 mm in size with ulceration; and 4) undifferentiated cancer up to 20 mm in size with no ulceration, as with the expanded criteria of the guidelines.

The histological criteria for the ESD to be considered curative were as follows: 1) lateral and vertical margins negative for the lesion, and 2) intramucosal cancer (m) or minute submucosal penetration (sm1, up to 500 μm into the submucosal layer) with no venous or lymphatic invasion by microscopic tissue examination.

### Examinations performed before and after ESD of gastric lesions

The examinations were scheduled before and after ESD. Two days before ESD, the first plain chest radiography and blood examinations were performed on an outpatient basis. ESD was conducted in the afternoon on the day of admission. On the second hospital day (postoperative day [POD] 1), plain chest radiography, blood tests, esophagogastroduodenoscopy, and chest/abdominal CT were performed. Blood tests for leukocyte count and C-reactive protein (CRP) were repeated on the fourth hospital day (POD 3). Axillary temperature was checked 1 hour after ESD and at 06:00, 14:00, and 20:00 daily thereafter. Patients without clinical perforations or major bleeding requiring blood transfusion or surgery started drinking water 1 day after ESD and eating soft food 2 days after ESD. A normal diet was allowed at discharge, usually 7 or 8 days after ESD.

### ESD procedure

The ESD was performed using a gastroscope with a single working channel and water jet function (GIF-Q260J; Olympus Optical Co., Tokyo, Japan), and a cap attachment (D-201-11804; Olympus, or F-030; Top Corporation, Tokyo, Japan). The gastric lesion was resected using either a Flex-Knife (KD-630L; Olympus), a Dual-Knife (KD-650L/Q; Olympus), or an insulated-tip diathermic knife (IT-OM-Knife, IT2-Knife, KD-610L, or KD-611L; Olympus). We typically used the Flex-Knife or the Dual-Knife for the ESD procedures. However, for lesions located in the middle third of the stomach, the IT-OM/IT2-knife was selected because it could be placed in a straight position against the lesion.

After chromoendoscopy using 0.25% indigo carmine was performed to clarify the border of the lesion, the circumference was marked using the Flex-Knife or Dual-Knife in swift coagulation mode (effect 3, output 50W) approximately 2–5 mm outside the lesion. Subsequently, several milliliters of high-molecular-weight hyaluronic acid solution containing indigo carmine and epinephrine were injected into the submucosal layer to lift up the lesion on a fluid cushion. Thereafter, an incision of the mucosal layer outside the marking dots was made using the Flex-Knife, the Dual-Knife, or the IT-OM/IT2-Knife in dry cut mode (effect 3, output 60W) to separate the lesion from the surrounding non-neoplastic mucosa. Subsequent direct dissection of the submucosal layer was performed with the Flex-Knife, the Dual-Knife, or

the IT-OM/IT2-Knife in swift coagulation mode (effect 3, output 50W) to remove the lesion. When massive bleeding occurred or exposed vessels were visible on the ulcer base during the ESD procedure, heat coagulation was performed with a hemostatic forceps (FD-410LR; Olympus) in soft coagulation mode (effect 5, output 80W). Throughout the procedure (including marking, incision of the gastric mucosa, dissection at the submucosal layer, and coagulation of exposed vessels), high-frequency energy as described above was supplied by a VIO300D generator (Erbe, Tübingen, Germany). All the procedures were conducted under conscious sedation and analgesia using standard doses of diazepam, hydroxyzine hydrochloride, and pentazocine.

### Definition of ESD complications

#### Pyrexia

Pyrexia was defined as a body temperature exceeding 37.5°C after ESD, regardless of the duration of the febrile period.

#### Endoscopically visible perforation during ESD

The diagnosis of a perforation was made by direct endoscopic observation of an extramural organ or fat through the muscle layer during ESD. We generally treated this complication by immediate closure of the perforation hole using an endoclip (Olympus). If tension pneumoperitoneum developed, decompression was performed using an 18- or 20-gauge puncture needle. In patients where complete closure was not obtained endoscopically, we moved to surgery. When the perforation was closed endoscopically and the patient's condition was stable, we continued the ESD procedure to complete the resection. Thereafter, the patient was managed conservatively on bed-rest with nasogastric suction, peripheral venous nutritional support, and broad-spectrum antibiotics until the pyrexia resolved.

#### Intra-abdominal transmural air leak

Intra-abdominal transmural air leaks were first reported as a complication by Onogi et al [21]. As previously reported by this group, these air leaks were detected by plain abdominal CT at POD 1 as the presence of focal free air close to the stomach. However, these leaks were not detectable during ESD and were not observed on plain chest radiography. This complication was followed-up without any specific treatment.

#### Aspiration pneumonia

Aspiration pneumonia was diagnosed based on the presence of an obvious pneumonia shadow on plain chest CT 1 day after ESD in patients without pneumonia shadows before ESD. We treated this complication with intravenous antibiotics and with antifebriles.

#### Antibiotics and antifebriles

Antibiotics were indicated for febrile patients with (1) findings of pneumonia on CT at POD 1 or (2) clinical findings such as pyrexia or respiratory symptoms after ESD.

Antifebriles were prescribed to fifteen patients with pyrexia and shivering in this study. The agent was acetaminophen, ketoprofen, sulpirine, or diclofenac sodium, and was given once (median).

#### Analysis parameters

Demographic and ESD-related parameters included patient age and sex, location of the gastric lesion, resection diameter, tumor diameter, indications according to the criteria of the guidelines, histopathological diagnosis, endoscopic findings of the artificial

ulcer base at the end of ESD, and operation time. Post-ESD parameters were hospital stay, presence or absence of pyrexia, presence or absence of pneumonia on chest CT imaging at POD 1, peripheral leukocyte count, and serum CRP level. The gastric locations were categorized as the upper third (U), middle third (M), lower third of the stomach (L), or the remnant stomach. *En bloc* resection was defined as resection occurring in a single piece, as opposed to piecemeal resection in multiple pieces. Operation time was measured from the start of circumferential marking to the completion of the resection.

### Statistical analysis

Values are expressed as the number (percentage) of patients or the median (range). Differences in categorical variables between groups were examined by the  $\chi^2$  test or by Fisher's exact test when required. The nonparametric Kruskal-Wallis test was used for the comparison of continuous variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a logistic model for multivariate analysis, and receiver operating characteristic (ROC) analysis was used to detect cut-off points for continuous variables. A  $P < 0.05$  was considered statistically significant. All statistical analyses were conducted with JMP version 8.0 (SAS Institute, Cary, North Carolina, USA).

## Results

### Incidence of post-ESD complications and the characteristics of pyrexia

The demographic and clinical characteristics of the 471 patients and the details of the 485 ESD procedures are summarized in **Table 1**. Of the 346 lesions in which the adenocarcinoma was resected according to the conventional or expanded criteria, 324 (93.6%) were removed curatively by ESD.

The incidence of ESD-related complications is summarized in **Table 2**. ESD complications occurred as perforations in 5 patients (1.1%), postoperative bleeding in 20 patients (4.2%), intra-abdominal transmural air leaks in 43 patients (9.1%), pneumonia (as detected by chest CT at POD 1) in 68 patients (14.4%), and pyrexia above 37.5 °C in 117 patients (24.8%). No atelectasis appeared anew on CT at POD 1 except for patients with an atelectasis shadow on chest radiography before ESD. Among the 68 patients who were diagnosed as pneumonia by chest CT, 40 patients (58.8%) had pyrexia. Meanwhile, 19.1% of patients without the typical findings of pneumonia (77/403 patients) became febrile. These findings indicate that the incidence of pyrexia was markedly higher in patients with pneumonia than in those without pneumonia ( $P < 0.001$ ). In addition, 65.8% of the patients with pyrexia (77/117 patients) did not show the typical findings of pneumonia by chest CT at POD 1.

As shown in **Table 3**, 93.2% (109/117) of the patients developed pyrexia within 1 day postoperatively. By contrast, only one patient (0.9%) developed pyrexia on the sixth day postoperatively. The pyrexia lasted less than two days in 82.1% (96/117) of the patients (median, 1 day; range, 1–36 days). No significant difference was observed in the duration of the pyrexia between the pneumonia patients (median, 2 days; range 1–36 days) and those without pneumonia (median, 1 day; range, 1–8 days). Sixty-eight of the 117 pyrexia patients (58.1%) received antibiotics. Moreover, the ratio of patients treated with antibiotics was higher among the pneumonia patients (33/40, 82.5%) than among those without pneumonia (35/77, 45.5%,  $P < 0.001$ ).

**Table 1** Demographic and endoscopic submucosal dissection (ESD)-related characteristics of the patients.

Demographic characteristics	
Total number of patients	471
Total number of lesions	485
Sex (male/female)	350/121
Age (years)	73 (26–92)
ESD-related characteristics	
Location of lesion (upper/middle/lower/remnant)	107/191/180/7
Resection diameter (mm)	35 (9–110)
Tumor diameter (mm)	17 (3–75)
En-block resection rate	482/485 (99.4%)
Histopathology (adenocarcinoma/adenoma/hyperplastic polyp/carcinoid)	381/99/3/2
Criteria (guideline/expanded/extra) in lesions with adenocarcinoma	222/124/35
Curative resection rate (curative/non-curative) in lesions with adenocarcinoma without extra criteria	324/22 (93.6%)
Operation time (minutes)	49 (8–379)
Hospital stay (days)	8 (3–35)

Values are expressed as the number (percentage) of patients or the median (range).

**Table 2** Incidence of ESD-related complications.

	Number of patients	Incidence
Pyrexia above 37.5 °C after ESD	117	24.8%
Pneumonia (detected by CT at POD 1)	68	14.4%
Transmural air leak (detected by CT at POD 1)	43	9.1%
Postoperative bleeding	20	4.2%
Perforation	5	1.1%

Values are expressed as the number and percentage of patients. POD: postoperative day; CT: computed tomography.

**Table 3** Onset and duration of pyrexia after ESD in 117 patients.

	Number of patients	Incidence
Onset of pyrexia after ESD		
Operation day	14	12.0%
POD 1	95	81.2%
POD 2	7	6.0%
POD 3	0	0%
POD 4	0	0%
POD 5	0	0%
POD 6	1	0.9%
Duration of pyrexia after ESD		
1 day	69	59.0%
2 days	27	23.1%
3 days	8	6.8%
4 days	5	4.3%
5 days	4	3.4%
6 days	1	0.9%
7 days or more	3	2.6%

POD: postoperative day.

### Outcome of post-ESD complications

All 471 patients were discharged after a median hospital stay of 8 days (range, 3–35 days; **Table 1**). As shown in **Table 4**, the hospital stay was longer in patients with complications (median, 8 days; range 5–35 days) than in those without complications (median, 8 days; range, 3–21 days;  $P = 0.0002$ ). The length of the

**Table 4** Hospital stay according to the presence or absence of ESD-related complications.

	Patients with ESD-related complications	Days	Patients without ESD-related complications	Days	P value
Any complication	160	8 (5–35)	311	8 (3–21)	0.0002
Pyrexia	117	8 (7–35)	354	8 (3–21)	n.s.
Pneumonia (detected by CT at POD 1)	68	8 (5–35)	403	8 (3–29)	n.s.
Postoperative bleeding	20	9.5 (7–20)	451	8 (3–35)	<0.0001
Perforation	5	10 (5–35)	466	8 (3–21)	0.0001

Statistical significance was tested by the Kruskal-Wallis test. Values are expressed as the number of patients or the median (range). CT: computed tomography; n.s.: not statistically significant; POD: postoperative day.

hospital stay was not affected by pyrexia or pneumonia, but was longer in patients treated with antibiotics (median, 8 days; range, 5–35 days) than in those not treated with antibiotics (median, 8 days; range, 3–21 days,  $P=0.0381$ ). The patients with bleeding (median, 9.5 days; range, 7–20 days) required longer hospital care than those without bleeding (median, 8 days; range, 3–35 days;  $P<0.0001$ ). In the twenty bleeding patients, no one received surgery, however, six patients required blood transfusion. The hospital stay of the transfusion patients was 17 days (range, 8–35 days) and was longer than that of the transfusion-free patients (median, 8 days; range, 3–21 days;  $P<0.0001$ ). Among the five perforation patients, two were closed endoscopically, two were recovered by conservative therapies, and one required surgery. The hospital stay of these patients was 10 days (range, 5–35 days) and was longer than that of unperforated patients (median, 8 days; range, 3–21 days;  $P=0.0001$ ).

### Clinical and laboratory characteristics of patients with or without post-ESD pyrexia

The clinical and ESD parameters of patients with or without post-ESD pyrexia (Table 5). The location and histopathological diagnosis of multiple resected lesions were compared based on the findings of the primary lesions. When compared to patients without pyrexia, those with pyrexia showed an increased resection diameter (median, 40 mm vs. 35 mm;  $P<0.0001$ ), tumor diameter (median, 20 mm vs. 16 mm;  $P=0.0133$ ), and operation time (median, 57 minutes vs. 48 minutes;  $P=0.0082$ ). Age (median, 75 years vs. 72.5 years;  $P=0.0006$ ), the incidence of the female gender (34.2% vs. 22.9%;  $P=0.0174$ ), and the curative resection rate (86.7% vs. 95.3%,  $P=0.0113$ ) were lower in the patients with pyrexia.

Among the complications after ESD, the rate of pneumonia detected by CT at POD 1 was higher in the patients with pyrexia (34.2% vs. 7.9%,  $P<0.0001$ ). Compared to patients without pyrexia, those with pyrexia had elevated serum levels of CRP at POD 1 (0.58 mg/dl vs. 0.28 mg/dl,  $P<0.0001$ ) and POD 3 (3.99 mg/dl vs. 1.81 mg/dl,  $P<0.0001$ ).

### Multivariate analysis of risk factors for post-ESD pyrexia

Among the variables identified in Table 5, age (OR: 1.03, 95% CI: 1.00–1.06,  $P=0.0310$ ), resection diameter (OR: 1.07, 95% CI: 1.03–1.10,  $P<0.0001$ ), and the female gender (OR: 2.05, 95% CI: 1.19–3.53,  $P=0.0100$ ) were identified by multivariate analysis as significant independent risk factors for pyrexia. The occurrence of pneumonia (OR: 5.81, 95% CI: 3.16–10.86,  $P<0.0001$ ) and increased CRP level at POD 1 (OR: 1.73, 95% CI: 1.34–2.35,  $P<0.0001$ ) were identified as significant independent risk factors for pyrexia among the post-ESD parameters (Table 6).

In 403 patients without pneumonia, age, non-curative resection, resection diameter, tumor diameter, and operation time were significant risk factors for pyrexia by univariate analysis (Table 7). By multivariate analysis, age (OR: 1.05, 95% CI: 1.02–1.08,  $P=0.0029$ ) and resection diameter (OR: 1.03, 95% CI: 1.01–1.05,  $P=0.0009$ ) were identified as significant independent risk factors for pyrexia (Table 7). With respect to the independent risk factors of post-ESD pneumonia, operation time (OR: 1.01, 95% CI: 1.00–1.01,  $P=0.0025$ ) and increased CRP level at POD 1 (OR: 1.48, 95% CI: 1.23–1.85,  $P<0.0001$ ) were identified.

### Cut-off values for an at-risk age, resection size, operation time, and serum CRP levels at POD 1

ROC analysis revealed the cut-off values for an at-risk age, resection diameter, and serum CRP levels at POD 1 for pyrexia as a complication were 68 years (sensitivity, 79.5%; specificity, 37.3%), 35.0 mm (71.6%, 48.2%), and 0.65 mg/dl (49.6%, 82.5%), respectively. Meanwhile, the cut-off values for a high-risk operation time and serum CRP level at POD 1 for pneumonia were 60 min (51.5%, 66.2%) and 0.45 mg/dl (64.7%, 64.1%), respectively.

### Discussion

ESD is regarded as the first line therapy for early stage gastric tumors; however, gastric ESD requires great skill to complete the procedure safely [3, 10, 23]. Moreover, complications such as bleeding, perforation, pneumonia, and pyrexia may occur at a certain rate even when the ESD is performed with care [15]. Although pyrexia seems to be a common complication of ESD as related to many other complications, the exact incidence and critical risk factors for pyrexia are largely unknown. To our knowledge, no previous study has focused on the clinicopathological characteristics of pyrexia after gastric ESD procedure. In addition, this study provided comprehensive and comparative information, including pneumonia findings on chest CT at POD 1, injury of the muscularis propria on the ESD ulcer, and transmural air leaks [21].

Pyrexia occurred in 24.8% of patients after gastric ESD and persisted for a median of one day. The results from the multivariate analysis and ROC curve analysis revealed that an age greater than 68 years, a resection diameter of > 35.0 mm, and increased serum CRP level at POD 1 were independent risk factors for pyrexia. Further, pneumonia detected by chest CT at POD 1 was the largest cause of pyrexia because 34.2% of pyrexia patients developed pneumonia. The results from the sub-analysis of patients without pneumonia demonstrated that age and resection diameter were still independent risk factors for pyrexia, whereas operation time



**Table 5** Clinical and laboratory characteristics of patients with or without post-ESD pyrexia.

Patient demographic characteristics	Pyrexia (n = 117)	No pyrexia (n = 354)	P value
Female	40 (34.2%)	81 (22.9%)	0.0174
Age (years)	75 (51–89)	72.5 (26–92)	0.0006
<b>ESD-related characteristics</b>			
Location of the primary lesion (upper/middle/lower/remnant)	20/52/43/2	87/130/132/5	n.s.
Resection of multiple lesions	4 (3.4%)	10 (2.8%)	n.s.
Histopathology of the primary lesion (carcinoma/adenoma/hyperplastic polyp/carcinoid)	90/27/0/0	282/67/3/2	n.s.
Criteria (guideline/expanded/extra) for lesions with adenocarcinoma	44/39/7	169/85/28	0.0186
Curative resection rate (curative/non-curative) for lesions with adenocarcinoma without extra criteria	72/11 (86.7%)	242/12 (95.3%)	0.0113
Resection diameter (mm)	40 (16–105)	35 (9–110)	<0.0001
Tumor diameter (mm)	20 (4–65)	16 (3–75)	0.0133
Operation time (minutes)	57 (14–279)	48 (8–379)	0.0082
<b>Complications</b>			
Pneumonia (detected by CT at POD 1)	40 (34.2%)	28 (7.9%)	<0.0001
Perforation	3 (2.6%)	2 (0.6%)	n.s.
Transmural air leak (detected by CT at POD 1)	15 (12.8%)	28 (7.6%)	n.s.
Postoperative bleeding	6 (5.1%)	14 (4.0%)	n.s.
Injury to the muscularis propria on the ulcer	32 (27.4%)	74 (20.1%)	n.s.
<b>Laboratory tests</b>			
Leukocyte count (/μL)			
Before ESD	5080 (2270–9980)	5485 (1160–11400)	n.s.
POD 1	8720 (2570–17680)	8110 (1050–15970)	n.s.
POD 3	6630 (1880–12940)	6100 (2330–13180)	n.s.
C-reactive protein (mg/dl)			
Before ESD	0.06 (0.02–6.17)	0.06 (0.02–6.27)	n.s.
POD 1	0.58 (0.05–13.82)	0.28 (0.02–7.31)	<0.0001
POD 3	3.99 (0.16–14.59)	1.81 (0.05–18.60)	<0.0001

Statistical significance was tested by the Chi-square test (Fisher's exact test when required) or by the Kruskal-Wallis test. Values are expressed as the number (percentage) of patients or the median (range). CT: computed tomography; n.s.: not statistically significant; POD: postoperative day.

and serum CRP level at 1 POD were variables for predicting the risk of developing pneumonia.

Several possibilities could explain the development of post-ESD pyrexia, including treatment methods, devices, injury to the muscularis propria on the ulcer, and infection of the wound during the procedure. We have previously reported that patients with transmural air leaks after ESD had a high incidence of pyrexia [21]. Moreover, the presence of the transmural air leak was associated with a larger resection size, longer procedure time, and exposure of the muscularis propria on the ulcer base [21]. However, in the present study, only a larger resection diameter remained as significant independent risk factor for pyrexia even when patients did not develop pneumonia. Although neither blood nor urine cultures were conducted in this study, gastric ESD shows a low risk for bacteremia [20]. Hence, we consider that a larger wound *per se* and its subsequent healing process might induce inflammatory responses associated with pyrexia. As compared to ordinary peptic ulcers, post-ESD wounds are made with more invasive injury in a shorter time, specifically with electrical heat burns for dissection and hemostasis. Therefore, a larger post-ESD wound and its subsequent healing process might cause pyrexia at higher incidence. Consistent with the possible role of wound size in post-ESD pyrexia, several reports have demonstrated a larger ESD diameter increases the risk of perforation and postoperative bleeding [17,18]. Future experimental and clinical confirmation will be required to confirm the role of wound size in the occurrence of post-ESD pyrexia.

In this study and a previous report from our institution, we defined pyrexia as a body temperature exceeding 37.5 °C, regardless

**Table 6** Multivariate analysis of risk factors for post-ESD pyrexia.

	OR	95%CI	P value
Female	2.05	1.19–3.53	0.0100
Age	1.03	1.00–1.06	0.0310
Resection diameter	1.07	1.03–1.10	<0.0001
Pneumonia detected by CT at POD 1	5.81	3.16–10.86	<0.0001
Serum level of C-reactive protein at POD 1	1.73	1.34–2.35	<0.0001

Statistical significance was tested by logistic model. OR: odds ratio; CI: confidence interval.

of the duration of the febrile period [21]. When another definition of pyrexia as a body temperature exceeding 38.0 °C is applied [20], post-ESD pyrexia occurred in 61 patients (13.0%). Among them, 24 patients (39.3%) were diagnosed with pneumonia by chest CT. The incidence of pneumonia was not significantly different between the two definitions.

In the present trial, pneumonia occurred in 68 patients (14.4%) after gastric ESD. In a large retrospective study, Akasaka et al. reported that the incidence of pneumonia was 1.6% (19 of 1188 patients) [16], which was lower than that found in the present study. However, in the previous study, plain chest radiography was performed only when the attending physician suspected postoperative pneumonia based on the clinical symptoms. Another group reported an incidence of 2.3% and diagnosed the pneumonia by a similar procedure [24]. Importantly, Watari et al. reported that 66.7% of the patients with CT-detected pneumonia

**Table 7** Univariate and multivariate analysis of risk factors for post-ESD pyrexia in patients without pneumonia (N = 403).

	Univariate analysis			Multivariate analysis		
	OR	95%CI	P value	OR	95%CI	P value
Age	1.05	1.02 – 1.09	0.0006	1.05	1.02 – 1.08	0.0029
Non-curative resection	1.81	1.01 – 3.24	0.0474	1.98	0.60 – 6.11	n.s.
Resection diameter	1.03	1.01 – 1.04	0.0010	1.03	1.01 – 1.05	0.0009
Tumor diameter	1.02	1.00 – 1.04	0.0285	0.96	0.91 – 1.01	n.s.
Operation time	1.01	1.00 – 1.02	0.0169	1.00	0.99 – 1.01	n.s.

Statistical significance was tested by a logistic model. OR: odds ratio; CI: confidence interval.

after ESD had no abnormal findings on plain chest radiography [19]. Together with the results of these previous reports [16, 19, 24], the present findings suggest that chest CT examination should be conducted to increase the accuracy of the diagnosis of pneumonia after ESD.

In the recent guidelines of the American Society for Gastrointestinal Endoscopy and the new British guidelines, the efficacy of antibiotic prophylaxis for preventing pyrexia and pneumonia associated with endoscopic procedures is not broached as a topic [25, 26]. These guidelines recommend antibiotic use for groups with a high risk of severe infection, including biliary infections, or highly invasive procedures involving the piercing of the gastrointestinal wall; however, the standard ESD procedure is not included in the criteria [20, 25, 27]. Therefore, it is necessary to conduct studies to determine if the prophylactic use of antibiotics is required to prevent pyrexia and pneumonia after ESD. It should be noted that no significant differences in hospital stay were observed among the patients with or without pyrexia in the present study. We believe the improvement of the pyrexia through accurate diagnosis and early treatment by administration of antibiotics might have contributed to this outcome. Although the pyrexia patients without findings of pneumonias might have taken severe courses, including delayed perforation or aggravation of inflammation, the appropriate approach had not been conducted these patients. Hence, we made an addition to estimate a clinical relevance of the pyrexia without findings of pneumonias. The chest CT performed at POD 1 enabled us to find chest X-ray negative pneumonia at an early stage. Therefore, we conclude that the early diagnosis of pneumonia, using CT, and starting therapy in the early phase is an effective strategy for easing the patient burden.

In conclusion, the results of the present study demonstrated that an age over 68 years, the female gender, a resection diameter of >35.0mm, an increased serum CRP level at POD 1, and pneumonia as a complication were significant independent risk factors for pyrexia after gastric ESD. Therefore, particular attention should be focused on performing ESD carefully in patients with these risk factors. Furthermore, a reduction in the operation time might be effective for preventing pneumonia and therefore pyrexia in at least some patients. CT examination is recommended for the early diagnosis and treatment of pneumonia. Future studies should address whether these efforts can reduce the complications of pyrexia and pneumonia, which would enable wider application of gastric ESD without extending hospital stay.

## Abbreviations



CI	confidence interval
CRP	C-reactive protein
CT	computed tomography
EMR	endoscopic mucosal resection
ESD	endoscopic submucosal dissection
OR	odds ratio
POD	postoperative day
ROC	receiver operating characteristic.

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