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ORIGINAL ARTICLE

Pneumonia After Endoscopic Resection for Gastric Neoplasm

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Abstract
Background Pneumonia following endoscopic procedures may affect the clinical course and prolong hospital stay.
Aim To investigate the incidence and risk factors for pneumonia after endoscopic resection (ER) for gastric neoplasm.
Methods Subjects who underwent ER for gastric neoplasm at the Asan Medical Center from January 1997 to March 2013 were included. To investigate risk factors, control patients were randomly selected from these subjects.
Results Of the 7,149 subjects who underwent ER for gastric neoplasm, 44 (0.62 %) developed pneumonia. The median age of these 44 patients was 68 years (range 31–82 years), and the male to female ratio was 3:1. Twenty-five of the pneumonia patients (56.8 %) were smokers, and 8 (18.2 %) had underlying pulmonary diseases. The median procedure time was 23 min (range 2–126 min), and pathologic diagnoses included adenocarcinoma ($n = 29$), dysplasia ($n = 10$), and hyperplastic polyp ($n = 5$). Compared with the control group, smoking (current smoker vs. never smoker, odds ratio [OR] 2.366, $p = 0.021$), total procedure time (OR 1.011, $p = 0.048$), and hemostasis time (OR 1.026, $p = 0.028$) were risk factors for the development of pneumonia. In multivariate analysis, age >65 years (OR 2.073, $p = 0.031$), smoking (current smoker vs. never smoker, OR 2.324, $p = 0.023$), and hemostasis time (OR 1.025, $p = 0.038$) were independent risk factors. All patients recovered from pneumonia, and the duration of hospital stay did not differ between patients with pneumonia and the control group ($p = 0.077$).
Conclusions Whereas old age, smoking, and longer hemostasis time are risk factors for pneumonia, its incidence after ER is not associated with clinically significant adverse outcomes.

Keywords Pneumonia · Gastric neoplasms · Gastrointestinal endoscopy · Conscious sedation

Introduction

Endoscopic resection (ER) has been widely accepted as an effective minimally invasive treatment for gastric neoplasm. Compared with conventional endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) has made en bloc resection more possible for large tumors and tumors in more difficult locations [1, 2]. However, ESD is a technically difficult and time-consuming procedure and may have a higher risk of complications including bleeding and perforation [1, 3, 4].

Most endoscopic procedures are performed under conscious sedation without airway management [4–8].

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Because therapeutic endoscopy including ER generally lasts longer than conventional endoscopy, more sedatives are required to maintain acceptable level of sedation. Hence, the possibility of sedation-related adverse events including pulmonary complications may be increased when performing therapeutic endoscopy. Pneumonia after ER can prolong hospital stay, leading to greater costs, and may lead to clinically significant adverse outcomes [9]. In contrast, pulmonary infiltrates detected by chest radiography in the absence of respiratory symptoms sometimes recover without additional treatment. This variety of clinical manifestations may make it difficult to define the development of pneumonia, as well as to make a decision regarding additional managements. Therefore, appropriate risk assessment and proper management are required to perform ER safely. However, little is currently known about the characteristics and risk factors associated with pneumonia as an adverse event arising after ER. In our study, we investigated the incidence and risk factors for pneumonia after ER for gastric neoplasm.

Methods

Patients

All 10,392 patients who underwent ER for gastric neoplasm at the Asan Medical Center from January 1997 to March 2013 were eligible for enrollment in this study. Of these, 3,243 patients did not undergo chest radiography after the procedure and were therefore excluded. Of the remaining 7,149 patients, 44 patients were found to have pulmonary infiltration on chest radiography. To investigate the risk factors for pneumonia after ER, a control cohort with tenfold the number of the patients with pneumonia ($n = 440$) was randomly selected for the analyses. A flowchart for patient selection is depicted in Fig. 1. Because conscious sedation itself is associated with the risk of pneumonia, we included patients who underwent ER in our study cohort regardless of the type of procedures they received.

Patient-related factors (age, sex, smoking habit, and comorbidity), tumor-related factors (tumor location, number of lesions, maximal dimension of the resected specimen, and histologic differentiation), procedure-related factors (total procedure time, resection time, and hemostasis time), and clinical parameters (symptoms, antibiotics use, and duration of hospital stay) were evaluated using medical records. The histologic classification and tumor location fulfilled the criteria of the Japanese Research Society for Gastric Cancer [10].

Endoscopic Resection

Endoscopic resection was performed with the patient in the left lateral decubitus position under conscious sedation using intravenous midazolam and pethidine with or without propofol. During the procedure, at least 2 L/min of nasal oxygen was administered and blood pressure, heart rate, and peripheral oxygen saturation were monitored [11]. In

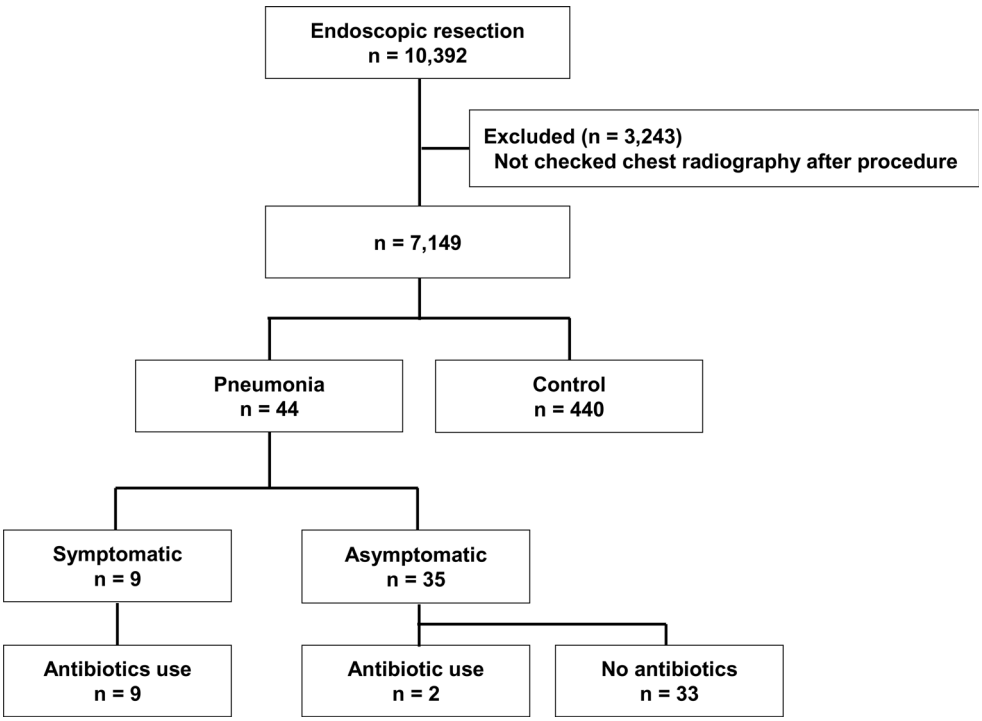

Fig. 1 Flowchart of this study

patients with co-morbidities such as renal dysfunction and liver dysfunction, the sedative dosages were chosen carefully. When using midazolam, we routinely gave flumazenil at the end of the procedure.

Chest radiography was performed on the same day after the procedure to identify possible complications such as perforation in all of the patients included in this study. In addition, chest radiography was performed when the attending physician suspected pneumonia based on the clinical presentation. After the absence of perforation was confirmed, a second-look endoscopic examination was performed to exclude bleeding on day 2 after ER. All patients were admitted on the day before ER and were usually discharged 2 days after the procedure. Thus, the hospital stay for patients without any complications was 4 days based on the clinical protocol of our hospital.

Definitions

The total procedure time was measured from the beginning of the marking around the tumor to the removal of the endoscope, including any time required for hemostasis. Resection time was defined as the period from marking to detachment of the resected specimen. Hemostasis time was the time required to control immediate bleeding. The correlation coefficient between the total procedure time and hemostasis time was 0.716 ($p = 0.01$).

En bloc resection was defined as the lesion being resected in one piece. Complete resection of en bloc-resected tumors was defined by lateral tumor-free margins of more than 2 mm and vertical tumor-free margins of more than 0.5 mm on histologic examination. When the lesion required removal of multiple segments, the piecemeal-resected specimens were reconstructed as completely as possible.

Several types of pulmonary syndromes can arise after aspiration, including aspiration pneumonitis and aspiration pneumonia. Aspiration pneumonitis reflects a chemical injury of lung, whereas aspiration pneumonia has an infectious etiology. In our present study, the definition of pneumonia was based on a chest radiography finding of the presence of new or progressive infiltrates, consolidation, or pleural effusion in patients who had no evidence of pneumonia on chest radiography before the procedure. We further reviewed the chest radiography results and symptoms of patients who developed pneumonia and categorized the patients as pneumonia with or without symptoms.

Statistical Analysis

The risk of pneumonia was assessed by case–control analysis. Univariate analysis was performed using logistic regression model by computation of odds ratio (OR) and corresponding 95 % confidence intervals (CI). Multivariate analysis was performed using a logistic regression model with a stepwise backward elimination procedure. Differences between pneumonia with and without symptoms were determined using the T test or chi-square test, as appropriate. When the data were not normally distributed or when the sample size was small, the Mann–Whitney U test or Fisher's exact test was used instead of the T test or chi-square test. A p value <0.05 was considered statistically significant. A receiver operator characteristic (ROC) curve was constructed by plotting sensitivity (true-positive rate) against 1-specificity (false-positive rate) over all possible threshold levels of hemostasis time which is related to the development of pneumonia. All statistical analyses were performed using SPSS 18.0 (Chicago, IL, USA) software.

Results

Among the 7,149 subjects in our study cohort, 44 patients (0.62 %) developed pneumonia after ER. Pathologic diagnoses in this subgroup included adenocarcinoma in 29 patients, dysplasia in 10 patients, and gastric hyperplastic polyp in five patients. The median age of these 44 patients was 68 years (range 31–82 years), and the male to female ratio was 3:1. Of these cases, 17 (38.6 %) were current smokers and eight (18.2 %) were ex-smokers. In addition, eight patients had underlying pulmonary diseases such as asthma ($n = 4$), sequelae of pulmonary tuberculosis ($n = 2$), chronic obstructive pulmonary disease ($n = 1$), interstitial lung disease ($n = 1$), and a history of lung cancer ($n = 1$). The clinical characteristics of these 44 patients with pneumonia are shown in Table 1.

Among our cohort of 44 pneumonia patients, EMR was performed in five patients (11.4 %), ESD was performed in 35 patients (79.5 %), and polypectomy was performed in four patients (10.5 %). All 44 patients were sedated with intravenous midazolam (median 0.06 mg/kg, range 0.01–0.15 mg/kg), and none showed oxygen desaturation during the procedure. With respect to the size of the resected specimen, it was less than 10 mm in 12 cases (27.3 %), 10–20 mm in 21 cases (47.7 %), and equal to or more than 20 mm in 11 cases (25.0 %). All except for three of these patients (93.2 %) achieved complete resection, and the median total procedure time was 23 min (range 2–126 min).

The most common location of the pneumonic infiltrations was the left lower lung field ($n = 39$, 88.6 %), followed by the right lung field and the bilateral lung fields. Nine patients (20.5 %) had fever and were treated with empirical intravenous antibiotics. No patient had bacteremia. When comparing the symptomatic patients with asymptomatic patients, there was no difference in age,

Table 1 Clinical characteristics of the patients who developed pneumonia after endoscopic resection

Age (years)	68 (31–82)
Male sex	33 (75.0)
Comorbidity	
Pulmonary disease[a]	8 (18.2)
Other comorbidity[b]	9 (20.5)
Smoking	
Never smoker	19 (43.2)
Ex-smoker	8 (18.2)
Current smoker	17 (38.6)
Number of lesion	
1	37 (86.0)
2	6 (14.0)
≥3	1 (0.2)
Location	
Upper third	5 (11.4)
Middle third	8 (18.2)
Lower third	31 (70.5)
Resected specimen size (mm)	16 (1–80)
Pathologic diagnosis	
Adenocarcinoma	29 (65.9)
Dysplasia	10 (22.7)
Hyperplastic polyp	5 (11.4)
Procedure time (min)	
Total time	23 (2–126)
Resection time	16.5 (1–80)
Hemostasis time	7.5 (1–80)
En bloc resection	44 (100.0)
Complete resection	41 (93.2)
Pneumonic infiltration	
Left lung field	33 (75.0)
Right lung field	4 (9.1)
Bilateral lung fields	7 (15.9)

Variables are presented as a number (%) or median (range)

[a] Underlying pulmonary disease: asthma, chronic obstructive lung disease, bronchiectasis, sequelae of pulmonary tuberculosis, interstitial lung disease, and history of lung cancer

[b] Other comorbidities: cardiovascular disease, renal disease, liver cirrhosis, and diabetes

smoking status, underlying pulmonary disease, or procedure time between the two groups. The median hospital stay was 8 days (range 4–19 days) for symptomatic patients and 4 days (range 2–8 days) for patients without symptoms ($p < 0.001$) (Table 2). All of these patients recovered from pneumonia, although one patient was transferred to the intensive care unit and received mechanical ventilator care. This patient had shown respiratory symptoms a week before the procedure, but there were no complaints at the time of admission. This patient

Table 2 Comparison between the symptomatic and asymptomatic study patients with pneumonia

	Symptomatic ($n = 9$)	Asymptomatic ($n = 35$)	p value
Age (years)	68 (42–82)	67 (31–77)	0.792
Male sex	8 (88.9)	25 (71.4)	0.411
Comorbidity			
Pulmonary disease[a]	0 (0.0)	8 (22.8)	0.175
Other comorbidity[b]	3 (33.3)	6 (17.2)	0.329
Smoking			0.231
Never smoker	2 (22.2)	17 (48.6)	
Ex-smoker	3 (33.3)	5 (14.3)	
Current smoker	4 (44.4)	13 (37.1)	
Resected specimen size (mm)	23 (1–53)	16 (3–80)	1.000
Midazolam (mg/kg)	0.06 (0.04–0.08)	0.06 (0.01–0.15)	0.753
Procedure time (min)			
Total time	23 (17–57)	23 (2–126)	0.668
Resection time	16 (8–52)	17 (1–80)	0.606
Hemostasis time	6 (3–18)	8 (1–66)	0.731
Antibiotics use	9 (100.0)	2 (5.7)	<0.001
Hospital stay (days)	8 (4–19)	4 (2–8)	<0.001

Variables are presented as a number (%) or median (range)

[a] Underlying pulmonary disease: asthma, chronic obstructive lung disease, sequelae of pulmonary tuberculosis, interstitial lung disease, and a history of lung cancer

[b] Other comorbidities: cardiovascular disease, renal disease, liver cirrhosis, and diabetes

developed fever after the procedure, and a chest radiography revealed a new pulmonary infiltration of a rapidly progressive nature, at which point he was transferred to the intensive care unit and received mechanical ventilator care. There was no identified pathogen in this case other than pneumococcal urinary antigen positivity. The patient was extubated on the sixth hospital day and finally discharged after 17 days of hospital stay.

Compared with the control group, smoking, total procedure time, and hemostasis time were identified as risk factors for the development of pneumonia (Table 3). Multivariate analysis showed that an age above 65 years, smoking, and a longer hemostasis time were independent risk factors for pneumonia (Table 4). True-positive rate against false-positive rate of hemostasis time was plotted in relation to the development of pneumonia. Based on the ROC curve, hemostasis time with optimal sensitivity and specificity was about 7 min (Fig. 2). When performed the logistic regression analysis, the estimated OR was 2.510 (95 % CI 1.314–4.795) with p value of 0.005 and area under the ROC curve of 0.682. Submucosal fibrosis or scar formation was detected in five of our pneumonia patients

Table 3 Risk factors for pneumonia after endoscopic resection (univariate analysis)

	Pneumonia ($n = 44$)	Control ($n = 440$)	OR (95 % CI)	p value
Age >65 years	25 (56.8)	191 (43.4)	1.715 (0.918–3.207)	0.091
Male sex	33 (75.0)	308 (70.0)	1.286 (0.631–2.621)	0.489
Pulmonary disease[a]	8 (18.2)	40 (9.1)	2.222 (0.967–5.107)	0.06
Smoking				
Never smoker	19 (43.2)	227 (51.6)	1.00	0.066
Ex-smoker	8 (18.2)	113 (25.7)	0.846 (0.359–1.991)	0.702
Current smoker	17 (38.6)	100 (22.7)	2.031 (1.013–4.071)	0.046
Submucosal fibrosis	5 (11.4)	41 (9.6)	1.027 (0.451–3.232)	0.708
Resected specimen size (mm)	16 (1–80)	15 (1–75)	1.012 (0.990–1.035)	0.288
Midazolam (mg/kg)	0.06 (0.01–0.15)	0.06 (0.01–0.19)	0.12 (0.00–17,151.8)	0.783
Procedure time (min)				
Total time	23 (2–126)	18 (1–164)	1.011 (1.000–1.021)	0.048
Resection time	16.5 (1–80)	12 (1–144)	1.010 (0.996–1.025)	0.166
Hemostasis time	7.5 (1–80)	5 (0–87)	1.026 (1.003–1.049)	0.028

Variables are presented as a number (%) or median (range)

CI confidence interval, *OR* odds ratio

[a] Underlying pulmonary disease: asthma, chronic obstructive lung disease, bronchiectasis, sequelae of pulmonary tuberculosis, interstitial lung disease, and a history of lung cancer

Table 4 Risk factors for pneumonia after endoscopic resection (multivariate analysis)

	OR (95 % CI)	p value
Age >65 years	2.073 (1.070–4.016)	0.031
Smoking		
Never smoker	1	
Ex-smoker	0.748 (0.311–1.798)	0.516
Current smoker	2.324 (1.121–4.817)	0.023
Hemostasis time	1.025 (1.001–1.049)	0.038

Variables are presented as a number (%) or median (range)

CI confidence interval, *OR* odds ratio

(11.4 %), but there was no association found between ulcerations or scars and the risk of pneumonia ($p = 0.708$). The use of a proton pump inhibitor (PPI) was reported in 4.5 % (2/44) of patients with pneumonia and 4.1 % (18/440) of the control patients, but PPI use did not increased the risk of pneumonia (OR 1.116, 95 % CI 0.250–4.978, $p = 0.885$). Regarding the 440 control patients, EMR was performed in 70 cases (18.2 %), ESD was performed in 312 cases (70.9 %), polypectomy was performed in 34 cases (7.7 %), and ablation using argon plasma coagulation was performed in 14 cases (3.2 %). The type of procedure used did not show statistically significant difference between the pneumonia patients and the control group ($p = 0.694$). The duration of hospital stay was not significantly different between the patients with pneumonia (median 4 days, range 2–19 days) and the control group (median 4 days, range 2–12 days) ($p = 0.077$).

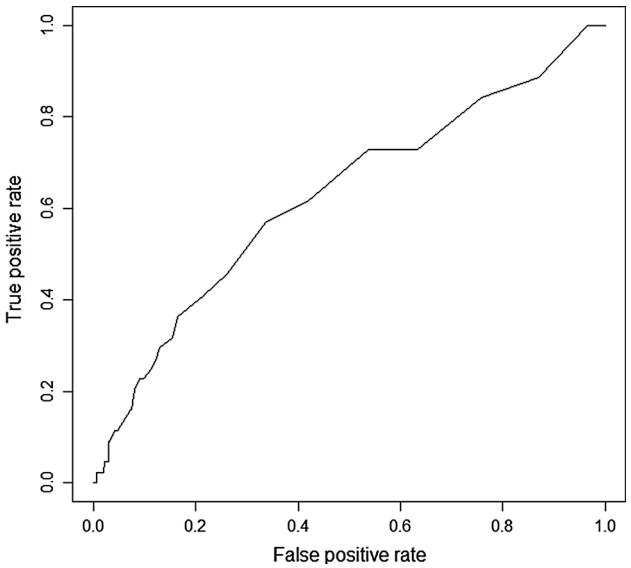

Fig. 2 Receiver operating characteristic curve for hemostasis time. The sensitivity and 1-specificity at the hemostasis time of 7 min were 0.568 and 0.337, respectively

Discussion

In our present study, we investigated the incidence and risk factors for pneumonia in a cohort of patients who received ER for gastric neoplasm. Among the 7,149 patients who underwent ER at our hospital, the incidence of pneumonia was 0.62 %, with 20.5 % of these affected patients showing symptoms. Compared with the control group, old age (>65 years), smoking, and a longer hemostasis time were found to be independent risk factors for pneumonia. All of

the pneumonia patients in our current study recovered after conservative management, and there was no significant difference in the length of hospital stay between the pneumonia and the control groups. Our data suggest that pneumonia is one of the complications of ER and can be associated with higher costs, but not with clinically serious outcomes.

The incidence of pneumonia after ER in our present study is lower than that of other studies, which ranged from 1.6 to 6.6 % [4, 5, 12, 13]. One possible explanation for this discrepancy may be the difference in the procedure times between previous studies (usually over 80 min) and our current study (median 23 and 18 min in the pneumonia and the control group, respectively). Previous studies have shown that a longer procedure time is associated with the development of pneumonia [3–5, 7, 12]. In addition, the procedure time is longer in cases of ulceration, scar, large lesions, or for lesions located in the upper portion of the stomach, and these factors are thus related to the risk of pneumonia [2]. In contrast to these earlier results, neither the size, tumor location, nor the presence of fibrosis or scarring showed any association with pneumonia in our present study. Moreover, there was no statistically significant difference based on the type of procedure, although the technical difficulty varies between endoscopic procedures.

The total procedure time and hemostasis time were found to be risk factors for the development of pneumonia, but multivariate analysis revealed the hemostasis time to be the only independent risk factor. During hemostatic procedures, we usually use a significant amount of water to wash and clear the lesion, so that the gastric content increases with time. The lower and upper esophageal sphincters prevent passive regurgitation from the stomach to the esophagus and from the esophagus to the pharynx, but the tone of the sphincters is reduced in patients under conscious sedation. As gastric distension persists, the risk of belching and aspiration increases, which means that the risk of pneumonia may be higher in such cases. In this regard, frequent suction of gastric fluid and avoidance of excessive air expansion help to prevent development of aspiration pneumonia [3]. Additional protective measures, such as the use of an overtube or endotracheal tube may prevent aspiration; however, predicting the procedure time or hemostasis time is difficult, and further studies are needed to clarify their impact [14, 15].

During ER, the abolition or impairment of the gag reflex due to local pharyngeal anesthesia, intravenous sedation, and mechanical interference with the laryngeal closure and upper esophageal sphincter by the endoscope can predispose patients to aspiration of gastric contents [16, 17]. Because patients are in the left lateral decubitus position during the procedure, aspiration pneumonia often occurs on the left side of the lung, as shown in our present study and in previous reports [3]. Compared with patients under deep sedation, patients under conscious sedation via a midazolam injection still demonstrate a gag reflex. However, while the gag reflex and cough reflex are functional under these conditions, this does not necessarily mean that aspiration will not occur, as the laryngeal closure reflex is impaired after the administration of intravenous benzodiazepine [18]. This is particularly problematic in elderly patients, and old age is considered an important risk factor for aspiration pneumonia [4, 5, 19]. Patients are also at risk of aspiration after completion of the procedure because of the difference in the half-life between local pharyngeal anesthesia and intravenous sedatives, and this is why patients should remain recumbent until the local anesthetic has worn off [20].

Aspiration of sterile gastric contents induces the development of pneumonitis, not always leading to pneumonia, while that of colonized oropharyngeal material induces pneumonia [21]. In contrast to aspiration pneumonia, the majority of patients with aspiration pneumonitis do not require treatment with antibiotics. Previous reports confirmed that the use of antibiotics did not affect the length of hospital stay or prognosis in patients without respiratory symptoms or fever [12]. In our present study, the hospital stay of patients with symptoms was longer than that of asymptomatic patients, and all patients with symptoms were treated with antibiotics. However, all patients recovered, with no patients showing bacteremia. These results support current guidelines that do not recommend the use of prophylactic antibiotics in such settings [22, 23].

This study has several limitations. First, the incidence of pneumonia may be underestimated because aspiration during endoscopy may not lead to radiological changes immediately after the procedure. In accordance with our clinical protocol, patients are discharged 2 days after ER, and the duration of hospital stay may therefore not be sufficient to allow for detectable changes on chest radiography. Recently, a prospective study using computed tomography (CT) reported a higher incidence of pneumonia (6.6 %) than that of our present study, with 66.7 % of these patients showing no abnormal findings on chest radiographs, but positivity for pneumonia by CT [13]. In addition, our current study was retrospective, and a considerable portion of the patients who underwent ER at our hospital was excluded because they did not undergo chest radiography after the procedure. This may have contributed to a selection bias. Second, we did not evaluate operator-related factors in our current analysis. The endoscopic skill level of the treating physician affects the procedure time and also the rate of possible treatment complications after ER, which may cause a learning curve bias [24]. However, the procedure times at our institution were shorter than

those of other reports, reflecting a high skill level of the endoscopists at our hospital. Another weakness of our study is that we could not assess the performance status of each patient. Because patients with more favorable performance status may be selected for ER, this may also have resulted in a selection bias in our cohort. Finally, although we randomly selected a tenfold of control patients to investigate the risk factors for the development of pneumonia after ER and this was a reasonable approach in terms of providing statistical power, this could also be associated with a selection bias.

In conclusion, our current analyses identified pneumonia as a complication of ER and revealed that old age, smoking, and a longer hemostasis time were risk factors for the development of pneumonia. Although the length of hospital stay may be longer in symptomatic patients, it may not lead to clinically significant outcomes. Appropriate risk stratification and adequate protective measures are important, and these findings may be useful for physicians to make a decision to treatment in patients showing pulmonary infiltration.

Conflict of interest The authors declare no potential conflicts of interest.

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