



Adverse Events Associated With Peroral Endoscopic Myotomy Affecting Extended Hospital Stay: A Multi-center Retrospective Study in South Korea

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Background/Aims

To analyze various adverse events (AEs) related to the peroral endoscopic myotomy (POEM) procedure and to analyze whether these AEs are related to an extended hospital stay.

Methods

Patients admitted for POEM for esophageal motility disorders from August 2012 to February 2020 at 5 centers were retrospectively collected. Length of hospital stay, AEs during or after the POEM procedure were analyzed.

Results

Of the 328 patients, 63.1% did not have any AEs, but 2.4% had major AEs, and 33.4% had minor AEs. Major AEs included mucosal injury, bleeding, and hemothorax, accounting for 1.5%, 0.6%, and 0.3%, respectively. Among the minor AEs, pneumoperitoneum was the most common gas-related AEs. Among non-gas-related minor AEs, pneumonia was the most common at 4.6%, followed by pain, fever, and pleural effusion. All major AEs had meaningful delayed discharge and significantly extended hospital stay compared to the no AEs group (median differences range 4.5-9.0 days). Among gas-related minor AEs, except for 4 cases of emphysema, the extended hospital stay was meaningless. All non-gas-related minor AEs was associated with a significant prolongation of hospital stay compared to that in the no AEs group (median differences range 2.0-4.0 days).

Conclusions

In conclusion, most gas-related minor AEs do not significantly affect the patient's clinical course. However, subcutaneous emphysema and minor non-gas related AEs such as pneumonia, pain, fever, and pleural effusion can prolong the hospital stay, therefore careful observation is required. Efforts will be made to reduce major AEs that significantly prolong hospitalization.

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Key Words

Achalasia; Adverse events; Endoscopic myotomy; Esophageal motility disorder; Hospital stay

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Introduction

Peroral endoscopic myotomy (POEM) is a minimal invasive endoscopic procedure that reduces the lower esophageal sphincter (LES) pressure by creating a myotomy in an area with abnormal muscle relaxation or contraction in the esophagus and/or stomach. POEM was first performed by Inoue et al¹ to treat achalasia and its utility has been expanded to treat various esophageal motility disorders such as distal esophageal spasm (DES) and jackhammer esophagus.

POEM is a relatively safe procedure; however, several major and minor adverse events (AEs) can occur during POEM procedure, including mucosal injury, esophageal perforation, bleeding requiring intervention, subcutaneous emphysema, pneumothorax, pneumomediastinum, pneumoperitoneum, and pleural effusion.²⁻⁴ Most AEs are self-resolved and can be treated conservatively. Mucosal defects can be closed using clips, fibrin glue, over-the-scope clips, or an endoscopic suture device.⁵⁻⁸ Bleeding can be treated by endoscopic hemostasis.⁹ Pneumoperitoneum can usually be managed with needle aspiration, and most cases of pleural effusion and pneumothorax resolve spontaneously, even though severe pleural effusions require thoracotomy with drainage. Mediastinitis, a major complication of POEM but uncommon, often requires surgical drainage. Delayed bleeding is rare and can be treated conservatively in most cases by observation or transfusion.^{10,11}

POEM has consistently showed clinical, manometric, and functional efficacy that is comparable to that of laparoscopic Heller myotomy (LHM), providing a safe and effective alternative to LHM.^{12,13} Early pooled meta-analysis also showed a shorter length of hospital stay for POEM than for LHM.¹⁴ However, the majority of recent studies show that the length of hospital stay for POEM and LHM has been quite similar,^{15,16} although shorter hospital stays for POEM compared to LHM continue to be reported.^{13,17} Various major and minor AEs related to the POEM procedure may be related to the prolongation of hospital stay, however this has not been proven. The discharge time after POEM procedure varies from institution to institution. In particular, as far as we know, there is no consensus on how long hospitalization should be required when an adverse event related to the POEM procedure occurs. From this background, the purpose of this study is to analyze various AEs related to the POEM procedure and to analyze whether these AEs are related to an extended hospital stay.

Materials and Methods

Patient and Methods

This retrospective, multicenter study was performed at 5 centers (Eunpyeong St. Mary's Hospital, Asan Medical Center, Gangnam Severance Hospital, Severance Hospital, and Bucheon Soonchunhyang Hospital) in South Korea. A total of 328 patients with esophageal motility disorder admitted for POEM between August 2012 and February 2020 were included. Demographic data, previous treatment, length of myotomy, procedural time, length of hospital stay, and AEs during or after the POEM procedure were collected and analyzed. The diagnosis of esophageal motility disorders and classification of achalasia type were according to the Chicago classification version 3.0.¹⁸ The underlying disease, drug use, previous treatment history, AEs, and length of hospital stay were investigated from the patients' medical records. Myotomy length, procedure time, and AEs that occurred during the procedure were determined from the POEM procedure records. The study was approved by the institutional review board of each participating Center (IRB No. XC21RCDI0022). In addition, this study has been registered at the Clinical Research Information Service (KCT0005940).

Peroral Endoscopic Myotomy Procedures

All patients were placed under general anesthesia, and CO₂ was used for insufflation. POEM was performed as previously described.¹ After incising the mucosal layer, a submucosal tunnel was created that was extended 2 cm to 3 cm into the gastric cardia. Subsequently, a selective circular muscle myotomy was performed. The length of the myotomy was adjusted according to the achalasia subtype or category of esophageal motility disorders (6 cm to 8 cm above the LES in type I and type II achalasia and calibrated according to manometric extent in type III achalasia or DES or jackhammer esophagus). Lastly, the tunnel opening was closed using endoscopic clips from the anal side to the oral side. POEM was performed by 1 endoscopist (2 centers), 2 endoscopists (2 centers), or 3 endoscopists (1 center). All patients received nothing by mouth for 24 hours after POEM. Intravenous antibiotics and proton-pump inhibitors were administered before the procedure and were continued for a minimum of 3 days after the procedure. Patients underwent esophagography to rule out perforation or leakage between postoperative days 1 and 3.

Adverse Events

Major AEs were defined as conditions that resulted in vital sign instability, intensive care unit stay, hospital readmission, conversion to open surgery, invasive postoperative procedures, blood transfusion, or hospitalization because of functional impairment of the patient. Minor AEs were defined as AEs that required clinical intervention but did not qualify as major AEs. Minor AEs were classified as gas-related (pneumoperitoneum, subcutaneous emphysema, pneumomediastinum, and pneumoretroperitoneum) or non-gas-related (pneumonia, pain, fever, and pleural effusion). Fever was defined as a temperature of 38°C or higher, and post-POEM pain was defined as severe pain requiring administration of narcotic analgesics after the POEM procedure. Other minor AEs, such as diarrhea and pharyngeal laceration during over-tube insertion, were classified as “other” AEs.

Definition of Delayed Discharge

Delayed discharge was defined as discharge being delayed by more than 2 days in the POEM admission protocol set by each institution. Meaningful delayed discharge was defined by excluding delayed discharge cases that were not for medical reasons (patient request, delayed esophagography reservation, etc.).

Statistical Methods

Data are expressed as median (interquartile range, IQR) or mean \pm standard deviation. Categorical variables were analyzed using the chi-square test or Fisher’s exact test. Continuous variables were analyzed using the Mann-Whitney *U* test. The Hodges–Lehmann method was used to estimate median differences with 95% confidence intervals for length of hospital stay outcomes. The significance level of the analysis was set to 5%, and 2-sided tests were conducted. A *P*-value of less than 0.05 was considered significant. All statistical analyses were performed using SPSS version 18.0 (SPSS, Chicago, IL, USA).

Results

Patient Characteristics

A total of 328 patients who underwent POEM were included, 50% of which were women. Patient characteristics are summarized in Table 1. Most of the patients (*n* = 307, 93.6%) were diagnosed with achalasia. Most patients had undergone no prior treatment; however, 19.5% of patients underwent endoscopic

balloon dilatation, 3.7% of patients underwent botox injection, and 1.5% of patients underwent LHM or POEM. The median length of hospital stay after POEM was 5.0 days (IQR 4.0–6.0), and 43 (13.1%) patients had meaningful delayed discharge due to AEs.

Table 1. Patient Characteristics

Variables	N = 328
Age (yr)	50.0 \pm 17.2
Sex (M/F)	164/164
Previous illness	
None	177 (59.8)
Hypertension	48 (16.2)
Diabetes mellitus	23 (7.8)
Others ^a	58 (19.6)
Medication history	
None	249 (84.1)
Anti-platelets	12 (4.1)
Warfarin	2 (0.7)
NOAC	2 (0.7)
Steroids	2 (0.7)
Others	10 (3.4)
Diagnosis	
Type I	121 (36.9)
Type II	138 (42.1)
Type III	48 (14.6)
Distal esophageal spasm	4 (1.2)
Jackhammer esophagus	4 (1.2)
EGJ outflow obstruction	6 (1.8)
Unclassified (manometry fail, etc)	7 (2.1)
Previous treatment	
Naïve	242 (73.8)
Balloon dilatation	64 (19.5)
Botox injection	12 (3.7)
Heller’s myotomy	5 (1.5)
POEM	5 (1.5)
Esophageal myotomy length (cm)	8.5 (6.2–10.0)
Gastric myotomy length (cm)	3.0 (2.0–3.0)
POEM procedure time (min)	70.0 (55.0–87.0)
Length of hospital stay after POEM (days)	5.0 (4.0–6.0)
Meaningful discharge delay due to adverse events	43 (13.1)

^aHeart disease (coronary artery disease, atrial fibrillation, and congestive heart failure), cerebrovascular disease (cerebrovascular accident and Parkinson’s disease), etc.

M, male; F, female; NOAC, novel oral anti-coagulant; EGJ, esophagogastric junction; POEM, peroral endoscopic myotomy.

Data are presented as mean \pm SD, n, n (%), or median (interquartile range [IQR]).

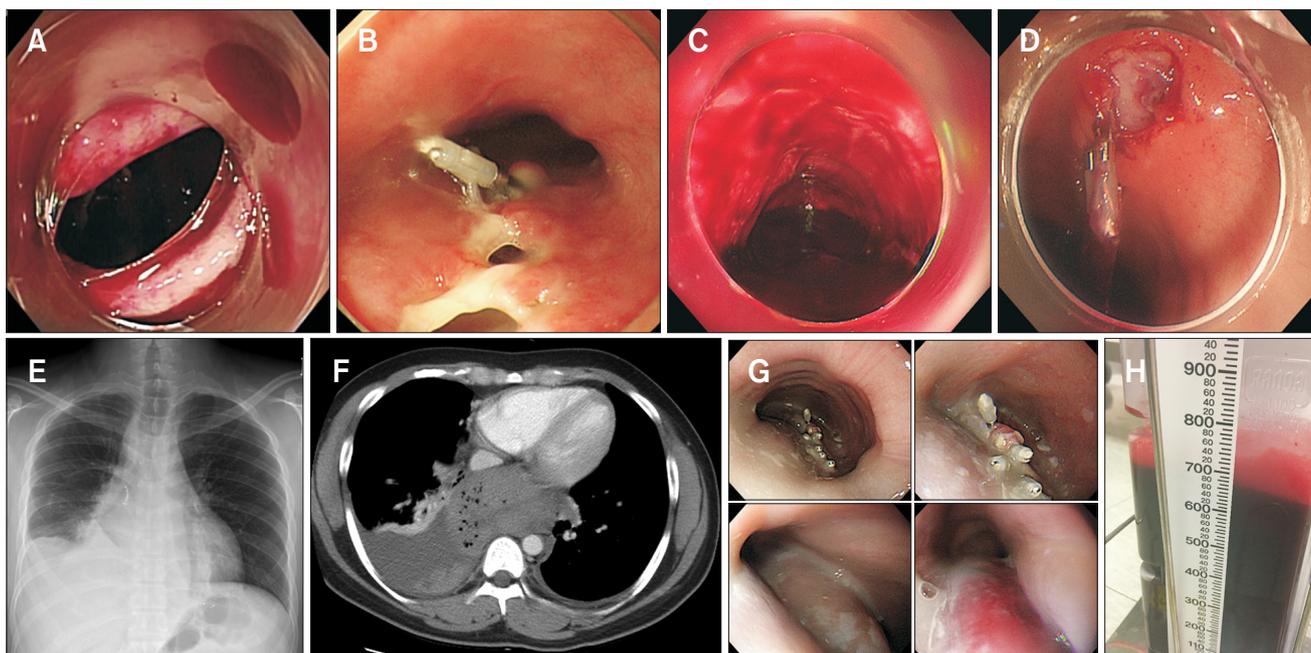


Figure. Major adverse events during or after peroral endoscopic myotomy (POEM) that included mucosal injury (A, B), bleeding (C, D), and hemothorax (E-H). Gastric mucosa (cardia) laceration during POEM (A), clipping site mucosal perforation (B), incision site bleeding (C) with exposed vessel (D), chest X-ray performed due to severe chest pain 2 days after POEM and showing mediastinum widening (E), CT scan showing an esophageal rupture with hemothorax (F), endoscopy revealing large submucosal tunnel hematoma (G), immediately after insertion of the chest tube, 700 mL of blood was drained (H).

Adverse Events of Peroral Endoscopic Myotomy

Of the 328 patients, 207 patients (63.1%) did not have any AEs, but 8 patients (2.4%) had major AEs, and 110 patients (33.4%) had minor AEs. Major AEs included mucosal injury (Figure A and B), bleeding (Figure C and D), and hemothorax (Figure E-H), accounting for 1.5%, 0.6%, and 0.3%, respectively. Among the minor AEs, pneumoperitoneum was the most common gas-related AEs, representing 15.5% followed by subcutaneous emphysema, pneumomediastinum, and pneumoretroperitoneum. Among the AEs not related to gas, pneumonia was the most common at 4.6%, followed by pain, fever, and pleural effusion. Other AEs not directly related to the POEM procedure were diarrhea and pharyngeal laceration (Table 2).

Comparison of Delayed and No Delayed Discharge Groups

Patients with delayed discharge (n = 43) and patients with no delayed discharge (n = 285) were analyzed separately. In the delayed group, the median length of hospital stay was 6 days, and in the non-delayed group, the median length of hospitalization was 4

Table 2. Analysis of the Frequency of Peroral Endoscopic Myotomy Adverse Events

Adverse events	n (%)
None	207 (63.1)
Major	
Mucosal injury	5 (1.5)
Bleeding	2 (0.6)
Hemothorax	1 (0.3)
Minor	
Gas-related	
Pneumoperitoneum	51 (15.5)
Subcutaneous emphysema	16 (4.9)
Pneumomediastinum	6 (1.8)
Pneumoretroperitoneum	2 (0.6)
Not related to gas	
Pneumonia	15 (4.6)
Pain	9 (2.7)
Fever	8 (2.4)
Pleural effusion	3 (0.9)
Others	
Diarrhea	2 (0.6)
Pharyngeal laceration	1 (0.3)
Total	328 (100.0)

Table 3. Comparison of Delayed and No Delayed Discharge Groups

Variables	No delayed discharge (n = 285)	Delayed discharge (n = 43)	P-value
Age (yr)	50.1 ± 17.2	50.0 ± 17.0	0.965
Sex (M/F)	141/144	23/20	0.624
Previous illness			0.302
None	150 (52.6)	27 (62.8)	
HTN	36 (12.6)	12 (27.9)	
DM	20 (7.0)	3 (7.0)	
Others	45 (15.8)	13 (30.2)	
Previous medical history			0.614
None	205 (71.9)	36 (83.7)	
Anti-platelet	9 (3.2)	3 (7.0)	
Warfarin	1 (0.4)	1 (2.3)	
NOAC	2 (0.7)	0 (0.0)	
Steroid	1 (0.4)	1 (2.3)	
Others	8 (2.8)	2 (4.6)	
Diagnosis			0.727
Type I	108 (37.9)	13 (30.2)	
Type II	116 (40.7)	22 (51.2)	
Type III	41 (14.4)	7 (16.3)	
Distal esophageal spasm	4 (1.4)	0 (0.0)	
Jackhammer esophagus	4 (1.4)	0 (0.0)	
EGJ outflow obstruction	5 (1.8)	1 (2.3)	
Unclassified (manometry fail, etc)	7 (2.5)	0 (0.0)	
Previous treatment			0.655
Naïve	206 (73.6)	36 (75.0)	
Balloon dilatation	53 (18.9)	11 (22.9)	
Botox injection	11 (3.9)	1 (2.1)	
Heller's myotomy	5 (1.8)	0 (0.0)	
POEM	5 (1.8)	0 (0.0)	
Esophageal myotomy length (cm)	9.0 (6.0-10.0)	8.0 (7.0-10.0)	0.509
Gastric myotomy length (cm)	3.0 (2.0-3.0)	3.0 (2.0-3.0)	0.739
POEM procedure time (min)	68.0 (54.0-85.3)	70.0 (56.7-99.2)	0.261
Hospital admission after POEM (day)	4.0 (3.0-5.0)	6.0 (5.0-8.0)	< 0.001

M, male; F, female; HTN, hypertension; DM, diabetes mellitus; NOAC, novel oral anticoagulants; EGJ, esophagogastric junction; POEM, peroral endoscopic myotomy.

Data are presented as mean ± SD, n, n (%), or median (interquartile range [IQR]).

days ($P < 0.001$). There was no significant difference was observed between the delayed discharge group and the non-delayed group in patients characteristics, diagnosis, previous treatment, and characteristics related to the POEM procedure (Table 3).

Meaningful Delayed Discharge Compared to No Delayed Discharge Group

Major AEs such as mucosal injury, bleeding, and hemothorax all had meaningful delayed discharge and significantly extended hospital stay compared to the no AEs group. Among the gas-related minor AEs, pneumoperitoneum and subcutaneous emphysema showed significant prolongation of hospital stay compared to the no AEs group. However, except for 4 cases of subcutaneous emphysema, the extended of hospital stay was meaningless. All non-gas-related minor AEs were associated with a significant prolongation of hospital stay compared to that in the no AEs group. Antibiotic-related diarrhea after the procedure and pharynx laceration caused by overtube insertion during the procedure also prolonged the hospital stay, but the difference was not statistically significant (Table 4).

Discussion

In this multicenter retrospective study, we analyzed the basic characteristics of patients, POEM procedure data, factors influencing hospital stay. Major AEs and non-gas-related minor AEs related to POEM significantly prolonged hospital stay. Whereas in minor AEs related to gas, only a few cases had significant prolongation of hospital stay.

The incidence of major AEs of POEM in previous studies ranges from 0.5% to 3.3%.¹⁹⁻²² In a meta-analysis by Akintoye et al,⁴ the incidence of serious AEs was low, with mucosal perforation and clinically meaningful bleeding being reported in only 0.7% and 0.2% of patients, respectively. Mucosal injuries are common AEs during POEM and most of these can be identified and managed during POEM procedure. A history of submucosal fibrosis, previous myotomy (LHM or POEM), mucosal edema, and a long submucosal tunnel more than 13 cm are predisposing factors for mucosal injury.²³ In our study, the incidence of major AEs was not as high at 1.5% for mucosal perforation, 0.6% for bleeding, and 0.3% for hemothorax, and all of these major AEs significantly extended hospital stays.

Insufflation-related events, including subcutaneous emphysema (7.5%), pneumothorax (1.2%), pneumomediastinum (1.1%), and pneumoperitoneum (6.8%), are common during POEM but usually do not convert to clinically significant AEs.² The use of CO₂,

Table 4. Meaningful Delayed Discharge Compared to No Delayed Discharge Group

Adverse events	n (%)	Meaningful delayed discharge (n)	Admission period after POEM (day)	Median differences ^a	P-value ^a
None	207 (63.1)	0	4.0 (3.0-5.0)		
Major					
Nucosal injury	5 (1.5)	4	14.5 (12.4-23.0)	9.0 (7.0-13.0)	0.008
Bleeding	2 (0.6)	2	10.0 (6.0-14.0)	4.5 (1.0-11.0)	0.017
Hemothorax	1 (0.3)	1	13.0 (13.0-13.0)	9.0 ^b	0.072
Minor					
Gas-related					
Pneumoperitoneum	51 (15.5)	0	5.0 (4.0-6.0)	1.0 (0.0-1.0)	< 0.001
Subcutaneous Emphysema	16 (4.9)	4	6.0 (6.0-7.6)	3.0 (2.0-3.0)	< 0.001
Pneumomediastinum	6 (1.8)	0	4.5 (3.0-6.1)	0.0 (-1.0-2.0)	0.479
Pneumoretroperitoneum	2 (0.6)	0	4.0 (3.0-5.0)	1.0 (0.0-2.0)	0.155
Non-gas- related					
Pneumonia	15 (4.6)	11	6.0 (5.0-7.0)	2.0 (1.0-3.0)	< 0.001
Pain	9 (2.7)	9	5.0 (5.0-7.0)	2.0 (1.0-2.0)	0.001
Fever	8 (2.4)	8	6.0 (5.0-6.6)	2.0 (1.0-3.0)	< 0.001
Pleural effusion	3 (0.9)	1	8.0 (5.5-8.8)	4.0 (1.0-5.0)	0.009
Others					
Diarrhea	2 (0.6)	2	5.5 (5.0-6.0)	1.0 (0.0-3.0)	0.068
Pharynx laceration	1 (0.3)	1	7.0 (7.0-7.0)	3.0 ^b	0.080
Total	328 (100.0)	43	5.0 (4.0-6.0)		

^aCompare with no adverse events group, Hodges-Lehmann location shift (95% CI).

^b95% CI cannot be obtained since n = 1.

Data are presented as n (%) or median (interquartile range).

that has a higher diffusion capacity than air, has markedly reduced the occurrence of insufflation-associated AEs, and even if it occurs, CO₂ can be absorbed quickly and the related symptoms may be mild.²⁴ In this study, CO₂ was used in all cases to reduce gas-related AEs and even though pneumoperitoneum and subcutaneous emphysema significantly extended the hospitalization period, the extended of hospital stay was meaningless except for 4 cases of subcutaneous emphysema. These gas-related AEs are not life threatening, but increase patient anxiety owing to abdominal distension and facial and skin swelling, which were the cause of the extended hospitalization period.

Among the non-gas-related AEs, pneumonia, post-POEM pain, fever, and pleural effusion showed significant prolongation of the hospital stay. Pneumonia can be caused by aspiration of the esophageal contents before or during the POEM procedure. Therefore, it is necessary to check posteroanterior chest imaging before the procedure to check for aspiration pneumonia. During the procedure, aspiration may occur during the intubation process after induction of anesthesia. Therefore, it is also important to prevent aspiration by suctioning the aspirate from the esophagus by perform-

ing an endoscopy before the procedure on the day of the POEM procedure.

Pain after POEM is commonly reported; most patients are easily managed with oral analgesics and rarely need long-term narcotics.²⁵ Benias et al²⁶ followed 103 POEM patients and demonstrated that the most common reason for hospitalization was post-POEM pain. However, post-POEM pain was not a predictor of poor outcomes, and many patients in the cohort were not routinely hospitalized. Li et al¹⁹ reported that only 10% of their cohort had severe post-POEM pain that required narcotics. Misra et al²⁵ analyzed the characteristics and medications required for patients with post-POEM pain and found that pain scores decreased significantly within 2 days after POEM, and patients' pain did not require a high dose or long use of opioids. In this study, 9 (2.7%) patients had a meaningful extension of hospital stay due to post-POEM pain. These patients complained of pain to the extent that they needed narcotic analgesics.

The learning curve for POEM has not been well studied. Previous multicenter studies noted that half of the treatment failures were patients from the initial 10 cases at participating centers,

suggesting a learning curve effect on outcomes.²⁷ Other studies have shown that the learning curve of POEM is approximately 15 cases^{28,29} with subsequent cases characterized by a reduction in both procedure times and technical errors. Hungness et al³⁰ reported that POEM performed after 15-case learning curve provided durable symptomatic relief in 94% of patients with non-spastic achalasia and 90% of patients with type 3 achalasia/spastic esophageal motility disorders, with a low rate of complications.³⁰ Patel et al³¹ showed that efficiency was attained after 40 cases and mastery after 60 cases. It is thought that the occurrence of major AEs decreases when the learning curve reaches plateaus due to improved proficiency in the POEM procedure. In this study, AEs were analyzed for 5 practitioners who performed more than 30 POEMs, and major AEs tended to decrease when more than 30 POEMs were performed (data not shown). In addition, minor AEs appear to occur regardless of the skill level of the procedure, however, it is difficult to determine because the number of patients with complications is small. We also analyzed risk factors for AEs, however the underlying disease, medication history, type of motility disorder, previous treatment history, myotomy length, and procedure time that were investigated in this study did not correlate with the occurrence of AEs or prolonged hospital stay. Further large-scale prospective study is needed in the future.

The limitation of this study is that it is a retrospective study, so the POEM patient management protocol of the 5 participating hospitals may be slightly different and the timing of discharge may be slightly different. However, pre- and post-procedure antibiotics, use of proton pump inhibitor, and the use of CO₂ gas in all cases were similarly matched, so the possible bias was considered to be minimized. In particular, we tried to minimize bias by defining and analyzing delayed discharge as “discharge being delayed by more than 2 days in the POEM admission protocol set by each institution.” Despite the limitations of a retrospective study, it is considered to be of clinical significance as it is the first complication analysis study conducted on a large number of patients at multiple centers.

In conclusion, most gas-related minor AEs do not significantly affect the patient's clinical course. However, subcutaneous emphysema and minor non-gas related AEs such as pneumonia, pain, fever, and pleural effusion can prolong the hospital stay, therefore careful observation is required. Efforts will be made to reduce major AEs that significantly prolong hospitalization. This data is expected to be helpful in determining an appropriate hospitalization period in the future.

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Author contributions: Ju Yup Lee analyzed data and prepared the manuscript drafted; Chul-Hyun Lim designed the study, collected data, and supervised the writing of this manuscript; Su Jin Hong, Do Hoon Kim, Hwoon-Yong Jung, Young Hoon Youn, Da Hyun Jung, and Jun Chul Park collected data and supervised the study; and Hee Seok Moon supervised the writing of the manuscript. All authors have read and approved the final draft of this article.

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