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Original Article

Risk factors for adverse outcomes at various phases of endoscopic ultrasound-guided treatment of pancreatic fluid collections: Data from a multi-institutional consortium

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Objectives: No comprehensive study has examined short- and long-term adverse outcomes of endoscopic ultrasound (EUS)-guided treatment of pancreatic fluid collections (PFCs) including walled-off necrosis (WON) and pseudocysts.

Methods: In a multi-institutional cohort of 357 patients receiving EUS-guided treatment of PFCs (228 with WON and 129 with pseudocysts), we examined PFC type-specific risk factors for procedure-related adverse events (AEs), clinical failure, and recurrence. Odds ratios (ORs) and hazard ratios (HRs) with 95% confidence intervals (CIs) were computed using the logistic and Cox regression models, respectively, adjusting for potential confounders.

Results: Adverse events were observed predominantly in WON, and risk factors were WON extension to the pelvis (OR 2.49; 95% CI 1.00–6.19) and endoscopic necrosectomy (OR 5.15; 95% CI 1.61–16.5). Risk factors for clinical failure in WON treatment included higher Charlson Comorbidity Index (OR for ≥3 vs. ≤2, 2.58; 95% CI 1.05–6.35), extension to the pelvis (OR 3.63; 95% CI 1.57–8.43), nonuse of a lumen-apposing metal stent (OR 2.88; 95% CI 1.10–7.54), and percutaneous drainage (OR 3.73; 95% CI 1.27–10.9). Patients with pseudocysts extending to the paracolic gutter and the need for more than two endoscopic/percutaneous procedures had ORs for clinical failure of 5.28 (95% CI 1.10–25.3) and 5.52 (95% CI 1.61–18.9), respectively. Pseudocysts requiring the multigateway approach were associated with a high risk of recurrence (HR 4.00; 95% CI 1.11–11.6).

Conclusion: The adverse outcomes at various phases of EUS-guided PFC treatment may be predictable based on clinical parameters. Further research is warranted to optimize treatment strategies for high-risk patients.

Trial registration: UMIN-Clinical Trials Registry (UMIN000044130).

Key words: cohort study, endoscopy, endosonography, pancreatitis, stent

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INTRODUCTION

PANCREATIC FLUID COLLECTIONS (PFCs) following severe acute pancreatitis have been classified into walled-off necrosis (WON) and a pseudocyst based on the status of the internal contents (necrotic vs. nonnecrotic, respectively).[1] When symptomatic PFCs become unamenable to conservative management, the patients are referred to interventional programs.[2–5] With the increasing popularity of endoscopic ultrasound (EUS)-guided transmural interventions in this setting, PFCs requiring treatment are commonly managed via nonsurgical procedures.[6–12] The emerging treatment modality of lumen-apposing metal stents (LAMS) has accelerated the trend toward the nonsurgical treatment through serving as a transmural port for safe and effective endoscopic necrosectomy (EN) following EUS-guided drainage of WON.[4,7,13]

Despite the reported effectiveness of EUS-guided treatment of PFCs, attention should be paid to adverse outcomes at various treatment phases,[14] including procedure-related adverse events (AEs), treatment failure, and PFC recurrence.[15–23] EUS-guided drainage and subsequent EN have an inherent risk of AEs,[24,25] which may result in fatal outcomes.[26] In addition, a substantial fraction of patients with symptomatic PFCs undergo treatment failure, and thus, require salvage treatment options including surgery.[3,4] From the perspective of long-term patient care, recurrence following successful PFC treatment can raise a burden on the patients, and thus, high-risk patients should be monitored intensively during follow-up.[15,17] Optimizing treatment strategies based on the individual risk profile of respective AEs would help tailor short- and long-term patient management and further improve clinical outcomes of PFC patients treated by EUS-guided treatment.[4,8] However, the relative rarity of PFCs requiring EUS-guided interventions has inhibited a comprehensive investigation of the predictive factors for adverse outcomes in large populations. WON and pseudocysts have been analyzed collectively in a majority of the prior studies, and therefore, differential associations of PFC types with the risks of adverse outcomes remain largely unknown.

To address those clinical unmet needs, we leveraged data derived from a large multi-institutional cohort of patients receiving EUS-guided treatment of PFCs. We examined risk factors for major adverse outcomes during the treatment course: i.e. (i) procedure-related AEs; (ii) clinical failure; and (iii) recurrence of PFC. Utilizing the large sample size, we additionally examined the differences in risk factors for adverse outcomes by PFC types (WON vs. pseudocysts).

METHODS

Study design

THE AIM OF this multicenter retrospective cohort study was to examine incidences of and risk factors for adverse outcomes at various phases of EUS-guided treatment of PFCs. Study end-points were adverse outcomes including procedure-related AEs (including mortality), clinical failure in PFC resolution, and recurrence after PFC resolution (Fig. 1a). We examined specific risk factor profiles for respective PFC types (i.e. WON or pseudocysts). The current study was conducted by the WONDERFUL (WON anD pERipancreatic FlUid coLlection) study group, which consisted of expert endoscopists, gastroenterologists, interventional radiologists, and epidemiologists at 11 high-volume centers in Japan (Appendix S1).[5,27] All authors had access to the study data and reviewed and approved the final article.

Written informed consent for the procedure was obtained from all patients, and consent for the use of the retrospective data for research was obtained on an opt-out basis. The study was designed and implemented according to the guidelines in the Declaration of Helsinki. The study was approved by the Ethics Committee at each center and was registered with UMIN-CTR (registration number UMIN000044130).

Study population

Using a clinical endoscopy database at each center, we identified consecutive patients who had undergone EUS-guided transmural drainage of PFCs from January 2010 through November 2020. We categorized PFCs into WON or pancreatic pseudocysts according to the revised Atlanta classification;[1] in brief, a PFC was considered WON if there was necrosis in pancreatic or peripancreatic tissue; otherwise, it was considered a pseudocyst. The differential diagnosis of pancreatic pseudocysts and WON was determined at each center. We collected the data on imaging studies (computed tomography [CT] and magnetic resonance imaging) before and after EUS-guided PFC drainage in the DICOM (Digital Imaging and Communications in Medicine) format. A single investigator (T.Saito), blinded to other clinical data, conducted a centralized review of the images for the diagnosis of PFC types (pseudocysts vs. WON). Disagreements in the diagnosis were resolved through discussions with each center. We excluded patients receiving nonendoscopic management of PFCs and patients with postoperative fluid collections (Fig. 1b). Utilizing a standardized study database constructed via the Microsoft Access software (Microsoft Japan, Tokyo, Japan),

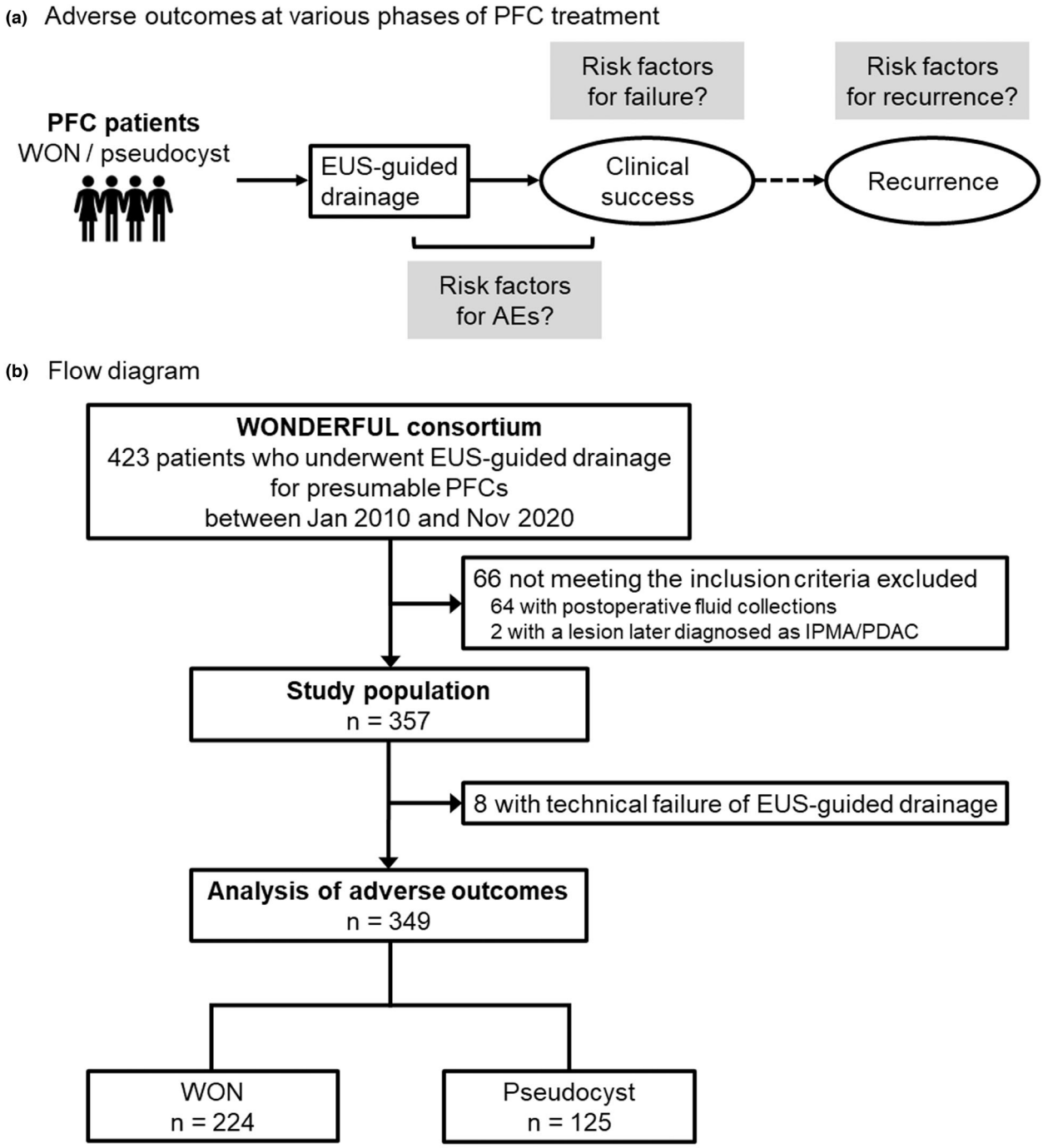

Figure 1 Study outline. (a) Adverse outcomes at various phases of endoscopic ultrasound (EUS)-guided interventions for pancreatic fluid collections (PFCs). (b) Flow diagram of selection of patients undergoing EUS-guided interventions for pancreatic fluid collections. AE, adverse event; IPMA, intraductal papillary mucinous adenoma; PDAC, pancreatic ductal adenocarcinoma; WON, walled-off necrosis.

study physicians reviewed medical charts and collected the following clinical data: patient demographics, radiological features of PFCs, details of all endoscopic and nonendoscopic procedures, AEs, and PFC recurrence during follow-up. The details of the extension status of PFCs are described in Appendix S1.

Study end-points

The technical success of EUS-guided drainage was defined as a successful placement of at least one transmural stent in a targeted PFC. Procedure-related AEs (e.g. bleeding, peritonitis, pancreatitis, stent migration) were graded as mild, moderate, or severe according to the American Society for Gastrointestinal Endoscopy lexicon guidelines for AEs of endoscopic procedures[28] and were classified as early (≤14 days of the index procedure) or late (>14 days).[28] AEs associated with percutaneous procedures were also classified according to the lexicon criteria. Clinical success was defined as reduction in the PFC size to ≤2 cm or removal of all transmural and percutaneous stents/catheters with relief of symptoms associated with PFCs. Time to clinical success was defined as time from the initial EUS-guided drainage to clinical success, the last follow-up, or death, whichever came first. Clinical failure was defined when clinical success was not achieved within 6 months of the initial EUS-guided drainage or salvage surgery was conducted. Recurrence of the PFC was defined as the occurrence of a new PFC or exacerbation of the treated PFC on cross-sectional imaging studies following clinical success.[21] Time to PFC recurrence was defined as time from documentation of clinical success to PFC recurrence, the last follow-up, or death, whichever came first. The patients were followed up until April 30, 2022.

EUS-guided and adjunctive interventions for PFCs

The details of the endoscopic and nonendoscopic interventions are described in Appendix S1.

Statistical analysis

Our primary analyses were assessments of associations of clinical parameters with adverse outcomes of EUS-guided treatment of PFCs in multivariable models. We used the logistic regression model for analyses of AEs and clinical failure (binary outcome variables) to calculate the odds ratios (ORs) with 95% confidence intervals (CIs) and the Cox proportional hazards regression model for analyses of time to PFC recurrence to calculate hazard ratios (HRs) with 95% CIs. Univariable analyses were conducted by entering each of the variables listed in the corresponding tables. Potential risk factors with $P < 0.05$ in the univariable analyses were further examined in a multivariable model to identify independent risk factors with adjustment for potential confounding factors. In analyses of PFC recurrence, patients without PFC recurrence were censored at the timepoint of the last follow-up. Cumulative probabilities of clinical success and PFC recurrence were estimated using the Kaplan–Meier product-limit method and were compared using the log-rank test.

We used the two-sided α level of 0.05 for statistical significance in all analyses. Given the exploratory nature of the current study, we did not take multiple comparisons into account for the statistical significance. The JMP statistical software (version 16.2; SAS International, Cary, NC, USA) was used for all statistical analyses.

RESULTS

Patient characteristics

WITHIN OUR MULTICENTER consortium, we analyzed 357 patients undergoing EUS-guided treatment for PFCs (Fig. 1b and Table 1). Technical success was achieved in 349 (98%) out of 357 patients. Causes of technical failures were failed stent insertion (n = 5), failed guidewire placement (n = 2), and an abandoned procedure due to nonfluid contents in the WON (n = 1).

Types of PFCs and adverse outcomes

In multivariable analyses, WON patients were more likely to undergo AEs and clinical failure and less likely to undergo recurrence following clinical success compared to pseudocyst patients (Table S1). Kaplan–Meier analyses yielded consistent results. Median times to clinical success were 53 days (95% CI 56–69 days) and 23 days (95% CI 26–40 days) in the WON and pseudocyst groups, respectively (Fig. 2a). Median times to recurrence were 189 days (95% CI 75–418 days) and 394 days (95% CI 245–895 days) in the WON and pseudocyst groups, respectively (Fig. 2b).

Risk factors for procedure-related AEs

As our primary analyses, we examined clinical parameters in relation to adverse outcomes of EUS-guided treatment of PFCs. First, we examined risk factors for moderate or higher AEs that occurred predominantly in WON patients (14% vs. 3.2% in the WON and pseudocysts groups,

Table 1 Clinical and treatment characteristics of patients undergoing endoscopic ultrasound (EUS)-guided interventions for pancreatic fluid collections (PFCs), overall or by type of PFC

Characteristic[†]	All cases (*n* = 357)	Type of PFC	
		WON (*n* = 228)	Pseudocyst (*n* = 129)
Patient characteristic			
Age, years	61 (21–87)	63 (21–87)	59 (26–82)
Sex			
Male	279 (78)	171 (75)	108 (84)
Female	78 (22)	57 (25)	21 (16)
CCI			
0	170 (47)	114 (50)	56 (43)
1–2	124 (35)	79 (35)	45 (35)
≥3	63 (18)	35 (15)	28 (22)
ICU stay	42 (12)	39 (17)	3 (2.3)
Preprocedural organ failure			
0	321 (90)	196 (86)	125 (97)
1	13 (3.6)	10 (4.4)	3 (2.3)
≥2	23 (6.4)	22 (9.6)	1 (0.8)
Preprocedural WBC, $\times 10^3/\mu L$	8.3 (1.3–52.8)	9.4 (1.3–36.6)	7.4 (2.6–52.8)
Preprocedural CRP, mg/dL	7.7 (0–38.7)	8.3 (0–38.7)	6.1 (0–36.0)
Preprocedural albumin, mg/dL	2.8 (1.1–4.9)	2.7 (1.1–4.8)	3.1 (1.4–4.9)
Preprocedural amylase, IU/L	119 (10–3245)	105 (10–3245)	151 (11–2085)
PFC characteristic			
Etiology of AP			
Alcohol	98 (27)	62 (27)	36 (28)
Biliary	53 (15)	49 (21)	4 (3.1)
Acute exacerbation of chronic pancreatitis	51 (14)	12 (5.3)	39 (30)
Idiopathic	44 (12)	36 (16)	8 (6.2)
ERCP-related	34 (9.5)	32 (14)	2 (1.6)
Others	77 (22)	37 (16)	40 (31)
Indication of EUS-guided drainage			
Infection	221 (62)	167 (73)	54 (42)
Abdominal pain	70 (20)	35 (15)	35 (27)
Expanding collection	53 (15)	19 (8.3)	34 (26)
Others	13 (3.6)	7 (3.1)	6 (4.7)
Location of PFC			
Body to tail of the pancreas	196 (55)	111 (49)	85 (66)
Head of the pancreas	49 (14)	27 (12)	22 (17)
Entire pancreas	112 (31)	90 (39)	22 (17)
Extension area[‡]			
Right side of the body	126 (35)	107 (47)	19 (15)
Paracolic gutter	96 (27)	85 (37)	11 (8.5)
Pelvic cavity	59 (17)	50 (22)	9 (7)
Multiple collections	165 (46)	125 (55)	40 (31)
Encapsulation of collection			
Fully encapsulated	256 (72)	160 (70)	96 (74)
Partially encapsulated	88 (25)	59 (26)	29 (22)
Unclassifiable	13 (3.6)	9 (3.9)	4 (3.1)
Size of PFC, cm[§]	10.0 (2.4–26.3)	12.6 (3.5–26.3)	7.0 (2.4–20.0)
Ascites	80 (22)	58 (25)	22 (17)
Injury of the main pancreatic duct			
Complete disruption	44 (12)	32 (14)	12 (9.3)
Partial disruption	64 (18)	33 (14)	31 (24)

Table 1 (*Continued*)

Characteristic[†]	All cases (*n* = 357)	Type of PFC	
		WON (*n* = 228)	Pseudocyst (*n* = 129)
Intact	242 (68)	157 (69)	85 (66)
Unknown	7 (2.0)	6 (2.6)	1 (0.8)
Procedure[¶]			
Route of the initial EUS-guided drainage			
Transgastric	324 (93)	210 (94)	114 (91)
Transduodenal	24 (6.9)	14 (6.3)	10 (8.0)
Transesophageal	1 (0.3)	0 (0.0)	1 (0.8)
Stent type			
Plastic stent	260 (74)	153 (68)	107 (86)
Metal stent	89 (26)	71 (32)	18 (14)
LAMS	62	48	14
BFMS	12	11	1
Others	15	12	3
Nasocystic catheter placement	242 (69)	161 (72)	81 (65)
Time from AP onset to the drainage, days	52 (8–810)	54 (10–713)	45 (8–810)
Multigateway approach	49 (14)	40 (18)	9 (7.2)
Percutaneous drainage	31 (8.9)	27 (12)	4 (3.2)
Endoscopic necrosectomy	107 (31)	107 (48)	0 (0.0)
Salvage surgical intervention	18 (5.2)	17 (7.6)	1 (0.8)
Removal of all transmural stents	186 (53)	122 (54)	64 (51)
Duration of transmural stent placement, days	108 (1–1885)	115 (9–1885)	73 (1–1087)
ERCP	90 (26)	48 (21)	42 (34)
Placement of a pancreatic stent	57 (16)	27 (12)	30 (24)
Removal of a pancreatic stent	47 (82)	23 (85)	24 (80)
Duration of pancreatic stent placement, days	126 (9–571)	154 (9–510)	100 (21–571)

[†]Values are expressed as numbers (%) or medians (ranges).
[‡]Multiple extension areas might be assigned for a single case.
[§]Defined as the maximum diameter of the largest collection.
[¶]Eight cases (four each with walled-off necrosis [WON] and pseudocysts) with technical failure were excluded.
AP, acute pancreatitis; BFMS, biflanged metal stent; CCI, Charlson Comorbidity Index; CRP, C-reactive protein; ERCP, endoscopic retrograde cholangiopancreatography; ICU, intensive care unit; LAMS, lumen-apposing metal stent; WBC, white blood cell.

respectively; Table 2). In analyses of WON patients (Tables 3, S2), WON extension to the pelvic cavity and requirement of EN were independent risk factors for moderate to severe AEs with multivariable ORs of 2.49 (95% CI 1.00–6.19) and 5.15 (95% CI 1.61–16.5), respectively. In the total study population, 41 patients underwent bleeding as the most common AE. Hemostasis was achieved in all the cases, although 14 patients required transarterial embolization. Two out of 15 patients with peritonitis were managed via a rescue surgery (one with duodenal perforation due to a migrated transpapillary pancreatic stent and one with procedure-related perforation of the WON wall). The in-hospital mortality rate was higher in WON patients than in pseudocyst patients (9.8% vs. 2.4%, respectively; Table 2).

Risk factors for clinical failure in PFCs

A majority of clinical failures was observed in WON patients, with a rate of 22% compared to 12% in pseudocyst patients (Table 2). In analyses of patients with WON (Tables 3, S3), higher levels of Charlson Comorbidity Index (CCI),[29] WON extension to the pelvic cavity, non-LAMS use, and requirement of percutaneous drainage were risk factors for clinical failure, with multivariable ORs of 2.58 (95% CI 1.05–6.35; for ≥3 vs. ≤2), 3.63 (95% CI 1.57–8.43), 2.88 (95% CI 1.10–7.54), and 3.73 (95% CI 1.27–10.9), respectively. On the other hand, the multigateway approach was associated with low clinical failure rates (multivariable ORs 0.24 [95% CI 0.07–0.86]) (Fig. 3). In analyses of patients with pseudocysts (Tables 3, S3), the

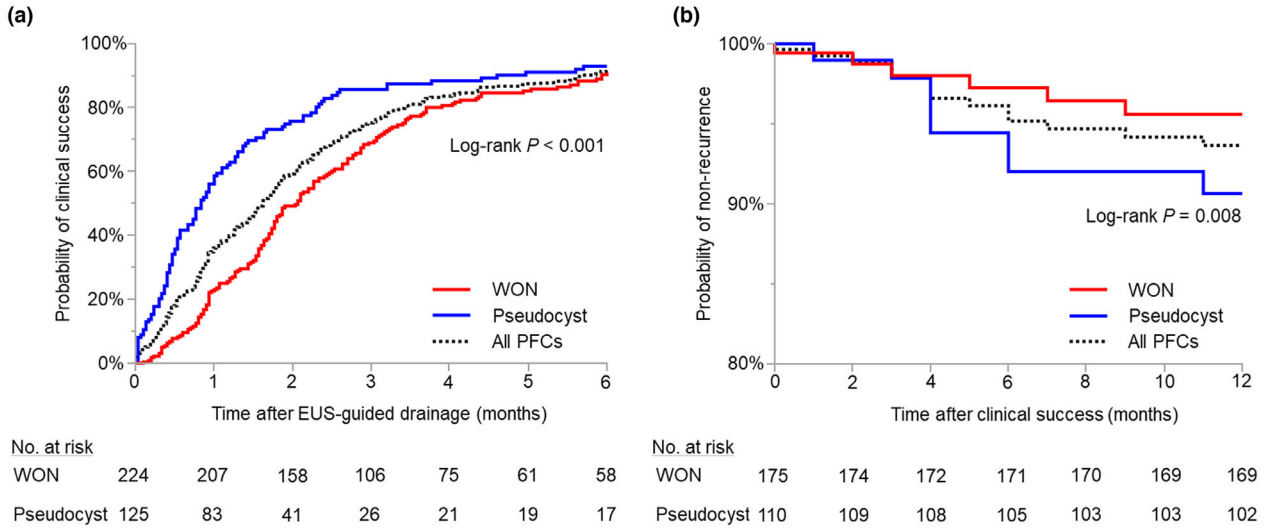

Figure 2 Kaplan–Meier curves of times to (a) clinical success and (b) recurrence following clinical success among patients undergoing endoscopic ultrasound (EUS)-guided interventions for pancreatic fluid collections (PFCs). *P*-values are shown for the log-rank test comparing walled-off necrosis (WON) and pseudocysts.

lesions extending to the paracolic gutter and need for more than two endoscopic/percutaneous procedures were associated with a high risk of clinical failure with multivariable ORs of 5.28 (95% CI 1.10–25.3) and 5.52 (95% CI 1.61–18.9), respectively. The additional treatment modalities following EUS-guided drainage of pseudocysts are summarized in Table S4. Salvage surgery was required for 18 patients with a median duration of 42 days (interquartile range, 30–52 days) following the initial EUS-guided PFC drainage. Uncontrolled infection was the most common indication for the surgery.

Risk factors for recurrence after resolution of PFCs

During the median follow-up time of 25 months (interquartile range, 9–56 months) for censored cases, we documented PFC recurrence in 25 (8.8%) out of 285 patients with clinical success (Table 2). The number of events was small in the WON group, and therefore we examined risk factors for collection recurrence in the pseudocyst group (Tables 3, S5). The patients requiring the multigateway approach had a high risk of recurrence, with multivariable HRs of 4.00 (95% CI 1.11–11.6). The multigateway approach was more likely to be taken for a large pseudocyst, multiple collections, and pseudocysts extending to the entire pancreas, the paracolic gutter, and/or the pelvic cavity (Table S6).

DISCUSSION

IN THIS LARGE multi-institutional series of patients receiving EUS-guided treatment of PFCs, we documented differential repertoires of adverse outcomes at three treatment phases by distinctive types of PFCs (WON vs. pseudocysts). Utilizing the detailed data on clinical features, interventions, and follow-up, we successfully identified clinically relevant parameters associated with the short- and long-term adverse outcomes. Our data may help stratify PFC patients in terms of risks of various adverse outcomes, and thereby, inform treatment strategies as well as post-treatment surveillance programs.

To date, few studies have investigated the predictive factors for adverse outcomes along the time sequence of EUS-guided treatment of PFCs (Table 4).[16–19,24,30–35] In the current study, clinically significant AEs were observed mostly in patients with WON rather than in patients with pseudocysts, and bleeding was the most common type of AE. WON lesions extending to the pelvic cavity and requiring repeated EN procedures supposedly predispose the patients to the risk of bleeding events. In line with these findings in this study, several procedural factors have been shown to be risk factors for bleeding (e.g. the number of endoscopic procedures[17] and tract dilation[25]). In addition, studies suggest that anatomical factors may also be associated with the bleeding risk (e.g. vascular formation on the internal wall of the PFC[16,25]). Contrast-enhanced CT

Table 2 Short- and long-term clinical outcomes of patients undergoing endoscopic ultrasound-guided interventions for pancreatic fluid collections (PFCs), overall or by type of PFC

Outcome[†]	All cases (n = 349)	Type of PFC		P-value
		WON (n = 224)	Pseudocyst (n = 125)	
Adverse event[‡]				
Total	62 (18)	56 (25)	6 (4.8)	<0.001
Bleeding	41 (12)	38 (17)	3 (2.4)	–
IVR embolization for bleeding	14 (4.0)	11 (4.9)	3 (2.4)	–
Peritonitis	15 (4.3)	14 (6.3)	1 (0.8)	–
Stent migration	10 (2.9)	10 (4.5)	0 (0.0)	–
Respiratory complication	2 (0.6)	2 (0.9)	0 (0.0)	–
Pancreatitis	1 (0.3)	1 (0.4)	0 (0.0)	–
Others	3 (0.9)	1 (0.4)	2 (1.6%)	–
Severity[§]				0.880
Mild	31 (8.9)	29 (13)	2 (1.6)	–
Moderate	30 (8.6)	27 (12)	3 (2.4)	–
Severe	9 (2.6)	8 (3.6)	1 (0.8)	–
Fatal	2 (0.6)	2 (0.9)	0 (0.0)	–
Timing of adverse events				0.980
During procedure	49 (14)	45 (20)	4 (3.2)	–
Early (≤14 days)	13 (3.7)	12 (5.4)	1 (0.8)	–
Late (>14 days)	10 (2.9)	9 (4.0)	1 (0.8%)	–
Short-term outcome				
Clinical success	285 (82%)	175 (78%)	110 (88%)	0.014
Time to clinical success, days	41 (1–182)	53 (3–182)	23 (1–171)	<0.001
No. of procedures until clinical success	2 (1–22)	4 (1–22)	1 (1–8)	<0.001
No. of EN sessions until clinical success	0 (0–19)	1 (0–19)	–	<0.001
Total procedure time until clinical success, min	101 (10–5359)	190 (10–5359)	55 (10–431)	<0.001
Length of hospital stay, days	36 (5–851)	52 (8–851)	24 (5–110)	<0.001
Mortality	25 (7.2%)	22 (9.8%)	3 (2.4%)	0.005
Long-term outcome[¶]				
Follow-up, months	25 (1–140)	25 (1–135)	26 (1–140)	0.680
PFC recurrence after clinical success	25 (8.8%)	8 (4.6%)	17 (15)	0.002
Time to recurrence, days	251 (17–1884)	189 (17–560)	394 (43–1884)	0.270

[†]Values are expressed as numbers (%) or medians (ranges). Categorical variables were compared using the chi-squared test or Fisher's exact test, as appropriate, and continuous variables were compared using the Wilcoxon rank-sum test or Student's t test, as appropriate.
[‡]Multiple adverse events might be assigned for a single case.
[§]Graded according to the American Society for Gastrointestinal Endoscopy lexicon guidelines.
[¶]Sixty-four cases (49 with WON and 15 with pseudocysts) with clinical failure were excluded.
EN, endoscopic necrosectomy; IVR, interventional radiology; WON, walled-off necrosis.

can provide valuable information on the vascular status and the possibility of pseudoaneurysms, and therefore, prudent examinations of this imaging modality are important. Our large sample size allowed us to investigate the PFC type-specific profile of risk factors for clinical treatment failure both in WON and pseudocysts. WON extending to the pelvic cavity[12] and pseudocysts extending to the paracolic gutter[23,36] were associated with clinical treatment failure. In patients with WON, the CCI was inversely associated with the clinical success rate, suggesting the clinical relevance of patients' systemic conditions and organ functions to successful completion of endoscopic treatment of WON. Interestingly, the multigateway approach for WON, which might be used in difficult-to-treat lesions,[37] was associated with a low rate of clinical failure, supporting the importance of determining drainage routes in a moment-to-moment manner. Pseudocysts, by definition, consist of liquid components and are expected to shrink by EUS-guided drainage alone. Our findings suggest that ineffective drainage due to the pseudocyst massiveness characterized by extension to the paracolic gutter may impair drainage efficiency, and the need for multiple procedures may be

Table 3 Multivariable analyses of risk factors for adverse outcomes at various phases of endoscopic ultrasound (EUS)-guided interventions for pancreatic fluid collections (PFCs)

	No. of cases	No. of events (%)	Multivariable OR (95% CI)[§]	*P*-value
Risk factor for AEs[†] (WON)				
Preprocedural organ failure				
≤1	202	23 (11)	1.00 (referent)	–
≥2	22	9 (41)	2.39 (0.78–7.32)	0.130
Location of WON				
Body to tail of the pancreas	108	10 (9.3)	1.00 (referent)	–
Head of the pancreas	27	7 (26)	2.22 (0.60–8.22)	0.190
Entire pancreas	89	15 (17)	1.05 (0.35–3.12)	0.480
Extension to the right side of the body				
Absent	118	10 (8.5)	1.00 (referent)	–
Present	106	22 (21)	1.66 (0.58–4.78)	0.350
Extension to the pelvic cavity				
Absent	175	19 (11)	1.00 (referent)	–
Present	49	13 (27)	2.49 (1.00–6.19)	0.049
Endoscopic necrosectomy				
No	117	6 (5.1)	1.00 (referent)	–
Yes	107	26 (24)	5.15 (1.61–16.5)	0.006
No. of endoscopic/percutaneous procedures				
≤2	76	4 (5.3)	1.00 (referent)	–
≥3	148	28 (19)	1.03 (0.26–4.11)	0.970
Risk factor for clinical failure (WON)				
CCI				
≤2	190	37 (19)	1.00 (referent)	–
≥3	34	12 (35)	2.58 (1.05–6.35)	0.039
Extension to the pelvic cavity				
Absent	175	29 (17)	1.00 (referent)	–
Present	49	20 (41)	3.63 (1.57–8.43)	0.003
Full encapsulation				
No	66	21 (32)	1.00 (referent)	–
Yes	158	28 (18)	0.50 (0.23–1.08)	0.077
Stent type				
LAMS	59	7 (12)	1.00 (referent)	–
Non-LAMS	165	42 (25)	2.88 (1.10–7.54)	0.031
Multigateway approach				
No	184	45 (24)	1.00 (referent)	–
Yes	40	4 (10)	0.24 (0.07–0.86)	0.028
Percutaneous drainage				
No	197	37 (19)	1.00 (referent)	–
Yes	27	12 (44)	3.73 (1.27–10.9)	0.016
Endoscopic necrosectomy				
No	117	32 (27)	1.00 (referent)	–
Yes	107	17 (16)	0.58 (0.27–1.24)	0.160
Risk factor for clinical failure (pseudocyst)				
Location of pseudocyst				
Pancreatic body/tail	82	6 (7.3)	1.00 (referent)	–
Pancreatic head	21	3 (14)	1.78 (0.35–9.08)	0.900
Entire pancreas	22	6 (27)	3.84 (0.98–15.0)	0.120
Extension to the paracolic gutter				
Absent	114	11 (9.6)	1.00 (referent)	–
Present	11	4 (36)	5.28 (1.10–25.3)	0.038

Table 3 (*Continued*)

	No. of cases	No. of events (%)	Multivariable OR (95% CI)[§]	*P*-value
No. of endoscopic/percutaneous procedures				
≤2	99	7 (7.1)	1.00 (referent)	–
≥3	26	8 (31)	5.52 (1.61–18.9)	0.007
	No. of cases	No. of events (%)	Multivariable HR (95% CI)[¶]	*P*-value
Risk factor for recurrence (pseudocyst)[‡]				
Multigateway approach				
No	104	13 (13)	1.00 (referent)	–
Yes	6	4 (67)	4.00 (1.11–11.6)	0.036
Pancreatic stent placement				
No	82	8 (9.8)	1.00 (referent)	–
Yes	28	9 (32)	2.34 (0.87–6.32)	0.089

[†]Moderate or severe adverse events (AEs) were analyzed as an outcome variable.
[‡]Fifteen cases with clinical failure were excluded.
[§]A univariable analysis was conducted by entering each of the following variables: age (<70 vs. ≥70 years), sex (male vs. female), Charlson Comorbidity Index (CCI) (≤2 vs. ≥3), preprocedural organ failure (≤1 vs. ≥2 organs), preprocedural white blood cells (WBC) (<10,000 vs. ≥10,000/μL), preprocedural C-reactive protein (CRP) (<10 vs. ≥10 mg/dL), etiology of acute pancreatitis (AP) (alcohol vs. nonalcohol), indication of EUS-guided drainage (infection vs. abdominal pain vs. expanding collection vs. others), location of PFC (the entire pancreas vs. head of the pancreas vs. body to tail of the pancreas), PFC extension to the right side of the body (absent vs. present), PFC extension to the paracolic gutter (absent vs. present), PFC extension to the pelvic cavity (absent vs. present), multiple collections (no vs. yes), fully encapsulation of PFC (no vs. yes), size of PFC (<15 vs. ≥15 cm), an injury of the main pancreatic duct (no vs. yes [complete or partial disruption]), route of the initial EUS-guided drainage (transgastric vs. transduodenal vs. transesophageal), stent type (lumen-apposing metal stent [LAMS] vs. non-LAMS), time from AP onset to the drainage (<4 vs. ≥4 weeks), multigateway approach (no vs. yes), percutaneous drainage (no vs. yes), endoscopic necrosectomy (no vs. yes), and number of procedures (≤2 vs. ≥3) (data shown in Tables S2 and S3). The variables with $P < 0.05$ in the univariable analyses were entered in multivariable analyses.
[¶]A univariable analysis was conducted by entering each of the following variables: age (<70 vs. ≥70 years), sex (male vs. female), CCI (≤2 vs. ≥3), preprocedural organ failure (≤1 vs. ≥2 organs), preprocedural WBC (<10,000 vs. ≥10,000/μL), preprocedural CRP (<10 vs. ≥10 mg/dL), etiology of AP (alcohol vs. nonalcohol), indication of EUS-guided drainage (infection vs. abdominal pain vs. expanding collection vs. others), location of PFC (the entire pancreas vs. head of the pancreas vs. body to tail of the pancreas), PFC extension to the right side of the body (absent vs. present), PFC extension to the paracolic gutter (absent vs. present), PFC extension to the pelvic cavity (absent vs. present), multiple collections (no vs. yes), fully encapsulation of PFC (no vs. yes), size of PFC (<15 vs. ≥15 cm), an injury of the main pancreatic duct (no vs. yes [complete or partial disruption]), route of the initial EUS-guided drainage (transgastric vs. transduodenal vs. transesophageal), stent type (LAMS vs. non-LAMS), time from AP onset to the drainage (<4 vs. ≥4 weeks), multigateway approach (no vs. yes), percutaneous drainage (no vs. yes), removal of all transmural stents (no vs. yes), pancreatic stent placement (no vs. yes), and number of procedures (≤2 vs. ≥3) (data shown in Table S4). The variables with $P < 0.05$ in the univariable analyses were entered in multivariable analyses.
CI, confidence interval; HR, hazard ratio; OR, odds ratio.

correlated with treatment failure. Taken together, our findings support that it is crucial to consider intensive intervention strategies for the successful treatment of PFCs while minimizing the risk of bleeding.

No large studies have examined risk factors for posttreatment PFC recurrence (Table 4). The recurrence rate was higher in pseudocysts (15%) than in WON (4.6%). Acute exacerbation of chronic pancreatitis was the most common etiology of pseudocysts. The underlying pancreatic duct stricture and/or stones, if untreated, can cause recurrence after the initial clinical success. Furthermore, the abstinence from alcohol is often difficult in cases with alcoholic chronic pancreatitis, which may also contribute recurrent attacks of pancreatitis and lead to recurrent PFC. The current study implicated that patients with pseudocysts treated by the multigateway approach might be at 4-fold higher risk of recurrence following clinical treatment success. This subgroup of patients with pseudocysts were more likely to have not only multiple collections, but also a collection extending across a large area. There is a possibility that the severity of the primary pancreatitis may be positively correlated with the risk of recurrence of pancreatitis or pancreatic ductal disruption.[4] Pseudocysts, if not managed properly, would result in substantial comorbidities, including, but not limited to, pancreatic ascites and/or pleural effusions. Evidence suggests that patients with disconnected pancreatic duct syndrome may be at high risk of PFC recurrence.[21,27,38] Prolonged placement of a transluminal plastic stent may

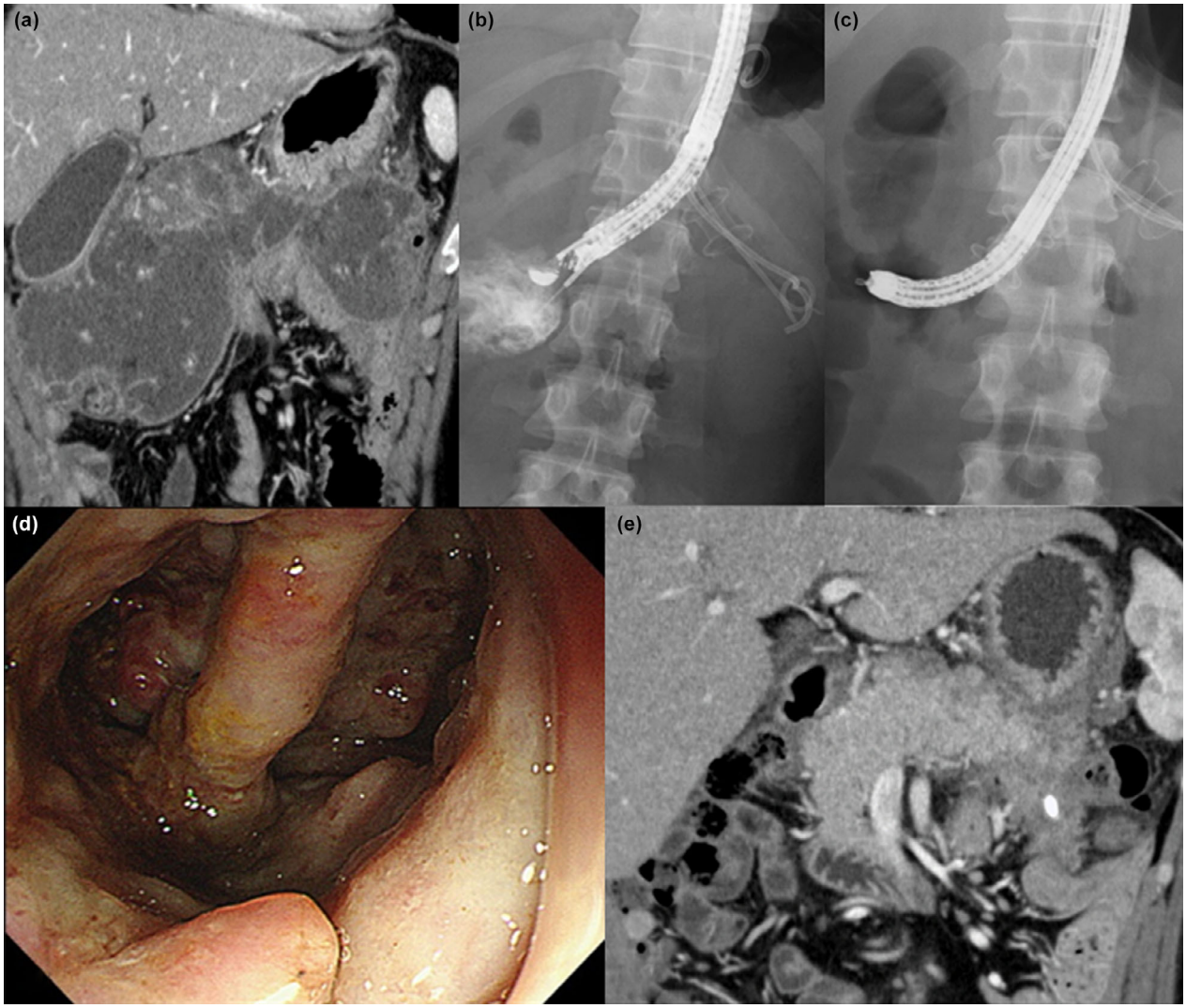

Figure 3 A large walled-off necrosis (WON) with clinical success achieved after multiple endoscopic sessions. (a) Contrast-enhanced computed tomography (CT) demonstrated a large WON extending both to the head and tail of pancreas. (b) Second lumen-apposing metal stent (LAMS) was deployed as the multigateway approach. (c) Endoscopic necrosectomy was performed through each LAMS. (d) After several sessions of endoscopic necrosectomy, necrotic tissue was completely removed. (e) Contrast-enhanced CT confirmed clinical success.

mitigate the risk of recurrence in this setting.[15,20] Therefore, our data suggest that patients with massive pseudocysts treated by the multigateway approach should be screened for the pancreatic ductal disruption/disconnection to consider the indication of long-term placement of a plastic stent and be monitored prudently at the outpatient clinic.

Our study has notable strengths, including the use of the large multicenter cohort highly annotated with clinical, treatment, and follow-up data. Our large sample size allowed us to examine risk factors for adverse outcomes specifically for PFC subgroups (WON vs. pseudocysts). Nonetheless, limitations should also be acknowledged. There might have been interinstitutional heterogeneity in the selection of adjunctive treatment options and rescue surgical interventions, as well as the interval and method of patient follow-up at the outpatient clinic. Therefore, our findings should be validated in independent cohorts. Nonetheless, the pooled analysis of data based on various treatment strategies in different settings ensured the generalizability of our findings.

Table 4 Summary of major studies reporting adverse outcomes among patients undergoing endoscopic ultrasound-guided interventions for pancreatic fluid collections (PFCs) (studies including ≥200 PFC patients with a study period starting in 2010 or later)

Author	Country	Study period	Type of PFC, *n*			Stent type	Adverse events		Clinical failure		Recurrence of PFC	
			Total	WON	PC		%	Risk factors	%	Risk factors	%	Risk factors
Sharaiha *et al.*[18]	USA	2010–14	230	–	230	SEMS, PS	24.0	PS (vs. SEMS) No. of sessions	10.0	NA	2.4	NA
Siddiqui *et al.*[19]	USA	2010–15	313	313	–	LAMS, SEMS, PS	28.0	PS/LAMS (vs. SEMS)	10.0	PS (vs. SEMS)	0	NA
Brimhall *et al.*[24]	USA	2011–16	249	197	52	LAMS, PS	21.0	NA	9.2	NA	5.2	NA
Messallam *et al.*[30]	USA	2011–18	204	204	–	LAMS	13.0	NA	19.0	Non-use of H_2O_2	NA	NA
Yang *et al.*[17]	Canada, Germany, Italy, USA	2012–16	205	–	205	LAMS, PS	14.0	Younger age No. of sessions	9.3	Long procedure time Pancreatic stent placement	15.0	NA
Yan *et al.*[31]	USA	2012–16	271	271	–	LAMS	22.0	NA	13.0	No or elective EN	2.5	NA
Lakhtakia *et al.*[32]	India	2013–15	205	205	–	BFMS	3.9	NA	3.5	NA	2.5	NA
Fugazza *et al.*[33]	Italy, 8 other countries	2013–17	304	151	153	LAMS	24.0	WON Tract dilation	10.0	NA	8.9	NA
Parsa *et al.*[34]	Germany, Italy, Spain, UK, USA	2014–18	306	306	–	LAMS	17.0	NA	8.2	NA	8.2	NA
Khan *et al.*[35]	Australia, New Zealand, Singapore, Thailand	2016–19	202[†]	81	107	LAMS	25.0	NA	11.0	NA	9.2	NA
Facciorusso *et al.*[16]	Italy	2016–20	516	269	247	LAMS	15.0	Pancreatic duct injury Abnormal vessels Low hospital volume	8.3	NA	7.4	NA
Current study	Japan	2010–20	357	228	129	LAMS, BFMS, SEMS, PS	18.0	(WON) Extension to the pelvis EN	18.0	(WON) High CCI Extension to the pelvis Non-LAMS (vs. LAMS) No conduct of the multi-gateway approach Percutaneous drainage (PC) Extension to the paracolic gutter Need for three or more procedures	8.8	(PC) Multigateway approach

[†]The remaining 14 patients received endoscopic ultrasound-guided drainage for postoperative PFCs.
BFMS, biflanged metal stent; CCI, Charlson Comorbidity Index; EN, endoscopic necrosectomy; H_2O_2, hydrogen peroxide; LAMS, lumen-apposing metal stent; NA, not available; PC, pseudocyst; PS, plastic stent; SEMS, self-expandable metal stent; WON, walled-off necrosis.

In summary, we demonstrated distinctive risk factor profiles of patients with WON and pseudocysts for adverse outcomes occurring along the endoscopy-based treatment sequence. We identified not only risk factors for adverse outcomes (e.g. PFC extension to the pelvic cavity for AEs), but also favorable parameters and strategies associated with better clinical outcomes. Prospective studies are warranted to elucidate the beneficial effects of modified treatment protocols based on the individual risk factor profile on clinical outcomes of patients referred to EUS-guided treatment of PFCs.

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CONFLICT OF INTEREST

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DATA TRANSPARENCY STATEMENT

THE DEIDENTIFIED DATA and analytic methods used in the current study will be available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

ADDITIONAL SUPPORTING INFORMATION may be found in the online version of this article at the publisher's web site.

Table S1 Types of pancreatic fluid collections (PFCs) and adverse outcomes among patients undergoing endoscopic ultrasound-guided interventions for PFCs.

Table S2 Univariable analyses of predictive factors for adverse events of endoscopic ultrasound-guided interventions for walled-off necrosis.

Table S3 Univariable analyses of predictive factors for clinical failure of endoscopic ultrasound-guided interventions for pancreatic fluid collections.

Table S4 Treatment details in patients undergoing more than two interventions for pancreatic pseudocysts.

Table S5 Univariable analyses of predictive factors for recurrence following clinical success of endoscopic ultrasound-guided interventions for pancreatic pseudocysts.

Table S6 Clinical characteristics of patients undergoing endoscopic ultrasound-guided interventions for pseudocysts, by requirement of the multigateway approach.

Appendix S1 Participating centers, extension status of pancreatic fluid collections (PFCs), and endoscopic ultrasound (EUS)-guided and adjunctive interventions for PFCs.