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Common Practice of Percutaneous Drainage in Necrotising Pancreatitis—A Multicentre Retrospective Study (DRACULA)

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Keywords: drainage | flushing | necrosis | pancreatitis

ABSTRACT

Background and Aims: Acute necrotising pancreatitis carries high mortality, especially if infected necrosis occurs. While percutaneous drainage may be required when internal drainage is not feasible, reliable guidelines for managing percutaneous drains are lacking. This study aimed to assess the common practice of percutaneous drainage therapy for infected pancreatic necrosis.

Methods: This retrospective study among 29 tertiary care centres included all patients hospitalised for necrotising acute pancreatitis from 01/2016 until 12/2022 with at least one percutaneous drain. The length of hospital stay was the primary endpoint, with mortality as the secondary endpoint. Between-group comparisons were conducted using the ratio of restricted mean survival time (RMST) after adjusting for confounders.

Results: 585 patients (67% male) from 29 tertiary care centres in 15 countries in Europe, Canada and Bolivia were included in the analysis. Length of hospitalisation or mortality did not differ between the flushed (n = 398) and non-flushed groups (RMST ratio 1.04, p-value = 0.42 and RMST ratio 1.05, p-value = 0.1 respectively). Mortality was significantly lower in those patients who received a combination of percutaneous and internal drains (dual-modality drainage, n = 243) as compared to those who

Abbreviations: ANC, acute necrotic collection; DMD, dual-modality drainage; DRACULA, drainage and flushing therapy in necrotising pancreatitis; eCRF, electronic case report form; ICU, intensive care unit; IMC, intermediate care unit; RAC, revised Atlanta classification; RMST, Restricted Mean Survival Time; WOPN, walled-off pancreatic necrosis.

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received percutaneous drains only (RMST ratio 1.05, p-value = 0.01). Flushing with antibiotics as compared to saline was not associated with shorter length of hospital stay or lower mortality (RMST ratio 0.98, p-value = 0.78 and 0.97, p-value = 0.48 respectively).

Conclusions: This study reveals notable differences in therapeutic concepts and flushing management for percutaneous drains. While flushing itself was not associated with a shorter length of hospitalisation or lower in-hospital mortality, a lower mortality was observed when internal and percutaneous drainage were used in combination.

Clinical Trial Registration: The study was prospectively registered in the German Clinical Trials Register (Deutsches Register Klinischer Studien, DRKS) under the registration number DRKS00032231.

1 | Introduction

The development of necrotic collections is a serious complication of pancreatitis as it is associated with significant morbidity and mortality [1, 2]. While acute pancreatitis is among the most common non-malignant causes for hospital admission in gastroenterology [1, 3], only 5%–10% of patients progress to necrotising pancreatitis [1, 2, 4]. Although a substantial proportion of pancreatic necrotic collections regress spontaneously, infection can lead to a septic course, organ failure and death, driving mortality as high as 35% [5]. While early organ failure and death in acute pancreatitis can occur independently of infection, infected necrosis represents a particularly challenging complication that considerably impacts outcome [2, 5, 6]. Therefore, in addition to antibiotic therapy, interventional drainage and even necrosectomy are often required. Although these interventions involved surgical necrosectomies in the past, the superiority of minimally invasive approaches has been demonstrated in recent years [7]. Whenever feasible, endoscopic transmural therapy should be attempted [8, 9]. However, percutaneous drainage can also be chosen, either alone or in combination with endoscopic drainage [10]. It is hypothesised that flushing of these catheters resolves necrotic collections and prevents drain occlusion and is recommended in current guidelines [3, 10, 11]. Data on the optimal management of percutaneous drains is currently lacking. While neither the German [3] nor American [10] guidelines offer specific recommendations, only the ESGE guideline provides recommendations [11] on the handling of percutaneous drains and whether and which flushing regimen should be chosen, albeit missing reliable base data. Therefore, the best approach for patients requiring percutaneous drainage remains unclear. In this multicentre, retrospective study, the current practice of percutaneous drainage therapy of necrotising pancreatitis was systematically investigated for the first time.

2 | Material and Methods

2.1 | Study Design

DRACULA is a multicentre retrospective study aiming to investigate the current practice of percutaneous drainage therapy for necrotising pancreatitis, focusing on the number and type of percutaneous drains, flushing regimens, combination with internal drains, and how this influences length of hospital stay and mortality. The study included all adult patients (≥ 18 years old) with necrotising acute pancreatitis who received at least one percutaneous drainage for the treatment of acute necrotic collection (ANC) or walled-off pancreatic necrosis (WOPN) as defined by the revised Atlanta Classification [4] at the participating high-volume tertiary centres between January 2016 and December 2022. Patients were identified from hospital discharge records (Figure 1A).

Acute pancreatitis was diagnosed and classified according to the Revised Atlanta Classification criteria [4]. The location of necrotic collections was classified into peripancreatic, paracolic, pelvic, and other locations (Figure 1B). The diameter of drains was recorded on a French Catheter Scale (Fr). All variables are detailed in the appendix.

In order to allow comparability, different groups were defined based on the type of drainage. Since all patients had at least one percutaneous drain, we grouped those patients with exclusively percutaneous drains into one group. If the patient had received at least one internal drain as well, they were assigned to the dual-modality drainage group (DMD). Flushing frequency was categorised into once or twice daily, three or four times daily and continuous flushing. Patients who received other flushing regimens were excluded (n = 38). Lumina of external drains were divided into drains < 20 Fr and ≥ 20 Fr [12]. Patients were categorised into either group if they only received drains of this size and into the combined group if they had received both drains < 20 Fr and ≥ 20 Fr.

The primary outcome was the length of hospital stay, and the secondary outcome was all-cause mortality, both restricted to events occurring within 90 days from the initial diagnosis of pancreatitis. Patients who died within this period were right-censored on day 91.

Data collection was conducted using the open-source electronic data capture (EDC) software LCARS-M2 [13]. Central analysis was performed on de-identified data.

2.2 | Statistics

We summarised continuous variables as means with standard deviations or medians with interquartile ranges as appropriate using the t-test or the Mann-Whitney U test for comparison. Categorical variables were reported as absolute numbers and frequencies and compared using the Chi-square test or Fisher's exact test. In survival analysis, confounding factors were determined a priori based on clinical expertise, including age, sex, aetiology, disease severity, intensive care unit (ICU) stay, year of hospitalisation, case volume of study site, number of necrotic

Key Summary

- Summarise the established knowledge on this subject
  - Percutaneous drainage as well as endoscopic drainage can be used for the treatment of necrotic collections in pancreatitis
  - Management of percutaneous drains, including flushing and combination with endoscopic drains, is unclear
- What are the significant and/or new findings of this study?
  - Very heterogeneous therapeutic regimens across participating pancreas centres
  - No differences in hospitalisation or mortality for flushing versus no flushing
  - No differences in hospitalisation or mortality for flushing with antibiotics versus saline
  - Lower mortality in patients with dual-modality drainage

collections, antibiotic use, maximum size of necrotic collection, and multiple locations of necrotic collections. When comparing between groups, we applied inverse probability treatment weighting (IPTW) to address confounding, with weights estimated from the propensity score model. Stürmer trimming [14], with 2.fifth/97.fifth percentile cut points, was implemented to reduce estimate bias, and standardised mean differences were examined pre- and post-IPTW adjustment to evaluate baseline balance (Figures S1–S7) [15]. The weighted Kaplan-Meier curves were used to display the cumulative probability of hospital stay and mortality over a 90-day period. To detect proportional hazards assumption violations, we used the ratio of restricted mean survival time (RMST) [16], which compares the average length of hospital stay or survival between two groups from time 0 to the prespecified day 90. The standard error of RMST was estimated using 2500 bootstrap replications. Missing values were handled with multiple imputations using 20 imputations, and results from survival analysis were pooled across imputations [17]. We used predictive mean matching for continuous variables, logistic regression for binary variables, and the random forest method for categorical variables, incorporating clinical variables of interest, the confounders listed above, and the outcome variables. A two-sided p-value of 0.05 was used. Due to the exploratory nature of this study, the Šidák correction was applied only for comparisons across multiple groups [18]. All statistical analyses were conducted using R (version 4.4.1). The R packages that were used are listed in the appendix.

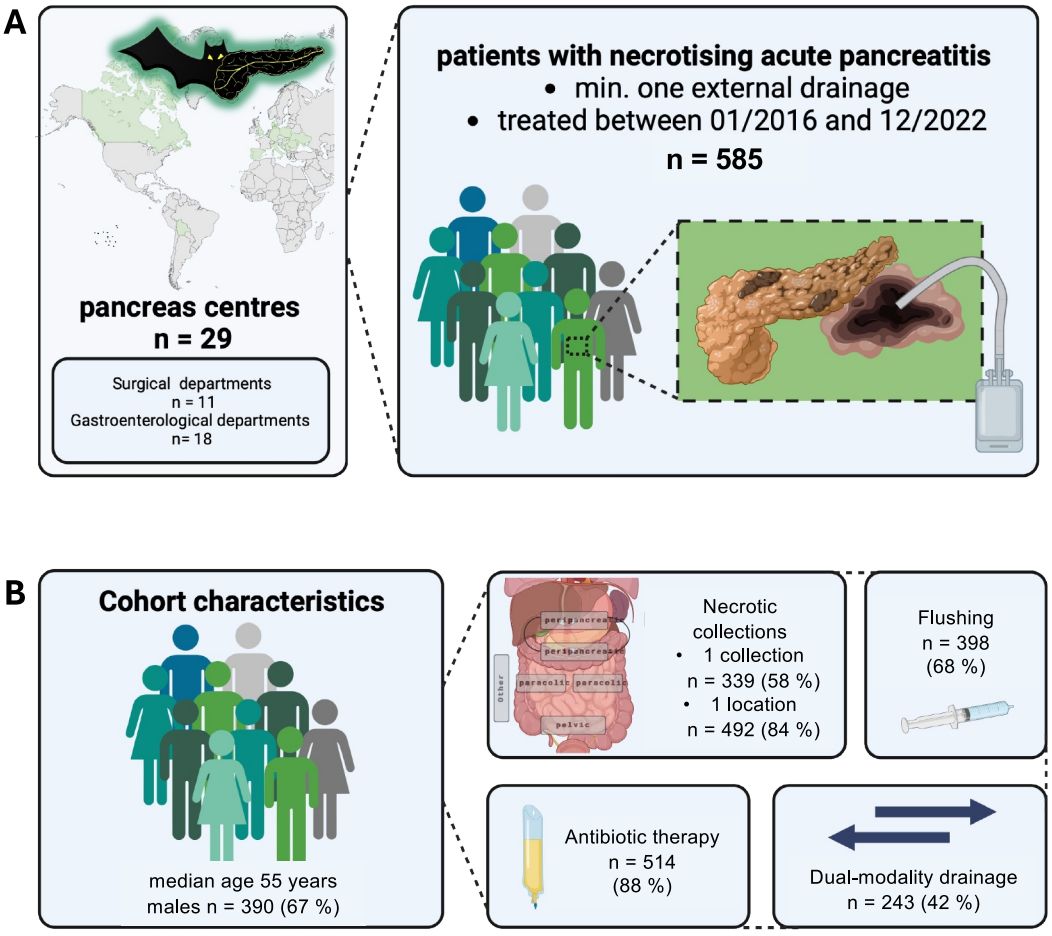

FIGURE 1 | Study design and cohort. (A) 29 pancreas centres, mostly European, both gastroenterological and surgical, took part in the study. (B) 585 patients were analysed. Baseline characteristics are also displayed in Table 1.

2.3 | Ethics

The study was reviewed and approved by the LMU Munich ethics committee on March 23rd, 2023 (internal record 23–0163). All participating centres also obtained ethical approvals according to local regulations. The study was prospectively registered in the German Clinical Trials Register (Deutsches Register Klinischer Studien, DRKS) under the registration number DRKS00032231.

3 | Results

3.1 | Study Population

A total of 585 patients with necrotising pancreatitis and at least one percutaneous drain were included from 29 centres from 15 countries. Apart from one Canadian and one Bolivian centre, all other participating centres were European. All centres were university hospitals, with 18 providing over 1000 hospital beds. Both surgical (11/29) and gastroenterological (18/29) departments participated. Endoscopic drainage was available at almost all centres (25/29). Details of the participating centres can be found in the appendix. Cohort characteristics are presented in Table 1.

In brief, 390 (66.7%) were males, median age was 55 years (IQR 44–66 years). Alcohol and gallstones accounted for 63.2% of the cases (n = 370). The majority of cases were severe acute pancreatitis (n = 365, 62.4%). The overall mortality rate was 12.5% (n = 73), while three centres, all surgical, reached mortality rates of 38%–43%. The median length of hospitalisation was 72 days, with no apparent outliers of single centres. Mortality in patients admitted to ICU (n = 401) was 17.7% (n = 71), compared to just 0.5% in those not needing ICU (n = 1). 57.9% of patients (n = 339) had one necrotic collection and 39.2% had two or more (n = 229). Percutaneous drains (n = 1140) were inserted using CT-guidance in 35.6% (n = 406), ultrasound-guidance in 30.1% (n = 353) and surgically in 21.6% (n = 246). When implanted surgically, general practice was open surgery in 15 centres, while VARD is the standard procedure in 6 centres and laparoscopic insertion in 6 centres. We observed bleeding in 2.2% (n = 25) of percutaneous drains, with the majority (n = 18) occurring in surgically placed percutaneous drains, and in 6.9% (n = 21) of endoscopically placed drains. Drains were placed for a median of 41 days, while multiple drains were often placed at overlapping times.

3.2 | Flushing

A total of 68.0% of patients (n = 398) received flushing. The baseline characteristics of the flushed and non-flushed groups are displayed in Table 1. In the entire cohort, the average length of hospitalisation did not differ significantly between the flushed and non-flushed groups, with an RMST ratio (flushing vs. no flushing) of 1.04 (95% CI: 0.95, 1.14, p value: 0.42) (Figure 2A). Median drainage duration was longer in the group that was flushed (43 vs. 34 days). In the exclusively percutaneously drained patients, we did not see a difference in length of hospitalisation either, with an RMST ratio (flushing vs. no flushing) of 1.03 (95% CI: 0.95, 1.11, p value: 0.54) (Figure 2B). Likewise, we could not see a difference in mortality in the entire cohort, with an RMST ratio (flushing vs. no flushing) of 1.05 (95% CI: 0.99, 1.10, p value: 0.1) (Figure 2C), or in those exclusively percutaneously drained, with an RMST ratio (flushing vs. no flushing) of 1.03 (95% CI: 0.95, 1.11, p value: 0.54) (Figure 2D). The ICU admission rate was 68.88% (n = 274) and 67.9% (n = 127) in the flushed and non-flushed groups.

3.3 | Dual-Modality Drainage (DMD)

In this cohort of patients with at least one percutaneous drain, 41.5% (n = 243) were treated with both a percutaneous and an internal drain, thus receiving dual-modality drainage (DMD). Median drainage duration was longer in the DMD group than in the percutaneous only group (66 vs. 30 days). When comparing DMD to percutaneous drains alone, we did not observe a difference in length of hospital stay with a RMST ratio (DMD vs. percutaneous) of 0.98 (95% CI: 0.92, 1.06, p value: 0.67) (Figure 3A). However, there was a significantly lower overall mortality in the DMD group, with an RMST ratio (DMD vs. percutaneous) of 1.05 (95% CI: 1.01, 1.09, p value: 0.01) (Figure 3B). When examining flushing in the DMD group, we observed that those who received flushing had a significantly longer hospital stay, with an RMST ratio (flushing vs. no flushing) of 1.18 (95% CI: 1.00, 1.38, p value: 0.04), corresponding to an average of 9.8 (95% CI: 0.7, 18.8) days longer (Figure 3C). Yet no difference in mortality was found, with an RMST ratio (flushing vs. no flushing) of 1.05 (95% CI: 0.98, 1.13, p value: 0.2) (Figure 3D).

3.4 | Flushing Regimens

Flushing regimens exhibited significant heterogeneity. Of the patients, 50.1% (n = 183) were flushed three times daily, while 6.0% (n = 22) were flushed only once daily, 22.2% (n = 81) twice daily, 10.4% (n = 38) 4x daily, and 11.2% (n = 41) received continuous irrigation. The cumulative daily flushing volume within 24 h showed considerable variability with an IQR of 30–750 ml. Categorising flushing regimens and volume allowed comparison of the groups. However, we did not observe any difference in the length of hospital stay regarding the flushing regimen (Figure 4A) or flushing volume (Figure 4B).

3.5 | Flushing Fluid

Saline was used for flushing in 71.8% (n = 245) of patients, while Ringer's lactate was used in 0.6% (n = 2). Antibiotics and antiseptics were used in 6.7% (n = 23) and 18.2% (n = 62) respectively. For statistical purposes, we grouped patients flushed with saline and Ringer's lactate together, and those flushed with antibiotics and antiseptics in another group. Flushing with saline solution was not associated with a change in length of hospitalisation, with an RMST ratio (Antibiotics/Antiseptics vs. NaCl) of 0.98 (95% CI: 0.86, 1.12, p value: 0.78), Figure 4C) or mortality (RMST ratio (Antibiotics/Antiseptics vs. NaCl) of 0.97 (95% CI: 0.88, 1.06, p value: 0.48)).

TABLE 1 | Patient characteristics at baseline.

Parameter[a]	Total ($n = 585$)	Flushing ($n = 398$)	No flushing ($n = 187$)	*p*-value *a*	Percutaneous only ($n = 342$)	DMD ($n = 243$)	*p*-value *b*
Age (years)	55 (44–66)	54 (41–65)	59 (48–68)	< 0.001	55 (44–66)	56 (44–66)	0.848
Sex							
Male	390 (66.7)	276 (69.3)	114 (61)	0.056	228 (66.7)	162 (66.7)	> 0.999
Year of admission							
2016–2019	299 (51.1)	209 (52.5)	90 (48.1)	0.368	163 (47.7)	136 (56)	0.058
2020–2022	286 (48.9)	189 (47.5)	97 (51.9)		179 (52.3)	107 (44)	
Aetiology of acute pancreatitis							
Alcohol	157 (26.8)	115 (28.9)	42 (22.5)	0.211	98 (28.7)	59 (24.3)	0.127
Gallstones	213 (36.4)	144 (36.2)	69 (36.9)		113 (33)	100 (41.2)	
Other	215 (36.8)	139 (34.9)	76 (40.6)		131 (38.3)	84 (34.6)	
Severity of acute pancreatitis							
Severe	365 (62.4)	249 (62.6)	116 (62)	0.425	227 (66.4)	138 (56.8)	0.049
Non-severe	211 (36.1)	141 (35.4)	70 (37.4)		111 (32.5)	100 (41.2)	
Missing	9 (1.5)	8 (2)	1 (0.5)		4 (1.2)	5 (2.1)	
Number of necrotic collections							
1	339 (57.9)	193 (48.5)	146 (78.1)	< 0.001	201 (58.8)	138 (56.8)	0.604
2	149 (25.5)	124 (31.2)	25 (13.4)		82 (24)	67 (27.6)	
> 2	80 (13.7)	71 (17.8)	9 (4.8)		47 (13.7)	33 (13.6)	
Missing	17 (2.9)	10 (2.5)	7 (3.7)		12 (3.5)	5 (2.1)	
Anatomical distribution of necrotic collections							
(Peri)pancreatic	478 (81.7)	304 (76.4)	174 (93)	< 0.001	270 (78.9)	208 (85.6)	0.052
Paracolic	129 (22.1)	120 (30.2)	9 (4.8)	< 0.001	90 (26.3)	39 (16)	0.004
Pelvic	28 (4.8)	22 (5.5)	6 (3.2)	0.309	13 (3.8)	15 (6.2)	0.259
Other	55 (9.4)	45 (11.3)	10 (5.3)	0.031	33 (9.6)	22 (9.1)	0.921
Maximum size of necrotic collections (cm)	12.5 (9–16)	13 (10–17)	11 (8–14.9)	< 0.001	12 (8.1–15)	14 (10–18)	< 0.001
Missing	74 (12.6)	13 (3.3)	61 (32.6)		66 (19.3)	8 (3.3)	
Flushing	398 (68)	398 (100)	0 (0)	—	233 (68.1)	165 (67.9)	> 0.999
Direction of drainages							
Percutaneous only	342 (58.5)	233 (58.5)	109 (58.3)	> 0.999	342 (100)	0 (0)	—
DMD	243 (41.5)	165 (41.5)	78 (41.7)		0 (0)	243 (100)	
Lumen of drains							
< 20 Fr only	309 (52.8)	238 (59.8)	71 (38)	< 0.001	198 (57.9)	111 (45.7)	< 0.001
≥ 20 Fr only	77 (13.2)	44 (11.1)	33 (17.6)		35 (10.2)	42 (17.3)	
Both	127 (21.7)	112 (28.1)	15 (8)		45 (13.2)	82 (33.7)	
Missing	72 (12.3)	4 (1)	68 (36.4)		64 (18.7)	8 (3.3)	
Length of hospitalisation within 90 days (days)	72 (42–90)	71 (45–90)	78 (35–90)	0.782	74 (45–90)	71 (40–90)	0.029
ICU	401 (68.5)	274 (68.8)	127 (67.9)	0.796	244 (71.3)	157 (64.6)	0.072
Missing	2 (0.3)	1 (0.3)	1 (0.5)		2 (0.6)	0 (0)	
Antibiotic therapy	514 (87.9)	387 (97.2)	127 (67.9)	< 0.001	279 (81.6)	235 (96.7)	< 0.001
Mortality within 90 days	73 (12.5)	48 (12.1)	25 (13.4)	0.755	52 (15.2)	21 (8.6)	0.025

[a]Continuous variables are summarised as median (interquartile range), categorical variables are summarised as count (frequency). Numbers in brackets are %, if not indicated otherwise. *a*: flushing versus no flushing; *b*: percutaneous only versus DMD.

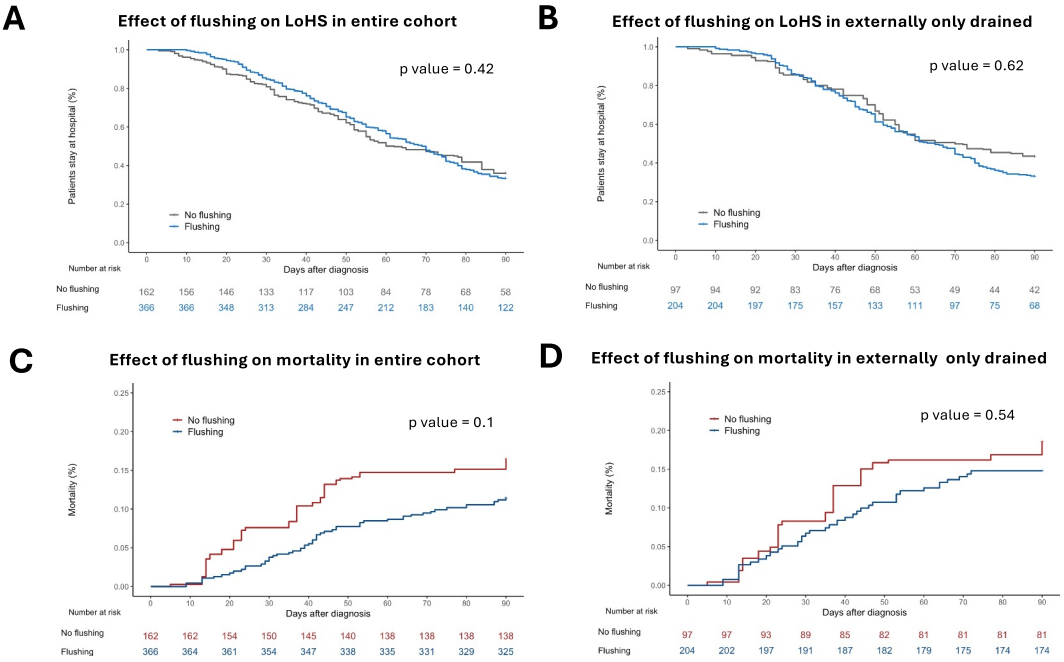

FIGURE 2 | Flushing of necrotic collections does not impact length of hospital stay (LoHS) or mortality. (A) There is no difference in LoHS for flushed patients in the entire cohort [RMST ratio (flushing vs. no flushing) of 1.04 (95% CI: 0.95, 1.14, *p* value: 0.42)] or (B) in patients who were solely externally drained [RMST ratio (flushing vs. no flushing) of 0.97 (95% CI: 0.86, 1.09, *p* value: 0.62)]. (C) Mortality is not affected by flushing in the entire cohort [RMST ratio (flushing vs. no flushing) of 1.05 (95% CI: 0.99, 1.10, *p* value: 0.1)] nor (D) in externally-only drained patients that were flushed [RMST ratio (flushing vs. no flushing) of 1.03 (95% CI: 0.95, 1.11, *p* value: 0.54)].

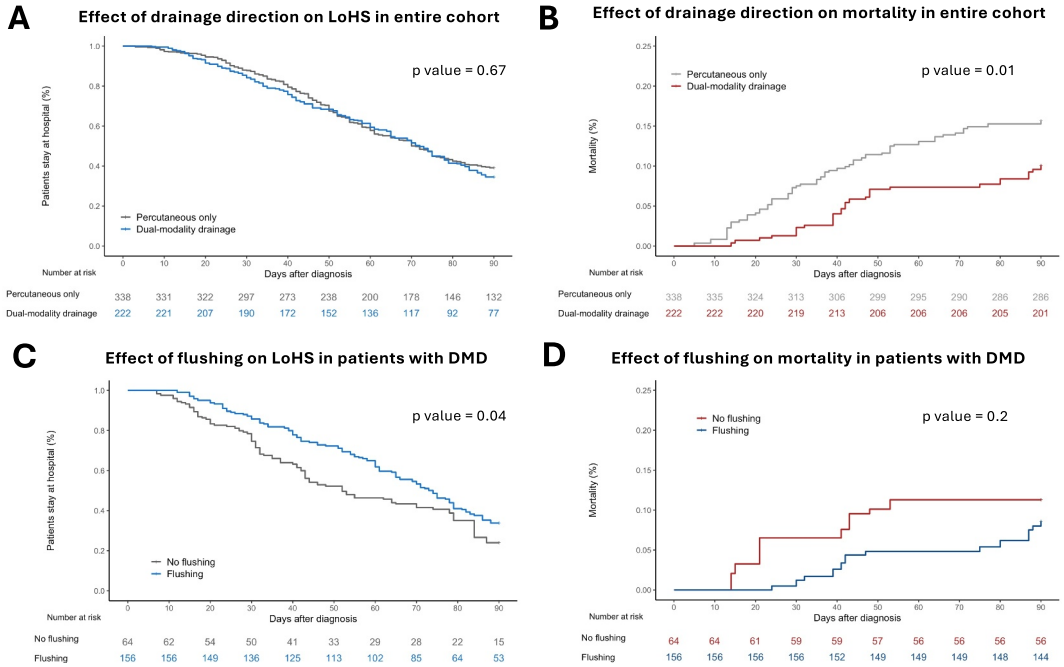

FIGURE 3 | Dual-modality drainage compared with external drainage only is associated with lower mortality. (A) The average LoHS between the two groups is not statistically significant, with a RMST ratio (DMD vs. external) of 0.98 (95% CI: 0.92, 1.06, *p* value: 0.67). (B) Patients with dual-modality drainage present a statistically lower mortality with a RMST ratio (DMD vs. external) of 1.05 (95% CI: 1.01, 1.09, *p* value: 0.01). In the group of patients with DMD, (C) we observed a significantly longer length of hospital stay for those that were flushed with a RMST ratio (flushing vs. no flushing) of 1.18 (95% CI: 1.00, 1.38, *p* value: 0.04). (D) At the same time, there is no difference in mortality in the flushed subgroup [RMST ratio (flushing vs. no flushing) of 1.05 (95% CI: 0.98, 1.12, *p* value: 0.2)].

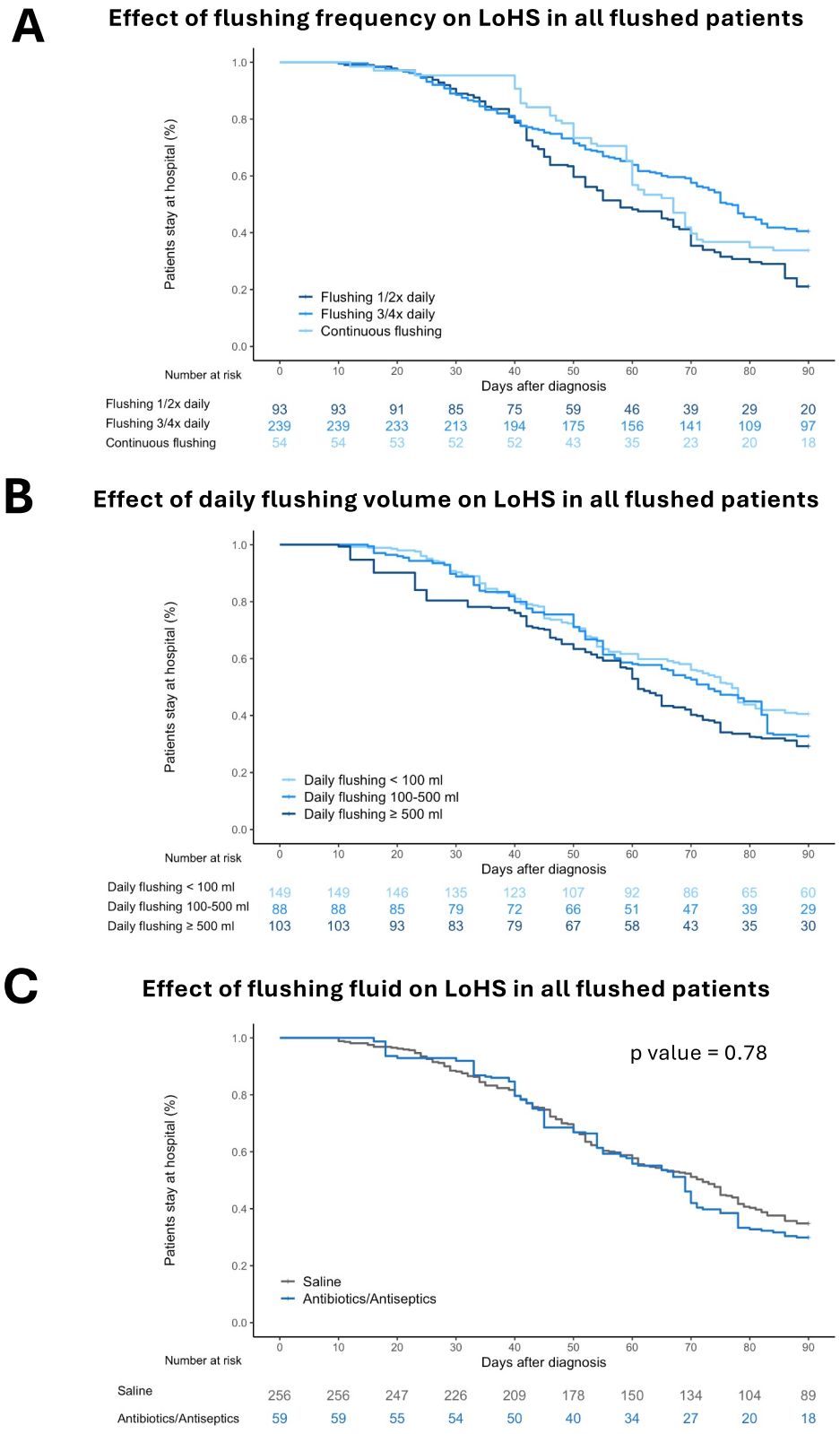

FIGURE 4 | Flushing frequency, volume or fluid is not associated with length of hospital stay. Flushing regimens and daily volumes showed great heterogeneity between the different centres. (A) There was no difference in length of hospital stay with regard to flushing frequency (3/4x daily vs. 1/2x daily: p-value = 0.13; continuous vs. 1/2x daily: p-value = 0.66; continuous vs. 3/4x daily: p-value = 1.00). (B) Flushing volume was not associated with a difference in length of hospital stay (100–500 vs. < 100: p-value = 1.00, ≥ 500 vs. < 100: p-value = 0.61, ≥ 500 vs. 100–500: p-value = 0.88). (C) Considering the flushing fluid, flushing with sodium chloride or Ringer Lactate was compared to flushing with antiseptic solutions. There was no significant difference in length of hospital stay [RMST ratio (Antibiotics/antiseptics vs. saline) of 0.98 (95% CI: 0.86, 1.12, p value: 0.78)] for either fluid.

3.6 | Drain Size

To ensure comparability, we examined drainage catheter lumina in patients who were treated exclusively with percutaneous drains. The median size of large-bore catheters was 38 Fr, while the median size of small-bore catheters was 12 Fr. Of the patients, 57.9% (n = 198) received small-bore catheters only. However, we also observed that 13.2% (n = 45) had both small-bore and large-bore percutaneous catheters. When comparing these groups, no difference was observed in the length of hospital stay (Figure 5A) or mortality (Figure 5B).

3.7 | Pathogen Detection

In our cohort, pathogens were identified in the necrotic collections of 68.5% of patients (n = 401). We observed a significantly

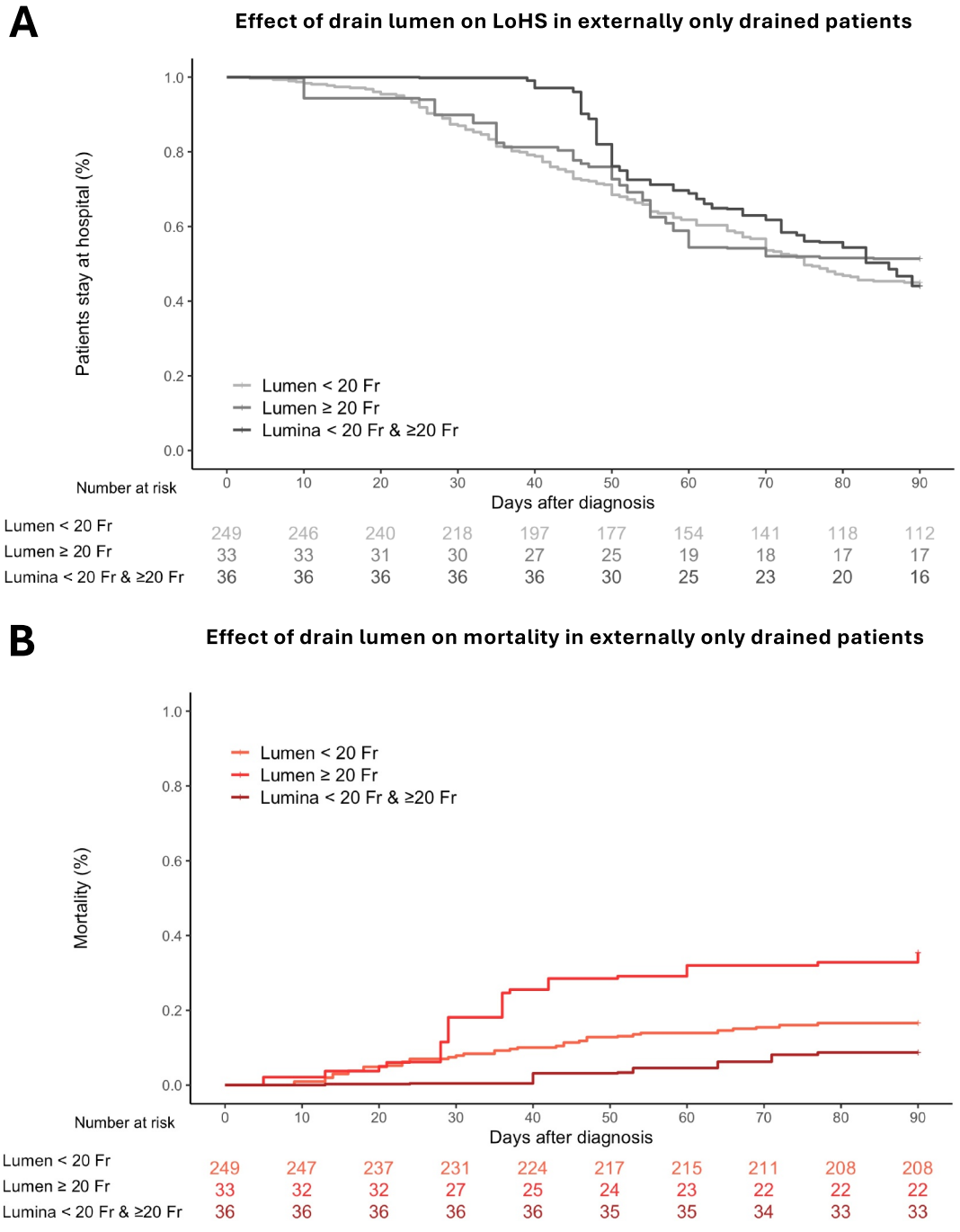

FIGURE 5 | The diameter of drains in patients with external drainage only does not affect the length of hospital stay. In patients with external drains only, we categorised the lumen of drains as large bore (≥ 20 Fr) or small bore (> 20 Fr). Some patients received a combination. (A) lumen of drain was not associated with a different length of hospital stay (≥ 20 Fr only vs. < 20 Fr only: p-value = 1.00; combination vs. < 20 Fr only: p-value = 0.39; combination vs. ≥ 20 Fr only: p-value = 0.94) (B) nor a difference in mortality (≥ 20 Fr only vs. < 20 Fr only: p-value = 0.58; combination vs. < 20 Fr only: p-value = 0.13; combination vs. ≥ 20 Fr only: p-value = 0.12).

longer length of hospital stay in those patients, with an RMST ratio (pathogens detected vs. pathogens not detected) of 1.19 (95% CI: 1.07, 1.33, *p* value: 0.002).

4 | Discussion

Necrotising pancreatitis poses high morbidity and mortality, especially in patients with infected necrotic collections [2, 5]. Drainage has been established as an efficient and necessary intervention in such cases, especially with minimally invasive endoscopic drainage being the standard of care [3, 7–10]. However, robust guidelines are lacking in necrotic collections that are not endoscopically accessible [3, 10, 11]. In this large multicentre analysis of 585 patients from 29 tertiary care centres hospitalised between 2016 and 2022 for necrotising pancreatitis treated with at least one percutaneous drain, we observed considerable variability in therapeutic approaches between and even within the centres. After extensive bias correction, we did not see a correlation between flushing itself, specific flushing regimens, percutaneous drain sizes and length of hospitalisation or mortality. We did, however, observe a significantly lower mortality in those patients who received a combination of both percutaneous and internal drains (dual-modality drainage) compared to percutaneous drainage only.

We were able to assemble a large multi-centre cohort of patients with acute necrotising pancreatitis treated with percutaneous drainage, including data on flushing at the drainage level. The majority of patients in this cohort suffered from a severe pancreatitis, aligning with the expected disease severity in this cohort. The distribution of pancreatitis aetiologies with gallstones (36%) and alcohol (27%) as the most common causes is consistent with the literature [19]. We observed a median length of hospitalisation of 72 days, in line with published data [7, 20–22]. In our cohort, the mortality rate was 12.5%, which is lower than in other reported cohorts with necrotising pancreatitis in mixed settings [5, 23]. This lower mortality may reflect the exclusion of patients who died early in the disease course before drainage could be performed. Additionally, treatment at specialised centres may have improved outcomes [24], where cohorts of patients with necrotising pancreatitis have been reported with mortality rates of 7%–18% [25–27]. Thus, the mortality in our cohort appears to fall within the expected range for high volume centres. While percutaneous drainage may cause complications such as fistulation and bleeding, we observed bleeding in 2.2% of patients, within the expected 1.1%–7.3% range reported in the literature [27, 28]. Fistulation rates were not specifically recorded. The ICU admission rate was high, at 69%, and this was associated with an increase in mortality as expected. The high ICU admission rate likely reflects the inclusion of severely ill patients in this cohort, while criteria for ICU entry admission varied by region and may also be driven by ICU capacity and reimbursement. Drainage duration was long, with a median of 41 days, and overlapping placements of drainages were common, hampering comparisons of outcomes with regard to drainage duration.

Although hypothesised to improve drainage efficacy, our study does not demonstrate a clear advantage of percutaneous flushing of pancreatic necrotic collections. Prior studies have often not reported on flushing [25] or systematically compared different flushing regimens. In studies where flushing was reported, the regimen was often thrice daily [21, 27, 29–31], the predominant frequency also reported in our cohort. When recorded, flushing volumes ranged from 10 ml [21] to 50 ml [29], a variation also observed in our cohort. As in our cohort, saline appeared to be the most commonly used fluid [21, 27, 29, 30], although different forms of antimicrobial fluids have been tested, such as hydrogen peroxide [32], streptokinase [33] or iodine [34]. Antibiotics and antiseptics were used in 25% of cases in our cohort, yet the substances were not specified in more detail. We did not observe any benefit from flushing with antibiotics or antiseptic fluids compared with flushing with saline. Given the concerns over antibiotic multi-resistance and higher costs for antibiotic or antiseptic fluids, we conclude that flushing with saline is sufficient for effective management.

The optimal lumen size of percutaneous catheters remains controversial. Large-bore catheters have traditionally been considered superior for drainage [12]. However, other studies, including a meta-analysis, did not demonstrate a clear advantage of large-bore catheter lumens [35]. Large-bore catheters offer the possibility of performing endoscopy within the catheter, yet they are associated with a higher risk of fistulation [9], thereby also increasing morbidity and length of hospitalisation. In our cohort, catheter size was not correlated with either length of hospital stay or mortality. While it would have been clinically valuable to assess the impact of drain upsizing on patient outcomes, this study did not capture longitudinal data on drain size changes throughout the treatment period.

Within our cohort, we identified a subgroup that was also treated with additional internal drains, thereby receiving so-called dual-modality drainage (DMD). This subgroup of patients exhibited a significantly lower mortality than exclusively percutaneously drained patients. However, given the retrospective design, this finding demonstrates an association rather than establishing causality. However, low mortality and favourable outcomes for patients receiving dual-modality treatment compared with percutaneous drains have been reported before [31, 36]. This finding also aligns with current data supporting a minimally invasive step-up approach for necrotising pancreatitis [7] and evidence suggesting that endoscopic drainage may be preferred when technically feasible [8, 9]. It is arguable that the benefit arises from the establishment of a flushing circuit, establishing a form of debridement [31, 36]. At the same time, flushing in DMD patients was associated with a longer length of hospitalisation. This may represent a selection bias arising from unmeasured confounding factors, with flushing being reserved for patients with more complex clinical presentations or inadequate initial drainage response.

4.1 | Strength and Limitations

Key strengths of this study include its multicentric design and the relatively large sample size achieved for necrotising pancreatitis, which strengthens the validity of our subgroup analyses in this complex clinical condition. The robust cohort size is particularly notable given the relative rarity of this pathology, providing

sufficient power to detect meaningful differences in practice patterns and outcomes across participating centres.

However, it is important to note that the majority of centres were based in Europe. Hence, apart from the Bolivian centre, all centres are from the 'Western hemisphere', which may limit global comparability. All participating centres were large pancreatic specialist centres, adhering to current recommendations [3, 10, 11]. Necrotising pancreatitis is a complex disease with a heterogeneous disease course and numerous comorbidities. Consequently, the analysis of this retrospective dataset was limited due to its heterogeneity. It is likely that standard operating procedures were not consistently implemented across many participating centres. The major limitation of this study is its retrospective nature. Henceforth, establishing uniform parameters to measure drainage therapy was challenging and causal conclusions could not be drawn. Additionally, the use of length of hospital stay as the primary outcome may be influenced by varying discharge protocols across the participating international centres, although it has been used in other pancreatitis studies in the past [35, 36]. Moreover, our cohort represents a highly selected, particularly severely ill population, potentially limiting generalisability for patients with milder courses of pancreatitis.

5 | Conclusion

Our study demonstrates that therapeutic approaches concerning drainage and flushing practices differ notably even among centres. This variability is largely due to the lack of data and the absence of specific guideline recommendations. In this exploratory analysis, we found that no specific flushing regimen was associated with a shorter length of hospitalisation or lower in-hospital mortality. Mortality was lower in patients receiving dual-modality drainage. Furthermore, our data suggest that flushing with antibiotics or antiseptics was not superior to flushing with saline. Ultimately, future randomised studies remain to provide evidence for the most appropriate percutaneous drainage therapy in patients with acute necrotising pancreatitis.

Author Contributions

M.V., S.S., J.M. and G.B. designed the study. All authors collected data. Y.X. analysed, M.V. and S.S. interpreted data. M.V., S.S., Y.X. and G.B. wrote the manuscript. All authors critically reviewed and approved the final version of the manuscript.

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Ethics Statement

The study was reviewed and approved by the LMU Munich ethics committee on March 23rd, 2023 (internal record 23–0163). All participating centres also obtained ethical approvals according to local regulations.

Conflicts of Interest

The authors have nothing to report.

Data Availability Statement

The raw data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Figure S2.1: Balance of confounding variables between groups (flushing vs. no flushing). Standardised mean differences (SMD) are presented before and after inverse probability treatment weighting (IPTW). **Figure S2.2**: Balance of confounding variables between groups (flushing vs. no flushing among externally only drained). Standardised mean differences (SMD) are presented before and after inverse probability treatment weighting (IPTW). **Figure S2.3:** Balance of confounding variables between groups (flushing vs. no flushing among dual-modality drainage). Standardised mean differences (SMD) are presented before and after inverse probability treatment weighting (IPTW). **Figure S3:** Balance of confounding variables across all lumen type pairs among externally only drained patients. Standardised mean differences (SMD) are presented before and after inverse probability treatment weighting (IPTW). **Figure S4:** Balance of confounding variables between groups (flushing with saline vs. flushing with antibiotics or antiseptics). Standardised mean differences (SMD) are presented before and after inverse probability treatment weighting (IPTW). **Figure S5:** Balance of confounding variables across all flushing regimen pairs. Standardised mean differences (SMD) are presented before and after inverse probability treatment weighting (IPTW). **Figure S6:** Balance of confounding variables across all flushing volume pairs. Standardised mean differences (SMD) are presented before and after inverse probability treatment weighting (IPTW). **Figure S7:** Balance of confounding variables between groups (detection of pathogens vs. no detection of pathogens). Standardised mean differences (SMD) are presented before and after inverse probability treatment weighting (IPTW).

Appendix

Table of Participating Centres

Continent	Country	City	Participating centre	The type of hospital	Total number of hospital beds	Department	Included patients
Europe	Belgium	Brussels	Hôpital Universitaire de Bruxelles	University hospital	1048	Gastroenterology	24
	Croatia	Zagreb	University Hospital Centre Sestre Milosrdnice	University hospital	853	Gastroenterology	1
	Denmark	Copenhagen	Pancreatitis Centre East, Gastrounit, Copenhagen University Hospital	University hospital	1120	Gastroenterology	20
	Germany	Erlangen	UK Erlangen	University hospital	1300	Surgery	10
		Freiburg	Department of General and Visceral Surgery, Centre for Surgery, Medical Centre University of Freiburg	University hospital	2050	Surgery	23
		Gießen	Department of General, Visceral, Thoracic and Transplant Surgery, University Hospital of Giessen	University hospital	1146	Surgery	7
		Göttingen	Gastroenterology, Gastrointestinal Oncology and Endocrinology, University Medical Centre Goettingen	University hospital	1600	Gastroenterology	18

(Continues)

(Continued)

Continent	Country	City	Participating centre	The type of hospital	Total number of hospital beds	Department	Included patients
		Hamburg	University Medical Centre Hamburg-Eppendorf	University hospital	1730	Gastroenterology	20
		Hannover	Hannover Medical School, Department of General, Visceral and Transplant Surgery	University hospital	1520	Surgery	21
		Leipzig	Klinik und Poliklinik für Onkologie, Gastroenterologie, Hepatologie und Pneumologie, Universitätsklinikum Leipzig	University hospital	1450	Gastroenterology	20
		Munich	Department of Medicine II, LMU University Hospital	University hospital	2000	Gastroenterology	44
			Department of Internal Medicine II, School of Medicine, University Hospital rechts der Isar	University hospital	1161	Gastroenterology	25
		Oldenburg	Department of Internal Medicine and Gastroenterology, University Hospital Oldenburg	University hospital	832	Gastroenterology	10
		Ulm	Division of Interdisciplinary Pancreatology, Department of Internal Medicine I, Ulm University Hospital, Ulm, Germany	University hospital	1200	Gastroenterology	20
	Hungary	Pécs	Institute for Translational Medicine, University of Pécs	University hospital	400	Gastroenterology	21
		Szeged	Szeged	University hospital	1790	Gastroenterology	2
	Italy	Bologna	Department of medical and surgical science (DIMEC)	University hospital	1535	Surgery	11
	Poland	Kielce	Collegium Medicum Uniwersytet Jana Kochanowskiego	University hospital	717	Surgery	16
	Portugal	Guimaraes	Hospital da Senhora da Oliveira	University hospital	663	Gastroenterology	19
	Romania	Timisoara	Division of Gastroenterology and Hepatology, Department of Internal Medicine II, Centre for Advanced Research in Gastroenterology and Hepatology, "Victor Babeş" University of Medicine and Pharmacy, "Pius Brinzeu" Emergency County Hospital Timişoara	University hospital	1070	Gastroenterology	10
	Serbia	Belgrade	Clinic for General Surgery, Military Medical Academy	University hospital	1200	Surgery	26
	Spain	Pamplona	Hospital Universitario de Navarra	University hospital	300	Gastroenterology	26
		Valladolid	Digestive Diseases Department. Hospital Clínico Universitario	University hospital	777	Gastroenterology	9
	United Kingdom	Exeter	Royal Devon University Healthcare NHS Foundation Trust, Department of Upper GI Surgery	University hospital	843	Surgery	11
		Newcastle Upon Tyne	Department for HPB Surgery, Freeman Hospital	University hospital	800	Surgery	56
	Ukraine	Lviv	Lviv Regional Clinical Hospital, Lviv, Ukraine	University hospital	1200	Surgery	45
		Poltava	Poltava State Medical University, Department of Surgery #3	University hospital	235	Surgery	12
North America	Canada	Toronto	The Centre for Therapeutic Endoscopy and Endoscopic Oncology, St. Michael's Hospital, University of Toronto	University hospital	1286	Gastroenterology	50
South America	Bolivia	La Paz	Bolivian Japanese Gastroenterology Institute, La Paz	University hospital	36	Gastroenterology	8

Definitions of Necrotic Collections in Acute Pancreatitis

Necrotising pancreatitis and necrotic collections were defined as per the revised Atlanta classification for acute pancreatitis (Banks (2013) [4]).

Necrotising Pancreatitis [4]:

- Inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis
- *CECT criteria*:
  - Lack of pancreatic parenchymal enhancement by intravenous contrast agent and/or
  - Presence of findings of peripancreatic necrosis (see below—ANC and WON)

Acute Necrotic Collection (ANC) [4]:

- A collection containing variable amounts of both fluid and necrosis associated with necrotising pancreatitis; the necrosis can involve the pancreatic parenchyma and/or the peripancreatic tissues
- *CECT criteria*:
  - Occurs only in the setting of acute necrotising pancreatitis
  - Heterogeneous and non-liquid density of varying degrees in different locations (some appear homogeneous early in their course)
  - No definable wall encapsulating the collection
  - Location—intrapancreatic and/or extrapancreatic

Walled-off Pancreatic Necrosis (WOPN) [4]:

- A mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well-defined inflammatory wall. WON usually occurs more than 4 weeks after the onset of necrotising pancreatitis.
- *CECT criteria*:
  - Heterogeneous with liquid and non-liquid density with varying degrees of loculations (some may appear homogeneous)
  - Well defined wall, that is, completely encapsulated
  - Location—intrapancreatic and/or extrapancreatic
  - Maturation usually requires 4 weeks after onset of acute necrotising pancreatitis

List of R Packages

Base packages

- stats
- graphics
- grDevices
- utils
- datasets
- methods
- base

Other attached packages:

- ggsci_3.2.0
- survminer_0.4.9
- ggpubr_0.6.0
- kableExtra_1.4.0
- mutoss_0.1–13
- mvtnorm_1.3-1
- cobalt_4.5.5
- WeightIt_1.3.0
- survival_3.7–0
- lattice_0.22–6
- mice_3.16.0
- lubridate_1.9.3
- forcats_1.0.0
- stringr_1.5.1
- dplyr_1.1.4
- purrr_1.0.2
- readr_2.1.5
- tidyr_1.3.1
- tibble_3.2.1
- ggplot2_3.5.1
- tidyverse_2.0.0
- readxl_1.4.3

Packages Loaded via a Namespace (and not Attached):

- tidyselect_1.2.1
- viridisLite_0.4.2
- fastmap_1.2.0
- TH.data_1.1-2
- digest_0.6.37
- rpart_4.1.23
- timechange_0.3.0
- lifecycle_1.0.4 magrittr_2.0.3
- compiler_4.4.1
- rlang_1.1.4
- tools_4.4.1
- plotrix_3.8-4
- utf8_1.2.4
- yaml_2.3.10
- data.table_1.16.0
- ggsignif_0.6.4
- knitr_1.48
- xml2_1.3.6
- abind_1.4-8
- multcomp_1.4–26
- withr_3.0.1
- BiocGenerics_0.50.0
- nnet_7.3–19
- grid_4.4.1

- stats4_4.4.1
- fansi_1.0.6
- jomo_2.7-6
- multtest_2.60.0
- xtable_1.8-4
- colorspace_2.1-1
- scales_1.3.0
- iterators_1.0.14
- MASS_7.3–61
- cli_3.6.3
- rmarkdown_2.28
- crayon_1.5.3
- generics_0.1.3
- km.ci_0.5-6
- rstudioapi_0.16.0
- tzdb_0.4.0
- minqa_1.2.8
- splines_4.4.1
- cellranger_1.1.0
- survMisc_0.5.6
- vctrs_0.6.5
- boot_1.3–31
- glmnet_4.1-8
- Matrix_1.7–0
- sandwich_3.1-1
- carData_3.0–5
- car_3.1-2
- hms_1.1.3
- rstatix_0.7.2
- mitml_0.4-5
- ystemfonts_1.1.0
- foreach_1.5.2
- glue_1.7.0
- nloptr_2.1.1
- pan_1.9
- codetools_0.2–20
- stringi_1.8.4
- shape_1.4.6.1
- gtable_0.3.5
- lme4_1.1–35.5
- munsell_0.5.1
- pillar_1.9.0
- htmltools_0.5.8.1
- KMsurv_0.1-5
- R6_2.5.1
- evaluate_1.0.0
- Biobase_2.64.0
- backports_1.5.0
- broom_1.0.6
- Rcpp_1.0.13
- gridExtra_2.3
- svglite_2.1.3
- nlme_3.1–166
- xfun_0.47 zoo_1.8–12
- pkgconfig_2.0.3