Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Boxhoorn L, van Dijk SM, van Grinsven J, et al. Immediate versus postponed intervention for infected necrotizing pancreatitis. N Engl J Med 2021;385:1372-81. DOI: 10.1056/NEJMoa2100826

SUPPLEMENTARY APPENDIX

"Immediate versus postponed intervention for infected necrotizing pancreatitis"

This trial was registered with ISRCTN registry (ISRCTN33682933).

The trial protocol is published in *Trials.* 2019 Apr 25;20(1):239.

CONTENT

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METHODS

Eligibility criteria

Inclusion criteria

- Proven infected necrotizing pancreatitis (0–35 days after the onset of disease) or clinical suspected infected necrosis (15–35 days after the onset of disease) *(Box S2. Criteria for diagnosing infected necrotizing pancreatitis*)
- Catheter drainage of the necrotic collection is technically feasible, as deemed by the acute pancreatitis expert panel and/or treating physician
- Age ≥ 18 years

Exclusion criteria

- Onset of acute pancreatitis more than 35 days ago
- Indication for emergency laparotomy in the situation of an abdominal catastrophe (e.g. bleeding, bowel perforation or abdominal compartment syndrome)
- Previous retroperitoneal intervention for necrotizing pancreatitis (ascites drainage and (emergency) laparotomy without opening the bursa were permitted)
- Documented chronic pancreatitis (according to the M-ANNHEIM criteria)[1]

Process of evaluating patients prior to randomization

Hospitalized patients with acute pancreatitis were followed from hospital admission in the collaborating hospitals of the Dutch Pancreatitis Study Group by the study coordinators. All patients who developed necrotizing pancreatitis were pro-actively assessed for the presence of infected necrosis. The nationwide online multidisciplinary expert panel of Dutch Pancreatitis Study Group was consulted when infected necrosis was suspected or proven, to evaluate the eligibility for randomization and indication for intervention, similar as in the PANTER, PENGUIN and TENSION trial.[2–5] The expert panel received a case description and CT images, provided via the treating physician. Within 24 hours, the members of the expert panel individually assessed whether they suspected infected necrosis, if fine-needle aspiration would be advised, and if there was an indication for intervention. Last, the eligibility for randomization in the POINTER trial evaluated. The expert panel was also used to identify

eligible patients in non-participating centers. These patients could then be transferred, if clinically appropriate, to a study center. The expert panel advice was discussed with the treating physicians, who made the final decision whether to intervene and/or randomize the patient in the POINTER trial.

Randomization

Patients were randomly assigned in a 1:1 ratio to immediate catheter drainage or postponed catheter drainage. Randomization was performed by the study coordinators using a centrally operated computer system (ALEA system) that used variable block randomization for allocation concealment. Randomization was stratified according to presence of organ failure at the time of randomization, disease duration (≤20 days or ≥21-35 days), and hospital volume (high- or low-volume centers). Patients, physicians, and investigators were aware of the assigned treatment group.

Treatment groups

Immediate catheter drainage

Immediate catheter drainage included catheter drainage within 24 hours after diagnosing infected necrosis, after starting (or continuing) broad-spectrum antibiotic treatment. Broad-spectrum antibiotics were tailored based on culture and antibiotics sensitivity results. In case of insufficient clinical improvement within the first 72 hours after initial catheter drainage, additional drainage was performed by either an additional drainage procedure, drain revision or upsizing to a larger drain size. If drainage was clinically unsuccessful, minimally invasive necrosectomy was performed once the peripancreatic and/or pancreatic collection developed into walled-off necrosis. Lack of clinical improvement was defined as (multiple) organ failure or increasing inflammatory parameters (temperature, C-reactive protein and leukocyte count).

Postponed catheter drainage

Postponed catheter drainage included treatment with broad-spectrum antibiotics and supportive treatment, aimed to postpone the drainage procedure until peripancreatic necrosis became largely or fully encapsulated (i.e. walled-off necrosis). If patients presented with collections that were already largely or fully encapsulated when infection was diagnosed, an initial conservative approach with antibiotics was first started. Catheter drainage was then only performed in case of clinical deterioration

or lack of clinical improvement despite antibiotic treatment. Broad-spectrum antibiotics were tailored based on culture and antibiotics sensitivity results. In case of insufficient clinical improvement within the first 72 hours after initial catheter drainage, additional drainage was performed by either an additional drainage procedure, drain revision or upsizing to a larger drain size. If drainage was clinically unsuccessful, minimally invasive necrosectomy was performed. Lack of clinical improvement was defined as new organ failure or increasing inflammatory parameters (temperature, C-reactive protein and leukocyte count).

Step-up approach in both groups

Both a endoscopic and surgical step-up approach were permitted. In the surgical step-up approach, the preferred technique for surgical necrosectomy was by videoscopic assisted retroperitoneal debridement (VARD). In the endoscopic step-up approach, endoscopic transluminal necrosectomy was performed. In both the immediate and the postponed drainage groups, treatment was not restricted to one intervention technique: in endoscopically treated patients, additional percutaneous interventions were allowed and vice versa. The step-up approach was performed according to the step-up approach in the PANTER and TENSION trial, and described in more detail below.[3,5]

Endoscopic step-up approach

As first step in endoscopic step-up approach, endoscopic ultrasound guided transluminal drainage was performed. Endoscopic ultrasound (EUS) was used to visualize the size, location, and content of the necrotic collection once patients were sedated. Subsequently, the collection was punctured through the gastric or duodenal wall in order to create a fistulous tract. This was followed by balloon dilation of the fistulous tract and placement of two double-pigtail plastic stents (7 Fr). A nasocystic catheter was then positioned within the necrosis and flushed with 1 liter saline/24 hours for post-procedural irrigation.

As described before, endoscopic transluminal necrosectomy was performed if endoscopic transluminal drainage was clinically unsuccessful. During this procedure, the fistulous tract with the double-pigtail stents in situ was first dilated up to 15–20 mm, and then accessed with a therapeutic gastroscope to remove the remaining necrotic tissue with dedicated instruments.

Surgical step-up approach

As first step in the surgical step-up approach, a percutaneous 14 Fr drain was placed in the collection using CT- or ultrasound guidance. The preferred route was through the left retroperitoneum, and if not possible, transabdominal. Drains were flushed with 50 ml saline every 8-hours. There was no maximum number of drains. Drains could be upsized up to 22 Fr drains.

As described before, surgical necrosectomy was performed if drainage was clinically unsuccessful. The preferred technique for surgical necrosectomy was by videoscopic assisted retroperitoneal debridement (VARD).[3,5] VARD is a minimally invasive retroperitoneal procedure, in which the retroperitoneal drain is used for guidance. During this procedure, the remaining necrotic tissue is removed from the collection with video-assistance. Afterwards, a continuous post-operative lavage system was positioned within the necrosis.

Supportive treatment

Management of acute pancreatitis is extensively described in the 2013 International Association of Pancreatology (IAP)/American Pancreatic Association (APA) guidelines.[6] Patients were in general managed in accordance with the IAP/APA guideline, and received fluid resuscitation, pain management and (oral, if not tolerated enteral) feeding accordingly.

Antibiotic prophylaxis was, in line with the guideline, not administered. Selective decontamination of the digestive tract was allowed when patients were admitted to the intensive care unit. In clinically deteriorating patients with signs of infection, blood-, urine-, sputum-, and/or ascites cultures were collected and diagnostic imaging (e.g. chest X-ray and contrast-enhanced abdominal CT) was conducted. In case of suspicion of infected necrosis, fine-needle aspiration (FNA) could be performed. FNA was not used for screening of infected necrosis. Targeted antibiotics were given when a primary focus of infection was found. In case of high suspicion of infected necrosis and persistent clinical deterioration, broad spectrum antibiotics, in accordance with the IAP/APA guideline, were started empirically.

Quality of life

Patients were asked to complete the Short-Form-36 (SF-36) questionnaire at 3 and 6 months.[7] Given the high percentage of patients with missing data (from 16 of 48 surviving patients (33%) in the immediate drainage group at 3 months and 14 of 48 surviving patients (29%) at 6 months vs. 17 of 44

surviving patients (39%) in the postponed drainage group at 3 and 6 months), we chose to not report the SF-36 data.

Predefined and post-hoc subgroup analyses

Exploratory analyses were performed to examine the effect of interaction between treatment and predefined subgroups (presence of organ failure, disease duration, and hospital volume) on the primary end point (Table S3a-c). Additionally, a post-hoc subgroup analysis was performed to evaluate the first drainage procedure (endoscopic transluminal drainage vs. percutaneous catheter drainage) in both groups (Table S5). Last, we performed a post-hoc sensitivity analysis for the primary end point, excluding all patients with necrosis extending >5 cm down the retrocolic gutter (Table S11).

Box S1. Definitions of the primary and secondary end points

End point	Definition
Primary end point	Comprehensive Complication Index (CCI), including all complications between randomization and 6 months follow-up, graded according to the Clavien-Dindo classification.[8–10]
Secondary end points	
New onset organ failure	Organ failure occurring after randomization and not present 24 hours before randomization: **- Pulmonary**: a PaO2 < 60 mmHg despite FiO2 30% or the need for mechanical ventilation **- Cardiovascular**: a systolic blood pressure < 90 mmHg despite adequate fluid resuscitation or need for vasopressor support **- Renal**: a serum creatinine > 177 mmol/L after rehydration or need for hemofiltration or hemodialysis (in case patients already suffered from renal insufficiency before this episode of AP [creatinine > 177 umol/L] this does not count as renal failure)
Multiple organ failure	Failure of 2 or more organ systems (respiratory, cardiovascular or renal) at the same moment.
Bleeding requiring intervention	Bleeding requiring surgical, radiological, or endoscopic intervention.
Perforation of a visceral organ requiring intervention	Perforation requiring surgical, radiological, or endoscopic intervention.
Enterocutaneous fistula requiring intervention	Secretion of fecal material from a percutaneous drain or drainage canal after removal of drains or from a surgical wound, either from small or large bowel; confirmed by imaging or during surgery.
Pancreaticocutaneous fistula	Output through a percutaneous drain or drainage canal after removal of drains from a surgical wound, or any measurable volume of fluid with an amylase content >3 times the serum amylase level.
Incisional hernia	Incisional hernia is defined as full-thickness discontinuity in abdominal wall and bulging of abdominal contents, with or without obstruction.
Wound infection	A superficial incisional SSI (surgical site infection) and must meet the following criterion: infection occurs within 30 days after the operative procedure and involves only skin and

	subcutaneous tissue of the incision and the patient has at least 1 of the following: - Purulent drainage from the superficial/deep incision but not from the organ/space component of the surgical site - Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision - At least 1 of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon and is culture positive or not cultured. A culture-negative finding does not meet this criterion - An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathological or radiologic examination - Diagnosis of superficial/deep incisional SSI by the surgeon or attending physician
Exocrine pancreatic insufficiency	• Oral pancreatic-enzyme supplementation required to treat clinical symptoms of steatorrhea 6 months after randomization; this requirement was not present before onset of pancreatitis • Fecal elastase <0.2 gram and the need for pancreatic enzyme supplementation; this requirement was not present before onset of pancreatitis.
Endocrine pancreatic insufficiency	The need for insulin or oral anti-diabetic drugs; this requirement was not present before onset of acute pancreatitis.

Box S2. Criteria for diagnosing infected necrotizing pancreatitis

Day 0-14 after onset of disease: proven infected necrosis	**Day 15-35 after onset of disease: proven or suspected infected necrosis**
Gas within (peri)pancreatic necrosis on contrast-enhanced computed tomography (CT)	Gas within (peri)pancreatic necrosis on contrast-enhanced computed tomography (CT)
Positive gram stain or culture of fine-needle aspiration from (peri)pancreatic necrosis	Positive gram stain or culture of fine-needle aspiration from (peri)pancreatic necrosis
	Clinical signs of infection without another focus than infected necrosis for 3 consecutive days[1]

[1] Either persistent (multiple) organ failure in patients admitted to the intensive care unit, or 2 of the 3 elevated inflammatory parameters (temperature (>38.5 ^{0}C), C-Reactive Protein or leukocyte count) during 3 consecutive days in patients on regular wards (with no other infection focus). These clinical criteria alone are considered sufficiently reliable only after the initial 14 days of acute pancreatitis.

Comprehensive Complication Index

Background

The Comprehensive Complication Index (CCI) was developed to evaluate all postoperative complications with their respective severities.[8–10] The CCI is calculated as the sum of all complications weighted for their severity: the final formula yields a continuous scale to rank the severity of any combination of complications from 0 to 100 in a single patient.[8,9]

Rationale for primary end point

We chose the Comprehensive Complication Index (CCI) as primary end point, because previous studies supported the validity of the CCI as a more sensitive tool than traditional morbidity end points in surgical trials.[8,9] Moreover, in the development of the CCI, complications were rated by both patients and physicians, and therefore includes the patient's perspective.

Calculation of CCI

As defined in our published protocol, all complications other than pre-existent complications (e.g. treatment for infected (peri)pancreatic necrosis) occurring after randomization until 6 months follow-up, were graded according to the Clavien-Dindo classification (Box S3).[11] Subsequently, the CCI calculated. The formula to calculate the CCI is presented below.[9] As shown, each Clavien-Dindo complication grade has an attributed severity weight. This weight was calculated from physicians' and patients' perspective of harm.[8] For example, Clavien-Dindo grade I complications have lower weight than Clavien-Dindo grade III complications (300 vs. 4450), as presented in the formula.

Box S3. Clavien-Dino Classification, adapted from Dindo *et al*.[10]

Grades	Definition	Treatment
Grade I	Any deviation from the normal postoperative course.	No pharmacological or surgical, endoscopic or radiological interventions. Acceptable therapeutic regimens: drugs, such as anti-emetics, antipyretics, analgesics, diuretics, electrolytes and physoptherapy. This grade also includes wound infections opened at bedside.
Grade II	Normal course altered.	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. This grade includes blood transfusions, antibiotics and total parenteral nutrition.
Grade III	Complications that require surgical, endoscopic or radiologic intervention.	Sub-classified into: • Grade IIIa: complications that require an intervention performed under local anesthesia. • Grade IIIb: complications that require an intervention under general or epidural anesthesia.
Grade IV	Life-treating complications requiring intensive care unit support.	Sub-classified into: • Grade IVa: single organ dysfunction • Grade IVb: multi-organ dysfunction
Grade V	Death of a patient.	-

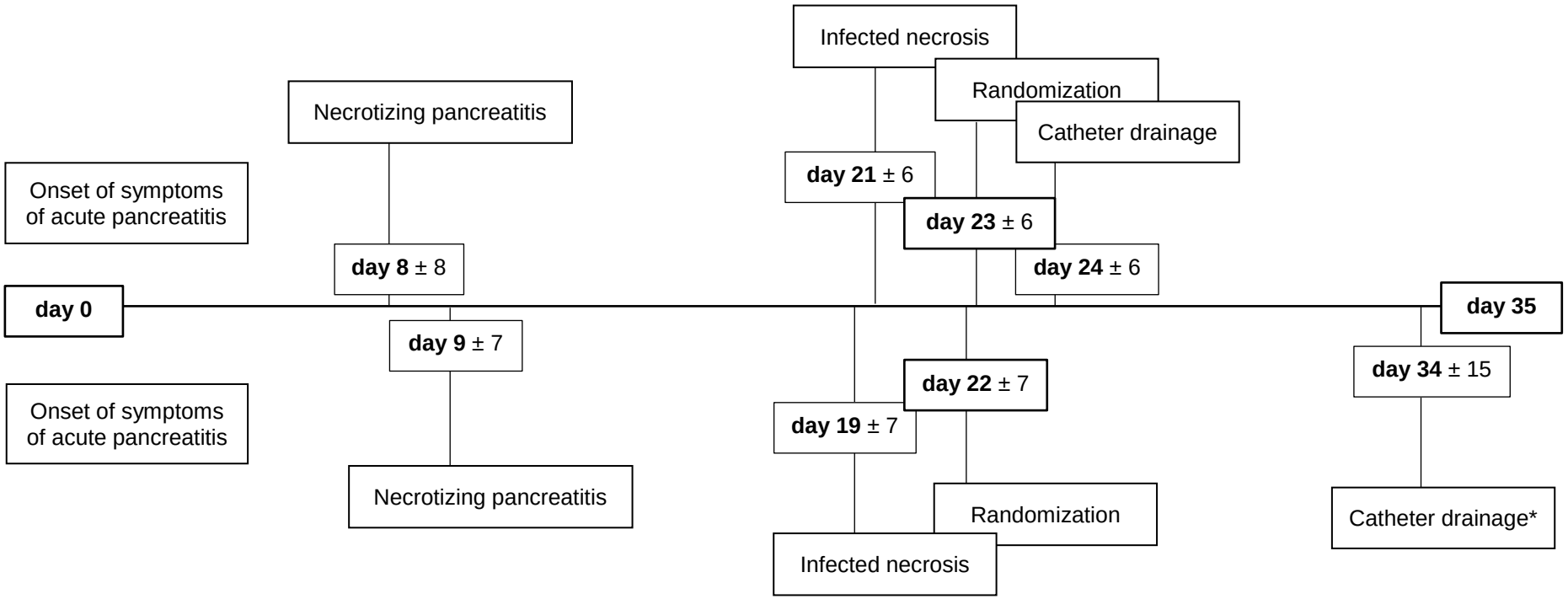
Comprehensive Complication Index formula, adapted from Slankamenac *et al.*

$$CCI = \frac{\sqrt{(CD1 * 300) + (CD2 * 1750) + (CD3a * 2750) + (CD3b * 4550) + (CD4a * 7200) + (CD4b * 8550)}}{2}$$

CCI = Comprehensive Complication Index, CD = Clavien-Dindo Classification

Figure S1. Timeline for both intervention groups

Immediate catheter drainage (*n* = 55)



Postponed catheter drainage (*n* = 49)

Data are mean ± SD
* In the postponed drainage group, 19 of 49 patients (39%) were treated conservatively.

Figure S2. Encapsulation of necrosis in immediate and postponed drainage group

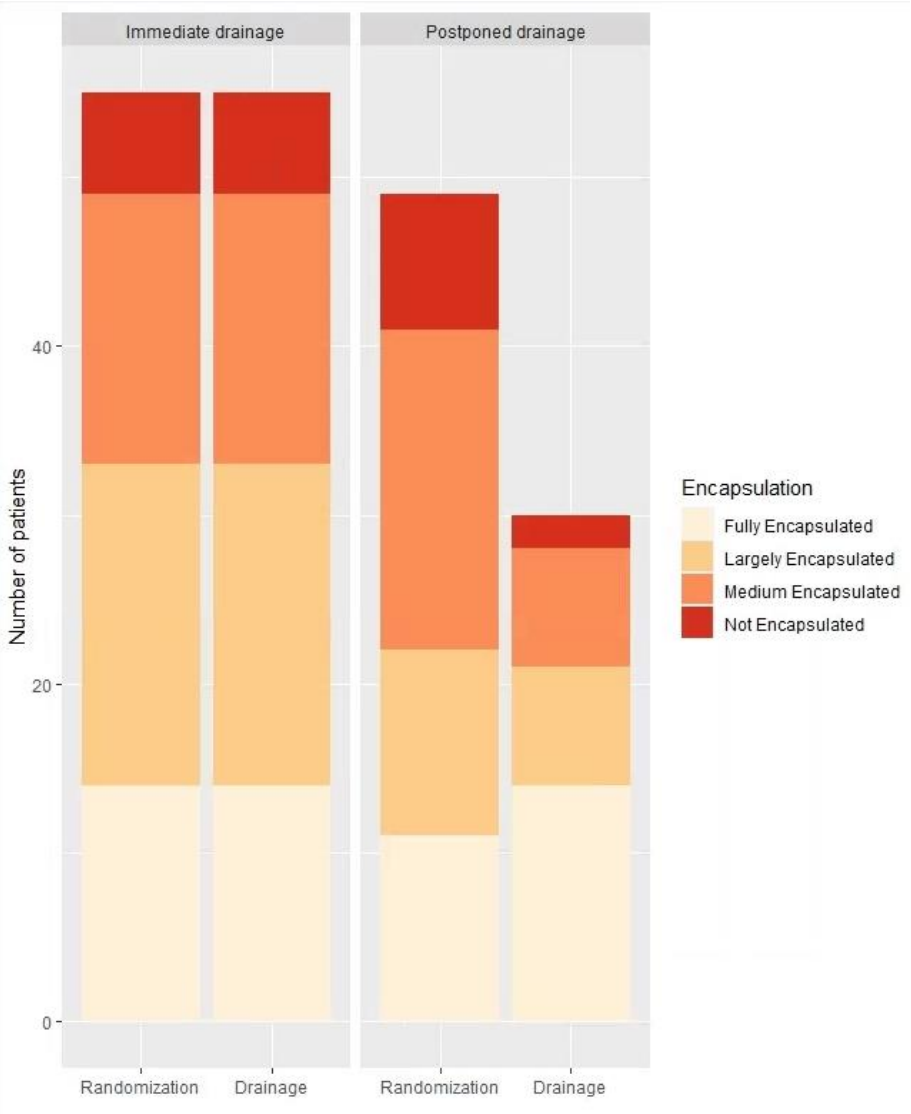


Figure S3. Disease severity in postponed drainage group at drainage

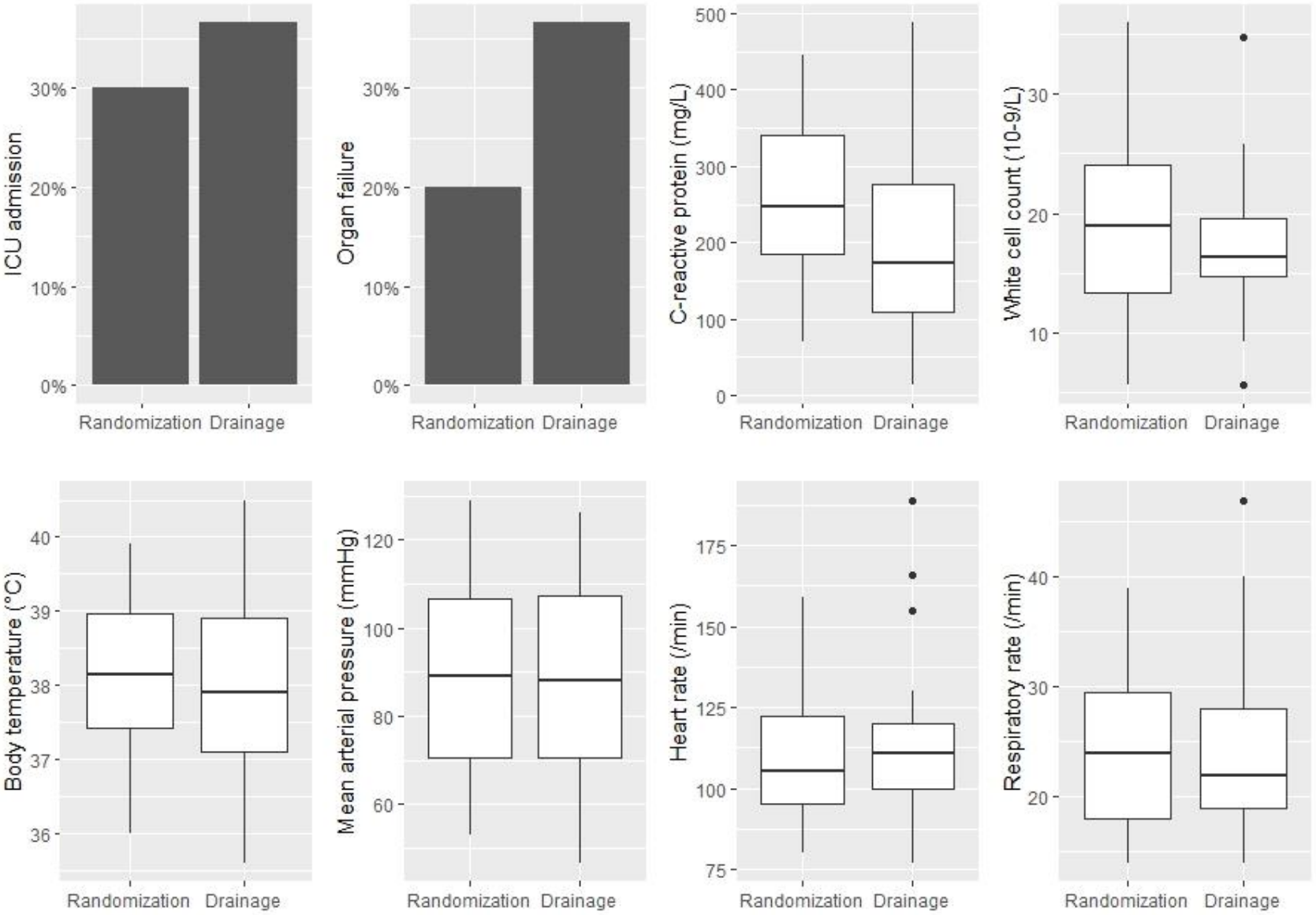


Table S1. Baseline characteristics (continued)

Characteristics	Immediate catheter drainage (*n* = 55)	Postponed catheter drainage (*n* = 49)
Cause of pancreatitis – no. (%)		
Gallstones	36 (65)	29 (59)
Alcohol abuse	8 (15)	7 (14)
Other*	11 (20)	13 (27)
Body-mass index – mean ± SD	30 ± 5	29 ± 6
ASA class on admission – no. (%)		
I: Healthy status	4 (7)	2 (4)
II: Mild systemic disease	24 (44)	23 (47)
III: Severe systemic disease	27 (49)	24 (49)
Necrosis extending >5 cm down the retrocolic gutters§ – no. (%)	33 (61)	23 (47)
Disease severity~		
APACHE ll score – median (IQR)¥	12 (8-14)	11 (9-14)
Modified Glasgow score – median (IQR) †	2 (1-3)	2 (1-2)
Modified MODS score – median (IQR)‡	0 (0-2)	0 (0-2)
SOFA score – median (IQR)	0 (0-2)	1 (0-2)
C-reactive protein (mg/L)[1] – median (IQR)	226 (164-310)	221 (133-322)
White cell count (10^{-9}/L) – median (IQR)	16 (12-21)	17 (12-24)
Organ failure – no. (%)	13 (24)	8 (16)
Respiratory	12 (22)	8 (16)
Cardiovascular	8 (15)	6 (12)
Renal	7 (13)	6 (12)
Antibiotic treatment at randomization – no. (%)	53 (96)	49 (100)
Tertiary referral – no. (%)	21 (38)	19 (39)

Data are n (%), mean (SD), or median (IQR). [1] Data missing in 4 patients.
ASA = American Society of Anesthesiologists, APACHE = Acute Physiology and Chronic Health Evaluation, MODS = Multiple Organ Dysfunction Syndrome, SOFA = Sequential Organ Failure Assessment
* Includes medication, hypertriglyceridemia, and unknown aetiology.
§ Data were derived from the contrast-enhanced CT performed before randomization.
~ Data were based on maximum values during the 24 hours before randomization.
¥ APACHE II score ranges from 0 to 71, with higher scores indicating more severe disease.
† Modified Glasgow score ranges from 0 to 8, with higher scores indicating more severe disease.
‡ Modified MODS scores range from 0 to 24, with higher scores reflecting more severe organ dysfunction.

Table S2. Timeline in each intervention group

Interval (days)	Immediate catheter drainage (*n* = 55)	Postponed catheter drainage (*n* = 49)
Onset of symptoms to diagnosis of acute pancreatitis (days) – mean ± SD	1 ± 2	0 ± 1
Onset of symptoms to necrotizing pancreatitis/necrotic collection (days) – mean ± SD	8 ± 8	9 ± 7
Diagnosis of necrotizing pancreatitis to infection (days) – mean ± SD	12 ± 9	10 ± 8
Diagnosis necrotizing pancreatitis/necrotic collection to randomization (days) – mean ± SD	15 ± 9	13 ± 8
Diagnosis infected necrosis to randomization[1] (days) – mean ± SD	2 ± 2	3 ± 4
Diagnosis infected necrosis to catheter drainage[1,2] (days) – mean ± SD	3 ± 3	15 ± 15
Randomization to catheter drainage[2] (days) – mean ± SD	1 ± 1	13 ± 15

Data are mean ± SD

[1] The day of diagnosing infected necrosis was either the day that a positive gram stain or culture from a fine-needle aspiration was obtained, or the day that gas configurations within pancreatic and/or peripancreatic necrosis were present on contrast-enhanced CT, or in patients with clinical signs of infected necrosis, the day that antibiotics were started for infected necrosis.

[2] In the postponed drainage group, 19 of 49 patients (39%) were treated conservatively.

Table S3a. Outcome of study participants with (multiple) organ failure at randomization

	Patients with (multiple) organ failure (*n* = 21)		
Outcome	**Immediate catheter drainage (*n* = 13)**	**Postponed catheter drainage (*n* = 8)**	**Mean difference (95% CI)**
Primary end point			
Comprehensive Complication Index – mean (95% CI)	81 (71 to 91)	87 (65 to 103)	-6 (-26 to 17)

Data are mean (95% CI).

Table S3b. Outcome of study participants with a disease duration ≤20 days at randomization

	Patients with disease duration ≤20 days (*n* = 42)		
Outcome	**Immediate catheter drainage (*n* = 19)**	**Postponed catheter drainage (*n* = 23)**	**Mean difference (95% CI)**
Primary end point			
Comprehensive Complication Index – mean (95% CI)	67 (57 to 76)	62 (50 to 75)	5 (-12 to 20)

Data are mean (95% CI)

Table S3c. Outcome of study participants in three high-volume centers

	Patients randomized in high-volume hospitals (*n* = 42)		
Outcome	**Immediate catheter drainage (*n* = 22)**	**Postponed catheter drainage (*n* = 20)**	**Mean difference (95% CI)**
Primary end point			
Comprehensive Complication Index – mean (95% CI)	55 (44 to 68)	58 (44 to 74)	-3 (-22 to 16)

Data are mean (95% CI)

Table S4. Model summary and coefficients of the linear regression model

	Dependent variable: Comprehensive Complication Index
Predictor	***β* (95% CI)**
Constant	47.57 (35.45 to 59.70)
Drainage group (immediate vs. postponed catheter drainage)	-0.67 (-16.64 to 15.30)
Organ failure at randomization	35.34 (15.47 to 55.21)
Disease duration at randomization (≤20 days)	6.65 (-7.94 to 21.23)
Expected high-volume centers	3.66 (-11.30 to 18.62)
Drainage group * organ failure at randomization	-3.13 (-28.77 to 22.52)
Drainage group * disease duration at randomization (≤20 days)	10.53 (-10.19 to 31.24)
Drainage group * expected high-volume centers	-11.70 (-32.40 to 8.99)
Observations	104
R^2	0.26
Residual Std. Error	25.95 (df = 96)
F Statistic	4.69 (df = 7; 96)

Table S5. Post-hoc analysis: first drainage procedure in both intervention groups

Outcome	**Immediate catheter drainage (*n* = 55)**	**Postponed catheter drainage (*n* = 30)**[1]
First drainage procedure		
Endoscopic transluminal drainage – no. (%)	31 (56)	20 (67)
Image-guided percutaneous drainage – no. (%)	24 (44)	10 (33)

Data are n (%).

[1] In the postponed drainage group, 19 of 49 patients (39%) were treated conservatively.

Table S6. Results of the per-protocol analysis[#]

Outcome	Immediate catheter drainage (*n* = 51)	Postponed catheter drainage (*n* = 48)	Relative Risk/ Mean difference (95% CI)	P-value
Primary end point				
Comprehensive Complication Index – mean (95% CI)	57 (49 to 65)	57 (49 to 66)	0 (-12 to 11)	0.94
Secondary end points				
Mortality – no. (%)	7 (14)	4 (8)	0.61 (0.19 to 1.94)	
New-onset organ failure – no. (%)*	12 (24)	10 (21)	0.89 (0.42 to 1.86)	
Bleeding – no. (%)	7 (14)	10 (21)	1.52 (0.63 to 3.67)	
Perforation of a visceral organ or enterocutaneous fistula – no. (%)	4 (8)	4 (8)	1.06 (0.28 to 4.01)	
Pancreaticocutaneous fistula – no. (%)	5 (10)	4 (8)	0.85 (0.24 to 2.98)	
Incisional hernia – no. (%)	0 (0)	0 (0)	-	
Wound infection – no. (%)	0 (0)	1 (2)	-	
Exocrine insufficiency – no. (%)				
Use of enzymes	19 (37)	19 (40)	1.06 (0.65 to 1.75)	
Fecal elastase <200 mg/g[1]	24 (50)	14 (33)	0.65 (0.39 to 1.09)	
Endocrine insufficiency – no. (%)	11 (22)	10 (21)	0.97 (0.45 to 2.07)	
Clavien-Dindo score ≥ III complication – no. (%)	38 (75)	39 (81)	1.09 (0.88 to 1.35)	
Total number of surgical, endoscopic and radiological interventions for infected necrosis – mean (95% CI)	4.4 (3.6 to 5.3)	2.6 (1.8 to 3.7)	1.8 (0.5 to 3.0)	
Days in ICU after randomization – mean (95% CI)	12 (6 to 24)	12 (6 to 23)	0 (-11 to 11)	
Days in hospital after randomization – mean (95% CI)	57 (48 to 68)	52 (40 to 66)	5 (-12 to 20)	

Data are n (%) or mean (95% CI). ICU = intensive care unit

Risk ratios are for immediate catheter drainage compared with postponed catheter drainage.

[#] Including only the patients who adhered to the treatment protocol that they were allocated to.

* New-onset organ failure was defined as organ failure that was not present at randomization.

[1] Data missing in 8 patients.

Table S7. Adverse events[#]

Adverse event	Immediate catheter drainage (*n* = 55)	Postponed catheter drainage (*n* = 49)	P-value
Total no. of adverse events*	**255**	**210**	
Gastrointestinal			
Ascites – no. (%)	7 (13)	7 (14)	1.00
Ascitic fluid infection – no. (%)	2 (4)	1 (2)	1.00
Candidiasis (oral/esophageal) – no. (%)	6 (11)	4 (8)	0.75
Biliary leak – no. (%)	0 (0)	1 (2)	0.47
Choledocholithiasis – no. (%)	2 (4)	5 (10)	0.25
Cholecystitis – no. (%)	0 (0)	1 (2)	0.47
Cholecystectomy (biliary etiology) – no. (%)	6 (11)	8 (16)	0.57
Cholangitis – no. (%)	2 (4)	2 (4)	1.00
Cholestasis – no. (%)	0 (0)	1 (2)	0.47
Clostridium infection – no. (%)	7 (13)	1 (2)	0.06
Galbladder perforation – no. (%)	0 (0)	1 (2)	1.00
Gastric adenocarcinoma – no. (%)	0 (0)	1 (2)	0.47
Gastroparesis – no. (%)	6 (11)	5 (10)	1.00
High-output stoma – no. (%)	1 (2)	0 (0)	1.00
Jejunal stenosis – no. (%)	1 (2)	1 (2)	1.00
Nutritional problems – no. (%)	30 (55)	29 (59)	0.69
Endoscopic placement of feeding tube – no. (%)	26 (47)	24 (49)	1.00
Cortrak-assisted feeding tube insertion – no. (%)	8 (15)	7 (14)	1.00
Parenteral nutrition – no. (%)	5 (9)	4 (8)	1.00
Liver abcess – no. (%)	1 (2)	1 (2)	1.00
Peristomal abscesses – no. (%)	0 (0)	1 (2)	0.47
Reflux esophagitis – no. (%)	0 (0)	1 (2)	0.47
Cardiovascular			
Acute coronary syndrome – no. (%)	1 (2)	0 (0)	0.47
Angina pectoris – no. (%)	0 (0)	1 (2)	0.47
Atrial fibrillation – no. (%)	4 (7)	3 (6)	1.00
Cardiac arrhythmias – no. (%)	2 (4)	0 (0)	0.50
Cardiac asthma – no. (%)	1 (2)	0 (0)	1.00
Cardiomyopathy – no. (%)	1 (2)	0 (0)	1.00

Congestive heart failure – no. (%)	3 (5)	3 (6)	1.00
Fluid overload – no. (%)	12 (22)	6 (12)	0.30
Hypertension – no. (%)	4 (7)	1 (2)	0.37
Pericarditis – no. (%)	1 (2)	0 (0)	1.00
Pulmonary			
Aspiration pneumonia – no. (%)	0 (0)	2 (4)	0.22
Atelectasis – no. (%)	0 (0)	1 (2)	0.47
Pleural effusion – no. (%)	8 (15)	4 (8)	0.40
Pneumonia – no. (%)	5 (9)	3 (6)	0.72
Pneumothorax – no. (%)	1 (2)	0 (0)	1.00
Pulmonary embolism – no. (%)	2 (0)	0 (0)	0.50
Neurological			
Cerebrovascular accident – no. (%)	1 (2)	0 (0)	1.00
Delirium – no. (%)	8 (15)	9 (18)	0.61
Hemiparesis – no. (%)	1 (2)	0 (0)	1.00
Pressure neuropathy – no. (%)	2 (4)	1 (2)	1.00
Renal/urinary tract			
Electrolyte disorders – no. (%)	26 (47)	27 (55)	0.44
Hematuria – no. (%)	0 (0)	1 (2)	0.47
Hydronephrosis – no. (%)	1 (2)	0 (0)	1.00
Urinary tract infection – no. (%)	8 (15)	2 (4)	0.10
Musculoskeletal system			
Arthritis – no. (%)	1 (2)	0 (0)	1.00
Clavicle fracture – no. (%)	1 (2)	0 (0)	1.00
Gout – no. (%)	1 (2)	0 (0)	1.00
ICU required weakness – no. (%)	4 (7)	3 (6)	1.00
Tendinitis – no. (%)	0 (0)	1 (2)	0.47
Dermatologic			
Abdominal wall hematoma – no. (%)	0 (0)	1 (2)	0.47
Cellulitis – no. (%)	1 (2)	0 (0)	1.00
Dermatomycosis – no. (%)	2 (1)	1 (2)	1.00
Exanthema – no. (%)	0 (0)	2 (4)	0.22
Impaired wound healing – no. (%)	1 (2)	1 (2)	1.00
Intertrigo – no. (%)	1 (2)	0 (0)	1.00

Paracolostomy abscess – no. (%)	0 (0)	1 (2)	0.47
Pressure ulcers – no. (%)	2 (4)	4 (8)	0.42
Stomatitis – no. (%)	0 (0)	1 (2)	0.47
Urticaria – no. (%)	0 (0)	1 (2)	0.47
Hematologic			
Anemia – no. (%)	17 (31)	12 (24)	0.52
Thrombocytopenia - no. (%)	0 (0)	2 (4)	0.22
Heparin induced thrombocytopenia – no. (%)	1 (2)	1 (2)	1.00
Hypertriglyceridemia – no. (%)	0 (0)	1 (2)	0.47
Infected aortic graft – no. (%)	1 (2)	0 (0)	1.00
Neutropenia – no. (%)	0 (0)	1 (2)	0.47
Phlebitis – no. (%)	5 (9)	3 (6)	0.72
Splenic vein or deep vein thrombosis – no. (%)	7 (13)	8 (16)	0.38
Thrombophlebitis – no. (%)	0 (0)	1 (2)	0.47
Other			
Adrenal insufficiency – no. (%)	1 (2)	0 (0)	0.47
Adenocarcinoma of unknown primary site – no. (%)	0 (0)	1 (2)	0.47
Allergy (e.g. contrast) – no. (%)	3 (5)	0 (0)	0.26
Anxiety disorder – no. (%)	0 (0)	1 (2)	0.47
Bacteremia – no. (%)	9 (16)	8 (16)	1.00
Benzodiazepine overdose – no. (%)	1 (2)	0 (0)	1.00
CMV infection – no. (%)	1 (2)	0 (0)	1.00
Drug allergy – no. (%)	1 (2)	2 (4)	0.60
Herpes simplex conjunctivitis – no. (%)	1 (2)	0 (0)	1.00

Data are n (%).

[#] The above mentioned adverse events and some of the major complications that were defined as secondary endpoints, were used to calculate the Comprehensive Complication Index (CCI) for each patient. Pre-existent complications prior to randomization were not included in the CCI.

* Patients could have more than one adverse event, therefore no statistical testing was performed.

Table S8. Number of patients per Clavien-Dindo classification

Outcome	Immediate catheter drainage (*n* = 55)	Postponed catheter drainage (*n* = 49)	Relative Risk (95% CI)
Clavien-Dindo grade I – no. (%)	41 (75)	35 (71)	1.04 (0.83 to 1.32)
Clavien-Dindo grade II – no. (%)	47 (85)	33 (67)	1.27 (1.01 to 1.59)
Clavien-Dindo grade IIIa – no. (%)	36 (65)	37 (76)	0.87 (0.68 to 1.11)
Clavien-Dindo grade IIIb – no. (%)	9 (16)	11 (22)	0.73 (0.33 to 1.61)
Clavien-Dindo grade IVa – no. (%)	9 (16)	6 (12)	1.34 (0.51 to 3.49)
Clavien-Dindo grade IVb – no. (%)	3 (5)	8 (16)	0.33 (0.09 to 1.19)

Data are n (%).

Table S9. Sample size by participating center

Participating center	Total per center (n)
Amsterdam UMC, location AMC	18
St. Antonius Hospital	17
Meander Medical Center	10
OLVG	7
Amphia Hospital	6
Erasmus MC University Medical Center	6
Gelre Hospital	6
Maasstad Hospital	4
Medisch Spectrum Twente	4
Maastricht University Medical Center+	4
University Medical Center Groningen	4
Radboud University Medical Center	3
Medical Center Leeuwarden	3
Isala Clinics	2
Jeroen Bosch Hospital	2
Maxima Medical Center	2
Albert Schweitzer Hospital	1
Leiden University Medical Center	1
Reinier de Graaf Gasthuis	1
University Medical Center Utrecht	1
Amsterdam UMC, location VUMC	1
Hospital Gelderse Vallei	1
Total	**104**

Table S10. Imaging received by both intervention groups

	Immediate catheter drainage (*n* = 55)	Postponed catheter drainage (*n* = 49)
Diagnostic imaging		
CT abdomen – mean ± SD	5.7 ± 3.9	5.1 ± 4.8
CT chest – mean ± SD	0.4 ± 0.9	0.6 ± 1.8
Abdominal ultrasound – mean ± SD	0.8 ± 1.1	0.8 ± 1.4
X-ray chest – mean ± SD	4.0 ± 4.6	4.2 ± 6.0
X-ray abdomen – mean ± SD	0.9 ± 1.4	0.7 ± 1.2
MRI/MRCP – mean ± SD	0.1 ± 0.4	0.1 ± 0.3
Image-guided therapeutic procedures		
Endoscopy		
Endoscopic retrograde cholangiopancreatography – mean ± SD	0.1 ± 0.3	0.3 ± 0.7
Endoscopic transluminal drainage – mean ± SD	0.8 ± 0.8	0.5 ± 0.7
Endoscopic transluminal necrosectomy – mean ± SD	1.1 ± 1.9	0.6 ± 1.6
Endoscopic feeding tube placement – mean ± SD	1.4 ± 1.5	1.0 ± 1.2
Radiology		
Image-guided percutaneous catheter drainage – mean ± SD	2.3 ± 2.6	1.4 ± 2.4
Ascites drainage – mean ± SD	0.2 ± 0.7	0.1 ± 0.5
Pleural drainage – mean ± SD	0.1 ± 0.3	0.1 ± 0.4
X-guided percutaneous transhepatic biliary drainage – mean ± SD	0.1 ± 0.6	0.0 ± 0.2
Ultrasound-guided percutaneous transhepatic biliary drainage – mean ± SD	0.1 ± 0.3	0.0 ± 0.0
Ultrasound-guided gallbladder drainage – mean ± SD	0.0 ± 0.0	0.0 ± 0.1

Data are mean ± SD.

Table S11. Post-hoc sensitivity analysis excluding patients with necrosis extending > 5 cm down the retrocolic gutter

	Patients without necrosis > 5 cm in retrocolic gutter (*n* = 42)		
Outcome	**Immediate catheter drainage (*n* = 22)**	**Postponed catheter drainage (*n* = 26)**	**Mean difference (95% CI)**
Primary end point			
Comprehensive Complication Index – mean (95% CI)	48 (37 to 61)	57 (47 to 70)	-9 (-25 to 7)

Data are mean (95% CI).

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