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Short-term and Long-term Outcomes of a Disruption and Disconnection of the Pancreatic Duct in Necrotizing Pancreatitis: A Multicenter Cohort Study in 896 Patients

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INTRODUCTION: **Necrotizing pancreatitis may result in a disrupted or disconnected pancreatic duct (DPD) with the potential for long-lasting negative impact on a patient's clinical outcome. There is a lack of detailed data on the full clinical spectrum of DPD, which is critical for the development of better diagnostic and treatment strategies.**

METHODS: **We performed a long-term *post hoc* analysis of a prospectively collected nationwide cohort of 896 patients with necrotizing pancreatitis (2005–2015). The median follow-up after hospital admission was 75 months (P25–P75: 41–151). Clinical outcomes of patients with and without DPD were compared using regression analyses, adjusted for potential confounders. Predictive features for DPD were explored.**

RESULTS: **DPD was confirmed in 243 (27%) of the 896 patients and resulted in worse clinical outcomes during both the patient's initial admission and follow-up. During hospital admission, DPD was associated with an increased rate of new-onset intensive care unit admission (adjusted odds ratio [aOR] 2.52; 95% confidence interval [CI] 1.62–3.93), new-onset organ failure (aOR 2.26; 95% CI 1.45–3.55), infected necrosis (aOR 4.63; 95% CI 2.87–7.64), and pancreatic interventions (aOR 7.55; 95% CI 4.23–13.96). During long-term follow-up, DPD increased the risk of pancreatic intervention (aOR 9.71; 95% CI 5.37–18.30), recurrent pancreatitis (aOR 2.08; 95% CI 1.32–3.29), chronic pancreatitis (aOR 2.73; 95% CI 1.47–5.15), and endocrine pancreatic insufficiency (aOR 1.63; 95% CI 1.05–2.53). Central or subtotal pancreatic necrosis on computed tomography (OR 9.49; 95% CI 6.31–14.29) and a high level of serum C-reactive protein in the first 48 hours after admission (per 10-point increase, OR 1.02; 95% CI 1.00–1.03) were identified as independent predictors for developing DPD.**

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DISCUSSION: **At least 1 of every 4 patients with necrotizing pancreatitis experience DPD, which is associated with detrimental, short-term and long-term interventions, and complications. Central and subtotal pancreatic necrosis and high levels of serum C-reactive protein in the first 48 hours are independent predictors for DPD.**

KEYWORDS: disconnected pancreatic duct syndrome; pancreatic duct leak; pancreatic necrosis

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/C847

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INTRODUCTION

Necrosis of the pancreatic parenchyma in acute pancreatitis may result in the integrity loss of the pancreatic duct. This can either be a partial disruption or a complete disconnection of the pancreatic duct (1–3), both resulting in leakage of pancreatic fluid leading to persistent or recurrent peripancreatic collections, pancreatic ascites, or external pancreatic fistulas (2–14).

A disrupted or disconnected pancreatic duct (DPD) is an increasingly reported entity (2–17), with estimated incidence rates varying from 10% to 50% (9,15,16,18). This may be due to a lack of a standardized and evidence-based diagnostic workup (19–21). Several distinct diagnostic modalities are reported to be used in daily clinical practice to diagnose DPD (2,6,9,10,13,22–25).

Moreover, the exact clinical impact of DPD remains unclear (26), with a lack of study into the long-term health implications of DPD in patients with necrotizing pancreatitis. It is generally believed that DPD has a large detrimental impact on a patient's clinical burden and is associated with high healthcare resource utilization (6,9,10,13,16,27). In particular, DPD has been linked to endocrine pancreatic insufficiency after necrotizing pancreatitis (28–30). However, studies on this topic do not cover the entire clinical spectrum of patients with necrotizing pancreatitis; primarily focused on reporting specific clinical outcomes, with either small sample sizes or selected study populations (e.g., only patients undergoing a certain invasive intervention). Only a few studies have addressed other long-term consequences of DPD; however, these studies were generally conducted retrospectively in small selected populations (13,16,27–30). In particular, data on late presentation of consequences of DPD, such as recurrent pancreatitis and chronic pancreatitis, are lacking.

The treatment for DPD range widely from conservative options to invasive radiological, endoscopic, or surgical interventions (14). International treatment guidelines include conflicting recommendations regarding the choice of treatment plan (19–21). This is driven by a lack of understanding on the treatment outcomes across the entire DPD population because most studies report only on selected patients undergoing specific treatment modalities (31). There are currently no tools to predict which patients are at a greater risk of developing DPD. A predictive tool would aid in determining an appropriate treatment plan early in the disease course to prevent further complications and improve patient health outcomes.

Therefore, more data are needed on the full clinical spectrum and predictive indicators of DPD to ultimately improve the timing and choice of diagnostic and treatment strategies. We performed a long-term analysis on a nationwide prospectively collected patient cohort to evaluate the incidence, diagnosis, clinical outcomes, and treatment of DPD in necrotizing pancreatitis. Furthermore, we designed a prediction model for the development of DPD.

METHODS

Study design and population

We performed a *post hoc* analysis of patients included in the prospective nationwide registry of acute pancreatitis (PWN-CORE) of the Dutch Pancreatitis Study Group. A subset of patients in the registry has been included in previously published randomized trials (32,33). For this study, we selected all patients older than 18 years with necrotizing pancreatitis who were treated between November 1, 2005, and December 31, 2015, in 27 hospitals. Patients were excluded in cases of definite chronic pancreatitis according to the M-ANNHEIM criteria (34), pancreatic carcinoma during the index hospital admission, or traumatic etiology of pancreatitis. PWN-CORE and each of the trials were approved by a central medical ethics committee and by each participating hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki. We adhered to the Strengthening the Reporting of Observational studies in Epidemiology guidelines (35). Written informed consent was provided for all patients. Treatment of acute pancreatitis was according to the international guidelines for management of acute pancreatitis (20,21). The Dutch Association for patients with pancreatic disease, the Alvleesklierevereniging, was actively involved in the design of the abovementioned trials and registration cohort. Their board members were also present during research meetings of the Dutch Pancreatitis Study Group.

Definitions

Acute pancreatitis was diagnosed according to the revised Atlanta classification, that is, at least 2 of 3 of the following criteria: (i) clinical presentation with abdominal pain, (ii) serum amylase or lipase levels exceeding 3 times the upper limit of normal, and/or (iii) abdominal imaging–confirmed diagnosis of acute pancreatitis (36). All patients underwent computed tomography (CT) during index admission. Necrotizing pancreatitis was defined as a CT severity index score of 3 or higher (37). An expert pancreatic radiologist (T.L.B.) reviewed all available abdominal radiological images. This review included assessment of the CT severity index (as assessed on the first available CT $\geq$5 days after onset of disease), the presence and location of peripancreatic collections and (peri)pancreatic necrosis, and the presence of DPD. In daily clinical practice, not all patients who might have had DPD underwent routine evaluation of the pancreatic duct through imaging. Because we wanted to cover the entire spectrum of DPD, we approached the occurrence of DPD pragmatically and made the following distinction: (i) no DPD; (ii) possible DPD, and (iii) confirmed DPD. Patients were classified *post hoc* by the study team using a standardized approach.

Confirmed DPD was defined by the presence of 1 or more of the following: (i) (radiological) confirmation by: (A) endoscopic

retrograde cholangiopancreaticography (ERCP); (a) extravasation of contrast medium from the ductal system or (b) a cutoff or blowout of the pancreatic duct with inability to demonstrate the upstream pancreatic duct; (B) magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP): an interruption of pancreatic ductal continuity (24,38–40); or (C) fluoroscopic fistulography: a connection between the pancreatic duct and the external environment (25,41–45) or (ii) functional confirmation: an amylase level in external drain fluid, more than 1 day after placement of the percutaneous catheter drain, exceeding 3 times the upper limit of normal amylase serum level (46). Based on the available data, no distinction could be made between the presence of a partial disruption or circumferential disconnection with the current data.

Possible DPD was defined as 1 or more of the following criteria and without meeting the criteria for confirmed DPD: (i) morphological signs on imaging, defined as central or subtotal pancreatic necrosis, (ii) amylase or lipase levels exceeding 3 times the upper limit of normal in fluid obtained during endoscopic drainage (not from percutaneous catheter drain fluid), (iii) the presence of other types of internal pancreatic fistula defined as a connection between the pancreas and any other organ depending on the site of the fistula (pleural and common bile duct), and (iv) the need for long-term (≥90 days) percutaneous catheter drainage without an amylase measurement in drain fluid.

Other outcomes included endoscopic and radiological diagnostics for DPD, time to diagnosis, and resolution of DPD (defined as the date of last intervention without the need for a follow-up intervention, when no new interventions are required with an endoscopic drain still in place, or the date of removal of the last percutaneous catheter drain). Clinical outcomes included the following: mortality, early and overall transient and persistent organ failure, abdominal compartment syndrome, gastrointestinal complications, infected necrosis, a number of pancreatic interventions (e.g., radiological/endoscopic/surgical), readmission, long-term complications of endocrine and exocrine pancreatic insufficiency, recurrent pancreatitis, and definite chronic pancreatitis according to the M-ANNHEIM criteria (34). Clinical outcomes were reported only when occurring more than 7 days after admission; the 7-day cutoff value has been deliberately chosen and was based on the hypothesis that DPD occurs during necrosis. Because necrosis generally develops in the first week, we also expect DPD to develop around that time. Therefore, we included only the clinical outcome that occurred more than 7 days after admission. Detailed definitions for these outcomes were established after a careful review of the current literature in research meetings of the Dutch Pancreatitis Study Group and are summarized in the Supplementary Appendix Table S1 (see Supplementary Digital Content 1, http://links.lww.com/AJG/C847).

Data collection

Using a standardized case-record form, clinical data were collected prospectively during the initial hospital admission, and follow-up data were collected retrospectively in January 2020. If at any time before or during follow-up a patient was transferred to a different hospital, all the required follow-up data were retrieved from the relevant hospitals. All data were imported by 1 author (H.C.T.) in Open Clinica and verified by a second author (S.M.v.D.). Discrepancies were resolved by consensus during research meetings of the Dutch Pancreatitis Study Group. All authors had access to the study data and reviewed and approved the final manuscript.

Statistical analysis

Patient and disease characteristics and diagnostic modalities were described, for both patients with confirmed DPD and those with possible DPD. Short-term and long-term clinical outcomes and interventions were compared across all categories of patients (confirmed, without DPD, and possible DPD). Multivariate regression analyses were performed to adjust for potential confounders. The clinical outcome was defined as the dependent variable. The covariates varied by clinical outcome and were a combination of the following: presence of confirmed (or in case of the multivariate sensitivity analysis also possible) DPD, age, sex, American Society of Anesthesiologists (ASA) classification, presence of parenchymal necrosis, extent of necrosis, occurrence of infected necrosis, and occurrence of early onset of organ failure after admission (all covariates included per outcome are listed in the supplementary appendix and were based on clinical reasoning, baseline differences, and current literature; see Supplementary Appendix Table S2, Supplementary Digital Content 1, http://links.lww.com/AJG/C847). Because multiple comparisons (n = 20) were performed, the Bonferroni correction was applied. A corrected P value of <0.0025 was considered significant. Two univariate sensitivity analyses were performed: (i) comparing patients without DPD with patients in whom DPD was confirmed with an amylase level exceeding 3 times the upper limit and (ii) comparing patients with functional DPD with patients with only imaging-based DPD. The different treatment strategies for a confirmed DPD were described and visualized using a Sankey diagram. This included radiological/endoscopic/surgical pancreatic interventions for both confirmed DPD and for infected necrosis because, in daily practice, there is often an overlap across both indications in the event of an intervention.

Second, a prediction model was designed to identify predictive indicators for the development of a confirmed DPD. We fitted a multivariable logistic regression model both with and without restricted cubic splines to identify potential nonlinear relationships between predictors and the outcome. Predictors were identified based on clinical reasoning among members of the study group. The choice of the predictors was further supported by univariate analysis of the patient characteristics (see Supplementary Appendix Table S2, Supplementary Digital Content 1, http://links.lww.com/AJG/C847) and using a full model strategy using 6 variables: age, sex, ASA classification, leukocyte count at admission, C-reactive protein (CRP) at admission, and pattern of parenchymal necrosis. Owing to the limited number of cases, the ASA classification was categorized into ASA I (reference), ASA II, and ASA ≥III. Likewise, we decided to reduce the patterns of parenchymal necrosis to (i) no necrosis (reference), (ii) central or subtotal, and (iii) right, left, or diffuse, while neglecting the percentage of necrotizing tissue that was involved. Missing values were multiply imputed using the R-package MICE. We generated 50 data sets and pooled the results across the data sets using Rubin rules. Model discrimination was evaluated in the derivation data using the c-statistic (i.e., area under the receiving operator curve). Neither internal nor external validation was attempted because this model was conceived for exploratory purposes only.

Descriptive data were reported as mean with SD when normally distributed and as median with the 25th and 75th percentiles (P25–P75) when not normally distributed. Categorical data

were shown as frequencies and percentages. Statistical comparison was performed using the Fisher exact test or χ^2 test for categorical data and the Student *t* test or the Mann-Whitney *U* test for continuous data. A *P* value <0.05 (not corrected) or <0.0025 (corrected) was considered statistically significant. We calculated risk ratios and (adjusted) odds ratios (OR) with their respective 95% confidence intervals (CI). Statistical analysis was performed using R, R version 3.6.1 (2019-07-05).

RESULTS

Between November 2005 and December 2015, 2,289 patients with acute pancreatitis were included in the prospective registry. Of this cohort, 896 patients had necrotizing pancreatitis and were included in this study (Figure 1). The median follow-up duration after hospital admission was 75 months (P25–P75: 41–151). Patient and disease characteristics are summarized in Table 1.

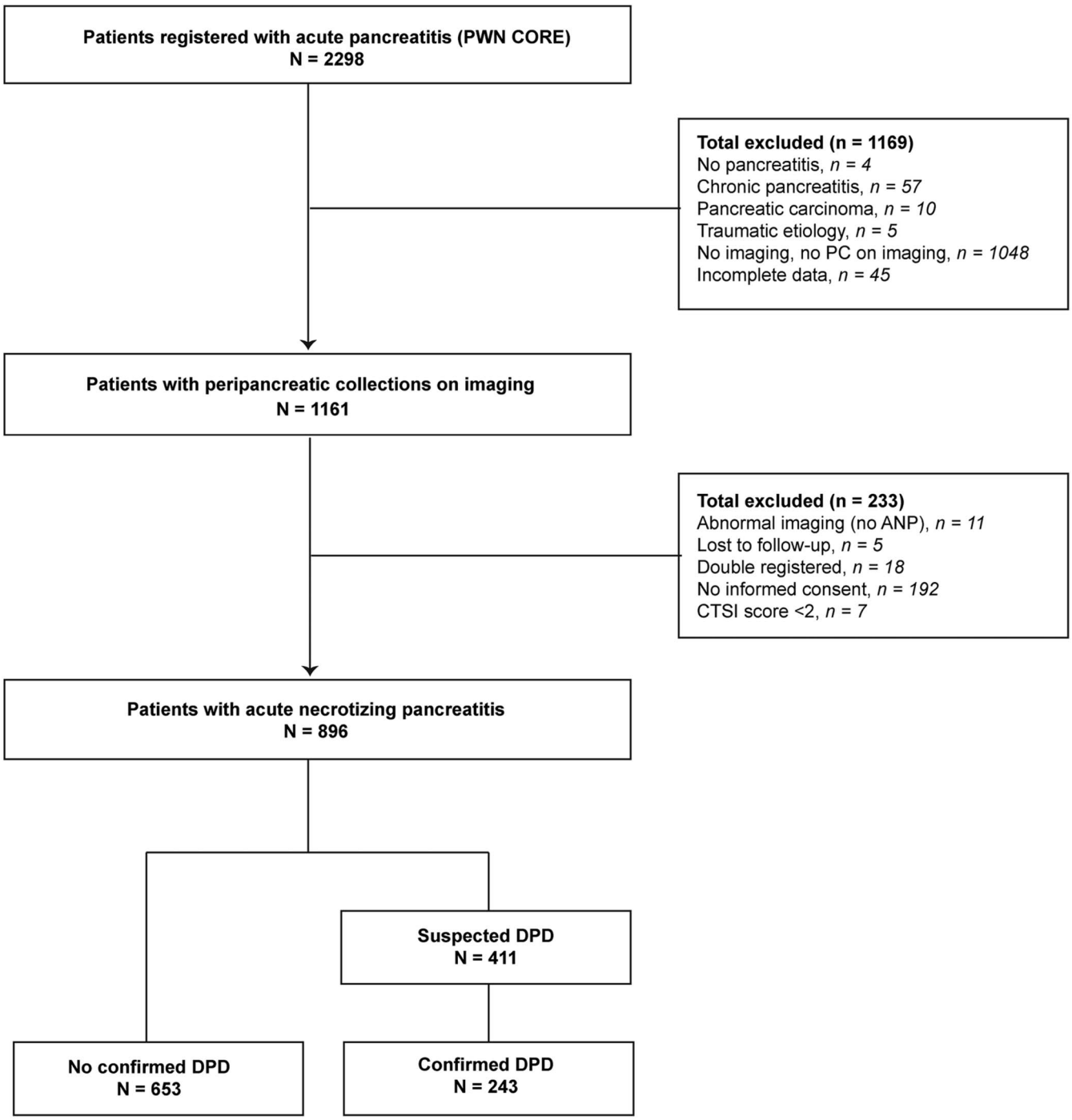

Figure 1. Flowchart of patient inclusion. ANP, acute necrotizing pancreatitis; CTSI, computed tomography severity index; DPD, disruption or disconnection of the pancreatic duct; N, number; PC, peripancreatic or pancreatic collection; PWN CORE Dutch Acute Pancreatitis Registry.

Table 1. Patient and disease characteristics in 896 patients with necrotizing pancreatitis

	Overall (N = 896)	No DPD (N = 653)	Confirmed DPD (N = 243)
Age (yr)	58 (47–69)	59 (47–70)	58 (46–68)
Male sex	571 (64)	402 (62)	169 (70)
Etiology			
Biliary	432 (48)	320 (49)	112 (46)
Alcohol	159 (18)	120 (18)	39 (16)
Post-ERCP	31 (4)	26 (4)	5 (2)
Idiopathic	180 (20)	122 (19)	58 (24)
Other	94 (11)	65 (10)	29 (12)
Medical history			
Cardiovascular	377 (42)[a]	281 (43)[cc]	96 (40)[t]
Pulmonary	91 (10)[b]	65 (10)[dd]	26 (11)[u]
Chronic renal	28 (3)[c]	21 (3)[ee]	7 (3)[v]
Diabetes mellitus	108 (12)[d]	81 (12)[ff]	27 (11)[w]
ASA classification			
1	298 (33)	223 (34)	75 (31)
2	471 (53)	336 (52)	135 (56)
3	123 (14)	91 (14)	32 (13)
4	4 (0.4)	3 (1)	1 (0.4)
Smoking, yes	130 (15)[e]	87 (13)[gg]	43 (18)[x]
Alcohol use, yes	357 (67)	255 (67)	102 (68)
BMI	27.1 (25–30.7)[f]	26.9 (25–30.7)[hh]	27.4 (25.1–30.8)[y]
Laboratory values			
Leukocytes (10^9/L)	18.2 (14.4–22.2)[g]	18 (14.3–21.9)[ii]	18.6 (14.8–23)[z]
CRP (mg/L)	297 (216–377)[h]	289 (201–359)[jj]	334 (239–425)[aa]
Imaging severity			
CT severity index	6 (4–8)[i]	5 (4–6)[kk]	8 (6–10)
Parenchymal necrosis	542 (60)[j]	330 (51)	212 (87)
Right	15 (2)	11 (2)	4 (2)
Left	52 (6)	43 (7)	9 (4)
Central	233 (26)	104 (16)	129 (53)
Subtotal	76 (8)	34 (5)	42 (17)
Diffuse	161 (18)	136 (21)	25 (10)
Extent of necrosis	[j]		[bb]
<30%	259 (29)	186 (56)	73 (30)
30%–50%	132 (15)	76 (23)	56 (23)
>50%	150 (17)	68 (21)	82 (34)
Extrapancreatic necrosis only	354 (40)	323 (49)	31 (13)
Follow-up	75 (41–151)	76 (41–151)	72 (40–150)

Data are presented as n (%) or median (interquartile range).
Missing patients: a = 3, b = 3, c = 3, d = 2, e = 477, f = 494, g = 82, h = 125, i = 8, j = 1 missing data on pattern and extent of parenchymal necrosis, k = 2, l = 2, m = 2, n = 2, o = 167, p = 217, q = 39, r = 52, s = 1, t = 1, u = 1, v = 1, w = 1, x = 126, y = 130, z = 26, aa = 34, bb = 1, cc = 2, dd = 2, ee = 2, ff = 1, gg = 351, hh = 364, ii = 56, jj = 91, kk = 1.
ASA, American Society of Anaesthesiologists; BMI, body mass index; CRP, C-reactive protein; CT, computed tomography; DPD, disruption or disconnection of the pancreatic duct; ERCP, endoscopic retrograde cholangiopancreaticography; N, number.

Diagnosis

A possible DPD occurred in 415 of 896 patients (46%), and DPD was confirmed in 243 of 896 patients (27%). Time to diagnosis for confirmed DPD was 57 (P25–P75: 28–116) days after admission. Univariate comparison of patient characteristics for patients with and without DPD is provided in the supplementary appendix (see Supplementary Appendix Table S2, Supplementary Digital Content 1, http://links.lww.com/AJG/C847). Of the 243 patients with confirmed DPD, the diagnosis was based on imaging findings in 103 patients (42%). In 55 of the 103 patients (53%), the diagnosis was also confirmed through an amylase level in drain fluid exceeding 3 times the upper limit. In most patients, DPD was confirmed with either MRI/MRCP (n = 37, 36%), ERCP (n = 26, 25%), or on both MRI/MRCP and ERCP (n = 20, 19%). In 204 of 320 (64%) patients who underwent a percutaneous catheter drainage, amylase level was measured with a median of 16,300 U/L (P25–P75: 1,905–63,070). In 140 of 243 patients (58%), DPD was confirmed only by an amylase level exceeding 3 times the upper limit (median 24,001 U/L; P25–P75: 5,952–65,550) in drain fluid after a median of 22 days (P25–P75: 2–66) after the first intervention. The median number of amylase measurements in these patients was 3 (P25–P75: 1–5). More details on diagnostic modalities used for diagnosing a confirmed DPD are summarized in the supplementary appendix (see Supplementary Appendix Table S3, Supplementary Digital Content 1, http://links.lww.com/AJG/C847).

Clinical outcome

Infected necrosis occurred in 481 of the 896 patients (54%). Invasive intervention of the pancreas was performed in 465 patients (52%). A total of 223 patients (25%) died during initial admission or follow-up thereafter; cause of death was directly related to pancreatitis in 106 patients (48%). In 245 of 896 patients (27%) a pancreatic fistula was identified, in whom DPD could not always be confirmed. The most frequently reported type of pancreatic fistula was a pancreato-cutaneous fistula (n = 186, 45%). All morphological characteristics and functional findings of DPD are listed in Table 2. Univariate analyses regarding clinical outcomes, pancreatic interventions, and long-term complications in patients with and without confirmed DPD are presented in the supplementary appendix (see Supplementary Appendix Table S4, Supplementary Digital Content 1, http://links.lww.com/AJG/C847).

The results of the multivariate analyses, fit to quantify the independent effect of confirmed DPD on the different clinical outcomes and need for interventions occurring more than 1 week after admission, are summarized in Table 3. A confirmed DPD was associated with new-onset intensive care unit admission (adjusted OR [aOR] 2.52; 95% CI 1.62–3.93), persistent or new-onset organ failure (aOR 2.80; 95% CI 1.71–4.60 and a OR 2.26; 95% CI 1.45–3.55), and with the occurrence of infected necrosis (aOR 4.63; 95% CI 2.87–7.64). Associations were also found between confirmed DPD and pancreatic intervention (aOR 7.55; 95% CI 4.23–13.96), additional pancreatic intervention (aOR 2.62; 95% CI 1.57–4.42), and pancreatic interventions during follow-up (aOR 9.71; 95% CI 5.37–18.30). Patients with a confirmed DPD were more frequently readmitted (aOR 3.40; 95% CI 2.21–5.33), particularly for readmissions related to reintervention (aOR 3.19; 95% CI 1.94–5.36). Furthermore, a confirmed DPD was associated with a higher risk of recurrent pancreatitis (aOR 2.08; 95% CI 1.32–3.29), chronic pancreatitis (aOR 2.73; 95% CI 1.47–5.15), and endocrine pancreatic insufficiency (aOR 1.63; 95% CI 1.05–2.53). Multivariate sensitivity analyses, fit to quantify the independent effect of possible DPD on the different clinical outcomes and need for interventions occurring more than 1 week after admission, are summarized in Supplementary Appendix Table S5 (see Supplementary Digital Content 1, http://links.lww.com/AJG/C847). A univariate sensitivity analysis comparing patients without DPD with patients with DPD confirmed solely by an amylase level exceeding 3 times the upper limit did not show any differences in outcome (see Supplementary Appendix Table S6, Supplementary Digital Content 1, http://links.lww.com/AJG/C847). In a second univariate analysis, a worse clinical outcome was found for patients with functional DPD compared with patients with only imaging-based DPD (see Supplementary Appendix Table S7, Supplementary Digital Content 1, http://links.lww.com/AJG/C847).

Table 2. Morphological characteristics and functional findings of a disrupted or disconnected pancreatic duct

	Confirmed DPD (N = 243 [27%])	Possible DPD (N = 415 [46%])
Morphological characteristics*	169 (70)[a]	310 (75)[f]
DPD on imaging	103 (42)	NA
Functional: High amylase in percutaneous drain fluid	194 (84)[b]	NA[g]
Clinical findings		
High amylase during ETD	10 (13)[c]	19 (13)[h]
Pancreatic fistula present†	188 (77)	194 (47)
Long-term drainage	96 (40)[d]	114 (28)[i]
Recurrent collection	93 (38)[e]	120 (29)[j]
Pancreatic fistula (n = 198)	190 (78)	197 (47)
Pancreatic cutaneous fistula (n = 186)	183 (75)	186 (45)
Pancreatic abdominal fistula (n = 27)	27 (11)	27 (7)
Pancreatic pleural fistula (n = 11)	10 (4)	11 (3)
Pancreatic CBD fistula (n = 7)	5 (2)	7 (2)

Data are presented as n (%).
*Central or subtotal necrosis.
†Excluding fistulas of the gastrointestinal tract.
a = 3 missing, b = in 11 patients, no percutaneous intervention was performed, c = in 166 patients, no ETD was performed, and in 67 patients, ETD was performed with low amylase in drain fluid or no amylase measurement, d = 2 missing patients, 29 patients died before removal of drain, e = in 15 patients, no follow-up CT was performed, in 13 patients, no intervention was performed and therefore not applicable, 34 patients died within 6 months after discharge before recurrent collection could occur, f = 3 missing, g = in 48 patients, no percutaneous intervention was performed, h = in 270 patients, no ETD was performed, and in 126 patients, ETD was performed with low amylase or no amylase measurement, i = 2 missing patients, 48 patients died before removal of drain, and j = in 40 patients, no follow-up CT was performed, in 36 patients, no intervention was performed and therefore not applicable, 65 patients died within 6 months after discharge before recurrent collection could occur.
CBD, common bile duct; CT, computed tomography; DPD, disrupted or disconnected pancreatic duct; ETD, endoscopic transluminal drainage; NA, not available.

Table 3. Comparison of patients with and without confirmed DPD and its association with clinical outcome, interventions, and long-term complications occurring more than 7 days after admission

	Overall (N = 896)	Confirmed DPD		OR (95% CI)*	*P* value†
		No (N = 653)	Yes (N = 243)		
Death pancreatitis related					
Death after 7 d	98 (11)	62 (10)	36 (15)	1.26 (0.74–2.14)	0.389
ICU admission					
Ongoing	231 (31)[c]	132 (23)[i]	99 (56)[c]	6.81 (2.83–17.02)	<**0.001**
New onset	218 (25)[d]	27 (21)[i]	30 (31)[c]	2.52 (1.62–3.93)	<**0.001**
Organ failure					
Ongoing	173 (48)[e]	95 (15)[t]	78 (32)[n]	2.80 (1.71–4.60)	<**0.001**
Ongoing MOF	115 (71)[f]	57 (63)	58 (79)	3.11 (1.78–5.45)	<**0.001**
New onset	204 (56)[a]	109 (17)[b]	95 (40)[i]	2.26 (1.45–3.55)	**0.001**
New onset MOF	142 (71)[e]	74 (69)[i]	68 (74)[bb]	2.32 (1.40–3.85)	**0.001**
Infected necrosis	442 (50)[a]	245 (38)[c]	197 (81)[n]	4.63 (2.87–7.64)	<**0.001**
Gastrointestinal complications‡	123 (14)[a]	51 (8)[i]	72 (30)[b]	3.00 (1.87–4.88)	<**0.001**
Interventions					
Pancreatic intervention	459 (52)	238 (99)	221 (98)	7.55 (4.23–13.96)	<**0.001**
Percutaneous catheter drainage	319 (36)	141 (22)	178 (73)	6.29 (4.14–9.67)	<**0.001**
Need for additional intervention	355 (77)	161 (68)	194 (86)	2.62 (1.57–4.42)	<**0.001**
Follow-up intervention	83 (18)	22 (9)	61 (27)	9.71 (5.37–18.30)	<**0.001**
Ascites drainage	77 (9)	26 (4)[n]	51 (21)[b]	5.15 (2.93–9.30)	<**0.001**
Readmission					
Readmission	601 (68)	403 (62)	198 (81)	3.40 (2.21–5.33)	<**0.001**
For reintervention	118 (20)	38 (9)	80 (40)	3.19 (1.94–5.36)	<**0.001**
Long-term complications					
Recurrent pancreatitis	196 (25)[j]	124 (21)[z]	72 (30)[cc]	2.08 (1.32–3.29)	**0.002**
Chronic pancreatitis	84 (11)[k]	42 (7)[aa]	42 (17)[dd]	2.73 (1.47–5.15)	**0.002**
Endocrine pancreatic insufficiency	241 (30)[l]	130 (23)[aa]	111 (46)[ee]	1.63 (1.05–2.53)	0.030
Exocrine pancreatic insufficiency	160 (20)[m]	86 (15)[aa]	74 (34)[ff]	1.35 (0.85–2.15)	0.200

Data are presented as n (%) or median (interquartile range).
*Binomial regression (binary data): patients (n = 8) who died in the first week after admission were excluded for analysis.
†After the Bonferroni correction was applied, the correct *P* value considered statistically significant was <0.0025.
‡Including gastrointestinal fistulas.
The statistically significant *P* values are stated in bold.
Missing patients: a = 5, b = 2, c = 4, d = 7, e = 9, f = 17, g = 10, h = 183, i = 3, j = 105, k = 109, l = 102 patients excluded within 1 year after admission and therefore excluded in case potential outcome was not reached yet, m = 103 patients excluded within 1 year after admission and therefore excluded in case potential outcome was not reached yet, n = 1, o = 12, p = 38, q = 40, r = 40, s = 41, t = 8, u = 23, v = 67, w = 69, x = 62, y = 63, z = 73, aa = 75, bb = 6, cc = 32, dd = 33, ee = 26, and ff = 28.
CI, confidence interval; DPD, disrupted or disconnected pancreatic duct; ICU, intensive care unit; MOF, multiple organ failure; N, number; OR, odds ratio; SOF, single organ failure.

Treatment

The wide range of treatment strategies for patients with confirmed DPD is shown in the Sankey diagram (Figure 2). Overall, 33 of 243 patients (14%) died before resolution of DPD. DPD was resolved in the remaining 208 patients with 138 of 208 patients (66%) requiring only 1 step of treatment. After the last step of treatment for DPD, 45 of 208 patients (22%) had a recurrent peripancreatic collection that did not require intervention; this condition occurred most frequently after percutaneous catheter drainage as the final step of treatment. The median duration to resolution of DPD was 182 (P25–P75: 103–452) days.

Conservative treatment (i.e., no invasive intervention), was initiated in 14 patients (6%) with a confirmed DPD. No data on drug therapy were available. Four patients (29%) had a recurrent peripancreatic collection. Three of the 4 patients (75%) underwent endoscopic transluminal drainage.

Percutaneous catheter drainage was the first treatment step in 184 patients (76%) with confirmed DPD. Percutaneous catheter drainage during the index admission was sufficient for 108 patients (59%), with the remaining 76 patients (41%) requiring other types of invasive interventions. Of the 108 patients who required only percutaneous catheter drainage, 27 (25%) had recurrent peripancreatic collections during follow-up that were

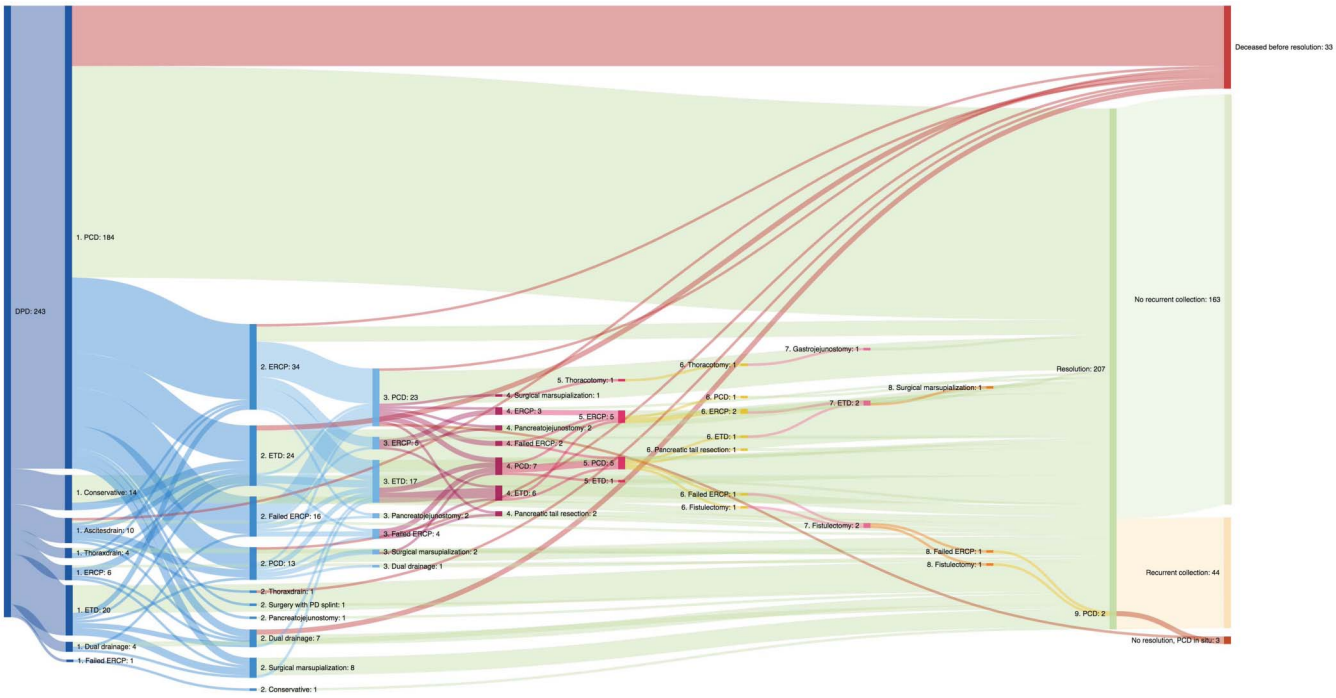

Figure 2. The Sankey diagram of different treatment steps in 243 patients with a confirmed disrupted or disconnected pancreatic duct. Resolution of DPD was defined as the date the patient underwent the last endoscopic or surgical intervention or in case a percutaneous catheter drain was left during the last intervention, the date the last percutaneous catheter drain was removed. DPD, disruption or disconnection of the pancreatic duct; ERCP, endoscopic retrograde cholangiopancreaticography; ETD, endoscopic transluminal drainage; PCD, percutaneous catheter drainage; PD, pancreatic duct.

treated conservatively. The median time to resolution of DPD for patients treated only with percutaneous catheter drainage was 131 days (P25–P75: 87–206).

Endoscopic transluminal drainage was performed as a first treatment step in 20 patients (8%), with removal of the plastic pigtails in 15 of the 20 patients (75%). In 9 of the 15 patients (60%), an additional invasive intervention was required after removal of the plastic pigtails. The median time until resolution was 112 days (P25–P75: 55–153). In 76 patients (31%), whose treatment did not initiate with endoscopic transluminal drainage, endoscopic transluminal drainage was performed as part of a follow-up procedure. This resulted in resolution of DPD in 51 patients (76%). In 6 of the patients (9%), peripancreatic collections recurred after removal of the last plastic pigtails.

Endoscopic retrograde cholangiopancreatography was the initial treatment in 5 patients (2%). In 61 patients (25%), an ERCP with stent placement into the pancreatic duct was attempted in conjunction to other treatment modalities with successful stent placement in 42 patients (69%). In 2 patients (5%), the disruption of the pancreatic duct could be bridged, whereas in 19 patients (45%), the disruption could not be bridged and the stent was therefore left either transpapillary or in the necrotic cavity. A follow-up intervention was performed in 34 patients (81%) who underwent ERCP with successful stent placement.

Surgery was performed in none of the patients as initial treatment. A total of 22 patients (9%) eventually underwent surgery, which resulted in resolution of DPD in 19 patients (86%). The following surgical interventions were performed: surgical cystgastrostomy of a peripancreatic collection (n = 12), distal pancreatectomy (n = 4), pancreatojejunostomy (n = 5), gastrojejunostomy (n = 1), surgery with a splint to bridge the defect in the pancreatic duct (n = 1), and fistulectomy (n = 2). DPD was not resolved after surgery in 2 patients (9%) and still required a percutaneous catheter drain *in situ* at the last round of follow-up (1 after fistulectomy and 1 after both surgical cystgastrostomy and fistulectomy).

Predictive indicators of DPD

The prediction model for developing confirmed DPD in patients with necrotizing pancreatitis is summarized in Table 4. The following 2 factors were independent predictors of DPD: central or subtotal pancreatic necrosis on CT (OR 9.49; 95% CI 6.31–14.29) and high levels of serum CRP in the first 48 hours of admission (OR 1.02 per 10-point increase; 95% CI 1.00–1.03).

DISCUSSION

In this first long-term analysis of a nationwide prospective cohort, 27% of 896 patients with necrotizing pancreatitis had a confirmed DPD, which was associated with worse short-term and long-term outcomes. Central and subtotal pancreatic necrosis on imaging and high levels of serum CRP in the first 48 hours were independent predictors for DPD.

In accordance with the current guidelines (19–21) and a recent survey (47), DPD was most frequently diagnosed on MRCP and ERCP. The reported sensitivity of (secretin)-MRCP is lower than that of ERCP, but does not carry the risks of procedure-related complications (24,38–40). Because sensitivity of 100% was demonstrated for amylase measurements in drain fluid (43,48,49), we have chosen to consider this as a diagnostic tool to confirm DPD. However, each patient in the study did not consistently receive measurement of amylase levels in external drain fluid and standardized imaging leading to delayed or even missed diagnoses of

Table 4. Predictive features for DPD in patients with necrotizing pancreatitis

	aOR (95% CI)	*P* value
Predictive features for developing a disrupted or disconnected pancreatic duct (n = 243) (AUC 0.79)		
Age[a,b]	0.93 (0.88–1.00)	0.023
Male	1.18 (0.83–1.70)	0.357
ASA II	1.39 (0.95–2.05)	0.091
ASA ≥III	1.23 (0.70–2.15)	0.478
Leukocytes[c]	1.01 (0.95–1.07)	0.711
CRP[d,b]	1.02 (1.00–1.03)	0.010
Pattern parenchymal necrosis		
Central or subtotal	9.49 (6.31–14.29)	<0.001
Right, left, or diffuse	1.35 (0.82–2.23)	0.243

Missing data were multiply imputed. The discriminative ability of the model to predict confirmed DPD was excellent on the internal data set, with a c-statistic (i.e., area under the receiver operating curve) of 0.79.
aOR, adjusted odds ratio; ASA, American Society of Anesthesiologists; AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; DPD, disrupted or disconnected pancreatic duct.
[a]In steps of 5 years.
[b]A slightly nonlinear association was found with the outcome.
[c]Highest leukocytes in the first 48 hours after admission in steps of 3.
[d]Highest CRP in the first 48 hours after admission in steps of 10.

the DPD. Our diagnosis of DPD at a median of 57 days after admission was made *post hoc* for study purposes. Therefore, during their admission, DPD was probably not recognized as such in all patients and could have been identified more frequently and earlier. These findings, alongside with the apparent negative clinical impact of DPD, clearly indicate that structured diagnostics should be performed in the future in these patients.

Necrosis of the pancreatic parenchyma in acute pancreatitis results in the loss of viable pancreatic tissue and the potential loss of pancreatic duct integrity. Spontaneous resolution may occur in the instances when the pancreatic tail is also affected and/or pancreatic tissue atrophies. If the tail remains intact, patients will experience clinical consequences (19,50) caused by a continuous leakage of pancreatic fluid, which may result in persistent or recurrent peripancreatic collections, pancreatic ascites, or external pancreatic fistula (2,3,7–12). Based on our findings, DPD leads to extended hospital stays, frequent interventions, and a higher risk of complications. In this study, DPD was clearly associated with an increase, including repeat, interventions during admission, and long-term follow-up, in line with previous studies (9,10,13,16,27).

Of more importance, our study was the first to demonstrate an association between the presence of DPD and a more severe disease course, such as new intensive care unit admission more than 1 week after admission, persistent and new-onset organ failure, and recurrent and chronic pancreatitis. In line with previous studies, we also found DPD to be associated with a higher risk of endocrine pancreatic insufficiency, probably caused by atrophy of upstream pancreatic tissue during subsequent years because of ductal hypertension (28–30). A potential shortcoming of our study was the definition used for endocrine pancreatic insufficiency, which was based on the use of antidiabetic medication rather than the results of laboratory test on serum glucose. It is to note we deliberately chose to include only clinical outcome events that arose >7 days after admission because presently there is insufficient data to determine a definite time of development of DPD. Given the data limitation, we hypothesized that DPD develops in line with necrosis, typically occurring in the first week after admission (51).

In general, persistent peripancreatic collections in the presence of DPD do not resolve spontaneously without intervention. In this study, percutaneous catheter drainage was still the first choice of treatment for infected necrosis. After this treatment, however, DPD maintains the production of pancreatic fluids, which leads to therapeutic failure. In most of the patients treated only with percutaneous catheter drainage, spontaneous resolution of DPD occurred without follow-up interventions. However, the average duration of drainage was almost 5 months, which may have a negative impact on the patients' quality of life.

At present, endoscopic transluminal drainage is the preferable first step in the treatment for infected necrosis (6,33,52); the primary benefit of which is a decrease in the number of patients with a pancreatic cutaneous fistula. However, the presence of DPD may, however, guide the choice to initially use a lumen-apposing metal stent (LAMS) or plastic double pigtails stent and whether to leave the plastic pigtails *in situ*. In our study, only a few patients with confirmed DPD underwent endoscopic transluminal drainage as the first step for either infected necrosis or DPD. However, we may have missed patients with proven DPD who underwent endoscopic drainage as an initial treatment. Because the endoscopic drainage route prevents clinical problems such as a pancreato-cutaneous fistula, DPD is less often diagnosed because a lack of clinical symptoms, thereby reducing the number of confirmed DPD cases in the patient population in the study. The available literature suggests that endoscopic transluminal drainage is sufficient to prevent DPD's clinical problems at a success rate ranging from 81% to 100% (7,10,30,31,50). In line with previous studies, after removal of the plastic pigtails, repeat intervention was required in 60% of the patients with DPD in this study. This outcome favors long-term indwelling transmural plastic stents, given this treatment is known to be safe and efficient (1,30,53,54). Nonetheless, in the clinical setting, LAMS can still be used if preferred. It is, however, recommended that patients are screened for DPD before the LAMS are removed, so that the LAMS can be replaced with plastic pigtails when DPD is present. This emphasizes once more the importance of a standardized diagnostic protocol for patients with a potential DPD.

Today, evidence-based guidelines do not recommend specific treatment for DPD. In this study, the management of DPD varied widely, from conservative to surgical intervention. A previous systematic review by our group extensively compared treatments for DPD and presented high pooled success rates for all the different treatment strategies (31). Most studies preferred internal drainage with endoscopic management by placing a stent during ERCP (1,7,11,23,25,31,42,55–58). In 69% of the patients in whom an ERCP was attempted in our study, a pancreatic duct stent was successfully placed; bridging of the disruption occurred in only 2 patients. It should be noted, data on the location of the stent were not available for all patients. Even if ERCP was successful, a follow-up intervention was often required (81%). This indicates that pancreatic duct stenting is a technically difficult procedure in necrotizing pancreatitis with a relatively low success rate. The low success rate may be because the detached part of the pancreas is

often inaccessible and therefore cannot be drained successfully. In addition, the treatment success rate of stent placement may be related to the degree and location of DPD (39,50,57,59), with a high risk of stent migration and recurrence rate (1). This again emphasizes the importance of accurate diagnosis of DPD and its degree. Furthermore, new-onset infected necrosis occurred in all 5 patients who underwent pancreatic duct stenting (59), in line with a previous study in which all patients who underwent prophylactic stenting of the pancreatic duct developed infected necrosis. These results implicate that stenting the pancreatic duct in the presence of sterile necrosis is not recommended, reducing the early treatment options for DPD.

Surgery is widely regarded as the cornerstone of DPD treatment and is considered as standard of care by 1 guideline (19). In this study, only 3% of patients with DPD underwent pancreatic surgery, contrary to a previous study in which 68% underwent surgery (60). This may be explained by their relatively rapid switch to surgical intervention (after a median of 128 [P25–P75: 20–2,430] days), while patients in our study had resolution of the DPD with percutaneous catheter drainage only after a median of 131 days. Conversely, the current evolution of advanced endoscopy is expected to increase the use of surgery in patients with DPD. In addition to endoscopic transluminal drainage of recurrent peripancreatic collections with maintenance of long-term transluminal stents, endoscopic ultrasound–guided pancreatogastrostomy is increasingly reported and carries a minimal risk of diabetes (3,7,61,62). Conversely, adequate surgery may provide a definite solution, safeguarding patients from the burden of multiple procedures and prolonged morbidity, as seen in patients with chronic pancreatitis (17,63,64). The 2 patients with insufficient result of surgery may suggest that if surgery is performed, a distal pancreatectomy—usually including splenectomy—is the approach with the highest success rate and shelters patients undergoing from multiple procedures. However, distal pancreatectomy results in a significant risk of insulin-dependent diabetes. Increasingly, islet auto transplantation from the excised tail is used to avoid the risk of surgically induced or worsened diabetes (65–68), though this technique may not be possible in patients with an atrophic or damaged tail.

The findings of our study have several implications for clinical practice. Ideally by the end of the first week of admission, implementation of a standardized diagnostic work-up for DPD in patients at high risk for DPD (i.e., subtotal and central necrosis) enables individually curated patient care and a likely reduction in healthcare costs. The wide range of treatment options for DPD paired alongside the poor clinical outcome in patients with DPD makes it a complex clinical challenge. A potential solution would be to implement a step-up treatment algorithm for patients with DPD, gradually transitioning from minimally invasive to more invasive surgical procedures. Timely intervention in patients with DPD should be considered to prevent potential complications; however, this should be investigated further.

To our knowledge, this study is the first large nationwide multicenter cohort study based on prospectively collected data with a long-term follow-up covering the entire clinical spectrum of DPD in necrotizing pancreatitis. However, this study has some limitations. First, it composes of a *post hoc* analysis, albeit of prospectively collected data, lacking a standardized diagnostic approach. As a result, the incidence of DPD may be underrepresented, and relevant data may be lacking, such as the relationship between drain output volume and the degree of DPD (i.e., partial or complete DPD). The degree of DPD is a particularly important data point that is lacking because it may influence the treatment success rate (39,50,57,59). In addition, treatment for infected necrosis and DPD are intertwined and cannot always be specifically assigned to 1 of the 2 entities. More broadly, a specific treatment is not always listed as the starting point of DPD treatment in patients with DPD. To prevent bias, we therefore take the first step of treatment for infected necrosis as the first step in the treatment for DPD. Given the uncertainty of the indication and timing of the reported treatments (i.e., confounding by indication), alongside the range of treatments used, we were unable to make a valid comparison between different treatments or to investigate the impact of the interventions for DPD on clinical outcomes. Separately, there is a high incidence of infected necrosis in our cohort, which is not a completely representative reflection of the clinical practice; this incidence rate could be explained by the fact that patients were registered with the Dutch Pancreatitis Study Group to participate in randomized studies regarding infected necrosis, which may have influenced the incidence rate. Unfortunately, patients did not undergo a predefined diagnostic work-up; therefore, we cannot rule out that the other patients by definition did not have DPD. Second, patients did not follow a predefined treatment protocol, which may have induced bias. On the contrary, this study is a reflection of what happens in current clinical practice. Our study sets out clear points on where future research should focus, starting with a well-designed diagnostic study to identify all patients with DPD, including the degree, and to identify predictive factors for DPD. Subsequently, a prospective clinical intervention study is needed to investigate the best treatment algorithm for patients with clinical consequences of DPD.

In conclusion, DPD occurs in at least 1 in every 4 patients with necrotizing pancreatitis. Diagnosis of DPD seems to be often missed because of a lack of standardized diagnostics. Development of standard diagnostic tools and treatment plans is important because DPD seems to be a major factor in determining short-term and long-term complications in the clinical course of necrotizing pancreatitis. High levels of serum CRP in the first 48 hours after admission and central or subtotal pancreatic necrosis on CT were identified as independent predictors for developing DPD. These findings can be leveraged to guide diagnostic and therapeutic strategies in clinical practice and develop future clinical studies.

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CONFLICTS OF INTEREST

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Specific author contributions: H.C.T. collected and entered all data. S.M.v.D. verified all entered data. T.L.B. reviewed all abdominal radiological images. H.C.T. and R.v.d.S. performed the statistical analysis. H.C.T. drafted the manuscript. S.M.v.D., R.A.H., C.S.W., D.S.U., L.B., R.v.d.S., N.H., L.B.r., P.v.D., L.K., S.K., J.-W.P., R.d.R., T.R., R.Q., M.P.S., A.C.I.T.L.T., N.V., F.V., R.L.J.v.W., E.v.G., B.J.W., I.Q.M., M.J.B., J.v.H., M.G.B., R.P.V., T.L.B., R.C.V., and H.C.v.S. coauthored the writing of the manuscript. All authors critically assessed the study design, included patients in the study, edited the manuscript, and read and approved the final manuscript.

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Data transparency statement: Data are available upon reasonable request from the corresponding author.

Study Highlights

WHAT IS KNOWN

- ✓ Necrotizing pancreatitis may result in a disrupted or disconnected pancreatic duct (DPD), resulting in persistent or recurrent peripancreatic collections and external pancreatic fistulas.
- ✓ There is a wide variance in the reported incidence rate of DPD, and a standardized diagnostic approach for DPD is lacking.

WHAT IS NEW HERE

- ✓ DPD occurs in at least 1 in every 4 patients with necrotizing pancreatitis.
- ✓ Central and subtotal pancreatic necrosis on imaging and high levels of serum C-reactive protein in the first 48 hours are independent predictors for DPD and could enable early diagnoses.
- ✓ DPD is associated with worse short-term and long-term patient outcomes.

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