Original research

Long-term follow-up study of necrotising pancreatitis: interventions, complications and quality of life

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2023-329735).

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Received 16 February 2023
Accepted 7 January 2024
Published Online First 24 January 2024

► http://dx.doi.org/10.1136/gutjnl-2024-331915

To cite: Hollemans RA, Timmerhuis HC, Besselink MG, *et al*. *Gut* 2024;**73**:787–796.

ABSTRACT

Objective To describe the long-term consequences of necrotising pancreatitis, including complications, the need for interventions and the quality of life.

Design Long-term follow-up of a prospective multicentre cohort of 373 necrotising pancreatitis patients (2005–2008) was performed. Patients were prospectively evaluated and received questionnaires. Readmissions (ie, for recurrent or chronic pancreatitis), interventions, pancreatic insufficiency and quality of life were compared between initial treatment groups: conservative, endoscopic/percutaneous drainage alone and necrosectomy. Associations of patient and disease characteristics during index admission with outcomes during follow-up were assessed.

Results During a median follow-up of 13.5 years (range 12–15.5 years), 97/373 patients (26%) were readmitted for recurrent pancreatitis. Endoscopic or percutaneous drainage was performed in 47/373 patients (13%), of whom 21/47 patients (45%) were initially treated conservatively. Pancreatic necrosectomy or pancreatic surgery was performed in 31/373 patients (8%), without differences between treatment groups. Endocrine insufficiency (126/373 patients; 34%) and exocrine insufficiency (90/373 patients; 38%), developed less often following conservative treatment ($p<0.001$ and $p=0.016$, respectively). Quality of life scores did not differ between groups. Pancreatic gland necrosis >50% during initial admission was associated with percutaneous/endoscopic drainage (OR 4.3 (95% CI 1.5 to 12.2)), pancreatic surgery (OR 3.2 (95% CI 1.1 to 9.5) and development of endocrine insufficiency (OR13.1 (95% CI 5.3 to 32.0) and exocrine insufficiency (OR6.1 (95% CI 2.4 to 15.5) during follow-up.

Conclusion Acute necrotising pancreatitis carries a substantial disease burden during long-term follow-up in terms of recurrent disease, the necessity for interventions and development of pancreatic insufficiency, even when treated conservatively during the index admission. Extensive (>50%) pancreatic parenchymal necrosis seems to be an important predictor of interventions and complications during follow-up.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Conservative treatment for sterile necrosis and a minimally invasive step-up approach for infected necrosis has shown good clinical results in the short term.

⇒ Following an initial episode of necrotising pancreatitis, patients are at risk for recurrent pancreatitis, chronic pancreatitis and pancreatic insufficiency. However, previous studies make no distinction between patients treated conservatively and for each type of intervention and follow-up periods are relatively short.

WHAT THIS STUDY ADDS

⇒ During long-term follow-up after a primary episode of necrotising pancreatitis, 26% of the patients are readmitted for an episode of recurrent pancreatitis, 13% require additional drainage, 8% require pancreatic surgery, 34% developed endocrine pancreatic insufficiency and 38% developed exocrine pancreatic insufficiency. Although both conservative and invasively treated patients developed endocrine and exocrine pancreatic insufficiency, it occurred more often following invasive treatment ($p<0.001$ and $p=0.016$, respectively).

⇒ Patients with >50% pancreatic gland necrosis are at higher risk for pancreatic drainage, surgery and endocrine and exocrine pancreatic insufficiency during follow-up.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A thorough protocol for follow-up after a first episode of necrotising pancreatitis should be developed and implemented, aimed at preventing disease recurrence and adequate management of pancreatic insufficiencies, regardless of initial treatment.

INTRODUCTION

In the treatment of acute necrotising pancreatitis, conservative treatment for sterile necrosis and a minimally invasive approach towards infected necrosis have shown good short-term and long-term clinical results.[1–8] International guidelines are unanimous in their advice on if and when to proceed with interventional treatment during the initial episode of necrotising pancreatitis.[9–14] The guidelines, however, withhold on recommendations for the long-term follow-up of patients after necrotising pancreatitis, especially when patients were initially treated conservatively. Previously published studies on long-term outcomes still have a relatively short follow-up with medians ranging from 13 to 90 months. Moreover, these studies report mostly on results of selected patients undergoing one specific type of treatment modality for (infected) necrosis[7 8 15 16] or different invasive treatment modalities (eg, endoscopy, minimally invasive and invasive surgery) are analysed as one group.[17 18] It is, therefore, difficult to obtain an overview of the entire clinical spectrum of necrotising pancreatitis and what the consequences are of each type of treatment during long-term follow-up. Long-term outcomes of the group of initially conservatively treated patients are especially unknown. Lastly, contrasting results have been reported on the occurrence of newly diagnosed endocrine and exocrine insufficiency after a primary episode of necrotising pancreatitis.[19 20]

Given the above, more data are needed on the risk of recurrent disease, the need for (re)interventions, occurrence of endocrine and exocrine pancreatic insufficiency, and the quality of life following especially conservative, and also invasive treatment of necrotising pancreatitis many years after the initial episode of necrotising pancreatitis. Analysing patients according to the three steps of the currently advised step-up approach for necrotising pancreatitis (ie, conservative treatment, catheter drainage and necrosectomy) is of special interest and no study thus far providing these data is available. Awareness of these late interventions and complications as a consequence of initial conservative and invasive treatment may guide structured follow-up and inform patients on their prognosis.

We, therefore, performed a long-term follow-up analysis of an unselected prospective cohort of patients with necrotising pancreatitis according to treatment during the index admission. We focused on recurrent admissions, late-onset complications, interventions and quality of life for more than 10 years after the first disease episode.

METHODS

Study design

A long-term analysis of a previously established prospective cohort of patients with necrotising pancreatitis was performed. These patients were originally included in a prospective observational study in 1 of the 8 university medical centres or in 1 of the 13 large teaching hospitals of the Dutch Pancreatitis Study Group between June 2005 and October 2008 during patient enrolment in the randomised PANTER trial.[3] This cohort comprised 447 patients with necrotising pancreatitis. Short-term outcome of these patients was previously reported.[2 3] The long-term outcome of the 88 patients in the PANTER trial has already been published.[8] The current study included the surviving patients of the entire unselected cohort of 447 patients with necrotising pancreatitis. Necrotising pancreatitis was determined by a review of all available abdominal radiological images (CT, MRI and MR cholangio-pancreatography) by an expert pancreatic radiologist (TLB). The study was conducted in accordance with the Declaration of Helsinki. We adhered to the STROBE guidelines for observational studies.[21] The Dutch Association for patients with pancreatic disease, the 'Alvleeskliervereniging' was actively involved in the design of the study. Their board members are also present during research meetings of the Dutch Pancreatitis Study Group.

Data collection and follow-up

For study purposes, patient visits were planned between June 2014 and March 2015. Patients were invited by letter to participate in the follow-up study. Subsequent communication was by letters, telephone calls or outpatient visits. After written informed consent was obtained, patients were invited for an outpatient visit. Quality of life questionnaires (EuroQOL 5 Dimension (EQ-5D)[22] and Short Form 36-item Health Survey (SF-36))[23] were sent to patients between June 2014 and March 2015. Visits were scheduled in hospitals where patients were initially treated, or in case of a rehousing of the patient, in another participating centre. Using a predefined, standardised case-record form, the coordinating investigator (RAH) performed the outpatient visits on multiple patient factors with special attention to readmissions, (pancreatic) radiological, endoscopic and surgical interventions, pain, gastrointestinal complaints (bloating, cramps, steatorrhoea and diarrhoea) and use of antidiabetic medication or pancreatic enzymes during years following the index admission. The quality of life questionnaires were evaluated and completed as necessary. Stool samples were collected at the first round of follow-up for measurement of pancreatic exocrine insufficiency. Faecal elastase-1 was measured in a single stool sample using Schebo Biotech KIT (Elisa). If available, faecal elastase-1 measurements were also collected by electronic chart reviews. When appropriate, physical examination was performed with special attention to abdominal pain and incisional hernias. Additional data collection and verification of data at (referring) hospitals, general practitioners and pharmacies were performed in 2015 and—to obtain long-term follow-up extending beyond 10 years—in 2020. All data were collected by one author (RAH or HCT) and subsequently verified by a second author (RAH or HCT).

Outcome measures

Outcomes included recurrent pancreatitis (as defined by the revised Atlanta classification[24]) and chronic pancreatitis (as defined by the M-ANNHEIM[23] diagnostic criteria for definite chronic pancreatitis). Pancreatitis-related emergency admissions and pancreatitis-related complications were also evaluated. Invasive interventions associated with necrotising pancreatitis included: endoscopic retrograde cholangiopancreatography, endoscopic transluminal drainage procedures, percutaneous catheter drainage procedures and surgical procedures. 'Pancreatic surgery' included marsupialisation, pancreatojejunostomy and pancreatic resection. 'Surgery for complications' included surgical procedures performed as a consequence of necrotising pancreatitis or prior (invasive) treatment for necrotising pancreatitis, for example, reversal of a colostomy following bowel ischaemia or hepaticojejunostomy as a result of ductal stenosis. Cholecystectomies and incisional hernia corrections are reported separately and are not included in 'surgery for complications'. Mortality was also reported.

New-onset endocrine pancreatic insufficiency following index admission was defined as the need to start oral antidiabetic medication or insulin. Exocrine pancreatic insufficiency was defined as a faecal elastase-1 level of <200 µg/g faeces.[24 25] Medication used for pancreatic endocrine or exocrine insufficiency was verified through contact with general practitioners and pharmacies.

Quality of life at long-term follow-up was evaluated using two validated questionnaires (both translated and validated for the Dutch population); the EQ-5D and the SF-36 (Medical Outcomes Trust, Boston, Massachusetts, USA).[22 26–28] We incorporated the Izbicki pain score in all follow-up interviews, which is frequently used in patients with chronic pancreatitis to assess frequency and intensity of pain attacks, use of pain medication and restriction from daily activities.[29]

Statistical analysis

Data are presented as occurrence of outcomes in the total cohort and subsequently in three main subgroups categorised according to treatment during index admission: (1) patients undergoing conservative treatment only, that is, without invasive intervention: the 'conservative group'; (2) patients treated with catheter drainage (endoscopic transluminal or radiological percutaneous) only, without the need for endoscopic or surgical necrosectomy: the 'drainage only group' and (3) patients treated with necrosectomy (endoscopic, minimally invasive surgical or open): the 'necrosectomy group'. We categorised patients in this manner in order to provide an overview in which patient groups are compared according to the currently advised treatment method for necrotising pancreatitis, namely the step-up approach. Continuous outcome measures are presented as mean±SD or median and IQRs (P25–P75) as appropriate. For categorical data, the χ^2 test was used and in case of small numbers, the Fisher's exact test. For continuous data, the independent sample t-test/one-way analysis of variance or Mann-Whitney U test/Kruskal Wallis test were used, as appropriate.

Exploratory analyses were performed regarding the difference in outcome in both the SF-36 as the EQ-5D questionnaires following the different treatment strategies (ie, conservative, drainage only and necrosectomy) or when major invasive intervention during follow-up was required. The difference in outcome in both the SF-36 as the EQ-5D questionnaires was also explored for patients with or without exocrine and endocrine pancreatic insufficiency.

Secondary, associations between the baseline characteristics (1) aetiology; (2) parenchymal necrosis or only extrapancreatic necrosis; (3) percentage of pancreatic necrosis (ie, <30%, 30%–50% or >50%); (4) location of pancreatic necrosis (ie, left, right, central, subtotal or diffuse) and 5) invasive treatment during index admission and the outcome measures (1) recurrent pancreatitis, (2) catheter drainage, (3) major surgery (ie, necrosectomy, other pancreatic surgery or surgery for complications), (4) endocrine insufficiency, (5) exocrine insufficiency and (6) development of chronic pancreatitis, were assessed using logistic regression. All associations were adjusted for age and American Society of Anesthesiologists (ASA) class during index admission and sex. Results are presented as ORs with 95% CIs. Analyses were performed using SPSS V.26.0 (IBM). Values of $p<0.05$ were considered statistically significant.

RESULTS

Of the 447 patients included in the original prospective cohort, 58 patients (13%) died during index admission. Sixteen patients (4%) were lost to follow-up. The remaining 373 patients were included in the analysis. A patient inclusion flow chart is shown in figure 1. Baseline characteristics and treatment during index admission of the 373 included patients are presented in table 1. The mean follow-up time for the patients who were known to be alive at the time of analyses was 13.5 years (range 12–15.5 years) after index admission.

Recurrence, complications and interventions

All events during long-term follow-up are reported in table 2. A total of 97 out of 373 patients (26%) were readmitted for recurrent pancreatitis, with no differences between the conservative (n=155/232), drainage (n=24/43) and necrosectomy groups (n=69/96; p=0.18). When readmitted, conservatively treated patients had a shorter length of hospital stay, as compared with patients from the drainage only group, whom subsequently had a shorter length of hospital stay compared with patients from the necrosectomy group.

In 84/373 patients (23%), no events related to necrotising pancreatitis occurred, meaning that these patients were neither readmitted to the hospital for events associated with the index admission nor did they develop chronic pancreatitis or used antidiabetic medication or supplemental pancreatic enzymes. Such

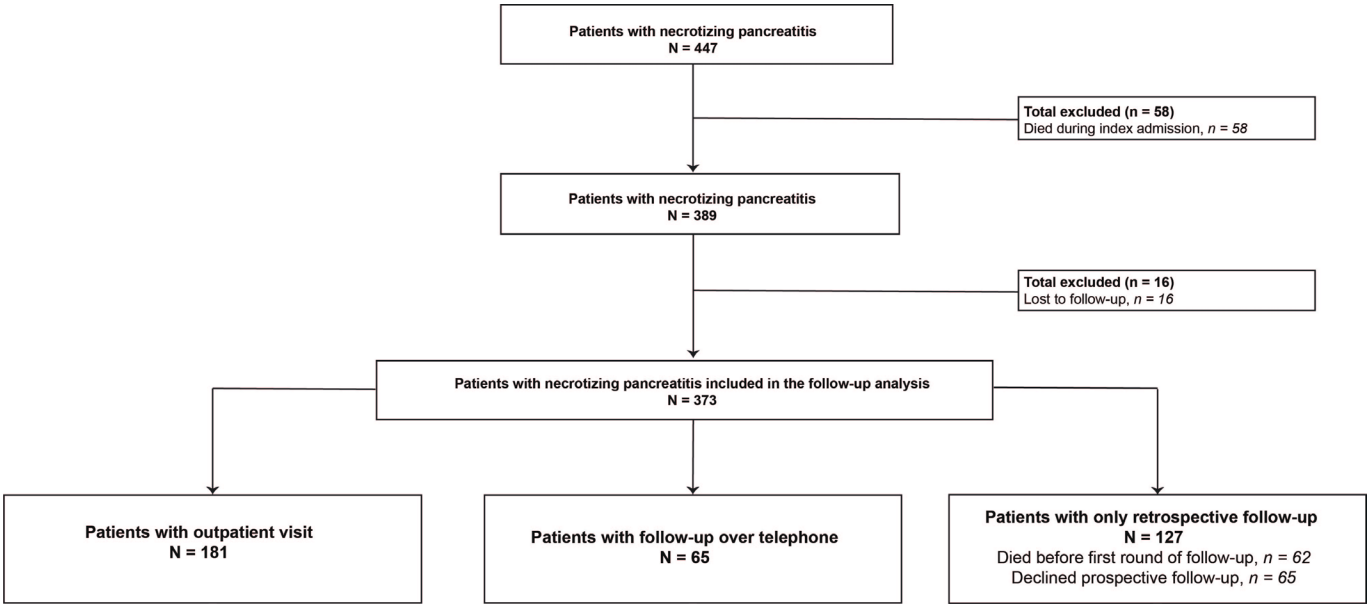

Figure 1 Flow chart patient inclusion.

Table 1 Characteristics at time of index admission of 373 patients with necrotising pancreatitis included in long-term follow-up*

	All patients N=373	Conservative N=232	Drainage only N=43	Necrosectomy N=96	P value
Age	57 (44–69)	56 (43–70)	58 (44–73)	58 (46–67)	0.893
Male sex—N (%)	238 (64)	139 (60)	23 (54)	74 (77)	0.005
Aetiology—N (%)					0.855
Biliary	182 (49)	113 (49)	19 (44)	50 (52)	
Alcohol	84 (22)	51 (22)	9 (21)	22 (23)	
Other	32 (9)	22 (9)	5 (12)	5 (5)	
Unknown	75 (20)	46 (20)	10 (23)	19 (20)	
ASA class on admission—N (%)					0.248
I (healthy status)	111 (30)	74 (32)	11 (26)	25 (26)	
II (mild systemic disease)	217 (58)	131 (56)	23 (53)	62 (65)	
III (severe systemic disease)	45 (12)	27 (12)	9 (21)	9 (9)	
Parenchymal necrosis—N (%)	192 (51)	84 (36)	32 (74)	77 (80)	<0.001
Extrapancreatic necrosis only—N (%)	181 (49)	148 (64)	11 (26)	19 (20)	<0.001
CT severity index	5 (4–8)	4 (4–6)	6 (4–8)	8 (6–10)	<0.001
Extent of pancreatic necrosis—N (%)					0.002
<30%	77 (40)	45 (54)	15 (47)	18 (23)	
30%–50%	58 (30)	18 (21)	11 (34)	29 (38)	
>50%	57 (30)	21 (25)	6 (19)	30 (39)	
Primary infection of necrosis—N (%)	128 (34)	8 (3)	38 (88)	82 (85)	
Invasive intervention—N (%)					
None	232 (62)	232 (100)	0	0	
Emergency laparotomy†	5 (1)*	0	0	3 (3)	
Catheter drainage only	43 (11)	0	43 (100)	0	
Catheter drainage followed by necrosectomy	45 (12)	0	0	45 (47)	
Primary necrosectomy	51 (14)	0	0	51 (53)	

*Two patients underwent emergency laparotomy without further pancreatic intervention and are not included in further analyses.
†Numbers are reported as numbers with percentages, median with IQRs (P25–P75) or mean with SD.
ASA, American Society of Anesthesiologists.

an uneventful follow-up occurred more frequently in patients from the conservative and drainage only group (27% and 28% respectively) compared with the necrosectomy group (9%; p=0.002).

Progression to chronic pancreatitis occurred in 50/373 patients (13%): in 27/232 patients (12%) following conservative treatment, in 10/43 patients (23%) following drainage only and 13/96 patients (14%) following necrosectomy.

The majority of patients (67%) were readmitted to the hospital during follow-up for additional treatment related to the index admission (eg, pancreatic interventions, recurrent pancreatitis and cholecystectomies).

During follow-up, 47/373 patients (13%) needed one or more endoscopic or percutaneous catheter drainage procedures as treatment for symptomatic pancreatic fluid collections. In 26 patients (55%), this was in addition to invasive treatment during index admission. Percutaneous and endoscopic catheter drainage modalities during follow-up were used in a similar number of patients. In the remaining 21 patients (45%), who were treated conservatively initially, drainage was performed during follow-up at a median of 7.6 months (P25–P75, 5.6–18.7) after start of the initial admission. Indication for drainage was new-onset infected necrosis in 4/21 patients (19%) and for symptomatic collections in 17/21 patients (81%). Drainage in these patients was performed exclusively endoscopically in 17 patients (81%) and in combination with percutaneous catheter drainage in four patients (19%). In addition to catheter drainage during follow-up, six patients (13%) needed endoscopic transluminal necrosectomy, one patient underwent surgical marsupialisation and one patient underwent surgical gastrojejunostomy because of a persisting gastric outlet obstruction following multiple endoscopic catheter drainages and development of chronic pancreatitis.

Surgical and endoscopic procedures performed during follow-up years as a consequence of the index disease or treatment are described in detail in table 2. Overall pancreatic intervention (pancreatic necrosectomy or other pancreatic surgery) was performed in 31/373 patients (8%) at a median of 13 months (P25–P75, 6–36) following the initial episode of necrotising pancreatitis. Pancreatic necrosectomy (endoscopic or surgical) was performed at a median of 5 months (P25–P75, 3–7.5) after the initial episode. These pancreatic procedures were evenly distributed between treatment groups. Surgery for complications in the 'conservative' and 'drainage only' groups was mainly performed for complications following invasive interventions during follow-up (eg, incisional hernia following cholecystectomy), whereas most surgery for complications in the 'necrosectomy' group consisted of correcting incisional hernias and colostomy reversal following necrosectomy during index admission.

Overall, 126/373 patients (34%) developed endocrine insufficiency following necrotising pancreatitis (table 2). In patients from the conservative group this occurred less often (23%; p<0.001), as compared with the patients who underwent an intervention (drainage only; 33% or necrosectomy; 62%). Of the 126 patients who developed endocrine insufficiency, 36 patients (29%) were discharged from index admission with antidiabetic medication and 89 patients (71%) started using antidiabetic medication at a median of 40 months (P25–P75, 20–73) after discharge from index admission. Development of endocrine insufficiency did not differ between patients who underwent different methods

Table 2 Readmissions, invasive interventions and long-term consequences during long-term follow-up in 373 patients with necrotising pancreatitis*

	Treatment during index admission				
	All patients N=373	Conservative N=232	Drainage only N=43	Necrosectomy N=96	P value
Recurrent pancreatitis—N (%)	97 (26)	61 (26)	11 (26)	25 (26)	1.00
No of admissions	1 (1–3)	1 (1–3)	1 (1–4)	1 (1–2)	0.97
Chronic pancreatitis†—N (%)	50 (13)	27 (12)	10 (23)	13 (14)	0.12
Recurrent hospital admission related to pancreatitis—N (%)	249 (67)	155 (67)	24 (56)	69 (72)	0.18
No of admissions	2 (1–3)	1 (1–3)	2 (1–5)	3 (2–5)	0.01
Days of admission	11 (5–25)	8 (3–21)	13 (5–48)	17 (9–43)	0.01
Catheter drainage of pancreatic fluid collection—N (%)	47 (13)	21 (9)	7 (16)	19 (20)	0.02
Percutaneous	19 (5)	4 (2)	5 (12)	10 (10)	
Endoscopic	33 (9)	21 (9)	2 (5)	10 (10)	
Surgery‡—N (%)	198 (53)	114 (49)	19 (44)	64 (67)	0.007
Pancreatic necrosectomy	1 (0)	0	0	1 (1)	–
Other pancreatic surgery	23 (6)	11 (5)§	4 (9)¶	8 (8)**	0.31
For complications after necrotising pancreatitis	31 (8)	6 (3)††	2 (5)‡‡	23 (24)§§	<0.001
Incisional hernia repair	42 (11)	6 (3)	2 (5)	33 (34)	<0.001
Cholecystectomy	158 (42)	107 (46)	12 (30)	38 (40)	0.12
Endoscopy—N (%)					
Pancreatic necrosectomy	8 (2)	6 (3)	1 (2)	1 (1)	–
ERCP	56 (15)	30 (13)	7 (16)	19 (20)	0.28
Balloon dilatation duodenum	1 (0)	0	0	1 (1)	–
Endocrine insufficiency¶¶—N (%)	126 (34)	53 (23)	14 (33)	59 (62)	<0.001
Oral antidiabetic medication	93 (74)	40 (75)	11 (79)	42 (71)	0.80
Insulin dependent	71 (56)	29 (55)	6 (43)	36 (61)	0.47
Exocrine insufficiency—N (%)	239 (64)	132 (57)	29 (67)	76 (79)	
Faecal elastase-1 level***	269±176	293±184	301±148	217±159	0.01
<200 µg/g—N (%)	90 (38)	44 (33)	7 (24)	38 (50)	0.02
200+—N (%)	149 (62)	88 (67)	22 (76)	38 (50)	
Pancreatic enzyme replacement therapy†††	72 (19)	31 (13)	7 (16)	34 (36)	<0.001
Uneventful follow-up‡‡‡—N (%)	83 (22)	61 (26)	12 (28)	10 (11)	0.01
Death—N (%)	96 (26)	62 (27)	13 (30)	21 (22)	0.57
Related to pancreatitis	7 (7)	3 (5)	2 (15)	2 (10)	
Unrelated to pancreatitis	82 (86)	53 (85)	10 (77)	19 (90)	
Unknown	7 (7)	6 (10)	1 (8)	0	

Data are missing in one patient.
*Numbers are reported as numbers with percentages, median with IQRs (P25–P75) or mean with SD. Two patients who underwent emergency laparotomy but no subsequent pancreatic intervention are not included in the subgroups.
†Based on M-ANNHEIM diagnostic criteria.
‡Any kind of surgery performed as a consequence of or related to the index episode or following episodes of necrotising pancreatitis.
§Five marsupialisation's, two pancreatojejunostomies, one distal pancreatectomy, two Whipple's procedures and one total pancreatectomy.
¶Two marsupialisation's, one pancreatojejunostomy and one distal pancreatectomy.
**Four marsupialisation's, two pancreatojejunostomies and two distal pancreatectomies.
††Two hemicolectomies, two gastrojejunostomies, three surgically drained wound abscesses and one laparotomy for bleeding postmarsupialisation.
‡‡One enterocutaneous fistula correction and short bowel resection due to obstruction/stenosis.
§§Eleven enterocutaneous fistula/ileostomy/colostomy corrections, five surgically drained wound abscesses, three gastrojejunostomies, four hepaticojejunostomies, two laparotomies for bleeding and one hemicolectomy.
¶¶Defined as the need for oral antidiabetic medication or insulin not present before the initial episode of necrotising pancreatitis. Data are missing in one patient.
***Faecal elastase-1 test was performed in 132 patients (57%) in the conservative group, in 29 patients (67%) in the drainage group and in 76 patients (79%) in the necrosectomy group
†††Percentages. Data are missing in one patient.
‡‡‡No recurrent admission related to necrotising pancreatitis, no new-onset (medication for) endocrine or exocrine insufficiency.
ERCP, endoscopic retrograde cholangiopancreatography.

of necrosectomy (ie, endoscopic, minimally invasive surgical or open: online supplemental table 1).

Faecal elastase levels were measured in 239/373 patients (64%). Exocrine insufficiency (ie, faecal elastase-1 levels <200 µg/g faeces) was diagnosed in 90/239 patients (38%). In 33% of patients of the conservative group, 24% of patients of the drainage group and 50% of patients of the necrosectomy group, exocrine insufficiency developed (p=0.016). Of the 90 patients with faecal elastase-1 levels <200 µg/g faeces, 46 patients (51%) used pancreatic enzymes. Of the remaining 44 patients (49%) who did not use pancreatic enzymes, only 11 patients (25%) reported abdominal complaints (n=8) and pain (n=8) and 33 patients (75%) were free of symptoms. In total, 72 patients (19%) used pancreatic enzymes during follow-up, of whom 46 patients (64%) had faecal elastase-1 levels <200 µg/g faeces, 15 patients (21%) had normal faecal elastase-1 levels and 11 patients (15%) were not tested. Development of exocrine insufficiency did not differ between patients who underwent different methods of necrosectomy during index admission (online supplemental table 1).

A total of 96 out of 373 patients (26%) died during follow-up. Seven deaths (7%) were directly related to pancreatic disease; three following multiple organ failure from recurrent acute pancreatitis, one following infectious complications after endoscopic transluminal drainage, one following massive bleeding following endoscopic catheter

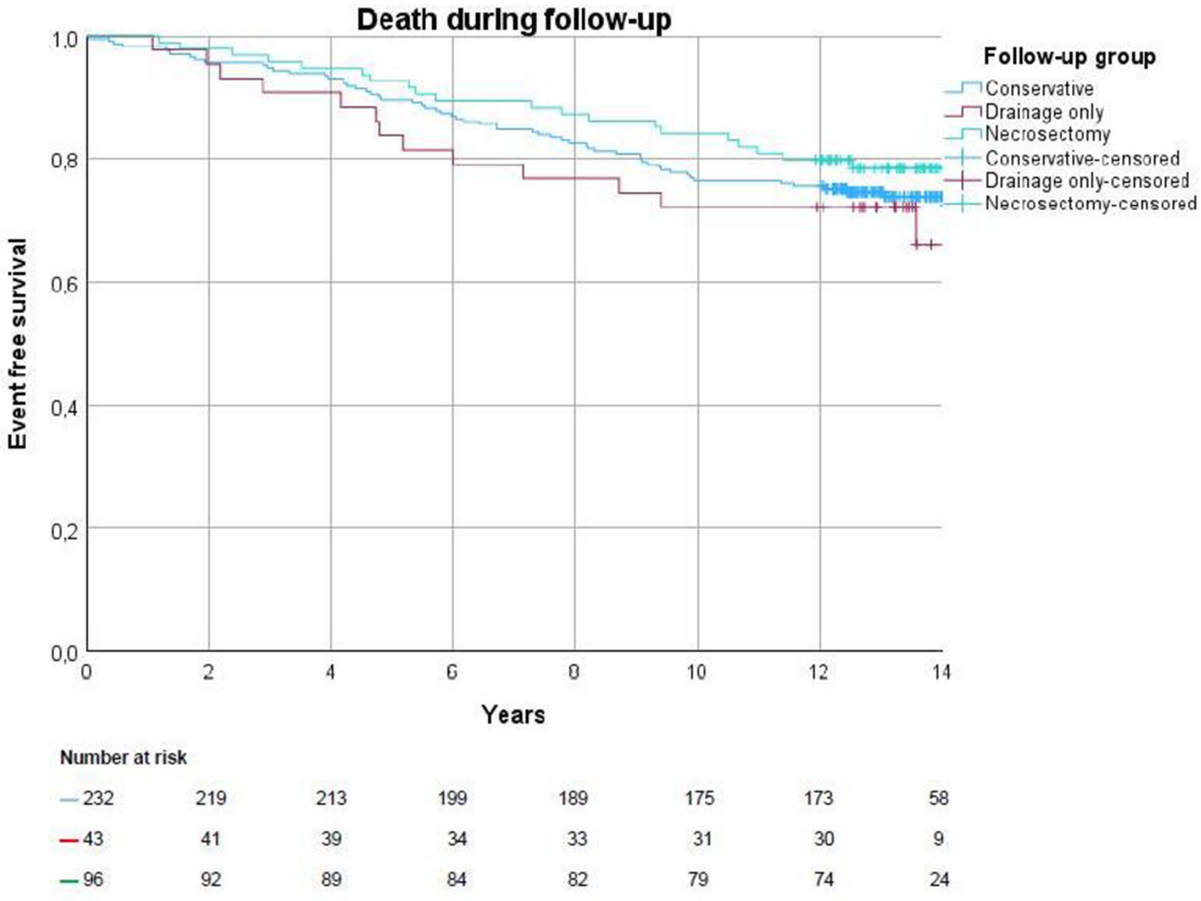

Figure 2 Kaplan-Meier curve of death during follow-up.

drainage, one following postoperative complications after hepaticojejunostomy for common bile duct stenosis and one following pancreatic carcinoma. Men (N=60) who died during follow-up had a mean age of 62.6 years (SD 14.0) at index admission and their mean age at death was 69.3 years (SD 13.8 years). Women (N=36) who died during follow-up had a mean age of 69.6 (SD13.8) at index admission and 75.8 years (SD 15.1) at death. A Kaplan-Meier survival curve categorised according to treatment modality is plotted and presented in figure 2.

Timing of several interventions and events during follow-up (catheter drainage, pancreatic necrosectomy, other pancreatic surgery, surgery for complications, incisional hernia repair, cholecystectomy and endocrine insufficiency) were plotted in Kaplan-Meier curves and provided in online supplemental figures 1–7.

Pain and abdominal complaints

In total, 244 out of 373 patients (65%) provided information on abdominal pain and other abdominal complaints (bloating, diarrhoea and anamnestic steatorrhoea) which started after the index admission. Twenty per cent of the patients from the conservative group reported pain, as did 39% of patients from the drainage group and 42% of patients from the necrosectomy group (p=0.001). In patients who reported pain, a median Izbicki score of 35 (P25–P75, 25–53) was reported and scores in the different treatment groups were similar.

In total, 78 patients (32%) reported one or more abdominal complaints. Patients from the conservative group reported abdominal complaints less often than patients from the drainage and necrosectomy groups (23% vs 35% vs 47%, respectively, p=0.001). All information on pain and abdominal complaints is provided in online supplemental table 4.

Quality of life

The SF-36 and EQ-5D questionnaires were completed by 243 of 373 patients (65%). Scores were similar between groups in all domains. The scores in physical component of the SF-36 in all groups were slightly lower than the 50±10 score in the general population, whereas the scores the mental component were not (table 3).

Patients who underwent endoscopic or percutaneous catheter drainage, necrosectomy or major surgery during follow-up had statistically significant lower EQ-5D scores (UK value 0.76 (P25–P75, 0.69–0.97)) and health state score (UK value 70 P25–P75, (56–80)), as compared with patients who did not (UK value 0.81 (P25–P75, 0.73–1.00) and UK value 76 (P25–P75, 70–85)), respectively: online supplemental table 2). Quality of life scores did not differ significantly between patients with and without new-onset endocrine insufficiency except for a slight difference in health state score (UK value 78; P25–P75, 68–85 and UK value 75; P25–P75, 60–80, respectively; p=0.03), nor were there differences in the scores of patients with and without new-onset exocrine insufficiency or in the scores of patients with both endocrine and exocrine insufficiency, as compared with patients with neither endocrine nor exocrine insufficiency (online supplemental table 3).

Table 3 Quality of life after long-term follow-up in 243 patients treated for necrotising pancreatitis*

		Treatment during index admission			
	All patients N=373	Conservative N=232	Drainage only N=43	Necrosectomy N=96	P value†
Questionnaires completed—no (%)	243 (65)	136 (59)	30 (70)	75 (78)	0.002
SF-36 US standard					
Physical	45±12	46±12	44±11	43±12	0.13
Mental	51±11	51±11	53±10	51±10	0.70
SF-36 Dutch standard					
Physical	46±12	47±12	45±11	44±12	0.16
Mental	49±11	49±11	51±10	49±10	0.66
EQ-5D					
UK values	0.80 (0.69–1.00)	0.81 (0.73–1.00)	0.74 (0.69–1.00)	0.80 (0.69–1.00)	0.46
Dutch values	0.84 (0.78–1.00)	0.84 (0.78–1.00)	0.81 (0.72–1.00)	0.84 (0.77–1.00)	0.44
Health state score	75 (65–85)	75 (68–85)	75 (60–80)	75 (65–80)	0.44

*Groups were compared as appropriate with the one-way ANOVA or Kruskal-Wallis test.
†Data are reported as means±SD as is custom in reporting results of the SF-36 questionnaire and as median (P25–P75) in the EQ-5D questionnaire. Two patients who underwent emergency laparotomy but no pancreatic intervention were not included in the subgroup analyses for quality of life.
ANOVA, analysis of variance; EQ-5D, EuroQOL 5 Dimension; SF-36, Short Form 36-item Health Survey.

Patients characteristics and associations with outcome during follow-up

Pancreatic necrosis, as opposed to extrapancreatic necrosis only, was associated with all outcomes during follow-up; endoscopic or percutaneous catheter drainage (adjusted OR 6.0 (95% CI 2.6 to 14.0), major surgery (adjusted OR 5.2 (95% CI 2.1 to 13.0), endocrine (adjusted OR 5.0 (95% CI 3.0 to 8.2) and exocrine insufficiency (adjusted OR 3.9 (95% CI 2.1 to 7.2) and chronic pancreatitis (adjusted OR 2.2 (95% CI 1.1 to 4.2).

In patients with pancreatic necrosis, >50% of gland necrosis were associated with endocrine (adjusted OR 13.1 (95% CI 5.3 to 32) and exocrine insufficiency (adjusted OR 6.1 (95% CI 2.4 to 15.5). Subtotal necrosis was associated with endocrine insufficiency (adjusted OR 23.7 (95% CI 3.1 to 183.4) and all patients with subtotal necrosis developed pancreatic exocrine insufficiency. Also, predominantly central gland necrosis was associated with catheter drainage (adjusted OR 3.7 (95% CI 1.8 to 7.8)) and other pancreatic interventions (adjusted OR 5.2 (95% CI 2.2 to 12.1)). Predominantly right-sided pancreatic necrosis was associated with development of chronic pancreatitis (adjusted OR 8.2 (95% CI 1.6 to 42.1)).

Endoscopic or percutaneous catheter drainage only during index admission was associated with the development of chronic pancreatitis (adjusted OR 2.5 (95% CI 1.1 to 5.8)). Patients who underwent necrosectomy during index admission were at increased risk for both endocrine as exocrine insufficiency (adjusted OR 5.1 (95% CI 3.0 to 8.6) and adjusted OR 1.9 (95% CI 1.1 to 3.5), respectively).

All patient characteristics and associations are provided in online supplemental table 5.

DISCUSSION

This is the largest and longest long-term follow-up study on patients from entire clinical spectrum of necrotising pancreatitis reported thus far. Our study provides unique insights in the late sequelae of necrotising pancreatitis following different treatment groups of conservative treatment, catheter drainage only or necrosectomy. Three-quarters of the 373 patients suffered from a necrotising pancreatitis-related event during long-term follow-up. Recurrent pancreatitis occurred in about a quarter of all patients and 6% of all patients underwent pancreatic surgery, regardless of their initial treatment. Patients who were originally treated conservatively were less likely to undergo additional drainage procedures or surgery for complications and were less likely to develop new-onset endocrine and exocrine pancreatic insufficiency. Necrosis of more than 50% of the pancreatic parenchyma on CT during index admission was strongly associated with catheter drainage and endoscopic/surgical pancreatic interventions and the development of pancreatic endocrine and exocrine insufficiency during long-term follow-up.

Previous studies have reported on follow-up of patients with necrotising pancreatitis. All these studies, however, focused on specifically selected subgroups of necrotising pancreatitis. One combined retrospective and prospective study evaluated endoscopic and surgical interventions during follow-up (44 months) of 86 patients treated with endoscopic transluminal necrosectomy (N=75) and subsequent surgical necrosectomy (N=11) for infected necrotising pancreatitis.[16] Interventions during follow-up consisted mainly of endoscopic drainage and pancreatic surgery was infrequent.[16] Comparison with our study is difficult, as inclusion of patients and baseline characteristics differ substantially. A retrospective follow-up study of 197 patients with necrotising pancreatitis demonstrated a substantially higher rate of pancreatic surgery (36%) as compared with our study (6%) and demonstrated that patients with pancreatic ductal injury during index admission are more likely to require surgery during follow-up. This difference could be explained by the difference in patient selection, since the authors categorised the patients by pancreatic ductal anatomy.[17] Another retrospective analysis from Italy included 631 patients with mild (N=558) and severe (N=73) pancreatitis and showed invasive pancreatic intervention during follow-up (52 months) in only nine patients.[18] Unfortunately, prevalence of (extra)pancreatic necrosis was not reported. A recent follow-up study (7 years) of the TENSION trial, comparing the endoscopic step-up approach with the surgical step-up approach, has shown that the endoscopy group needed fewer interventions than the surgery group. Pancreatic insufficiency and quality of life did not differ between groups.[6]

International guidelines recommend a step-up approach for necrotising pancreatitis, ranging from conservative treatment with maximal supportive care to performing invasive intervention stepwise (ie, endoscopic or percutaneous drainage followed, if needed, by necrosectomy).[12 13] The patients in our cohort were prospectively included in hospitals of the Dutch Pancreatitis Study group between 2005 and 2008. During this time,

minimally invasive treatment methods (ie, retroperitoneal percutaneous and endoscopic transluminal drainage) were upcoming, but not yet the standard approach. Direct open necrosectomy was still considered a reasonable first choice of treatment and a subset of our study population was randomised to either the step-up approach or direct open necrosectomy.[3] It, therefore, remains unclear how many of the patients would have recovered without (direct open) necrosectomy if a less invasive procedure or conservative therapy was primarily initiated and if the late-onset complications subsequently would have been different. We separately analysed the outcomes of patient undergoing different types of treatment of the initial episode of necrotising pancreatitis to provide guidance during follow-up for each of these subgroups. Our aim was not to designate a 'best treatment for infected necrosis', since not all patients can be treated conservatively and might benefit more from invasive treatment and vice versa.

Endocrine and exocrine pancreatic insufficiency are well-known outcome measures of follow-up studies on pancreatitis in general and necrotising pancreatitis in particular, as development of pancreatic insufficiency following pancreatitis is mainly attributed to loss of vital pancreatic tissue.[30] It was, therefore, not surprising that we found a high percentage of pancreatic necrosis and subsequently necrosectomy during the initial admission as a risk factor for developing pancreatic insufficiency. This may, in part, be explained by the fact that patients with pancreatic gland necrosis are those who more often need necrosectomy.[31] A systematic review yielded comparable results as in the current study on incidence of exocrine insufficiency following necrotising pancreatitis (32% and 38%, respectively).[20] Unfortunately, studies included in the systematic review reported insufficient data to perform subgroup analyses on extent of pancreatic necrosis.[20] Similarly, new-onset endocrine insufficiency was found in 34% of all patients, which corresponds to the findings in a systematic review including 1102 patients (30%).[19] This study demonstrated that severity of disease, classified according to clinical course during index admission (ie, mild or severe) by the determinant based classification,[32] had minimal effects in the development of endocrine insufficiency.[19] Acute pancreatitis, however, is a disease with a very broad clinical spectrum and in our opinion categorising patients as mild or severe during index admission is of limited value for follow-up studies, as it does not specify the impairment (ie, necrosis) of the pancreatic gland.[32 33] Furthermore, the recent publication of a long-term follow-up study of the randomised PANTER trial has shown that patients from the step-up group, who underwent fewer necrosectomies, had less pancreatic exocrine insufficiency at final follow-up and also trended towards less endocrine insufficiency, while pancreatic necrosis was similar between groups.[8] These data suggest that necrosectomy procedures directly contribute to a decrease in pancreatic functional capacity in subsequent years. These results emphasise the importance of acknowledging extent of pancreatic necrosis during index admission. We, therefore, believe that classifying patients according to the presence of parenchymal necrosis, the location and extent of pancreatic necrosis—especially for follow-up studies—is more suitable. We recommend the well acknowledged CT Severity Index (CTSI).[34]

A remarkable finding was that 44 out of 90 patients (49%) with faecal elastase-1 levels below 200 µg/g faeces were not on pancreatic enzyme replacement therapy, whereas 15 patients (17%) with faecal elastase-1 levels above 200 µg/g faeces were. Eleven patients (25%) with faecal elastase-1 levels below 200 µg/g faeces who were not on enzyme replacement therapy reported abdominal complaints. These complaints might be indicative of substantial pancreatic exocrine insufficiency and these patients may potentially benefit from enzyme replacement therapy. If untreated, pancreatic exocrine insufficiency can lead to malnutrition, weight loss and deficiency of fat-soluble vitamins (A, D, E, K) and mineral deficiencies that can cause metabolic bone disease. Of the 15 patients on pancreatic enzyme replacement therapy with faecal elastase-1 levels above 200 µg/g faeces, 8 still reported abdominal complaints. Their complaints, therefore, might not have been attributable to pancreatic exocrine insufficiency and hence their enzyme therapy may be unnecessary. This underlines the importance of early and accurate diagnosis of pancreatic exocrine insufficiency.

Quality of life following acute pancreatitis was recently summarised in a systematic review, highlighting the large number of tools used to asses quality of life, and the large variance in follow-up time after which quality of life was assessed, which precluded definitive conclusions.[35] It appears that perceived quality of life is impaired at least during the first 1–2 years following the admission for acute pancreatitis and that increasing severity of disease may have a negative impact.[35–37] Our study is novel since we compared quality of life in (1) subgroups of different interventions during index admission and (2) included subgroup analyses for treatment during follow-up. Unexpectedly, we found similar quality of life scores in all subgroups. This may be explained by the long interval between the index admission and time of quality of life measurement. As time passes, patients may get accustomed to their (residual) symptoms and medicine use for endocrine and/or exocrine insufficiency, and perceived quality of life may be similar compared with patients free of these disabilities.

One of the more remarkable findings in our opinion was the finding that patients treated by catheter drainage were more likely to develop chronic pancreatitis than patients treated with necrosectomy. Although we are aware no causal relationship can be concluded from this finding, the hypothesis that pancreatic necrosis in need of necrosectomy potentially protects a patient from developing chronic pancreatitis is intriguing. Also noteworthy, it seems plausible that patients developing chronic pancreatitis, given the nature of the disease, were admitted more frequently and underwent more extensive treatment than other patients during our follow-up. Chronic pancreatitis contributes significantly to healthcare consumption and accordingly contributes to the results of our study.

In our study, 96 patient died during follow-up, at a mean age for men and women of 69.3 years and 75.8 years, respectively. Life expectancy for men and women in the Netherlands at time of our data collection in 2020 was 79.7 and 83.1 years, respectively.[38] Although it is difficult to extrapolate these numbers directly to our patient population, they seem to indicate a significant loss of life expectancy in patients following necrotising pancreatitis. Similar results on loss of life expectancy were shown in a recent follow-up study from Hungary, including a very large number (N=2613) of patients following an episode of acute pancreatitis. The authors performed an 8-year follow-up and showed a threefold higher incidence rate of death (in person-years) for their patients compared with the general population.[39] This observation is remarkable and emphasises the importance of continued care of pancreatitis patients during follow-up.

Some limitations of our study need to be acknowledged. First, no laboratory test to assess endocrine insufficiency was performed as part of our study. Although follow-up on endocrine insufficiency after necrotising pancreatitis is common practice in the Netherlands during the first recovery phase, subclinical disease at our long-term follow-up may have been missed and

our findings, therefore, may be an underestimation of the actual problem. Second, no imaging studies were routinely performed. Complications such as pancreatic calcifications as indicators of chronic pancreatitis, or pancreatic fluid collections/cysts remaining after the index admission may have been missed. This precludes statements on morphological changes following an episode of necrotising pancreatitis from this study. Third, quality of life questionnaires were not collected at regular time intervals following discharge (eg, annually). This precludes judgement on alterations in quality of life in the years following recovery of necrotising pancreatitis and on potential differences between treatment groups. Fourth, although the response rate of around 65% for the active follow-up including questionnaires and faecal elastase-1 testing was acceptable, this does mean that in around 35% of patients data on these quality of life and pancreatic exocrine insufficiency outcomes were not available. These data did not appear to be missing at random, because a post hoc analysis (online supplemental table 6) demonstrated that patients with missing data had a higher age, more comorbidity (ie, higher ASA class), higher Acute Physiology and Chronic Health Evaluation II (APACHE-II) score at admission, lower CTSI score and less pancreatic parenchymal necrosis. We cannot rule out that this has led to bias. The main findings and conclusions regarding these outcomes may, therefore, not be generalisable to the subgroup of patients with higher age, more comorbidity, higher APACHE-II scores and less extensive necrosis on imaging. We did not perform an additional analysis to adjust the comparative outcome analyses of the different treatment groups (ie, conservative treatment, drainage, necrosectomy) for the abovementioned baseline characteristics, because these factors are likely to have influenced the decision/indication to perform certain treatments. Adjusting for these variables may thus dilute our prognostic findings that patients undergoing more invasive treatment suffered from more abdominal complaints and a higher risk of pancreatic exocrine insufficiency. Our findings of associations between more invasive treatment and a higher rate of abdominal complaints and pancreatic exocrine insufficiency, therefore, may not be directly extrapolated to a clinically less severe patient population or to a frail patient population. Finally, the initial hospital admissions were in the period 2005–2008. Since then, the invasive management of infected necrotising pancreatitis has evolved from an open approach to a minimally invasive approach. Consequently, how patients were treated in our cohort may not fully reflect current practice as more patients are primarily treated conservatively or by minimally invasive methods. Our study, however, does provide clear insights in the long-term results of all treatment strategies currently available.

In light of future perspectives on the follow-up of necrotising pancreatitis, two points need to be addressed. First, invasive interventions (ie, catheter drainage, endoscopic and surgical procedures) were scarce during the second period of our follow-up (2015–2020) and mostly occurred in a small subset of patients. Only few patients who did not already undergo such interventions during the first follow-up period had their first 'pancreatitis-related' intervention in the later stage of our follow-up (data not shown). We, therefore, feel it is not necessary for future studies to extend follow-up periods to longer than 10 years. Second, given the outcomes of this study, we feel it is appropriate to include long-term recommendations in future acute pancreatitis guidelines, as they may aid clinicians in their assessment of diagnostics, treatment and in their guidance of recovering patients. Our advice for treating physicians would be to locally implement a structured follow-up on all patients with necrotising pancreatitis. After an initial measurement of faecal elastase-1 levels during the initial episode, a standardised outpatient visit around 3–6 months after discharge should be planned. This outpatient visit includes a follow-up faecal elastase-1 measurement, a detailed history on abdominal complaints suggestive for exocrine insufficiency or residual symptoms indicative of intra-abdominal complications (eg, fluid collections, pancreatic ductal alterations) and blood glucose measurement. Additional laboratory tests and imaging can subsequently be performed if indicated.

In conclusion, the disease burden during long-term follow-up of necrotising pancreatitis is substantial in terms of disease recurrence, pancreatic insufficiency, pancreatic drainage and surgery, also patients who were initially treated conservatively. This warrants a systematic follow-up of all patients, especially those with over >50% of pancreatic necrosis, after an initial episode of necrotising pancreatitis. Incorporating advices on follow-up in future guidelines could facilitate its implementation in clinical practice.

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Contributors RAH performed the outpatient visits, RAH and HCT collected and entered all data, RAH and HCT verified all entered data. TLB reviewed all abdominal radiological images. RAH performed the statistical analysis. RAH and HCT drafted the manuscript. RAH, HCT, MGB, MB, PvD, E-JvG, MH, JH, SH, JEV-H, LMK, ERM, J-WP, RQ, TR, GPvdS, MPS, BWMS, MS, ACITLT, NGV, FV, RPV, RLJvW, TLB, RCV and HCvS 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. RAH is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by METC Utrecht 04-289/E. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request from the corresponding author.

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