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Minimally invasive versus open necrosectomy for necrotizing pancreatitis:

A systematic review and individual patient data meta-analysis

short title: Comparison of pancreatic necrosectomy methods

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Summary

Background and aims Minimally invasive necrosectomy compared with open necrosectomy might improve outcomes in necrotizing pancreatitis, especially in critically ill patients. Evidence from large comparative studies is lacking.

Methods We combined individual patient data from 15 published and unpublished cohorts (51 hospitals; 8 countries) on pancreatic necrosectomy for necrotizing pancreatitis. Death rates were compared in patients undergoing open necrosectomy or minimally invasive necrosectomy (i.e. minimally invasive surgical or endoscopic necrosectomy). We adjusted for confounding by three types of analyses: logistic regression, stratification according to predicted risk of death at baseline (low: <5%, intermediate: ≥5% to <15%, high: ≥15% to <35%, and very-high: ≥35%), and propensity-score matching.

Results Among 1980 patients with necrotizing pancreatitis, 1167 underwent open necrosectomy, 467 underwent minimally invasive surgical necrosectomy, and 346 underwent endoscopic necrosectomy. There was a lower risk of death for minimally invasive surgical necrosectomy (odds ratio, 0.53; 95%-CI, 0.34 to 0.84; P=0.006) and endoscopic necrosectomy (odds ratio, 0.19; 95%-CI, 0.06 to 0.61; P=0.005). After risk stratification and propensity-score matching, minimally invasive surgical necrosectomy remained associated with a lower risk of death than open necrosectomy in the very-high-risk group (42/111 versus 59/111; risk ratio, 0.70; 95%-confidence interval, 0.52 to 0.95; P=0.02). Endoscopic necrosectomy was associated with a lower risk of death than open necrosectomy in the high-risk group (3/40 versus 12/40; risk ratio, 0.27; 95%-CI, 0.08 to 0.88; P=0.03) and in the very-high-risk group (12/57 versus 28/57; risk ratio, 0.43; 95%-CI, 0.24 to 0.77; P=0.005).

Conclusions In high-risk patients with necrotizing pancreatitis, minimally invasive surgical and endoscopic necrosectomy reduced death rates compared with open necrosectomy.

Key-words: pancreatitis, necrosis, surgery, minimally invasive, endoscopy

Introduction

Approximately 20% of patients with acute pancreatitis develop necrosis of the pancreas and peripancreatic tissue.[1] These patients have a prolonged disease course with a high risk of complications such as multiple organ failure, secondary infection of the necrosis, and death.[1,2] Many patients with necrotizing pancreatitis ultimately need to undergo pancreatic necrosectomy.[1-4]

Death rates after pancreatic necrosectomy recently reported by international expert centers vary from 0% to 25%.[5-12] This variation may be explained by differences in case-mix or by differences in treatment strategies. Several changes in the treatment of patients with necrotizing pancreatitis have occurred over the last 20 years. First, the timing of intervention has shifted from very early in the disease course to around 3-4 weeks after onset of symptoms.[3,4,13] Second, the indication for necrosectomy has changed from sterile necrosis to predominantly infected necrosis.[3,4,14] Third, catheter drainage is now often the first step in treatment before necrosectomy.[15] Finally, as an alternative to open necrosectomy, minimally invasive necrosectomy (i.e. minimally invasive surgical necrosectomy and endoscopic necrosectomy) is increasingly being performed.[7-10,12]

Minimally invasive necrosectomy is thought to be beneficial by inducing less surgical stress, thereby lowering the pro-inflammatory response, especially in already critically ill patients.[16,17] Studies that directly compare minimally invasive necrosectomy with open necrosectomy for clinical outcomes are lacking. A few retrospective studies have been performed but these were mostly small and hampered by selection bias and confounding.[12,18] The only available randomized trial included only 20 patients.[17] Because necrotizing pancreatitis is a complex and relatively rare disease, it is unlikely that a trial with a sufficiently large sample size to study mortality will ever be performed. It therefore remains unclear if minimally invasive necrosectomy reduces death rates, especially in the context of other recent changes in the treatment of necrotizing pancreatitis. As a result, open necrosectomy remains a valid option and is still practiced worldwide.[3,11,19,20]

In this international collaborative project we combined individual patient data from published and unpublished cohorts on pancreatic necrosectomy in expert centers worldwide. We compared death rates of open necrosectomy with minimally invasive necrosectomy in a large number of patients, which allowed several approaches to adjust for confounding. We hypothesized that minimally invasive necrosectomy reduced death rates.

Methods

Study design

We combined data from patients undergoing pancreatic necrosectomy in 51 hospitals who were included in 15 cohorts from expert pancreatic centers in the United States and Canada (n=4), The United Kingdom (n=4), Germany (n=2), Hungary (n=2), The Netherlands (n=1), India (n=1), and Brazil (n=1). The cohorts were identified by a predefined systematic literature search. A total of 13 cohorts were published previously.[6-10,19,21-27] For 4 of these cohorts[7,10,19,24] additional patients were included of whom the data were unpublished and two cohorts consist of entirely unpublished data. Details on the search, eligibility criteria, included cohorts and quality assessment/risk of bias of individual studies are available in the appendix (p 4). Once the corresponding author of a cohort agreed to participate, original and additional individual patient data regarding baseline characteristics, method of intervention, and clinical outcomes were collected. All data were anonymized. The Institutional review boards of the participating centers approved study protocols, if appropriate. The study design was predefined and prospectively registered (www.crd.york.ac.uk/PROSPERO: CRD42014008995). We adhered to the MOOSE guidelines for reporting meta-analyses of observational cohort studies and the PRISMA-IPD guidelines for meta-analysis of individual participant data.[28,29]

Data collection

Data were collected in a standardized manner using an electronic case record form for the following baseline variables: sex, age, tertiary referral, cause of pancreatitis, catheter drainage before necrosectomy, time from hospital admission to necrosectomy, APACHE-II score and organ failure ≤24 hours before necrosectomy, documented infection of necrosis, and year of necrosectomy. Method of necrosectomy (i.e. open necrosectomy, minimally invasive surgical necrosectomy or endoscopic necrosectomy), complications, and death were also recorded. Detailed definitions are provided in the appendix (p 5). Data were checked for consistency and plausibility. Data were missing in eight of the 13 baseline variables, with a range of 0.2% to 4.7%. Missing data were imputed by multiple imputation using chained equations. More information on missing data and imputation is available in the appendix (p 6).

Statistical analysis

Patients undergoing open necrosectomy were compared with patients undergoing minimally invasive surgical necrosectomy and with patients undergoing endoscopic necrosectomy. The primary end point was in-hospital death during index admission. Readmissions within 10 days after discharge from index admission were considered as part of the index admission. We anticipated that certain prognostic baseline variables that are associated with death, such as measures of disease severity, would not be evenly distributed among treatment groups. This could be due to selection bias in the individual cohorts or because clinical severity played a role in deciding which method of necrosectomy was performed (i.e. confounding by indication or confounding by severity).[30] To adjust for these and other forms of confounding, we performed three types of analyses.

First, the association between different methods of necrosectomy and death was evaluated using multivariable logistic regression. The following potential confounding factors were included as covariates, if associated with death in univariable analysis ($P<0.1$): study cohort, sex, age, tertiary referral, cause of pancreatitis, year of necrosectomy, previous catheter drainage, APACHE-II score, cardiovascular failure, pulmonary failure, renal failure, documented infected necrosis, and time since hospital admission. Variables were excluded using stepwise backward elimination ($P>0.05$).

Second, patients were stratified according to their predicted risk of death at baseline. The aim of this approach was twofold: 1) to study the effect of necrosectomy in different subgroups of disease severity because it was anticipated that the beneficial effect of minimally invasive necrosectomy is greater in more severely ill patients; and 2) to adjust for differences in disease severity between the groups of open necrosectomy and minimally invasive surgical necrosectomy or endoscopic necrosectomy which could have occurred due to selection. A prediction model for the risk of death determined at baseline (i.e. within 24 hours before necrosectomy) was developed using the data from patients undergoing open necrosectomy (i.e. the control group).[31] The model was based on known parameters for disease severity as a result of pancreatitis and for pre-existing co-morbidity, and included the following predictors: study cohort, age, APACHE-II score, cardiovascular failure, pulmonary failure, and renal failure. Performance of the model was very good with an area under the curve of 0.85. We chose this method as opposed to classifying severity by the recently revised Atlanta classification[1] or the

determinant-based classification of acute pancreatitis severity[32] because we specifically wanted to determine disease severity at the time of necrosectomy, in contrast with severity of pancreatitis in general.

Using this model, patients in each treatment group were assigned to one of four baseline categories of predicted risk of death: low (<5%); intermediate (≥5% to <15%); high (≥15% to <35%); or very high (≥35%). Further details on the prediction model and risk stratification are available in the appendix (p 6-7). In each risk group, patients undergoing open necrosectomy were compared with patients undergoing minimally invasive surgical necrosectomy and with patients undergoing endoscopic necrosectomy.

Third, and building on the second analysis, patients in each risk group were matched using their propensity-score to achieve cohorts of patients with similar baseline characteristics. The propensity-score is the probability of treatment assignment conditional on observed baseline characteristics and allows one to design and analyze an observational study so that it mimics some of the characteristics of a randomized trial.[33] We developed a non-parsimonious multivariable logistic regression model to estimate a propensity-score for minimally invasive surgical necrosectomy and endoscopic necrosectomy. Details of the individual variables included in the model are provided in the appendix (p 7). Patients undergoing minimally invasive surgical necrosectomy or endoscopic necrosectomy were matched 1:1 with patients undergoing open necrosectomy using their propensity-score with the nearest-neighbour-matching algorithm without replacement (a caliper width equal to 0.2 of the standard deviation of the logit score was used). Standardized differences were estimated for all the baseline covariates to assess imbalance before matching and balance after matching. A standardized difference of less than 10% indicates appropriate balance.[33]

Results of multivariable regression analysis are given as odds ratios and 95%-confidence intervals (CI). Differences in death rates were tested with the chi-square test in the unmatched cohorts and with the McNemar's test for paired data in the matched cohorts. Comparisons of death rates are presented as risk ratios. All tests were two-tailed and P values of less than 0.05 were considered statistically significant.

Predefined subgroup analyses were performed for patients with infected necrosis and for patients who underwent previous catheter drainage. Several other sensitivity analyses were performed (appendix p 7-8).

Results

Study population

We included 1980 patients who underwent pancreatic necrosectomy; a total of 1167 underwent open necrosectomy, 467 patients underwent minimally invasive surgical necrosectomy, and 346 underwent endoscopic necrosectomy. Baseline characteristics for the entire study population and per study cohort are presented in the appendix (pp 14-16). A total of 325 out of 1980 patients (16%) in the study died.

Logistic regression adjusted-analysis

The following baseline characteristics (i.e. within 24 hours before necrosectomy) were associated with death in multivariable regression analysis: study cohort, year of necrosectomy, age, APACHE-II score, cardiovascular failure, pulmonary failure, and renal failure (appendix pp 18). While adjusting for these potential confounders, minimally invasive surgical necrosectomy and endoscopic necrosectomy remained associated with a lower risk of death: odds ratio 0.53 (95%-CI, 0.34 to 0.84); P=0.006 and odds ratio 0.19 (95%-CI, 0.06 to 0.61); P=0.005, respectively.

Baseline death risk–stratified-analysis

Using a multivariable prediction model (appendix p 19), patients were stratified according to their predicted risk of death at baseline. Stratification was considered successful because there were no major differences in predicted risk of death for patients undergoing open necrosectomy, minimally invasive surgical necrosectomy, and endoscopic necrosectomy, respectively: low-risk group: median 2% ([interquartile range (IQR)], 1% to 3%) vs. median 3% (IQR, 0% to 4%) vs. median 4% (IQR, 2% to

4%); intermediate-risk group: median 9% (IQR, 7% to 11%) vs. median 9% (IQR, 7% to 12%) vs. median 10% (IQR, 8% to 12%); high-risk group: median 24% (IQR, 18% to 29%) vs. median 22% (IQR, 19% to 29%) vs. median 22% (IQR, 19% to 27%); very high-risk group: median 52% (IQR, 43% to 64%) vs. median 58% (IQR, 45% to 78%) vs. 51% (IQR, 42% to 72%).

Baseline characteristics in each risk group are presented in Tables 1 and 2. Even though the predicted risk of death rates were comparable among treatment groups, some imbalance for individual baseline characteristics remained, as indicated by standardized mean differences greater than 10%.

Actual death rates in each risk group are shown in Figure 1. In the higher risk groups, fewer patients undergoing minimally invasive surgical necrosectomy and fewer patients undergoing endoscopic necrosectomy died.

Propensity-score–matched analysis

A total of 376 patients who underwent minimally invasive surgical necrosectomy were matched with 376 patients who underwent open necrosectomy and a total of 198 patients who underwent endoscopic necrosectomy were matched with 198 patients who underwent open necrosectomy. The matched cohorts were well balanced for all baseline characteristics because none of the standardized differences exceeded 10% (Tables 1 and 2).

Actual death rates in the matched cohorts in each risk group are shown in Figure 1. Minimally invasive surgical necrosectomy was associated with a lower risk of death than open necrosectomy in the very high-risk group; risk ratio 0.70 (95%-CI, 0.52 to 0.95); P=0.02. Endoscopic necrosectomy was associated with a lower risk of death than open necrosectomy in the high-risk group: risk ratio 0.27 (95%-CI, 0.08 to 0.88); P=0.03; and the very high-risk group: risk ratio 0.43 (95%-CI, 0.24 to 0.77); P=0.005; with judgment suspended in the intermediate-risk group: risk ratio 0.14 (95%-CI, 0.02 to 1.10); P=0.06.

Subgroup and sensitivity analyses

The baseline death risk–stratified analysis and propensity-score matched–analysis were also performed in the subgroups of patients with documented infected necrosis (403 patients [86%] in the minimally invasive surgical group, 197 patients [57%] in the endoscopic group and 885 patients [76%] in the open necrosectomy group) and in patients who underwent previous catheter drainage (436 patients [93%] in the minimally invasive surgical group, 178 patients [51%] in the endoscopic group and 210 patients [18%] in the open necrosectomy group). Baseline characteristics for the matched and the unmatched cohorts and their actual death rates are provided in the appendix (pp 20-35). Results were in line with the primary analyses.

As alternative risk stratification, patients were stratified according to their APACHE-II score within 24 hours before necrosectomy (i.e. <7, ≥7 to <11, ≥11 to <15, and ≥15) and matched with propensity-score matching (appendix pp 36-41). Similar to the primary analyses, minimally invasive surgical necrosectomy and endoscopic necrosectomy were associated with a lower actual death rate in the higher APACHE-II groups (appendix pp 42-43).

In addition to death, other study outcomes included postoperative complications (i.e. bleeding and pancreatic fistula), number of necrosectomies, and hospital stay after necrosectomy. In the matched cohorts, bleeding occurred in 5 - 19% of patients and was more frequent in the higher risk of death groups. There was no statistically significant difference between minimally invasive necrosectomy methods and open necrosectomy. Pancreatic fistula occurred in 4 - 35% of patients, was more frequent in patients at lower risk of death and occurred more often in patients who underwent open necrosectomy. Overall, patients who underwent minimally invasive surgical necrosectomy had the longest hospital stay after necrosectomy (median 32 - 54 days), followed by open necrosectomy (median 21 - 52 days) and endoscopic necrosectomy (5 - 42 days). The number of necrosectomies was highest in the endoscopic groups (median 3 - 4), followed by the minimally invasive surgical groups (median 2 -3) and open necrosectomy groups (median 1). Detailed results with respect to these outcomes for the unmatched cohorts and matched cohorts in each risk group are provided in the appendix (pp 44-47).

Discussion

In this international collaborative study involving 1980 patients with necrotizing pancreatitis from 51 hospitals across eight countries, minimally invasive surgical necrosectomy or endoscopic necrosectomy compared with open necrosectomy significantly decreased mortality among high-risk patients. This benefit of minimally invasive techniques remained apparent after adjustment for confounding by several different analyses.

A large number of, mostly retrospective, cohort studies have reported outcomes of patients undergoing minimally invasive pancreatic necrosectomy. Few studies, however, have directly compared minimally invasive necrosectomy with open necrosectomy. One meta-analysis of four studies compared 215 patients undergoing minimally invasive surgical necrosectomy with 121 patients undergoing open necrosectomy.[18] Mortality was 17% after minimally invasive surgical necrosectomy vs. 30% after open necrosectomy (odds ratio 0.43; 95%-CI, 0.01-8.60; P=0.06). This meta-analysis, however, suffered from significant heterogeneity. Another single center study compared 274 patients undergoing minimally invasive surgical necrosectomy with 120 patients undergoing open necrosectomy; mortality was 15% vs. 23% (P=0.06).[12] Our study, with individual patient data, differed from these earlier studies because of its much larger sample size and, as a consequence, the possibility to analyze different risk groups and to adjust for the effects of confounding and selection bias.

How can the lower death rates after minimally invasive necrosectomy be explained? It is well known that, in various diseases, minimally invasive surgical techniques induce less surgical stress and thereby lead to a lower systemic pro-inflammatory response as compared with open surgery.[34,35] This was also demonstrated in necrotizing pancreatitis: in the only randomized trial that compared endoscopic necrosectomy with surgical necrosectomy (a total of 20 patients), endoscopic necrosectomy reduced the levels of the pro-inflammatory cytokine interleukin (IL)-6 during the 7 days after the procedure.[17] The more pronounced pro-inflammatory response invoked by open necrosectomy may facilitate organ failure or worsen pre-existing organ failure, especially in patients who are already suffering from a severe inflammatory condition such as necrotizing pancreatitis.[15] This seems of particular importance because organ failure is the main determinant for mortality in patients with necrotizing pancreatitis, especially in the presence of infected necrosis.[36] The same trial that demonstrated lower levels of IL-6 after endoscopic necrosectomy also showed lower rates of post-

procedure multiple organ failure.[17] A reduction in multiple organ failure with less surgical stress was also seen in another randomized trial that compared primary catheter drainage with open necrosectomy in 88 patients with necrotizing pancreatitis.[15] In contrast with these previous trials,[15,17] we did not study the rate of organ failure as a surrogate outcome. Our study was designed to evaluate the most relevant clinical endpoint of mortality, with a sufficiently large number of patients, even in the subgroups of the most severely ill patients. The concept of lowering mortality by reducing the pro-inflammatory response by limiting surgical stress in already critically ill patients is not new. It is also the rationale for the well-established concept of 'damage control surgery' in trauma patients.[37] Similar to patients with necrotizing pancreatitis, these patients suffer from a systemic inflammatory response as a result of multiple injuries.[38] Several studies have shown that early extensive orthopedic trauma surgery acts as 'a second hit' that induces pro-inflammatory cytokines and multiple organ failure.[39] To lower mortality in trauma patients early surgical intervention therefore only consists of short duration, life-saving operations (e.g. to control for bleeding), whereas lengthy fracture repairs are performed at a later stage when the systemic inflammatory state has subsided and the patient is able to sustain the extensive operative burden.[37,39]

Our results suggest that patients with necrotizing pancreatitis who are severely ill should undergo minimally invasive surgical or endoscopic necrosectomy instead of open necrosectomy, given the expertise in these minimally invasive techniques is available. In the propensity score matched analysis, we did not find significantly lower death rates in the low- and intermediate-risk groups. These patients, who are in a relatively stable clinical condition, seem capable of sustaining the larger surgical stress and pro-inflammatory hit induced by open necrosectomy. Another explanation may be that, due to their lower *a priori* risk of death, the subgroup of less severely ill patients was too small to detect a difference in death between methods of necrosectomy. This is supported by the wide 95%-confidence intervals observed in these groups (Figure 1). One could therefore argue that open necrosectomy is still a reasonable treatment option in these patients. However, other reasons to prefer minimally invasive necrosectomy techniques are lower rates of pancreatic fistula as shown in our study and lower rates of long-term complications such as incisional hernias and endocrine or exocrine pancreatic insufficiency.[15,17]

Our study does not have the preferred design of a randomized trial and it is therefore possible that hidden confounding factors may have influenced results. For instance, the included cohorts did not

capture data on preoperative imaging, such as extent and location of peripancreatic necrosis on computed tomography. Theoretically, these factors may have influenced the decisions to perform minimally invasive or open necrosectomy. Small and centrally located peripancreatic collections may be more easily accessible by endoscopy whereas collections extending to the paracolic gutter may prefer a surgical approach. Notably, not all patients with necrotizing pancreatitis are candidates for minimally invasive techniques. A small minority of patients with extensive collections may only be suitable for open surgical approach. There may also be hidden confounders associated with the time period in which necrosectomy was performed: e.g. supportive treatment on the intensive care may have improved over the years. Unfortunately, year of necrosectomy could not be included as variable in the propensity score matching because patients treated by primary open necrosectomy largely originated from the older cohorts included in our study. We did, however, compensate for this possible time effect by including study cohort as a variable in the prediction model used to stratify patients according to their risk of death. A randomized trial with a sample size large enough to detect a difference in mortality will be very difficult to realize and no such trial is currently planned. Large observational studies therefore yield the best available evidence to guide clinical decision making in this severe and complex disease. Because patients from 51 hospitals across eight countries and three continents were included in this study, we believe our results are generalizable to patient populations with necrotizing pancreatitis worldwide.

In conclusion, among severely ill patients with necrotizing pancreatitis, minimally invasive surgical necrosectomy and endoscopic necrosectomy were associated with lower death rates than open necrosectomy.

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Figure 1 Death rates in patients undergoing minimally invasive surgical necrosectomy and endoscopic necrosectomy as compared with patients undergoing open necrosectomy.

Index:

Shown are actual death rates for patients undergoing minimally invasive surgical necrosectomy (Panel A) and endoscopic necrosectomy (Panel B) as compared with patients undergoing open necrosectomy in unmatched cohorts and propensity-score matched cohorts. Patients are stratified in four risk groups based on predicted death at baseline (Low: <5%, Intermediate: ≥5% to <15%, High: ≥15% to <35% and Very high: ≥35%) which was determined by a multivariable prediction model incorporating study cohort, APACHE-II score, cardiovascular failure, pulmonary failure, and renal failure in the 24 hours before necrosectomy.

Table 1. Baseline characteristics before and after propensity-score matching of patients undergoing minimally invasive surgical necrosectomy or open necrosectomy.*

Characteristic	Before matching			After matching		
	Minimally invasive surgical necrosectomy (N = 97)	**Open necrosectomy (N = 377)**	**Standardized difference %**	**Minimally invasive surgical necrosectomy (N = 87)**	**Open necrosectomy (N = 87)**	**Standardized difference %**
Low risk of death (< 5%)						
Male sex - no. (%)	65 (68)	276 (73)	12.7	63 (72)	61 (70)	4.1
Age	43 ± 12	44 ± 13	9.5	44 ± 12	45 ± 14	5.7
Cause - no. (%)						
Gallstones	50 (51)	111 (29)	46.2	40 (46)	38 (44)	5.5
Alcohol	28 (29)	177 (47)	38.0	28 (32)	27 (31)	1.5
Other	19 (20)	89 (24)	9.7	19 (22)	22 (25)	8.0
APACHE-II score[†]	6.0 ± 3.4	7.7 ± 4.2	47.0	6.3 ± 3.4	6.0 ± 3.7	6.3
Cardiovascular failure - no. (%)[†‖]	0 (0)	7 (2)	19.7	0 (0)	0 (0)	0
Pulmonary failure - no. (%)[†‡]	3 (3)	30 (8)	21.2	3 (3)	3 (3)	0.5
Renal failure - no. (%)[†¶]	2 (2)	10 (3)	4.2	2 (2)	2 (2)	3.9
Documented infected necrosis - no. (%)[£]	88 (91)	279 (74)	47.0	79 (90)	79 (90)	0.6
Tertiary referral - no. (%)	77 (80)	205 (55)	56.3	68 (78)	68 (78)	1.2
Time since hospital admission - days	56 ± 53	51 ± 133	5.2	56 ± 54	66 ± 158	7.6
	Minimally invasive surgical necrosectomy (N = 119)	**Open necrosectomy (N = 343)**	**Standardized difference %**	**Minimally invasive surgical necrosectomy (N = 108)**	**Open necrosectomy (N = 108)**	**Standardized difference %**
Intermediate risk of death (≥ 5% to < 15%)						
Male sex - no. (%)	82 (69)	229 (67)	5.1	74 (69)	73 (68)	2.0
Age	54 ± 15	53 ± 14	5.9	54 ± 14	55 ± 13	6.2
Cause - no. (%)						
Gallstones	65 (55)	139 (40)	29.2	56 (52)	53 (49)	5.3
Alcohol	29 (24)	119 (35)	23.0	28 (26)	30 (28)	3.3
Other	25 (21)	85 (25)	9.6	24 (22)	25 (23)	2.6
APACHE-II score[†]	7.9 ± 3.0	10.0 ± 4.1	57.9	8.2 ± 2.8	8.1 ± 3.5	4.6
Cardiovascular failure - no. (%)[†‖]	3 (3)	65 (19)	53.2	3 (3)	3 (3)	5.8
Pulmonary failure - no. (%)[†‡]	8 (7)	113 (33)	68.1	8 (8)	6 (6)	8.4
Renal failure - no. (%)[†¶]	5 (4)	42 (12)	29.7	5 (5)	4 (4)	6.0
Documented infected necrosis - no. (%)[£]	95 (80)	270 (79)	3.2	87 (81)	88 (82)	2.0
Tertiary referral - no. (%)	95 (80)	208 (61)	43.3	84 (78)	82 (76)	4.3
Time since hospital admission - days	48 ± 41	30 ± 27	50.0	43 ± 33	41 ± 36	5.1

Table 1. (Continued)

	Minimally invasive surgical necrosectomy (N = 120)	Open necrosectomy (N = 225)	Standardized difference %	Minimally invasive surgical necrosectomy (N = 70)	Open necrosectomy (N = 70)	Standardized difference %
High risk of death (≥ 15% to < 35%)						
Male sex - no. (%)	65 (54)	140 (62)	17.5	43 (61)	44 (63)	4.1
Age	57 ± 13	58 ± 14	7.1	59 ± 13	59 ± 14	4.2
Cause - no. (%)						
Gallstones	72 (60)	88 (39)	43.0	35 (50)	36 (51)	1.7
Alcohol	31 (25)	81 (36)	23.2	21 (30)	21 (30)	0.6
Other	17 (15)	56 (25)	26.3	14 (20)	13 (19)	3.0
APACHE-II score[†]	10.1 ± 4.3	12.8 ± 4.2	62.2	11.3 ± 3.9	11.2 ± 3.5	0.9
Cardiovascular failure - no. (%)[†‖]	25 (21)	98 (44)	51.2	20 (29)	22 (31)	4.3
Pulmonary failure - no. (%)[†‡]	25 (21)	145 (65)	97.6	23 (32)	24 (34)	4.8
Renal failure - no. (%)[†¶]	7 (6)	65 (29)	64.7	7 (10)	7 (10)	2.8
Documented infected necrosis - no. (%)[£]	97 (81)	182 (81)	0.5	60 (85)	61 (87)	3.3
Tertiary referral - no. (%)	99 (83)	160 (71)	27.4	58 (83)	58 (83)	0.4
Time since hospital admission - days	35 ± 22	24 ± 19	56.4	29 ± 14	29 ± 22	1.6
	Minimally invasive surgical necrosectomy (N = 131)	**Open necrosectomy (N = 222)**	**Standardized difference %**	**Minimally invasive surgical necrosectomy (N = 111)**	**Open necrosectomy (N = 111)**	**Standardized difference %**
Very high risk of death (≥ 35%)						
Male sex - no. (%)	81 (62)	146 (66)	8.2	68 (62)	70 (63)	2.6
Age	63 ± 12	62 ± 14	5.5	62 ± 12	63 ± 13	0.9
Cause - no. (%)						
Gallstones	74 (56)	99 (44)	23.7	62 (56)	66 (60)	7.3
Alcohol	37 (29)	66 (30)	2.3	30 (27)	29 (26)	1.2
Other	20 (15)	57 (26)	26.8	19 (17)	16 (14)	8.5
APACHE-II score[†]	16.8 ± 5.7	16.6 ± 5.3	3.3	17.0 ± 5.7	17.1 ± 5.5	1.2
Cardiovascular failure - no. (%)[†‖]	91 (69)	179 (81)	25.9	81 (74)	84 (76)	5.8
Pulmonary failure - no. (%)[†‡]	90 (69)	182 (82)	30.9	79 (72)	78 (70)	2.0
Renal failure - no. (%)[†¶]	59 (45)	123 (55)	21.0	53 (48)	50 (45)	4.4
Documented infected necrosis - no. (%)[£]	123 (94)	154 (69)	67.3	103 (93)	105 (95)	7.5
Tertiary referral - no. (%)	115 (88)	168 (76)	31.4	95 (86)	92 (83)	5.4
Time since hospital admission - days	30 ± 15	22 ± 18	50.3	30 ± 15	28 ± 19	8.9

* Plus-minus values are means ± SD. A value of less than 10.0% of the standardized difference indicates a negligible difference between groups. Patients are stratified in four risk groups based on predicted death at baseline which was determined by a multivariable prediction model incorporating study cohort, APACHE-II score, cardiovascular failure, pulmonary failure, and renal failure in the 24 hours before necrosectomy (details on prediction model in appendix p 6).

† within 24 hours before necrosectomy.

|| Circulatory systolic blood pressure <90 mm Hg, despite adequate fluid resuscitation, or need for inotropic catecholamine support.

‡ PaO2 <60 mm Hg, despite FIO2 of 30%, or need for mechanical ventilation.

¶ Creatinine level >177 µmol/liter after rehydration or need for hemofiltration or hemodialysis.

£ Positive microbiological culture from fine-needle aspiration before necrosectomy or from first catheter drainage before necrosectomy or from primary necrosectomy.

Table 2. Baseline characteristics before and after propensity-score matching of patients undergoing endoscopic necrosectomy or open necrosectomy.*

Characteristic	Before matching			After matching		
	Endoscopic necrosectomy (N = 31)	**Open necrosectomy (N = 377)**	**Standardized difference %**	**Endoscopic necrosectomy (N = 29)**	**Open necrosectomy (N = 29)**	**Standardized difference %**
Low risk of death (< 5%)						
Male sex - no. (%)	22 (71)	276 (73)	5.3	21 (72)	21 (72)	1.4
Age	39 ± 11	44 ± 13	49.4	39 ± 11	40 ± 10	1.1
Cause - no. (%)						
Gallstones	10 (32)	111 (29)	6.3	8 (28)	8 (28)	0.3
Alcohol	8 (26)	177 (47)	45.2	8 (28)	8 (28)	0.3
Other	13 (42)	89 (24)	39.8	13 (44)	13 (44)	0.1
APACHE-II score†	3.3 ± 2.9	7.7 ± 4.2	124.8	3.7 ± 2.9	3.1 ± 2.8	10.0
Cardiovascular failure - no. (%)†‖	0	7 (2)	19.5	0	0	0
Pulmonary failure - no. (%)†‡	0	30 (8)	42.4	0	0	0
Renal failure - no. (%)†¶	0	10 (3)	23.4	0	0	0
Documented infected necrosis - no. (%)£	12 (39)	279 (74)	76.5	11 (38)	12 (41)	8.4
Tertiary referral - no. (%)	25 (81)	205 (55)	57.8	23 (79)	23 (79)	3.2
Time since hospital admission – days	88 ± 118	51 ± 133	29.7	89 ± 121	86 ± 203	7.6
	Endoscopic necrosectomy (N = 120)	**Open necrosectomy (N = 343)**	**Standardized difference %**	**Endoscopic necrosectomy (N = 72)**	**Open necrosectomy (N = 72)**	**Standardized difference %**
Intermediate risk of death (≥ 5% to < 15%)						
Male sex - no. (%)	85 (71)	229 (67)	9.2	49 (68)	48 (67)	2.4
Age	50 ± 14	53 ± 14	2.1	53 ± 14	54 ± 13	3.6
Cause - no. (%)						
Gallstones	57 (48)	139 (40)	14.3	33 (46)	34 (47)	1.2
Alcohol	29 (24)	119 (35)	23.4	20 (28)	21 (29)	3.1
Other	34 (28)	85 (25)	8.0	19 (26)	17 (24)	4.7
APACHE-II score†	6.5 ± 3.1	10.0 ± 4.1	96.7	7.4 ± 2.8	7.4 ± 3.6	0.5
Cardiovascular failure - no. (%)†‖	0	65 (19)	68.1	0	0	0
Pulmonary failure - no. (%)†‡	1 (1)	113 (33)	94.5	1 (1)	1 (1)	6.7
Renal failure - no. (%)†¶	0	42 (12)	52.9	0	0	0
Documented infected necrosis - no. (%)£	59 (49)	270 (79)	64.3	46 (64)	47 (65)	3.1
Tertiary referral - no. (%)	80 (67)	208 (61)	12.8	46 (64)	45 (63)	1.0
Time since hospital admission – days	48 ± 51	30 ± 27	42.9	36 ± 30	37 ± 29	2.9

Table 2. (Continued)

	Endoscopic necrosectomy (N = 133)	Open necrosectomy (N = 225)	Standardized difference %	Endoscopic necrosectomy (N = 40)	Open necrosectomy (N = 40)	Standardized difference %
High risk of death (≥ 15% to < 35%)						
Male sex - no. (%)	68 (51)	140 (62)	22.9	23 (58)	25 (63)	9.2
Age	59 ± 12	58 ± 14	6.0	60 ± 13	60 ± 14	1.5
Cause - no. (%)						
Gallstones	66 (50)	88 (39)	21.5	16 (40)	18 (45)	5.1
Alcohol	27 (20)	81 (36)	35.8	13 (32)	12 (30)	3.5
Other	40 (30)	56 (25)	11.7	11 (28)	10 (25)	2.8
APACHE-II score†	8.9 ± 2.9	12.8 ± 4.2	105.2	10.6 ± 2.8	10.5 ± 2.7	5.4
Cardiovascular failure - no. (%)†‖	11 (8)	98 (44)	88.2	9 (23)	10 (25)	4.5
Pulmonary failure - no. (%)†‡	7 (5)	145 (65)	158.9	7 (18)	7 (18)	1.5
Renal failure - no. (%)†¶	2 (2)	65 (29)	82.6	2 (5)	3 (8)	6.2
Documented infected necrosis - no. (%)£	76 (57)	182 (81)	53.3	32 (80)	32 (80)	2.7
Tertiary referral - no. (%)	96 (72)	160 (71)	2.1	29 (73)	31 (78)	9.3
Time since hospital admission - days	59 ± 84	24 ± 19	57.7	27 ± 15	27 ± 20	3.5
	Endoscopic necrosectomy (N = 62)	**Open necrosectomy (N = 222)**	**Standardized difference %**	**Endoscopic necrosectomy (N = 57)**	**Open necrosectomy (N = 57)**	**Standardized difference %**
Very high risk of death (≥ 35%)						
Male sex - no. (%)	40 (65)	146 (66)	2.3	37 (65)	35 (61)	5.0
Age	64 ± 14	62 ± 14	10.9	63 ± 14	63 ± 14	0.4
Cause - no. (%)						
Gallstones	37 (60)	99 (44)	30.6	34 (59)	33 (58)	0.6
Alcohol	14 (22)	66 (30)	16.1	14 (25)	13 (23)	4.6
Other	11 (18)	57 (26)	19.7	9 (16)	11 (19)	5.3
APACHE-II score†	16.0 ± 6.2	16.6 ± 5.3	11.9	16.2 ± 6.4	16.4 ± 5.3	2.8
Cardiovascular failure - no. (%)†‖	33 (53)	179 (81)	60.5	33 (58)	34 (60)	4.3
Pulmonary failure - no. (%)†‡	35 (56)	182 (82)	57.6	35 (61)	34 (60)	1.3
Renal failure - no. (%)†¶	18 (29)	123 (55)	55.3	18 (32)	16 (28)	6.2
Documented infected necrosis - no. (%)£	50 (81)	154 (69)	26.8	46 (81)	46 (81)	0.2
Tertiary referral - no. (%)	48 (77)	168 (76)	3.8	45 (79)	43 (76)	6.7
Time since hospital admission - days	36 ± 24	22 ± 18	65.0	33 ± 17	33 ± 22	2.9

* Plus-minus values are means ± SD. A value of less than 10.0% of the standardized difference indicates a negligible difference between groups. Patients are stratified in four risk groups based on predicted death at baseline which was determined by a multivariable prediction model incorporating study cohort, APACHE-II score, cardiovascular failure, pulmonary failure, and renal failure in the 24 hours before necrosectomy (details on prediction model in appendix p 6).

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£ Positive microbiological culture from fine-needle aspiration before necrosectomy or from first catheter drainage before necrosectomy or from primary necrosectomy.