Algorithm-based care versus usual care for the early recognition and management of complications after pancreatic resection in the Netherlands

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Algorithm-based care versus usual care for the early recognition and management of complications after pancreatic resection in the Netherlands: an open-label, nationwide, stepped-wedge cluster-randomised trial


**Summary**

**Background** Early recognition and management of postoperative complications, before they become clinically relevant, can improve postoperative outcomes for patients, especially for high-risk procedures such as pancreatic resection.

**Methods** We did an open-label, nationwide, stepped-wedge cluster-randomised trial that included all patients having pancreatic resection during a 22-month period in the Netherlands. In this trial design, all 17 centres that did pancreatic surgery were randomly allocated for the timing of the crossover from usual care (the control group) to treatment given in accordance with a multimodal, multidisciplinary algorithm for the early recognition and minimally invasive management of postoperative complications (the intervention group). Randomisation was done by an independent statistician using a computer-generated scheme, stratified to ensure that low–medium-volume centres alternated with high-volume centres. Patients and investigators were not masked to treatment. A smartphone app was designed that incorporated the algorithm and included the daily evaluation of clinical and biochemical markers. The algorithm determined when to do abdominal CT, radiological drainage, start antibiotic treatment, and remove abdominal drains. After crossover, clinicians were trained in how to use the algorithm during a 4-week wash-in period; analyses comparing outcomes between the control group and the intervention group included all patients other than those having pancreatic resection during this wash-in period. The primary outcome was a composite of bleeding that required invasive intervention, organ failure, and 90-day mortality, and was assessed by a masked adjudication committee. This trial was registered in the Netherlands Trial Register, NL6671.

**Findings** From Jan 8, 2018, to Nov 9, 2019, all 1805 patients who had pancreatic resection in the Netherlands were eligible for and included in this study. 57 patients who underwent resection during the wash-in phase were excluded from the primary analysis. 1748 patients (885 receiving usual care and 863 receiving algorithm-centred care) were included. The primary outcome occurred in fewer patients in the algorithm-centred care group than in the usual care group (73 [8%] of 863 patients vs 124 [14%] of 885 patients; adjusted risk ratio [RR] 0.48, 95% CI 0.38–0.61; p<0.0001). Among patients treated according to the algorithm, compared with patients who received usual care there was a decrease in bleeding that required intervention (47 [5%] patients vs 51 [6%] patients; RR 0.65, 0.42–0.99; p=0.046), organ failure (39 [5%] patients vs 92 [10%] patients; 0.35, 0.20–0.60; p=0.0001), and 90-day mortality (23 [3%] patients vs 44 [5%] patients; 0.42, 0.19–0.92; p=0.029).

**Interpretation** The algorithm for the early recognition and minimally invasive management of complications after pancreatic resection considerably improved clinical outcomes compared with usual care. This difference included an approximate 50% reduction in mortality at 90 days.

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**Introduction** Postoperative complications occur in more than 20% of patients after major surgery and are the greatest contributors to health-care use and costs.1,2 Despite continuous improvements in a wide range of health-care processes during the past decades, postoperative complications are not always preventable.3 It has been suggested that the focus on improving outcomes should therefore include the timely recognition and management of complications.4,5
Research in context

Evidence before this study

We searched PubMed, Embase, and the Cochrane Library for articles in any language published from database inception to June 20, 2016, before the start of this study, and updated the search on August 20, 2021 with search terms “diagnosis”, “management”, “pancreatic resection”, and “complications”, and synonyms. We found no studies that evaluated a multimodal intervention for recognition and management of complications after pancreatic resection. We found many observational studies that evaluated different diagnostic modalities for postoperative pancreatic fistula. We published a systematic review on this topic in 2020. Our 2020 review included all diagnostic tests that showed an association with postoperative pancreatic fistula in at least two cohorts. Identified variables were body temperature, C-reactive protein, white blood cell count, serum amylase amount, drain amylase amount, non-serous drain efflux, and peripancreatic fluid collections on CT scan. To our knowledge, no randomised trials have been published on complication management after pancreatic resection. However, several observational studies suggested the superiority of a minimally invasive treatment strategy compared with reoperation.

Added value of this study

To our knowledge, our study provides the first high-quality evidence that early recognition and minimally invasive management of complications after pancreatic resection, before they become clinically relevant, can interrupt the cascade of events that lead to organ failure and death. This effect was measured both in high-volume centres and in low–medium-volume hospitals.

Implications of all the available evidence

The multidisciplinary, multimodal algorithm for daily bedside use was designed using data from our mandatory nationwide audit, guideline inventories, Dutch national meetings and international consensus meetings, and a comprehensive systematic review of the literature. The algorithm was therefore based on the best available evidence. After combining this evidence with our study findings, we believe that after pancreatic resection, all patients should receive a structured daily evaluation to aid the early recognition and management of complications before these become clinically relevant. This provision will considerably improve clinical outcomes and decrease the failure to rescue rate, which is an international priority in surgical practice and among policy makers. Our simple to use and low-cost algorithm, and the method for its implementation, can be modified easily for use in other types of surgery. Future studies could evaluate further improvements to the algorithm and the adaptation of the algorithm in other clinical contexts.

Methods

Study design and participants

The Care After Pancreatic Resection According to an Algorithm for Early Detection and Minimally Invasive Management of Pancreatic Fistula versus Current Practice (PORSCH) trial is a Dutch, nationwide, stepped-wedge cluster-randomised controlled trial. In the Netherlands, pancreatic surgery is centralised to centres that do at least 20 pancreaticoduodenectomies per year. All 17 Dutch centres doing pancreatic surgery, including all eight university hospitals, participated in this study, and we included all patients having pancreatic resection for all indications. There were no exclusion criteria for centres or patients (ie, nationally, all patients were included).

However, recognising the early signs of complications before they lead to clinical deterioration is a challenge. Noticing subtle changes in vital signs, biochemical markers, and radiological features requires members of a multidisciplinary medical team to have the appropriate training and experience. Improving the failure to rescue rate (ie, reducing mortality after major complications) has emerged as a main target for quality improvement by the international surgical community. There is a clear need for studies to develop effective interventions that can be implemented broadly to improve failure to rescue rates worldwide. Pancreatic resection is an example of a complex operation with a high risk (30–73% of patients) of postoperative complications. The most common complication is pancreatic fistula, which results in an intra-abdominal leak of amylase-rich fluid that can lead to life-threatening consequences, such as sepsis, bleeding, and multiple organ failure. In patients with clinically relevant pancreatic fistula, mortality is 12–18%. Outcomes after pancreatic resection have improved since the centralisation of such surgery to high-volume centres owing to a focus on the technical aspects of the surgery, process measures, and institutional factors, such as improvements in prehabilitation, anaesthesiology, and the quality of postoperative support in intensive care units. Nevertheless, even in high-volume centres, complications after pancreatic resection remain a serious problem. Furthermore, most patients worldwide have such surgery in low-volume or medium-volume centres. Reported nationwide 90-day mortality rates after pancreatic resection range from 7% to 12%. Improving failure to rescue rates has therefore been prioritised in pancreatic surgery.

We designed a multimodal algorithm for the early recognition and minimally invasive management of postoperative complications in patients having pancreatic resection for all indications. We hypothesised that implementation of this multimodal algorithm would result in better clinical outcomes than after usual care.
Randomisation and masking
As per the stepped-wedge cluster-randomised trial design, all centres (clusters) delivered usual care (control group) at the start of the study and crossed over to care according to the algorithm (intervention group). At the end of the trial, all centres had crossed over to the intervention group. Randomisation of the timing of crossover for each centre was done by an independent statistician using a computer-generated scheme, and was stratified to ensure that low–medium-volume centres alternated with high-volume centres in randomisation order. Randomisation order was concealed from patients and the investigators, except for the local principal investigator, who was informed at the start of the trial of the time of crossover for that centre. Patients and investigators were not masked to treatment.

Procedures
The process of designing the algorithm included a comprehensive systematic review of the literature, and an inventory of the guidelines on postoperative care, several retrospective studies, and consensus meetings.23 To reduce the risk of the contamination of usual care, only one pancreatic surgeon from each centre was involved in the study design. The final evidence-based algorithm was reviewed by an advisory committee of three international pancreatic experts from high-volume centres; further details are provided in the appendix (pp 8–9). Adverse events that might be related to the study intervention were discussed at regular study meetings that were open to all clinicians from the centres that had crossed over to the intervention. The study was done in accordance with the Declaration of Helsinki. We adhered to the CONSORT guidelines for stepped-wedge cluster-randomised trials.23 The study protocol has been published previously.20

and to advise on how to proceed with the management of postoperative complications.

For each patient, daily evaluation using the algorithm was done from postoperative day 3 to postoperative day 14 (figure 1). The algorithm focused on the early recognition of complications through the standardised evaluation of vital signs, abdominal drain output, and serum inflammatory markers (ie, white blood cell count and C-reactive protein). If predefined cutoff values were exceeded, an abdominal CT scan was indicated.

Figure 1: An overview of the multimodal, multidisciplinary algorithm for the early recognition and management of complications after pancreatic resection
ULN=upper limit of normal.

Appendix (pp 8–9) and in the study protocol.20 Protocol adherence was monitored continuously using an online platform by the study coordinators, who were not involved in clinical care. This online platform was also the basis of a smartphone app that facilitated use of the algorithm (appendix p 11). Adverse events that might be related to the study intervention were discussed at regular study meetings that were open to all clinicians from the centres that had crossed over to the intervention. The study was done in accordance with the Declaration of Helsinki. We adhered to the CONSORT guidelines for stepped-wedge cluster-randomised trials. The study protocol has been published previously.20

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After crossover, clinicians were trained in how to use the algorithm during a 4-week wash-in period. Training consisted of on-site presentations for all surgeons and resident medical officers, nursing staff, diagnostic and interventional radiologists, and intensive care staff. A nationwide online expert panel of authors who were pancreatic surgeons and interventional radiologists was available to assess clinical cases and radiological imaging and to advise on how to proceed with the management of postoperative complications.

For each patient, daily evaluation using the algorithm was done from postoperative day 3 to postoperative day 14 (figure 1). The algorithm focused on the early recognition of complications through the standardised evaluation of vital signs, abdominal drain output, and serum inflammatory markers (ie, white blood cell count and C-reactive protein). If predefined cutoff values were exceeded, an abdominal CT scan was indicated.
Evaluation of CT scans was standardised, focusing on radiological signs of postoperative pancreatic fistula and other postoperative complications. The complete list of criteria for assessment of CT scans is shown in the appendix (p 24). In the case of inadequately drained intra-abdominal fluid that was possibly related to a postoperative complication, radiological drainage was recommended. Treatment with intravenous antibiotics was indicated in all patients with pancreatic fistula or a systemic inflammatory response syndrome (in patients with an indication for a CT scan according to the algorithm). The algorithm also focused on the removal of abdominal drains, to ensure removal occurred as early as possible to help prevent infection. The algorithm also included daily assessment by the treating pancreatic surgeon, who was responsible for making final clinical decisions (appendix pp 20–23). An intraoperative drain was placed in all patients, whereas other surgical technique details were left to the discretion of local surgeons.

After entering all data in the smartphone app, the algorithm produced advice on the indication for CT scan, radiological drainage, antibiotic treatment, and removal of drains. An impression of the smartphone app is supplied in the appendix (p 25). A version of the Pancreatic surgery smartphone app has been modified for daily clinical use (see also appendix p 11).

Outcomes
The primary outcome was a composite of the most severe postoperative complications: bleeding that required invasive intervention, new-onset organ failure, and death either during admission or within 90 days after resection, and the outcome was met if any of these events occurred. The three components of the primary outcome were each analysed individually as secondary outcomes. Other predefined secondary outcomes included postoperative pancreatic fistula, postoperative bile leak, gastrointestinal leak, chyle leak, delayed gastric emptying, number and timing of CT scans, antibiotic treatment, radiological drainage, reoperations, intensive care unit (ICU) admission, length of ICU stay, length of hospital stay, readmission rate, number of patients receiving adjuvant chemotherapy, and costs. A complete list of all secondary outcomes and definitions is included in the appendix (pp 12–13, 18). Outcomes were assessed up to 90 days after initial pancreatic resection or, if patients were still admitted after 90 days, until discharge.

Data were collected using a web-based predefined case record form. In addition, baseline data were extracted from the mandatory prospective Dutch Pancreatic Cancer Audit.28 All data were checked for accuracy and completeness of the source data by researchers not involved in clinical care. Before statistical analysis, data for all potential primary outcomes were individually assessed by members of a masked adjudication committee consisting of authors who were pancreatic surgeons and interventional radiologists, and disagreements were resolved during a plenary consensus meeting with masking still in effect.

Statistical analysis
Sample size calculation was done for the subgroup of patients who were to have pancreatoduodenectomy to ensure adequate power for this population. We assumed an expected relative reduction of 50% in the incidence of the primary outcome after pancreatoduodenectomy, on the basis of 13·8% of patients, a two-sided α of 0·05, a power of 80%, an intracluster correlation of 0·009, and a cluster autocorrelation of 1·901,22,24 which resulted in a required sample size of 1186 patients having a pancreatoduodenectomy in the 17 centres. The planned study duration was therefore 22 months, on the basis of typical patient numbers per month. The total sample size was expected to be 25% higher than the planned sample size, because all types of pancreatic resection were included. A planned interim analysis was done at 11 months to allow for the study duration to be extended if enrolment was less than 47·5% of the planned sample size.

Analyses were done according to the intention-to-treat principle, comparing patients assigned to usual care with patients assigned to algorithm-centred care. Date of pancreatic resection (ie, before or after the planned crossover date) determined which study group patients were in. As predefined, patients having pancreatic resection during the wash-in period were excluded from analyses. Missing baseline data were imputed using multiple imputation. The study protocol defined mixed-effects logistic regression analyses of the binary outcomes with odds ratio (OR) as the measure of effect size. However, because risk ratios (RRs) are preferred to ORs in terms of interpretation, collapsibility, and reduced susceptibility to sparse-data bias, for the final analyses we used mixed-effects Poisson regression with cluster-robust SEs to estimate the shown RRs and 95% CIs. Time-to-event analyses (ie, from the date of the initial pancreatic resection to 90 days postoperatively) were done using shared-frailty Cox proportional hazards model. Count data were analysed using a zero-inflated negative binomial model. All analyses were adjusted for the study design (ie, we used the hospital as a random effect, normalised calendar time as a fixed effect, and the volume strata as a fixed effect) and baseline variables (all fixed effect) associated with the primary outcome (ie, male sex, increasing age, American Society of Anaesthesiologists classification >2, pancreatoduodenectomy vs other types of pancreatic resection) or postoperative pancreatic fistula (ie, soft pancreatic texture, small-diameter pancreatic duct, increasing blood loss during pancreatic resection, and underlying disease that is not either pancreatitis or pancreatic adenocarcinoma). Normalisation of calendar time was achieved by subtraction of the numerical
representation of the calendar date from the group mean, divided by the SD. Total hospital costs included hospital and intensive care unit admission, laboratory tests, diagnostic imaging, endoscopy, radiological interventions, and surgical procedures. Outpatient hospital costs and other health-care costs were not included. Mean costs are shown with two-sided bias-corrected and accelerated 95% CIs derived by bootstrapping with 5000 samples. A two-sided p value below 0·05 indicated statistical significance. For statistical analysis we used R studio (version 1.3.959). For details on the statistical analysis, including several exploratory analyses, see the appendix (p 14). We did not use a data monitoring committee. This trial was registered in the Netherlands Trial Register, number NL6671.

Role of the funding source
The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
All 17 centres doing pancreatic surgery in the Netherlands were randomly assigned a crossover date. One centre stopped doing pancreatic surgery before crossover to the intervention. From Jan 8, 2018, to Nov 9, 2019, a total of 1805 patients had pancreatic resection in the Netherlands and all of these patients were eligible and included in this study. 885 (49%) patients received usual care (control group), 57 (3%) patients underwent resection during the wash-in phase, and 863 (48%) patients received algorithm-centred care (intervention group; figure 2, appendix p 19). No patients were lost to follow-up. Baseline characteristics are provided in table 1.

Use of the algorithm in the smartphone app was completed 9308 times. On 7631 (94%) of 8137 included patient-days (ie, postoperative days 3–14), data were entered into the smartphone app algorithm. A CT scan was done in 814 (75%) of 1086 times that it was recommended by the app. The app recommendation to administer antibiotics was followed 253 (70%) of 360 times. The app recommendation on drain removal was followed 253 (70%) of 360 times. A total of two complications that might have been related to minimally invasive drainage were reported (one perforation of the stomach and one bowel perforation; 0·2% of all drainage procedures).

The primary outcome occurred in 73 (8%) of 885 patients in the intervention group and in 124 (14%) of 885 patients in the control group (adjusted RR 0·48, 95% CI 0·38–0·61; p<0·0001; table 2). Bleeding that required intervention occurred in 5% (47 patients) in the intervention group versus 6% (51 patients) in the control group (adjusted RR 0·65, 95% CI 0·42–0·99; p=0·046). New-onset organ failure, including failure of all individual organ systems, occurred less often in the intervention group than in the control group (39 patients [5%] vs 92 patients [10%], adjusted RR 0·35, 95% CI 0·20–0·60; p=0·0001). 90-day mortality was lower in the intervention group than in the control group (23 patients [3%] vs 44 patients [5%], adjusted RR 0·42, 95% CI 0·19–0·92; p=0·029).

Results of other clinical events and health-care use are shown in table 3. It appeared that CT scan, antibiotic treatment, and radiological drainage were done more often and earlier in patients in the intervention group than patients in the control group. Patients in the intervention group less often had reoperation or admission to the intensive care unit than patients in the control group (table 3). Mean total costs per patient were €23 202 (95% CI 22 024 to 24 498) in the intervention group and €23 450 (95% CI 22 100 to 24 450) in the control group (mean difference €248, −1395 to 1890; appendix p 30). Results of other secondary outcomes are provided in the appendix (pp 31–46). Results were consistent across all predefined exploratory analyses (appendix pp 31–46). In the subgroup of patients undergoing pancreaticoduodenectomy, the primary outcome occurred in 56 (9%) of 643 patients in the intervention group and in 105 (16%) of 671 patients in the control group (adjusted RR 0·46, 95% CI 0·34–0·61). In this subgroup, 90-day mortality was 3% in the intervention group (17 of 643 patients) and 5% in the control group (35 of 671 patients; adjusted RR 0·40, 95% CI 0·18–0·85).

The lower proportion of people with the primary outcome in the intervention group compared with in the control group occurred both in low–medium-volume centres (25 [9%] of 291 patients vs 42 [14%] of 294 patients, adjusted RR 0·49, 95% CI 0·25–0·68) and in high-volume centres (48 [8%] of 572 patients vs 82 [14%] of 591 patients adjusted RR 0·46, 95% CI 0·32–0·66). Compared with the
control, the intervention also reduced 90-day mortality in both low–medium-volume centres (8 [3%] of 291 patients vs 20 [7%] of 294 patients, adjusted RR 0·35, 95% CI 0·11–1·16) and high-volume centres (15 [3%] of 572 patients vs 20 [7%] of 294 patients, adjusted RR 0·35, 95% CI 0·24–0·50).

Discussion
This stepped-wedge cluster randomised trial showed that the use of a novel algorithm for the early recognition and management of postoperative complications in patients undergoing pancreatic resection greatly improved clinical outcomes, including an approximate 50% reduction of mortality nationwide. Our findings support a strategy in which all patients have a structured daily evaluation to identify and treat complications before they become clinically relevant. The smartphone app that was designed for bedside use of the algorithm can be used for this purpose.

Pancreatic resection is an operation done widely, mostly in patients with malignant disease who usually have a survival likelihood of only a few years. Pancreatic resection is also done in patients with chronic pancreatitis and prophylactically in young patients with asymptomatic pancreatic cysts. In all patients, the effect of severe complications is crucial in the shared decision-making process about doing major abdominal surgery. In our study, 90-day mortality before introduction of the intervention was 5%, which is higher than mortality of less than 2% reported by international expert centres. This difference might be explained by the fact that we studied 90-day mortality, whereas other studies often report 30-day mortality. In patients with pancreatic resection, 90-day mortality is generally twice as high as 30-day mortality. A systematic review of 44 studies on the effect of centralisation of pancreatic surgery provision showed 90-day mortality of 9–16% in low-volume centres and 0–5% in high-volume centres. Furthermore, we studied mortality on a nationwide level, which reflected outcomes that were not explained by the fact that we studied 90-day mortality, whereas other studies often report 30-day mortality. In patients with pancreatic resection, 90-day mortality is generally twice as high as 30-day mortality. A systematic review of 44 studies on the effect of centralisation of pancreatic surgery provision showed 90-day mortality of 9–16% in low-volume centres and 0–5% in high-volume centres. Furthermore, we studied mortality on a nationwide level, which reflected outcomes that were not only for selected expert centres. At the national level, 90-day mortality ranges from 7–12% in Europe and the USA.

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Sex</th>
<th>Intervention (n=863)</th>
<th>Control (n=885)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>427 (49%)</td>
<td>444 (50%)</td>
</tr>
<tr>
<td>Male</td>
<td>436 (51%)</td>
<td>441 (50%)</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>65·7 (11·6)</td>
<td>65·0 (11·7)</td>
</tr>
</tbody>
</table>

Table 2: Primary outcome and contributory secondary outcomes for algorithm-based care versus usual care after pancreatic resection surgery
The rationale for the multimodal, multidisciplinary algorithm is based on two concepts. The first is the timely identification of complications before they become clinically relevant. Complications of abdominal operations can lead to sudden clinical deterioration, with a cascade of sepsis, multiple organ failure, then death.27 There is often a short time period in which early signs of these complications might be visible on CT scan before there are clinical consequences. For this reason, the algorithm recommends an abdominal CT scan once a particular threshold of subtle changes in vital signs and serum inflammatory markers is reached, even in patients with no clinical suspicion of complications. Use of the algorithm resulted in an increase in number of CT scans done in the intervention group. Patients in the intervention group also had their first CT scan a mean of 2 days earlier than patients in the control group. These findings support the efficacy of the algorithm with regard to the timely identification of complications.

The second concept behind the algorithm is the timely treatment of complications, using a minimally invasive approach rather than reoperation. Patients in the

### Table 3: Secondary outcomes for algorithm-based care versus usual care after pancreatic resection surgery

<table>
<thead>
<tr>
<th>Clinical events†</th>
<th>Intervention (n=863)</th>
<th>Control (n=885)</th>
<th>Adjusted risk ratio (95% CI)*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative pancreatic fistula</td>
<td>239/863 (28%)</td>
<td>187/885 (21%)</td>
<td>1.23 (0.97-1.56)</td>
<td>0.084</td>
</tr>
<tr>
<td>Postoperative bile leak‡</td>
<td>66/864 (10%)</td>
<td>57/871 (8%)</td>
<td>0.90 (0.60-1.33)</td>
<td>0.59</td>
</tr>
<tr>
<td>Gastroenterostomy leak‡</td>
<td>8/863 (1%)</td>
<td>11/871 (2%)</td>
<td>0.88 (0.30-2.62)</td>
<td>0.82</td>
</tr>
<tr>
<td>Chyle leak</td>
<td>61/863 (7%)</td>
<td>69/885 (8%)</td>
<td>0.95 (0.59-1.54)</td>
<td>0.84</td>
</tr>
<tr>
<td>Delayed gastric emptying</td>
<td>134/863 (16%)</td>
<td>144/885 (16%)</td>
<td>1.17 (0.76-1.80)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

### Health-care resource use

#### Abdominal CT scans

<table>
<thead>
<tr>
<th>Description</th>
<th>Intervention (n=863)</th>
<th>Control (n=885)</th>
<th>Adjusted rate ratio (95% CI)§</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients having CT scan</td>
<td>562/863 (65%)</td>
<td>473/885 (53%)</td>
<td>1.18 (1.01-1.36)</td>
<td>0.031</td>
</tr>
<tr>
<td>Median CT scans per patient§</td>
<td>1 (0-2)</td>
<td>1 (0-2)</td>
<td>1.23 (1.00-1.53)</td>
<td>0.049</td>
</tr>
<tr>
<td>Total CT scans per study group</td>
<td>1533</td>
<td>1189</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Median postoperative day of first CT scan</td>
<td></td>
<td></td>
<td>5 (3-12)</td>
<td>7 (5-13)</td>
</tr>
</tbody>
</table>

#### Antibiotics

<table>
<thead>
<tr>
<th>Description</th>
<th>Intervention (n=863)</th>
<th>Control (n=885)</th>
<th>Adjusted rate ratio (95% CI)§</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients receiving antibiotics</td>
<td>395/863 (46%)</td>
<td>335/885 (38%)</td>
<td>1.19 (0.97-1.48)</td>
<td>0.10</td>
</tr>
<tr>
<td>Median duration of antibiotics treatment, days§</td>
<td>2 (0-8)</td>
<td>0 (0-7)</td>
<td>1.02 (0.71-1.46)</td>
<td>0.91</td>
</tr>
<tr>
<td>Median postoperative day of start of antibiotic treatment</td>
<td></td>
<td></td>
<td>7 (4-11)</td>
<td>8 (5-15)</td>
</tr>
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</table>

#### Radiological drainage

<table>
<thead>
<tr>
<th>Description</th>
<th>Intervention (n=863)</th>
<th>Control (n=885)</th>
<th>Adjusted rate ratio (95% CI)§</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients undergoing radiological drainage</td>
<td>252/863 (29%)</td>
<td>207/885 (23%)</td>
<td>1.21 (0.93-1.57)</td>
<td>0.16</td>
</tr>
<tr>
<td>Median radiological drainage procedures per patient§</td>
<td>0 (0-1)</td>
<td>0 (0-0)</td>
<td>1.05 (0.73-1.52)</td>
<td>0.77</td>
</tr>
<tr>
<td>Total radiological drainage procedures per study group</td>
<td>505</td>
<td>474</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Median postoperative day of first drainage</td>
<td></td>
<td></td>
<td>8 (5-11)</td>
<td>9 (7-13)</td>
</tr>
</tbody>
</table>

#### Reoperation

<table>
<thead>
<tr>
<th>Description</th>
<th>Intervention (n=863)</th>
<th>Control (n=885)</th>
<th>Adjusted rate ratio (95% CI)§</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients having reoperation</td>
<td>42/863 (5%)</td>
<td>70/885 (8%)</td>
<td>0.63 (0.43-0.92)</td>
<td>0.017</td>
</tr>
<tr>
<td>Median reoperations per patient§</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0.55 (0.31-0.99)</td>
<td>0.045</td>
</tr>
<tr>
<td>Total reoperations per study group</td>
<td>50</td>
<td>86</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Median postoperative day of surgical drain removal</td>
<td></td>
<td></td>
<td>5 (3-9)</td>
<td>5 (4-8)</td>
</tr>
</tbody>
</table>

#### Intensive care unit admission

<table>
<thead>
<tr>
<th>Description</th>
<th>Intervention (n=863)</th>
<th>Control (n=885)</th>
<th>Adjusted rate ratio (95% CI)§</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients admitted to the intensive care unit after postoperative day 3 (ie, new-onset ICU admission)</td>
<td>57/863 (7%)</td>
<td>80/885 (9%)</td>
<td>0.57 (0.43-0.76)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Median length of intensive care unit stay, days**</td>
<td>4 (3-9)</td>
<td>4 (2-8)</td>
<td>1.19 (0.74-1.81)</td>
<td>0.47</td>
</tr>
<tr>
<td>Median length of hospital stay, days</td>
<td></td>
<td></td>
<td>11 (8-18)</td>
<td>10 (7-15)</td>
</tr>
<tr>
<td>Readmission to hospital</td>
<td>168/863 (20%)</td>
<td>188/885 (21%)</td>
<td>1.04 (0.84-1.29)</td>
<td>0.70</td>
</tr>
<tr>
<td>Adjuvant chemotherapy††</td>
<td>172/220 (52%)</td>
<td>185/219 (58%)</td>
<td>1.02 (0.87-1.22)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Data are n/N (%), mean (SD), or median (IQR) unless otherwise stated. All analyses were adjusted for calendar time, pancreatic texture, diameter pancreatic duct, blood loss pancreatic resection, underlying disease, sex, age (years), American Society of Anaesthesiologists classification, type of pancreatic resection, and hospital volume. *Mixed-model Poisson regression analyses adjusted with the random intercept at hospital level. **Cox proportional hazard ratio (HR) for which HRs greater than 1 indicate a shorter time to event in the intervention group than in the control group. **The conditional rate ratio from a zero-inflated negative binomial regression model; zero-inflated inverted odds ratio 0.52 (95% CI 0.31-0.87). ††Calculated in a subset of patients with pancreatic adenocarcinoma who survived the index hospital admission (330 [38%] of 863 patients in the control group vs 319 [36%] of 885 patients in the intervention group).
intervention group had treatment with antibiotics and radiological drainage more often, and earlier, than patients in the control group. Fewer patients in the intervention group had reoperation. It is known that general anaesthesia required for surgery and the pro-inflammatory second hit of the surgical trauma might worsen the physiological downwards spiral of organ failure in critically ill patients. The benefits of radiological drainage have long been recognised in the treatment of complications after elective pancreatic surgery, but few studies have been done on this topic.

One observational study suggested that radiological drainage decreases complications and death compared with primary reoperation for pancreatic fistula. Our study provides further evidence for this concept.

Although the individual changes in clinical management induced by use of the algorithm might not appear large, the combined effect of changes led to a clinically relevant reduction in the primary outcome. We did not investigate the potential beneficial effect of each individual component of the algorithm, including a general awareness of the patient’s wellbeing owing to the daily clinical assessment by a pancreatic surgeon. This possibility could be a focus for future research, and potentially lead to a leaner algorithm. It might be that the use of modern technology, such as artificial intelligence, can facilitate the decision to operate, the identification and mitigation of modifiable risk factors, and decisions regarding postoperative management. These modalities are gaining popularity in many fields of medicine but have been little studied in surgery.

The main strength of our study is its generalisability to everyday surgical practice. The nationwide effect of the intervention was similar in subgroups in both low–medium-volume and high-volume centres in the Netherlands. This result supports the notion that, even in centres with substantial experience in pancreatic surgery, outcomes for patients could be improved further by using a standardised and increasingly intensive approach for the early recognition and management of complications. The parameters for the algorithm include vital signs and serum inflammatory markers that are already widely used in daily practice. CT scans and radiological drainage are also commonly available techniques. This usage implies that implementation of the algorithm is feasible in most countries, regardless of potential differences to the health-care system of the Netherlands. However, it does require the commitment of the clinicians involved, and hospital capacity to do diagnostic and interventional radiological procedures in around two-thirds of patients after surgery. We found no apparent downsides from the use of the algorithm. Total costs were not increased. The algorithm was safe, low cost, and easy to use, which was underlined by the use of a smartphone app to complete the algorithm. Nevertheless, we observed that in some centres it was challenging to adhere persistently to the recommendations given by the algorithm. Compliance by the treating pancreatic surgeons was 70–83%, which can be considered a limitation of our study. The effect of the algorithm might have been even greater if adherence had been higher. However, the observed amount of adherence can still be considered quite high, given that it is counterintuitive for clinicians to do diagnostics or inventions in patients who do not show any clinical signs of a postoperative complication. Although the result did not reach statistical significance, there appeared to be an increase in the incidence of pancreatic fistula in the intervention group. This increase was expected because radiological drainage and antibiotic treatment was recommended in the algorithm at a low threshold, which is classified as grade B pancreatic fistula according to international definitions. However, it has been recognised that adequately drained grade B pancreatic fistula are of little clinical significance. This view is supported by our finding of a substantial reduction in the primary endpoint of major complications and death in the intervention group. There appears to be a specific number needed to treat for abdominal CT, antibiotics, and radiological drainage in patients who are not clinically ill, to prevent one potentially fatal event as a result of a pancreatic fistula, and to thereby reduce the failure to rescue rate. In addition, data might be subject to sparse-data bias.

Failure to rescue has become an internationally endorsed, publicly reported quality measure for all types of surgery with potentially life-threatening complications. The early recognition and management of postoperative complications has been proposed as the main focus to decrease mortality in elective surgery patients. In our study, the first randomised clinical trial on this topic, failure to rescue decreased from 15% (44 of 290) to 8% (23 of 301) of patients with major complications (appendix p 32). We are not aware of other algorithms that have been studied to improve the early detection and timely management of postoperative complications. We only included patients having pancreatic resection, which might question the generalisability of our study to other patient populations. However, in the future, the algorithm could be modified to study its use in other diseases or surgical procedures that have a high risk of postoperative complications (eg, major liver resection, colorectal, gastric, and oesophageal surgery).

In conclusion, our study showed that compared with usual care, the early recognition and minimally invasive management of complications after pancreatic resection reduced the composite outcome of bleeding requiring invasive intervention, organ failure, and death.

Contributors
FJS, MGB, ORB, CHvE, IQM, and HGvS conceived the study. MGB, ORB, CHvE, MA, MvdK, OMvD, DvdH, CvdL, KPvL, AM, IQM, and
HCvS formed the expert panel. MGB, TLB, ORB, CHvE, BGK, DvdH, KPVl, IQM, and HCvS were members of the masked adjudication committee. FJS and ACH coordinated the study conduct and data collection. FJS, ACH, and LAD did the data analyses and verified the data, supervised ChvW and HCvS. FJS and HCvS drafted the manuscript, with assistance from all coauthors. All authors critically assessed the study design, enrolled patients in the study, edited the manuscript, and approved the final manuscript. All authors had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

Declaration of interests
CvdL is the Secretary of the Dutch Society of Interventional Radiology (unpaid position). CHvE’s institution received payments from Pfizer, Bionerieux, Da Volterra, and MSD and he has a European Patent Application with Da Volterra, University Antwerp, and University Medical Centre Utrecht Holdings. All other authors declare no competing interests.

Data sharing
Data (anonymised) from this study will be made available upon request, subject to review and approval by the study steering committee, the Dutch Pancreatic Cancer Group, institutional review boards (if appropriate), and a signed data access agreement. Requests including a detailed study proposal should be directed to h.vansantvoort@umcutrecht.nl.

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