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# Impact of Complications After Pancreatoduodenectomy on Mortality, Organ Failure, Hospital Stay, and Readmission

## *Analysis of a Nationwide Audit*

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**Objective:** To quantify the impact of individual complications on mortality, organ failure, hospital stay, and readmission after pancreatoduodenectomy.

**Summary of Background Data:** An initial complication may provoke a sequence of adverse events potentially leading to mortality after pancreatoduodenectomy. This study was conducted to aid prioritization of quality improvement initiatives.

**Methods:** Data from consecutive patients undergoing pancreatoduodenectomy (2014–2017) were extracted from the Dutch Pancreatic Cancer Audit. Population attributable fractions (PAF) were calculated for the association of each complication (ie, postoperative pancreatic fistula, postpancreatectomy hemorrhage, bile leakage, delayed gastric emptying, wound infection, and pneumonia) with each unfavorable outcome [ie, in-hospital mortality, organ failure, prolonged hospital stay (>75th percentile), and unplanned readmission), whereas adjusting for confounders and other complications. The PAF represents the proportion of an outcome that could be prevented if a complication would be eliminated completely.

**Results:** Overall, 2620 patients were analyzed. In-hospital mortality occurred in 95 patients (3.6%), organ failure in 198 patients (7.6%), and readmission in 427 patients (16.2%). Postoperative pancreatic fistula and postpancreatectomy hemorrhage had the greatest independent impact on mortality [PAF 25.7% (95% CI 13.4–37.9) and 32.8% (21.9–43.8), respectively] and organ failure [PAF 21.8% (95% CI 12.9–30.6) and 22.1% (15.0–29.1), respectively]. Delayed gastric emptying had the greatest independent impact on prolonged hospital stay [PAF 27.6% (95% CI 23.5–31.8)]. The impact of individual complications on unplanned readmission was smaller than 11%.

**Conclusion:** Interventions focusing on postoperative pancreatic fistula and postpancreatectomy hemorrhage may have the greatest impact on in-hospital mortality and organ failure. To prevent prolonged hospital stay, initiatives should in addition focus on delayed gastric emptying.

**Keywords:** complications, pancreas, quality improvement, surgery

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Resection combined with (neo)adjuvant chemotherapy provides the best chance of long term survival in patients with pancreatic ductal adenocarcinoma.[1–3] Pancreatoduodenectomy, however, remains associated with a 40%–60% risk of postoperative complications and subsequent 2%–5% risk of in-hospital mortality, even in high-volume centers.[4–6]

It is well recognized that individual complications may lead to a sequence of other complications and unfavorable outcomes (ie, mortality, organ failure, prolonged hospital stay, and readmission).[7,8] To improve quality of care and decrease costs after pancreatoduodenectomy, initiatives focus on the prevention, and optimal treatment

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of complications. To allocate healthcare and research resources most efficiently, initiatives should target those complications that have the greatest impact on reducing these unfavorable outcomes. Several studies have described the incidence of complications and outcomes after pancreatic resection.[9–11] However, simple data on the frequency are not sufficient to estimate the impact of a complication on the population undergoing pancreatoduodenectomy.

In this context, the population attributable fraction (PAF) is a useful measure as it represents the fraction of all patients with a specific unfavorable outcome (eg, mortality) that can be attributed to a specific exposure (eg, postoperative pancreatic fistula).[12–14] A specific strength of the PAF is that it incorporates both the frequency of an exposure and the likelihood that an outcome will occur in the presence of this exposure. Consequently, previous studies that utilized the PAF in surgery have identified several complications with a larger impact on a population level, than previously assumed.[15–19] This provided new insights and therewith facilitated more targeted quality improvement programs, which may be of considerable interest in the field of pancreatic surgery.

The aim of this study was to quantify the impact of individual complications (ie, postoperative pancreatic fistula, postpancreatectomy hemorrhage, bile leakage, delayed gastric emptying, wound infection, and pneumonia) on mortality, organ failure, hospital stay, and readmission after pancreatoduodenectomy in a national, prospective cohort.

## METHODS

All consecutive patients who underwent a pancreatoduodenectomy for a presumed pancreatic, periampullary or duodenal (pre)malignancy or pancreatitis from January 2014 to December 2017 in the Netherlands as registered in the Dutch Pancreatic Cancer Audit (DPCA) were analyzed. All patients were prospectively registered in the DPCA. Participation in the DPCA is mandatory for all pancreatic surgery centers in the Netherlands, each performing a minimum of 20 pancreatoduodenectomies annually.[20] Patients were excluded if they received preoperative chemo(radio)therapy, for this was only administered within (randomized) trials in The Netherlands (n = 136), or in case of essential missing data on postoperative complications (n = 28). The Medical Research Ethics Committee of the University Medical Center Utrecht reviewed the study and waived the need for informed consent. The study was conducted according to the declaration of Helsinki and according to STROBE guidelines[21].

### Data Extraction and Outcome Measures

Data extracted from the DPCA included patient and treatment-related characteristics (ie, age, sex, body mass index, weight loss, Eastern Cooperative Oncology Group performance score, American Society of Anesthesiologists classification, comorbidity to calculate the Charlson Comorbidity Index (ie, history of diabetes, liver disease, malignancy, infectious diseases, kidney disease, cardiovascular disease, pulmonary disease, neurologic disease, connective tissue disease, and gastrointestinal disease), surgical approach (open or minimally invasive), additional venous, arterial or visceral resection(s), diameter of the pancreatic duct, pancreatic texture and tumor histology). Furthermore, pancreatectomy specific complications (ie, postoperative pancreatic fistula, postpancreatectomy hemorrhage, bile leakage, chyle leakage, and delayed gastric emptying), general complications (ie, wound infection and pneumonia), and outcomes (ie, mortality, organ failure, length of hospital stay, and unplanned readmission rate) were extracted from the DPCA. Pancreatectomy specific complications were defined in accordance to International Study Group on Pancreatic Surgery (ISGPS)/Internatinal Study Group on Liver Surgery (ISGLS) definitions. Only clinically relevant grade B/C complications were included in the analysis.[22–26] Diagnosis of wound infection, pneumonia and organ failure was based on clinical features; no predefined diagnosis was adapted in the DPCA. Data were registered up to 30 days after pancreatic resection or – if length of admission exceeded 30 days – during entire hospital admission.

Unfavorable outcomes were in-hospital mortality, organ failure, prolonged hospital stay, and unplanned readmissions. Prolonged hospital stay was defined as a duration exceeding the 75th percentile in this cohort (ie, >18 days).

### Statistical Analysis

We evaluated the association between each complication (ie, postoperative pancreatic fistula, postpancreatectomy hemorrhage, bile leakage, delayed gastric emptying, wound infection, and pneumonia) and each study outcome (ie, in-hospital mortality, organ failure, prolonged hospital stay, and unplanned readmission rate).

The association of each complication–outcome pair was analyzed with adjustment for confounders. Potential confounding pathways between complications and study unfavorable outcomes were visualized in a Directed Acyclic Graph (dagitty.net/mIrLv6X; supplementary appendix Fig. S1, http://links.lww.com/SLA/C13).[27] The pathways were based on previously published studies and, whenever substantial evidence was lacking, on expert consensus.[23,24,26,28–32] The identified minimal sufficient set of confounders included: sex, age, body mass index, Eastern Cooperative Oncology Group performance score, American Society of Anesthesiologists classification, Charlson Comorbidity Index, surgical approach (open vs. minimally invasive), additional arterial, venous or visceral resection, tumor histology (malignant vs benign/premalignant) and hospital volume (<50 vs ≥50 pancreatic resections annually, based on the median annual volume in Dutch centers).

A complete set of baseline characteristics was created by multiple imputation using 10 iterations. All baseline and outcome variables were included as predictors for imputation.[33] The relation between each complication–outcome pair represented by the adjusted risk ratio (aRR) was evaluated using a modified Poisson regression analysis robust with standard error variance and adjustment for the minimal sufficient set of confounders as mentioned before and the presence of other complications.[34] The risk adjusted population attributed fraction (PAF) was calculated for each significantly associated complication-outcome pair. The PAF represents the proportion of an unfavorable outcome that would be prevented when the given complication could be eliminated entirely.[12–14,35] Two sensitivity analyses were performed. First, for hemorrhage could be caused by postoperative pancreatic fistula (ie, mediation instead of confounding), the effect of postoperative pancreatic fistula on in-hospital mortality was also evaluated without adjustment for post-pancreatectomy hemorrhage. Second, for textbook outcomes define prolonged hospital stay as longer than the 50th percentile (ie, >12 days), a sensitivity analysis was performed to evaluate the impact of complication this outcome.[36]

Because we did not have data on the onset date of complications, we assumed that all complications were present before the unfavorable outcome. Because grade B/C delayed gastric emptying by definition occurs 8–14 days after pancreatic resection, including patients who died within this time period might cause an underestimation of the effect due to immortal time bias. Therefore, patients who died on or before postoperative day 14 were excluded from all analyses on delayed gastric emptying.[37] Wound infection and pneumonia were only registered in 2016 and 2017 and; therefore, analysis of the impact of these complications was limited to those years in which these complications were registered. Chyle leakage was only registered in 2017, and was; therefore, not included in the analysis.[25]

Hospital stay and unplanned readmission were analyzed only in patients surviving the index hospitalization.

Statistical analysis was performed in IBM SPSS Statistics 25 and in R (version 3.5.1) using R-language ''Feather Spray'' (version 0.3.3) and the ''mice'' (version 3.3.0), ''sandwich'' (version 2.5–0) and ''AF'' (version 0.1.4) packages. Binary variables were presented as count with percentage. Normally distributed continuous data were presented as mean with standard deviation; variables with a skewed distribution were presented as median with interquartile range (IQR). A 2-sided *P*-value <0.05 was considered statistically significant.

## RESULTS

A total of 2620 patients undergoing pancreatoduodenectomy were eligible for analysis. Median age was 68 years (IQR 60–74) and 1474 patients (56.1%) were male. Pancreatoduodenectomy was performed for a presumed malignancy in 2017 patients (79.1%). Baseline characteristics are presented in Table 1.

Data on postoperative complications and study outcomes are presented in Table 2. Overall, 1672 patients experienced at least one complication (63.8%). Most common complications were delayed gastric emptying (488 patients, 18.6%) and postoperative pancreatic fistula (379 patients, 14.5%). In-hospital mortality occurred in 95 patients (3.6%) and organ failure in 198 patients (7.9%). Median time to death was 12 days (IQR 7–26 days); 50/95 patients died on or before postoperative day 14 and were excluded from all analyses concerning delayed gastric emptying. Median length of hospital stay was 12 days (IQR 8–18). A total of 427 patients (16.6%) were readmitted after initial discharge from the hospital.

aRR's for each complication-outcome pair are presented in (Tables 3–6). Postoperative pancreatic fistula [aRR 2.86 (95% CI 1.76–4.65)] and postpancreatectomy hemorrhage [aRR 6.09 (95% CI 3.80–9.76)] were associated with in-hospital mortality. All evaluated complications except bile leakage showed an association with organ failure, of which postpancreatectomy hemorrhage had the strongest association [aRR 3.14 (2.27–4.34)]. All complications were associated with prolonged hospital stay, however, the strongest association was with delayed gastric emptying [aRR 2.99 (95% CI 2.60–3.44)]. Postoperative pancreatic fistula, postpancreatectomy hemorrhage, bile leakage, and delayed gastric emptying were associated with unplanned readmission (Table 6).

The risk-adjusted PAF's for each complication-outcome pair are given in (Tables 3–6), and visualized in Fig. 1. Postoperative pancreatic fistula and postpancreatectomy hemorrhage had the greatest impact on in-hospital mortality. Complete elimination of these complications in the current cohort would result in an anticipated 25.7% (95% CI 13.4–37.9) and 32.8% (95% CI 21.9–43.8) decrease in in-hospital mortality, respectively. Additionally, postoperative pancreatic fistula and postpancreatectomy hemorrhage had the highest impact on organ failure [PAF 21.8% (95% CI 12.9–30.6), PAF 22.1% (95% CI 15.0–29.1), respectively]. Wound infection and pneumonia also affected organ failure considerably [PAF 18.0% (95% CI 8.2–27.8), PAF 18.9% (95% CI 9.4–28.4), respectively]. Delayed gastric emptying had the highest impact on prolonged hospital stay [PAF 27.6% (95% CI 23.5–31.8)]. All PAF's for readmission rate were relatively small, with postoperative pancreatic fistula having the greatest impact [PAF 10.6 (95% CI 6.0–15.1)]. The impact of all other complications on the unfavorable outcomes was relatively small.

In addition, a sensitivity analysis was performed to evaluate the role of postoperative pancreatic fistula as a mediator to postpancreatectomy hemorrhage. Overall, 86/214 patients with postpancreatectomy hemorrhage also suffered from postoperative pancreatic fistula (40.2%) showing an aRR of 3.94 (95% CI 2.52–6.17) of postoperative pancreatic fistula on mortality without adjustment for postpancreatectomy hemorrhage; the PAF was 29.9% (95% CI 18.4–41.4). The sensitivity analysis on length of hospital stay exceeding the 50th percentile (ie, >12 days) were similar to the outcomes presented in the manuscript (ie, >18 days) and presented in the Supplementary Appendix, http://links.lww.com/SLA/C13.

**TABLE 1.** Baseline Characteristics

| | Pancreatoduodenectomy n = 2620 | Missing Values |
|---|---|---|
| Age (yr)† | 68 (60–74) | 0 (0.0) |
| Sex ratio (M:F) | 1474 (56.1): 1146 (43.9) | 0 (0.0) |
| BMI (kg/m$^2$)† | 25 (22–27) | 120 (4.6) |
| Weight loss‡ | 1150 (52.9) | 448 (17.1) |
| ECOG performance status | | 223 (8.6) |
| 0 | 1160 (48.3) | |
| 1 | 989 (41.2) | |
| ≥2 | 248 (10.3) | |
| ASA classification | | 0 (0.0) |
| I | 369 (14.1) | |
| II | 1647 (62.8) | |
| III | 596 (22.7) | |
| IV | 8 (0.0) | |
| Charlson comorbidity index | | 31 (1.2) |
| 0–1 | 453 (17.4) | |
| 2–3 | 1330 (51.4) | |
| 4–5 | 672 (26.0) | |
| ≥6 | 134 (5.2) | |
| Surgical approach | | 49 (1.9) |
| Open procedure | 2204 (85.7) | |
| Minimally invasive | 367 (14.3) | |
| Additional resections | | |
| Arterial | 38 (1.5) | 23 (0.8) |
| Venous§ | 136 (5.2) | 25 (1.0) |
| Visceral | 220 (8.9) | 139 (5.3) |
| Diameter pancreatic duct† | 4 (2–7) | 1114 (42.5) |
| Soft texture pancreas | 1476 (61.6) | 255 (8.6) |
| Tumor histology | | 69 (2.6) |
| Pancreatic ductal adenocarcinoma | 1082 (42.4) | |
| Distal cholangiocarcinoma | 380 (14.9) | |
| Ampullary carcinoma | 338 (13.2) | |
| Duodenal carcinoma | 187 (7.3) | |
| IPMN | 184 (7.2) | |
| Neuroendocrine neoplasm | 127 (5.0) | |
| Chronic pancreatitis | 80 (3.1) | |
| Other | 173 (6.8) | |
| Operated in high volume center* | 1457 (55.6) | 0 (0.0) |

Values in parenthesis are percentages unless indicated otherwise.
*Performing >50 pancreatic resections annually.
†Median with interquartile range.
‡>5% of original weight.
§Wedge or segment of portal vein or superior mesenteric vein.
ASA indicates American Society of Anesthesiologists; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; F, female; IPMN, intraductal papillary mucinous neoplasm; kg, kilogram; m$^2$, square meter; M, male.

## DISCUSSION

This study identified the complications after pancreatoduodenectomy with the greatest attributable risk to unfavorable outcomes (ie, mortality, organ failure, hospital stay, and readmission). Postoperative pancreatic fistula and postpancreatectomy hemorrhage attributed considerable to all unfavorable outcomes and accounted for 25.7% and 32.8% of the total in-hospital mortality, respectively. Delayed gastric emptying had the greatest impact on prolonged

**TABLE 2.** Postoperative Complications

| | Pancreatoduodenectomy n = 2620 | Missing Values |
|---|---|---|
| Postoperative complications | | |
| Postoperative pancreatic fistula[§] | | 0 (0.0) |
| Grade B | 278 (10.6) | |
| Grade C | 101 (3.8) | |
| Postpancreatectomy hemorrhage | | 0 (0.0) |
| Grade B | 99 (3.8) | |
| Grade C | 115 (4.4) | |
| Postoperative bile leakage | | 0 (0.0) |
| Grade B | 99 (3.7) | |
| Grade C | 38 (1.5) | |
| Delayed gastric emptying | | 0 (0.0) |
| Grade B | 269 (10.2) | |
| Grade C | 219 (8.3) | |
| Postoperative chyle leakage[‡] | | 1933 (73.8) |
| Grade B | 54 (7.9) | |
| Grade C | 2 (0.0) | |
| Wound infection[‡] | 127 (10.2) | 1375 (52.4) |
| Pneumonia[‡] | 93 (7.5) | 1379 (52.6) |
| Study outcomes | | |
| Mortality | 95 (3.6) | 0 |
| Organ failure | | 109 (4.2) |
| Single organ failure | 110 (4.4) | |
| Multi organ failure | 88 (3.5) | |
| Hospital stay[†] | 12 (8–18) | 37 (1.4) |
| Prolonged hospital stay[*] | 621 (24.0) | 37 (1.4) |
| Unplanned readmission | 427 (16.6) | 41 (1.6) |

Values in parenthesis are percentages unless indicated otherwise.
[*]Extending stay of 75% of patients in this cohort (ie, >18 d).
†Calculated over survivors; median with interquartile range.
‡Only registered for year 2017 (Chyle leakage) and years 2016 and 2017 (wound infection and pneumonia).
[§]2005 definition.

hospital stay. The impact of evaluated complications on readmission was relatively small (maximum risk adjusted attribution of 10.6%).

Although the reported incidence of postpancreatectomy hemorrhage is relatively low (ca. 8%), it had the highest impact on in-hospital mortality and organ failure in this study.[38–40] Postoperative pancreatic fistula had the second largest impact on mortality and organ failure. Postoperative pancreatic fistula may lead to bleeding, and thereby to unfavorable outcomes such as organ failure, and death.[39,41–43] If bleeding is a mediator rather than a confounder in the association between postoperative pancreatic fistula and unfavorable outcomes, it is incorrect to adjust for the impact of postpancreatectomy hemorrhage whereas evaluating the impact of postoperative pancreatic fistula on unfavorable outcomes. Therefore, an additional sensitivity analysis was performed to evaluate the impact of postoperative pancreatic fistula on in-hospital mortality without adjusting for postpancreatectomy hemorrhage, demonstrating a slightly increased impact of fistula on mortality; from 25.7% to 29.9%.

Complications in general are associated with prolonged hospital stay after surgery.[44] In this study, a strong association between delayed gastric emptying and prolonged hospital stay was identified (estimated PAF 27.6%). A plausible explanation is that adequate oral intake is generally accepted as a criterion before hospital discharge. Recent analyses showed that unplanned readmissions were mainly related to infectious complications, dehydration, and malnutrition.[45,46] Unfortunately, factors associated with the latter two were not registered in the DPCA. This might explain why in the current analysis 75% of the readmissions could not be attributed to a specific complication.

An advantage of calculating the PAF compared to other measures of impact is that it enables determination of the burden of complications on a population level. As a result, our analysis may be used to guide quality improvement initiatives to specifically target those complications that have the greatest clinical and/or economic impact.[7,18] PAF calculations were recently conducted in other surgical fields.[15–19] Goense et al evaluated the impact of complications after esophagectomy and found pulmonary complications and anastomotic leakage to have the greatest overall impact on in-hospital mortality, prolonged hospital stay, reoperations and unplanned readmissions.[19] Scarborough et al concluded that anastomotic leakage has a large impact on in-hospital mortality and resource use after colonic resection, which was concerning because current quality improvement programs focus on other complications showing estimated PAF's of less than 10%.[18] The impact of complications after pancreatic resection on the entire population undergoing pancreatoduodenectomy has, to the best of our knowledge, not yet been evaluated.

Strengths of this study include the population-based, nationwide design; the prospective mandatory data collection and large sample size.[20] Calculation of risk-adjusted PAF's provides a simple but comprehensive overview of the overall impact of a complication on outcomes on a population level. Analysis was not only adjusted for patient and treatment related confounders, but also for all other complications, as some patients developed more than one complication. There were also several limitations. It was assumed that the unfavorable outcomes were at least partially caused by the complications, although the likelihood of developing complications can be influenced by the study unfavorable outcomes. For example, the risk of pneumonia might increase when length of hospital stay is prolonged, causing an overestimation of the effect due to reversed

**TABLE 3.** Adjusted Attributions of Complications to In-hospital Mortality

| Postoperative Complication | Proportion Who Died[*] | Adjusted Relative Risk[†] | *P* | Adjusted PAF (%) | *P* |
|---|---|---|---|---|---|
| Postoperative pancreatic fistula | 38 of 379 (10.0) | 2.86 (1.76–4.65) | <0.001 | 25.7 (13.4–37.9) | <0.001 |
| Postpancreatectomy hemorrhage | 38 of 214 (17.7) | 6.09 (3.80–9.76) | <0.001 | 32.8 (21.9–43.8) | <0.001 |
| Bile leakage | 10 of 137 (7.3) | 1.40 (0.74–2.61) | 0.30 | — | — |
| Delayed gastric emptying[‡] | — | — | — | — | — |
| Wound infection[§] | 2 of 127 (1.6) | 0.28 (0.06–1.22) | 0.09 | — | — |
| Pneumonia[§] | 4 of 93 (4.3) | 1.60 (0.58–4.45) | 0.81 | — | — |

Values in parenthesis are
[*]Percentages and
†95% confidence intervals.
‡Not calculated, for 50/95 patients were excluded in this analysis.
§Calculated over years 2016–2017.
PAF indicates population attributable fraction.

**TABLE 4.** Adjusted Attributions of Complications to Organ Failure

| Postoperative Complication | Proportion With Organ Failure* | Adjusted Relative Risk† | *P* | Adjusted PAF (%) | *P* |
|---|---|---|---|---|---|
| Postoperative pancreatic fistula | 84 of 362 (23.2) | 2.29 (1.72–3.32) | <0.001 | 21.8 (12.9–30.6) | <0.001 |
| Postpancreatectomy hemorrhage | 67 of 210 (31.9) | 3.14 (2.27–4.34) | <0.001 | 22.1 (15.0–29.1) | <0.001 |
| Bile leakage | 27 of 129 (20.9) | 1.47 (0.99–2.19) | 0.06 | — | — |
| Delayed gastric emptying‡ | 66 of 449 (14.7) | 1.46 (1.01–2.10) | 0.04 | 11.4 (0.6–22.2) | 0.04 |
| Wound infection§ | 23 of 125 (18.4) | 2.46 (1.59–3.82) | <0.001 | 18.0 (8.2–27.8) | <0.001 |
| Pneumonia§ | 25 of 90 (27.7) | 2.79 (1.69–4.59) | <0.001 | 18.9 (9.4–28.4) | 0.002 |

Values in parenthesis are.
*Percentages and.
†95% confidence intervals.
‡Calculated over 2570 patients surviving to postoperative day 14 with overall mortality of 45 (1,7%).
§Calculated over years 2016–2017.
PAF indicates population attributable fraction.

**TABLE 5.** Adjusted Attributions of Complications to Prolonged Hospital Stay‡

| Postoperative Complication | Proportion With Prolonged Stay* | Adjusted Relative Risk† | *P* | Adjusted PAF (%)† | *P* |
|---|---|---|---|---|---|
| Postoperative pancreatic fistula | 232 of 334 (69.4) | 2.09 (1.81–2.41) | <0.001 | 15.5 (12.3–18.7) | <0.001 |
| Postpancreatectomy hemorrhage | 110 of 169 (65.1) | 1.33 (1.11–1.60) | 0.002 | 4.9 (2.8–7.0) | <0.001 |
| Bile leakage | 100 of 124 (80.6) | 2.09 (1.73–2.52) | <0.001 | 7.1 (5.1–9.1) | <0.001 |
| Delayed gastric emptying | 322 of 461 (69.8) | 2.99 (2.60–3.44) | <0.001 | 27.6 (23.5–31.8) | <0.001 |
| Wound infection§ | 52 of 121 (43.0) | 1.27 (1.01–1.58) | 0.04 | 3.3 (0.0–6.4) | 0.04 |
| Pneumonia§ | 51 of 85 (60.0) | 1.51 (1.20–1.89) | <0.001 | 5.1 (2.2–8.0) | <0.001 |

Values in parenthesis are.
*Percentages and.
†95% confidence intervals.
‡Calculated over survivors; prolonged stay >18 d.
§Calculated over years 2016–2017.
PAF indicates population attributable fraction.

causality. Another example is probably the association between wound infection and organ failure. Unfortunately, the DPCA does not include data on sequence of complications and unfavorable outcomes. Conversely, an underestimation of the impact can be caused by immortal time bias, for example, induced by early mortality.[37] To minimize this effect, patients who died within 14 days after pancreatoduodenectomy were excluded from the delayed gastric emptying analysis. However, as a result, the PAF estimates for delayed gastric emptying are only applicable for patients surviving the first 14 days after resection. Another limitation was that no uniform definitions for organ failure, pneumonia and wound infection were adopted in the DPCA. Consequently, reporting bias might be introduced. For example, pneumonia is more likely to be reported when it leads to organ failure or even death, which might lead to an overestimated impact. Additionally, we assumed that our directed acyclic graph included all potential confounding pathways. Nevertheless, the risk of unregistered or unknown confounders remains. Also, patients who underwent neoadjuvant (radio)chemotherapy were excluded from our analysis, because this is currently not considered standard practice in The Netherlands and was only administered in (randomized) trials. This potentially leads to participation and performance bias, resulting in better outcomes of these patients as compared to a nationwide cohort. We believe this limits the generalizability to centers where neoadjuvant treatment is standard of care. To create a homogeneous patient group, these patients were excluded from this analysis. Lastly, results of this study might not be generalizable to all hospitals individually or outside the Netherlands, as local postoperative monitoring and complication

**TABLE 6.** Adjusted Attributions of Complications to Unplanned Readmission‡

| Postoperative Complication | Proportion Readmitted* | Adjusted Relative Risk† | *P* | Adjusted PAF (%)† | *P* |
|---|---|---|---|---|---|
| Postoperative pancreatic fistula | 107 of 328 (32.6) | 1.78 (1.42–2.24) | <0.001 | 10.6 (6.0–15.1) | <0.001 |
| Postpancreatectomy hemorrhage | 55 of 173 (31.7) | 1.64 (1.12–1.91) | 0.005 | 4.0 (0.9–7.1) | 0.01 |
| Bile leakage | 40 of 126 (31.7) | 1.54 (1.14–2.09) | 0.005 | 3.3 (0.7–5.9) | 0.01 |
| Delayed gastric emptying | 121 of 456 (26.5) | 1.35 (1.09–1.67) | 0.005 | 7.1 (1.9–12.1) | 0.007 |
| Wound infection§ | 25 of 124 (20.2) | 0.94 (0.64–1.38) | 0.72 | — | — |
| Pneumonia§ | 18 of 86 (20.9) | 0.83 (0.53–1.31) | 0.42 | — | — |

Values in parenthesis are.
*percentages and.
†95% confidence intervals.
‡Calculated over survivors.
§Calculated over years 2016–2017.
PAF indicates population attributable fraction.

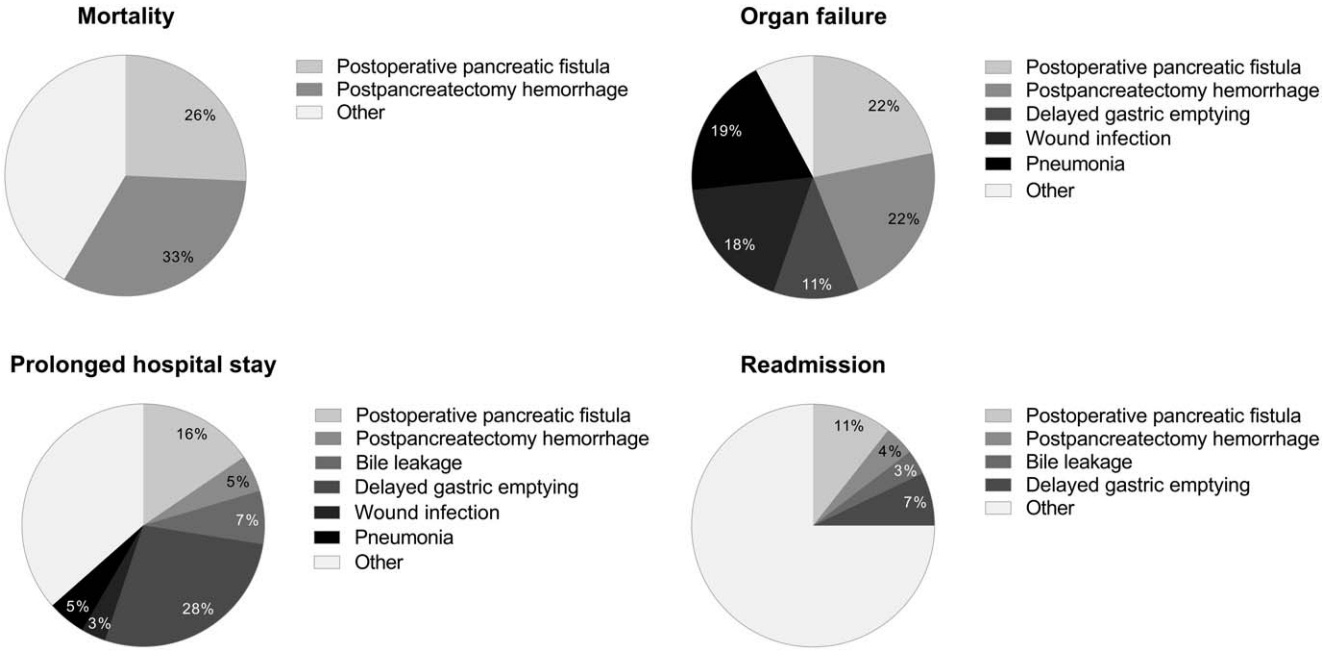


**FIGURE 1.** Risk-adjusted population attributed fractions for each complication-outcome pair showing a significant association.

management might lead to different outcomes. To address this potential source of bias, we have adjusted the analyses by hospital volume for pancreatic resections.

Postoperative pancreatic fistula and associated postpancreatectomy hemorrhage had the greatest attribution to in-hospital mortality in this study. In addition, a recent analysis showed these complications were strongly associated with both the risk of not receiving adjuvant chemotherapy and time to commence adjuvant chemotherapy, which are likely to influence survival.[47] Despite many initiatives to prevent postoperative pancreatic fistula, the incidence of this potentially fatal complication remains as high as 15%.[48–50] We hypothesize that early recognition and adequate drainage of postoperative pancreatic fistula might mitigate the risk of subsequent postpancreatectomy hemorrhage, organ failure, and mortality.[51] To investigate this hypothesis, we are currently conducting the nationwide PORSCH trial (NCT03400280), a quality improvement program to evaluate the implementation of a standardized best practice algorithm for postoperative care in the 17 centers of the Dutch Pancreatic Cancer Group (ie, all centers performing pancreatic surgery in The Netherlands).

In conclusion, quality improvement programs to reduce mortality after pancreatoduodenectomy should primarily focus on prevention and adequate management of postoperative pancreatic fistula and postpancreatectomy hemorrhage. To reduce hospital stay, the focus should be on delayed gastric emptying.

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