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VARIATION IN HOSPITAL MORTALITY AFTER PANCREATODUODENECTOMY IS RELATED TO FAILURE TO RESCUE RATHER THAN MAJOR COMPLICATIONS: A NATIONWIDE AUDIT

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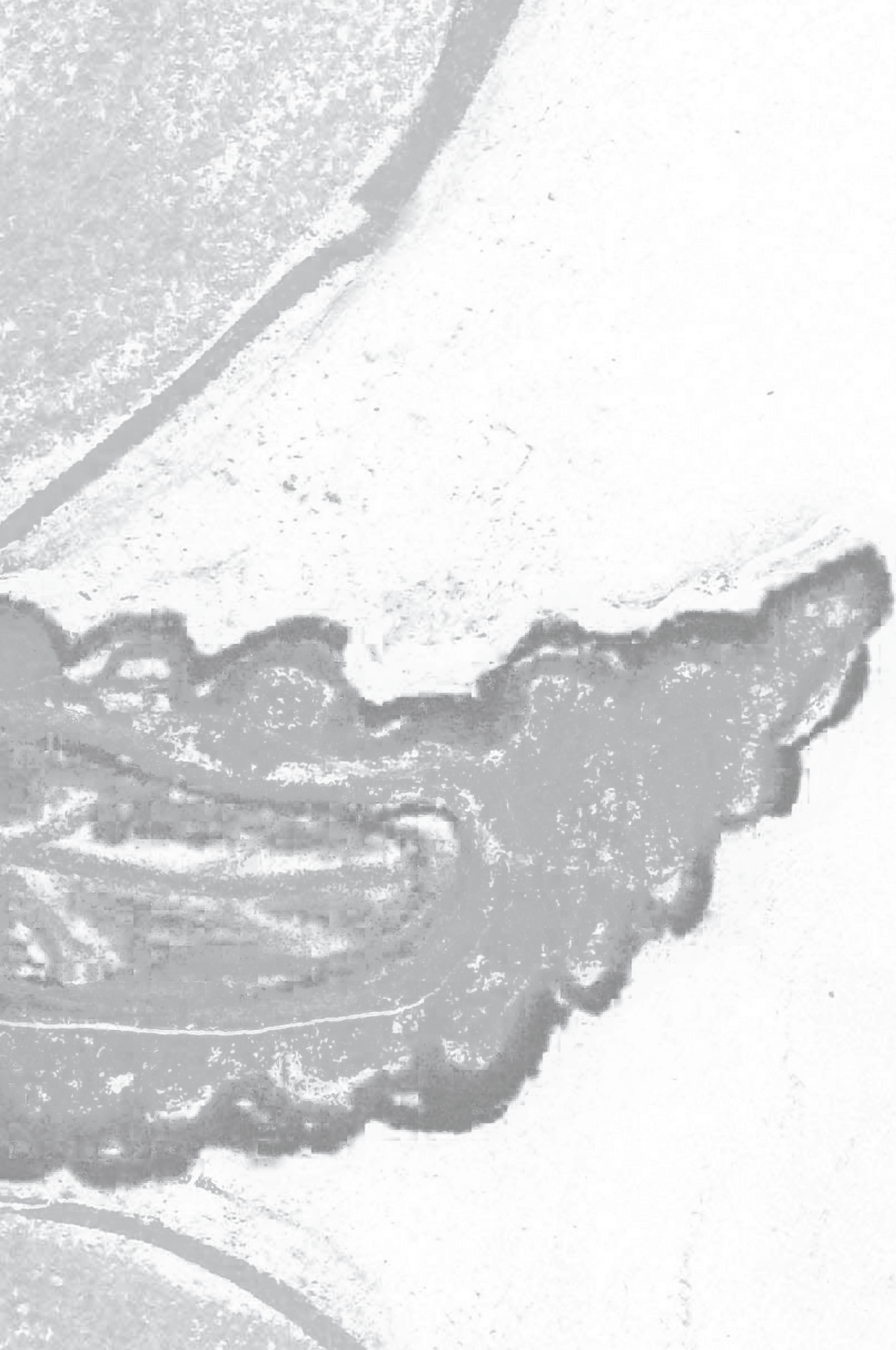


ABSTRACT

Background: In the mandatory nationwide Dutch Pancreatic Cancer Audit, rates of major complications and Failure to Rescue (FTR) after pancreatoduodenectomy between low- and high-mortality hospitals are compared, and independent predictors for FTR investigated.

Methods: Patients undergoing pancreatoduodenectomy in 2014 and 2015 in The Netherlands were included. Hospitals were divided into quartiles based on mortality rates. The rate of major complications (Clavien-Dindo ≥3) and death after a major complication (FTR) were compared between these quartiles. Independent predictors for FTR were identified by multivariable logistic regression analysis.

Results: Out of 1.342 patients, 391 (29%) developed a major complication and in-hospital mortality was 4.2%. FTR occurred in 56 (14.3%) patients. Mortality was 0.9% in the first hospital quartile (4 hospitals, 327 patients) and 8.1% in the fourth quartile (5 hospitals, 310 patients). The rate of major complications increased by 40% (25.7% vs 35.2%) between the first and fourth hospital quartile, whereas the FTR rate increased by 560% (3.6% vs 22.9%). Independent predictors of FTR were male sex (OR = 2.1, 95%CI 1.2–3.9), age >75 years (OR = 4.3, 1.8–10.2), BMI ≥30 (OR = 2.9, 1.3–6.6), histopathological diagnosis of periampullary cancer (OR = 2.0, 1.1–3.7), and hospital volume <30 (OR = 3.9, 1.6–9.6).

Conclusions: Variations in mortality between hospitals after pancreatoduodenectomy were explained mainly by differences in FTR, rather than the incidence of major complications.

INTRODUCTION

The strong demand for transparency in health care outcomes is leading to increasing comparison of hospital performances. The strongest and most acknowledged performance indicator is undoubtedly postoperative mortality. Higher mortality rates have traditionally been thought to be the consequence of higher complication rates. Recent studies, however, suggested that not the occurrence of a complication but its treatment drives differences in mortality. Failure to rescue (FTR), first described by Silber et al., is defined as the death of a patient due to a major postoperative complication.[1,2] FTR has shown to be more responsible for differences in mortality rates between hospitals following various surgical procedures, compared to differences in complication rates.[3–8]

FTR is an indicator of the management of complications and may distinguish a high-mortality from a low-mortality hospital. The association of various factors with the occurrence of FTR has therefore been investigated and includes mainly hospital structural factors such as patient volume, staffing levels, and technology status.[7,9–11] FTR is especially a relevant topic in pancreatic surgery, as pancreatic surgery remains associated with high complication rates of around 50% and major complication rates up to 30%.[12,13] Nationwide analyses of FTR in pancreatic surgery are however lacking.

In 2013, the Dutch Pancreatic Cancer Audit (DPCA) was launched. Registration of patients undergoing pancreatic surgery in the DPCA is mandatory for the Dutch pancreatic centers, each of who performs at least 20 pancreatoduodenectomies (PDs) annually. Our objective was to compare major complication and FTR rates between hospitals with high and low mortality after PD. The second objective was to develop a prognostic model to predict FTR.

METHODS

Patients and methods

Under Dutch law, no Institutional Review Board (IRB) approval or informed consent was required for this study. All patients undergoing PD for a (suspected) pancreatic- or periampullary neoplasm between January 1st 2014, and December 31st 2015, who were registered in the DPCAwere included. All 18 pancreatic centers in the Netherlands participate in the audit, each performing a minimum of 20 PDs annually. The DPCA has demonstrated over 90% case ascertainment and over 95% data accuracy.[14]

Scatterplots with regressions analyses were used to investigate the correlation between mortality, major complications, and FTR. Additionally, hospitals were grouped into quartiles of hospitals based on mortality rates. The rates of major complications and FTR were compared between these groups. The incidence of specific complications in patients with FTR was also assessed between the quartiles. Regression analysis was used to explore the association of FTR with patient and tumor characteristics, and hospital volume.

Data collection

Within the DPCA a wide range of anonymized clinicopathological variables, and outcomes are prospectively collected. Length of follow-up is 30 days after primary hospital discharge. Data are collected prospectively by health care professionals per center independently. Retrieved baseline characteristics were age, sex, body mass index (kg/m2), Eastern Cooperative Oncology Group (ECOG) performance status, presence of diabetes (insulin and non-insulin dependent), and neoadjuvant therapy. Collected outcomes were tumor size (centimeters), pathologic TNM stage, histopathologic diagnosis, resection margin, overall complications, major complications (Clavien–Dindo score ≥ III), postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE), postpancreatectomy hemorrhage (PPH), bile leakage (BL), and mortality.[15–19]

Predictive factors for failure to rescue

Logistic regression analysis was used to identify independent factors associated with FTR. Potential predictive factors included were sex, age, BMI, ECOG performance status, hospital volume, histopathological diagnosis, and hospital type (university or nonuniversity), and were based on previously identified risk factors for complications and mortality.[20] Hospital volume was categorized as <30, 30–39 and ≥40 PDs per year.[21] Additionally, a nomogram was created to predict the risk of FTR based on independent risk factors.

Definitions

Mortality was defined as in-hospital mortality. Overall complications consisted of all surgical and non-surgical complications. Major complication was defined as any Clavien–Dindo grade ≥III complication.[15] Procedure specific complications were graded according to the International Study Group on Pancreatic Surgery (ISGPS) definitions for POPF, DGE, and PPH and the International Study Group on Liver Surgery (ISGLS) for BL, respectively.[16–18] Clinically relevant (CR) complications were defined as grade B or grade C procedure specific complications. Failure to rescue was defined as in-hospital mortality in a patient with a major complication.

Statistical analysis

Data were analyzed using IBM SPSS statistics version 21 (IBM, Armonk, New York, USA). Distribution of the data was checked with histograms and box plots. Normally distributed continuous data were presented as mean with standard deviation and non-normally distributed continuous data were presented as median with interquartile range as appropriate. Categorical data were presented as frequency with percentage. Chi-square test was used to compare means. Sensitivity analysis was performed by excluding all patients with DGE as the only major complication. Spearman's correlation (r) was used to determine correlation between mortality and major complications, and between mortality and FTR. Predictors of FTR were assessed in a standard multivariable logistic regression. Characteristics with a p-value <0.20 in a univariable analysis were entered into the multivariable model. Outcomes of the multivariable analysis were reported as odds ratio (OR) with the corresponding 95% confidence interval (CI). Two-sided p-values <0.05 were considered statistically significant. Age and BMI were categorized into three groups for the nomogram (<65, 65–74, or ≥75 years and ≤24.9, 25.0–29.9, or ≥30.0 kg/m2, respectively). The risk score for each patient was calculated using odds ratios. Total risk scores were divided into categories and assessed for FTR incidence. The categories were increased in size to generate fewer categories, until four risk categories remained. While decreasing the number of risk categories, it was noted that FTR was equally distributed among the risk categories. Model performance was assessed by measuring discrimination (ability to discriminate between participants with or without an event) and calibration (ability to quantify the observed absolute risk). The discriminative ability of the model was examined by calculating the area under the curve for the receiver operating characteristic (ROC) with 95%CI. Calibration of the model was determined by calculating the Hosmer–Lemeshow χ^2 statistic. An internal bootstrap was performed using 300 bootstrap samples in R (Version 3.3.1; R Foundation for Statistical Computing).

RESULTS

Patients and outcomes

In total, 1342 patients undergoing PD were included. Over half of patients were male (57%) with a mean age of 66 (SD 11) years. In-hospital mortality was 4.2%. Histopathological diagnosis was pancreatic ductal adenocarcinoma in 560 (42%) patients, and periampullary (distal bile duct, duodenum, ampulla) carcinoma in 432 (32%) patients (Table 1).

A total of 889 (66.2%) patients experienced a complication whereas 391 (29.1%) patients experienced a major complication. A total of 56 patients died after a major complication, corresponding to a FTR rate of 14.3% (56/391). In total, 182 (13.6%) patients had a grade B/C POPF, 127 (9.5%) a grade B/C PPH, and 239 (17.8%) patients a grade B/C DGE.

Table 1. Baseline characteristics

	Patients (n= 1342)
Female sex	578 (43)
Age [years; mean (SD)]	66 (11)
<65	514 (38)
65-74	526 (39)
≥75	302 (23)
BMI [kg/m2; mean (SD)]	25 (5)
≤24.9	706 (53)
25.0 - 29.9	427 (32)
≥30.0	152 (11)
ECOG performance score[a]	
1	608 (49)
≥2	621 (51)
Diabetes	301 (22)
Neo-adjuvant therapy	49 (4)
Hospital volume	
<30	258 (19)
30-39	422 (31)
≥40	662 (49)
Hospital type	700 (52)
Academic	642 (48)
Non-academic	
Tumor size [cm; mean (SD)]	2.9 (2)
Pathologic T stage (in case of pancreatic-, ampullary- or distal cholangiocarcinoma, n=990)*,[b]	
1	94 (10)
2	145 (15)
3	646 (68)
4	60 (6)
Pathologic N1 stage	721 (54)
Pathologic M1 stage	28 (2)
Histopathological diagnosis	
Pancreatic carcinoma	560 (42)
Periampullary carcinoma[d]	432 (32)
Other[e]	350 (26)
Resection margin[c]	
R0	909 (74)
R1 (<1 mm to closest margin)	321 (26)

Data are expressed as n (%) unless otherwise specified.
* T stage is only registered in case of pancreatic, ampullary or distal bile duct tumor.
[a] Unknown in 113 (8%) patients.
[b] Unknown in 45 (3%) patients.
[c] Unknown in 112 (8%) patients
[e] Other diagnosis includes intraductal papillary mucinous neoplasm (6%), pancreatic neuroendocrine tumor (5%), pancreatic or papillary adenoma (2%), pancreatitis (2%), serous cystadenoma (1%), solid pseudopapillary neoplasm (1%), and a remaining group of 135 (10%) patients in who diagnosis was missing. SD, standard deviation. BMI, body mass index. WHO, World Health Organization. Cm, centimeters. Mm, millimeters.

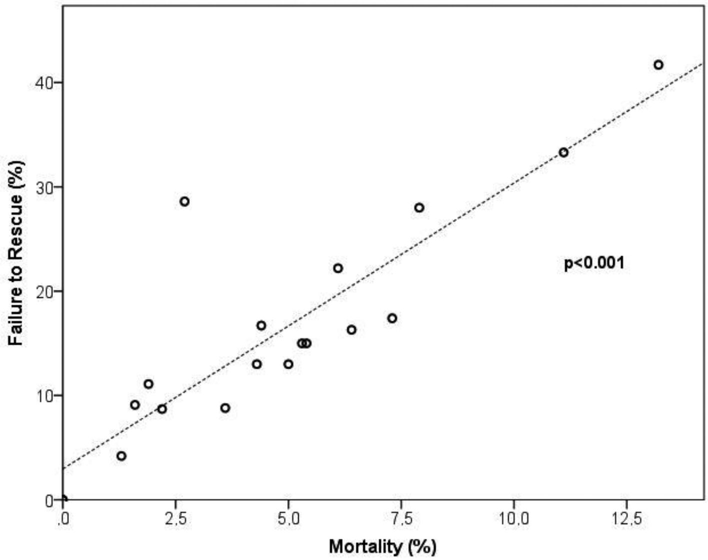
Variation between hospitals

Between hospitals, the mortality rate varied from 0% to 13.2%. Whereas a strong correlation between mortality and FTR was found ($r = 0.84$, $p < 0.001$, Fig. 1a), the correlation between mortality and major complications was weaker ($r = 0.47$, $p < 0.001$, Fig. 1b).

Fig. 2 demonstrates the variation in mortality, major complication rate, and FTR between the hospital quartiles based on mortality. In the first quartile (with the lowest mortality), the average mortality rate was 0.9%, whereas this was 8.1% in the fourth quartile. The rate of major complications increased by 40% between the first and the fourth quartile (25.7%–35.2%), whereas the FTR increased by 560% between the first and fourth quartile (3.6%–22.9%) (see Fig. 3).

There were no significant differences between the quartiles in the incidence of CR-POPF, CR-PPH, CR-DGE or CR-BL in patients who died with a major complication. The incidence of patients who died with a major complication and CR-POPF was 0% (0 out of 3) in the first hospital quartile (with the lowest mortality), 18.2% (2 out of 11) in the second quartile, 41.2% (7 out of 17) in the third quartile, and 56.0% (14 out of 25) in the fourth quartile ($p = 0.08$). The incidence of patients dying with a major complication and CR-PPH was 0% (0 out of 3) in the first quartile, 36.4% (4 out of 11) in the second quartile, 35.3% (6 out of 17) in the third quartile, and 48.0% (12 out of 25) in the fourth quartile ($p = 0.41$). The incidence of patients dying with a major complication and CR-BL was 0% (0 out of 3), 9.1% (1 out of 11), 5.9% (1 out of 17) and 16.7% (4 out of 24) in the first, second, third and fourth quartiles, respectively.

In a sensitivity analysis, excluding all 71 patients with DGE as the only major complication (Clavien–Dindo ≥ III) outcomes did not change. The rate of major complications increased by 50% between the first and the fourth quartile (21.9%–32.6%, $p = 0.003$). FTR increased by 490% between the first and fourth quartile (4.4%–25.8%, $p < 0.001$).



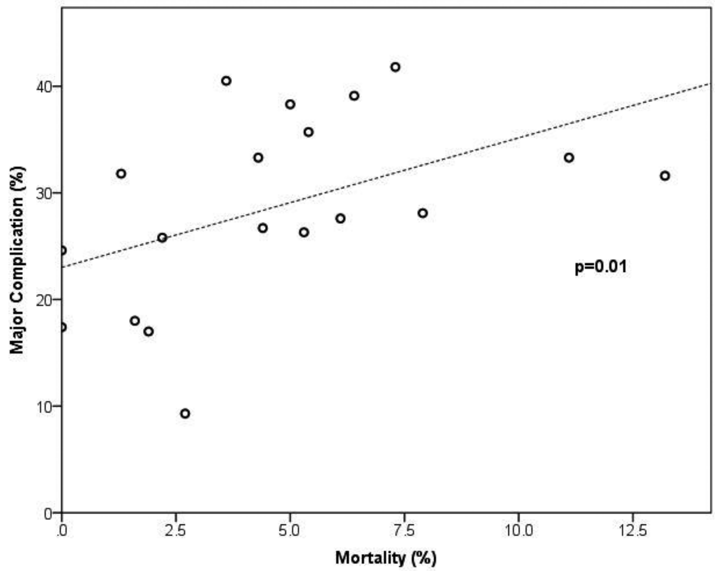


Figure 1 Scatterplots of hospital mortality and failure to rescue (a) or major complication rate (b). P-values indicate Spearman correlation

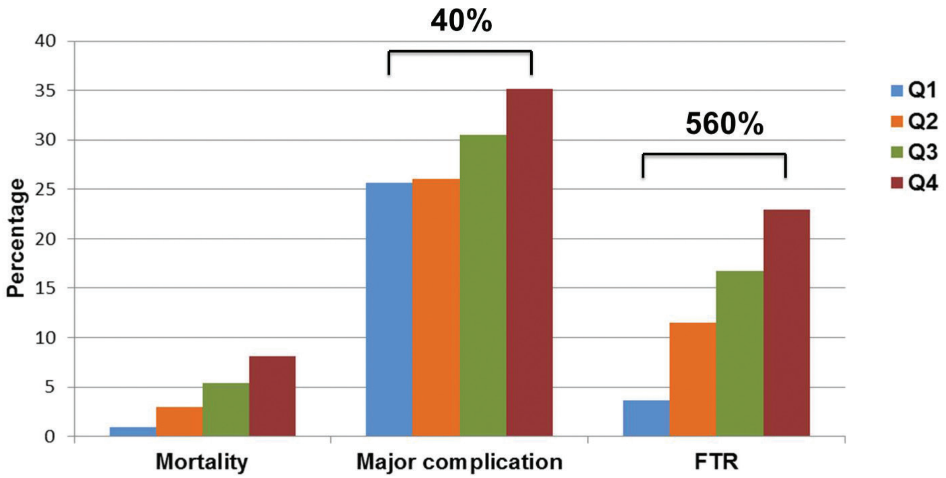


Figure 2 Variation in mortality, major complication rate, and failure to rescue rate after pancreatoduodenectomy between hospital quartiles based on mortality Q1; lowest mortality rate. Q4; highest mortality rate. FTR, failure to rescue; Q, quartile

Risk factors for failure to rescue

Male sex, advanced age, high BMI, ECOG performance status above 1, annual hospital volume below 30 PDs, and a diagnosis of periampullary cancer were associated with a significantly increased odds ratio of FTR in a univariable analysis. Hospital type (academic or non-academic) was not associated with FTR rate on univariable analysis (Table 2). On multivariable analysis, male sex (OR 2.1, 95%CI 1.1–4.0), age (OR 1.1, 95%CI 1.0–1.1), BMI (OR 1.1, 95%CI 1.0–1.1), hospital volume below 30 PDs annually (OR 3.89, 95%CI 1.58–9.61), and a diagnosis of periampullary cancer (OR 2.0, 95%CI 1.1–3.7) were independently associated with FTR.

All independent prognostic factors were included in the nomogram (Fig. 3). Outcomes of multivariable analysis with categorized values of age and BMI are available in the Supplementary Table. Based on the total number of points accrued over all 5 factors, patients are divided into three risk groups: very low risk, low risk, and high risk. Incidence of FTR in these groups was 2%, 4%, and 12%, respectively. Area under the ROC for the risk scores was 0.73 (95%CI 0.66–0.81) indicating good discriminative ability. The Hosmer–Lemeshow χ^2 statistic gave a p-value >0.99 indicating good calibration ability. After internal validation, area under the ROC was 0.72 indicating good internal validity.

Table 2 Multivariable analysis of predictors of mortality after a major complication (i.e. Failure to Rescue) in pancreatoduodenectomy

	N	Univariable			Multivariable		
Characteristics		**OR**	**95%CI**	**P-value**	**OR**	**95%CI**	**P-value**
Male Sex	764	2.13	1.17-3.89	0.01	2.10	1.10-3.98	0.02
Age (cont.)	1,342	1.06	1.03-1.10	<0.001	1.06	1.03-1.11	0.001
BMI (kg/m2, cont.)	1,342	1.06	1.02-1.10	0.01	1.06	1.01-1.11	0.02
ECOG >1	621	2.09	1.02-4.26	0.04	1.56	0.72-3.46	0.26
Hospital volume							
≥40	662	Ref			-		
30-39	422	1.15	0.64-2.04	0.64	1.70	0.84-3.51	0.14
<30	258	3.89	1.58-9.61	0.003	2.47	1.12-5.10	0.04
Diagnosis							
Pancreatic cancer	560	Ref			-		
Periampullary cancer[a]	432	2.01	1.09-3.70	0.03	2.29	1.18-4.49	0.02
Other	350	0.98	0.46-2.10	0.95	1.31	0.57-2.99	0.53
Non-academic hospital	642	1.27	0.74-2.17	0.38			

OR, odds ratio. BMI, body mass index. ECOG, Eastern Cooperative Oncology Group.
[a] Cancer of duodenum, distal bile duct, or ampulla.

DISCUSSION

This nationwide study shows striking differences in major complication and FTR rates between hospitals with high and low mortality after PD. Varying mortality rates between hospitals seemed to be explained to a much larger extent by varying FTR, than by varying complication rates. This was clearly illustrated by the 560% increase in FTR between the first and fourth hospital mortality quartile, compared to a 40% increased rate of major complications between these quartiles. Higher volume centers (at least 40 PDs annually) displayed the lowest FTR rates compared to lower volume hospitals. A nomogram was able to stratify patients into very low (2%), low (4%), and high (12%) FTR risk based on both patient and hospital characteristics.

This study uses data from a mandatory nationwide audit on pancreatic surgery to study FTR and only reports on patients undergoing PD. This audit contains more than 150 variables per patient, each with strict data definitions and extensive registration of clinicopathological characteristics. Previous studies investigating FTR,[3,4,7,9,22,23] used large scale administrative datasets which are known to be hampered by inaccurate registration of (the severity of) complications.[24,25] Previous studies on FTR have focused on high-risk surgery including pancreatic resections of all types – including both PD and distal pancreatectomy, with known differences in outcome.[3,4,7,9,22,23] The magnitude of increase in FTR was 560% in the current study as compared to 525% and 1150% in two previous studies investigating FTR among patients undergoing pancreatic resection (all types).[3,9] Contrary to previous studies we were able to include patients of all ages[3,7,23] and included all nationwide pancreatic centers instead of only dedicated participating centers.[4]

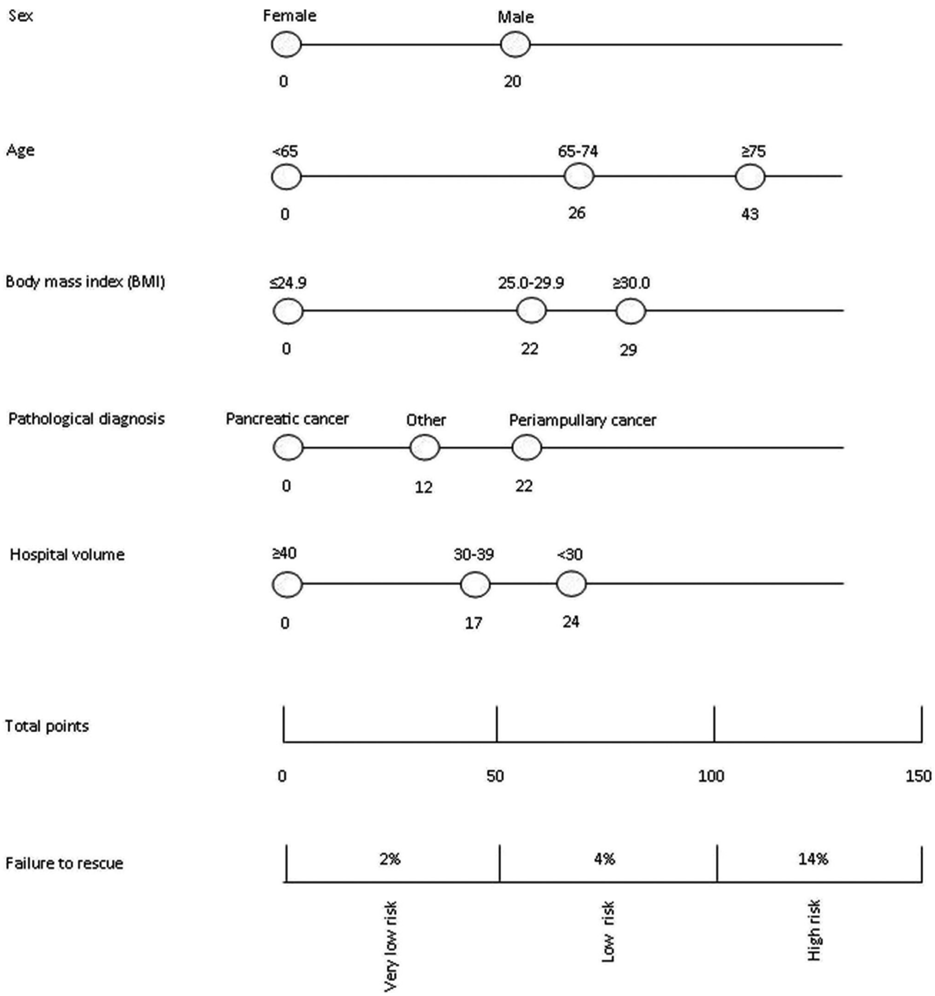


Figure 3 Nomogram for failure to rescue following pancreatoduodenectomy for cancer. Points acquired for each of the five variables (sex, age, BMI, diagnosis, hospital volume) are added. At the total points axis, a vertical line to the failure to rescue rate axis shows risk of FTR. ECOG, Eastern Cooperative Oncology Group. Periampullary refers to duodenum, distal bile duct and ampulla. Other diagnosis includes intraductal papillary mucinous neoplasm, pancreatic neuroendocrine tumor, pancreatic or papillary adenoma, pancreatitis, serous cystadenoma, solid pseudopapillary neoplasm

Most reports on mortality rates after PD originate from individual, high-volume, expert centers. Studies on a national level usually report higher mortality rates. Nationwide in-hospital mortality found in the present study (4.2%) seems lower compared to other recent nationwide reports e.g. from the U.S. (6–7%) and Italy (8.1%).[26–28] A recent nationwide study from Germany reported a 7.7% in-hospital mortality rate after PD.[29] The rate of major complications (29%) found in this study is comparable to reports from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP).[30,31]

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The identification of FTR as a key explanation for varying mortality rates after PD between hospitals has important implications for clinical practice and future research. Clinical research has focused mainly on the prevention of complications. Future studies should focus on strategies to improve early detection and management of major complications, including differences in infrastructure between centers (e.g. interventional radiology, nurse to patient ratio). In previous investigations, escalation of care has been proposed to reduce FTR by "the recognition and communication of patient deterioration to a senior colleague".[11,32,33] Factors that may hamper escalation of care include lack of established protocol or support of team members, hierarchy, and understaffing. Improvements in each item may lead to better outcomes.

Several previous studies have identified lower hospital volume as a risk factor for FTR.[7,8,22,23] The nomogram demonstrates that hospital volume PDs was the only risk factor for FTR that can be modified. For patients, the nomogram can be useful in preoperative counseling and shared-decision making. As clinicopathological points in the nomogram (age, sex, BMI, pathological diagnosis) cannot be influenced only transferring the patient for surgery to a higher volume center could improve outcome. Future research should investigate if there are strategies regarding the detection and management of major complications in higher volume centers which may be transferred to lower volume centers, to reduce FTR. Alternately, it is possible that solely the treatment of a larger volume of complications is responsible for lower FTR in high volume centers. Unfortunately, because were constrained to the data registered in the DPCA, we could not study which specific aspects of complication management (e.g. screening for complications, timing of intervention, type of intervention) in high-volume hospitals were responsible for the observed lower FTR rates.

Future studies should evaluate whether hospital volume is associated with better escalation of care. Surgical experience is only one factor for escalation of care. Experience of the whole team (e.g. the night nurse, the resident on call, the interventional radiologist) involved in the care for a patient with a major complication after a PD is equally important. In high-volume hospitals all members of the team may be more experienced in recognizing and treating complications after PD. Detailed clinical pathways for detection and management major complications after PD may have the potential to reduce FTR in both low- and high-volume hospitals but this concept needs to be tested in future prospective studies.[34] Furthermore, in the present study there were no significant differences in the incidence of (grade B/C) procedure related complications between the quartiles in patients who died with a major complication. However, there was a large increase in the incidence of CR-POPF across the hospital quartiles in patients who died with a major complication: 0% in the first hospital quartile (with the lowest mortality), and 56% in the fourth hospital quartile. Unfortunately, we were limited by relatively low event sizes and due to the design of the audit cannot determine if specific interventions were performed for POPF. Future studies should investigate the effect of differences in treatment strategies for POPF on FTR. For example, complication management is increasingly shifting towards non-operative interventions and therefore, away from the surgeon.[35]

Other factors such as hospital technology or teaching status, number of hospital beds, level of ICU, average daily census, nurse-to-patient ratio, or patient co-morbidities could also be associated with variation in FTR.[7,9,10,36] Contrary to previous studies, in our study hospital teaching status was not related to FTR.[7,9] This can probably be explained by the centralization of pancreatic surgery in the Netherlands, which has been accompanied by a significant decrease in postoperative mortality (9.8%–5.1% between 2004 and 2009).[37] Prior to centralization, university hospitals in the Netherlands demonstrated better outcomes compared to non-university hospitals.[38]

Our study has some limitations. We were not able to determine the primary cause of patients' death. Therefore, we cannot indisputably claim that higher mortality is caused by worse FTR. However, the vast majority of mortality after PD is caused by procedure related complications.[12] Furthermore, the series of events following a major complication often obscures the primary cause of death.[39] Some variation in the incidence of major complications between the mortality quartiles may be explained by differences in strategies in case of DGE (the most common complication after PD). However, in a sensitivity analysis excluding all patients with DGE as the only major complication, the results did not change. Due to the design of the audit we were not able to determine the number of complications per patient. Therefore, it is possible that in the highest hospital quartiles of mortality, there were relatively more patients with more than one complication. Differences in mortality could then also be attributed to more (procedure related) complications in some patients. However, we were able to determine the number of patients with more than one procedure specific major complication, i.e. POPF, PPH, DGE and BL. This was limited to less than 10% of patients, and the distribution was not significantly different between the hospital quartiles.

This study has several strengths compared to previous studies. The DPCA includes all 18 pancreatic centers in the Netherlands, all of whom are high volume by the definition of 20 PDs per year, and therefore allows evaluation of FTR on a national level. This eliminates the selection bias seen in previous studies.[3,4,7,9,22,23,40] Furthermore, the DPCA does not rely on administrative data assuring correct coding of procedures, complications, and severity grading.

In conclusion, variation in hospital mortality after PD on a nationwide level is probably explained to a much larger extent by differences in FTR rather than complication rates. Higher volume centers (at least 40 PDs annually) displayed lower FTR rates compared to lower volume hospitals. Therefore, hospitals and future studies should focus on methods to reduce FTR.

Collaborators

The Dutch Pancreatic Cancer Group is grateful for all collaborators of the Dutch Pancreatic Cancer Audit, including Thomas M. Van Gulik, MD PhD (department of Surgery, Academic Medical Center, Amsterdam); Sebastiaan Festen, MD PhD and Tom M. Karsten, MD PhD (department of Surgery, Onze Lieve Vrouwe Gasthuis, Amsterdam); Peter P Coene, MD PhD (Maasstad ziekenhuis, Rotterdam, all the Netherlands).

REFERENCES

1. Silber JH, Rosenbaum PR, Schwartz JS, Ross RN, Williams SV. (1995) Evaluation of the complication rate as a measure of quality of care in coronary artery bypass graft surgery. J Am Med Assoc 274:317–323.
2. Ghaferi AA, Birkmeyer JD, Dimick JB. (2009) Variation in hospital mortality associated with inpatient surgery. N Engl J Med 361:1368–1375.
3. Ghaferi AA, Birkmeyer JD, Dimick JB. (2009) Complications, failure to rescue, and mortality with major inpatient surgery in medicare patients. Ann Surg 250:1029–1034.
4. Wong SL, Revels SL, Yin H, Stewart AK, McVeigh A, Banerjee M et al. (2015) Variation in hospital mortality rates with inpatient cancer surgery. Ann Surg 261:632–636.
5. Edwards FH, Ferraris VA, Kurlansky PA, Lobdell KW, He X, O'Brien SM et al. (2016) Failure to rescue rates after coronary artery bypass grafting: an analysis from the society of thoracic surgeons adult cardiac surgery database. Ann Thorac Surg 102:458–464.
6. Tevis SE, Carchman EH, Foley EF, Heise CP, Harms BA, Kennedy GD. (2016) Does anastomotic leak contribute to high failure-to-rescue rates? Ann Surg 263:1148–1151.
7. Sheetz KH, Dimick JB, Ghaferi AA. (2016) Impact of hospital characteristics on failure to rescue following major surgery. Ann Surg 263:692–697.
8. Tamirisa NP, Parmar AD, Vargas GM, Mehta HB, Kilbane EM, Hall BL et al. (2016) Relative contributions of complications and failure to rescue on mortality in older patients undergoing pancreatectomy. Ann Surg 263:385–391.
9. Ghaferi AA, Osborne NH, Birkmeyer JD, Dimick JB. (2010) Hospital characteristics associated with failure to rescue from complications after pancreatectomy. J Am Coll Surg 211:325–330.
10. Henneman D, van Leersum NJ, Ten Berge M, Snijders HS, Fiocco M, Wiggers T et al. (2013) Failure-to-rescue after colorectal cancer surgery and the association with three structural hospital factors. Ann Surg Oncol 20:3370–3376.
11. Johnston MJ, Arora S, King D, Bouras G, Almoudaris AM, Davis R et al. (2015) A systematic review to identify the factors that affect failure to rescue and escalation of care in surgery. Surgery 157:752–763.
12. Cameron JL, He J. (2015) Two thousand consecutive pancreaticoduodenectomies. J Am Coll Surg 220:530–536.
13. McMillan MT, Allegrini V, Asbun HJ, Ball CG, Bassi C, Beane JD et al. (2017) Incorporation of procedure-specific risk into the ACS-NSQIP surgical risk calculator improves the prediction of morbidity and mortality after pancreatoduodenectomy. Ann Surg 265:978–986.
14. van Rijssen LB, Koerkamp BG, Zwart MJ, Bonsing BA, Bosscha K, van Dam RM et al. (2017 Oct) Nationwide prospective audit of pancreatic surgery: design, accuracy, and outcomes of the Dutch Pancreatic Cancer Audit. HPB 19:919–926.
15. Dindo D, Demartines N, Clavien PA. (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240:205–213.
16. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J et al. (2005) Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 138:8–13.
17. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR et al. (2007) Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 142:761–768.
18. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ et al. (2007) Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 142:20–25.
19. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L et al. (2011) Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. Surgery 149:680–688.
20. Roberts KJ, Sutcliffe RP, Marudanayagam R, Hodson J, Isaac J, Muiesan P et al. (2015) Scoring system to predict pancreatic fistula after pancreaticoduodenectomy: a UK Multicenter Study. Ann Surg 261: 1191–1197.
21. van der Geest LG, van Rijssen LB, Molenaar IQ, de Hingh IH, Groot Koerkamp B, Busch OR et al. (2016) Volume-outcome relationships in pancreatoduodenectomy for cancer. HPB 18:317–324.
22. Amini N, Spolverato G, Kim Y, Pawlik TM. (2015) Trends in hospital volume and failure to rescue for pancreatic surgery. J Gastrointest Surg 19:1581–1592.

23. Ghaferi AA, Birkmeyer JD, Dimick JB. (2011) Hospital volume and failure to rescue with high-risk surgery. Med Care 49:1076–1081.
24. Jencks SF, Williams DK, Kay TL. (1988) Assessing hospital-associated deaths from discharge data. The role of length of stay and comorbidities. J Am Med Assoc 260:2240–2246.
25. Iezzoni LI, Foley SM, Daley J, Hughes J, Fisher ES, Heeren T. (1992) Comorbidities, complications, and coding bias. Does the number of diagnosis codes matter in predicting in-hospital mortality? J Am Med Assoc 267:2197–2203.
26. Hyder O, Dodson RM, Nathan H, Schneider EB, Weiss MJ, Cameron JL et al. (2013) Influence of patient, physician, and hospital factors on 30-day readmission following pancreatoduodenectomy in the United States. JAMA Surg 148:1095–1102.
27. McPhee JT, Hill JS, Whalen GF, Zayaruzny M, Litwin DE, Sullivan ME et al. (2007) Perioperative mortality for pancreatectomy: a national perspective. Ann Surg 246:246–253.
28. Balzano G, Zerbi A, Capretti G, Rocchetti S, Capitanio V, Di Carlo V. (2008) Effect of hospital volume on outcome of pancreaticoduodenectomy in Italy. Br J Surg 95:357–362.
29. Nimptsch U, Krautz C, Weber GF, Mansky T, Grutzmann R. (2016) Nationwide in-hospital mortality following pancreatic surgery in Germany is higher than anticipated. Ann Surg 264:1082–1090.
30. Hallet J, Mahar AL, Tsang ME, Lin Y, Callum J, Coburn NG et al. (2015) The impact of peri-operative blood transfusions on post-pancreatectomy short-term outcomes: an analysis from the American College of Surgeons National Surgical Quality Improvement Program. HPB 17:975–982.
31. Parikh P, Shiloach M, Cohen ME, Bilimoria KY, Ko CY, Hall BL et al. (2010) Pancreatectomy risk calculator: an ACS-NSQIP resource. HPB 12:488–497.
32. Johnston M, Arora S, Anderson O, King D, Behar N, Darzi A. (2015) Escalation of care in surgery: a systematic risk assessment to prevent avoidable harm in hospitalized patients. Ann Surg 261:831–838.
33. Ghaferi AA, Dimick JB. (2015) Understanding failure to rescue and improving safety culture. Ann Surg 261:839–840.
34. Johnston MJ, King D, Arora S, Cooper K, Panda NA, Gosling R et al. (2014) Requirements of a new communication technology for handover and the escalation of patient care: a multi-stakeholder analysis. J Eval Clin Pract 20:486–497.
35. Tol JA, Busch OR, van Delden OM, van Lienden KP, van Gulik TM, Gouma DJ. (2014) Shifting role of operative and nonoperative interventions in managing complications after pancreatoduodenectomy: what is the preferred intervention? Surgery 156:622–631.
36. Chiulli LC, Stephen AH, Heffernan DS, Miner TJ. (2015) Association of medical comorbidities, surgical outcomes, and failure to rescue: an analysis of the Rhode Island hospital NSQIP database. J Am Coll Surg 221:1050–1056.
37. de Wilde RF, Besselink MG, van der Tweel I, de Hingh IH, van Eijck CH, Dejong CH et al. (2012) Impact of nationwide centralization of pancreaticoduodenectomy on hospital mortality. Br J Surg 99:404–410.
38. van Roest MH, van der Aa MA, van der Geest LG, de Jong KP. (2016) The impact of socioeconomic status, surgical resection and type of hospital on survival in patients with pancreatic cancer. A populationbased study in The Netherlands. PLoS One 11, e0166449.
39. Silber JH, Rosenbaum PR. (1997) A spurious correlation between hospital mortality and complication rates: the importance of severity adjustment. Med Care 35:OS77–92.
40. Spolverato G, Ejaz A, Hyder O, Kim Y, Pawlik TM. (2014) Failure to rescue as a source of variation in hospital mortality after hepatic surgery. Br J Surg 101:836–846.

APPENDIX A. SUPPLEMENTARY DATA

eTable 1. Multivariable analysis of factors associated with Failure to Rescue

	Multivariable		
Characteristics	**OR**	**95%CI**	**P-value**
Male Sex	2.02	1.05-3.87	0.03
Age			
<65	-		
65-74	2.58	1.12-5.91	0.03
≥75	4.33	1.84-10.17	0.001
BMI			
≤24.9	-		
25.0 - 29.9	2.16	1.13-4.16	0.02
≥30.0	2.89	1.26-6.63	0.01
ECOG >1	1.39	0.63-3.10	0.42
Hospital volume			
≥40	-		
30-39	1.69	0.84-3.42	0.15
<30	2.44	1.20-4.99	0.02
Diagnosis			
Pancreatic cancer	-		
Periampullary cancer*	2.20	1.12-4.32	0.02
Other	1.19	0.52-2.76	0.67

* Cancer of duodenum, distal bile duct, or ampulla. OR, odds ratio. BMI, body mass index. ECOG, Eastern Cooperative Oncology Group.