

Predicting Successful Catheter Drainage in Patients With Pancreatic Fistula After Pancreatoduodenectomy

F. Jasmijn Smits, MD, Hjalmar C. van Santvoort, MD, PhD,* Marc G. Besselink, MD, PhD,† Djamila Boerma, MD, PhD,* Olivier R. Busch, MD, PhD,† Ronald M. van Dam, MD, PhD,‡ Casper H. van Eijck, MD, PhD,§ Sebastiaan Festen, MD, PhD,|| Erwin van der Harst, MD, PhD,¶ Ignace H. de Hingh, MD, PhD,# Koert P. de Jong, MD, PhD,** Inne H. Borel Rinkes, MD, PhD,* and I. Quintus Molenaar, MD, PhD* on behalf of the Dutch Pancreatic Cancer Group*

Objectives: The objective of this study was to identify predictors for successful minimally invasive catheter drainage (ie, survival without relaparotomy) for pancreatic fistula after pancreatoduodenectomy.

Methods: Included were consecutive patients undergoing catheter drainage as first intervention for pancreatic fistula after pancreatoduodenectomy (2005–2013) in 9 Dutch centers. Possible prognostic factors for successful catheter drainage (ie, survival without relaparotomy) were selected using Akaike information criterion.

Results: Included were 227 patients after 2196 pancreatoduodenectomies. Primary catheter drainage was successful in 175 (77%) of 227 patients. Multivariable logistic regression revealed the following negative prognostic factors for success: male sex (odds ratio [OR], 0.46; 95% confidence interval [CI], 0.21–1.00; $P = 0.049$), higher age (for every 5 years over 50; OR, 0.69; 95% CI, 0.57–0.84; $P < 0.001$), and respiratory failure at time of catheter drainage (OR, 0.10; 95% CI, 0.03–0.33; $P < 0.001$). A prognostic model incorporating these factors yielded an area under the curve of 0.76 and demonstrated a success range of 98% to 14%.

Conclusions: Male sex, higher age, and respiratory failure are associated with a low success rate of catheter drainage in patients with pancreatic fistula after pancreatoduodenectomy. These patients might benefit from an intensified postoperative monitoring for early detection and management of pancreatic fistula to prevent respiratory failure.

Key Words: pancreatic carcinoma, pancreatic leakage, amylase, complication management, multicenter

(*Pancreas* 2019;48: 811–816)

In patients with pancreatic malignancy, resection followed by adjuvant chemotherapy provides the best chance of long-term

survival.^{1–3} Pancreatic surgery, however, is complex and associated with a high risk of postoperative complications.^{4–6} One of the most severe complications is postoperative pancreatic fistula, in which there is leakage of enzyme rich pancreatic juice into the abdomen.^{7–9} A large meta-analysis demonstrated an incidence of clinically relevant pancreatic fistula of 12% after pancreatoduodenectomy.⁶

Leakage of enzyme-rich fluid might cause bleeding through vessel erosion and a systemic inflammatory response, potentially leading to organ failure and death.^{7,8,10} To prevent these severe complications, clinically relevant pancreatic fistula should be identified at an early stage and treatment should be prompt. Invasive management of clinically relevant pancreatic fistula is either through relaparotomy or minimally invasive catheter drainage. A minimally invasive management strategy, with percutaneous catheter drainage as the first step, appears to be the best approach. Percutaneous catheter drainage is associated with a better clinical outcome, including lower mortality, as compared with primary relaparotomy.^{11–13} However, despite efforts to optimize the management of pancreatic fistula, clinically relevant postoperative pancreatic fistula is still associated with a mortality of 18% to 39%.^{6,8,12,14}

One of the difficulties in the management of pancreatic fistula is the early distinction between a biochemical leak, a clinically relevant but mild leak and the life-threatening subtype of pancreatic fistula.^{7,8,10} According to the International Study Group on Pancreatic Surgery definition, all types include efflux of amylase rich fluid through an abdominal drain. However, only patients with a clinically relevant leak require a change in postoperative management.⁹ Inadequate management of pancreatic fistula increases the risk of progression to the life-threatening subtype, with a high risk of bleeding, organ failure, and death. In this subgroup, patients clinically deteriorate under initial treatment (ie, minimally invasive catheter drainage) and often require a relaparotomy.^{9,10} Early identification of this subgroup of patients can be useful in patient counseling and communication with clinicians and to determine the postoperative management strategy for pancreatic fistula in an individual patient.

Therefore, the aim of this study was to identify predictors for successful minimally invasive catheter drainage (ie, survival without relaparotomy) as first invasive intervention in the treatment of postoperative pancreatic fistula after pancreatoduodenectomy.

MATERIALS AND METHODS

Design and Study Population

For this retrospective observational study, a cohort of 328 consecutive patients with severe pancreatic fistula after pancreatoduodenectomy (January 2005 to September 2013)

From the *Department of Surgery, Regional Academic Cancer Center Utrecht: University Medical Center Utrecht and St Antonius Hospital, Utrecht, The Netherlands; †Department of surgery, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam; ‡Department of Surgery, Maastricht University Medical Center, Maastricht; §Department of Surgery, Erasmus Medical Center, Rotterdam; ||Department of Surgery, Onze Lieve Vrouwe Gasthuis, Amsterdam; ¶Department of Surgery, Maasstad Hospital, Rotterdam; #Department of Surgery, Catharina Hospital, Eindhoven; and **Department of Surgery, University Medical Center Groningen, Groningen, The Netherlands. Received for publication July 26, 2018; accepted April 22, 2019.

Address correspondence to: I. Quintus Molenaar, MD, PhD, Department of Surgery, University Medical Centre Utrecht, internal mail G04.228, PO Box 85500, 3508 GA, Utrecht, The Netherlands (e-mail: i.q.molenaar@umcutrecht.nl).

The authors declare no conflict of interest.

Supplemental digital contents are available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.pancreasjournal.com).

Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

DOI: 10.1097/MPA.0000000000001334

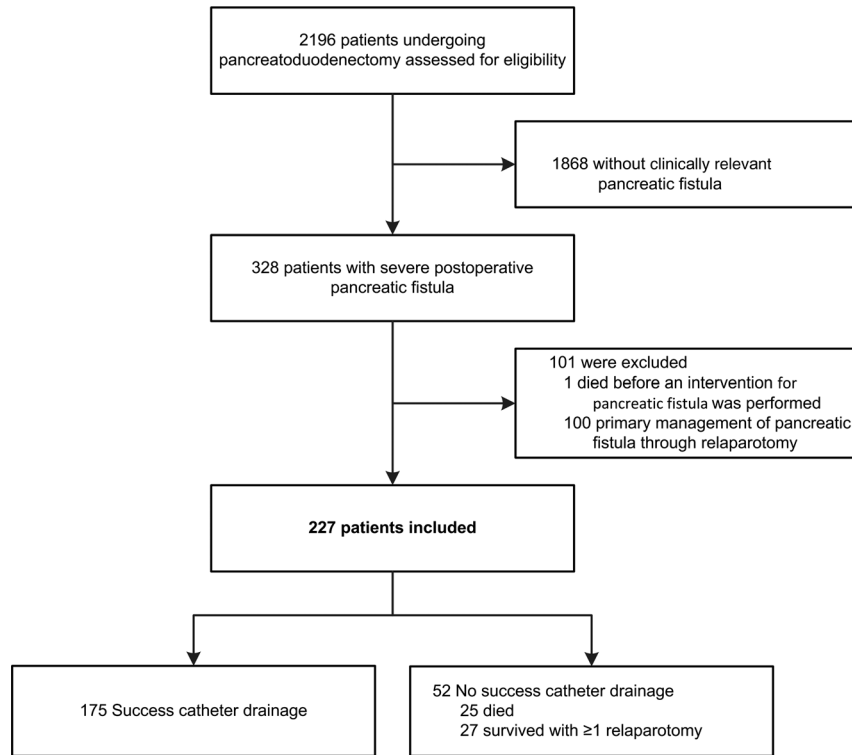


FIGURE 1. Flow chart of patient inclusion.

in 9 centers of the Dutch Pancreatic Cancer Group were evaluated for eligibility. Clinical outcomes of this cohort were previously described.¹² This study was reviewed by the medical ethical committee, and the need for informed consent was waived.

This study was conducted in accordance to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis statement.¹⁵ Included in the current analysis were all patients undergoing prolonged (ie, discharge with preoperatively placed drain in place) or additional minimally invasive catheter drainage as primary intervention for pancreatic fistula after pancreatoduodenectomy. Excluded were patients undergoing relaparotomy as primary intervention for pancreatic fistula (see inclusion flow chart in Fig. 1). Success of

catheter drainage was defined as in-hospital survival without the need for relaparotomy. Pancreatic fistula was defined in accordance to the International Study Group on Pancreatic Fistula.¹⁴ All relevant definitions were provided in Table 1.

Data Collection

All data were retrospectively collected for the initial analysis using a predefined, standardized case record form through systematic patient file search or from existing prospective databases. The following baseline characteristics were evaluated: patient demographics (ie, sex, age, American Society of Anesthesiologists classification on admission, body mass index [BMI], preoperative weight loss, preoperative cholestasis [ie,

TABLE 1. Definitions

Outcome	Definition
Success of catheter drainage	Discharge alive without need for relaparotomy
Postoperative pancreatic fistula	Amylase in drain fluid on or after postoperative day three of at least three times the upper level of normal serum amylase ⁴
Clinically relevant pancreatic fistula	Requiring prolonged (ie, discharge with preoperatively placed drain in place) or additional minimally invasive catheter drainage or relaparotomy (with eg, surgical drainage or completion pancreatectomy)
Preoperative cholestasis	Need for preoperative biliary drainage; jaundice at physical examination or elevation of last preoperative bilirubin over upper limit of normal serum value.
Organ failure	Adapted from Bardley ³⁵
Pulmonary	PaO ₂ <60 mm Hg, despite FiO ₂ of 0.3, or need for mechanical ventilation
Circulatory	Systolic blood pressure <90 mm Hg, despite adequate fluid resuscitation, or need for inotropic support
Renal	Creatinine level >177 μmol/L after rehydration or need for hemofiltration or hemodialysis

PaO₂ indicates partial pressure of arterial oxygen; FiO₂, fraction of inspired oxygen.

jaundice, increased bilirubin level and the need for preoperative biliary drainage), pancreatoduodenectomy details (ie, procedure, operative time, placement of surgical abdominal drain), first postoperative serum amylase level, postoperative pathology diagnosis (ie, pancreatic adenocarcinoma or pancreatitis vs other diagnoses), disease severity at 24 hours or less before primary minimally invasive catheter drainage for pancreatic fistula (ie, Acute Physiology and Chronic Health Evaluation II [APACHE II] score,¹⁶ systemic inflammatory response syndrome [SIRS], white blood cell count, and organ failure [ie, pulmonary, renal, or circulatory failure]). In addition, number of invasive interventions before first intervention for pancreatic fistula and timing of first catheter drainage for pancreatic fistula (ie, days after index pancreatic resection), in-hospital mortality, and the need for relaparotomy after primary catheter drainage were collected. All definitions are provided in Table 1.

Length of follow-up was equal to length of index admission, in which readmission within 10 days after discharge was considered to be part of the index admission.

Statistical Analysis

Patients were divided into 2 groups based on the success of catheter drainage. The relation between possible predictors and success of catheter drainage was evaluated using univariable logistic regression analysis. All predictors possibly associated with the success of catheter drainage in univariable analysis ($P < 0.1$) were included in multivariable logistic regression analysis. The Akaike information criterion (AIC), combining the number of variables in the model and the likelihood function, was used to determine the best performing model. The lower the AIC, the better the model fit for the prognostic model.¹⁷ The discriminatory ability of the model was expressed in the area under the curve in the receiver operating characteristics curve (ROC). The model was internally validated using 500 bootstrap resamples. Regression coefficients obtained for the multivariable logistic regression analysis were visualized in a nomogram. This nomogram provides prognostic information on the predicted success of catheter drainage for each patient.

To use a complete dataset for logistic regression, we used multiple imputation for missing data in baseline characteristics. Initial analysis showed missing data in BMI (7%), weight loss (4%), length of surgery (3%), first postoperative serum amylase (18%), and white blood cell count (2%). The imputation model was created using all baseline characteristics as predictors. Pooled data from the imputed dataset with 5 dummy cases for each patient were used for the construction of a prediction model. After checking assumptions in the possible predictors, age was transformed into steps for every 5 years and was truncated. The cut points (ie, <50 years and >80 years, respectively) were based on clinical relevance and chosen so every group contained at least 10 patients.

Normally distributed continuous data were presented as mean (standard deviation [SD]), and data with skewed distribution, as median (interquartile range [IQR]). Outcomes of regression analysis are presented as odds ratio (OR) with a 95% confidence interval (CI). A 2-tailed $P < 0.05$ was considered statistically significant. All analyses were performed in SPSS version 21.0 (IBM, Armonk, NY).

RESULTS

Patients

In the entire cohort of 2196 consecutive patients undergoing pancreatoduodenectomy, 328 patients (15%) developed clinically relevant pancreatic fistula (grade B/C). Clinical outcomes of this

cohort were described previously.¹² Included in this analysis were all 227 consecutive patients undergoing catheter drainage as first intervention for pancreatic fistula. Catheter drainage was successful (ie, survival without the need for relaparotomy) in 175 patients (77%). Forty patients (18%) underwent 1 or more relaparotomies after primary catheter drainage. Completion pancreatectomy was performed in 7 patients (3%). Mortality during admission in patients undergoing primary catheter drainage for pancreatic fistula was 11% (25 patients), 12 of these patients died without undergoing a relaparotomy (see Fig. 1).

Baseline characteristics are shown in Table 2. The first catheter drainage was performed at a median of 9 days after pancreatoduodenectomy (IQR, 6–13). Catheter drainage was performed percutaneous in 196 patients (86%) and transgastric in 2 patients (1%). A total of 29 patients (13%) were discharged with the peroperatively placed drain in place without undergoing additional catheter drainage. In 121 patients (53%), 1 drainage procedure was performed, 47 patients (21%) underwent 2 drainages, 22 patients (10%) underwent 3 drainages, and 37 patients (16%) underwent 4 or more drainage procedures. A median of 1 invasive intervention was performed to resolve pancreatic fistula (IQR, 1–3). Clinical outcomes are presented in Table 3.

Prediction of Successful Catheter Drainage

Outcomes of univariable logistic regression are shown in Supplementary Table 1, <http://links.lww.com/MPA/A726>. Potential negative predictors for successful catheter drainage ($P < 0.1$ in univariable logistic regression) were the following: male sex, higher age, preoperative cholestasis, APACHE II score, the presence of any form of organ failure, and the presence of respiratory failure at time of first intervention. In multivariable analysis, the best performing model (ie, with the lowest AIC) included the following negative predictors: male sex (OR, 0.46; 95% CI, 0.21–1.00; $P = 0.049$); higher age (ie, for every additional 5 years over 50, truncated at 80; OR, 0.70; 95% CI, 0.57–0.84; $P < 0.001$); and the presence of respiratory failure in 24 hours before first catheter drainage (OR, 0.10; 95% CI, 0.03–0.33; $P < 0.001$). This model was internally validated using 500 bootstrap resamples, showing no major indication for bias. Therefore, all variables were included in the final model (Table 4). This model yielded an area under the curve of 0.76 (95% CI, 0.68–0.83; see Supplementary Fig. 1, <http://links.lww.com/MPA/A726>).

The prognostic value of each of these variables is visualized in a nomogram in Figure 2. This nomogram was designed using intercept and regression coefficients of the independent predictors in the final model. Each patient is awarded a number of points based on their characteristics at time of intervention (eg, 0 points for reference values; 2 points for male sex, 0–7 points for every 5 years over 50 years of age, and 6 points for the presence of respiratory failure at time of first intervention). The sum of these points correlates to a predicted percentage for the success of catheter drainage: for example, a female patient of 49 years without respiratory failure has a success chance of 98% (0 points); a male patient of 85 years with respiratory failure has a success chance of only 14% (15 points).

DISCUSSION

In this multicenter cohort of patients undergoing minimally invasive drainage for pancreatic fistula after pancreatoduodenectomy, male sex, higher age, and the presence of respiratory failure were negatively associated with the success of catheter drainage (ie, survival without the need for relaparotomy). Because respiratory failure is the only independent predictor that can be influenced, we believe clinical outcomes could be improved

TABLE 2. Baseline Characteristics*

Characteristics	Primary Catheter Drainage (n = 227)
Sex, male, n (%)	147 (65)
Age, median (IQR), y	65 (59–72)
ASA classification on admission, n (%)	
I: Healthy status	50 (22)
II: Mild systemic disease	150 (66)
III: Severe systemic disease	27 (12)
BMI, mean (SD), kg/m ^{2†}	26.4 (3.6)
Preoperative weight loss, median (IQR), kg‡	2 (0–6)
Preoperative cholestasis, n (%)§	165 (73)
Jaundice, n (%)	137 (60)
Serum bilirubin, median (IQR), µmol/L	15.5 (8.0–56.8)
Biliary drainage, n (%)	122/226 (54)
Pancreatoduodenectomy details	
Pylorus preserving pancreatoduodenectomy, n (%)	183 (81)
Operative time, median (IQR), min [¶]	294 (241–373)
Placement surgical abdominal drain, n (%)	225 (99)
First postoperative serum amylase, median (IQR), U/L [#]	295 (58–657)
Low-risk pathologic disease (ie, pancreatic adenocarcinoma or pancreatitis), n (%)	62 (27)
Disease severity 24 h before first intervention	
APACHE II score, median (IQR)**	8 (6–10)
SIRS, n (%) ^{††}	99 (44)
White blood cell count, median (IQR), ×10 ⁹ /L ^{‡‡}	15 (12–21)
Organ failure, n (%)	27 (12)
Respiratory failure, n (%)	17/226 (8)
Renal failure, n (%)	11 (5)
Circulatory failure, n (%)	9 (4)
Previous invasive interventions, n (%)	10 (4)
Timing first catheter drainage after resection, median (IQR), d	9 (6–13)

*Normal distributed values are presented as mean (SD).

†Calculated in 212 patients.

‡Calculated in 220 patients.

§Defined as jaundice, elevated bilirubin and/or need for preoperative biliary drainage.

^{||}Last peroperative value; calculated in 172 patients.

[¶]Calculated in 220 patients.

[#]Measured within the first 3 days after resection, calculated in 187 patients.

**Acute Physiology and Chronic Health Evaluation II scale from 0 to 71, higher scores for more severe disease.

††Systemic inflammatory response syndrome as defined by the American College of Chest Physicians and the Society of Critical Care Medicine.

‡‡Calculated in 222 patients.

ASA indicates American Society of Anesthesiologists.

through initiatives aiming to prevent respiratory failure in these patients. This might be achieved by implementation of an intensified postoperative monitoring strategy focused on early detection and early catheter drainage for pancreatic fistula. In addition, the proposed nomogram can be used to provide information on individual patient prognosis in patient counseling and communication with clinicians.

Even though the relation of these predictors with relaparotomy is not clear in patients undergoing pancreatic resection, all have been associated with the worst outcome in previous studies in other diseases. Male patients appear to be at greater risk of developing sepsis and are treated more aggressively, tend to undergo more invasive interventions, and are more frequently admitted to the intensive care unit.^{18–20} The sex difference in outcome might

be explained by the combination of chronic disease burden, social and environmental factors, and genetic predisposition causing differences in the host immune response.²¹ Higher age has been associated with more severe sepsis and increased mortality in critically ill patients, possibly partly owing to comorbidity.^{16,18,22} Organ failure can be considered a sign of more advanced stage of systemic inflammation, which could in itself be associated with a worse clinical outcome.^{16,18} We only found a negative association between respiratory failure and successful drainage. This might be explained by the fact that renal and circulatory failure occurred less often (see Table 2). These data suggest that early signs of sepsis, especially in elderly men, should promote a more aggressive search for and treatment of clinically relevant pancreatic fistula, because preemptive

TABLE 3. Clinical Outcomes

Outcome	Primary Catheter Drainage (n = 227)
Death, n (%)	25 (11)
Major complications after first intervention POPF, n (%)	58 (26)
New-onset single-organ failure, n (%)	46 (20)
New-onset multiple-organ failure, n (%)	25 (11)
Postpancreatectomy hemorrhage, n (%) [*]	40 (18)
Gastroenterostomy leakage, n (%) [*]	5 (2)
Bile leakage, n (%) [*]	17 (8)
Other complications after first intervention POPF, n (%)	
Delayed gastric emptying, n (%) [†]	
Grade B	0 (0)
Grade C	23 (11)
Acute pancreatitis, n (%) [‡]	11 (5)
Long-term complications, n (%)	
New-onset diabetes, n (%) [§]	28 (14)
New-onset exocrine pancreatic insufficiency, n (%) [§]	85 (43)
Hospitalization course	
New ICU admission after first intervention POPF, n (%)	67 (30)
Length of ICU stay, median (IQR), d [¶]	0 (0–2)
Length of hospital stay, median (IQR), d [¶]	29 (21–48)
Duration of pancreatic fistula, median (IQR), d ^{¶#}	28 (17–51)

^{*}Occurrence any time during admission after first intervention for pancreatic fistula, requiring intervention.

[†]Calculated over 186 patients.

[‡]Defined as elevated serum amylase and serum lipase in combination with abdominal pain or as seen on CT-scan or during relaparotomy.

[§]Occurrence within 90 days after date of admission.

^{||}After first intervention for pancreatic fistula.

[¶]Calculated over survivors.

[#]Time between pancreatoduodenectomy and removal of last abdominal drain or completion pancreatectomy.

POPF indicates postoperative pancreatic fistula; ICU, intensive care unit.

minimally invasive catheter drainage may prevent organ failure and subsequent mortality.

This study has several limitations. Because this was a retrospective study, there is an inevitable risk of confounding by indication. To limit the effect of bias, we have analyzed only objective, predefined predictors for success of catheter drainage (Table 1). Multiple imputation was used to deal with missing data, and therefore, we were able to include 226 complete cases in the logistic regression model. All patients were selected from 9 out of the 18 hospitals performing pancreatic surgery in the Netherlands. Even though we believe that the sample is representative for the other 9 hospitals, this could limit the external validity of this study. Finally, although we performed an internal bootstrap validation of our results, ideally, this model should be validated in an external cohort.

This study demonstrates the importance of good clinical decision-making, because respiratory failure is the only negative predictor for successful drainage that can be influenced. Future studies should focus on early adequate management of postoperative pancreatic fistula to prevent respiratory failure. Strict protocols to perform diagnostic imaging based on biochemical and clinical inflammatory parameters in the early postoperative phase after pancreatoduodenectomy should be evaluated to determine whether early management of pancreatic fistula can prevent organ failure and ultimately improves clinical outcome in these patients. The nationwide PORSCH trial aims to determine if an intensified, standardized *best practice* algorithm for early detection and minimally invasive management of pancreatic fistula leads to less major complications and mortality after pancreatic resection (NCT03400280).

TABLE 4. Risk Prediction Model for Success of Catheter Drainage

Characteristics	OR (95% CI)	Regression Coefficient	P	Points
Sex (male vs female)	0.46 (0.21–1.00)	−0.78	0.049	2
Respiratory failure at time of intervention (yes vs no)	0.10 (0.03–0.33)	−2.26	<0.001	6
Age (continuous; per 5 y; from 50 up to 80 y)	0.69 (0.57–0.84)	−0.37	<0.001	0–7
Intercept, 3.78.				

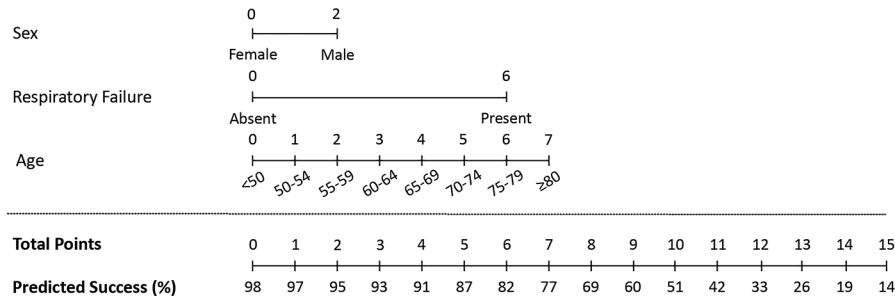


FIGURE 2. Nomogram for successful catheter drainage as first step in management of grade B/C pancreatic fistula after pancreatoduodenectomy. The presence or absence of each predictor is awarded points. The sum of these points (0 to 15 points) represents a success percentage of catheter drainage (98% to 14%, respectively). The probability of success of catheter drainage can be read from the bottom ruler shown in this figure.

Furthermore, this prediction model can be used to provide information on the prognosis of the individual patient. This information can help the clinician in communication with patients and their family and with fellow clinicians. It should be stressed that the proposed nomogram is not supposed to discourage a minimally invasive approach in patients with a low chance of predicted success (ie, elderly men with respiratory failure), because even those patients could benefit from a minimally invasive approach over relaparotomy.¹²

This study shows that the success of catheter drainage in patients with clinically relevant pancreatic fistula after pancreatoduodenectomy can accurately be predicted by using sex, age, and respiratory failure. Emphasis of future studies should be on the impact of intensive monitoring of patients to use early adequate management of pancreatic fistula before the phase of respiratory failure.

REFERENCES

1. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet*. 2017;389:1011–1024.
2. Neoptolemos JP, Moore MJ, Cox TF, et al. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma. *JAMA*. 2012;308:147–156.
3. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer. *JAMA*. 2013;310:1473–1481.
4. Sohn TA, Yeo CJ, Cameron JL, et al. Pancreaticoduodenectomy: role of interventional radiologists in managing patients and complications. *J Gastrointest Surg*. 2003;7:209–219.
5. Hidalgo M. Pancreatic cancer. *N Engl J Med*. 2010;362:1605–1617.
6. Hamoss JC, Ulrich AB, Hamoss JM, et al. Use and results of consensus definitions in pancreatic surgery: a systematic review. *Surgery*. 2014;155:47–57.
7. de Castro SM, Busch OR, van Gulik TM, et al. Incidence and management of pancreatic leakage after pancreatoduodenectomy. *Br J Surg*. 2005;92:1117–1123.
8. Fuks D, Piessen G, Huet E, et al. Life-threatening postoperative pancreatic fistula (grade C) after pancreaticoduodenectomy: incidence, prognosis, and risk factors. *Am J Surg*. 2009;197:702–709.

9. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. *Surgery*. 2017;161:584–591.
10. McMillan MT, Vollmer CM Jr, Asbun HJ, et al. The characterization and prediction of ISGPF grade C fistulas following pancreatoduodenectomy. *J Gastrointest Surg*. 2016;20:262–276.
11. Tol JA, Busch OR, van Delden OM, et al. Shifting role of operative and nonoperative interventions in managing complications after pancreatoduodenectomy: what is the preferred intervention? *Surgery*. 2014;156:622–631.
12. Smits FJ, van Santvoort HC, Besselink MG, et al. Management of severe pancreatic fistula after pancreatoduodenectomy. *JAMA Surg*. 2017;152:540–548.
13. Dellaportas D, Tympa A, Nastos C, et al. An ongoing dispute in the management of severe pancreatic fistula: pancreatosplenectomy or not? *World J Gastrointest Surg*. 2010;2:381–384.
14. Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery*. 2005;138:8–13.
15. Collins GS, Reitsma JB, Altman DG, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *Eur Urol*. 2015;67:1142–1151.
16. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13:818–829.
17. Bozdogan H. Model selection and Akaike's Information Criterion (AIC): the general theory and its analytical extensions. *Psychometrika*. 1987;52:345–370.
18. Mayr FB, Yende S, Linde-Zwirble WT, et al. Infection rate and acute organ dysfunction risk as explanations for racial differences in severe sepsis. *JAMA*. 2010;303:2495–2503.
19. Bos MM, Verburg IW, Dumaij I, et al. Intensive care admission of cancer patients: a comparative analysis. *Cancer Med*. 2015;4:966–976.
20. Valentin A, Jordan B, Lang T, et al. Gender-related differences in intensive care: a multiple-center cohort study of therapeutic interventions and outcome in critically ill patients. *Crit Care Med*. 2003;31:1901–1907.
21. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. *Virulence*. 2014;5:4–11.
22. Hollemans RA, Bollen TL, van Brunschot S, et al. Predicting success of catheter drainage in infected necrotizing pancreatitis. *Ann Surg*. 2016;263:787–792.