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# Risk stratification for postoperative pancreatic fistula using the pancreatic surgery registry StuDoQ|Pancreas of the German Society for General and Visceral Surgery

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ABSTRACT

*Background:* Postoperative pancreatic fistula (POPF) is a major factor for morbidity and mortality after pancreatic resection. Risk stratification for POPF is important for adjustment of treatment, selection of target groups in trials and quality assessment in pancreatic surgery. In this study, we built a risk-prediction model for POPF based on a large number of predictor variables from the German pancreatic surgery registry StuDoQ|Pancreas.

*Methods:* StuDoQ|Pancreas was searched for patients, who underwent pancreatoduodenectomy from 2014 to 2016. A multivariable logistic regression model with elastic net regularization was built including 66 preoperative und intraoperative parameters. Cross-validation was used to select the optimal model. The model was assessed via area under the ROC curve (AUC) and calibration slope and intercept.

*Results:* A total of N = 2488 patients were included. In the optimal model the predictors selected were texture of the pancreatic parenchyma (soft versus hard), body mass index, histological diagnosis pancreatic ductal adenocarcinoma and operation time. The AUC was 0.70 (95% CI 0.69–0.70), the calibration slope 1.67 and intercept 1.12. In the validation set the AUC was 0.65 (95% CI 0.64–0.66), calibration slope and intercept were 1.22 and 0.42, respectively.

*Conclusion:* The model we present is a valid measurement instrument for POPF risk based on four predictor variables. It can be applied in clinical practice as well as for risk-adjustment in research studies and quality assurance in surgery.



## Introduction

Postoperative pancreatic fistula (POPF) is one of the major factors for morbidity and mortality in pancreatic surgery. The International Study Group for Pancreatic Surgery (ISGPS) published in 2005 a definition and a classification of POPF, which have been widely accepted and used [1]. According to this definition, a pancreatic fistula is defined as any amylase-rich drainage fluid (>3 times the upper limit of institutional normal serum amylase activity) starting from the third day after surgery. POPF are then classified in grade A, grade B and grade C, according to the extent of

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the clinical impact. Grade A POPF have no impact on the postoperative course, grade B POPF alter the normal postoperative course, while the condition of the patient stays stable, and grade C POPF lead to severe complications such as organ failure with the need of intensive care or surgical intervention. In 2016, the ISGPS narrowed the definition of POPF to the clinically relevant POPF B and C [2]. While POPF B does not lead to higher mortality, the in-hospital death rate among patients with POPF C is as high as 35% and over one third of in-hospital deaths after pancreatoduodenectomy are contributed to POPF C [3,4]. Thus, assessing risk for POPF has a pivotal role when estimating overall risk in pancreatic surgery.

There has been considerable effort to develop a measurement tool for risk of POPF [5–8]. In a recent review, Sandini et al. described 10 clinical risk scores for POPF, published between 2008 and 2016 [5]. The most common parameters used in the development of predictive scores for POPF are the consistency of the pancreatic parenchyma and the diameter of the main pancreatic duct (MPD). While usually the consistency of the pancreatic parenchyma is subjectively assessed by the surgeon as soft or hard, the MPD is either used as a continuous or as a multicategorial parameter, measured at the resection plane of the pancreas. Since measurements of the MPD intraoperatively, especially when the pancreatic duct is small, might be impractical and imprecise, in the pancreatic surgery registry StuDoQ|Pancreas of the German Society for General and Visceral Surgery MPD has been recorded as a binary variable $<3$ mm versus $\geq 3$ mm [9]. Furthermore, there is an association of soft pancreatic parenchyma and small MPD that might cause the problem of multicollinearity in the regression models used to develop the prediction scores, and thus lead to instability of the models [10].

Another issue, when developing a predictive model for POPF, is the parameter selection, which usually has been based on univariable testing for significance or some prior knowledge, which might lead to selection bias and potentiating of uncertainties due to multiple testing.

In this study, we address the problems of parameter selection and multicollinearity using multivariable logistic regression with elastic net regularization [11] to develop a predictive model for POPF, using a large sample from the German pancreatic surgery registry StuDoQ|Pancreas [9].

## Methods

### *Study Design and Approval*

This is a retrospective, registry-based, explorative study. It was approved by the German Society for General and Visceral Surgery and the local ethics committee of the University of Lübeck.

### *Software*

All data processing and analysis was performed with R version 3.3.1. The following R packages were used: Hmisc, knitr, tables, xtable, stats, pROC, stringr, mice, Amelia, caret, ggplot2, gridExtra. The graphics were produced with the R packages ggplot2 and gridExtra.

### *Study population and parameters*

The study population consisted of all patients in StuDoQ|Pancreas with pancreatoduodenectomy from 2014 to 2016. A presentation and systematic quality evaluation of StuDoQ|Pancreas has been published in an international peer-reviewed journal [9]. After defining the dataset, the German Society for General and Visceral Surgery provided it in anonymized form for further analysis. The dataset was split into a training set and a test set according to the year of operation, with the cases from two years in the training set and the cases form the third year in the test set. Since the year of operation was coded in the process of anonymization, the splitting might not follow consecutive order of cases. The parameters studied are listed in Appendix A, Table A1.

### *Descriptive statistics and missing data analysis*

Descriptive statistics with median and range for continuous parameters and percentage of total for discrete parameters were calculated. Descriptive missing data analysis with percentage missing data per variable and per case as well as missing data patterns was performed. Assuming missing at random process, multiple imputation for missing data using the chained equations method was implemented with the R package mice [12]. For the imputation an extended dataset consisting of 104 clinically relevant parameters was used. Training and test sets were imputed separately. The imputation was repeated 5 times. After imputation, cases with missing values for POPF were excluded.

### *Univariable analysis*

Univariable logistic regression was used with the imputed training set to model association between POPF B/C and 66 preoperative and intraoperative parameters. Continuous parameters like operative time or age were modeled using the fractional polynomial method to test for non-linear effects [13]. Odds ratios (OR) were calculated and the Wald test was used to determine p values. Significance level was set at 0.05.

### *Elastic net POPF model*

The 66 preoperative and intraoperative parameters were included in a multivariable logistic regression model with elastic net regularization. The optimal regularization parameter L1 und L2 were set using 5-fold cross validation. To improve the stability of the model bootstrap-enhancement as in Bunea et al. was performed [14]. Here, 100-fold bootstrapping was performed on the original training set and the 5-fold imputation was repeated on each bootstrap dataset. The model building steps were repeated on each of the resulting 500 datasets and the relative frequency of the parameters selected in the models was calculated. Parameters selected in more than 90% of the models were included in the final model.

The discrimination power of the model was evaluated using the area under the ROC-curve (AUC) und the calibration via the slope and intercept of the regression line of the actual POPF rate over the predicted POPF rate [15]. The model performance was validated on the test set.

## Results

### *Descriptive and univariable analysis*

A total of $N = 2488$ patients were identified. Of these, 1671 were assigned to the training set and 817 to the test set. Appendix A, Table A1 displays the descriptive statistics including missing data percentage. In the training set, POPF B rate was 8.2%, POPF C - 6.3% and total POPF B/C - 14.5%. The 30-day mortality was 3.4%, in-hospital mortality - 4.6%. Of the patients, who died during postoperative hospital stay, 34.2% had POPF C and 28.4% of the patients with POPF C died during postoperative hospital stay.

In the test set, POPF B rate was 9.5% and POPF C rate - 5.9%, total

POPF B/C - 15.4%. The 30-day mortality was 2.7%, the in-hospital mortality - 3.7%. Of the patients with in-hospital death 27.6% had POPF C, while 19.5% of the patients with POPF C died during postoperative hospital stay.

The overall missing data 3.3% in the training dataset und 3.2% in the test dataset with similar distribution over variables in both datasets.

Statistically significant associations with POPF B/C are displayed in Table 1. The results for all parameters tested are listed in Appendix A, Table A1. Non-linearities were revealed for preoperative creatinine and body mass index (BMI), while only the association with BMI was statistically significant (Fig. 1).

*Elastic net Modell*

The following parameters were selected in more than 90% of the 500 bootstrap-enhanced elastic net models: soft pancreatic parenchyma – 99.8%, hart pancreatic parenchyma - 99.8%, histological diagnosis pancreatic ductal adenocarcinoma (PDAC) – 99.8%, BMI – 99.2%, operation time - 94.6%. The final model equation is

$$Probability\ (POPF\ B/C) = \frac{\exp(L)}{1+\exp(L)},,$$

where

**Table 1**
Statistically significant associations between POPF and parameters in the training set.

| Parameter | POPF N[a] (%) | | Univariable Analysis | |
|---|---|---|---|---|
| | POPF none/A | POPF B/C | OR (95% CI) | p value |
| **sex** | | | | |
| female | 611 (87.8) | 85 (12.2) | | |
| male | 807 (83.9) | 155 (16.1) | 1.38 (1.04–1.84) | 0.026 |
| **BMI [kg/m$^2$]** | | | | 0.001 |
| 20 to 25 | | | 1.73 (1.35–2.21) | |
| 26 to 30 | | | 1.35 (1.18–1.54) | |
| 31 to 35 | | | 1.20 (1.10–1.30) | |
| 36 to 40 | | | 1.12 (1.07–1.18) | |
| 41 to 45 | | | 1.08 (1.05–1.12) | |
| 45 to 50 | | | 1.06 (1.03–1.09) | |
| **need of care** | | | | |
| no | 1345.4 (86.1) | 218 (13.9) | | |
| yes | 72.6 (76.7) | 22 (23.3) | 1.87 (1.14–3.08) | 0.014 |
| **history of cerebrovascular event** | | | | |
| no | 1350 (86.1) | 218 (13.9) | | |
| yes | 68 (75.6) | 22 (24.4) | 2.00 (1.21–3.31) | 0.007 |
| **history of chronic pancreatitis** | | | | |
| no | 1208 (84.5) | 221 (15.5) | | |
| yes | 210 (91.7) | 19 (8.3) | 0.50 (0.30–0.81) | 0.005 |
| **hemoglobin [g/dl]** | | | 1.11 (1.02–1.20) per 1 g/dl increase | 0.011 |
| **AP [U/l]** | | | 0.99(0.85–0.97) per 100 U/dl increase | 0.029 |
| **histological diagnosis** | | | | |
| PDAC | 756.6 (91.0) | 74.6 (9.0) | | |
| ampullary carcinoma | 106.6 (76.8) | 32.2 (23.2) | 3.06 (1.93–4.87) | <0.001 |
| DBDC | 92.8 (80.8) | 22 (19.2) | 2.41 (1.42–4.06) | 0.001 |
| duodenal carcinoma | 37.6 (80.7) | 9 (19.3) | 2.43 (1.13–5.23) | 0.024 |
| IPMN/invasive IPMN | 90 (85.6) | 15.2 (14.4) | 1.71 (0.94–3.11) | 0.077 |
| MCN/SCN | 15 (61.5) | 9.4 (38.5) | 6.35 (2.68–15.04) | <0.001 |
| NET/cystic NET | 58.4 (80.7) | 14 (19.3) | 2.43 (1.29–4.57) | 0.006 |
| chronic pancreatitis | 137.6 (87.2) | 20.2 (12.8) | 1.49 (0.88–2.53) | 0.140 |
| benign lesion | 33 (68.5) | 15.2 (31.5) | 4.67 (2.42–9.01) | <0.001 |
| other | 90.4 (76.2) | 28.2 (23.8) | 3.16 (1.94–5.15) | <0.001 |
| **portal vein resection** | | | | |
| no | 1277 (85.0) | 226 (15.0) | | |
| yes | 141 (91.0) | 14 (9.0) | 0.56 (0.32–0.99) | 0.046 |
| **pancreatic parenchyma** | | | | |
| soft | 615 (79.9) | 155 (20.1) | | |
| hard | 453 (92.4) | 37 (7.6) | 0.32 (0.22–0.47) | <0.001 |
| **MPD** | | | | |
| <3 mm | 760 (83.0) | 156.2 (17.0) | | |
| >=3 mm | 658 (88.7) | 83.8 (11.3) | 0.62 (0.42–0.91) | 0.017 |
| **transection of the pancreas** | | | | |
| scalpel | 695 (88.4) | 90.8 (11.6) | | |
| stapler | 48.2 (84.0) | 9.2 (16.0) | 1.46 (0.69–3.11) | 0.325 |
| LigaSure© | 38 (77.6) | 11 (22.4) | 2.22 (1.09–4.51) | 0.028 |
| Ultracision© | 47.6 (74.8) | 16 (25.2) | 2.57 (1.39–4.76) | 0.003 |
| bipolar | 40.6 (78.7) | 11 (21.3) | 2.07 (1.03–4.19) | 0.042 |
| monopolar | 505.4 (85.0) | 89 (15.0) | 1.35 (0.98–1.86) | 0.070 |
| ultrasounddissector | 43.2 (76.9) | 13 (23.1) | 2.30 (1.19–4.45) | 0.013 |
| **Operation time [min]** | | | 1.16 (1.08–1.26) per 60 min | <0.001 |

POPF - postoperative pancreatic fistula, BMI - body mass index, AP - alkaline phosphatase, PDAC - pancreatic ductal adenocarcinoma, DBDC - distal bile duct carcinoma, NET - neuroendocrine tumor, MCN - mucinous cystic neoplasm, SCN – serous cystic neoplasm, IPMN - intraductal papillary mucinous neoplasm, MPD – main pancreatic duct.

[a] Absolute numbers N are given as the mean over the 5 imputed datasets.

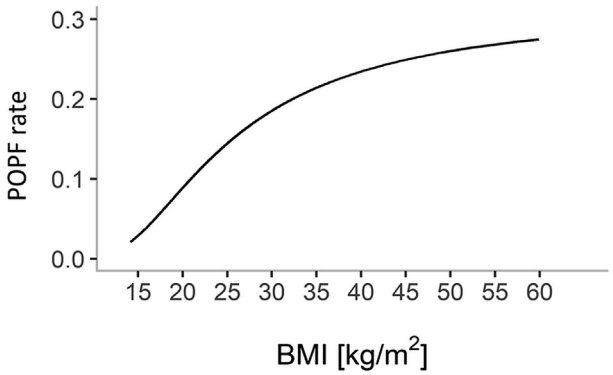


**Fig. 1.** Relationship between POPF B/C and BMI.

$$L = -1.651 - 2.715\frac{100}{BMI^2} + 0.239(soft\ parenchyma) - 0.234(hard\ parenchyma) + 1.470\frac{OP\ time}{1000} - 0.568(PDAC)$$

exp() being the exponential function.

On the training set the AUC was 0.70 (95%CI 0.69–0.70), the calibration slope 1.67 and the intercept 1.12. On the test set the AUC was 0.65 (95% CI 0.64–0.66), the calibration slope 1.22, the intercept 0.42. The calibration is visually presented in Fig. 2.

## Discussion

In the era of precision medicine, estimation and quantification of operative risk is of major importance in surgery. Being able to estimate the operative risk allows for an individual therapy concept but also to develop and target new therapeutics and operative techniques to a specific population at risk as well as for risk adjusted quality assurance.

Postoperative pancreatic fistula has acquired much attention due to its enormous impact on morbidity and mortality in pancreatic surgery. Individual risk factors have been extensively studied and several multivariable models for POPF risk prediction have been published. In this work, we present a novel model, based on a machine learning approach, using logistic regression with bootstrap-enhanced elastic net regularization. By applying this method, we address the problem of parameter reduction and were able to include over 60 preoperative and intraoperative variables in the model.

In the final model only 4 parameters have been selected. Unsurprisingly, one of those parameters is the consistency of the pancreatic parenchyma. In numerous analyses, it has been shown

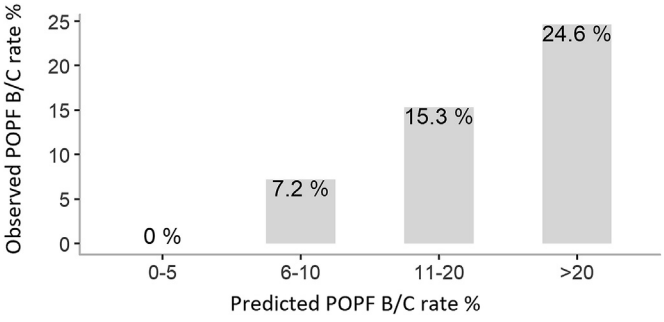


**Fig. 2.** Calibration of the model on the test set.

that soft pancreatic parenchyma is a risk factor for POPF B/C [7,16–18]. The consistency of the pancreatic parenchyma in the StuDoQ|Pancreas dataset has been determined by the surgeon, while palpating the gland intraoperatively. Although subjective, this method has been shown to correlated well with the objective method of measuring the hardness of the pancreas with a durometer [19].

Another predictor parameter in the model is BMI, that also has been shown to correlate with the POPF B/C rate. In some studies, BMI has been categorized according to the World Health Organization definition of obesity with cut-off being set at 25 kg/m$^2$ or 30 kg/m$^2$ [7,17]. Roberts et al. demonstrated an almost linear relationship between BMI and POPF B/C rate [10]. In our dataset a non-linear association describes better the empirical distribution of the data. As could be seen in Table 1, with raising BMI the odds ratios are becoming smaller. The results show, that already being slightly overweight leads to a significant increase in risk for POPF. We conclude that categorizing the parameter BMI might lead to loss of information.

In the model, histological diagnosis PDAC lowers the risk of POPF. In previously published studies PDAC and chronic pancreatitis have been combined in one group versus other pathologies [7,20]. In this study, we considered PDAC and chronic pancreatitis separately and only PDAC was selected in the final model. In accordance, in the univariable analysis POPF B/C rate for PDAC is lower than for chronic pancreatitis, although not statistically significant.

Interestingly, in the univariable analysis the POPF B/C rate for POPF and intraductal papillary mucinous neoplasm (IPMN) was not statistically significant, while that for mucinous cystic neoplasm (MCN) and serous cystic neoplasm (SCN) is much higher. Thus, whenever looking at the histological diagnosis as a risk factor for POPF, IPMN and other cystic lesions as well as PDAC and chronic pancreatitis should be considered separately.

Operation time was also selected by the model and there is an almost linear association between POPF B/C rate and operation time that is highly significant ($p < 0.001$), although the effect size is not large with odds ratio 1.164 for each hour of operation duration. Operation time mirrors the complexity of the operation as well as the experience of the surgical team and these are factors that might influence the risk of POPF. Other studies also demonstrated prolonged operation time as risk factor for POPF [3,21].

The model showed moderate discrimination with AUC = 0.70 on training set and AUC = 0.65 on the test set. The calibration slope and intercept on the training set show slight underfitting, presumably because of the elastic net regularization. On the test dataset, the slope of 1.22 and intercept 0.42 are much nearer to the perfect calibration with slope 1 and intercept 0. Some parameters like anastomosis technique and stent of the main pancreatic duct, that have been linked to POPF, were included but not selected in the final model equation. Previous studies on those parameters have shown controversial results about the effect of either pancreatogastrostomy versus pancreatojejunostomy and pancreatic duct stenting on POPF rate so our results are not surprising [16,22–24]. Other parameters like the use of somatostatin and the drainage use and management, that might alter the incidence and course of POPF, were not available, Yet, encompassing postoperative interventions such as drainage duration or somatostatin in a predictive model will require a much more complex dynamic risk model that considers also the time course of the POPF diagnosis, which is beyond the scope of the current study.

The model has the limitation that it uses the POPF definition from 2005 which is due to the retrospective nature of the study and data from 2014 to 2016. Furthermore, redefining Grade B and Grade C POPF according to the 2016 definition has been shown not to be

straightforward [25]. Since Grade B and C were combined as a target variable for the model, we do not expect any significant difference in the performance of our prediction model, when applied to data with the 2016 POPF-definition. Due to the relatively small case number of 2488 and splitting according to year of the operation, the splitting of the dataset might influence the results. The descriptive statistics show that both data sets are balanced, so we do not expect considerable influence. Furthermore, the test and training datasets were imputed separately to preserve their independence.

Comparing the current StuDoQ|Pancreas-based POPF prediction model to other well-established models like the Fistula Risk Score [20], the NSQIP-modified risk score [7], the POPF risk score of Roberts et al. [10] or the recently published alternative fistula risk score of Mungroop et al. [18], it contains similarly only a few easily available parameters. The current model does not involve the parameter diameter of the main pancreatic duct, which is a categorical variable in the FRS and NSQIP-modified risk score and continuous variable in the models of Roberts et al. and Mungroop et al. Thus, the current model allows estimation of POPF risk even when diameter of the main pancreatic duct is not available, which might be the case especially in retrospective studies und risk adjustment for quality assurance. The discrimination with AUC=0.70 and AUC=0.65 on the train and test set, respectively, are similar to those of the Fistula Risk Score [20] with AUC=0.716 on multicenter validation [26] and the NSQIP-modified risk score [7] with AUC = 0.70 and AUC =0.62 on train and test set, respectively. Yet those measures refer to different datasets and thus are not directly comparable. Because of the structure of the StuDoQ|Pancreas the FRS and the NSQIP-modified FRS cannot be applied to our dataset. Thus, a direct comparison of the performance scores on the current data set was not possible. Using elastic net, multiple imputation and bootstrapping we used a robust method, allowing for the primary inclusion of many parameters without the need of preselection and addressing the problem of multicollinearity. We detected non-linear associations in the case of BMI, a novel feature, that allows for more precise risk stratification.

## Conclusion

In conclusion, the model presented here is a valid measurement tool for POPF risk. It can be applied to guide the decision for surgery, drainage management, risk adjustment in research studies as well as quality assurance in surgery.

## Conflicts of interest

T. Keck and U. F. Wellner are members of the steering committee of StuDoQ|Pancreas.

## Acknowledgements

None.

## Appendix A

**Table A1**
Descriptive analysis of training and test sets and univariable analysis of association of POPF with selected parameters in the training set.

| Parameter | N (%*)/median (range) | | Univariable Analysis | |
|---|---|---|---|---|
| | Training set | Test set | OR (95% CI) | p value |
| **sex** | | | | |
| female | 700 (41.9) | 367 (44.9) | | |
| male | 971 (58.1) | 450 (55.1) | 1.38 (1.04–1.84) | 0.026 |
| missing (%**) | 0 | 0 | | |
| **age [years]** | 67.0 (20.0–88.0) | 67.0 (23.0–88.0) | 0.99 (0.98–1.01) per year | 0.399 |
| missing (%**) | 4 (0.2) | 2 (0.2) | | |
| **BMI [kg/m$^2$]** | 25.0 (12.8–59.9) | 24.9 (14.3–51.7) | | 0.001 |
| 20 to 25 | | | 1.73 (1.35–2.21) | |
| 26 to 30 | | | 1.35 (1.18–1.54) | |
| 31 to 35 | | | 1.20 (1.10–1.30) | |
| 36 to 40 | | | 1.12 (1.07–1.18) | |
| 41 to 45 | | | 1.08 (1.05–1.12) | |
| 45 to 50 | | | 1.06 (1.03–1.09) | |
| missing (%**) | 7 (0.4) | 2 (0.2) | | |
| **ASA score** | | | | |
| I | 105 (6.3) | 42 (5.1) | | |
| II | 781 (46.9) | 384 (47.0) | 1.36 (0.70–2.63) | 0.359 |
| III | 752 (45.2) | 376 (46.0) | 1.54 (0.80–2.96) | 0.199 |
| IV-V | 27 (1.6) | 15 (1.8) | 1.97 (0.62–6.27) | 0.252 |
| missing (%**) | 6 (0.4) | 0 | | |
| **need of care** | | | | |
| 30 days prior surgery | | | | |
| no (Karnosky Index $\geq$ 70%) | 1560 (94.3) | 772 (94.7) | | |
| yes (Karnosky Index $\leq$ 60%) | 95 (5.7) | 43(5.3) | 1.87 (1.14–3.08) | 0.014 |
| missing (%**) | 6 (1.0) | 2 (0.2) | | |
| **weight loss** | | | 0.82 (0.59–1.15) | 0.248 |
| >10% within 6 months prior surgery | | | | |
| no | 1208 (75.4) | 615 (77.3) | | |
| yes | 395 (24.6) | 181 (22.7) | | |
| missing (%**) | 68 (4.1) | 21 (2.6) | | |
| **alcohol abuse** | | | 1.34 (0.86–2.09) | 0.189 |
| within a year prior surgery | | | | |
| no | 1513 (91.0) | 744 (91.2) | | |

(*continued on next page*)

**Table A1** (*continued*)

| Parameter | N (%*)/median (range) | | Univariable Analysis | |
|---|---|---|---|---|
| | Training set | Test set | OR (95% CI) | p value |
| yes | 149 (9.0) | 72 (8.8) | | |
| missing (%**) | 9 (0.5) | 1 (0.1) | | |
| **smoking** | | | | |
| no | 980 (81.1) | 579 (83.7) | | |
| yes | 135 (11.2) | 68 (9.8) | 1.21 (0.74–1.97) | 0.443 |
| abstinence >1 year | 94 (7.8) | 45 (6.5) | 1.58 (0.96–2.60) | 0.069 |
| missing (%**) | 462 (27.6) | 125 (15.3) | | |
| **history of cerebrovascular event** | | | | |
| no | 1575 (94.6) | 781 (95.6) | | |
| yes | 90 (5.4) | 36 (4.4) | 2.00 (1.21–3.31) | 0.007 |
| missing (%**) | 6 (0.4) | 0 (0.0) | | |
| **heart failure** | | | | |
| no | 1418 (85.2) | 735 (90.0) | | |
| NYHA I | 94 (5.6) | 30 (3.7) | 1.82 (1.14–2.90) | 0.012 |
| NYHA II | 100 (6.0) | 36 (4.4) | 1.19 (0.68–2.08) | 0.543 |
| NYHA III-IV | 29 (1.8) | 12 (1.5) | 1.04 (0.36–3.05) | 0.939 |
| NYHA unknown | 23 (1.4) | 4 (0.5) | | |
| missing (%**) | 7 (0.4) | 0 (0.0) | | |
| **arterial hypertension** | | | | |
| no | 717 (43.0) | 400 (49.0) | | |
| yes | 950 (57.0) | 417 (51.0) | 1.16 (0.88–1.54) | 0.286 |
| missing (%**) | 4 (0.2) | 0 (0.0) | | |
| **platelet aggregation inhibitors** | | | | |
| not paused prior surgery | | | | |
| none | 1367 (82.3) | 667 (81.6) | | |
| ASS | 206 (12.4) | 114 (14.0) | 1.38 (0.94–2.04) | 0.101 |
| other | 87 (5.3) | 36 (4.4) | 1.53 (0.88–2.67) | 0.129 |
| missing (%**) | 11 (0.7) | 0 (0.0) | | |
| **coronary arterial disease** | | | | |
| no | 1455 (87.4) | 718 (87.9) | | |
| yes | 210 (12.6) | 99 (12.1) | 1.28 (0.87–1.89) | 0.216 |
| missing (%**) | 6 (0.4) | 0 (0.0) | | |
| **peripheral artery disease** | | | | |
| no | 1623 (97.5) | 801 (98.0) | | |
| yes | 42 (2.5) | 16 (2.0) | 0.62 (0.22–1.74) | 0.360 |
| missing (%**) | 6 (0.4) | 0 (0.0) | | |
| **COPD** | | | | |
| no | 1580 (94.8) | 787 (96.3) | | |
| yes | 86 (5.2) | 30 (3.7) | 1.07 (0.58–1.97) | 0.826 |
| missing (%**) | 5 (0.3) | 0 (0.0) | | |
| **Corticosteroids** | | | | |
| ≥ 7,5 mg prednisolon/day >6 mo until at least 3 mo prior surgery | | | | |
| no | 1649 (99.0) | 803 (98.3) | | |
| yes | 17 (1.0) | 14 (1.7) | 1.83 (0.59–5.67) | 0.294 |
| missing (%**) | 5 (0.3) | 0 (0.0) | | |
| **other immunosuppressive therapy** | | | | |
| until at least 3 mo prior surgery | | | | |
| no | 1647 (98.9) | 809 (99.0) | | |
| yes | 18 (1.1) | 8 (1.0) | 2.30(0.81–6.52) | 0.117 |
| missing (%**) | 6 (0.4) | 0 (0.0) | | |
| **diabetes mellitus** | | | | |
| no | 1246 (74.8) | 613 (75.0) | | |
| NIDDM | 222 (13.3) | 103 (12.6) | 0.90(0.60–1.37) | 0.624 |
| IDDM | 197 (11.8) | 101 (12.4) | 0.83(0.53–1.30) | 0.414 |
| missing (%**) | 6 (0.4) | 0 (0.0) | | |
| **new onset diabetes** | | | | |
| no | 1611 (96.8) | 783 (95.8) | | |
| yes | 53 (3.2) | 34 (4.2) | 0.47 (0.17–1.33) | 0.154 |
| missing (%**) | 7 (0.4) | 0 (0.0) | | |
| **history of acute pancreatitis** | | | | |
| no | 1507 (90.6) | 753 (92.2) | | |
| yes | 157 (9.4) | 64 (7.8) | 0.96 (0.60–1.54) | 0.863 |
| missing (%**) | 7 (0.4) | 0 (0.0) | | |
| **history of chronic pancreatitis** | | | | |
| no | 1432 (86.1) | 716 (87.6) | | |
| yes | 232 (13.9) | 101 (12.4) | 0.50 (0.30–0.81) | 0.005 |
| missing (%**) | 6 (0.4) | 0 (0.0) | | |
| **disseminated malignant disease** | | | | |
| no | 1622 (97.5) | 797 (97.6) | | |
| yes | 41 (2.5) | 20 (2.4) | 1.45 (0.66–3.17) | 0.356 |
| missing (%**) | 8 (0.5) | 0 (0.0) | | |
| **liver cirrhosis** | | | | |
| no | 1617 (97.7) | 798 (98.2) | | |
| yes | 38 (2.3) | 15 (1.8) | 1.10 (0.46–2.67) | 0.827 |

**Table A1** (*continued*)

| Parameter | N (%*)/median (range) | | Univariable Analysis | |
|---|---|---|---|---|
| | Training set | Test set | OR (95% CI) | p value |
| missing (%**) | 16 (1.0) | 4 (0.5) | | |
| **ascites** | | | | |
| no | 1633 (98.3) | 806 (98.7) | | |
| yes | 29 (1.7) | 11 (1.3) | 0.43 (0.10–1.83) | 0.256 |
| missing (%**) | 9 (0.5) | 0 (0.0) | | |
| **icterus** | | | | |
| no | 1256 (75.2) | 711 (87.0) | | |
| yes | 415 (24.8) | 106 (13.0) | 0.82 (0.59–1.14) | 0.227 |
| missing (%**) | 0 | 0 | | |
| **nausia** | | | | |
| no | 1333 (79.8) | 629 (77.0) | | |
| yes | 338 (20.2) | 188 (23.0) | 1.23 (0.89–1.71) | 0.211 |
| missing (%**) | 0 | 0 | | |
| **emesis** | | | | |
| no | 1533 (91.7) | 749 (91.7) | | |
| yes | 138 (8.3) | 68 (8.3) | 1.02 (0.62–1.68) | 0.936 |
| missing (%**) | 0 | 0 | | |
| **Pain** | | | | |
| no | 1047 (62.7) | 489 (59.9) | | |
| yes | 624 (37.3) | 328 (40.1) | 1.03 (0.77–1.36) | 0.857 |
| missing (%**) | 0 | 0 | | |
| **radio-/chemotherapy** | | | | |
| within 3 mo prior surgery | | | | |
| none | 1611 (96.8) | 793 (97.1) | | |
| chemotherapy | 29 (1.7) | 18 (2.2) | 0.94(0.33–2.73) | 0.913 |
| radio-/chemotherapy | 24 (1.5) | 6 (0.7) | 0.84 (0.25–2.85) | 0.781 |
| missing (%**) | 7 (0.4) | 0 (0.0) | | |
| **DHC stent** | | | | |
| no | 1082 (65.1) | 541 (66.2) | | |
| yes | 581 (34.9) | 276 (33.8) | 1.07(0.80–1.42) | 0.656 |
| missing (%**) | 8 (0.5) | 0 (0.0) | | |
| **Septic cholangitis** | | | | |
| 48 h prior to surgery | | | | |
| no | 1608 (96.7) | 797 (97.6) | | |
| yes | 55 (3.3) | 20 (2.4) | 0.73 (0.31–1.73) | 0.477 |
| missing (%**) | 8 (0.5) | 0 (0.0) | | |
| **hemoglobin** | 13.0 (6.3–19.3) | 12.9 (6.5–17.9) | 1.11 (1.02–1.20) per 1 g/dl increase | 0.011 |
| missing (%**) | 23 (1.4) | 36 (4.4) | | |
| **white blood cell count [1000/μl blood]** | 7.0 (2.5–39.0) | 7.2 (2.2–35.0) | 1.03 (0.99–1.18) per 1000/μl increase | 0.129 |
| missing (%**) | 53 (3.2) | 48 (5.9) | | |
| **creatinine [mg/dl]** | 0.8 (0.1–4.8) | 0.8 (0.1–4.9) | | 0.204 |
| **1 to 1.5 mg/dl** | | | 1.12 (0.92–1.37) | |
| **1.5 to 2 mg/dl** | | | 0.91(0.78–1.06) | |
| missing (%**) | 51 (3.1) | 56 (6.9) | | |
| **bilirubin [mg/dl]** | 0.9 (0.1–46.1) | 1.0 (0.1–43.0) | 0.92 (0.68–1.24) per 10 mg/dl increase | 0.576 |
| missing (%**) | 289 (17.3) | 103 (12.6) | | |
| **albumin [g/dl]** | 4.0 (0.4–9.1) | 4.0 (0.3–8.9) | 0.20 (0.01–4.01) per 10 mg/dl increase | 0.249 |
| missing (%**) | 783 (46.9) | 437 (53.5) | | |
| **amylase [U/l]** | 51.0 (0.1–3720.0) | 48.0 (1.4–1166.0) | 0.96 (0.84–1.10) per 100 U/l increase | 0.542 |
| missing (%**) | 764 (45.7) | 416 (50.9) | | |
| **lipase [U/l]** | 67.1 (0.0–9304.0) | 66.0 (3.0–9999.0) | 0.99 (0.96–1.03) per 100 U/l increase | 0.667 |
| missing (%**) | 492 (29.4) | 270 (33.0) | | |
| **AP [U/l]** | 149.5 (1.0–6972.0) | 165.0 (5.7–1895.0) | 0.99(0.85–0.97) per 100 U/dl increase | 0.029 |
| missing (%**) | 269 (16.1) | 159 (19.5) | | |
| **γ-GT [U/l]** | 149.0 (0.1–4576.0) | 174.0 (0.1–2628.0) | 0.85 (0.63–1.15) per 1000 U/dl increase | 0.299 |
| missing (%**) | 221 (13.2) | 137 (16.8) | | |
| **CRP [mg/l]** | 5.0 (0.0–660.0) | 4.9 (0.0–302.0) | 1.01 (0.97–1.06) per 10 mg/l increase | 0.555 |
| missing (%**) | 287 (17.2) | 167 (20.4) | | |
| **histological diagnosis** | | | | |
| PDAC | 836 (50.4) | 404 (49.6) | | |
| ampullary carcinoma | 138 (8.3) | 74 (9.1) | 3.06 (1.93–4.87) | <0.001 |
| DBDC | 115 (6.9) | 65 (8.0) | 2.41 (1.42–4.06) | 0.001 |
| duodenal carcinoma | 46 (2.8) | 21 (2.6) | 2.43 (1.13–5.23) | 0.024 |
| IPMN/invasive IPMN | 104 (6.3) | 39 (4.8) | 1.71 (0.94–3.11) | 0.077 |
| MCN/SCN | 24 (1.5) | 13 (1.6) | 6.35 (2.68–15.04) | <0.001 |
| NET/cystic NET | 76 (4.6) | 37 (4.5) | 2.43 (1.29–4.57) | 0.006 |
| chronic pancreatitis | 157 (9.5) | 64 (7.9) | 1.49 (0.88–2.53) | 0.140 |
| benign lesion | 48 (2.9) | 35 (4.3) | 4.67 (2.42–9.01) | <0.001 |
| other | 114 (6.9) | 63 (7.7) | 3.16 (1.94–5.15) | <0.001 |
| missing (%**) | 13 (0.8) | 2 (0.2) | | |
| **emergency operation** | | | | |
| yes | 26 (1.6) | 12 (1.5) | | |
| no | 1644 (98.4) | 805 (98.5) | 0.45(0.19–1.09) | 0.076 |

(*continued on next page*)

**Table A1** (*continued*)

| Parameter | N (%*)/median (range) | | Univariable Analysis | |
|---|---|---|---|---|
| | Training set | Test set | OR (95% CI) | p value |
| missing (%**) | 1 (0.1) | 0 (0.0) | | |
| **operation type** | | | | |
| PPPD | 1139 (68.2) | 492 (60.2) | | |
| Whipple | 532 (31.8) | 325 (39.8) | 1.27(0.95–1.69) | 0.104 |
| missing (%**) | 0 (0.0) | 0 (0.0) | | |
| **access technique** | | | | |
| open | 1540 (92.7) | 775 (95.3) | | |
| laparoscopic | 51 (3.1) | 7 (0.9) | 0.86 (0.36–2.07) | 0.723 |
| laparoscopic-assisted | 41 (2.5) | 23 (2.8) | 1.24 (0.54–2.82) | 0.616 |
| laparoscopic with conversion | 29 (1.7) | 8 (1.0) | 1.91(0.81–4.53) | 0.142 |
| missing (%**) | 10 (0.6) | 4 (0.5) | | |
| **portal vein resection** | | | | |
| no | 1516 (90.7) | 715 (87.5) | | |
| yes | 155 (9.3) | 102 (12.5) | 0.56 (0.32–0.99) | 0.046 |
| missing (%**) | 0 (0.0) | 0 (0.0) | | |
| **colon resection** | | | | |
| no | 1636 (97.9) | 806 (98.7) | | |
| yes | 35 (2.1) | 11 (1.3) | 0.98 (0.38–2.57) | 0.974 |
| missing (%**) | 0 (0.0) | 0 (0.0) | | |
| **liver resection** | | | | |
| no | 1637 (98.0) | 801 (98.0) | | |
| yes | 34 (2.0) | 16 (2.0) | 0.78 (0.27–2.25) | 0.651 |
| missing (%**) | 0 (0.0) | 0 (0.0) | | |
| **intestinal resection** | | | | |
| no | 1627 (97.4) | 790 (96.7) | | |
| yes | 44 (2.6) | 27 (3.3) | 0.75 (0.29–1.93) | 0.554 |
| missing (%**) | 0 (0.0) | 0 (0.0) | | |
| **gastric resection** | | | | |
| (other than antrectomy as part of the Whipple procedure) | | | | |
| no | 1620 (96.9) | 789 (96.6) | | |
| yes | 51 (3.1) | 28 (3.4) | 0.64 (0.25–1.62) | 0.340 |
| missing (%**) | 0 (0.0) | 0 (0.0) | | |
| **lymphadenectomy** | | | | |
| none | 81 (5.0) | 29 (3.6) | | |
| standard | 1410 (87.1) | 678 (84.5) | 1.00 (0.53–1.88) | 0.998 |
| extended | 128 (7.9) | 95 (11.8) | 1.04 (0.48–2.27) | 0.917 |
| missing (%**) | 52 (3.1) | 15 (1.8) | | |
| **pancreatic parenchyma** | | | | |
| soft | 773 (46.7) | 396 (48.9) | | |
| hard | 491 (29.7) | 231 (28.6) | 0.32 (0.22–0.47) | <0.001 |
| unknown | 391 (23.6) | 182 (22.5) | | |
| missing (%**) | 16 (1.0) | 8 (1.0) | | |
| **MPD** | | | | |
| <3 | 661 (39.9) | 344 (42.5) | | |
| >=3 | 535 (32.3) | 223 (27.6) | 0.62 (0.42–0.91) | 0.017 |
| not measured | 462 (27.9) | 242 (29.9) | | |
| missing (%**) | 13 (0.8) | 8 (1.0) | | |
| **transection of the pancreas** | | | | |
| scalpel | 769 (47.4) | 353 (44.1) | | |
| stapler | 55 (3.4) | 30 (3.6) | 1.46 (0.69–3.11) | 0.325 |
| LigaSure© | 48 (3.0) | 40 (5.0) | 2.22 (1.09–4.51) | 0.028 |
| Ultracision© | 64 (3.9) | 21 (2.6) | 2.57 (1.39–4.76) | 0.003 |
| bipolar | 51 (3.1) | 18 (2.2) | 2.07 (1.03–4.19) | 0.042 |
| monopolar | 581 (35.8) | 290 (36.2) | 1.35 (0.98–1.86) | 0.070 |
| ultrasounddissector | 56 (3.4) | 49 (6.1) | 2.30 (1.19–4.45) | 0.013 |
| missing (%**) | 47 (2.8) | 16 (2.0) | | |
| **Pancreatic anastomosis** | | | | |
| Pancreaticojejunostomy | 1345 (81.3) | 662 (81.6) | | |
| Pancreatogastrostomy | 290 (17.5) | 141 (17.4) | 1.32 (0.94–1.85) | 0.113 |
| missing (%**) | 16 (1.0) | 6 (0.7) | | |
| **MPD stent** | | | | |
| no | 1318 (79.6) | 642 (79.2) | | |
| yes | 338 (20.4) | 169 (20.8) | 1.32 (0.96–1.82) | 0.091 |
| missing (%**) | 15 (0.9) | 6 (0.7) | | |
| **duct-to-mucosa anastomosis** | | | | |
| no | 636 (38.7) | 296 (36.6) | | |
| yes | 1008 (61.3) | 512 (63.4) | 0.85 (0.64–1.12) | 0.237 |
| missing (%**) | 27 (1.6) | 9 (1.1) | | |
| **suture enhancement** | | | | |
| none | 1434 (87.0) | 686 (85.2) | | |
| fibrin | 38 (2.3) | 8 (1.0) | 0.67 (0.24–1.91) | 0.456 |
| Tachosil© | 36 (2.2) | 8 (1.0) | 2.19 (1.04–4.62) | 0.040 |
| seromuscular patch/Ligamentum terres hepatis patch | 22 (1.2) | 19 (2.4) | 0.29 (0.04–2.17) | 0.227 |
| omental patch | 65 (3.9) | 47 (5.8) | 0.60 (0.26–1.41) | 0.243 |

**Table A1** (*continued*)

| Parameter | N (%*)/median (range) | | Univariable Analysis | |
|---|---|---|---|---|
| | Training set | Test set | OR (95% CI) | p value |
| other | 54 (3.3) | 37 (4.6) | 0.71 (0.30–1.68) | 0.436 |
| missing (%**) | 22 (1.3) | 12 (1.5) | | |
| **antibiotics perioperative** | | | | |
| no | 74 (4.4) | 36 (4.4) | | |
| yes | 1589 (95.6) | 779 (95.6) | 1.42 (0.67–2.99) | 0.362 |
| missing (%**) | 8 (0.5) | 2 (0.2) | | |
| **RBC concentrates** | 0 (0–9) | 0 (0–10) | 0.87 (0.71–1.05) | 0.147 |
| missing (%**) | 20 (1.2) | 3 (0.4) | | |
| **Operation time [min]** | 318.0 (107.0–875.0) | 326.0 (74.0–823.0) | 1.16 (1.08–1.26) per 60 min | <0.001 |
| missing (%**) | 2 (0.1) | 2 (0.2) | | |
| **30-day-mortality %** | 3.4 | 2.7 | | |
| missing (%**) | 12 (0.7) | 1 (0.1) | | |

AP - alkaline phosphatase, ASA – American Society of Anesthesiologists, ASS - acetylsalicylic acid, BMI - body mass index, COPD - chronic obstructive disease, CRP – c-reactive protein, DBDC - distal bile duct carcinoma, DHC – ductus hepatocholedochus, γ-GT - γ-glutamyltransferase, IDDM - insulin-dependent diabetes mellitus, IPMN - intraductal papillary mucinous neoplasm, mo. – months, MPD – main pancreatic duct, MCN - mucinous cystic neoplasm, NET-neuroendocrine tumor, NIDDM – non-insulin dependent diabetes mellitus, PDAC- pancreatic ductal adenocarcinoma, POPF – postoperative pancreatic fistula, RBC - red blood cells, SCN – serous cystic neoplasm.
*- Percentage of non-missing.
**- Percentage of total.

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