



UNIVERSITA' DEGLI STUDI DI VERONA

DEPARTMENT OF SURGERY, DENTISTRY, PAEDIATRICS AND GYNAECOLOGY

DOCTORAL PROGRAM IN SURGICAL AND CARDIOVASCULAR SCIENCES

With the financial contribution of Pederzoli Hospital, Peschiera del Garda, Verona

XXXVII Cycle

**USE OF ARTIFICIAL INTELLIGENCE FOR RISK PREDICTION OF
POSTOPERATIVE COMPLICATION AFTER PANCREATODUODENECTOMY**

S.S.D. MED/18

Coordinator: Prof. Ruzzenente Andrea

Tutor: Prof. Ruzzenente Andrea, Dr. Butturini Giovanni, Dr. Giardino Alessandro

Doctoral Student: Dr. Tripepi Marzia

A handwritten signature in black ink, appearing to be 'M. Tripepi', written in a cursive style.

SOMMARIO

Introduzione: Nonostante i progressi nella gestione clinica e chirurgica, l'incidenza di complicanze dopo chirurgia pancreaticata rimane ancora alta (attestandosi attorno al 40-50%).

La morbilità postoperatoria può associarsi ad un prolungamento della degenza ospedaliera, ad un incremento della mortalità postoperatoria, ad un peggioramento della qualità di vita, ad un incremento dei costi ospedalieri ed infine anche ad un peggioramento degli esiti oncologici anche in conseguenza di un ritardo nell'erogazione della chemioterapia adiuvante.

Numerosi studi hanno indagato il rischio di sviluppare complicanze postoperatorie e sono stati elaborati differenti score predittivi per stratificare i pazienti in virtù del rischio di morbilità e mortalità postoperatoria. Tuttavia, questi score predittivi sono stati sviluppati mediante la statistica tradizionale che si basa su interazioni lineari tra variabili, contrariamente alle comorbidità e alle variabili che, nella pratica clinica, possono interagire tra loro anche in modalità differenti da quella lineare.

Al contrario, l'intelligenza artificiale e l'apprendimento automatico, grazie alla combinazione di un vasto numero di variabili in una interazione non lineare, può essere superiore alla statistica tradizionale nel predire gli esiti postoperatori.

Lo scopo principale del nostro studio è stato quello di indagare, mediante l'intelligenza artificiale, le variabili preoperatorie che possono predire lo sviluppo di complicanze postoperatorie dopo duodenocefalopancreasectomia (DCP) per patologia benigna e maligna e sviluppare un calcolatore in grado di definire per ciascun paziente il rischio reale di sviluppare almeno una complicanza postoperatoria dopo DCP.

Materiali e Metodi: nello studio sono stati inclusi 496 pazienti che sono stati sottoposti a DCP per patologia benigna e maligna presso il dipartimento di chirurgia epatobiliopancreatica dell'Ospedale Pederzoli (Peschiera del Garda, Verona) tra il 2011 ed il 2022.

È stato sviluppato un modello mediante il metodo della foresta casuale "random forest" per predire il rischio di sviluppare almeno una complicanza postoperatoria

dopo DCP. La popolazione dello studio è stata suddivisa in una coorte di addestramento (80%) ed una coorte di validazione (20%).

Risultati: il modello è risultato valido sia nella coorte di addestramento (AUC=0.87) che nella coorte di validazione (AUC=0.72). Le dodici variabili più influenti sono risultate: il dotto pancreatico dilatato, la perdita di peso superiore al 10% prima della chirurgia, la diagnosi di lesione cistica, il diabete, la pregressa chirurgia addominale, il livello sierico preoperatorio di CA 19.9, gli elevati livelli di bilirubina, la chemioterapia neoadiuvante, i dotti biliari dilatati, lo score ASA, l'approccio chirurgico e le diagnosi classificate come "altre" (GIST, groove pancreatitis, tumori duodenali).

Sulla base dell'algoritmo è stato sviluppato un calcolatore chiamato "PanRisk Calculator", disponibile online e facile da usare nella pratica clinica quotidiana.

Conclusioni: la predizione mediante intelligenza artificiale dello sviluppo di complicanze postoperatorie può contribuire a migliorare il planning preoperatorio, mettere in atto strategie postoperatorie di mitigazione delle complicanze e di conseguenza a migliorare gli esiti postoperatori.

ABSTRACT

Introduction: Despite advances in medical management, the incidence of complications after pancreatic surgery remains still high (between 40% to 50%). Morbidity could lead to a longer length of hospital stay, higher mortality, worse quality of life, higher hospital cost, and finally worsen oncologic outcome also in consequence of delay of adjuvant therapy.

Several studies have tried to investigate the preoperative risk of surgical complication and a lot of predictive scores have been proposed to stratify a patient's risk of postoperative morbidity and mortality; however, this predictive score has been developed with standard statistical methods, considering that the variables interact in a linear and additive fashion linear while the interaction of comorbidities and markers of disease could be different from linear.

Conversely, machine learning, thanks to the combination of a vast number of variables in a non-linear way, may be superior to the standard statistical methods currently used by clinicians to predict the postoperative outcome.

Our primary end point was to investigate through artificial intelligence the preoperative fields that could affect postoperative outcome after pancreaticoduodenectomy for benign and malignant disease and develop a calculator that can define the real risk of any postoperative complication for each patient candidate to pancreaticoduodenectomy.

Material and methods: 496 patients who underwent pancreaticoduodenectomy for benign and malignant tumors between 2011 and 2022 at the Department of Hepato-pancreatobiliary Surgery, Pederzoli Hospital (Peschiera del Garda, Verona) were retrospectively collected from a prospectively maintained database.

A random forest model was developed to predict the risk of any postoperative complication after pancreaticoduodenectomy. The study population has been divided in training cohort (80%) and a testing cohort (20%).

Results: The primary model evaluation metric was the area under the receiver operating characteristic curve (ROC-AUC) that was good as for training cohort (AUC= 0.87) as for testing cohort (AUC=0.72). The twelve most influential variables were dilated pancreatic duct, weight loss >10% prior to surgery, diagnosis

of cystic lesion, diabetes, previous abdominal surgery, preoperative CA 19.9 serum level, high bilirubin level, preoperative chemotherapy, dilated bile duct, ASA Score, Surgical Approach and “Other diagnosis” (GIST, groove pancreatitis, duodenal tumor).

A calculator called "PanRisk Calculator" has been developed based on the algorithm, which is available online and it is easy to use in daily clinical practice.

Conclusion: Preoperative machine learning prediction of the development of any postoperative complication may improve preoperative planning, postoperative mitigation strategy, and, subsequently, patient outcomes.

INDEX

SUMMARY.....	pag. 3
ABSTRACT.....	pag. 4
INTRODUCTION.....	pag. 7
MATERIALS AND METHODS.....	pag. 17
STATISTICAL ANALYSIS.....	pag. 21
RESULTS.....	pag. 22
DISCUSSION.....	pag. 31
CONCLUSIONS.....	pag. 38
REFERENCES.....	pag. 39

INTRODUCTION

Pancreatic surgery remains among the most complex general surgical procedures. Advances in medical management, improvements in patients' selection, as well as centralization of high-risk operation at high-volume hospitals have allowed a reduction in postoperative mortality, although the incidence of complications after pancreatic surgery remains still high (between 40% to 50%).(1-4)

Postoperative pancreatic fistula (POPF) and delayed gastric emptying (DGE) are the two most common, high-impact complications after pancreatoduodenectomy.(5, 6)

Postoperative complications are deleterious events for patients, impacting length of hospital stay (LOS) and perioperative mortality, reducing patient's quality of life, as well as increasing hospital costs.(4, 7-11)

Moreover, among patients with cancer, the occurrence of postoperative complication has been correlated with a worse recurrence free survival and worse overall survival.

In addition, the development of complication after surgery in cancer patients could cause an omission or delays in adjuvant chemotherapy following surgery. A study of American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) and the National Cancer Data Base (NCDB), collecting 2047 patients from 149 hospitals who underwent resection for stage I-III pancreatic adenocarcinoma showed a 23.2% rate of at least one serious complication. Moreover, the rate of adjuvant chemotherapy among patients free from complication was higher (61.8%) than among those who experienced a serious complication (43.6%) which can lead to a delay in adjuvant treatment administration (OR = 2.08, 95% CI: 1.42-3.05). (12)

The causes of complications after surgery are multifactorial with many studies reporting patient-, disease-, and even social- specific factors that influence the risk of morbidity. (4, 13-17) Furthermore, it is frequently observed in clinical practice that when multiple risk factors are present simultaneously in the same patient, their effects can be synergistic, significantly increasing the likelihood of complications (18-20). Some of risk factor for the development of postoperative complications

after pancreaticoduodenectomy commonly described in the literature may involve patient comorbidities already present preoperatively, such as malnutrition, cardiovascular disease or smoking, whereas others are typically disease-related and become evident intraoperatively, such as soft pancreatic texture, small pancreatic duct diameter, or adverse events as bleeding. Some other depends on surgical techniques or medical management. (i.e. type of pancreatic reconstruction, hospital and surgeon volume, nurse practice).(21)

Most efforts have been concentrated on managing complications once they have occurred postoperatively although anticipation of potentially severe complications and early detection of patients at risk represent another valuable strategy.

Both patients and clinicians would benefit from an accurate prediction of postoperative complication.(22) Accurately predicting the risk of a postoperative complication in the preoperative setting would allow an adequate selection of the patient before surgery and could drive the decision-making process by determining the necessary level of vigilance in the postoperative period favoring early interventions.(22, 23)

Moreover, considering that pancreatic cancer incidence is increasing in many western countries, older patient also undergo surgery, and, luckily, oncological treatments become increasingly available, make it of greatest importance to effectively decrease postoperative morbidity.(21, 24, 25)

As a result, in the literature there has been a growing interest in the prediction, prevention and management of postoperative complications after pancreatic surgery and several studies have tried to investigate the patients preoperative risk of surgical short-term outcome.(8, 12)

Traditional risk calculator

The need to stratify the risk and predict complications based on pre-surgical data have been extensively investigated.

The ASA (American Society of Anesthesiologists) score, one of the first and known worldwide, is an anesthesiologic risk classification based on a score assigned by a clinician following the subjective assessment of a patient's preoperative health.(26) Despite its wide variability determined by the subjectivity of the scoring, and

despite being related only to the patient's health status before surgery, it remains the most used tool for preoperative risk assessment among anesthesiologists.(27)

The ACS NSQIP (American College of Surgeon National Surgical Quality Improvement Program) risk score was proposed to predict patient specific risks of developing eight surgical complications occurring in the thirty postoperative days for more than 2500 surgical procedures. This score was developed using the ACS-NSQIP database including more than 20 preoperative variables (patient demographics and comorbidities) about over 4.3 million operations from 780 hospitals in the USA participating in ACS-NSQIP from 2013 to 2017.

This model showed a good performance in validation studies (c statistics = 0.81–0.94), while the use in clinical practice is limited by the amount of data required.(28)

Over the years, a lot of specific predictive scores have been developed with standard statistical methods to stratify a patient's risk of postoperative morbidity and mortality after pancreatic surgery.(21, 29-43).

Most risk scores try to predict the risk of postoperative pancreatic fistula (POPF), which is the most frequent and the most feared complication following pancreatic resection.

Some authors suggest that the estimation of the risk of developing POPF rely on parameters collected intraoperatively including, for example, the pancreatic gland texture, the diameter of pancreatic duct, blood loss and pathology while some others considered also preoperative data such as CT evaluation of Wirsung duct diameter and the BMI. (30, 33, 44)

The validated Fistula Risk Score (FRS) by Callery et al. predicts POPF based on gland texture, pancreatic duct diameter, intraoperative blood loss and pathology. This is a 10-point risk score where patients with scores of 0 point never showed POPF, while other patients showed an increasing risk of POPF depending on score (low risk:1 to 2 points; intermediate risk:3 to 6 points; high risk:7 to 10 points).(30) Despite the FRS is the most cited and best used POPF prediction model, a modified version has been proposed considering that intraoperative blood loss was found to be not significant in two recent external validation studies and it is often a missing field in big database. (45, 46)

In light of this, Mungroop et colleagues proposed an alternative FRS (a-FRS) using two databases for the model development [Dutch Pancreatic Cancer Audit (18 centers) and the University Hospital Southampton NHS] and other two databases for validation (University Hospital of Verona and University Hospital of Pennsylvania). The resulting “alternative FRS” (a-FRS) included 3 easily available variables (pancreatic texture, duct diameter, BMI) as predictor of POPF after pancreatoduodenectomy. The AUC after external validation was adequate (AUC= 0.78, 95% CI 0.74-0.82)(37)

Successively, the alternative FRS was updated (ua-FRS) including also sex male as risk factor and was validated in 952 patients who underwent pancreaticoduodenectomy with minimally invasive approach (MIPD) in 26 European hospitals, confirming a good discrimination in detecting POPF (AUC = 0.75, 95% CI 0.71–0.79).(41)

Moreover, Petrova et al. conducted a retrospective study on predictive model for POPF, using data from the German Pancreatic Surgery Registry (StuDoQ Pancreas). Among 2488 patients included in the analysis, 1671 (67.2%) were assigned to the training set and 817 (32.8%) to the test set. The optimal predictors selected for the model were texture of the pancreatic parenchyma (soft versus hard), BMI, pancreatic ductal adenocarcinoma and operation time. The AUC was 0.70 (95% CI 0.69-0.70) in the training and 0.65 (95% CI 0.64-0.66) in the validation set.(47)

Similarly, Chen et al. in a study on 921 consecutive patients who underwent PD between 2008 and 2013 proposed a scoring system based on a logistic regression model including body mass index, gland texture, the difference between the blood loss and transfusion and the pancreatic duct diameter.(34)

Differently, other reports proposed a risk score for development of clinically relevant POPF including only preoperative fields.

Yamamoto et colleagues proposed a risk score strictly based on 5 preoperative characteristics of the patient and the pancreatic cancer: main pancreatic duct index (defined as the ratio of the diameter of MPD to the diameter of the short axis of the pancreatic body), proximity of pancreatic lesion from portal vein on computed tomography, type of pancreatic disease, sex, and intra-abdominal thickness. This

scoring system, proved to have good discrimination ability in prediction of POPF in the validation group having a ROC with AUC =0.810.(48)

Roberts et al., in a study on 325 patients who underwent pancreaticoduodenectomy randomly divided into two group (“modelling set” and “validation set”) with a 2:1 ratio elaborated and validated a risk model for POPF including BMI and pancreatic duct width at preoperative CT scan as risk factor.(33)

Pancreatic texture results among the main element cited as risk factor for POPF in predictive risk model even though its evaluation is performed by the surgeon intraoperatively and therefore is subject to a certain individual variability.

In order to preoperatively assess the risk of soft pancreatic texture, Casadei et al., in a retrospective study on 208 patients who underwent pancreatic resection at S.Orsola-Hospital in Bologna, proposed three clinical fields (BMI, Wirsung duct size and coexisting periampullary diseases) as risk factors predictive of soft pancreas using the POPF rate as validating factors.(49).

Knowing preoperatively the extent of the postoperative risk can help the surgeon to better plan the therapeutic process and in case of confirmed indication for surgery can predispose to the implementation of mitigation strategies.

A recent study investigated the true predictive accuracy and generalizability of 14 risk models reported in the literature using a validation cohort that consisted of 1358 patients who underwent pancreatoduodenectomy in the Netherlands between 2018 and 2019, of which 341 (25%) developed a POPF. This study demonstrated that none of the 14 published fistula risk models seem to perform well in a large, nationwide, unselected prospective patient cohort. In line with previous retrospective validation studies, the highest AUC of this validation cohort (AUC= 0.70) was lower than that reported by the original studies.(50-56).

Nevertheless, the poor performance of traditional studies, combined with the wide variety of available risk models and the lack of standardization, makes their application in clinical practice challenging.(50, 57)

Role of Artificial intelligence in preoperative risk assessment

An upcoming technique to develop novel prediction models is machine learning modeling using artificial intelligence (AI).

Machine-learning techniques have been gaining popularity in the field of prediction of postoperative complications as a more comprehensive, “non-linear”, and accurate method to predict patient outcomes.(58)

Among the most widespread AI systems in predicting short-term postoperative outcome there are clinical data analysis systems and those for extrapolating data from the analysis of radiological images.

Clinical data analysis to predict outcome with artificial intelligence (AI)

A lot of studies have proposed risk model developed through the analysis of perioperative clinical data with artificial intelligence.

Bihorac et al. developed a machine learning (ML) algorithm (MySurgeryRisk) using single-center cohort of more than fifty thousand patients undergoing major surgery for predict the risk of postoperative complication and death. The algorithm uses existing clinical data in electronic health records to estimate the risk of developing one of eight major postoperative complications (acute kidney injury, sepsis, venous thromboembolism, intensive care unit admission > 48 hours, mechanical ventilation > 48 hours, wound, neurologic and cardiovascular complications) with AUC values ranging between 0.82 and 0.94 (99% CI 0.81–0.94), and death up to 24 months after surgery, with AUC values ranging between 0.77 and 0.83 (99% CI 0.76–0.85).(59)

Merath et al., using data from the ACS-NSQIP database about 15,657 patients who underwent hepatopancreatic (HP) and colorectal surgery between 2014 and 2016 developed a decision-tree learning algorithm to predict any 30-day postoperative complication as well as seventeen specific postoperative outcomes [incidence of superficial surgical site infection (SSI), deep incisional SSI, pulmonary embolism, organ space SSI, sepsis, wound dehiscence, urinary tract infection, deep vein thrombosis, myocardial infarction, pneumonia, unplanned intubation, stroke, cardiac arrest, septic shock, bleeding requiring transfusion, progressive renal insufficiency, and use of ventilator for > 48 h].This algorithm showed a good

predictive ability for the occurrence of any complication, with a c-statistic of 0.74 and a very high accuracy in predicting occurrence of specific 30-day postoperative complications (c-statistic range from 0.76 to 0.98).(60)

Han et al. proposed a ML algorithms developed through random forest (RF) and a neural network (NN) with or without recursive feature elimination (RFE) using preoperative and intraoperative data from 1769 patients who underwent pancreaticoduodenectomy at a single institution. This algorithm found 16 risk factors for POPF. According to the proposed risk factors, it is possible to individualize 3 macro-groups of risk: the *technically challenging group*, the *intraoperative volume status-related group*, and *poor general condition group*. In detail, the *technically demanding group* include factor potential difficulty in reconstructing the pancreatic-enteric anastomosis such as soft pancreas, small pancreatic duct, extra pancreatic absence of preoperative pancreatitis or low lipase level, absence of preoperative endoscopic biliary decompression, absence of neoadjuvant radiotherapy, and high BMI); the risk factors in the *intraoperative volume status-related group* include causes of dehiscence of the pancreatic enteric anastomosis in consequence of oedema and ischemia (large intraoperative fluid administration, concomitant portal vein-superior mesenteric vein resection, and low platelet count) and finally *the poor general condition group* include the presence of comorbidity and poor nutritional status (old age, underlying heart disease, low preoperative serum albumin level, and low ASA score). This algorithm showed a maximum AUC of 0.74.(61)

Sahara et al., developed a machine learning model to estimate the risk of “unpredicted death” (UD) among patients undergoing hepatopancreatic (HP) with a low estimated morbidity and mortality risk based on the NSQIP estimated probability (EP).

According to this decision tree model, patients age was noted to be the most important factor to predict UD after pancreatectomy, followed by preoperative albumin level, vascular resection and bleeding disorder. The model accuracy in prediction of UD after hepatopancreatic surgery among “low risk patients” of NSQIP EP was good with an AUC 0.807 compared with an AUC of only 0.662 for the NSQIP EP ($p < 0.001$). (62)

Preoperative imaging analysis to predict outcome with AI

AI has been also used for recognizing important features of pancreatic texture associated with an increased risk of POPF based on preoperative computed tomography.

Kambakamba et al. examined preoperative CT scan of 110 patients from a single institution and found that machine learning-based CT analysis provided an accurate prediction of the occurrence of clinically relevant POPF through pancreatic texture analysis (AUC= 0.95).(63)

Mu et colleagues, generated a deep-learning score (DLS) through a neural network able to identify the patients with higher risk of CR-POPF preoperatively using CT scan images. This score was firstly externally tested in a single center prospective cohort and successively was apply in a group of 513 patients underwent pancreaticoduodenectomy at three institutions which formed a training (70%) and a validation cohort (30%) randomly. The deep learning score offered significantly greater predictability compared to FRS in training (0.85 vs 0.78 in AUC, respectively), validation (0.81 vs 0.76 in AUC, respectively) and test (0.89 vs 0.73 in AUC, respectively) cohorts.

In particular, the DLS showed a higher accuracy in detecting patients with intermediate risk of POPF (FRS 3-6) when compared to FRS (test: 92.1% vs 65.8%, respectively) thanks to the ability of identify histo-morphological features related to pancreatic duct, parenchymal fibrosis, and remnant pancreatic tissue volume.(64)

Artificial intelligence or Standard statistical analysis: pros and cons

Most of traditional models are elaborated on logistic regression method, which is based on a linear correlation between independent and dependent variables. According to the traditional logistic regression method the probability of an outcome is related to a certain number of predictors.

These models have some advantages, including the fact that they are easy to use and to understand even in relation to the small number of input variables generally involved. Among limitations, there is that, in the real life, the interaction between comorbidities and risk factors can be different from linear and some variables can

vary their "weight" in terms of risk factors for the development of complications based on the presence/absence of other variables.(56)

Likewise, the number of variables that can interact within a linear logistic regression model is limited and this necessarily leads to an approach bias.

In addition, the predictors included in the standard statistical study are usually chosen using backward selection, and this technique prevents a variable from being reinserted once it has been eliminated.(65, 66)

Moreover, most of the available risk models that have been developed with standard statistical analysis use the same key risk factors, but with different cutoff values and this makes these models non-standardized and very heterogeneous.

Machine learning algorithms are increasingly promoted as they are less related to the above-mentioned problems.(67-69)

Nowadays, large amounts of data are available and incorporating all this information in clinical practice could be not so easy, however machine learning algorithms incorporate more variables than logistic regression and can detect non-linear relationships between independent and dependent variables.(70-72)

Artificial intelligence processes more information than traditional methods, and this can improve medical decision-making. The number of data that can be processed concerns both the size of the sample of patients but also the number of variables. (73, 74)

Moreover, thanks to a series of complex interactions between variables, machine learning can identify latent variables deduced from the interaction with other variables related to outcome; this can be an added value, especially in the context of the discovery of new risk factors for complications feared by clinicians such as POPF in pancreatic surgery.(56, 61)

AI can offer a more personalized medicine. In fact, AI provide, through the integration of details and large numbers of medical fields, recommendations tailored to patient specific characteristics, moving from population-level to patient-level of evidence.

Regarding the limitation, however, every AI system requires data to train on and perform its algorithm. To train efficient models, AI system need high-quality and often large datasets.

Second come the so-called black-box phenomenon, meaning that the models, and the interaction between variables, are not always interpretable and easy to discriminate for humans.(65, 71, 75) AI indeed can lack of transparency (that means the knowledge of the code of the algorithm and the data it was trained on), explainability (the comprehension of how the model produces the output troughs the input) and finally the interpretability (the ability of humans to understand the cause of a decision and to predict the model result).(76-78)

The "black box" nature of AI could present challenges in integrating its outputs into the complex clinical context or aligning them with existing scientific knowledge, particularly when aiming to drive new scientific discoveries.

Additionally, AI models are prone to overfitting, a phenomenon where the model becomes overly tailored to the training dataset, limiting its ability to generalize to new data.

MATERIAL AND METHOD

Patient population and study variables

Patients who underwent pancreaticoduodenectomy (open and robotic) for benign and malignant (primary or secondary) tumors between 2011 and 2022 at the Department of Hepato-pancreatobiliary Surgery, Pederzoli Hospital (Peschiera del Garda, Verona) were retrospectively collected from a prospectively maintained database.

Patient with missing data about preoperative or postoperative outcome categorical variables and patients who underwent emergent surgery were excluded from the analysis.

Data on preoperative, intraoperative, and postoperative outcomes has been collected.

In detail, patient demographic and clinicopathologic characteristics included age, sex, body mass index (BMI), smoking and weight loss >10% prior to surgery. Patient operative risk will be estimated using the American Society of Anesthesiologists physical status classification system (ASA score).(79)

Regarding comorbidities, those of interest will be Diabetes mellitus, Chronic obstructive pulmonary disease (COPD), Heart disease, Hypertension, Chronic Renal Failure (CRF) or dialysis.

Preoperative albumin, prealbumin, and bilirubin serum level before surgery has been included in the analysis. Moreover, history of previous abdominal surgery and data regarding the eventuality and the type of biliary stent placement [Percutaneous Transhepatic Biliary Drainage (PTBD) or Endoscopic biliary drainage, (EBD)] have been collected.

The type of lesion has been classified as Solid [pancreatic ductal adenocarcinoma (PDAC), cholangiocarcinoma (CCC), periampullary tumor, kidney metastasis, pseudopapillary tumor and endocrine tumor], Cystic (IPMN, serous tumor) or "Others" [gastrointestinal stromal tumor (GIST), groove pancreatitis and duodenal tumor].

Furthermore, data regarding Wirsung and bile duct diameter, vascular adjacency or invasion, tumor size and baseline resectability (all obtain with preoperative

multidetector CT (MDCT) and MRI with multiplanar reconstruction) have been included.

Preoperative chemotherapy and radiotherapy other than Serum carcinoembryonic antigen (CEA), and cancer antigen (CA 19.9) assays before surgery for patients with malignant disease have been included in the analysis.

As regard intraoperative data, type of surgical approach (open resection or minimally invasive approach), vascular resection and intraoperative blood loss has been reported.

Postoperative outcome has been defined as the development of any of this complication included in the analysis within 30 days after surgery: POPF according the 2016 updated definition of International Study Group for Pancreatic Surgery (ISGPS), bile leakage, enteric leakage, delay gastric emptying, chylous fistula intrabdominal abscess, acute pancreatitis, postoperative bleeding, gastrointestinal occlusion, sepsis, pulmonary complication, cardiac complication, kidney injury, wound infection, reoperation, readmission.

The severity of postoperative complications was graded according to the Clavien–Dindo classification system, and severe complications were defined as Clavien–Dindo grade ≥ 3 (80)

Moreover, data about discharge with abdominal drain and hospital death has been collected.

Surgical techniques and perioperative management

In cases of symptomatic jaundice, cholangitis or in case of delayed surgical resection or necessity of neoadjuvant chemotherapy a preoperative endoscopic or percutaneous biliary drainage was introduced.

In patients with a borderline resectable or locally advanced pancreatic cancer at the diagnosis, neoadjuvant treatment has been proposed after discussion at multidisciplinary team. All surgical procedures were performed by experienced five pancreatic surgeons at Pederzoli Hospital in Peschiera del Garda, Verona.

The main indications for a robotic approach were a mass small and resectable upfront.

Pancreatic anastomosis has always been performed as end to side pancreatico-jejunosomy (PJ).

An external pancreatic duct stent was placed based on the surgeon judgment about the pancreatic texture and duct diameter less than 3 mm and in this case the preferred anastomosis was the duct to mucosa pancreatojejunosomy.

Conversely, the end-to-side single layer pancreatojejunosomy was the standard anastomosis.

The entero-biliary anastomosis has been performed in single layer continuous in case of bile duct diameter more than 1 cm or a single layer interrupted suture in case of bile duct diameter lower than 1 cm.

The entero-entero anastomosis has been performed with interrupted or continuous stitches according to the surgeon's preference.

In all patients 2 drains were placed as follows: one behind the pancreatic and entero-entero anastomosis, another behind the entero-biliary anastomosis.

Serum and drain fluid amylase levels were routinely measured on postoperative days 1, 3, 5 and 7 if the drains were maintained.

Drains were removed in third postoperative day if there was not clinical and laboratory evidence of a leak.

Model development

Twenty-seven predictors (“features”) to be entered into the ML model were identified following consensus among the investigators based on clinical reasoning, literature review, and availability in the clinical setting. These features included demographics, comorbidities, laboratory results and tumor characteristics based on preoperative imaging.

A Random Forest machine learning model was developed.

This algorithm was selected based on its wide adoption in the literature due to its ability to accurately predict surgical outcomes.(81, 82) RF method is a kind of ensemble learning algorithm that builds multiple decision trees to produce the output. Thanks to “bagging methods” it creates different models by randomly sampling the training data and finally it produces the outcomes by combining the best model.(81)

A first Random Forest model was used to determine the optimal hyperparameters to maximize model accuracy.

After that, the top 12 predictors among 27 have been selected for the final Random Forest model.

The population was randomly divided into a training cohort (80%) to develop the model and a testing cohort (20%) to validate the model. A calculator based on the random forest model was developed and made available online.

Study outcome

The primary endpoint of the study was the development of an algorithm to predict the risk of any complication within 30 days after pancreaticoduodenectomy.

The secondary endpoint was to develop an easy-to-use calculator called “PanRisk Calculator” based on the developed algorithm and made it available online.

STATISTICAL ANALYSIS

For descriptive statistics, continuous variables were summarized as median and interquartile range (IQR) and compared using the independent t- test, while categorical variables were reported as frequencies and percentages (%) and compared using the Chi-squared test or Fisher's exact test, as appropriate, and a p-value <0.05 was considered statistically significant. In case of missing data Multiple Imputation by Chained Equations (MICE) method has been used for generating plausible numbers derived from distributions of and relationships among observed variables in the dataset.(83) The primary model evaluation metric was the area under the receiver operating characteristic curve (ROC-AUC). All statistical analyses were performed using R version 4.3.2 (R Foundation, Vienna, Austria).

RESULTS

Clinicopathological characteristics and surgical outcomes

Among 1072 patients who underwent pancreaticoduodenectomy between 2011 and 2022 at the Department of Hepato-pancreato-biliary Surgery, Pederzoli Hospital (Peschiera del Garda, Verona) 496 met the inclusion criteria and have been included in the study.

Table 1 provides the clinical-pathological details of the 496 patients.

The median age was 65.0 years (IQR 57–73), 272 (54.8%) patients were male, and the median BMI was 25.0 kg/m² (IQR 22.31-26.70).

About 40 % of the patients were current smoker while 181 (36.5%) patients had a preoperative weight loss of > 10%.

As regard comorbidity 123 (24.8%) patients had an ASA score higher than 2, 132 (26.6%) patients had diabetes mellitus, 54 (10.9%) heart disease and 253 (51%) blood hypertension while 212 (42.7%) underwent previous abdominal surgery.

Almost half of patients (46.2%) underwent endoscopic preoperative biliary drainage and only 5% underwent percutaneous transhepatic biliary drainage.

The most frequent diagnosis was a solid lesion of the pancreas in 427 (86.1%) patients. The others indication for surgery were: Cystic lesion in 52 patients (10.5%) and “Others diagnosis” in the remaining 17 patients (3.4%).

Pancreatic duct was dilatated in 363 (73.2%) patients while bile duct was more than 1 cm in more than half of patients (50.8%) who underwent pancreaticoduodenectomy.

The preferred surgical approach was open pancreaticoduodenectomy (93.3%).

The robotic approach increases over the years (staring from lower than 1% in 2019 to 4.2% in 2022) thanks to the improvement of surgeon learning curve and the higher availability of the robot itself.

Table 2 shows the surgical outcomes.

Almost half of patients (270, 54.4%) developed almost one postoperative complication, and the rate of severe complication (Dindo-Clavien ≥ 3) was around 19%.

As concerns the most feared complication, POPF, 56 patients (11.3%) developed a grade B POPF, and 18 (3.6%) developed a grade C POPF.

The rate of bile leakage was around 5% while that of the enteric leakage lower than 1%.

Among 50 patients (10.1%) suffered from postoperative delayed gastric emptying. Moreover, almost 20% of patients developed intra-abdominal abscess, 5.4% a wound infection and more than 4% developed a sepsis.

A chylous fistula occurred in 34 (6.9%) patients while 43 (8.7%) patients experienced an acute pancreatitis.

A postoperative bleeding involved 41 (8.3%) patients, and 52 patients (10.5%) required a reoperation for surgical complication. Indication for reoperation were the following: 5 cases (9.6%) of acute pancreatitis, 23 cases (44.2%) of bleeding, 3 cases (5.8%) of intestinal volvulus, 14 cases (26.9%) of peritonitis as consequence of anastomosis dehiscence, 3 cases (5.8%) of sepsis, and 4 cases (7.7%) of wound infection with wound dehiscence.

In addition, pulmonary complication occurred in 50 patients (10.1%) and cardiac complication in 68 (13.7%), while kidney injury in 13 (2.6%).

Moreover, both readmission rate and the rate of discharge with abdominal drain were around 7%. In-hospital mortality was 3.4%.

Table 3 shows clinical and surgical detail of patients stratified for the development or not of surgical complications.

Based on preoperative characteristics, there was no difference in age, sex and BMI between the group of patients who developed at least one complication and those who did not develop any complications.

The group of patients who developed almost one complication had higher rate of previous abdominal surgery (47.2%) compared to the group of patients who didn't develop almost one postoperative complication (37.3%), $p=0.029$.

Moreover, the group of patients who didn't develop complication had a higher level of Ca 19.9 (median 42, IQR 12-90-142.60) compared to the group with complication (median 31.60, IQR 9.60-105.45), $p= 0.043$.

The rate of dilated Wirsung duct (83.1%) and dilated bile duct (52.4%) was higher in the group who did not experience complication compared to the complication group (64.9%, $p < 0.001$ and 49.4%, $p = 0.528$, respectively).

No difference in the tumor stage at the diagnosis was found between the two groups. In detail, the majority of patients resulted resectable at the diagnosis (no complication group: 95.6%, any complication group 96.3%).

Neoadjuvant chemotherapy was also more frequent in the group without complication (32.4%) compared to the group with postoperative complication (20.7%), $p = 0.004$.

Conversely, the rate of preoperative radiotherapy was similar between the two groups (complication group 5.5%; no complication group 6.2%; $p = 0.848$).

The open approach was the preferred surgical method to perform pancreatic duodenectomy in more than 90% of cases in both groups under analysis.

The rate of vascular resection was quite higher in the group of patients who developed almost one complication ($n = 42$, 15.5%) compared to the group without complication ($n = 31$, 13.8%) but the difference was not significant ($p = 0.613$).

Development of machine learning models using random forest

Table 4 shows the twenty-seven predictors (“features”) selected to be entered into the first ML model.

The 12 most influential features included in the final model are represented in Figure 1.

After model development with hyperparameter tuning, the final Random Forest model showed an AUC of 0.87 in the training cohort and of 0.72 in the testing cohort (Figure 2).

Specifically, dilated pancreatic duct was the most important feature in predicting any postoperative complication, followed by weight loss $> 10\%$, diagnosis of cystic lesion, diabetes, previous abdominal surgery, preoperative CA 19.9 serum level, high bilirubin level, preoperative chemotherapy, dilated bile duct, ASA Score, Surgical Approach and “Other diagnosis” (GIST, groove pancreatitis, duodenal tumor).

To enable the clinical applicability of the model, a calculator of the probability of developing any postoperative complication after pancreaticoduodenectomy based on preoperative characteristics was developed and made available online (https://panriskcalculator.shinyapps.io/Panrisk_Calculator/)

Using the calculator, clinicians can input individual patient clinical characteristics to assess the probability of a developing of postoperative complication after pancreaticoduodenectomy.

Table 1: Clinical-pathological details of patients

VARIABLE	N (%), Median (IQR)
N	496
Age (yr)	65 (57-73)
Sex	
M	272(54.8)
F	224 (46.1)
BMI (kg/m ²)	25 (22.31-26.70)
Current smoker	201 (40.5)
Preoperative weight loss >10%	181 (36.5)
Comorbidity	332 (66.9)
Diabetes mellitus	132 (26.6)
Heart disease	54(10.9)
Hypertension	253 (51)
Chronic obstructive pulmonary disease (COPD)	28 (5.6)
Chronic kidney disease	13 (2.6)
Previous Abdominal Surgery	212 (42.7)
ASA SCORE:	
1-2	373 (75.2)
3-4	123 (24.8)
Preoperative biliary drainage:	
PTBD	26 (5.2)
EBD	229 (46.2)
Preoperative Total bilirubin level \geq 3 mg/dL)	70 (14.1)
Preoperative Albumin level (g/dL)	40.60 (37.90-42.62)
Preoperative Prealbumin level (g/dL)	0.20 (0.19-0.26)
Preoperative ca 19.9 level (U/mL)	34.30 (10.57-122.90)
Preoperative CEA level (ng/mL)	2.50 (1.70-3.80)
Diagnosis	
Solid lesion	427 (86.1)
Cystic lesion	52 (10.5)
Others	17 (3.4)
Baseline resectability	
Resectable	476 (96)
Borderline resectable	20 (4.0)
Vascular adjacency	185 (37.3)
Pancreatic duct diameter \geq 3 mm	363 (73.2)
Bile duct diameter \geq 1 cm	252 (50.8)
Preoperative radiological tumor size	26 (20-33)
Preoperative Chemotherapy	129 (26)
Preoperative Radiotherapy	29 (5.8)
Surgical Approach	
RPD	33 (6.7)
OPD	463 (93.3)
Blood loss (ml)	300 (200-420)
Vascular resection	73 (14.7)

Data are presented as median (IQR) for continuous variables and n (%) for categorical variables. Abbreviations: BMI, Body-Mass Index; COPD, Chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists physical status classification system; PTBD, Percutaneous Transhepatic Biliary Drainage (PTBD); EBD, Endoscopic Biliary Drainage; RPD, Robotic pancreaticoduodenectomy; OPD, Open Pancreaticoduodenectomy.

Table 2: Surgical outcomes

VARIABLE	N (%)
N	496
Overall complication	270 (54.4)
POPF	
Biochemical leak	38 (7.7)
Gade B	56 (11.3)
Grade C	18 (3.6)
Bile leakage	24 (4.8)
Enteric leakage	3 (0.6)
DGE	50 (10.1)
Intra-abdominal abscess	107 (21.6)
Chylous fistula	34 (6.9)
Acute pancreatitis	43 (8.7)
Bleeding	41 (8.3)
Gastrointestinal occlusion	3 (0.6)
Sepsis	23 (4.6)
Pulmonary complication	50 (10.1)
Cardiac complication	68 (13.7)
Kidney Injury	13 (2.6)
Wound infection	27 (5.4)
Reoperation	52 (10.5)
Readmission	38 (7.7)
Discharge with abdominal drain	37 (7.5)
Hospital death	17 (3.4)
Dindo-Clavien ≥ 3	94 (19.0)

Data are presented as N (%) for categorical variables. Abbreviations: POPF, Postoperative pancreatic fistula; DGE Delay Gastric Emptying.

Table 3: Clinical and surgical detail of patients stratified by the development or not of surgical complications.

VARIABLE	Any complication N (%), Median (IQR)	No Complication N (%), Median (IQR)	P value
N	270 (54.4)	225 (45.6)	
Age (yr)	66 (57.50-72.00)	65 (57.00-72.00)	0.478
Sex			
M	152 (56.1)	120 (53.3)	
F	119 (43.9)	105 (46.7)	0.587
BMI (kg/m ²)	25 (22.48-27.00)	24.82 (22.22-26.23)	0.197
Comorbidity	192 (70.8)	140 (62.2)	0.045
Diabetes mellitus	65 (24.0)	67 (29.8)	0.154
Current smoker	105 (38.7)	96 (42.7)	0.409
Heart disease	32 (11.8)	22 (9.8)	0.563
Hypertension	149 (55.0)	104 (46.2)	0.058
Pulmonary disease	14 (5.2)	14 (6.2)	0.697
Chronic kidney disease	7 (2.6)	6 (2.7)	1.000
Previous Abdominal Surgery	128 (47.2)	84 (37.3)	0.029
ASA SCORE:			
1-2	210 (77.5)	163 (72.4)	
3-4	61 (22.5)	62 (27.6)	0.211
Preoperative weight loss >10%	88 (32.5)	93 (41.3)	0.049
Preoperative biliary drainage:			
PTBD	12 (4.4)	14 (6.2)	
EBD	118 (43.5)	111 (49.3)	0.208
Preoperative Total bilirubin level \geq 3 mg/dL	44 (16.2)	26 (11.6)	0.155
Preoperative Albumin level (g/dL)	40.90 (38.20-43.05)	40.40 (37.80-42.50)	0.155
Preoperative Prealbumin level (g/dL)	0.20 (0.20-0.26)	0.20 (0.18-0.24)	0.441
Preoperative ca 19.9 level (U/mL)	31.60 (9.60-105.45)	42.00 (12.90-142.60)	0.043
Preoperative CEA level (ng/mL)	2.60 (1.70-4.05)	2.60 (1.70-3.90)	0.770
Diagnosis			
Solid lesion	227 (83.8)	200 (88.9)	
Cystic lesion	32 (11.8)	20 (8.9)	
Others	14 (4.4)	5 (2.2)	0.223
Baseline resectability			
Resectable	261 (96.3)	215 (95.6)	
Borderline resectable	10 (3.7)	10 (4.4)	0.819
Pancreatic duct diameter \geq 3 mm	176 (64.9)	187 (83.1)	<0.001
Bile duct diameter \geq 1 cm	134 (49.4)	118 (52.4)	0.528
Preoperative radiological tumor size mm	25(20.00-33.00)	26.00 (19.00-33.00)	0.705
Preoperative Chemotherapy	56 (20.7)	73 (32.4)	0.004
Preoperative Radiotherapy	15 (5.5)	14 (6.2)	0.848
Surgical Approach			
RPD	20 (7.4)	13 (5.8)	
OPD	251 (92.6)	212 (94.2)	0.588
Vascular resection	42 (15.5)	31 (13.8)	0.613

Data are presented as median (IQR) for continuous variables and n (%) for categorical variables. Abbreviations: BMI, Body-Mass Index; COPD, Chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists physical status classification system; PTBD, Percutaneous Transhepatic Biliary Drainage (PTBD); EBD, Endoscopic Biliary Drainage; RPD, Robotic pancreaticoduodenectomy; OPD, Open Pancreaticoduodenectomy.

Table 4: Twenty-seven predictors (“features”) selected to be entered into the first RF model.

VARIABLE
Age (yr)
Sex: M/F
BMI (kg/m ²)
Current smoker
Preoperative weight loss >10%
Diabetes mellitus
Heart disease
Hypertension
Chronic obstructive pulmonary disease (COPD)
Chronic kidney disease
Previous Abdominal Surgery
ASA SCORE: 1-2/3-4
Preoperative biliary drainage: PTBD/ EBD
Preoperative Total bilirubin level ≥ 3 mg/dL)
Preoperative Albumin level (g/dL)
Preoperative Prealbumin level (g/dL)
Preoperative ca 19.9 level (U/mL)
Preoperative CEA level (ng/mL)
Diagnosis: Solid lesion, Cystic lesion, Others
Baseline resectability: Resectable/Borderline resectable
Pancreatic duct diameter ≥ 3 mm
Bile duct diameter ≥ 1 cm
Radiological tumor size
Preoperative Chemotherapy
Preoperative Radiotherapy
Surgical Approach: RPD/OPD
Vascular resection

Abbreviations: RF, Random Forest; BMI, Body-Mass Index; COPD, Chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists physical status classification system; PTBD, Percutaneous Transhepatic Biliary Drainage (PTBD); EBD, Endoscopic Biliary Drainage; RPD, Robotic pancreaticoduodenectomy; OPD, Open Pancreaticoduodenectomy.

Figure 1: Illustration of the importance of the 12 most influential features included in the final Random Forest model

Pareto plot

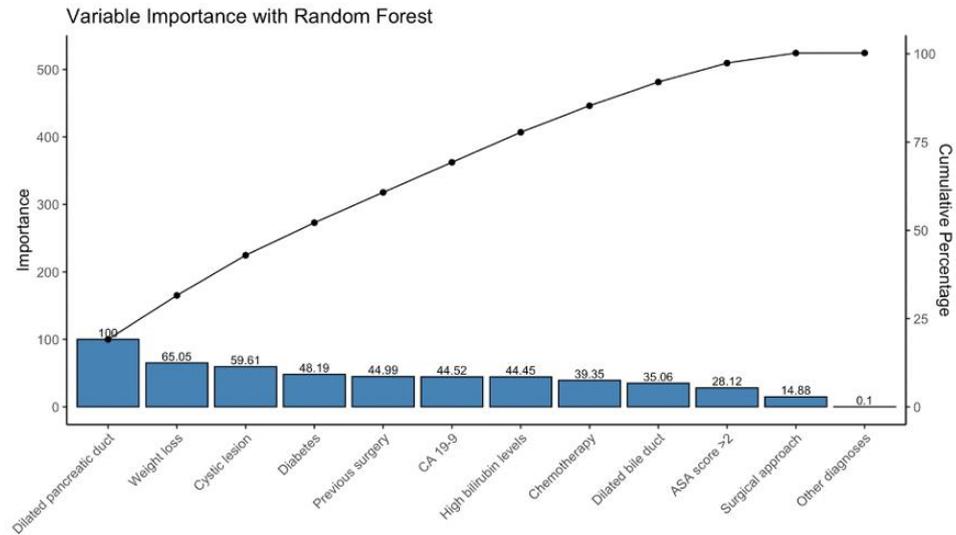
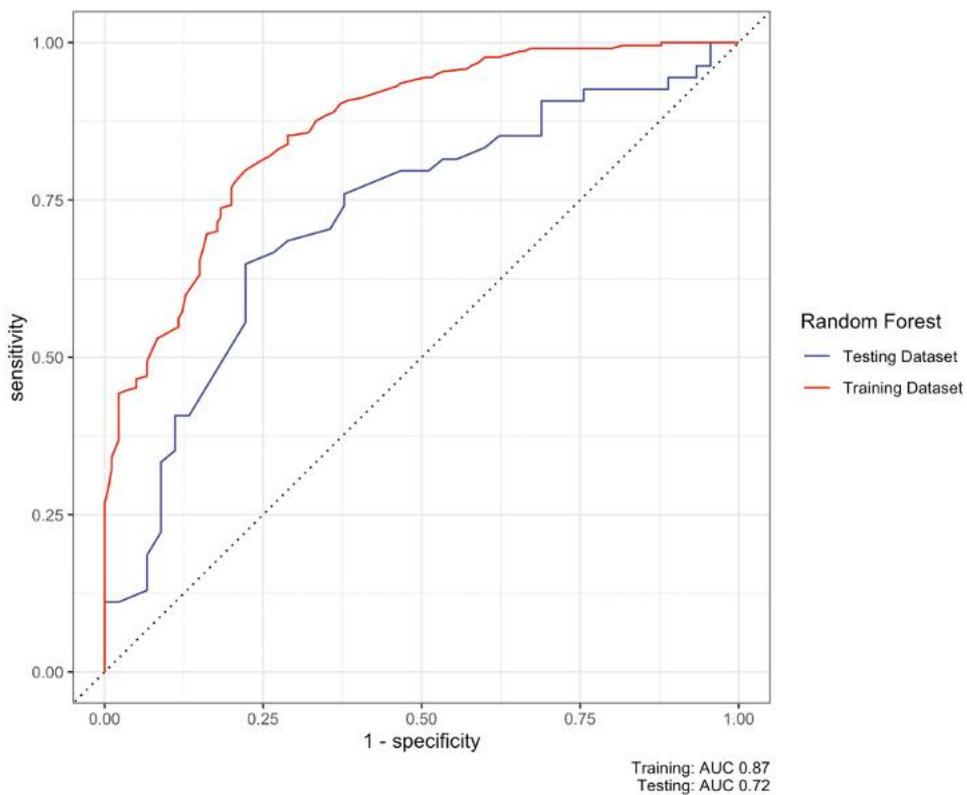


Figure 2: Receiver operating characteristic (ROC) curve of the RF model in the training and testing cohorts.

ROC



DISCUSSION

Pancreatic surgery remains a high-risk surgery with a considerable rate of morbidity and mortality. (4, 84-87)

Up to approximately 50% of patients who undergo pancreatic surgery could experience postoperative complications (eg, delayed gastric emptying (DGE), POPF, infection, bleeding) resulting in increased mortality, need for a higher level of care and management, longer length of postoperative hospital stays, higher hospital cost and reducing patient's quality of life.(4, 7-11)

Although some of these postoperative complications are unavoidable because of non-modifiable patient and surgical risk factors (eg, BMI, sex, soft pancreatic texture, broad and thick pancreas, duct diameter <3 mm, ongoing pancreatitis, high acinar cell density), others are potentially preventable through early identification of modifiable risk factors (eg, preoperative nutritional status, neoadjuvant treatment, intraoperative bleeding and liquid infusion) and the application of an appropriate mitigation strategy (eg, timely administration of antibiotics in postoperative care settings, active drain management based on drain fluid amylase, drain volume and characteristic, identifying bleeding complications early and managing with embolization and stent)(4, 21, 85, 87-89)

In this context, several risk predictor models have been developed to optimize patient selection as well as to stratify risk among patients. (62, 90-92)

For many years, predictive models have been built using traditional statistical methods such as the logistic regression model and relying mainly on intraoperative parameters. Pancreatic texture, Wirsung diameter and histology of the pancreatic lesion have been proposed among the most cited risk factors in the literature.(30, 37, 49)

However, the reduced performance of the standard statistical method can likely be attributed to two main factors: its reliance on a linear relationship between variables and the fact that predictive accuracy is generally tied to the internal validation of the data. Moreover, models often tend to adapt specifically to the data on which they were developed.(56)

Recently, ML has gained popularity and has been applied in different surgical areas for operative risk assessment.(93-97)

Thanks to their ability to identify and analyze complex nonlinear relationships among numerous variables, ML approaches could enhance the accuracy of risk assessment by leveraging the intricate interactions between risk factors that influence postoperative morbidity in pancreatic surgery. This random forest model showed very good performance in predicting the probability of developing complication. The maximum AUC of this model was considerable (AUC of 0.87 in the training cohort and of 0.72 in the testing cohort).

The result is satisfying, and the model is based on characteristics that can be identified or planned (surgical approach and the indication of vascular resection) preoperatively with the aim of being able to make a correct risk balance before surgery and consequently improve shared decision-making. Indeed, knowing the risk helps to adequately inform and involve the patient in decisions concerning the planned surgery.(62, 90-92)

Once the risk of developing complications has been identified with this RF model, it is possible to implement preoperatively optimization measures or adopt mitigation strategy in the postoperative course.

In this AI model the most important predictive factor for postoperative complication resulted the Wirsung duct diameter defined through the preoperative CT scan.

This AI-based risk prediction could help the surgeon adopt a personalized approach by better tailoring risk management to individual patients. Indeed, the preoperative knowledge of the risk of morbidity related to the pancreatic duct diameter, suggests the surgeon to adopt an intraoperative mitigation strategy in case of non-dilated Wirsung duct. Indeed, a smaller pancreatic duct is first of all difficult to reconstruct (it can accommodate only few stiches and the juxtaposition of the duct to bowel mucosa it can result difficult), and consequently also more predisposed to collapse and/or or dehisce.(30)

In addition, a small pancreatic duct is often an indication of the absence of a real underlying obstructive condition, so the pancreas also tends to be soft and less fibrous unlike what occurs after prolonged periods of obstruction to the outflow of

pancreatic juice with consequent dilation of the duct and fibrosis of the pancreas upstream of the obstruction.(30)

After a risk assessment, high-risk patients might be selected, for example, for the placement of external pancreatic stent to protect the pancreatic-enteric anastomosis and to perform a duct to mucosa double layer pancreatojejunostomy although even these fistula prevention techniques are not shared by all authors.(98-100)

Identification and optimization, thanks to our ML model, of modifiable factors as in case of weight loss before surgery and high preoperative bilirubin levels, allow to improve the patient's performance status before surgery.

In literature, weight loss more than 10% before surgery has been associated with an increase in postoperative complications across a variety of surgical procedures. (101-103)

Weight loss could be the indicator of a loss in muscle mass and increased energy expenditure typical of cachexia cancer related.(101)

For this reason, identifying this condition in advance enables the implementation of a pre-rehabilitation program based on a multimodal approach, including physical exercise and nutritional support. The goal is to improve the patient's performance status before surgery and reduce the risk of complications associated with poor muscle and nutritional health.(104)

Obstructive jaundice is generally the most common presentation in patients with pancreatic head cancer and it is associated with an increased risk of cholangitis, coagulopathy and decline organ function (e.g liver and kidney function).(105-107)

A potential strategy to mitigate the consequences of high bilirubin level is preoperative biliary drainage.(108) However, despite its theoretical advantages, in available literature, results of preoperative biliary drainage are controversial.

Sohn et al observed no differences in overall morbidity, mortality, and length of stay (LOS) between patients who underwent and those who did not undergo biliary drainage prior to pancreaticoduodenectomy.(109)

De Pastena et al., analyzing 1500 consecutive cases, showed that preoperative biliary drain does not increase major complication and mortality rates after pancreaticoduodenectomy, but it is associated with higher surgical site infection rate.(110)

Other authors have reported worse outcomes associated with preoperative biliary drainage, including increased risk of postoperative overall complications, surgical site infections, readmission rates, LOS, and mortality when compared to patients not undergoing biliary decompression.(111, 112)

The management of high bilirubin levels requires not only the decision whether to drain preoperatively but also which cut-off to consider as an indication for drainage since there is also a lot of heterogeneity on this.(110, 112)

In our analysis we used the cut off $>3\text{mg/dl}$ to define high bilirubin levels, and we usually made preoperative bile drainage in case of symptomatic or septic patients or in case of delayed surgical resection based on the waiting list or necessity of neoadjuvant chemotherapy in line with the recent Clinical Practice Guidelines in Oncology-NCCN Guidelines (113)

As regard comorbidity, diabetes mellitus (DM) resulted as a factor able to influence the short-term outcome after pancreaticoduodenectomy.

The role of diabetes mellitus (DM) in term of influence of short- term outcome is debated in literature. Some reports reported that DM was associated with increased abdominal complication and was an independent risk factor of POPF in patients undergoing PD for pancreatic cancer.(114-116) In addition, Hank et al, described an increased postoperative mortality in diabetic patients who underwent pancreaticoduodenectomy probably as consequence of contemporary advanced age, obesity, malnutrition, coexisting co-morbidities.(117)

Conversely, some other authors reported a protective effect of DM in term of decreased POPF thanks to the DM related less pancreatic fat and increased fibrosis in pancreatic remnant.(19, 118)

ML algorithm, thanks to a series of complex interactions between data offers the opportunity to discover latent variables that are unlikely to be observed but might be inferred from other variables related to outcome.(119, 120)

In this way, Ca 19.9 value resulted as a new factor able to influence postoperative morbidity, detected by our RF model.

In our series, patients who developed at least one postoperative complication exhibited lower serum levels of Ca 19.9 compared to those who did not experience postoperative morbidity. Interestingly, this finding contrasts with a previous report

investigating the role of Ca 19.9 in complications after pancreatic surgery. That study suggested that elevated levels of this tumor marker were associated with a higher risk of postoperative pancreatic fistula (POPF). However, it was based on a single-center retrospective analysis with a limited sample size, which may affect the generalizability of its conclusions.(121)

A possible explanation for our result lies in the slight predominance of solid lesions among patients without postoperative complications, even though this difference did not reach statistical significance. It is well established that Ca 19.9 levels tend to be higher in malignant tumors compared to cystic lesions and non-epithelial lesions, which could account for the observed trend.

This hypothesis aligns with the finding that the diagnosis of cystic lesions (e.g., IPMN, serous tumors) or other types of lesions (e.g., GIST, groove pancreatitis, duodenal tumors) was associated with postoperative morbidity in this model. Pathologies other than solid lesions and chronic pancreatitis are often linked to softer pancreatic parenchyma and non-dilated pancreatic ducts—two well-known risk factors for postoperative complications following pancreatectomy.(30)

The observation that Ca 19.9 levels correlate with postoperative complications is novel and adds an interesting dimension to existing literature, where the focus has often been on higher Ca 19.9 levels as marker of tumor stage, resectability and tumor response to chemotherapy.(122)(123)(124)

This finding may provide additional insights for risk stratification and preoperative planning, particularly in cases involving cystic or atypical lesions, in which often surgery is offered in unclear cases or possible pre-malignant behavior, guiding surgeons in anticipating postoperative risks.

Since the early 90s a meta-analysis of more than 2,600 patients supports the correlation between histopathology and pancreatic duct diameter and reports lower POPF in the setting of chronic pancreatitis (5%) and pancreatic cancer (12%).(125)

In our series, we observed that pathology diagnosis of cystic lesion (IPMN, serous tumor) or “other diagnosis” (GIST, groove pancreatitis, duodenal tumor) were related to the development of postoperative morbidity.

Interestingly, in our ML model, chemotherapy resulted as another factor able to influence the development of postoperative morbidity.

There are several reasons that could explain this result.

First, despite our main outcome is the overall morbidity, it is well known that generally POPF is the first complication that appears after pancreaticoduodenectomy which is followed by others complication such as post pancreatectomy hemorrhage or sepsis. The protective effect of chemotherapy in reducing postoperative complications, including POPF, remains unclear in the literature. One plausible explanation is that fibrotic pancreatic tissue provides better suture-holding capacity, reducing the likelihood of anastomotic leakage. Chemotherapy itself, along with the extended time to surgery in patients receiving neoadjuvant treatment, is thought to promote fibrosis in the pancreatic tissue, resulting in a firmer pancreatic consistency.(126, 127)

Moreover, neoadjuvant chemotherapy could also reduce the rate of vascular resections, in patients with vascular involvement at baseline stadiation, which are related to an increase of postoperative complication both in this model and in the available literature.(128, 129)

This study used a highly performant ML algorithm to develop a calculator which can accurately predict patient risk of overall morbidity within 30-day after pancreaticoduodenectomy.

The calculator we have developed is easily to use in clinical practice and requires the entry of readily available preoperative data. Furthermore, the proposed calculator offers valuable support in the thorough evaluation of surgical candidates, enhancing preoperative planning and ultimately contributing to better patient outcomes. In fact, in patients suffering from pancreatic cancer, in the event that the calculator we have developed suggests a high risk of complications, it is possible, for example, to consider a neoadjuvant chemotherapy treatment of three months before surgery as mitigation strategy.

Although this study shows the potential for using ML algorithms, it has several limitations.

First, due to the retrospective design of the study, selection bias is possible despite the database is prospectively collected. Furthermore, even though the use of a large database, this is a monocentric study and lack of variations in patient selection and perioperative management among different hospital should be considered.

Application of the model to a larger cohort and external validation are needed to evaluate the model's performance in other settings.

Additionally, the model considers as main outcome the presence or absence of 30-day postoperative complication, however a more detailed risk assessment (type and grade of complications) along with 90-days related morbidity and mortality will also be considered in future studies. To make this possible, a large amount of data is needed to implement the performance of the AI algorithm.

Moreover, the developed calculator needs to be tested in a prospective and multicentric way.

CONCLUSION

In conclusion, this study used a highly performant ML algorithm to develop an accurate tool to predict individualized patient risk of overall morbidity within 30-day after pancreaticoduodenectomy.

The present study highlights the presence of modifiable preoperative factors that can be addressed to reduce the likelihood of postoperative complications, as well as non-modifiable factors that, if recognized early, may suggest the application of mitigation strategies. Furthermore, the proposed calculator is a valuable support in the thorough evaluation of surgical candidates, enhancing preoperative planning and ultimately contributing to better patient outcomes.

REFERENCES

1. Haigh PI, Bilimoria KY, DiFronzo LA. Early postoperative outcomes after pancreaticoduodenectomy in the elderly. *Arch Surg.* 2011;146(6):715-23.
2. Simons JP, Shah SA, Ng SC, Whalen GF, Tseng JF. National complication rates after pancreatectomy: beyond mere mortality. *J Gastrointest Surg.* 2009;13(10):1798-805.
3. Spanheimer PM, Cyr AR, Liao J, Johlin FC, Hoshi H, Howe JR, et al. Complications and survival associated with operative procedures in patients with unresectable pancreatic head adenocarcinoma. *J Surg Oncol.* 2014;109(7):697-701.
4. Merath K, Chen Q, Bagante F, Akgul O, Idrees JJ, Dillhoff M, et al. Synergistic Effects of Perioperative Complications on 30-Day Mortality Following Hepatopancreatic Surgery. *J Gastrointest Surg.* 2018;22(10):1715-23.
5. Mirrieles JA, Weber SM, Abbott DE, Greenberg CC, Minter RM, Scarborough JE. Pancreatic Fistula and Delayed Gastric Emptying Are the Highest-Impact Complications After Whipple. *J Surg Res.* 2020;250:80-7.
6. Smits FJ, Verweij ME, Daamen LA, van Werkhoven CH, Goense L, Besselink MG, et al. Impact of Complications After Pancreatoduodenectomy on Mortality, Organ Failure, Hospital Stay, and Readmission: Analysis of a Nationwide Audit. *Ann Surg.* 2022;275(1):e222-e8.
7. Healy MA, Mullard AJ, Campbell DA, Dimick JB. Hospital and Payer Costs Associated With Surgical Complications. *JAMA Surg.* 2016;151(9):823-30.
8. Spolverato G, Yakoob MY, Kim Y, Alexandrescu S, Marques HP, Lamelas J, et al. Impact of complications on long-term survival after resection of intrahepatic cholangiocarcinoma. *Cancer.* 2015;121(16):2730-9.
9. Silber JH, Rosenbaum PR, Trudeau ME, Chen W, Zhang X, Kelz RR, et al. Changes in prognosis after the first postoperative complication. *Med Care.* 2005;43(2):122-31.
10. Tevis SE, Kennedy GD. Postoperative complications and implications on patient-centered outcomes. *J Surg Res.* 2013;181(1):106-13.
11. Idrees JJ, Johnston FM, Canner JK, Dillhoff M, Schmidt C, Haut ER, et al. Cost of Major Complications After Liver Resection in the United States: Are High-volume Centers Cost-effective? *Ann Surg.* 2019;269(3):503-10.
12. Merkow RP, Bilimoria KY, Tomlinson JS, Paruch JL, Fleming JB, Talamonti MS, et al. Postoperative complications reduce adjuvant chemotherapy use in resectable pancreatic cancer. *Ann Surg.* 2014;260(2):372-7.
13. Friese CR, Lake ET, Aiken LH, Silber JH, Sochalski J. Hospital nurse practice environments and outcomes for surgical oncology patients. *Health Serv Res.* 2008;43(4):1145-63.
14. Ghaferi AA, Osborne NH, Birkmeyer JD, Dimick JB. Hospital characteristics associated with failure to rescue from complications after pancreatectomy. *J Am Coll Surg.* 2010;211(3):325-30.
15. Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg.* 2002;236(4):397-406; discussion -7.

16. Cescon M, Vetrone G, Grazi GL, Ramacciato G, Ercolani G, Ravaioli M, et al. Trends in perioperative outcome after hepatic resection: analysis of 1500 consecutive unselected cases over 20 years. *Ann Surg.* 2009;249(6):995-1002.
17. Gleeson EM, Shaikh MF, Shewokis PA, Clarke JR, Meyers WC, Pitt HA, et al. WHipple-ABACUS, a simple, validated risk score for 30-day mortality after pancreaticoduodenectomy developed using the ACS-NSQIP database. *Surgery.* 2016;160(5):1279-87.
18. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery.* 2007;142(5):761-8.
19. Mathur A, Pitt HA, Marine M, Saxena R, Schmidt CM, Howard TJ, et al. Fatty pancreas: a factor in postoperative pancreatic fistula. *Ann Surg.* 2007;246(6):1058-64.
20. de Castro SM, Busch OR, van Gulik TM, Obertop H, Gouma DJ. Incidence and management of pancreatic leakage after pancreatoduodenectomy. *Br J Surg.* 2005;92(9):1117-23.
21. Joliat GR, Petermann D, Demartines N, Schäfer M. Prediction of Complications After Pancreaticoduodenectomy: Validation of a Postoperative Complication Score. *Pancreas.* 2015;44(8):1323-8.
22. Marchegiani G, Bassi C. Prevention, prediction, and mitigation of postoperative pancreatic fistula. *Br J Surg.* 2021;108(6):602-4.
23. Gleeson EM, Pitt HA, Mackay TM, Wellner UF, Williamsson C, Busch OR, et al. Failure to Rescue After Pancreatoduodenectomy: A Transatlantic Analysis. *Ann Surg.* 2021;274(3):459-66.
24. Hartwig W, Hackert T, Hinz U, Gluth A, Bergmann F, Strobel O, et al. Pancreatic cancer surgery in the new millennium: better prediction of outcome. *Ann Surg.* 2011;254(2):311-9.
25. Quero G, Pecorelli N, Paiella S, Fiorillo C, Petrone MC, Capretti G, et al. Pancreaticoduodenectomy in octogenarians: The importance of "biological age" on clinical outcomes. *Surg Oncol.* 2022;40:101688.
26. Lake AP WE. ASA classification and perioperative variables: graded anaesthesia score? . *Br J Anaesth*1997.
27. Moreno RP, Pearse R, Rhodes A, Groups ESOSEGotESoICMaESoAT. American Society of Anesthesiologists Score: still useful after 60 years? Results of the EuSOS Study. *Rev Bras Ter Intensiva.* 2015;27(2):105-12.
28. Bilimoria KY, Liu Y, Paruch JL, Zhou L, Kmieciak TE, Ko CY, et al. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. *J Am Coll Surg.* 2013;217(5):833-42.e1-3.
29. Matsui H, Shindo Y, Yamada D, Ogihara H, Tokumitsu Y, Nakajima M, et al. A novel prediction model of pancreatic fistula after pancreaticoduodenectomy using only preoperative markers. *BMC Surg.* 2023;23(1):310.
30. Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer CM. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. *J Am Coll Surg.* 2013;216(1):1-14.
31. Kim JY, Park JS, Kim JK, Yoon DS. A model for predicting pancreatic leakage after pancreaticoduodenectomy based on the international study group of

- pancreatic surgery classification. *Korean J Hepatobiliary Pancreat Surg.* 2013;17(4):166-70.
32. Kosaka H, Kuroda N, Suzumura K, Asano Y, Okada T, Fujimoto J. Multivariate logistic regression analysis for prediction of clinically relevant pancreatic fistula in the early phase after pancreaticoduodenectomy. *J Hepatobiliary Pancreat Sci.* 2014;21(2):128-33.
 33. Roberts KJ, Hodson J, Mehrzad H, Marudanayagam R, Sutcliffe RP, Muiesan P, et al. A preoperative predictive score of pancreatic fistula following pancreatoduodenectomy. *HPB (Oxford).* 2014;16(7):620-8.
 34. Chen JY, Feng J, Wang XQ, Cai SW, Dong JH, Chen YL. Risk scoring system and predictor for clinically relevant pancreatic fistula after pancreaticoduodenectomy. *World J Gastroenterol.* 2015;21(19):5926-33.
 35. Casadei R, Ricci C, Taffurelli G, Pacilio CA, Di Marco M, Pagano N, et al. Prospective validation of a preoperative risk score model based on pancreatic texture to predict postoperative pancreatic fistula after pancreaticoduodenectomy. *Int J Surg.* 2017;48:189-94.
 36. Kantor O, Talamonti MS, Pitt HA, Vollmer CM, Riall TS, Hall BL, et al. Using the NSQIP Pancreatic Demonstration Project to Derive a Modified Fistula Risk Score for Preoperative Risk Stratification in Patients Undergoing Pancreaticoduodenectomy. *J Am Coll Surg.* 2017;224(5):816-25.
 37. Mungroop TH, van Rijssen LB, van Klaveren D, Smits FJ, van Woerden V, Linnemann RJ, et al. Alternative Fistula Risk Score for Pancreatoduodenectomy (a-FRS): Design and International External Validation. *Ann Surg.* 2019;269(5):937-43.
 38. Puvaneswary M, Segasothy M. Analgesic nephropathy: ultrasonic features. *Australas Radiol.* 1988;32(2):247-50.
 39. Tabchouri N, Bouquot M, Hermand H, Benoit O, Loiseau JC, Dokmak S, et al. A Novel Pancreatic Fistula Risk Score Including Preoperative Radiation Therapy in Pancreatic Cancer Patients. *J Gastrointest Surg.* 2021;25(4):991-1000.
 40. Huang XT, Huang CS, Liu C, Chen W, Cai JP, Cheng H, et al. Development and Validation of a New Nomogram for Predicting Clinically Relevant Postoperative Pancreatic Fistula After Pancreatoduodenectomy. *World J Surg.* 2021;45(1):261-9.
 41. Mungroop TH, Klompmaker S, Wellner UF, Steyerberg EW, Coratti A, D'Hondt M, et al. Updated Alternative Fistula Risk Score (ua-FRS) to Include Minimally Invasive Pancreatoduodenectomy: Pan-European Validation. *Ann Surg.* 2021;273(2):334-40.
 42. Schuh F, Mihaljevic AL, Probst P, Trudeau MT, Müller PC, Marchegiani G, et al. A Simple Classification of Pancreatic Duct Size and Texture Predicts Postoperative Pancreatic Fistula: A classification of the International Study Group of Pancreatic Surgery. *Ann Surg.* 2023;277(3):e597-e608.
 43. Perri G, Marchegiani G, Partelli S, Crippa S, Bianchi B, Cinelli L, et al. Preoperative risk stratification of postoperative pancreatic fistula: A risk-tree predictive model for pancreatoduodenectomy. *Surgery.* 2021;170(6):1596-601.
 44. Pratt WB, Callery MP, Vollmer CM. Risk prediction for development of pancreatic fistula using the ISGPF classification scheme. *World J Surg.* 2008;32(3):419-28.

45. Shubert CR, Wagie AE, Farnell MB, Nagorney DM, Que FG, Reid Lombardo KM, et al. Clinical Risk Score to Predict Pancreatic Fistula after Pancreatoduodenectomy: Independent External Validation for Open and Laparoscopic Approaches. *J Am Coll Surg*. 2015;221(3):689-98.
46. Grendar J, Jutric Z, Leal JN, Ball CG, Bertens K, Dixon E, et al. Validation of Fistula Risk Score calculator in diverse North American HPB practices. *HPB (Oxford)*. 2017;19(6):508-14.
47. Petrova E, Lapshyn H, Bausch D, D'Haese J, Werner J, Klier T, et al. Risk stratification for postoperative pancreatic fistula using the pancreatic surgery registry StuDoQ|Pancreas of the German Society for General and Visceral Surgery. *Pancreatology*. 2019;19(1):17-25.
48. Yamamoto Y, Sakamoto Y, Nara S, Esaki M, Shimada K, Kosuge T. A preoperative predictive scoring system for postoperative pancreatic fistula after pancreaticoduodenectomy. *World J Surg*. 2011;35(12):2747-55.
49. Casadei R, Ricci C, Taffurelli G, D'Ambra M, Pacilio CA, Ingaldi C, et al. Are there preoperative factors related to a "soft pancreas" and are they predictive of pancreatic fistulas after pancreatic resection? *Surg Today*. 2015;45(6):708-14.
50. Pande R, Halle-Smith JM, Phelan L, Thorne T, Panikkar M, Hodson J, et al. External validation of postoperative pancreatic fistula prediction scores in pancreatoduodenectomy: a systematic review and meta-analysis. *HPB (Oxford)*. 2022;24(3):287-98.
51. Kang JS, Park T, Han Y, Lee S, Kim JR, Kim H, et al. Clinical validation of scoring systems of postoperative pancreatic fistula after pancreatoduodenectomy: applicability to Eastern cohorts? *Hepatobiliary Surg Nutr*. 2019;8(3):211-8.
52. Ryu Y, Shin SH, Park DJ, Kim N, Heo JS, Choi DW, et al. Validation of original and alternative fistula risk scores in postoperative pancreatic fistula. *J Hepatobiliary Pancreat Sci*. 2019;26(8):354-9.
53. Lao M, Zhang X, Guo C, Chen W, Zhang Q, Ma T, et al. External validation of alternative fistula risk score (a-FRS) for predicting pancreatic fistula after pancreatoduodenectomy. *HPB (Oxford)*. 2020;22(1):58-66.
54. Shinde RS, Acharya R, Chaudhari VA, Bhandare MS, Mungroop TH, Klompmaker S, et al. External validation and comparison of the original, alternative and updated-alternative fistula risk scores for the prediction of postoperative pancreatic fistula after pancreatoduodenectomy. *Pancreatology*. 2020;20(4):751-6.
55. Adamu M, Plodeck V, Adam C, Roehnert A, Welsch T, Weitz J, et al. Predicting postoperative pancreatic fistula in pancreatic head resections: which score fits all? *Langenbecks Arch Surg*. 2022;407(1):175-88.
56. Schouten TJ, Henry AC, Smits FJ, Besselink MG, Bonsing BA, Bosscha K, et al. Risk Models for Developing Pancreatic Fistula After Pancreatoduodenectomy: Validation in a Nationwide Prospective Cohort. *Ann Surg*. 2023;278(6):1001-8.
57. Sandini M, Malleo G, Gianotti L. Scores for Prediction of Fistula after Pancreatoduodenectomy: A Systematic Review. *Dig Surg*. 2016;33(5):392-400.
58. Carlos RC KC, Halabi S. Data science: big data, machine learning, and artificial intelligence. *J Am Coll Radiol*. 2018.
59. Bihorac A, Ozrazgat-Baslanti T, Ebadi A, Motaei A, Madkour M, Pardalos PM, et al. MySurgeryRisk: Development and Validation of a Machine-learning

- Risk Algorithm for Major Complications and Death After Surgery. *Ann Surg.* 2019;269(4):652-62.
60. Merath K, Hyer JM, Mehta R, Farooq A, Bagante F, Sahara K, et al. Use of Machine Learning for Prediction of Patient Risk of Postoperative Complications After Liver, Pancreatic, and Colorectal Surgery. *J Gastrointest Surg.* 2020;24(8):1843-51.
 61. Han IW, Cho K, Ryu Y, Shin SH, Heo JS, Choi DW, et al. Risk prediction platform for pancreatic fistula after pancreatoduodenectomy using artificial intelligence. *World J Gastroenterol.* 2020;26(30):4453-64.
 62. Sahara K, Paredes AZ, Tsilimigras DI, Sasaki K, Moro A, Hyer JM, et al. Machine learning predicts unpredicted deaths with high accuracy following hepatopancreatic surgery. *Hepatobiliary Surg Nutr.* 2021;10(1):20-30.
 63. Kambakamba P, Mannil M, Herrera PE, Müller PC, Kuemmerli C, Linecker M, et al. The potential of machine learning to predict postoperative pancreatic fistula based on preoperative, non-contrast-enhanced CT: A proof-of-principle study. *Surgery.* 2020;167(2):448-54.
 64. Mu W, Liu C, Gao F, Qi Y, Lu H, Liu Z, et al. Prediction of clinically relevant Pancreatico-enteric Anastomotic Fistulas after Pancreatoduodenectomy using deep learning of Preoperative Computed Tomography. *Theranostics.* 2020;10(21):9779-88.
 65. Ingwersen EW, Stam WT, Meijs BJV, Roor J, Besselink MG, Groot Koerkamp B, et al. Machine learning versus logistic regression for the prediction of complications after pancreatoduodenectomy. *Surgery.* 2023;174(3):435-40.
 66. Chowdhury MZI, Turin TC. Variable selection strategies and its importance in clinical prediction modelling. *Fam Med Community Health.* 2020;8(1):e000262.
 67. Hayashi H, Uemura N, Matsumura K, Zhao L, Sato H, Shiraishi Y, et al. Recent advances in artificial intelligence for pancreatic ductal adenocarcinoma. *World J Gastroenterol.* 2021;27(43):7480-96.
 68. Deo RC. Machine Learning in Medicine. *Circulation.* 2015;132(20):1920-30.
 69. Tu JV. Advantages and disadvantages of using artificial neural networks versus logistic regression for predicting medical outcomes. *J Clin Epidemiol* 1996. p. pp. 1225-31.
 70. LeCun Y, Bengio Y, Hinton G. Deep learning. *Nature.* 2015;521(7553):436-44.
 71. Schlanger D, Graur F, Popa C, Moiş E, Al Hajjar N. The role of artificial intelligence in pancreatic surgery: a systematic review. *Updates Surg.* 2022;74(2):417-29.
 72. Ramesh AN, Kambhampati C, Monson JR, Drew PJ. Artificial intelligence in medicine. *Ann R Coll Surg Engl.* 2004;86(5):334-8.
 73. Johnson AEWea. MIMIC-III, a freely accessible critical care database. . *Sci. Data* 3, 1600352016.
 74. Pollard TJe. The eICU Collaborative Research Database, a freely available multi- center database for critical care research. . *Sci. Data* 5, 1801782018.
 75. Guidi JL, Clark K, Upton MT, Faust H, Umscheid CA, Lane-Fall MB, et al. Clinician Perception of the Effectiveness of an Automated Early Warning and Response System for Sepsis in an Academic Medical Center. *Ann Am Thorac Soc.* 2015;12(10):1514-9.

76. Hernandez-Boussard T, Bozkurt S, Ioannidis JPA, Shah NH. MINIMAR (MINimum Information for Medical AI Reporting): Developing reporting standards for artificial intelligence in health care. *J Am Med Inform Assoc.* 2020;27(12):2011-5.
77. Miller T. Explanation in Artificial Intelligence: Insights from the Social Sciences. . arXiv e-prints arXiv:1706.07269 2017.
78. Kim B, Khanna, R. & Koyejo, O. Examples are not enough, learn to criticize! Criticism for interpretability. in *Advances in Neural Information Processing Systems* 2288–2296. 2016.
79. RD. D. New classification of physical status. *Anesthesiology.* . 1963.
80. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;240(2):205-13.
81. Kim D, You S, So S, Lee J, Yook S, Jang DP, et al. A data-driven artificial intelligence model for remote triage in the prehospital environment. *PLoS One.* 2018;13(10):e0206006.
82. Smith CL. Three doctor-writers and how they heal. *Pharos Alpha Omega Alpha Honor Med Soc.* 1988;51(2):6-12.
83. Li P, Stuart EA, Allison DB. Multiple Imputation: A Flexible Tool for Handling Missing Data. *JAMA.* 2015;314(18):1966-7.
84. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. *N Engl J Med.* 2011;364(22):2128-37.
85. Tamirisa NP, Parmar AD, Vargas GM, Mehta HB, Kilbane EM, Hall BL, et al. Relative Contributions of Complications and Failure to Rescue on Mortality in Older Patients Undergoing Pancreatectomy. *Ann Surg.* 2016;263(2):385-91.
86. Kutlu OC, Lee JE, Katz MH, Tzeng CD, Wolff RA, Varadhachary GR, et al. Open Pancreaticoduodenectomy Case Volume Predicts Outcome of Laparoscopic Approach: A Population-based Analysis. *Ann Surg.* 2018;267(3):552-60.
87. Chen Q, Beal EW, Kimbrough CW, Bagante F, Merath K, Dillhoff M, et al. Perioperative complications and the cost of rescue or failure to rescue in hepato-pancreato-biliary surgery. *HPB (Oxford).* 2018;20(9):854-64.
88. Ecker BL, McMillan MT, Allegrini V, Bassi C, Beane JD, Beckman RM, et al. Risk Factors and Mitigation Strategies for Pancreatic Fistula After Distal Pancreatectomy: Analysis of 2026 Resections From the International, Multi-institutional Distal Pancreatectomy Study Group. *Ann Surg.* 2019;269(1):143-9.
89. Parray AM, Chaudhari VA, Shrikhande SV, Bhandare MS. "Mitigation strategies for post-operative pancreatic fistula after pancreaticoduodenectomy in high-risk pancreas: an evidence-based algorithmic approach"-a narrative review. *Chin Clin Oncol.* 2022;11(1):6.
90. Simon R. Complications After Pancreaticoduodenectomy. *Surg Clin North Am.* 2021;101(5):865-74.
91. Loftus TJ, Tighe PJ, Filiberto AC, Efron PA, Brakenridge SC, Mohr AM, et al. Artificial Intelligence and Surgical Decision-making. *JAMA Surg.* 2020;155(2):148-58.
92. Solanki SL, Pandrowala S, Nayak A, Bhandare M, Ambulkar RP, Shrikhande SV. Artificial intelligence in perioperative management of major gastrointestinal surgeries. *World J Gastroenterol.* 2021;27(21):2758-70.

93. Pera M, Gibert J, Gimeno M, Garsot E, Eizaguirre E, Miró M, et al. Machine Learning Risk Prediction Model of 90-day Mortality After Gastrectomy for Cancer. *Ann Surg.* 2022;276(5):776-83.
94. Tseng PY, Chen YT, Wang CH, Chiu KM, Peng YS, Hsu SP, et al. Prediction of the development of acute kidney injury following cardiac surgery by machine learning. *Crit Care.* 2020;24(1):478.
95. Capretti G, Bonifacio C, De Palma C, Nebbia M, Giannitto C, Cancian P, et al. A machine learning risk model based on preoperative computed tomography scan to predict postoperative outcomes after pancreatoduodenectomy. *Updates Surg.* 2022;74(1):235-43.
96. Xue B, Li D, Lu C, King CR, Wildes T, Avidan MS, et al. Use of Machine Learning to Develop and Evaluate Models Using Preoperative and Intraoperative Data to Identify Risks of Postoperative Complications. *JAMA Netw Open.* 2021;4(3):e212240.
97. Zeng S, Li L, Hu Y, Luo L, Fang Y. Machine learning approaches for the prediction of postoperative complication risk in liver resection patients. *BMC Med Inform Decis Mak.* 2021;21(1):371.
98. Guo C, Xie B, Guo D. Does pancreatic duct stent placement lead to decreased postoperative pancreatic fistula rates after pancreaticoduodenectomy? A meta-analysis. *Int J Surg.* 2022;103:106707.
99. Xiong JJ, Altaf K, Mukherjee R, Huang W, Hu WM, Li A, et al. Systematic review and meta-analysis of outcomes after intraoperative pancreatic duct stent placement during pancreaticoduodenectomy. *Br J Surg.* 2012;99(8):1050-61.
100. Jiang Y, Chen Q, Wang Z, Shao Y, Hu C, Ding Y, et al. The Prognostic Value of External. *J Invest Surg.* 2021;34(7):738-46.
101. Mason MC, Garcia JM, Sansgiry S, Walder A, Berger DH, Anaya DA. Preoperative cancer cachexia and short-term outcomes following surgery. *J Surg Res.* 2016;205(2):398-406.
102. Cho SW, Tzeng CW, Johnston WC, Cassera MA, Newell PH, Hammill CW, et al. Neoadjuvant radiation therapy and its impact on complications after pancreaticoduodenectomy for pancreatic cancer: analysis of the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP). *HPB (Oxford).* 2014;16(4):350-6.
103. Doshi S, Abad J, Wells A, Chawla A. Weight loss during neoadjuvant chemotherapy impacts perioperative outcomes in patients undergoing surgery for pancreatic cancer. *Pancreatology.* 2023;23(8):1020-7.
104. Tripepi M, Pizzocaro E, Giardino A, Frigerio I, Guglielmi A, Butturini G. Telemedicine and Pancreatic Cancer: A Systematic Review. *Telemed J E Health.* 2023;29(3):352-60.
105. Sauvanet A, Boher JM, Paye F, Bachellier P, Sa Cuhna A, Le Treut YP, et al. Severe Jaundice Increases Early Severe Morbidity and Decreases Long-Term Survival after Pancreaticoduodenectomy for Pancreatic Adenocarcinoma. *J Am Coll Surg.* 2015;221(2):380-9.
106. van der Gaag NA, Kloek JJ, de Castro SM, Busch OR, van Gulik TM, Gouma DJ. Preoperative biliary drainage in patients with obstructive jaundice: history and current status. *J Gastrointest Surg.* 2009;13(4):814-20.
107. Strasberg SM, Gao F, Sanford D, Linehan DC, Hawkins WG, Fields R, et al. Jaundice: an important, poorly recognized risk factor for diminished survival in

- patients with adenocarcinoma of the head of the pancreas. *HPB (Oxford)*. 2014;16(2):150-6.
108. Sewnath ME, Karsten TM, Prins MH, Rauws EJ, Obertop H, Gouma DJ. A meta-analysis on the efficacy of preoperative biliary drainage for tumors causing obstructive jaundice. *Ann Surg*. 2002;236(1):17-27.
109. Sohn TA, Yeo CJ, Cameron JL, Pitt HA, Lillemoe KD. Do preoperative biliary stents increase postpancreaticoduodenectomy complications? *J Gastrointest Surg*. 2000;4(3):258-67; discussion 67-8.
110. De Pastena M, Marchegiani G, Paiella S, Malleo G, Ciprani D, Gasparini C, et al. Impact of preoperative biliary drainage on postoperative outcome after pancreaticoduodenectomy: An analysis of 1500 consecutive cases. *Dig Endosc*. 2018;30(6):777-84.
111. van der Gaag NA, Rauws EA, van Eijck CH, Bruno MJ, van der Harst E, Kubben FJ, et al. Preoperative biliary drainage for cancer of the head of the pancreas. *N Engl J Med*. 2010;362(2):129-37.
112. Mosquera C, Mitsakos AT, Guyton RL, Fitzgerald TL, Zervos EE. When Is It Safe to Proceed With Pancreaticoduodenectomy Without Biliary Decompression? *Am Surg*. 2021;87(5):825-32.
113. Tempero MA, Malafa MP, Al-Hawary M, Behrman SW, Benson AB, Cardin DB, et al. Pancreatic Adenocarcinoma, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2021;19(4):439-57.
114. Srivastava S, Sikora SS, Pandey CM, Kumar A, Saxena R, Kapoor VK. Determinants of pancreaticoenteric anastomotic leak following pancreaticoduodenectomy. *ANZ J Surg*. 2001;71(9):511-5.
115. Chu CK, Mazo AE, Sarmiento JM, Staley CA, Adsay NV, Umpierrez GE, et al. Impact of diabetes mellitus on perioperative outcomes after resection for pancreatic adenocarcinoma. *J Am Coll Surg*. 2010;210(4):463-73.
116. Cheng Q, Zhang B, Zhang Y, Jiang X, Yi B, Luo X, et al. Predictive factors for complications after pancreaticoduodenectomy. *J Surg Res*. 2007;139(1):22-9.
117. Hank T, Sandini M, Qadan M, Weniger M, Ciprani D, Li A, et al. Diabetes mellitus is associated with unfavorable pathologic features, increased postoperative mortality, and worse long-term survival in resected pancreatic cancer. *Pancreatology*. 2020;20(1):125-31.
118. Lin JW, Cameron JL, Yeo CJ, Riall TS, Lillemoe KD. Risk factors and outcomes in postpancreaticoduodenectomy pancreaticocutaneous fistula. *J Gastrointest Surg*. 2004;8(8):951-9.
119. Dreiseitl S, Ohno-Machado L. Logistic regression and artificial neural network classification models: a methodology review. *J Biomed Inform*. 2002;35(5-6):352-9.
120. Weng SF, Reys J, Kai J, Garibaldi JM, Qureshi N. Can machine-learning improve cardiovascular risk prediction using routine clinical data? *PLoS One*. 2017;12(4):e0174944.
121. Sugita H, Okabe H, Ogawa D, Hirao H, Kuroda D, Taki K, et al. Preoperative serum CA19-9 predicts postoperative pancreatic fistula in PDAC patients: retrospective analysis at a single institution. *BMC Surg*. 2022;22(1):367.
122. Santucci N, Facy O, Ortega-Deballon P, Lequeu JB, Rat P. CA 19-9 predicts resectability of pancreatic cancer even in jaundiced patients. *Pancreatology*. 2018;18(6):666-70.

123. Ahmad MU, Javadi CS, Chang JD, Forgó E, Delitto DJ, Dua MM, et al. Biochemical, Radiographic, or Pathologic Response to Neoadjuvant Chemotherapy in Resected Pancreatic Cancer: Which is Best? *Ann Surg.* 2024.
124. Bao QR, Frigerio I, Tripepi M, Marletta S, Martignoni G, Giardino A, et al. Prognostic value of major pathological response following neoadjuvant therapy for non resectable pancreatic ductal adenocarcinoma. *Pancreatology.* 2023;23(3):266-74.
125. Bartoli FG, Arnone GB, Ravera G, Bachi V. Pancreatic fistula and relative mortality in malignant disease after pancreaticoduodenectomy. Review and statistical meta-analysis regarding 15 years of literature. *Anticancer Res.* 1991;11(5):1831-48.
126. van Dongen JC, Suker M, Versteijne E, Bonsing BA, Mieog JSD, de Vos-Geelen J, et al. Surgical Complications in a Multicenter Randomized Trial Comparing Preoperative Chemoradiotherapy and Immediate Surgery in Patients With Resectable and Borderline Resectable Pancreatic Cancer (PREOPANC Trial). *Ann Surg.* 2022;275(5):979-84.
127. van Dongen JC, Wismans LV, Suurmeijer JA, Besselink MG, de Wilde RF, Groot Koerkamp B, et al. The effect of preoperative chemotherapy and chemoradiotherapy on pancreatic fistula and other surgical complications after pancreatic resection: a systematic review and meta-analysis of comparative studies. *HPB (Oxford).* 2021;23(9):1321-31.
128. Aoki S, Miyata H, Konno H, Gotoh M, Motoi F, Kumamaru H, et al. Risk factors of serious postoperative complications after pancreaticoduodenectomy and risk calculators for predicting postoperative complications: a nationwide study of 17,564 patients in Japan. *J Hepatobiliary Pancreat Sci.* 2017;24(5):243-51.
129. Castleberry AW, White RR, De La Fuente SG, Clary BM, Blazer DG, McCann RL, et al. The impact of vascular resection on early postoperative outcomes after pancreaticoduodenectomy: an analysis of the American College of Surgeons National Surgical Quality Improvement Program database. *Ann Surg Oncol.* 2012;19(13):4068-77.