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Machine learning-based prediction of postoperative pancreatic fistula after laparoscopic pancreaticoduodenectomy

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Abstract

Background Clinically relevant postoperative pancreatic fistula (CR-POPF) following laparoscopic pancreaticoduodenectomy (LPD) is a critical complication that significantly worsens patient outcomes. However, the heterogeneity of its risk factors and the clinical utility of predictive models remain to be fully elucidated. This study aims to systematically analyze the risk factors for CR-POPF and develop an optimized predictive model using machine learning algorithms, providing an evidence-based approach for individualized risk assessment in patients undergoing LPD.

Methods A retrospective study was conducted, including 210 patients with periampullary cancer who underwent laparoscopic pancreaticoduodenectomy (LPD) at the Hepatobiliary Surgery Center, Olympic Stadium Campus, Shandong Provincial Hospital Affiliated to Shandong First Medical University, from January 2017 to January 2024. Patients were classified into the clinically relevant pancreatic fistula (CR-POPF) group (n = 34) and the non-clinically relevant pancreatic fistula (non-CR-POPF) group (n = 176) according to the 2016 criteria of the International Study Group of Pancreatic Surgery (ISGPS). Potential risk factors were identified through intergroup comparisons, and independent risk factors were determined using univariate and multivariate logistic regression analyses. Based on these findings, a predictive model for CR-POPF was developed using machine learning algorithms.

Results CR-POPF was associated with higher BMI, monocyte levels, platelet count, total bilirubin, AST, ALT, and lower albumin. Pathological diagnosis of ampullary carcinoma and soft pancreatic texture were significantly more common in the CR-POPF group. Multivariate analysis identified soft pancreatic texture as an independent predictor (OR = 4.99, 95% CI: 1.93–12.86). Among all models, the random forest model showed the best performance (AUC = 0.747, sensitivity = 0.917, specificity = 0.574), using only preoperative variables such as age, gender, BMI, hypertension, diabetes, hemoglobin, platelets, AST, and ALT.

Conclusion Soft pancreatic texture was identified as an independent risk factor for postoperative pancreatic fistula following laparoscopic pancreaticoduodenectomy (LPD). The random forest model based on preoperative clinical variables enables individualized risk prediction, offering value for preoperative planning and postoperative care.

Keywords Laparoscopic pancreaticoduodenectomy, Clinically relevant postoperative pancreatic fistula, Postoperative complications, Machine learning, Predictive model

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Introduction

Pancreaticoduodenectomy (PD) is a classical surgical procedure for tumors located in the periampullary region including pancreatic head, ampulla, periampullary duodenum, and distal common bile duct. However,

its complexity and high risk of perioperative complications historically led to elevated postoperative mortality rates [1–3]. In recent years, advancements in surgical techniques, perioperative management, and minimally invasive surgery have promoted the increasing adoption of laparoscopic pancreaticoduodenectomy (LPD), demonstrating advantages such as reduced intraoperative blood loss and accelerated postoperative recovery [4,5]. Nevertheless, postoperative complications, particularly clinically relevant postoperative pancreatic fistula (CR-POPF), remain prevalent following LPD, occurring in approximately 10%–30% of patients, and significantly impacting patient prognosis and recovery [6,7].

Clinical studies indicate that several factors influence the occurrence of CR-POPF, including soft pancreatic texture, pancreatic duct diameter ≤ 3 mm, and elevated BMI [8–10]. However, most existing research has focused on identifying risk factors and developing predictive models based on open pancreaticoduodenectomy (OPD). Due to the distinct technical features of LPD, such as restricted laparoscopic working space and increased difficulty in pancreatoenteric anastomosis, the direct application of OPD-derived risk factors may lead to prediction biases. For example, although a small pancreatic duct diameter is widely recognized as a risk factor for CR-POPF in OPD, recent comparative studies have shown that its predictive value is significantly reduced in LPD patients [11]. The refined surgical techniques in LPD, such as improved laparoscopic precision, may reduce the impact of small pancreatic ducts on CR-POPF. In contrast, soft pancreatic texture is considered a more stable and important predictor in LPD surgery [2]. Therefore, identifying specific risk factors for CR-POPF in the context of LPD is crucial.

In predicting CR-POPF, traditional statistical methods like logistic regression can identify independent risk factors but have limited ability to capture complex, nonlinear relationships between variables, restricting their capability to integrate multidimensional clinical data for accurate prediction. In contrast, machine learning (ML) techniques have distinct advantages in big data analytics and pattern recognition, enabling the construction of highly accurate predictive models capable of handling nonlinear, high-dimensional, and intricate interactive relationships [12]. Recently, ML methods have increasingly been applied in the development of surgical predictive models for postoperative complications, tumor staging, and personalized treatment decisions [13–17]. Additionally, existing studies have applied machine learning (ML) methods in various areas of pancreatic surgery, including postoperative complication prediction, lymph node metastasis assessment, and individualized surgical decision-making. These ML models have demonstrated superior predictive accuracy, such as higher AUC, compared to traditional models [18–20]. However, research specifically using machine learning to predict CR-POPF after LPD remains relatively limited, and the clinical feasibility and predictive performance of existing models require further optimization.

Thus, this study aimed to identify independent risk factors for CR-POPF after LPD and to enhance the predictive accuracy of CR-POPF using ML models. The results aim to facilitate preoperative risk stratification, intraoperative decision-making, and postoperative management in high-risk LPD patients, thereby reducing the incidence of CR-POPF, improving patient outcomes, and advancing precision surgery practice.

Materials and methods

Patients

This study retrospectively analyzed data from 313 patients who underwent laparoscopic pancreatoduodenectomy (LPD) at our institution between January 2017 and January 2024. Patients were included if they met the following criteria: a) they underwent elective LPD; b) preoperative imaging indicated that the tumor was resectable, without invasion of major vascular structures or distant metastasis, according to National Comprehensive Cancer Network (NCCN) guidelines; and c) postoperative pathology confirmed a diagnosis of periampullary cancer. Based on these criteria, 255 patients were eligible for the study. Exclusion criteria were: a) patients who underwent open pancreatoduodenectomy or required conversion to open surgery during the procedure (25 cases); b) patients who received neoadjuvant chemotherapy (16 cases); and c) patients with incomplete or missing clinical data (4 cases). After applying these criteria, 210 patients were included in the final analysis. These patients were divided into two groups based on the occurrence of clinically relevant postoperative pancreatic fistula (CR-POPF):CR-POPF Group (34 patients) and Non-CR-POPF Group (176 patients).A detailed flowchart of the patient selection process is provided in Fig. 1.

Patient Characteristics and Outcome Variable

The primary outcome variable was clinically relevant postoperative pancreatic fistula (CR-POPF; grade B or C fistula), defined according to the 2016 criteria of the International Study Group on Pancreatic Surgery (ISGPS) [21]. Preoperative baseline characteristics included demographic data, comorbidities, and laboratory parameters assessing hematologic, hepatic, and renal function. Intraoperative variables consisted of pancreas texture, pancreatic duct diameter, operative time, and intraoperative blood loss.

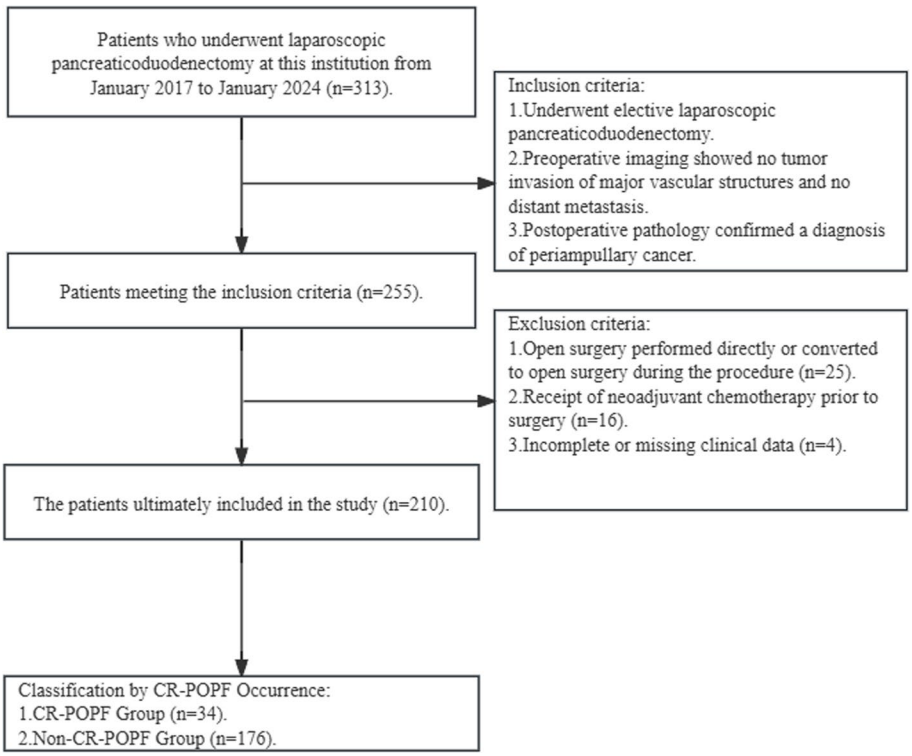

Fig. 1 Patient Screening and Group Division Flowchart

Statistical methods

All statistical analyses were performed using R software (Version 4.3.2; R Core Team, 2023). Categorical variables were summarized as absolute and relative frequencies, while continuous variables were expressed as mean ± standard deviation (SD) for normally distributed data and median with interquartile range (IQR) for non-normally distributed data. Comparisons between the clinically relevant postoperative pancreatic fistula (CR-POPF) group and the non-CR-POPF group were conducted using the independent samples t-test for normally distributed continuous variables, the Wilcoxon rank-sum test (Mann–Whitney U test) for non-normally distributed continuous variables, and the chi-square (χ^2) test for categorical variables. Four machine learning algorithms were employed to develop predictive models for clinical prognosis. The dataset was randomly split in a 7:3 ratio, with 70% of the data allocated to the training set for model construction and 30% to the validation set for performance evaluation. The predictive models were assessed using area under the curve (AUC), specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV). The significance level was set at $\alpha = 0.05$, with $P \leq 0.05$ considered statistically significant. For the Random Forest algorithm, we conducted hyperparameter tuning to optimize the number of trees in the decision tree. The results indicated that for Models 1, 2, 3, 4, and 5, the highest predictive accuracy on the training set was achieved when the number of trees was 60, 34, 41, 136, and 30, respectively (with a range of 1 to 500). The relationship between the number of trees in the Random Forest and model error is depicted in Appendix Figure 1.For the Support Vector Machine (SVM), we performed training and selection of kernel functions, considering both linear and polynomial kernels. In addition, hyperparameter tuning was carried out for the misclassification penalty parameter (C values = 0.0001, 0.001, 0.01, 1, 5, 10).Other institutions can apply our dataset using a 70:30 split for training and testing, with the random seed set to set.seed(123). By following the same hyperparameter tuning approach, they should be able to replicate the results obtained in this study. The machine learning models were primarily constructed using the Random Forest function from the Random Forest package and the tune.svm function from the e1071 package in R software (version 4.3.2) for building the Random Forest and Support Vector Machine models, respectively. Missing data were addressed using Complete Case Analysis, as the proportion of missing data in this study was minimal. Detailed information regarding the number of missing data points and their corresponding proportions can be found in Appendix Table 1. The highest missing

data rate was 5.238%, with only three variables showing a missing data rate greater than 5%. The majority of variables had missing data rates of less than 1%, and the proportion of variables with complete data was 45.4% (15/33). To improve the model's interpretability, we calculated the feature importance scores from the trained Random Forest model and visualized the variable importance using the Gini Index. The resulting plot illustrates the mean decrease in Gini impurity for each feature, providing insights into how each variable contributes to the model's predictive power. This evaluation was performed using the random Forest package's built-in functionality.

Results

Comparison of Preoperative Data Between Two Groups

Table 1 compares the preoperative general characteristics and laboratory parameters between the clinically relevant postoperative pancreatic fistula (CR-POPF) group (n = 34) and the non-clinically relevant postoperative pancreatic fistula (non-CR-POPF) group (n = 176). The results indicate no significant differences between the two groups in terms of sex, diabetes, hypertension, coronary heart disease (CHD), age, pulmonary ventilation reserve (VR%), left ventricular ejection fraction (LVEF), white blood cell count (WBC), hemoglobin (HGB), lymphocyte percentage (LYMPH%), neutrophil percentage (NEUT%), lymphocyte count (LYMPH#), neutrophil count (NEUT#), γ-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), prealbumin (PA), total protein (TP), creatinine (Cr), and blood urea nitrogen (BUN) (all P > 0.05). However, the CR-POPF group exhibited significantly higher BMI (P = 0.010), platelet count (PLT) (P = 0.038), monocyte count (MONO) (P = 0.002), total bilirubin (TBIL) (P = 0.032), aspartate aminotransferase (AST) (P = 0.021), and alanine aminotransferase (ALT) (P = 0.034) compared to the non-CR-POPF group. Conversely, albumin (ALB) levels were significantly lower in the CR-POPF group (P = 0.004).

Table 1 Comparison of Preoperative General Characteristics

Variables	non-CR-POPF	CR-POPF	t/Z/x^2	P-value
Gender				
Male	103 (58.5%)	21 (61.8%)	0.124	0.725
Female	73 (41.5%)	13 (38.2%)		
Diabetes				
No	140 (79.5%)	29 (85.3%)	0.599	0.439
Yes	36 (20.5%)	5 (14.7)		
Hypertension				
No	136 (77.3%)	25 (73.5%)	0.233	0.637
Yes	40 (20.5%)	9 (26.5%)		
CHD				
No	163 (92.6%)	32 (94.1%)	0.097	0.755
Yes	13 (7.4%)	2 (5.9%)		
Age(year)	60.03 ± 10.45	59.44 ± 9.973	0.305	0.761
BMI(kg/m^2)	23.10 ± 3.15	24.62 ± 3.14	−2.587	0.010*
VR%	85.95 ± 3.59	85.39 ± 3.68	0.811	0.418
LVEF	61.46 ± 1.24	61.45 ± 1.12	0.011	0.991
WBC(10^9/L)	6.38 ± 1.87	6.78 ± 2.25	−1.090	0.277
Hb(g/L)	120.54 ± 16.45	120.03 ± 19.36	0.161	0.872
PLT(10^9/L)	250.27 ± 88.50	284.06 ± 66.08	−2.084	0.038*
LYMPH(10^9/L)	1.47 ± 0.54	1.46 ± 0.47	0.118	0.960
MONO(10^9/L)	0.55 ± 0.19	0.67 ± 0.25	−3.146	0.002*
NEUT(10^9/L)	4.30 ± 2.01	4.65 ± 2.23	−0.888	0.375
AST(U/L)	67.50(31,140)	94.50(51,152.25)	−1.875	0.021*
ALT(U/L)	96.0(41.25,189.75)	145.0(63.75,229)	−0.888	0.034*
GGT(U/L)	425(98.5,688)	702.5(225,104.25)	−2.312	0.061
ALP(U/L)	323(160.5,510)	507(259.5,709)	−2.116	0.217
PA(mg/L)	162.09 ± 57.92	143.06 ± 43.73	1.738	0.084
ALB(g/L)	37.07 ± 4.37	34.36 ± 7.01	2.920	0.004*
TP(g/L)	62.60(59.30,67.08)	61.85(57.98,67.53)	−0.347	0.728
TBIL(μmol/L)	106.6(31.5,209.25)	159.7(63.77,299.65)	−2.140	0.032*
Cr(μmol/L)	52.4(36.1,65.4)	58.3(50.35,67.85)	−1.323	0.186
BUN(μmol/L)	5.10(4.10,9.70)	5.25(4.30,6.20)	−0.382	0.703

P < 0.05 was considered statistically significant

Comparison of Intraoperative Data

Table 2 compares the intraoperative characteristics between the non-clinically relevant postoperative pancreatic fistula (non-CR-POPF) group and the clinically relevant postoperative pancreatic fistula (CR-POPF) group. The results indicate a significant difference in pancreatic texture between the two groups, with a higher proportion of soft pancreas observed in the CR-POPF group compared to the non-CR-POPF group (52.9% vs. 18.9%, P < 0.001). No significant difference was found in pancreatic duct diameter between the two groups (P = 0.524). Similarly, operative time (P = 0.172) and intraoperative blood loss (P = 0.168) did not differ significantly between the groups. However, a significant difference was noted in pathological diagnosis, with a higher proportion of ampullary cancer in the CR-POPF group compared to the non-CR-POPF group (85.3% vs. 65.3%, P = 0.022). These findings suggest that soft pancreatic texture and ampullary cancer may be associated with an increased risk of clinically relevant postoperative pancreatic fistula, while pancreatic duct diameter, operative time, and intraoperative blood loss do not appear to be significant influencing factors.

Risk Factors for CR-POPF: Logistic Analysis

The variables with a P-value < 0.05 in Tables 1 and 2 were included in the multivariate logistic regression analysis. The results revealed that soft pancreatic texture was

Table 2 Comparison of Intraoperative Characteristics

Variables	non-CR-POPF	CR-POPF	t/Z/x^2	P-value
Pancreatic texture				< 0.001*
Soft	33(18.9%)	18(52.9%)	17.928	
Hard	142(81.1%)	16(47.1%)		
Pancreatic duct diameter(mm)	5.13 ± 1.35	5.29 ± 1.73	5.373	0.524
Operative time(min)	426.52 ± 91.47	450.41 ± 100.52	−1.372	0.172
Intraoperative blood loss(ml)	303.69 ± 100.81	329.71 ± 97.90	−1.384	0.168
Pathological Diagnosis Pancreatic Cancer Ampullary Cancer	61(34.7%) 115(65.3%)	5(14.7%) 29(85.3%)	5.264	0.022*

P < 0.05 was considered statistically significant

Table 3 Multivariate Logistic Regression Analysis

Risk Factor	B	Odds Ratio(OR)	95%CI	P-value
BMI	0.1138	1.12	0.97–1.29	0.112
PLT	0.0045	1.005	0.99–1.01	0.121
MONO%	0.0923	1.10	0.87–1.38	0.426
MONO	1.1075	3.03	0.26–34.59	0.373
AST	0.0064	1.01	1.00–1.01	0.082
ALT	−0.0046	0.995	0.99–1.00	0.139
ALB	−0.0583	0.94	0.83–1.07	0.374
TBIL	0.0021	1.002	0.99–1.01	0.281
Pancreatic texture	1.6070	4.99	1.93–12.86	0.001*
Pathological Diagnosis	0.7969	2.22	0.63–7.82	0.215

P < 0.05 was considered statistically significant

identified as an independent risk factor for pancreatic fistula (OR = 0.20, 95% CI: 0.08–0.52, P = 0.001), indicating that patients with a firm pancreas had a significantly lower risk of developing pancreatic fistula compared to those with a soft pancreas. Although BMI, AST, and pathological type had OR values greater than 1, suggesting a potential increase in the risk of pancreatic fistula, these factors did not reach statistical significance (P > 0.05). Additionally, preoperative factors such as platelet count, monocyte count, albumin, and total bilirubin showed no significant correlation with the occurrence of pancreatic fistula (P > 0.05). In conclusion, a soft pancreatic texture is an independent risk factor for CR-POPF, highlighting the clinical significance of pancreatic texture in predicting postoperative pancreatic fistula. However, the influence of other factors requires further investigation and validation. Detailed information is presented in Table 3.

Machine Learning Model for Predicting CR-POPF

To construct a predictive model for clinically relevant postoperative pancreatic fistula (CR-POPF), this study proposed five candidate models based on existing clinical research on factors influencing complications following laparoscopic pancreaticoduodenectomy and the relevant risk factors identified in this study. Four machine learning methods were employed: Random Forest (RF), Support Vector Machine with a Linear Kernel (SVM-L), Support Vector Machine with a Polynomial Kernel (SVM-P), and Logistic Regression (Logistic). The data were randomly split into a training set and a validation set at a ratio of 7:3, with 70% of the data used for model training and 30% for model validation. Model performance was evaluated using the Area Under the Curve (AUC), specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV). Detailed information on the models is provided in Table 4.

Predictive Model Analysis for CR-POPF

This study employed five candidate predictive models (Model 1 to Model 5) to predict clinically relevant postoperative pancreatic fistula (CR-POPF) using four machine learning algorithms: Random Forest (RF), Support Vector Machine with a Linear Kernel (SVM-L), Support Vector Machine with a Polynomial Kernel (SVM-P), and Logistic Regression (Logistic). The predictive performance of these models on the training and testing datasets is presented in Tables 5 and 6, respectively. On the training dataset, the Random Forest (RF) model demonstrated the best performance, achieving an AUC value of 1.000, along with specificity, sensitivity, negative predictive value (NPV), and positive predictive value (PPV) all equal to 1.000 (Table 5, Fig. 2). In the validation dataset, Model 4 (Age + Gender + BMI + Hypertension + Diabetes + HGB + PLT + ALT + AST) achieved the highest AUC value of 0.747, with a sensitivity of 0.917 and specificity of 0.574 (Table 6, Fig. 2). Appendix Figure 2 illustrates the predictive performance of Model 4 under the Random Forest algorithm, further emphasizing

Table 4 Candidate Models for CR-POPF Prediction

Model	Variables
Model 1	Age + Gender + BMI + Hypertension + Diabetes + Hb + WBC + ALB + PLT
Model 2	Age + Gender + BMI + Hypertension + Diabetes + Operation Duration + Pathological Diagnosis + Pancreas Texture + Pancreatic Duct Diameter
Model 3	Age + Gender + BMI + Hypertension + Diabetes + LYMPH% + WBC + MONO% + NEUT + LYMPH + MONO
Model 4	Age + Gender + BMI + Hypertension + Diabetes + HGB + PLT + ALT + AST
Model 5	Age + Gender + BMI + Hypertension + Diabetes + SCR + BUN + TBIL

Table 5 Predicted Results of Five Models for CR-POPF in Training Data

Model	Methods	Threshold	AUC	Spe	Sen	NPV	PPV
1	RF	0.600	1.000	1.000	1.000	1.000	1.000
	SVM-L	0.838	0.699	0.534	0.842	0.948	0.250
	SVM-P	0.851	0.947	0.922	0.947	0.990	0.692
	Logistic	0.210	0.810	0.816	0.737	0.944	0.424
2	RF	0.529	1.000	1.000	1.000	1.000	1.000
	SVM-L	0.839	0.686	0.771	0.550	0.900	0.314
	SVM-P	0.844	0.974	0.962	0.950	0.990	0.826
	Logistic	0.154	0.793	0.714	0.800	0.949	0.348
3	RF	0.598	1.000	1.000	1.000	1.000	1.000
	SVM-L	0.850	0.715	0.570	0.800	0.934	0.271
	SVM-P	0.832	0.929	0.950	0.850	0.969	0.773
	Logistic	0.171	0.782	0.700	0.800	0.946	0.348
4	RF	0.566	1.000	1.000	1.000	1.000	1.000
	SVM-L	0.868	0.613	0.822	0.471	0.902	0.308
	SVM-P	0.855	0.925	0.950	0.882	0.980	0.750
	Logistic	0.241	0.653	0.921	0.412	0.903	0.467
5	RF	0.567	1.000	1.000	1.000	1.000	1.000
	SVM-L	0.821	0.590	0.800	0.450	0.884	0.300
	SVM-P	0.831	0.904	0.952	0.800	0.962	0.762
	Logistic	0.129	0.760	0.600	0.850	0.955	0.288

Threshold, values above and equal to threshold was classed into the case group; AUC, area under the curve; Spe, specificity; Sen, Sensitivity; NPV: negative predict value; PPV: positive predict value. RF, random forest; SVM-L, support vector machine with linear kernel; SVM-P, support vector machine with polynomial kernel, Logistic, logistic regression model

the importance of different variables in the prediction process. The chart shows the Gini index (MeanDecreaseGini) for each variable, where a higher value indicates that the variable plays a more significant role in the model's predictions. Key variables such as BMI, PLT, and AST have higher importance, underscoring their crucial role in predicting clinically relevant postoperative pancreatic fistula (CR-POPF). In contrast, variables like age, gender, and diabetes contribute less to the model's performance. These results suggest that Model 4, utilizing the Random Forest algorithm, may be suitable for predicting CR-POPF in clinical practice.

Discussion

This study systematically analyzed data from 210 patients who underwent laparoscopic pancreaticoduodenectomy (LPD), revealing a clinically relevant postoperative pancreatic fistula (CR-POPF, defined as Grade B or C according to ISGPS) incidence of 16.2% (34/210). Compared to the non-CR-POPF group, patients in the CR-POPF group exhibited significant preoperative abnormalities, including higher body mass index (BMI), elevated peripheral blood monocyte ratio and absolute count, increased platelet count, elevated liver function markers (AST, ALT, and total bilirubin), and reduced albumin levels (all

Table 6 Predicted Results of Five Models for CR-POPF in Test Data

Model	Methods	Threshold	AUC	Spe	Sen	NPV	PPV
1	RF	0.725	0.604	0.853	0.385	0.879	0.333
	SVM-L	0.837	0.501	0.500	0.615	0.872	0.190
	SVM-P	0.872	0.567	0.912	0.308	0.873	0.400
	Logistic	0.170	0.563	0.691	0.538	0.887	0.250
2	RF	0.868	0.503	0.543	0.571	0.864	0.200
	SVM-L	0.840	0.502	0.800	0.357	0.862	0.263
	SVM-P	0.828	0.617	0.843	0.429	0.881	0.353
	Logistic	0.178	0.643	0.829	0.500	0.892	0.368
3	RF	0.610	0.527	0.970	0.231	0.865	0.600
	SVM-L	0.845	0.597	0.636	0.692	0.913	0.273
	SVM-P	0.846	0.607	0.545	0.769	0.923	0.250
	Logistic	0.146	0.618	0.758	0.538	0.893	0.304
4	RF	0.846	**0.747***	0.574	0.917	0.975	0.275
	SVM-L	0.853	0.609	0.471	0.917	0.970	0.234
	SVM-P	0.855	0.627	0.735	0.667	0.926	0.308
	Logistic	0.165	0.679	0.809	0.583	0.917	0.350
5	RF	0.950	0.586	0.300	0.929	0.955	0.210
	SVM-L	0.827	0.609	0.529	0.786	0.925	0.250
	SVM-P	0.866	0.639	0.400	0.929	0.966	0.236
	Logistic	0.209	0.594	0.343	0.929	0.960	0.220

Threshold, values above and equal to threshold was classed into the case group; AUC, area under the curve; Spe, specificity; Sen, Sensitivity; NPV: negative predict value; PPV: positive predict value. RF, random forest; SVM-L, support vector machine with linear kernel; SVM-P, support vector machine with polynomial kernel, Logistic, logistic regression model

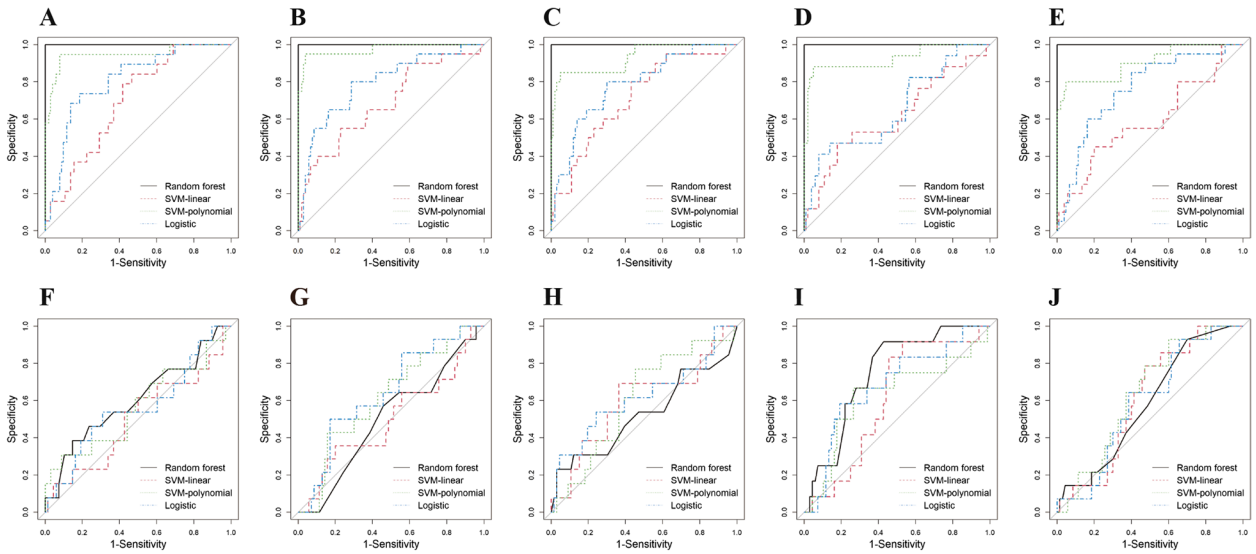

Fig. 2 The ROC curve for four machine learning algorithms in train and validation datasets (A to E: model 1 to model 5 in train datasets, respectively; F to J: model 1 to model 5 in validation datasets, respectively)

P < 0.05). Among intraoperative risk factors, soft pancreatic texture and tumor pathology were strongly associated with CR-POPF. The incidence of soft pancreas was significantly higher in the CR-POPF group than in the non-fistula group (52.9% vs. 18.9%, P < 0.001), and the proportion of non-pancreatic parenchymal tumors, such as ampullary carcinoma, was also significantly higher (85.3% vs. 65.3%, P = 0.022). Multivariate logistic

regression confirmed that soft pancreatic texture was the most significant independent risk factor for CR-POPF (OR = 4.99). Using these factors, multiple machine learning models were developed to predict postoperative pancreatic fistula. In the validation set, the random forest model (Model 4) demonstrated the best performance, achieving an area under the ROC curve (AUC) of 0.747 and a sensitivity of 91.7%. Notably, this model relies exclusively on preoperative variables, enhancing its clinical applicability. In our study, the Random Forest model achieved a perfect AUC of 1.0 on the training set, but this dropped to 0.747 in the validation set. This discrepancy suggests that the model may have overfitted the training data, capturing noise or irrelevant patterns, which led to poor generalization to unseen data. To address this issue, we employed a simple random split with a 70:30 ratio, training the model on 70% of the samples and validating it on the remaining 30% to reduce overfitting. We ultimately selected the model's performance on the validation set as the criterion for evaluating its predictive accuracy.

The identification of soft pancreatic texture as a core risk factor for CR-POPF is consistent with findings from studies on open pancreaticoduodenectomy (OPD) [22–24]. However, some predictors considered significant in open surgery, such as main pancreatic duct diameter and BMI, did not demonstrate independent predictive value in our LPD cohor [25,26].This discrepancy may arise from several factors. First, the relatively small sample size (210 patients) could have impacted the statistical sensitivity, leading to some variables failing to reach statistical significance. Second, differences in measurement techniques may also play a role. For example, the measurement of pancreatic duct diameter in laparoscopic surgery could be influenced by imaging resolution and the experience of the surgeon. Additionally, laparoscopic techniques may involve different handling of pancreatic tissue, with patients who have smaller pancreatic ducts potentially receiving more meticulous treatment during surgery. This could explain why these traditional risk factors may not be applicable in LPD. Future studies could consider increasing the sample size or utilizing more precise measurement techniques to further validate the predictive value of these variables.This study also identified several preoperative predictors that have been less frequently discussed in the existing literature, such as peripheral blood monocyte ratio and platelet count. These markers may reflect the patient's immune-inflammatory status and influence postoperative healing. Monocytes play a pivotal role in postoperative immune responses, and their functional state regulates inflammation through the release of cytokines such as IL-6 and IL-10. Additionally, monocytes participate in antigen presentation via HLA-DR molecules, which affects tissue repair and infection resistance. The activation state of preoperative monocytes has been associated with the incidence of postoperative sepsis, suggesting that monocyte dysfunction may be closely linked to the occurrence of pancreatic fistula. Future research should explore the specific mechanisms of monocyte-related factors and HLA-DR expression in the pathogenesis of pancreatic fistula, offering new targets for clinical intervention [27]. Additionally, our data support the association between hypoalbuminemia and increased postoperative complication risk, consistent with existing knowledge, as low albumin levels often indicate malnutrition and impaired healing capacity [28]. Regarding pancreatic tumor pathology, we observed a higher incidence of pancreatic fistula in patients with periampullary carcinoma compared to pancreatic head adenocarcinoma, likely due to the softer pancreatic texture and relatively narrower pancreatic ducts in periampullary carcinoma patients. This finding aligns with reports in open surgery literature: pancreatic head cancer is often associated with varying degrees of pancreatic fibrosis, reducing fistula risk, whereas periampullary carcinoma, lacking such fibrotic changes, carries a higher risk [29].

Moreover, machine learning algorithms in this study outperformed traditional logistic regression models. Models such as random forest can integrate multiple variables and capture complex nonlinear relationships, which may explain their superior performance. Similarly, other studies have demonstrated the advantages of machine learning models. For example, a large-sample analysis found that a preoperative prediction model based on XGBoost achieved an AUC of 0.72, outperforming traditional regression models [30]. Machine learning models can automatically identify nonlinear relationships between variables and outcomes, as well as higher-order interactions among variables. This makes them particularly suitable for integrating diverse data sources, such as clinical indicators, imaging features, and genomic information, thereby enhancing predictive performance on a more comprehensive basis [31].

Several risk scores and calculators are currently available to assess the risk of clinically relevant postoperative pancreatic fistula (CR-POPF) after pancreaticoduodenectomy. The most widely used in clinical practice is the Fistula Risk Score (FRS) proposed by Callery et al., which includes variables such as pancreatic texture, pathology, pancreatic duct diameter, and intraoperative blood loss, with an AUC ranging from 0.75 to 0.78 [32]. In comparison, the random forest model in this study fully leverages machine learning techniques to handle multidimensional and nonlinear data, giving it a distinct advantage in prediction over traditional methods, especially in handling

complex cases. Additionally, our machine learning model relies exclusively on preoperative variables, making it more clinically applicable than the FRS, as preoperative data are more easily accessible and do not rely on complex intraoperative factors. Nevertheless, the potential integration of the FRS with machine learning models remains a promising area for clinical application. Future studies could consider combining the two approaches, such as using machine learning algorithms to further explore the complex relationships between the FRS variables or incorporating the FRS results as an additional feature into machine learning models, thereby enhancing the model's overall predictive ability. This combination of both approaches could improve the accuracy of risk prediction while maintaining clinical feasibility. Furthermore, Al Abbas et al. developed a PD-specific risk calculator based on NSQIP data, which includes intraoperative variables like pancreatic texture and achieved an AUC of 0.696 [33]. The best-performing machine learning model in this study reached an AUC of 0.747, comparable to these studies. However, the performance of the model still falls short of the ideal clinical standard. For example, while the random forest model achieved an AUC of 0.747, indicating moderate discriminative ability, its specificity was relatively low (0.574), resulting in a high false-positive rate. This means that a significant proportion of low-risk patients were misclassified as high-risk, highlighting the need for further optimization to improve precision and reduce misclassification.

The machine learning model developed in this study can be used for individualized preoperative assessment of pancreatic fistula risk, offering significant clinical value. Based on preoperative risk predictions, healthcare teams can implement optimization measures for high-risk patients. In postoperative management, the model can also guide personalized monitoring strategies. High-risk patients identified by the model can receive closer monitoring and follow-up. For example, more frequent monitoring of drain fluid amylase levels can facilitate early detection and intervention for pancreatic fistula, thereby reducing the incidence of severe complications. Risk stratification can also enable more efficient allocation of medical resources, focusing monitoring efforts on high-risk patients and improving the efficiency and precision of perioperative management.

Despite its practical value, this study has several limitations. First, as a single-center retrospective analysis with a relatively small sample size (210 cases), the study may be subject to selection bias, and the model's generalizability requires validation in larger, multicenter populations. The lack of external validation limits the assessment of the model's applicability across different medical centers. Additionally, center-specific surgical techniques may influence the results, thereby affecting the model's generalizability and its application in other medical centers. Second, the model primarily relies on preoperative variables and does not incorporate potentially important intraoperative and postoperative factors, such as specific techniques for pancreaticojejunostomy or dynamic changes in postoperative drain fluid amylase levels. Additionally, factors such as pancreatic fibrosis degree and emerging biomarkers, which may influence fistula risk, were not included, potentially limiting the model's predictive accuracy. To address these limitations, future research will focus on the following areas: First, multicenter prospective studies with larger sample sizes will be conducted to validate and update the model, enhancing its reliability and external applicability. Second, efforts will be made to integrate emerging technologies such as radiomics into risk assessment, leveraging preoperative CT imaging to extract objective pancreatic features and improve the model's ability to quantify factors like pancreatic texture. With advancements in machine learning and big data, more sophisticated algorithms such as deep learning may further enhance model performance by integrating larger and more complex variable sets. While increasing model complexity, we will also prioritize interpretability, employing explainable artificial intelligence methods to enhance transparency in model decision-making. This will help clinicians understand the basis of model predictions, facilitating its translation into clinical practice.

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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Authors' contributions
WQC were responsible for writing the main manuscript text. WZ and WZJ contributed to the research and data collection. LFF and WZJ supervised the entire project and provided guidance throughout the research process. WZ prepared the figures and participated in data management. LFF performed the formal analysis and statistical analysis of the data. NQQ and CH contributed to the design of the methodology and provided feedback on the experimental design. LFF was responsible for the project administration. All authors reviewed and approved the final version of the manuscript.

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Data availability
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Biomedical Research Ethics Committee of Shandong Provincial Hospital (Approval No. SWYX2024-469). All methods were conducted in accordance with relevant guidelines and regulations, including the Declaration of Helsinki. Informed consent was not required due to the retrospective design of the study and the exemption granted by the IRB.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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