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The value of preoperative RDW for post-pancreatectomy haemorrhage and surgical prognosis in patients with pancreatic cancer: a retrospective study

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Abstract

Background Pancreatic ductal adenocarcinoma (PDAC) is a highly malignant tumor, and only some patients can receive surgical treatment. Complex surgical procedures combined with various postoperative complications seriously affect the prognosis of patients. It is very important to use appropriate biomarkers to prevent and predict the occurrence of complications. On the basis of our previous attention to red blood cell distribution width (RDW), this study aimed to investigate the correlation between RDW and the prognosis of pancreatic cancer patients.

Methods Patients who underwent elective radical resection of pancreatic tumors from January 2017 to June 2021 were retrospectively analyzed. Relevant clinical data were collected to evaluate the correlation between preoperative absolute RDW changes and post-pancreatectomy haemorrhage and clinical outcomes.

Results A total of 2268 patients were analyzed. We found that the preoperative RDW, preoperative LMR, anesthesia method, operation method, preoperative jaundice, operation with NSAIDs, and intravenous administration in patients with PDAC were significantly correlated with the infusion of albumin and R colloidal/crystal and post-pancreatectomy haemorrhage (PPH). In addition, sensitivity analysis revealed that preoperative RDW was associated with 30-day survival ($P = 0.026$), whereas PPH had a significant effect on in-hospital outcomes ($P = 0.002$), 30-day outcomes ($P < 0.001$) and 90-day outcomes ($P < 0.001$).

Conclusion The preoperative RDW may be a useful marker for predicting and evaluating PPH and short-term prognosis in patients with PDAC.

Keywords Pancreatic ductal adenocarcinoma, Red cell distribution width, Postoperative, Post-pancreatectomy haemorrhage, Prognosis

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Introduction

Pancreatic cancer (PC) is a highly malignant tumor. Among the histological classifications, PDAC is the most common type. This disease is characterized by rapid progression, high tumor invasiveness, and a low postdisease survival rate. Currently, it ranks fourth in terms of global cancer mortality rates, and its incidence is increasing annually [1]. According to current cancer statistics, more than half of patients diagnosed with PDAC present different degrees of tumor metastasis or poor systemic symptoms and are intolerant to such surgical treatments. Ultimately, only approximately one-fourth of PDAC patients can undergo surgical resection [2]. Nevertheless, with the innovation and development of medical technologies and equipment, there have been several alterations in the clinical treatment plans for patients with PDAC. In addition to traditional systemic therapy, numerous new treatment approaches, such as gene-targeted therapy and neoadjuvant chemotherapy, have emerged. However, the only means to achieve radical therapeutic purposes is surgical resection of the tumor and related tissues [3].

The choice of surgical approach is often based on the stage and location of the pancreatic tumor. For example, resectable (R-PHC) or borderline resectable (BR-PHC) pancreatic head cancers may be suitable for pancreaticoduodenectomy (PD), whereas other patients with extensive pancreatic tumors may require total pancreatectomy (TP) [4, 5]. The goal of surgical treatment is to relieve the pain caused by the tumor, but pancreatic surgery is complex and involves multiple organs and important blood vessels, which can cause varying degrees of impairment to various organ systems during the perioperative period, leading to a high incidence of postoperative complications, which seriously affects the prognosis and survival of patients [5, 6].

There are many kinds of complications after pancreatic surgery, such as postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE), and post-pancreatectomy haemorrhage (PPH). Based on the redefinition of postoperative complications of pancreatic closure by the International Study Group of Pancreatic Surgery (ISGPS), an increasing number of medical staff and medical researchers are paying attention to how to prevent and predict the occurrence of complications [7]. The high mortality rate of PPH has attracted our attention. ISGPS guidelines also clarify that the classification of PPH is based on the differences in time, location and severity. PPH can cause hematemesis and melena in mild cases, and hemodynamic instability can occur in severe cases, which can further affect multiple organ dysfunction and eventually lead to death.

All patients with PDAC received routine examination of peripheral blood before operation, and the inflammation-related indicators often attracted the attention of clinicians. However, a number of studies have found that red blood cell distribution width is a measure of the size variation of circulating red blood cells, and RDW has produced unexpected effects in many diseases. RDW is a routine parameter in the analysis of peripheral blood complete blood cell count, which is easy to obtain and can reflect the difference in red blood cell volume in the circulation system [8]. Research has shown that RDW can effectively predict the survival rate of patients with pneumonia. Furthermore, RDW is positively correlated with the occurrence of cardiovascular events [9, 10]. Similarly, in patients with rectal cancer, a direct association between RDW and tumor-related complications has also been observed [11].

We have noted the importance of RDW in disease prognosis analysis, yet its use is limited in conditions such as pancreatic tumors. Consequently, the objective of this study was to explore the influence of RDW on postoperative intra-abdominal bleeding and other complications, as well as short-term outcomes, in patients with pancreatic cancer. This will help offer a more robust foundation for clinical decision-making.

Materials and methods

Patient

This study adopted a retrospective approach to collect data from patients who underwent elective radical resection surgery for pancreatic tumors at Shanghai Changhai Hospital from January 2017 to June 2021 (see Fig. 1 for the patient selection process). The inclusion criteria were as follows: (1) aged ≥ 18 years; (2) underwent radical resection surgery for pancreatic tumors; and (3) complete clinical research data were available. The exclusion criteria were as follows: (1) a change in surgical procedure or not undergoing radical pancreatic resection; (2) total pancreatectomy; (3) severe cardio-cerebrovascular events during surgery; and (4) significant recording errors in the clinical research data. This study was conducted in accordance with the Helsinki Declaration, and was declared based on the ethical standards set by the National Health Commission of the People's Republic of China (Act No. 11 of 2016). It was approved by the Ethics Committee of the First Affiliated Hospital of Naval Medical University (CHEC2021–192), which waived the requirement for written informed consent.Given the retrospective nature of this study, no new biological samples were taken from the patients, and informed consent was waived.

Clinical characteristic data

The primary aim of this study was to investigate the impact of preoperative RDW on PPH in PDAC patients. The secondary objective was to determine the influence of the preoperative RDW on other complications and postoperative outcomes in these patients. All research

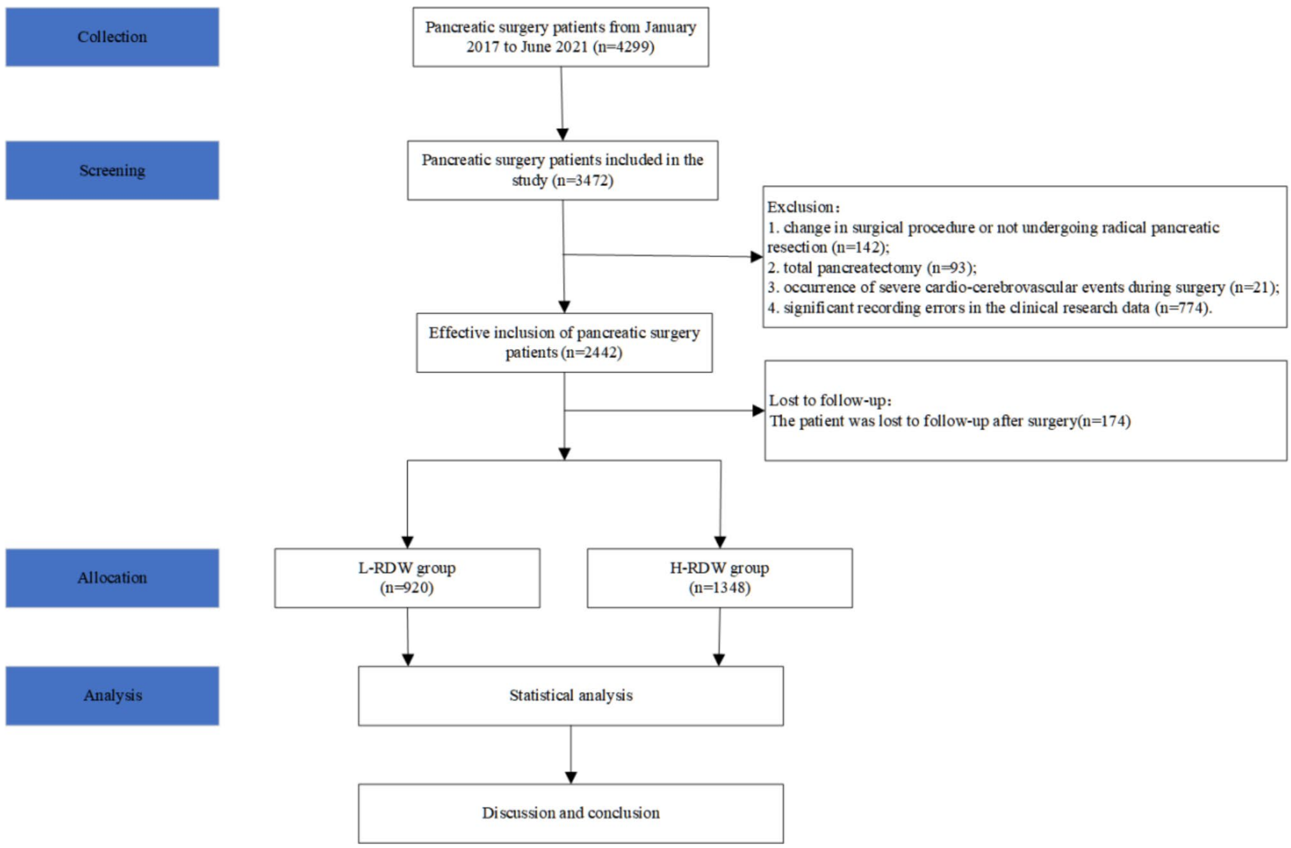

Fig. 1 Flow chart of the patient allocation

data, including demographic information, comorbidities, surgical details, anesthesia-related information, laboratory test results, postoperative complications, and patient outcomes at different time points after surgery, were extracted from completed medical records. The "preoperative" laboratory results included in the study were all blood indicators examined within 2 days prior to surgery. Composite inflammation indicators were calculated on the basis of laboratory results as follows: the systemic immune-inflammation index (SII) was the platelet count × neutrophil/lymphocyte ratio; the neutrophil-to-lymphocyte ratio (NLR) was the neutrophil/lymphocyte count; the platelet-to-lymphocyte ratio (PLR) was the platelet/lymphocyte count; the lymphocyte-to-monocyte ratio (LMR) was the lymphocyte/monocyte count; and the prognostic nutritional index (PNI) was the serum albumin concentration + 5 × lymphocyte count. The final in-hospital outcomes were categorized into discharge after recovery and nonrecovery, where nonrecovery included in-hospital mortality and patients with severe unstable vital signs who opted out of further life support treatment.

Postoperative complication definition

PPCs: Postoperative pulmonary complications (PPCs) were measured according to the European Joint Working Group published in 2015. Clinical diagnoses include respiratory failure, acute respiratory distress syndrome, respiratory tract infection, pleural effusion, atelectasis, pneumothorax and pulmonary edema [12].

PO-AKI: The diagnosis of postoperative acute kidney injury (PO-AKI) was based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria and required any of the following: an increase in serum creatinine ≥ 26.4 μmol/L (0.3 mg/dL) within 48 h; an increase in serum creatinine of ≥ 50% (equivalent to a 1.5-fold increase from the baseline normal value); and a urine output of less than 0.5 ml/kg/h that lasted for more than 6 h [13].

POPF: The diagnosis of postoperative pancreatic fistula (POPF) was based on the International Study Group on Pancreatic Surgery (ISGPS) criteria. The peritoneal drainage fluid amylase content was defined as 3 times or more higher than the upper limit of the normal value of serum amylase 3 days after surgery. It is related to clinical treatment and patient prognosis. The severity of pancreatic leakage can be divided into BL, B and C grades, among which the BL grade is "biochemical leak" (BL), and grades B and C are defined as clinically relevant pancreatic leakage [14].

DGE: The diagnosis of delayed gastric emptying (DGE) followed the ISGPS criteria if any of the following criteria were met: postoperative gastric tube indwelling for more than 3 days; the stomach tube was indwelling again because of recurrent symptoms such as vomiting after removal of the stomach tube. No solid food was allowed for one week or more after surgery [15].

Statistical analysis

Statistical analysis of the clinical study data was conducted via SPSS 26.0 software. The Youden index for "in-hospital nonrecovery" was calculated on the basis of the receiver operating characteristic (ROC) curve to determine the optimal cutoff value for RDW. The patient cohort was then divided into low RDW and high RDW groups. To reduce data bias and confounding variables in this retrospective study, 1:1 propensity score matching (PSM) was performed with predefined matching parameters: "preoperative tumor metastasis, age, BMI, preoperative jaundice, history of preoperative pancreatic treatment, and history of preoperative biliary stenting," to standardize the treatment and eliminate interfering factors between groups. For univariate analysis of clinical baseline data, independent sample t tests were used for normally distributed continuous data, presented as the mean (SD); Mann−Whitney U tests were used for non-normally distributed data, presented as the median (IQR). Categorical data were analyzed via χ2 tests and Fisher's exact tests and are presented as n (%). Sensitivity analysis involved logistic regression; the cohort study compared postoperative pancreatic fistula, postoperative intra-abdominal hemorrhage, AKI, cardio-cerebrovascular complications, pulmonary complications, postoperative infections, and patient outcomes. Cumulative survival rates were calculated via the Kaplan−Meier method, and log-rank tests were used to assess differences between groups. Cox proportional hazards regression was used for both univariate and multivariate analyses to identify prognostic factors related to OS. Hazard ratios (HRs) and 95% confidence intervals (CIs) were used to describe relative risk factors. All tests were two-sided, with a p value < 0.05 indicating statistical significance.

Results

Baseline and clinical characteristics of patients

A total of 2268 patients were included in this study. The optimal cutoff value of RDW was 12.8%, as determined by the Youden index, and the patients were divided into a low RDW group (L-RDW) and a high RDW group (H-RDW) according to the optimal cutoff value of RDW. The demographic data are summarized in Table 1. After PSM, the H-RDW group was significantly older than the H-RDW group was ($P = 0.007$). Preoperative laboratory examination revealed significant differences in the SII ($P < 0.001$), NLR ($P < 0.001$), PLR ($P < 0.001$), LMR ($P < 0.001$) and PNI ($P < 0.001$). This difference was mainly

Table 1 Baseline and clinical characteristics of patients

Variables	Before PSM			After PSM		
	L-RDW (*n* = 920)	H-RDW (*n* = 1348)	*P*	L-RDW (*n* = 920)	H-RDW (*n* = 789)	*P*
Age, mean (SD), y	59.3(12.1)	61.6(11.3)	<0.001*	59.3(12.1)	60.9 ± 11.9	0.007*
BMI, mean (SD), kg/m^2	22.9(3.1)	22.5(3.0)	<0.001*	22.9(3.1)	22.7 ± 3.1	0.071
SII, median (IQR)	406.1(273.0,591.1)	519.8(325.6,852.5)	<0.001*	406.1(273.0,591.1)	449.7(294.5,714.9)	<0.001*
NLR, median (IQR)	2.1(1.5,2.8)	2.5(1.8,3.8)	<0.001*	2.1(1.5,2.8)	2.3(1.6,3.3)	<0.001*
PLR, median (IQR)	129.5(99.0,167.6)	153.3(112.8,215.4)	<0.001*	129.5(99.0,167.6)	139.1(106.5,194.7)	<0.001*
LMR, median (IQR)	3.8(3.0,4.8)	3.0(2.2,4.0)	<0.001*	3.8(3.0,4.8)	3.4(2.5,4.4)	<0.001*
PNI, median (IQR)	48.9(45.7,52.1)	47.8(44.5,51.0)	<0.001*	48.9(45.7,52.1)	48.0(44.8,51.5)	<0.001*
Gender, (*n*/%), Male	548(59.6)	802(59.5)	0.974	548(59.6)	445(56.4)	0.186
Diabetes, (*n*/%)	187(20.3)	307(22.8)	0.165	187(20.3)	162(20.5)	0.916
Hypertension, (*n*/%)	314(34.1)	421(31.2)	0.148	314(34.1)	241(30.5)	0.115
Preoperative jaundice, (*n*/%)	126(13.7)	610(45.3)	<0.001*	126(13.7)	137(17.4)	0.036*
Pancreatic treatment history, (*n*/%)	24(2.6)	117(8.7)	<0.001*	24(2.6)	12(1.5)	0.118
Biliary stent, (*n*/%)	33(3.6)	128(9.5)	<0.001*	33(3.6)	49(6.2)	0.011*
Tumor metastasis, (*n*/%)	292(31.7)	561(41.6)	<0.001*	292(31.7)	255(32.3)	0.798
ASA			0.002*			0.061
I, (*n*/%)	28(3.0)	20(1.5)		28(3.0)	14(1.8)	
II, (*n*/%)	844(91.7)	1222(90.7)		844(91.7)	718(91.0)	
III, (*n*/%)	48(5.2)	106(7.9)		48(5.2)	57(7.2)	

**P* value was less than 0.05, with statistical significance. L-RDW, Low red blood cell distribution width group; H-RDW, High red blood cell distribution width group; SD, standard deviation; IQR, interquartile range; BMI, body mass index; SII, systemic immune inflammation index; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PNI, Prognostic nutritional index; ASA, American Society of Anesthesiologists Physical Status Classification System reflected in the higher preoperative inflammatory index and the lower nutritional index in the H-RDW group. When a retrospective analysis of surgery-related disease history was conducted, we also found that preoperative redundancy ($P = 0.036$) and the use of biliary stents ($P < 0.001$) were more common in the H-RDW group.

Analysis of perioperative-related factors

There were significant differences in the duration of anesthesia and operation, intraoperative blood loss, intraoperative blood transfusion rate, type of pancreatectomy, proportion of intraoperative vascular anastomosis, total hospital stay and postoperative hospital stay before and after PSM (Table 2). In addition, the proportion of patients in the L-RDW group who received intravenous infusions of human serum albumin ($P = 0.013$) and non-steroidal anti-inflammatory drugs (NSAIDs) ($P = 0.007$) was significantly greater than that in the H-RDW group.

Postoperative complications and in-hospital outcomes of patients with PDAC

There were significant differences in CCE ($P = 0.007$), PPCs ($P = 0.008$), DGE ($P = 0.002$), SSI ($P < 0.001$) and PPH ($P = 0.004$) between the two groups before PSM. However, only PPCs ($P = 0.008$), SSIs ($P = 0.027$) and PPH ($P < 0.001$) were significantly more common in the H-RDW group after PSM. The C-D grade of postoperative complications in the H-RDW group also showed a high-grade distribution ($P < 0.001$). The resulting in-hospital recovery rate ($P = 0.005$) was also higher in the L-RDW group than in the H-RDW group (Table 3).

Univariate and multivariate analyses of PPH were based on post-PSM

To evaluate the independent predictors of PPH in PDAC patients, univariate and multivariate logistic regression analyses were performed on the data after PSM. We found that preoperative RDW, preoperative LMR, anesthesia method, operation method, preoperative jaundice, surgery with NSAIDs, and intravenous infusion of

Table 2 Analysis of perioperative-related factors

Variables	Before PSM			After PSM		
	L-RDW ($n = 920$)	H-RDW ($n = 1348$)	P	L-RDW ($n = 920$)	H-RDW ($n = 789$)	P
Anesthesia duration, median (IQR), h	3.4(2.8,4.1)	3.8(3.2,4.3)	<0.001*	3.4(2.8,4.1)	3.5(2.9,4.3)	0.001*
Operation duration, median (IQR), h	2.7(2.1,3.4)	3.0(2.5,3.7)	<0.001*	2.7(2.1,3.4)	2.9(2.3,3.5)	<0.001*
Intraoperative urine output, median (IQR), L	0.4(0.2,0.5)	0.4(0.3,0.6)	<0.001*	0.4(0.2,0.5)	0.4(0.3,0.5)	0.218
Intraoperation bleeding, median (IQR), L	0.3(0.2,0.5)	0.4(0.2,0.6)	<0.001*	0.3(0.2,0.5)	0.3(0.2,0.6)	0.001*
Crystal, median (IQR), L	1.5(1.1,1.7)	1.5(1.1,1.7)	0.246	1.5(1.1,1.7)	1.5(1.1,1.7)	0.045*
Colloid, median (IQR), L	1.0(0.5,1.5)	1.0(0.5,1.5)	0.126	1.0(0.5,1.5)	1.0(0.5,1.0)	0.054
R colloidal /crystal, median (IQR)	0.7(0.3,1.0)	0.6(0.4,1.0)	0.538	0.7(0.3,1.0)	0.6(0.3,0.9)	0.013*
Total fluid, median (IQR), L	2.3(1.0,2.7)	2.5(2.0,3.0)	0.016*	2.3(1.0,2.7)	2.2(2.0,2.9)	0.958
Liquid infusion rate, median (IQR), ml/kg·h^{-1}	11.2(8.6,14.3)	10.9(8.5,13.6)	0.049*	11.2(8.6,14.3)	10.9(8.6,13.8)	0.143
Anesthesia method			0.173			0.013*
GA + TAP, *n* (%)	801(87.1)	1199(88.9)		801(87.1)	717(90.9)	
GA + TPVB, *n* (%)	119(12.9)	149(11.1)		119(12.9)	72(9.1)	
Operation method			<0.001*			<0.001*
PD, *n* (%)	425(46.2)	903(67.0)		425(46.2)	449(56.9)	
DP, *n* (%)	495(53.8)	445(33.0)		495(53.8)	340(43.1)	
Intravenous infusion of albumin, *n* (%)	288(31.3)	460(34.1)	0.161	288(31.3)	204(25.9)	0.013*
Intraoperative blood transfusion, *n* (%)	149(16.2)	384(28.5)	<0.001*	149(16.2)	197(25.0)	<0.001*
Intraoperative with NSAIDs, *n* (%)	659(71.6)	945(70.1)	0.433	659(71.6)	517(65.5)	0.007*
Vascular anastomosis, *n* (%)	136(14.8)	259(19.2)	0.006*	136(14.8)	157(19.9)	0.005*
Postoperative with somatostatin, *n* (%)	756(82.2)	1168(86.6)	0.004*	756(82.2)	658(83.4)	0.505
Pancreatic tumor texture			0.001*			0.207
Hard, *n* (%)	218(23.7)	366(27.2)		218(23.7)	196(24.8)	
Medium, *n* (%)	259(28.2)	440(32.6)		259(28.2)	246(31.2)	
Soft, *n* (%)	443(48.2)	542(40.2)		443(48.2)	347(44.0)	
TLOS, median (IQR), d	12(9,16)	13(10,19)	<0.001*	12(9,16)	13(10,18)	<0.001*
ICU days treatment, median (IQR), d	1(0,3)	2(1,3)	<0.001*	1(0,3)	1(1,3)	0.079
Days of treatment after surgery, median (IQR), d	8(6,12)	10(7,14)	<0.001*	8(6,12)	9(7,13)	<0.001*

*P value was less than 0.05, with statistical significance. L-RDW, Low red blood cell distribution width group; H-RDW, High red blood cell distribution width group; SD, standard deviation; IQR, interquartile range; GA, general anesthesia; TAP, transversus abdominis plane; TPVB, thoracic paravertebral block; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; NSAIDs, Nonsteroidal Antiinflammatory Drugs; TLOS, total length of stay; ICU, intensive care unit

Table 3 Postoperative complications and in-hospital outcomes of patients with PDAC

Variables	Before PSM			After PSM		
	L-RDW (*n* = 920)	H-RDW (*n* = 1348)	*P*	L-RDW (*n* = 920)	H-RDW (*n* = 789)	*P*
AKI, (*n*/%)	22(2.4)	48(3.6)	0.114	22(2.4)	21(2.7)	0.722
CCE, (*n*/%)	7(0.8)	30(2.2)	0.007*	7(0.8)	13(1.6)	0.089
PPCs, (*n*/%)	20(2.2)	57(4.2)	0.008*	20(2.2)	35(4.4)	0.008*
DGE, (*n*/%)	40(4.3)	101(7.5)	0.002*	40(4.3)	50(6.3)	0.066
SSI, (*n*/%)	95(10.3)	221(16.4)	<0.001*	95(10.3)	109(13.8)	0.027*
PPH, (*n*/%)	113(12.3)	225(16.7)	0.004*	113(12.3)	160(20.3)	<0.001*
POPF			0.196			0.436
B, (*n*/%)	44(95.7)	96(99.0)		44(95.7)	56(98.2)	
C, (*n*/%)	2(4.3)	1(1.0)		2(4.3)	1(1.8)	
Complications C-D grading			<0.001*			0.007*
I, (*n*/%)	342(90.2)	451(78.7)		342(90.2)	268(82.5)	
II, (*n*/%)	25(6.6)	65(11.3)		25(6.6)	27(8.3)	
III, (*n*/%)	10(2.6)	38(6.6)		10(2.6)	21(6.5)	
IV, (*n*/%)	0(0)	8(1.4)		0(0)	4(1.2)	
V, (*n*/%)	2(0.5)	11(1.9)		2(0.5)	5(1.5)	
Rehabilitation discharge, (*n*/%)	917(99.7)	1327(98.4)	0.005*	917(99.7)	778(98.6)	0.015*
Unrecovered discharge						
Treatment abandoning (Undead), (*n*/%)	2(0.2)	15(1.1)	0.015*	2(0.2)	8(1.0)	0.031*
Death, (*n*/%)	1(0.1)	6(0.4)	0.156	1(0.1)	3(0.4)	0.247

**P* value was less than 0.05, with statistical significance. L-RDW, Low red blood cell distribution width group; H-RDW, High red blood cell distribution width group; AKI, acute kidney injury; CCE, Cardiovascular And Cerebrovascular Events; PPCs, postoperative pulmonary complications; DGE, delayed gastric emptying; POPF, postoperative pancreatic fistula; SSI: surgical site infection; PPH, post-pancreatectomy haemorrhage; C-D grading: clavien-dindo grading

Table 4 Univariate and multivariate analyses of PPH were based on post-PSM

Variables	Univariate analysis			Multivariate analysis		
	OR	95%CI	*P*	OR	95%CI	*P*
RDW (High vs. Low)	1.172	1.094–1.255	<0.001*	1.152	1.069–1.243	<0.001*
LMR (High vs. Low)	1.051	0.977–1.130	0.181	1.107	1.020–1.202	0.016*
Anesthesia method (TPVB vs. TAP)	0.323	0.177–0.588	<0.001*	0.418	0.226–0.774	0.006*
Operation method (DP vs. PD)	2.030	1.549–2.660	<0.001*	1.967	1.467–2.639	<0.001*
Preoperative jaundice (Yes vs. No)	2.165	1.585–2.959	<0.001*	1.617	1.138–2.297	0.007*
Intraoperative with NSAIDs (Yes vs. No)	1.832	1.344–2.498	<0.001*	2.593	1.864–3.608	<0.001*
Intravenous infusion of albumin (Yes vs. No)	0.362	0.253–0.517	<0.001*	0.377	0.259–0.549	<0.001*
R colloidal/crystal (High vs. Low)	0.633	0.507–0.789	<0.001*	0.662	0.526–0.831	<0.001*

**P* value was less than 0.05, with statistical significance.RDW, red blood cell distribution width; LMR, lymphocyte to monocyte ratio; NSAIDs, nonsteroidal antiinflammatory drugs; PPH, Post-pancreatectomy haemorrhage

albumin and R colloidal/crystal were risk factors that could predict the occurrence of PPH (Table 4). To verify the fitting effect of the logistic regression model, discrimination and calibration were used for evaluation. The ROC curve was used to evaluate the performance of the model for discrimination. The AUC of RDW was 0.581 when PPH was affected only by RDW, and the AUC of the full model was 0.733 when factor analysis was used, with a sensitivity of 0.778 and a specificity of 0.628 for predicting PPH (Fig. 2A). Calibration, as measured by using a calibration curve to evaluate the predicted probability, revealed that the calibration curve of the model was close to the reference line, suggesting good agreement between the predicted probability and the actual probability (Fig. 2C). Moreover, we used the clinical decision curve (DCA) response to predict the clinical response rate of the model, and the full model factor adjustment achieved a better effect on the prevention of PPH than did the single adjustment of the preoperative RDW (Fig. 2B). Finally, we developed a nomogram to determine the relationships among the risk factors and better reflect the performance of each variable in driving PPH outcomes (Fig. 2D).

Postoperative complication risk factor analysis

Correlation analysis was conducted between all baseline characteristic variables with significant differences and different postoperative complications, and a heatmap was drawn to demonstrate the relationship between each variable (Fig. 3A). In addition, univariate logistic analysis of the independent risk factors between the preoperative RDW and different postoperative complications

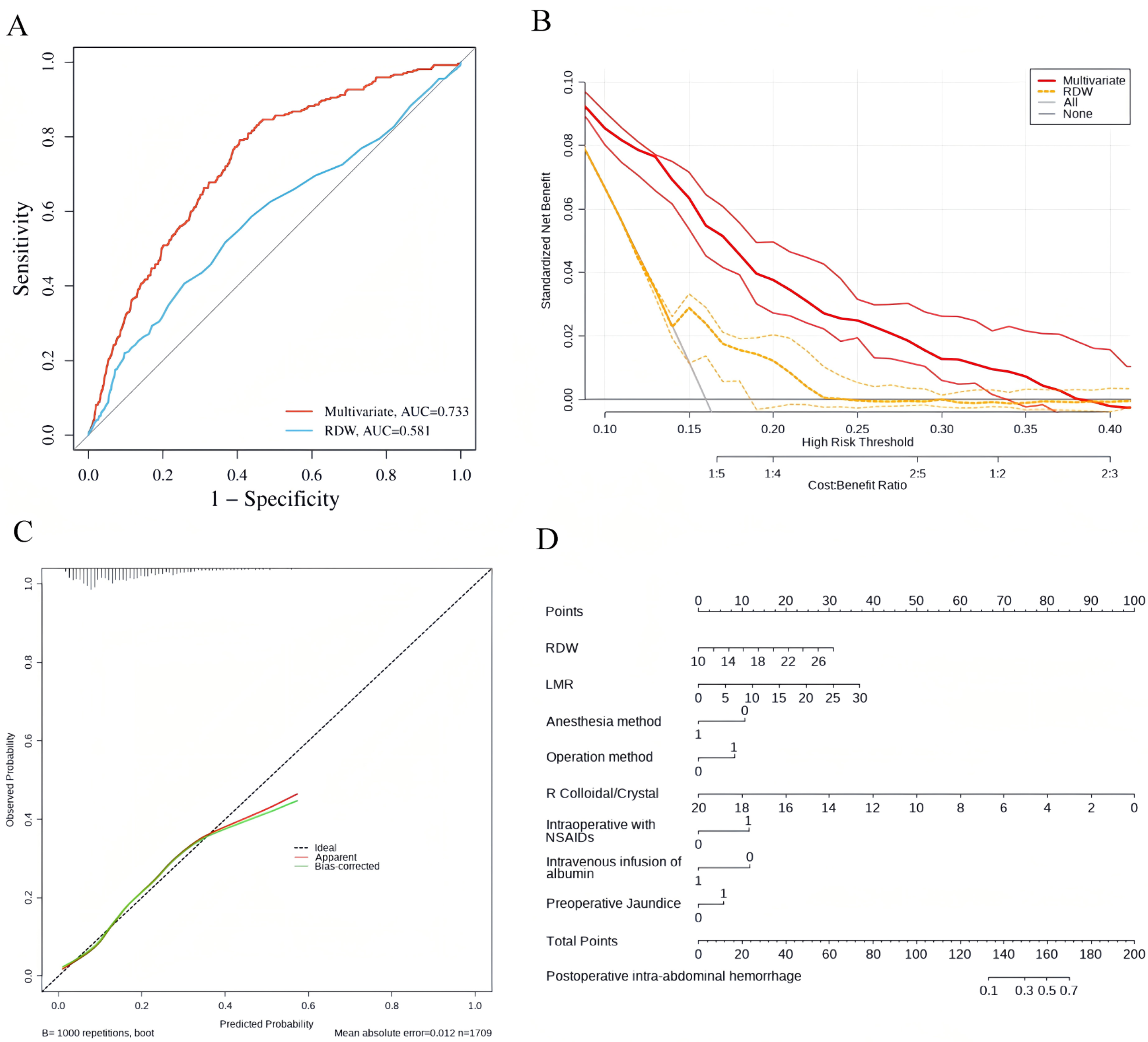

Fig. 2 Validation of independent predictors of PPH

suggested that a high preoperative RDW is associated with DGE (HR = 1.141, 95% CI 1.032–1.261), $P = 0.010$), and PPH (HR = 1.172, 95% CI 1.094–1.255, $P = 0.000$), SSI (HR = 1.112, 95% CI 1.030–1.201, $P = 0.007$), and CCE (HR = 1.209, 95% CI 1.026–1.426, $P = 0.024$) are independent risk factors. For overall postoperative complications, RDW was associated with a certain risk for C-D grade III patients (HR = 1.215, 95% CI 1.053–1.401; $P = 0.007$) (Fig. 3B).

Factors analysis of in-hospital non-rehabilitation outcomes after PSM

When the final in-hospital outcomes after surgery were compared, there was a significant difference in the rate of nonrecovery between the two groups. Univariate and multivariate logistic regression analyses via propensity score matching (PSM)-adjusted data revealed that PPH (OR = 10.420, 95% CI 2.338–46.439, $P = 0.002$), SSI (OR = 4.310, 95% CI 1.001–18.550, $P = 0.050$), CCE (OR = 16.080, $P = 0.050$), 95% CI 3.325–77.757, $P = 0.001$) and PPCs (OR = 22.566, 95% CI 5.583–91.201, $P < 0.001$) were independent risk factors for nonrecovery in hospitals (see Table 5). K-M analysis revealed that PPH had a significant effect on 30-day ($P < 0.001$) and 90-day ($P < 0.001$) survival. However, the preoperative RDW significantly affected the survival of patients within 30 days after surgery ($P = 0.026$) (Fig. 4).

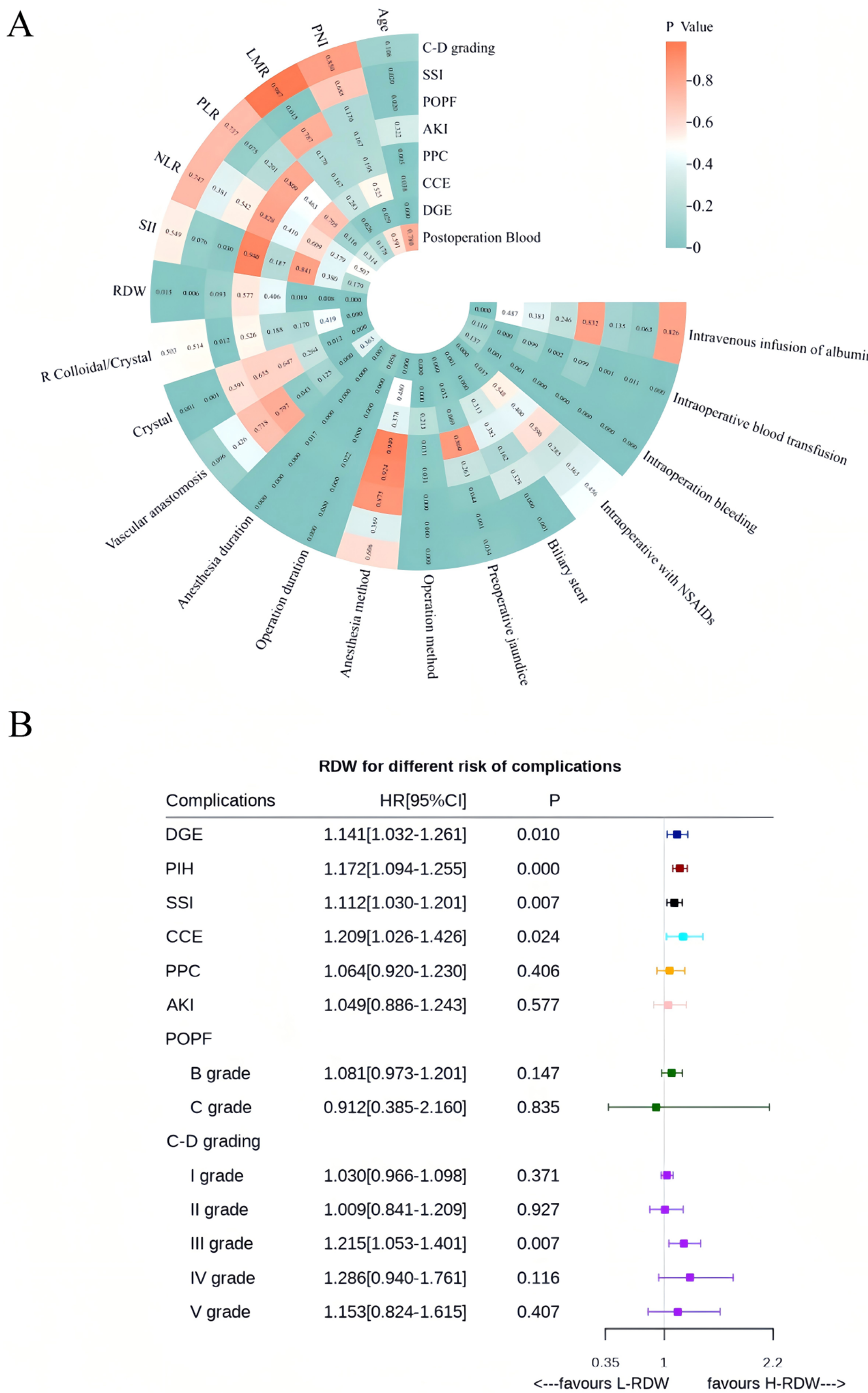

Fig. 3 Correlation between postoperative complications and multiple factors and RDW

Discussion

The surgical procedure for treating PDAC is extremely challenging, and its prognosis and outcome have attracted much attention. In addition to being closely related to tumor stage, a variety of perioperative factors affect survival, especially the occurrence of postoperative complications, which significantly reduce the survival rate and quality of life of patients [16]. To predict these complications more accurately, researchers are constantly exploring reliable biomarkers in peripheral blood.

Table 5 Factors analysis of in-hospital non-rehabilitation outcomes after PSM

Variables	Univariate analysis			Multivariate analysis		
	OR	95%CI	*P*	OR	95%CI	*P*
PIH	21.645	4.571-102.494	<0.001*	10.420	2.338–46.439	0.002*
SSI	11.371	3.181–40.645	<0.001*	4.310	1.001–18.550	0.050*
CCE	70.125	18.042-272.556	<0.001*	16.080	3.325–77.757	0.001*
PPCs	80.257	20.138-319.849	<0.001*	22.566	5.583–91.201	<0.001*

**P* value was less than 0.05, with statistical significance.PPH, post-pancreatectomy haemorrhage; SSI, surgical site infection; CCE, Cardiovascular And Cerebrovascular Events; PPCs, postoperative pulmonary complications

As an indicator that can reflect changes in red blood cell volume, RDW has become an indicator of red blood cell variability, and many studies have confirmed that RDW is correlated with the prognosis of a variety of diseases [17, 18]. A previous study revealed that the expression level of RDW in patients with different tumors was significantly different; for example, the expression of RDW in gastrointestinal tumors was greater than that in lung cancer and gynecological cancer [19].

Some studies have verified that RDW is positively correlated with tumor stage and can predict the prognosis of patients with different levels of pancreatic tumors. Studies have shown that when the expression of CA19-9 in patients increases, RDW also tends to increase20. However, research on RDW as a biomarker for evaluating or predicting postoperative complications and the prognosis of patients with pancreatic cancer is lacking. In this study, receiver operating characteristic (ROC) curve analysis was used to stratify RDW before surgery and verify the ability of RDW to predict PPH and survival. The results of the present study revealed that patients in the H-RDW group were generally older and that the proportion of patients with preoperative jaundice and biliary stent treatment was greater, which was directly related to functional decline and preoperative red blood cell wasting disease in elderly patients [21].

In addition, the preoperative multiple inflammation combination indices, such as the SII, NLR, PLR and LMR, in the H-RDW group were also significantly greater than those in the L-RDW group, which was similar to the results of most studies. In patients with gastrointestinal tumors, the RDW and inflammation combination index are increased before surgery, which could accurately predict the surgical prognosis of patients [22]. In conclusion, the preoperative basic condition of patients in the H-RDW group was poor, and the PNI value of the nutritional index was lower than that in the L-RDW group, suggesting that patients in this group may have experienced malnutrition before surgery [23]. Perioperative observation indices also revealed that patients in the H-RDW group had longer operation times and anesthesia times, more intraoperative blood loss and fluid infusion volume, and longer overall and postoperative hospital stays. These gaps were related to a higher rate of complex procedures in the H-RDW group, with nearly one in five patients undergoing a complex vascular anastomosis procedure during the procedure.

The postoperative complications of patients with PDAC vary. After PSM analysis, we found that the incidence of PPCs, SSIs and PPHs in the H-RDW group was much greater than that in the L-RDW group and that the proportion of patients with high C-D grades of postoperative complications was greater. In addition, in-hospital recovery and short-term (30-day and 90-day) survival rates were significantly lower in this group. This phenomenon of poor prognosis due to elevated preoperative RDWs has also been verified in recent studies [24, 25], but few studies on PDAC patients exist. Therefore, we further analyzed the risk factors associated with the identification of adverse outcomes. When all-cause analysis was performed, postoperative PPH, SSI, CCE and PPCs ultimately became the factors that seriously affected the in-hospital recovery of patients. After radical surgical treatment of patients with PDAC, traumatic stimulation causes various systems of the body to experience different degrees of stress. Coupled with the occurrence of complications, patients' circulatory, respiratory and coagulation systems have abnormal functions, which may threaten the life of patients in severe cases [26].

In view of the findings in the H-RDW group of patients, better provide me with clinical management basis. It is necessary to correct and deal with the inflammatory state in time before surgery, and pay close attention to the fluctuations of vital signs during the operation. In addition, because of the relatively high incidence of postoperative complications in this group of patients, we can also carry out preventive treatment for related complications before or during operation to ensure that the occurrence of postoperative complications is reduced or the occurrence grade of postoperative complications is reduced.

Reviewing the many postoperative complications in patients with PDAC, the presence of PPH caught our attention. Its occurrence produces many functional or organic changes in the body. With the progression of blood loss, the blood volume decreases to varying degrees, and hypoxia and hypoperfusion of tissues and organs occur one after another. Once important organs (such as the heart, brain, kidney, etc.) that are sensitive

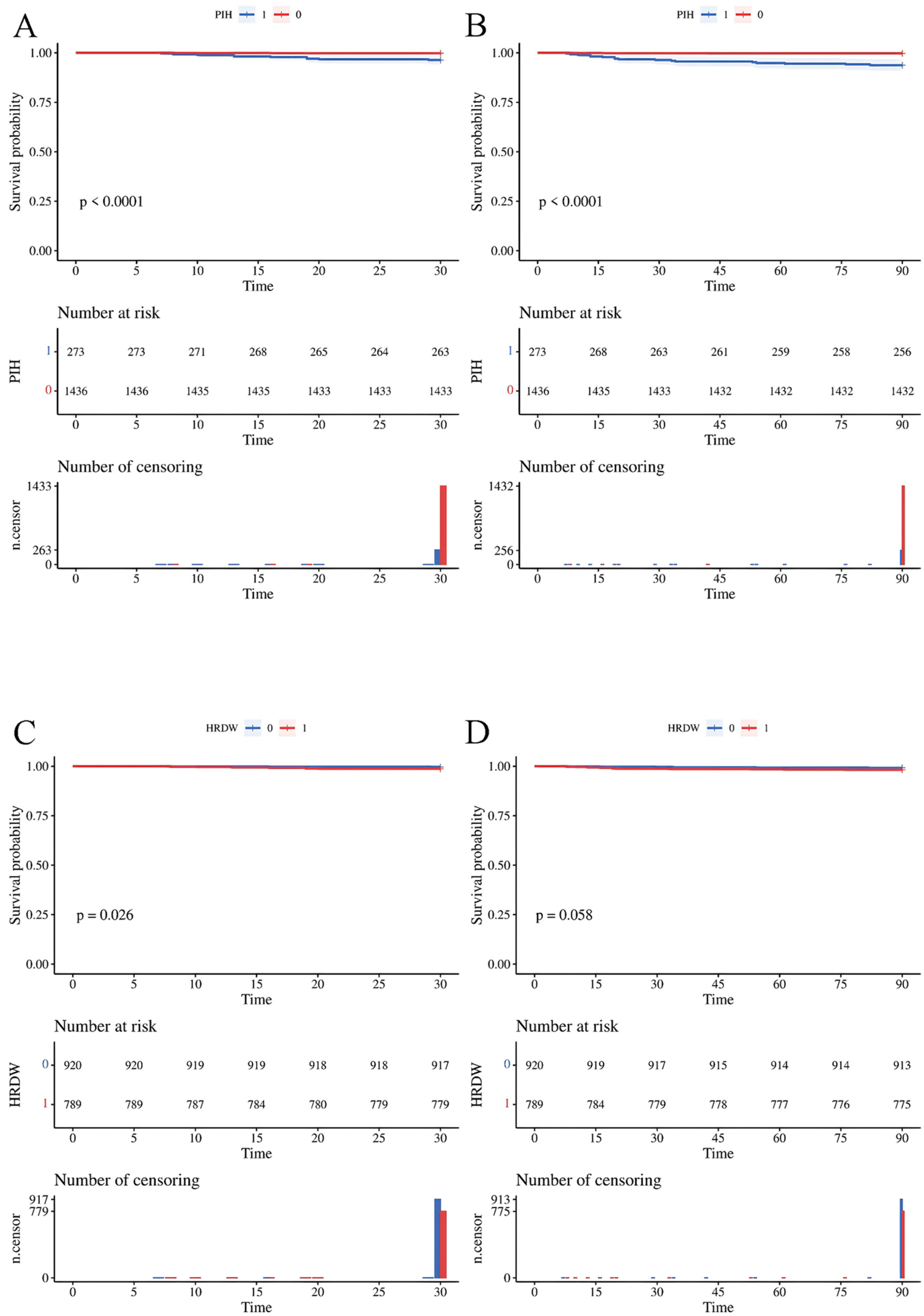

Fig. 4 Survival analysis of patients with pancreatic cancer after operation

to ischemia and hypoxia are damaged, severe dysfunction or failure may occur. In addition, the body's coagulation mechanism is disturbed, and the risk of abdominal infection increases. In conclusion, the occurrence and development of PPH seriously affects the prognosis of patients, increases postoperative discomfort, produces a series of stress reactions, and increases their psychological burden and anxiety. This not only affects the recovery of patients but also increases medical costs, prolongs the treatment time, and severe cases can even be life-threatening [27, 28].

Univariate and multivariate logistic analyses were used to construct a prediction model for PPH. The results showed that patients with preoperative anemia, jaundice and inflammation may have undergone compensatory changes and abnormal tissue metabolism before the operation. After complex surgery, special intraoperative medication and fluid infusion, the foundation for the occurrence and development of PPH is ultimately laid. Previous studies have shown that concomitant biliary tract diseases not only increase the chance of perioperative infection and activate the systemic inflammatory response but also promote postoperative bleeding [29]. In addition, studies have confirmed that the complexity of pancreatic surgery is also a risk factor for crisis events such as postoperative bleeding [30]. In the present study, the R colloidal/crystal ratio also emerged as a risk factor for PPH. A review of patients with PDAC revealed that patients with a higher ratio underwent more complex surgical procedures, more intraoperative blood loss, and greater fluctuations in blood system components during the perioperative period, which had an impact on coagulation function. On the basis of the results of the logistic analysis, receiver operating characteristic (ROC) curve analysis, calibration curve analysis, clinical decision curve analysis and nomogram analysis were used to further confirm the effectiveness of the risk factor prediction model and provide guidance for clinical work.

This retrospective study has certain limitations. First, due to selection bias and confounding factors, it is not possible to control for all variables that may affect the results. Therefore, we conducted PSM on the research data to eliminate or mitigate the effects of these factors. Second, regarding the occurrence of complications, a prospective design is usually more conducive to exploring causal relationships, but there may be various limitations in practical operation. Although the retrospective design has limitations, it may be the best approach in certain situations, especially when rare complications or long-term trends are studied. Finally, regarding the issue of sample sources for research, single center studies may indeed limit the generalizability of the results. There may be differences in patient populations in different regions, which may affect the applicability of the research results. To increase the external validity of the research, we are considering conducting a multicenter collaborative study for validation.

Conclusion

PPH is a common complication in PDAC patients and may affect their postoperative recovery and survival status. If the incidence of PPH can be reduced through intervention measures, it will undoubtedly have a positive effect on the prognosis of patients. In addition, changes in the preoperative RDW, as one of the factors affecting the occurrence and development of PPH, provide new ideas for clinical intervention. Monitoring and adjusting the RDW of patients may help prevent or alleviate the occurrence of PPH. Future research can explore the interaction mechanisms between RDWs and other related factors, as well as the optimal intervention strategies and timing.

Abbreviations

PC	Pancreatic cancer
PDAC	Pancreatic ductal adenocarcinoma
R-PHC	Resectable pancreatic head cancer
BR-PHC	Borderline resectable pancreatic head cancer
PD	Pancreaticoduodenectomy
TP	Total pancreatectomy
RDW	Red blood cell distribution width
SII	Systemic Immune-Inflammation Index
NLR	Neutrophil-to-lymphocyte ratio
PLR	Platelet-to-lymphocyte ratio
LMR	Lymphocyte-to-Monocyte Ratio
PNI	Prognostic Nutritional Index
PPH	Post-pancreatectomy haemorrhage
POPF	Postoperative pancreatic fistula
DGE	Delayed gastric emptying
PPCs	Postoperative pulmonary complications
PO-AKI	Postoperative acute kidney injury
BL	Biochemical leak
ISGPS	International Study Group of Pancreatic Surgery
KDIGO	Kidney Disease: Improving Global Outcomes
NSAIDs	Nonsteroidal Antiinflammatory Drugs

Supplementary information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions

Yuanqiang Dai: Methodology; Software; Formal analysis; Validation; Writing-Original Draft; Writing - Review & Editing. Ting Niu: Formal analysis; Validation; Writing - Original Draft. Yueying Wang: Investigation; Writing - Original Draft. Liangliang Lu: Investigation. Tianhua Cheng: Investigation. Jialin Li: Investigation. All authors read and approved the final manuscript.

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Data availability

All data generated or analyzed during this study are included in this published article. Data supporting the findings of this study are available from the First Affiliated Hospital of Naval Medical University, but the availability of these data is limited and the data is used under the license of the current study, so it is not publicly available. However, these data are available to authors on reasonable request here.

Declarations

Ethics approval and consent to participate
This study was performed in line with the principles of the Declaration of Helsinki. This study was approved by the ethics committee of the First Affiliated Hospital of Naval Medical University (CHEC2021-192).This study was retrospective and exempted patients from informed consent. This study strictly complies with the "Good Practice for Quality Management of Drug Clinical Trials" and the "Declaration of Helsinki".

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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