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ORIGINAL ARTICLE

Retrospective Study

Recurrence scoring system predicting early recurrence for patients with pancreatic ductal adenocarcinoma undergoing pancreatectomy and portomesenteric vein resection

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Abstract

BACKGROUND

Pancreatectomy with concomitant portomesenteric vein resection (PVR) enables patients with portomesenteric vein (PV) involvement to achieve radical resection of pancreatic ductal adenocarcinoma, however, early recurrence (ER) is frequently observed.

AIM

To predict ER and identify patients at high risk of ER for individualized therapy.

METHODS

Totally 238 patients undergoing pancreatectomy and PVR were retrospectively enrolled and were allocated to the training or validating cohort. Univariate Cox and LASSO regression analyses were performed to construct serum recurrence score (SRS) based on 26 serum-derived parameters. Uni- and multivariate Cox regression analyses of SRS and 18 clinicopathological variables were performed to establish a Nomogram. Receiver operating characteristic curve analysis was used to evaluate the predictive accuracy. Survival analysis was performed using Kaplan-Meier method and log-rank test.

RESULTS

Independent serum-derived recurrence-relevant factors of LASSO regression model, including postoperative carbohydrate antigen 19-9, postoperative carcinoembryonic antigen, postoperative carbohydrate antigen 125, preoperative albumin (ALB), preoperative platelet to ALB ratio, and postoperative platelets to lymphocytes ratio, were used to construct SRS [area under the curve (AUC): 0.855,

95%CI: 0.786–0.924]. Independent risk factors of recurrence, including SRS [hazard ratio (HR): 1.688, 95%CI: 1.075-2.652], pain (HR: 1.653, 95%CI: 1.052-2.598), perineural invasion (HR: 2.070, 95%CI: 0.827-5.182), and PV invasion (HR: 1.603, 95%CI: 1.063-2.417), were used to establish the recurrence nomogram (AUC: 0.869, 95%CI: 0.803-0.934). Patients with either SRS > 0.53 or recurrence nomogram score > 4.23 were considered at high risk for ER, and had poor long-term outcomes.

CONCLUSION

The recurrence scoring system unique for pancreatectomy and PVR, will help clinicians in predicting recurrence efficiently and identifying patients at high risk of ER for individualized therapy.

Key Words: Early recurrence; Portomesenteric vein resection; Pancreatic ductal adenocarcinoma; Recurrence score; Nomogram

Core Tip: Portomesenteric vein involvement is common in pancreatic ductal adenocarcinoma, which is correlated to the poor outcome, and needs individualized therapy. Pancreatectomy and portomesenteric vein resection (PVR) allow patients to achieve radical resection, however, early recurrence is frequently observed. This study constructed the first tailored recurrence scoring system unique for patients undergoing pancreatectomy and PVR, which consisted of Serum Recurrence Score and Recurrence Nomogram. With this scoring system, clinicians could predict early recurrence efficiently, and identify patients at high-risk of recurrence for individualized therapy timely, aiming to restrain the recurrence and improve the prognosis.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive malignant tumors in human neoplasms, with a five-year survival rate around 13%[1]. Radical resection remains the best therapeutic option that provides the long-term survival for patients with PDAC[2]. Because the majority of patients will develop distant metastases or locally advanced diseases, only 15%-20% are suitable candidates for surgery[3]. Portomesenteric vein (PV) involvement is frequent in patients with PDAC, and pancreatectomy with PV resection (PVR) is critical for achieving histologically margin-negative resection in this setting[4]. Although studies have demonstrated the safety and feasibility of pancreatectomy with PVR[5-8], the surgical and oncological outcomes remain poorly understood. The majority of the relevant literature argues that pancreatectomy with PVR provides no significant benefit of survival at the price of higher morbidity and mortality[9], however, several researchers have pointed out that selection bias resulting from the choice of baseline clinical features may have given rise to an underestimation of the benefits of this therapeutic intervention, suggesting that pancreatectomy with PVR could improve the long-term outcomes[10]. In a previous study, we demonstrated that radical resection and synchronous PVR in patients with PDAC could achieve comparable survivals to the standard approach, accompanied with no significantly serious complication[11].

Recent improvements in surgical techniques, radiological imaging, and perioperative management have facilitated access to pancreatectomy and PVR for more patients with PDAC and PV involvement. However, emerging evidence has showed that up to 80% of patients with PDAC undergoing radical resection will experience tumor recurrence within 2 years[12]. Moreover, 25%-37% of the cases of recurrence are likely to occur within 6 months postoperatively, which are denoted as early recurrence (ER). Patients with ER have extremely poor survivals that the median survival is around 9 months[13,14]. Although there is no data describing ER in this subgroup, estimates suggest that ER is far more frequently encountered in patients with PV involvement compared with those without due to the more advanced stages of tumors [15,16]. Accordingly, identifying patients at high risk of ER will facilitate the administration of individualized therapy, and promote the efficient treatment for patients suitable for pancreatectomy and PVR. Studies have found that tumor size, serum tumor markers, and venous invasion are independent prognostic factors for PDAC recurrence. Despite this, a tailored approach for the risk stratification of ER unique for patients undergoing pancreatectomy and PVR is currently lacking[17-19]. In patients with PV involvement, clinicopathological and biochemical parameters may change due to the variations of biological features of tumors. Therefore, the use of the values of the parameters and their cut-off values in patients with PV involvement based on previous readings, is highly inaccurate when attempting to predict ER. Thus, the development of a predictive system for ER unique to patients undergoing pancreatectomy and PVR, is critical for facilitating clinicians with a tool through which they can identify high-risk patients for individualized therapy.

In this study, we focused on serum-derived parameters to establish a comprehensive score in order to stratify the risk of ER. These were used to construct a nomogram, which would act in a concise manner to evaluate the risk of ER for patients undergoing pancreatectomy and PVR. Using this recurrence scoring system, clinicians will be able to perform a risk stratification of the recurrence efficiently and administer tailored therapies timely, with the aim of improving the long-term outcomes of patients with pancreatectomy and PVR.

MATERIALS AND METHODS

Study design and patients

This study was a retrospective analysis in a single center. All procedures were in accordance with the requirements of institutional ethical committee and the Helsinki Declaration (revised in 2013). A total of 727 patients with PDAC underwent pancreatectomy between January 2019 and December 2022 at this center. Among these, 277 underwent pancreatectomy and PVR.

The inclusion criteria were as follows: (1) Diagnosis of PDAC was confirmed by pathological examination; (2) No distant metastasis was found preoperatively or intraoperatively; (3) R0 resection with synchronous PVR was achieved; and (4) Adjuvant therapy such as chemotherapy or chemoradiotherapy was performed postoperatively. The exclusion criteria were as follows: (1) The tumor involving common hepatic artery, celiac axis, or superior mesenteric artery; (2) The patient who died within 90 days postoperatively, primarily due to surgical complication or organ dysfunction secondary to surgery rather than recurrence, that might skew the results; (3) Follow-up was not available or record could not be obtained; or (4) Evidence of other uncontrolled malignancies was found. In total, 39 patients were excluded according to the inclusion and exclusion criteria, including 13 patients (4.6%) who died within 90 days postoperatively, one patient (0.36%) with other uncontrolled malignancy, eight patients (2.8%) undergoing pancreatectomy with isolated metastasis found intraoperatively, and 17 patients (6.1%) without R0 resections. Ultimately, a total of 238 patients were recruited for this study.

Perioperative setup

Abdominal contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) was performed preoperatively in each patient, in order to exclude abdominal metastasis, pelvic metastasis or lung metastasis. The invasion extent of adjacent artery or vein was evaluated by both surgeons and radiologists. Positron emission tomography was applied in selected patients with indications of distant metastasis. Neoadjuvant chemotherapy (NAT) was adopted in patients with borderline resectable diseases according to the National Comprehensive Cancer Network guidelines[20]. Clinical and demographics data (age, sex, smoking, body mass index, diabetes mellitus, and symptoms) was collected. Serum-derived parameters [neutrophils, lymphocytes, monocytes, platelets, albumin (ALB), neutrophils to lymphocytes ratio, platelets to lymphocytes ratio (PLR), lymphocytes to monocytes, neutrophil to ALB ratio (NAR), and platelet to ALB ratio (PAR)], and serum tumor markers [carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), and CA125] were examined within one week before operation, and one month after operation. Preoperative biliary drainage was performed in patients with obstructive jaundice (serum total bilirubin > 250 μmol/L). Endoscopic retrograde biliary drainage was adopted if available, otherwise, percutaneous biliary drainage was conducted. Postoperative major complications (Clavien-Dindo score ≥ 3) were defined according to the Clavien-Dindo classification [21].

Surgical procedure

The pancreatectomies, including pancreaticoduodenectomy (PD), total pancreatectomy (TP), and distal pancreatectomy (DP) were conducted according to the preoperative evaluation and intraoperative exploration. Briefly, the procedures of PD, TP, or DP were performed as previously described[22]. The feasibility and manners of PVR were re-evaluated intraoperatively. PVR was carried out either by tangential resection (11.3%) with primary closure of the vein, or segmental resection (88.6%) with end-to-end anastomosis using vascular graft or not. Routine frozen-section examinations of margins, and dissections of regional lymph nodes were completed in each patient. Gastrointestinal reconstructions, including end-to-side pancreaticojejunostomy, end-to-side hepaticojejunostomy, and antecolic gastrojejunostomy were performed depending on the detailed types of pancreatectomies.

Pathological characteristics

Pathological parameters, including histological type, tumor site, tumor size, grade of tumor differentiation (poor differentiation: Grade III), perineural invasion, PV invasion (pathologically confirmed invasion of venous wall), and lymph node status, were extracted. The pathological stage was determined according to the 8th edition of the American Joint Committee on Cancer. R0 resection was defined in accordance with the consensus statement of the International Study Group of Pancreatic Surgery[23].

Follow-up

All enrolled patients were continuously followed up every month in the first 6 months after operation, then every 3 months in the following 6 months, thereafter every 3-6 months in the second year, finally once a year if no recurrence was observed within 2 years postoperatively. Blood tests were conducted during each follow-up. CT or MRI was performed every 3 months in the first year postoperatively, and then every 6 months in the second year. Abdominal venous

ultrasound was adopted to examine the patency of PV after operation, and all patients took aspirin (100 mg/day). Recurrence was evaluated not only following the criteria of RECIST guideline version 1.1[24], but also considering the continuous and progressive increases of serum tumor markers. Since patients who experience recurrence within 6 months had a significantly poorer prognosis compared with those beyond 6 months in this study, recurrence within 6 months post-surgery was defined as ER, while recurrence beyond 6 months or no recurrence was defined as delayed recurrence (DR). The types of recurrence were classified into liver metastasis, locoregional recurrence (soft tissue around vascular or surgical bed or remnant pancreas), lung metastasis, peritoneal or omental metastasis, and indeterminate site. The recurrence free survival (RFS) was defined as the period from the date of operation to the date of recurrence or the last follow-up. The overall survival (OS) was defined as the period from the date of operation to the date of death or the last follow-up.

Construction of serum recurrence score

From the original cohort, 238 cases were assigned to the training cohort (cases which were randomly sampled from the entire original cohort at a ratio of 70%), and the validating cohort (cases which were randomly sampled from the entire original cohort at a ratio of 50%). The different ratios for constructing the training and validating cohort, aimed to make full use of limited cases to randomly generate the training cohort for establishing a stable predictive system, as well as to randomly generate the validating cohort without excessively increasing the probability of overlapping cases (currently 23% of the original cohort) between these two cohorts. This design was chosen in order to ensure that reliable verifications were performed.

Univariate Cox regression analysis was performed to identify the serum-derived variables closely related to recurrence in the training cohort, and the variables with P value < 0.1 were then taken into least absolute shrinkage and selection operator (LASSO) regression analysis. Cross validations (5-fold) were adopted in the subsequent LASSO regression analysis (R package: Glmnet), and the appropriate lambda value (penalty coefficient) was determined to construct an optimal model. All included serum-derived variables and corresponding coefficients in the model constructed by LASSO regression were applied to establish the serum recurrence score (SRS) formula as follows:

$$SRS = Coefficient_1 \times Variable_1 + Coefficient_2 \times Variable_2 + \ldots + Coefficient_N \times Variable_N$$

In the training cohort, receiver operating characteristic (ROC) curve analysis was performed (R package: PROC), and area under the curve (AUC) was calculated to evaluate the accuracy of SRS for predicting ER. The time-dependent ROC curve was established to compare the accuracy of SRS in different time intervals postoperatively (R package: TimeROC). Survival analysis was carried out by Kaplan-Meier survival plot and log-rank test (R package: Survival and survminer) to provide prognosis stratification. ROC curve analysis and survival analysis were both performed in the validating cohort to verify the results.

Construction of the recurrence nomogram

Clinicopathological variables and SRS were used for univariate Cox regression analysis to screen out the potential risk factors of recurrence. Multivariate Cox regression analysis (factors with P value < 0.1 in the previous step) was performed to determine the independent risk factors of recurrence. Backward stepwise (likelihood ratio) method was adopted in the multivariate Cox regression model. A nomogram was established (R package: Rms) to provide a risk prediction for ER.

Statistical analysis

Continuous variables in normal distribution were presented as mean ± SD, and the variables in non-normal distribution were presented as median and interquartile range (IQR). Continuous variable was categorized by the cut-off value (R package: Survival), otherwise, the mean value was used. Categorical variables were presented as absolute number and percentage. For this retrospective study, the sample size was determined by the actual available cases in accordance to the inclusion and exclusion criteria. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test as appropriate. Continuous variables were compared using Student's t-test. P value < 0.05 of two-tailed tests was considered statistically significant. With the exception of cases with missing values for the analyzed variables, which were omitted temporarily before LASSO regression analysis or multivariate Cox regression analysis, all enrolled cases were included in this statistical analysis. Outliers of the variables analyzed were maintained in our analysis. Statistical analysis was performed using SPSS software 26.0 (SPSS Inc, Chicago, IL, United States).

RESULTS

Cohort characteristics

The cohort was comprised of 238 cases, including 165 assigned to the training cohort and 112 to the validating cohort. The clinicopathological features were compared between the training and validating cohorts (Table 1). Categorial variables with multiple levels were transformed into two-level variables in the aforementioned cohorts, including operation types (PD 74.5%, DP 9.7% and TP 15.8% *vs* PD 75%, DP 9.8% and TP 15.2%), tumor sites (head 53.9%, neck 39.4% and body/tail 6.7% *vs* head 60.7%, neck 34.8% and body/tail 4.5%), lymph node status (N0 43.6%, N1 34.6% and N2 21.8% *vs* N0 42%, N1 36.6% and N2 21.4%), and pathological stage (stage I 25.5%, stage II 52.7% and stage III 21.8% *vs* stage I 27.7%, stage II 50.9% and stage III 21.4%). No statistically significant difference was observed for these clinicopathological variables between the training and validating cohorts, with the exception of weight loss.

Table 1 Clinicopathological features, %

Features	Training cohort (*n* = 165)	Validation cohort (*n* = 112)	*P* value
Age (years)	61.46 ± 8.262	61.67 ± 8.237	0.836
Sex (male)	55.8	60.7	0.412
Smoking	15.2	15.2	0.995
BMI (kg/m^2)	22.0901 ± 2.68962	22.4009 ± 2.78960	0.355
Diabetes mellitus	38.8	38.4	0.947
Pain	69.7	63.4	0.273
Weight loss	23.6	13.4	0.035
Neoadjuvant chemotherapy	26.1	18.8	0.157
Jaundice	28.5	26.8	0.757
Operation types (PD[1])	74.5	75.0	0.932
Major complications	6.6	6.3	0.890
Tumor sites[2]	93.3	95.5	0.441
Tumor size (cm)	3.915 ± 1.6448	3.771 ± 1.6681	0.476
Poor differentiation	49.7	58.9	0.131
Perineural invasion	92.7	94.6	0.526
Portomesenteric vein invasion	49.7	50.9	0.845
Lymph node status (N0)	43.6	42.0	0.783
Pathological stage (stage III)	21.8	21.4	0.938
Recurrence	80.6	80.4	0.953
Early recurrence	42.5	42.7	1.000
Median OS (months)	16.40 (9.67-25.07)	15.60 (9.70-22.70)	0.626
Median RFS (months)	7.40 (2.97-14.85)	7.35 (3.00-15.10)	0.810

[1]Pancreaticoduodenectomy.
[2]Head or neck of pancreas.
BMI: Body mass index; PD: Pancreaticoduodenectomy; OS: Overall survival; RFS: Recurrence free survival.

The median follow-up period was 16.31 months (IQR: 9.78-25.56), the median RFS was 7.68 months (IQR: 3.27-15.57), and the median OS was 16.36 months (IQR: 9.92-25.63). Recurrence within 6 months (ER), beyond 6 months (DR), and no recurrence (DR) accounted for 41.4%, 39.3%, and 19.2% of the original cohort, respectively. The recurrence sites of ER and DR indicate that hepatic metastasis was more frequently observed during the ER stage, whereas locoregional recurrence was more common during the DR stage (Table 2). Additionally, the majority of the cases of recurrence were diagnosed by continuous and progressive increases in serum tumor markers and classified as indeterminate sites, which could not be identified by the imaging modalities. The median OS of patients with ER and DR were 9.70 months (IQR: 6.60-15.30) and 22.10 months (IQR: 15.65-31.90), respectively. Patients with ER had significantly poorer OS than those with DR (*P* value < 2e-16). The Kaplan-Meier survival plots were shown in Supplementary Figure 1.

Construction of SRS based on serum-derived factors

To identify the relevant recurrence factors, 26 perioperative serum-derived variables were investigated through univariate Cox regression analysis in the training cohort (Figure 1A). Briefly, 15 of the 26 variables with *P* value < 0.1 were included in the LASSO regression analysis. With an increasing lambda value, fewer variables were retained in the model (Figure 1B). As a result, the cross validation of LASSO regression analysis (Figure 1C) helped us determine the appropriate lambda value (lambda.1se: 0.182645) to construct the optimal model. Six variables, including Af_CA19-9, Af_CEA, Af_CA125, Pre_ALB, Pre_PAR, and Af_PLR, were incorporated into the final model, and their corresponding coefficients were applied to establish the SRS formula. The SRS of each case in both the training and validating cohorts was calculated as follows:

SRS = 0.66381928 × Af_CA19-9 + 0.08935077 × Af_CEA + 0.03762186 × Af_CA125 + 0.25404440 × Pre_ALB - 0.09664955 × Pre_PAR - 0.12718560 × Af_PLR

Table 2 Recurrence sites of early recurrence and delayed recurrence, %

Recurrence site	Recurrence (≤ 6 months)	Recurrence (> 6 months)
Liver	41.2	19.7
Lung	1.0	0.7
Locoregional metastasis	7.2	14.5
Peritoneal and omental metastasis	2.0	5.1
Indeterminate	48.4	29.1

Predicting ER based on SRS

To evaluate the accuracy of SRS in predicting ER, ROC curve analysis was performed to calculate the AUC of SRS and the aforementioned serum-derived variables. The corresponding ROC curves were plotted to compare the AUCs (Figure 2A). Statistically significant differences in the accuracy for predicting ER were observed between SRS and the serum-derived variables (Table 3). The time-dependent ROC curve showed that the AUC of SRS varied over time (Figure 2B), and revealed that the accuracy of SRS in predicting recurrence within 12 months was beyond 0.8, but decreased and then remained stable after 12 months (Table 4). Taken together, these results indicate that the most accurate predictive period of SRS was within 12 months. The results of ROC curve analysis in the validating cohort are provided in Supplementary Figure 2A and B, and Supplementary Tables 1 and 2.

Stratifying the prognosis of patients using SRS

SRS were transformed into two-categorial variables. The cut-off values of the variables are provided in Supplementary Table 3. ER accounted for the majority of the cases of recurrence in the high-SRS (SRS > 0.53) group compared with the low-SRS (SRS ≤ 0.53) group (80.43% *vs* 22.05%, *P* value = 2.719e-09) (Figure 2C). The high-SRS group was found to have a significantly poorer RFS compared with the low-SRS group [2.50 months (IQR: 1.625-4.425) *vs* 13.90 months (IQR: 6.57-23.72), *P* value = 3e-15; Figure 2D]. The high-SRS group showed a markedly poorer OS compared with the low-SRS group [12.45 months (IQR: 8.07-20.37) *vs* 18.95 months (IQR: 14.45-29.60), *P* value = 2e-06; Figure 2E]. The results of the validating cohort are provided in Supplementary Figure 2C-E.

Construction of the recurrence nomogram

The correlations between SRS and 18 clinicopathological variables were investigated (Supplementary Table 4). As a result, tumor site (head/neck), poor differentiation, and advanced stage were found to be correlated to a higher SRS (Figure 3A-C). SRS and 18 clinicopathological variables were analyzed *via* univariate Cox regression model, and the risk factors (*P* value < 0.1) were included in multivariate Cox regression model (Figure 3D and E). Pain, perineural invasion, PV invasion, and SRS were identified as the independent risk factors of recurrence.

The recurrence nomogram was constructed based on the independent risk factors mentioned above (Figure 4A). The recurrence nomogram score (RNS) was calculated according to the recurrence nomogram. ROC curve analysis was performed to evaluate the accuracy of the recurrence nomogram in predicting ER at different time points in both the training and validating cohorts (Figure 4B and Supplementary Figure 3A), indicating that the most accurate predictive period of RNS was within 6 months. The clinicopathological score (CS) for predicting recurrence based on the independent clinicopathological factors was also constructed, and the predictive accuracies of CS, RNS, and SRS were compared (Figure 4C and Supplementary Figure 3B). The predictive accuracy of RNS was superior to CS in both the training (*P* value = 1.99e-05) and validating cohorts (*P* value = 0.0298), but no significant difference was observed between RNS and SRS in both the training (*P* value = 0.478) and validating cohorts (*P* value = 0.946).

The cohort was divided into the high-risk (RNS > 4.23) and low-risk (RNS ≤ 4.23) groups according to the cutoff value of RNS. ER accounted for the majority of the cases of recurrence in the high-risk group compared with the low-risk group (72.88% *vs* 16.36%, *P* value = 4.467e-09) (Figure 4D and Supplementary Figure 3C). RFS was significantly better in the low-risk group compared with the high-risk group [14.60 months (IQR: 7.45-25.80) *vs* 2.70 months (IQR: 1.75-6.40), *P* value = 9e-13; Figure 5A]. Moreover, a better OS was observed in the low-risk group compared with the high-risk group [19.30 months (IQR: 14.90-31.05) *vs* 13.00 months (IQR: 7.85-19.80), *P* value = 5e-07; Figure 5B]. The PV_invasion group (*P* value = 0.036) and pain group (*P* value = 0.023) were associated with a significantly poorer RFS (Figure 5C and D), in contrast to the perineural_invasion group (*P* value = 0.1). The PV_invasion (*P* value = 0.032) and pain groups (*P* value = 0.017) were also associated with a significantly poorer OS (Figure 5E and F), in contrast to the perineural_invasion group (*P* value = 0.1). The results of survival analysis in the validating cohort are presented in Supplementary Figure 4. High risk of recurrence (RNS > 4.23) and PV invasion were associated with a poorer RFS and OS, whereas pain and perineural invasion were not correlated to RFS or OS in the validating cohort.

DISCUSSION

Patients with PV involvement who undergo pancreatectomy and PVR, are more likely to experience tumor recurrence or metastasis compared with those without[15]. This is more likely due to the factor that tumors with PV involvement are

Table 3 Predictive accuracy for early recurrence in training cohort

Training cohort	AUC	95%CI	*P* value
SRS	0.855	(0.786-0.924)	-
Af_CA19-9	0.795	(0.710-0.880)	0.0362
Af_CEA	0.677	(0.577-0.777)	0.000358
Pre_CA19-9	0.675	(0.576-0.774)	0.000518
Pre_CA125	0.641	(0.538-0.744)	0.00016
Pre_ALB	0.631	(0.526-0.735)	2.20e-05
Pre_NLR	0.563	(0.456-0.670)	1.52e-05
Af_CA125	0.559	(0.453-0.666)	5.14e-06
Af_NAR	0.550	(0.442-0.659)	7.92e-06
Pre_neutrophils	0.548	(0.441-0.655)	2.36e-06
Pre_CEA	0.541	(0.433-0.649)	1.13e-07
Pre_NAR	0.509	(0.402-0.616)	2.68e-07
Af_neutrophils	0.508	(0.401-0.615)	3.08e-08
Af_LMR	0.506	(0.399-0.614)	1.13e-07
Af_lympocytes	0.502	(0.394-0.611)	6.21e-08
Af_NLR	0.495	(0.387-0.603)	6.10e-08
Pre_monocytes	0.487	(0.378-0.595)	2.24e-08
Pre_LMR	0.486	(0.378-0.593)	1.49e-06
Af_monocytes	0.482	(0.375-0.589)	2.91e-07
Af_PAR	0.459	(0.349-0.569)	5.31e-06
Pre_PLR	0.458	(0.350-0.566)	7.86e-08
Pre_lymphocytes	0.457	(0.347-0.567)	1.41e-10
Af_PLR	0.435	(0.328-0.541)	3.88e-06
Af_platelets	0.432	(0.326-0.539)	4.54e-06
Af_ALB	0.428	(0.319-0.536)	1.99e-05
Pre_platelets	0.415	(0.309-0.521)	1.29e-05
Pre_PAR	0.397	(0.293-0.502)	9.95e-06

CA: Carbohydrate antigen; CEA: Carcinoembryonic antigen; ALB: Albumin; NLR: Neutrophils, lymphocytes ratio; PLR: Platelets to lymphocytes ratio; LMR: Lymphocytes to monocytes ratio; NAR: Neutrophil to albumin ratio; PAR: Platelet to albumin ratio; SRS: Serum recurrence score; AUC: Area under the curve.

more aggressive, providing an environment that favors tumor metastasis. Accordingly, measures that facilitate a risk stratification by recurrence in patients with PV involvement, are likely to contribute extensively to the provision of individualized therapy for target patients. However, at present, no tailored approach unique to patients undergoing pancreatectomy and PVR who are at high risk of recurrence exists.

In this study, the cohort was comprised of 238 patients with PV involvement who underwent pancreatectomy and PVR. As the median follow-up period was 16.31 months (IQR: 9.78-25.56), 34.5% of the patients were alive at the time of the final follow-up, and were classified as censored cases. Therefore, the median OS was 16.36 months (IQR: 9.92-25.63), relatively lower than previously reported values[25]. A plenty of patients (41.4%) experienced recurrence within 6 months, with hepatic metastasis (41.2%) or the aberrant increase of tumor markers (48.4%) accounting for the majority of cases of ER. This indicates that occult micro-metastasis may have been present at the time of surgery, as stated in a previous study[26]. Previous studies have found that NAT can eliminate micro-metastasis diseases, reduce tumor sizes, and increase the rate of R0 resection in patients with PV involvement[27,28]. Although NAT may be an alternative approach for decreasing ER in candidate patients undergoing pancreatectomy and PVR[29,30], we could not demonstrate that NAT was an independent factor of recurrence due to the low rate of NAT in this study. In addition to NAT, with respect to the high rate of ER, postoperative adjuvant therapy was important in patients undergoing pancreatectomy and PVR[31]. It is worth noting that the extent of regimens and treatment periods may be critical to suppress ER, given that all

Table 4 Time-dependent area under the curves of serum recurrence score in training cohort

Time intervals (months)	AUC	95%CI
6	0.8549938	(78.62-92.38)
12	0.8095726	(73.15-88.76)
18	0.7710402	(67.01-87.20)
24	0.7830021	(67.75-88.85)
30	0.7766629	(66.12-89.21)
36	0.7762760	(67.27-87.99)
42	0.7930477	(68.72-89.89)
48	0.7930477	(68.72-89.89)
54	0.7975818	(67.76-91.75)

AUC: Area under the curve.

enrolled patients received adjuvant therapy in this study. Moreover, patients with ER had a markedly poorer OS compared with those with DR [9.70 months (IQR: 6.60-15.30) *vs* 22.10 months (IQR: 15.65-31.90), *P* value < 2e-16], suggesting that the risk stratification of ER may help clinicians take therapeutic measures sooner, and therefore improve the likelihood of achieving a better prognosis among their patients.

Since patients underwent radical resections of tumors, the relapsed lesions at the very early stage would not be identified easily by the imaging modalities, and usually led to the aberrant increase of serum tumor markers. In this study, instances of recurrence were identified based on a continuous and progressive increase in serum tumor markers, which may not have been included in previous studies[17,18]. Therefore, both the rate of recurrence (80%) and the rate of ER (41.4%) were relatively higher in this study. However, this would help to establish a rational recurrence score system that is sensitive to ER in practical applications.

In this study, we developed a LASSO regression model based on the perioperative serum-derived parameters, from which SRS was constructed. To the best of our knowledge, SRS is the first recurrence score unique to patients undergoing pancreatectomy and PVR, which consists of four postoperative parameters (Af_CA19-9, Af_CEA, Af_CA125, and Af_PLR) and two preoperative parameters (Pre_ALB and Pre_PAR). Preoperative CA19-9, CEA, and CA125 were previously demonstrated as prognostic tumor markers of PDAC[32], while preoperative CA19-9 was identified as an important predictor for recurrence[33]. However, when preoperative and postoperative tumor markers were both used for LASSO regression analysis, postoperative CA19-9, CEA, and CA125 were found to play an outsized role in predicting recurrence compared with preoperative CA19-9, CEA, or CA125, in line with the findings that postoperative CA19-9, CEA, and CA125 are biomarkers predicting the operative outcomes of PDAC[34]. Preoperative predictors can help clinicians make better treatment decisions before surgery, while postoperative predictors can be used to achieve more accurate estimations of recurrence. Nutrition- and inflammatory-based parameters such as prognostic nutrition index, modified Glasgow prognostic score, and NAR have been demonstrated as prognostic indexes. However, whether they can be employed to predict recurrence remains unknown[17,18,35,36]. The findings of this study indicate that the combination of nutrition- and inflammatory-based parameters, and postoperative serum tumor markers can be used to improve the predictive accuracy for ER.

Applying SRS to predict ER in patients undergoing pancreatectomy and PVR, achieved an excellent predictive accuracy in both the training (AUC: 0.855) and validating (AUC: 0.773) cohorts. Compared with the findings of previous studies[17,18,37,38], SRS showed an extremely high predictive accuracy for recurrence during the ER stage (AUC > 0.854), and even performed well during the DR stage (AUC: 0.771-0.809). This indicates that SRS can predict recurrence efficiently and stably in patients undergoing pancreatectomy and PVR. LASSO regression analysis creates penalty coefficients that cause shrinkages of different variables according to their effects on the main outcome event, instead of removing the variables directly, in order to reduce the interference of collinearity to aid in the establishment of an optimal model. We speculate that the unique inclusion of the perioperative serum-derived factors in the LASSO regression model to construct SRS is one of the reasons for the outstanding performance of SRS.

Next, we used SRS to stratify patients with pancreatectomy and PVR into high-SRS group and low-SRS groups. Patients in the high-SRS group (SRS > 0.53) had a poorer RFS and a poorer OS compared with those in the low-SRS group. Adjuvant therapy has been proved to be an independent prognostic factor for patients with radical resections of PDAC, which is generally administered for 6 months postoperatively[39,40]. However, in this study, the results serve as a reminder to clinicians that the regular adjuvant therapy may be insufficient in patients undergoing pancreatectomy and PVR when their SRS are beyond 0.53. Moreover, SRS can be generated within one month postoperatively, which provides clinicians with a reliable reference for conducting an enhanced or extended treatment quickly for patients at high risk of ER.

Due to the excellent performance of SRS in predicting recurrence and stratifying prognosis, we combined SRS and clinicopathological parameters to construct a recurrence nomogram for patients with pancreatectomy and PVR. Independent risk factors, including pain, perineural invasion, PV invasion, and SRS were applied to establish the

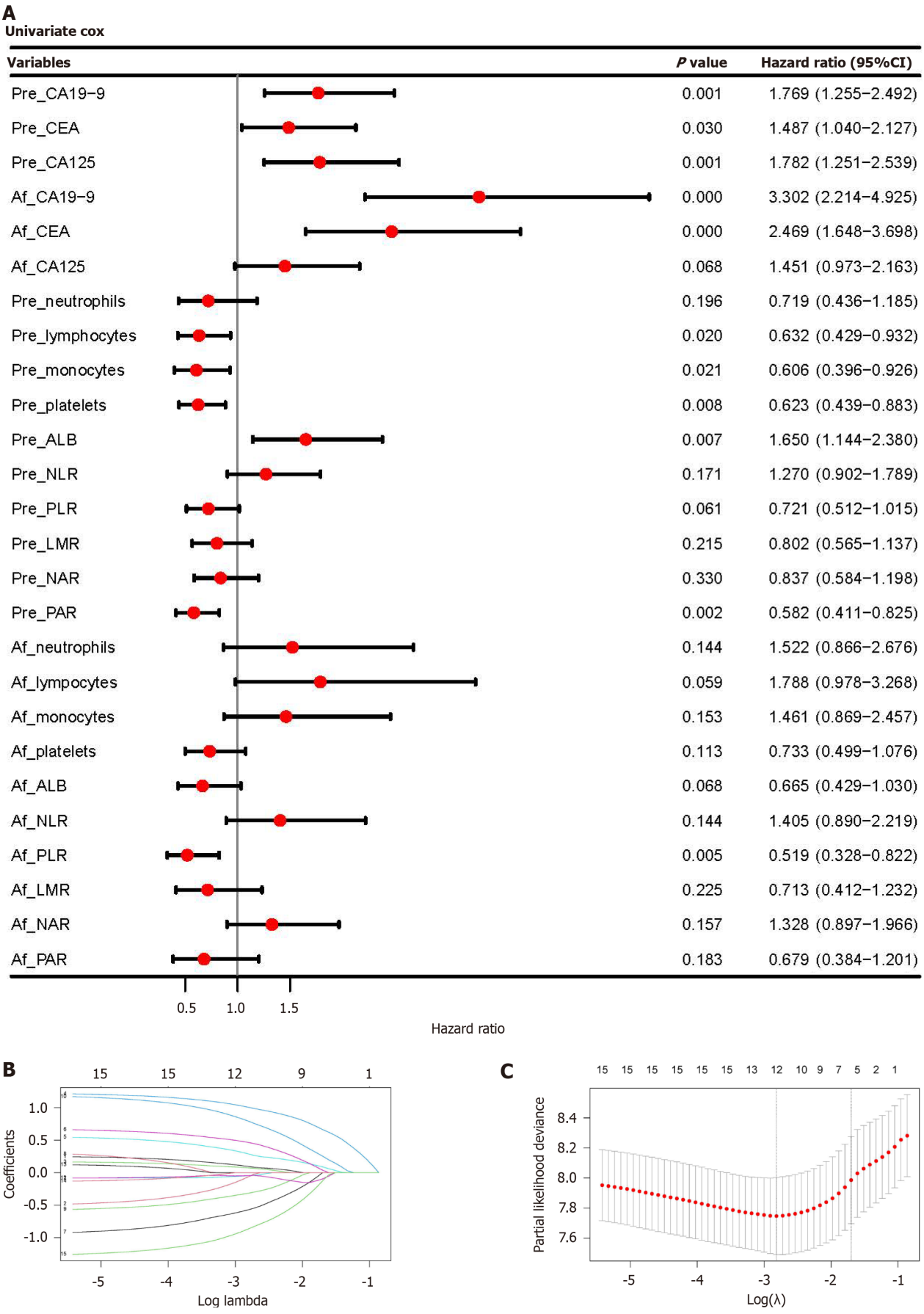


Figure 1 Construction of serum recurrence score based on perioperative serum-derived variables. A: Univariate Cox regression analysis and Forest plot of perioperative serum-derived variables; B: LASSO regression analysis of 15 serum-derived variables (*P* value < 0.1) and shrinkage coefficient diagram. Y-axis represents coefficients of variables, and X-axis represents the penalty coefficient (Lambda). As the log Lambda increases, more coefficients of variables will

decrease to zero; C: Cross validation (5-fold) of LASSO regression analysis. Dotted vertical line indicates the minimum and one standard error of Lambda values. The one standard error value of Lambda was used as the penalty coefficient. CA: Carbohydrate antigen; CEA: Carcinoembryonic antigen; ALB: Albumin; NLR: Neutrophils, lymphocytes ratio; PLR: Platelets to lymphocytes ratio; LMR: Lymphocytes to monocytes ratio; NAR: Neutrophil to albumin ratio; PAR: Platelet to albumin ratio.

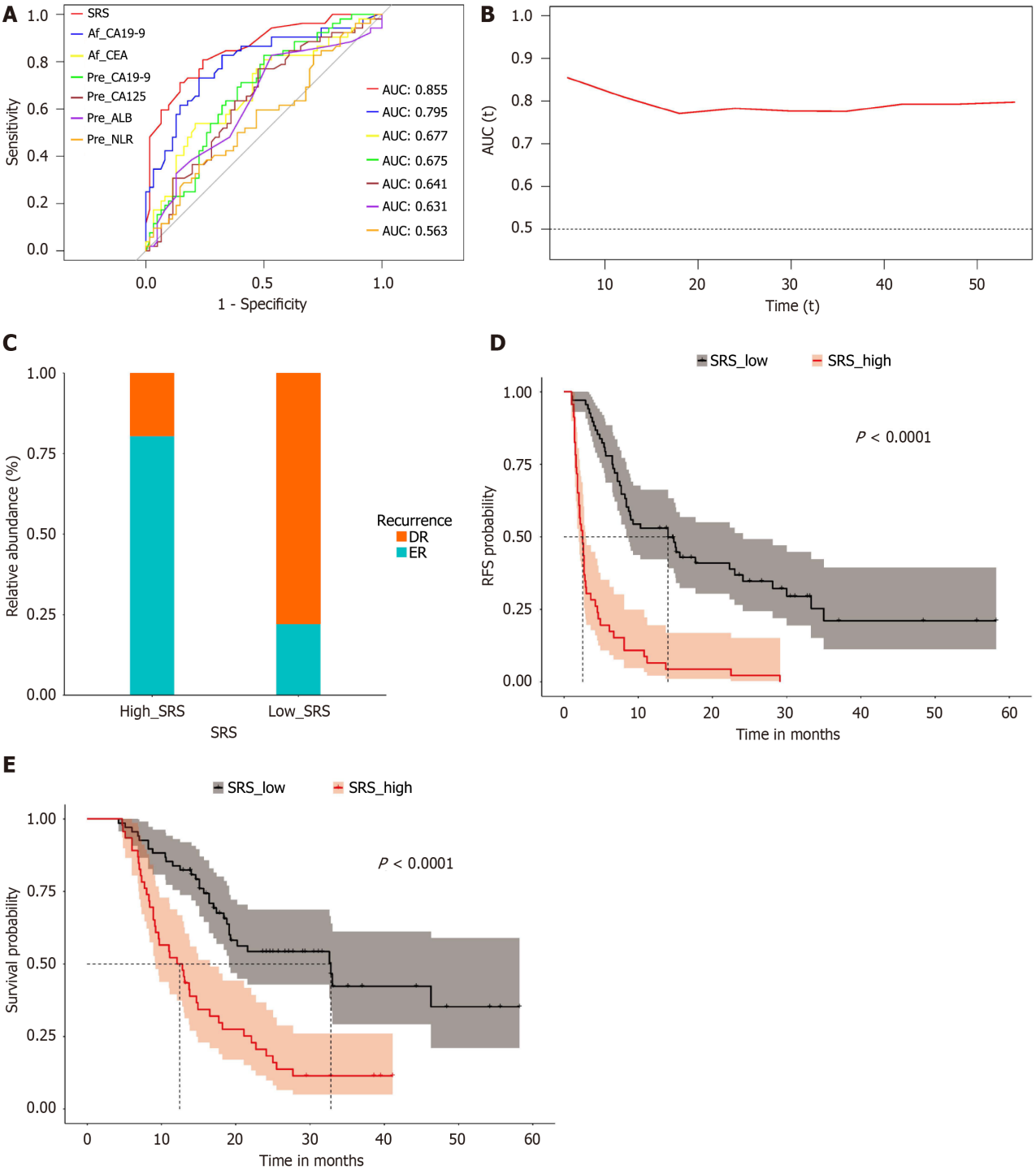
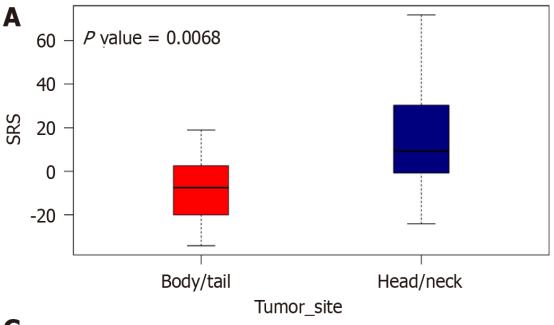
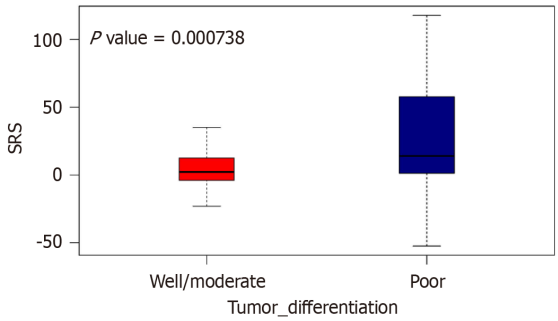
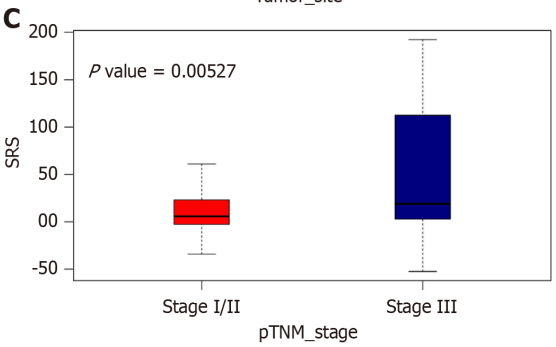


Figure 2 Receiver operating characteristics curve and survival analyses of serum recurrence score in the training cohort. A: Receiver operating characteristics (ROC) curves of serum recurrence score (SRS) and top six (AUC) serum-derived variables for predicting early recurrence (ER). The AUC of SRS was superior to the AUCs of other serum-derived variables; B: Time-dependent ROC curve of SRS for predicting recurrence, the AUCs of SRS varied over time (months); C: Stacked plot showing significantly different ratios of ER and delayed recurrence, in the high-SRS (SRS > 0.53) and low-SRS (SRS ≤ 0.53) groups, respectively (*P* value = 2.719e-09); D and E: Kaplan-Meier survival analysis for patients with high SRS and low SRS. The high-SRS group showed significantly poorer recurrence free survival and overall survival compared with the low-SRS group. SRS: Serum recurrence score; ROC: Receiver operating characteristics; AUC: Area under the curve; ER: Early recurrence.



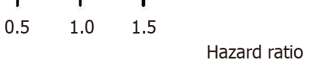




D

Univariate cox

Variables	*P* value	Hazard ratio (95%CI)
Operation types	0.551	0.890 (0.606–1.306)
Age	0.274	0.826 (0.586–1.163)
Gender	0.709	1.067 (0.758–1.503)
Smoking	0.164	0.702 (0.426–1.156)
BMI	0.462	0.879 (0.623–1.240)
DM	0.655	1.082 (0.766–1.528)
Pain	0.099	1.375 (0.942–2.008)
Weight_loss	0.778	0.944 (0.633–1.409)
Neoadjuvant chemotherapy	0.194	1.290 (0.879–1.894)
Jaundice	0.906	1.023 (0.698–1.501)
Tumor_site	0.515	1.252 (0.636–2.464)
Tumor_size	0.570	1.104 (0.784–1.555)
Tumor_differentiation	0.397	1.159 (0.824–1.631)
Perineural_invasion	0.030	2.337 (1.086–5.028)
Portomesenteric_vein_invasion	0.015	1.530 (1.085–2.156)
Lymphnode_metastasis	0.162	1.282 (0.905–1.816)
pTNM_stage	0.234	1.278 (0.854–1.914)
Complications	0.361	1.373 (0.696–2.709)
SRS	0.005	1.901 (1.217–2.969)



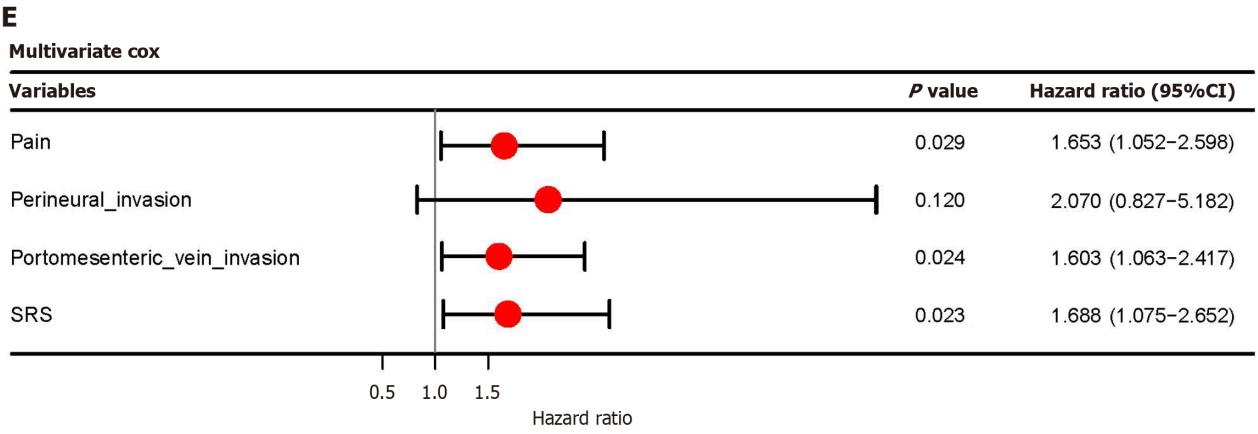


Figure 3 Construction of the recurrence nomogram. A-C: Correlations between serum recurrence score (SRS) and tumor site, tumor differentiation, and tumor stage. Higher SRS was observed in the head/neck group, the poor differentiation group, and the advanced stage group; D: Univariate Cox regression analysis and Forest plot of SRS and 18 clinicopathological variables; E: Multivariate Cox regression analysis and Forest plot of the independent risk factors of recurrence. SRS: Serum recurrence score.

recurrence nomogram, which is much more accessible in clinical practice. The recurrence nomogram consisted of one preoperative clinical parameter, two pathological parameters, and SRS. Perineural invasion (HR: 2.070, 95%CI: 0.827-5.182) and PV invasion (HR: 1.603, 95%CI: 1.063-2.417) indicate the aggressive characteristics of PDAC, which are closely related to recurrence[41,42]. Patients with pathologically confirmed invasion of PV accounted for 30%-80% of patients with PVR[43]. Whether PVR with PV invasion shows a poorer survival compared with PVR without PV invasion remains a topic of debate[44,45]. However, our findings suggest that patients undergoing pancreatectomy and PVR with PV invasion will tend to have a poorer RFS and OS compared with those without. Pain (HR: 1.653, 95%CI: 1.052-2.598) is a typical manifestation of advanced tumors, which is worthy of being taken into account preoperatively. RNS including SRS and the independent clinicopathological factors showed a superior predictive accuracy for ER compared with CS including only independent clinicopathological factors. This highlights the critical role of SRS in the recurrence nomogram. Using RNS, clinicians can identify those patients at high risk of ER when RNS is beyond 4.23, which is associated with a very poor prognosis. Although the stratification of candidate patients undergoing pancreatectomy and PVR preoperatively is a challenge, adopting the recurrence nomogram and RNS is likely to help refine current postoperative management strategies for patients undergoing pancreatectomy and PVR. Individual therapeutic approaches may include enhanced regimens of adjuvant therapy, extended treatments after regular adjuvant therapy, and close monitoring of hepatic metastasis by MRI or digital subtraction angiography in high-risk patients. Considering the most accurate predicting period of current scoring system was from 6 to 12 months post-surgery, tailored interventions for high-risk patients should be performed as soon as possible, lasting at least for one year postoperatively.

In this study a recurrence scoring system consisting of SRS and the recurrence nomogram was successfully constructed. Nevertheless, this study has some limitations. Firstly, due to relatively small sample size of the study cohort and as a retrospective analysis, we are unable to completely eliminate bias. Secondly, the results of this single-center research may be affected by preoperative evaluation, the surgical experience of clinicians, and perioperative management, which will need to be taken into account and evaluated through a multi-center study. Thirdly, although adjuvant therapies were conducted in all patients, the regimens and durations of adjuvant therapies might also affect recurrence, and should be investigated in the future. Lastly, since occult micro-metastasis may be present in the subgroup of PDAC, NAT is strongly recommended. Thus, applying this scoring system in patients undergoing NAT followed by pancreatectomy and PVR is a main objective of ours for future research.

CONCLUSION

In this study, SRS was constructed for the prediction of ER in patients undergoing pancreatectomy and PVR using LASSO regression analysis based on the serum-derived parameters and corresponding weights. In addition, this system was used to establish the recurrence nomogram, composed of the independent risk factors of recurrence, including SRS and three clinicopathological parameters. This represents the first tailored recurrence scoring system unique to patients undergoing pancreatectomy and PVR, which showed an excellent performance in predicting ER. In practical applications, this scoring system will allow clinicians to identify patients at high risk of ER after pancreatectomy and PVR, enabling them to take more active measures more quickly in order to prevent or delay recurrence.

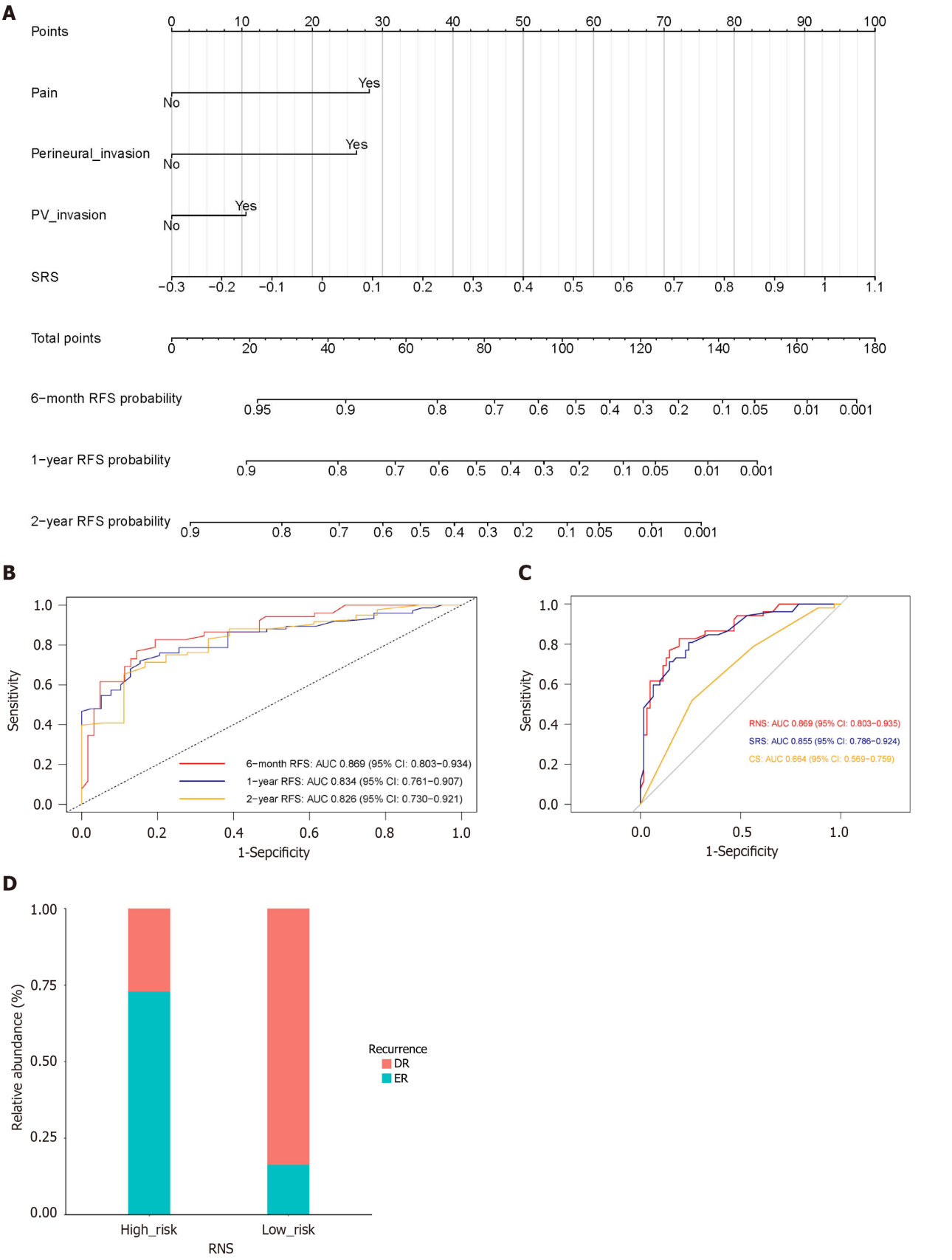


Figure 4 The Recurrence nomogram, and receiver operating characteristics curve analysis of recurrence nomogram score in the training cohort. A: The Recurrence Nomogram for predicting recurrence; B: Receiver operating characteristics (ROC) curves of recurrence nomogram score (RNS) for predicting recurrence in different time intervals; C: ROC curves of RNS, serum recurrence score, and clinicopathological score for predicting early recurrence (ER); D: Stacked plot showing significantly different ratios of ER and delayed recurrence, in the high-risk (RNS > 4.23) and low-risk groups (RNS ≤ 4.23), respectively (*P* value = 4.467e-09). ROC: Receiver operating characteristics; RNS: Recurrence nomogram score; SRS: Serum recurrence score; CS: Clinicopathological score; ER: Early

recurrence; DR: Delayed recurrence.

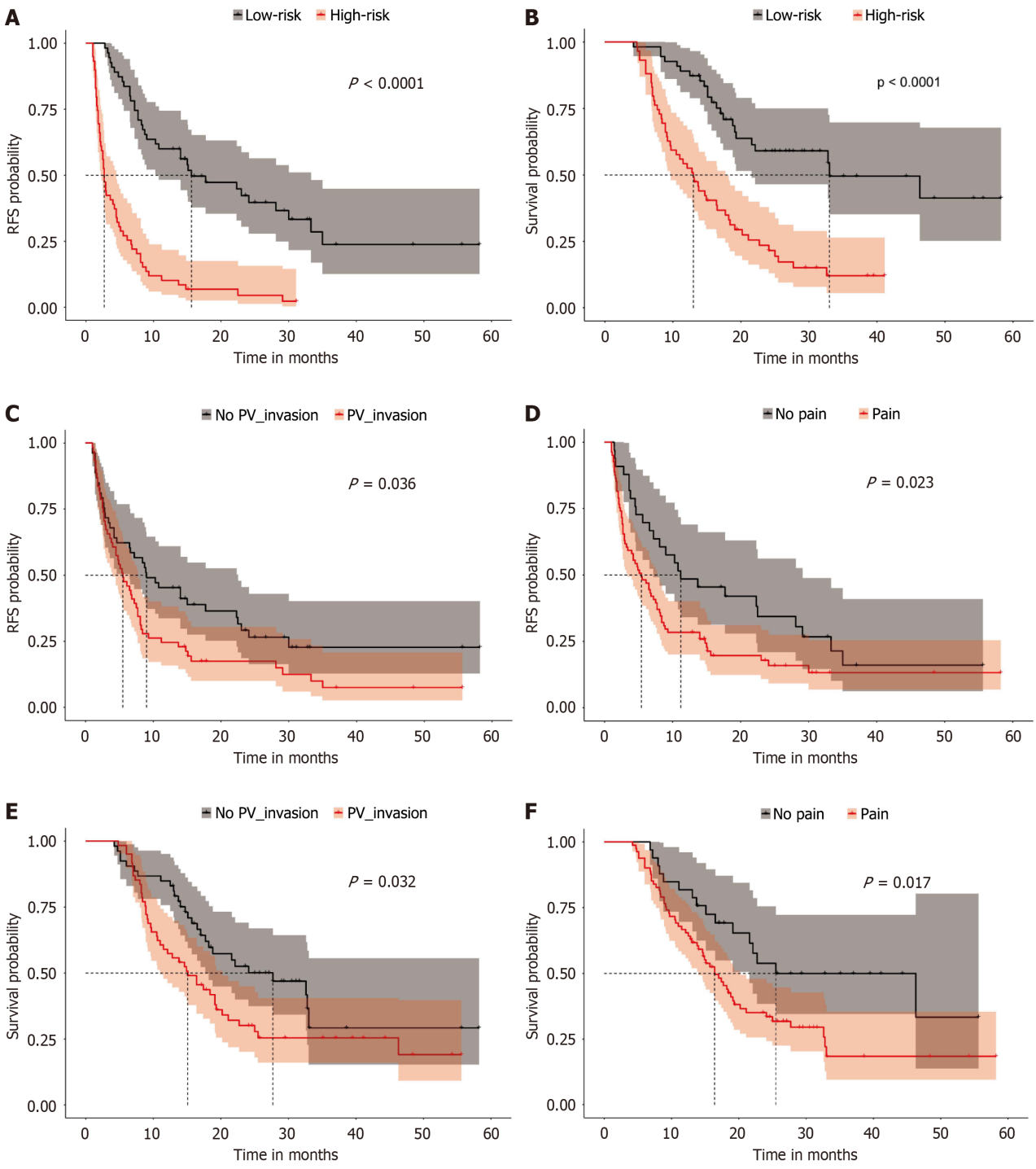


Figure 5 Survival analysis of recurrence nomogram score and clinicopathological variables in the training cohort. A and B: Kaplan-Meier survival plots for patients in the high-risk [recurrence nomogram score (RNS) > 4.23] and low-risk (RNS ≤ 4.23) groups. The high-risk group showed significantly poorer recurrence free survival (RFS) and overall survival (OS) compared with the low-risk group; C-F: Patients with portomesenteric vein invasion showed poorer RFS and OS than those without (C and E), and patients with pain showed poorer RFS and OS than those without (D and F). RNS: Recurrence nomogram score; RFS: Recurrence free survival; OS: Overall survival.

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FOOTNOTES

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Informed consent statement: This study retrospectively included data without any intervention for the patients. The informed consent document is not applicated.

Conflict-of-interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data sharing statement: All data and results of this study were presented in the article and the supplementary file. No additional data are available.

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