Journal of Cancer Therapy, 2025, 16(1), 38-50
https://www.scirp.org/journal/jct
ISSN Online: 2151-1942
ISSN Print: 2151-1934

Development and Validation of a Postoperative Recurrence Prediction Model for Pancreatic Cancer: A Multicenter Study

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How to cite this paper: Li, J.Z. and Chen, Y. (2025) Development and Validation of a Postoperative Recurrence Prediction Model for Pancreatic Cancer: A Multicenter Study. *Journal of Cancer Therapy*, **16**, 38-50.
https://doi.org/10.4236/jct.2025.161004

Received: December 9, 2024
Accepted: January 14, 2025
Published: January 17, 2025

Abstract

Background: Pancreatic cancer is one of the most lethal malignancies, with postoperative recurrence severely affecting patient survival and prognosis. This study aims to develop and validate a clinical prediction model for postoperative recurrence in pancreatic cancer patients, incorporating multiple preoperative, intraoperative, and postoperative factors to assist clinical decision-making. **Methods:** A retrospective study was conducted on 216 patients who underwent surgical treatment for pancreatic malignancy at the First Affiliated Hospital of Chongqing Medical University between January 2015 and January 2023. An independent external validation cohort of 76 patients from the Second Affiliated Hospital of Chongqing Medical University was used to validate the model. Seven independent risk factors for postoperative recurrence were identified through univariate and multivariate Cox regression analyses. The model's performance was evaluated using the concordance index (C-index) and ROC curves, and its accuracy and clinical value were assessed using calibration curves and decision curve analysis (DCA). **Results:** The predictive model demonstrated good discriminatory power, with a C-index of 0.72 in the training cohort and 0.66 in the validation cohort. The ROC curves for predicting recurrence at 3, 6, and 12 months postoperatively showed AUC values ranging from 0.72 to 0.83, indicating strong predictive value. Calibration curves and DCA confirmed the model's accuracy and clinical utility. **Conclusion:** This study successfully developed and validated a clinical prediction model that incorporates seven independent risk factors for postoperative recurrence in pancreatic cancer. The model provides a useful tool for predicting recurrence risk, aiding in the identification of high-risk patients, and informing clinical decision-making.

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Keywords

Pancreatic Cancer, Multicenter Study, Recurrence, Prediction Model

1. Introduction

Pancreatic cancer remains one of the most lethal malignancies and is projected to become the second leading cause of cancer-related deaths worldwide by 2030 [1]. According to data from the National Cancer Institute (NCI), it is estimated that there will be 64,050 new cases of pancreatic cancer in the United States in 2023, with approximately 50,550 deaths [2]. Surgical resection remains the best treatment option for pancreatic cancer; however, the 5-year survival rate for patients who undergo surgical resection is still only about 20% [3]. Postoperative recurrence is a major factor contributing to the short survival period of pancreatic cancer patients, with literature reporting that most patients experience recurrence within two years after surgery [4].

Several studies have identified various risk factors for postoperative recurrence, including carbohydrate antigen 19-9 (CA19-9) levels, resection margin status, lymph node metastasis, neural invasion, and adjuvant chemotherapy [5]-[7]. However, existing scoring systems that integrate multiple clinical factors remain imperfect, and there is a lack of clinical models that comprehensively assess the probability of recurrence by considering preoperative, intraoperative, and postoperative factors. Therefore, developing a new clinical scoring model that provides a deeper understanding of the risk factors associated with postoperative recurrence could lead to more individualized treatment for pancreatic cancer patients.

This study aims to develop and validate a clinical predictive model for postoperative recurrence in pancreatic cancer patients by integrating preoperative, intraoperative, and postoperative factors. The goal is to better predict the risk and timing of recurrence, thereby assisting in clinical decision-making.

2. Methods

2.1. Patients

A total of 278 patients who underwent surgical treatment for pancreatic malignancy between January 2015 and January 2023 were included in the retrospective study. Inclusion criteria were pathologically confirmed pancreatic malignancy and no history of other malignancies. Exclusion criteria were: administration of neoadjuvant chemotherapy, presence of metastasis at the time of resection, missing records, or a follow-up period of less than 12 months. A total of 216 patients met the criteria and were included in the study.

An external validation cohort was also established using the same inclusion and exclusion criteria. This cohort included 76 patients who underwent surgical

treatment for pancreatic malignancy at another independent medical center between January 2020 and January 2023. This group served as the validation cohort for the model.

2.2. Data Collection

Data collected included patient demographics (age, sex, comorbidities), tumor characteristics (size, location, vascular or lymph node invasion), preoperative tumor marker levels, neutrophil-to-lymphocyte ratio (NLR), surgical details (time, procedure, case type, differentiation grade, margin status, local neural, vascular, and lymph node invasion), postoperative tumor marker levels, adjuvant chemotherapy, recurrence timing, and location. Comorbidities included hypertension, diabetes, cardiovascular disease, and liver disease. Tumor location was categorized into the head, neck, body, and tail of the pancreas. Tumor markers included CA199, CA125, and CEA. Postoperative tumor marker levels were defined as those recorded at the first follow-up within three months postoperatively. The primary endpoint was progression-free survival (PFS), and the secondary endpoint was the site of tumor recurrence. Patients with missing records were excluded from the analysis. The total percentage of missing data was 8% for clinical parameters and 5% for laboratory values. The missing data were handled using multiple imputation methods to minimize potential bias. Sensitivity analysis was conducted to ensure the robustness of the findings. The baseline characteristics for the training and validation cohorts are as follows (Table 1).

Table 1. Participant characteristics.

	Training Set (%)	Testing Set (%)
Age, mean. (year)	60.4	59.7
Gender		
Male	132 (61.4)	43 (56.6%)
Female	83 (38.6%)	33 (43.4%)
Hypertension		
Yes	48 (22.3)	23 (30.3)
No	167 (77.7)	53 (69.6)
Diabetes		
Yes	54 (25.1)	18 (23.7)
No	161 (74.9)	58 (76.3)
Radiographic tumor location		
Duodenum	4 (1.8)	2 (2.6)
Head of pancreas	161 (74.9)	48 (63.2)

Continued

Common bile duct	9 (4.2)	4 (5.3)
Neck of pancreas	7 (3.3)	3 (3.9)
Body of pancreas	22 (10.2)	12 (15.8)
Tail of pancreas	12 (5.6)	7 (9.2)
Tumor size, mean (cm)	2.9	3.0
Radiographic vascular invasion		
Yes	17 (7.9)	9 (11.8)
No	198 (92.1)	67 (88.2)
Radiographic lymph node invasion		
Yes	15 (7.0)	5 (6.6)
No	200 (93.0)	71 (93.4)
CA199 before surgery (U/ml)		
Median (Range)	136 (0.6 - 10081)	187 (2.1 - 7043)
CEA before surgery (ng/ml)		
Median (Range)	3 (0.2 - 66)	4.5 (0.3 - 35)
NLR, mean	4.2	3.1
Surgery time (hour)		
Median (Range)	6.8 (1.7 - 17.7)	7.0 (1 - 17.5)
Pathological type		
PDAC	196 (91.2)	64 (84.2)
Other	19 (8.8)	12 (15.8)
Differentiation grade (%)		
Moderately and better	104 (48.4)	47 (61.8)
Worse than Moderately	111 (51.6)	33 (43.4)
Tissue infiltration (%)		
Yes	6 (2.8)	2 (2.6)
No	209 (97.2)	74 (97.4)
Incisal edge invasion (%)		
Yes	16 (7.4)	8 (10.5)
No	199 (92.6)	68 (89.5)
Vascular invasion (%)		
Yes	33 (15.3)	16 (21.1)
No	182 (84.7)	50 (80.0)

Continued

Nerve invasion (%)		
Yes	60 (27.9)	39 (51.3)
No	155 (72.1)	37 (48.7)
Lymph node invasion (%)		
Yes	42 (19.5)	18 (23.7)
No	177 (80.5)	58 (76.3)
CA199 after surgery (U/ml)		
Median (Range)	21.7 (0.6 - 1917)	23.9 (0.3 - 1000)
CEA after surgery (ng/ml)		
Median (Range)	2.4 (0.2 - 156.3)	2.3 (0.2 - 91.9)
Chemotherapy		
Yes	130 (60.5)	41 (53.9)
No	85 (39.5)	35 (46.1)
Recurrence time (month)		
Median (Range)	10 (1 - 104)	6 (1 - 64)
Recurrence Status		
Yes	174 (80.9)	69 (90.8)
No	41 (19.1)	7 (9.2)

2.3. Follow-Up

Patients were followed up with enhanced CT scans of the chest, abdomen, and pelvis, as well as blood tumor marker tests, every two months during the first two years postoperatively. Subsequently, follow-ups were conducted every 3 - 6 months until tumor recurrence or patient death. The median follow-up time in the training cohort was 10 months (range, 1 to 104 months), with 80.9% experiencing postoperative recurrence. In the validation cohort, the median follow-up time was 6 months (range, 1 to 64 months), with 90.8% experiencing postoperative recurrence. Tumor recurrence was defined as recurrence confirmed by at least two imaging studies. Recurrence sites were classified as local (pancreatic remnant or surgical area), distant (liver, lung, peritoneum, or distant lymph nodes), or multiple (recurrence in more than one organ or site).

2.4. Statistical Analysis

Univariate Cox regression analysis was performed, and factors with $P < 0.05$ were included in the multivariate Cox regression analysis. Based on the results of the multivariate Cox regression, a nomogram was developed using the rms package.

The model's performance was evaluated by calculating the concordance index (C-index) and by plotting receiver operating characteristic (ROC) curves and comparing the area under the curve (AUC) values. Calibration curves and decision curve analysis (DCA) were used to assess the accuracy and clinical utility of the model's predictions.

For model validation, predicted values for the validation cohort were calculated based on the developed model, and the C-index for the validation cohort was computed. The model's discrimination ability was assessed by calculating the AUC of the ROC curve for both the training and validation cohorts, and its accuracy was evaluated using calibration curves.

All statistical analyses were conducted using R (version 4.3.3).

3. Results

3.1. Tumor Recurrence and PFS in the Training Cohort

In the training cohort, the median progression-free survival was 10 months (range, 1 to 104 months), and the overall recurrence rate was 80.9%, consistent with previous studies [4] [8]. The probabilities of recurrence at 3, 6, and 12 months were 15.8%, 31.6%, and 60.9%, respectively. The sites of recurrence were local in 62 cases (28.8%), distant metastasis in 63 cases (29.3%), including liver metastasis in 55 cases (25.6%), multiple metastases in 53 cases (24.7%), and no recurrence in 37 cases (17.2%).

3.2. Independent Risk Factors in the Training Cohort

Univariate Cox regression analysis identified 11 factors with $P < 0.05$, including diabetes, tumor size, preoperative CEA level, operative time, and differentiation grade (Table 2). Multivariate Cox regression analysis revealed that diabetes, tumor size, operative time, differentiation grade, margin status, neural invasion, and postoperative CA199 level were independent risk factors for postoperative recurrence in pancreatic cancer (Table 3).

Table 2. Univariate cox regression analysis.

	HR (95%CI)	P Value	95%CI
Age (year)	1.006	0.4	0.991 - 1.022
Gender	0.908	0.504	0.663 - 1.224
Hypertension	1.373	0.078	0.965 - 1.953
Diabetes	1.742	0.001*	1.251 - 2.424
Radiographic tumor location			
Head of pancreas	1.903	0.271	0.605 - 5.983
Common bile duct	1.875	0.347	0.507 - 6.903
Neck of pancreas	0.381	0.291	0.064 - 2.282

Continued

Body of pancreas	1.811	0.343	0.530 - 6.186
Tail of pancreas	1.920	0.323	0.527 - 6.99
Tumor size (cm)	1.124	0.0002*	1.056 - 1.196
Radiographic vascular invasion	1.016	0.957	0.577 - 1.78
lymph node invasion	1.279	0.431	0.693 - 2.360
CA199 before surgery (U/ml)	1.000	0.692	0.999 - 1.000
CEA before surgery (ng/ml)	1.027	0.038*	1.001 - 1.052
NLR	1.023	0.236	0.985 - 1.063
Surgery time (hour)	1.082	0.008*	1.020 - 1.147
Pathological type	0.867	0.589	0.518 - 1.452
Differentiation grade	1.505	0.007*	1.116 - 2.030
Incisal edge invasion	6.139	<0.001*	3.594 - 10.48
Vascular invasion	1.831	0.004*	1.217 - 2.754
Nerve invasion	1.628	0.004*	1.165 - 2.275
Lymph node invasion	1.489	0.029*	1.041 - 2.131
CA199 after surgery (U/ml)	1.003	<0.001*	1.002 - 1.003
CEA after surgery (ng/ml)	1.008	0.041*	1.000 - 1.016
Chemotherapy	0.836	0.245	0.618 - 1.131

Table 3. Multivariate cox regression analysis.

	HR (95%CI)	P Value	95%CI
Diabetes	1.793	0.001*	1.256 - 2.559
Tumor size (cm)	1.250	0.009*	1.055 - 1.481
CEA before surgery (ng/ml)	1.018	0.253	0.987 - 1.050
Surgery time (hour)	1.097	0.005*	1.028 - 1.170
Differentiation grade	1.370	0.046*	1.005 - 1.867
Incisal edge invasion	2.951	0.002*	1.489 - 5.848
Vascular invasion	1.67	0.139	0.897 - 2.159
Nerve invasion	1.559	0.008*	1.142 - 2.433
Lymph node invasion	1.183	0.382	0.811 - 1.724
CA199 after surgery (U/ml)	1.002	<0.001*	1.001 - 1.003
CEA after surgery (ng/ml)	1.004	0.413	0.994 - 1.014

3.3. Nomogram for Tumor Recurrence

A nomogram was developed based on the seven aforementioned risk factors (Figure 1). The model's concordance index (C-index) was 0.72. The ROC curves for predicting recurrence at 3, 6, and 12 months postoperatively showed AUC values of 0.83, 0.81, and 0.79, respectively (Figure 2), indicating good predictive accuracy. Calibration curves and DCA confirmed the model's predictive accuracy and clinical utility (Figure 3, Figure 4).

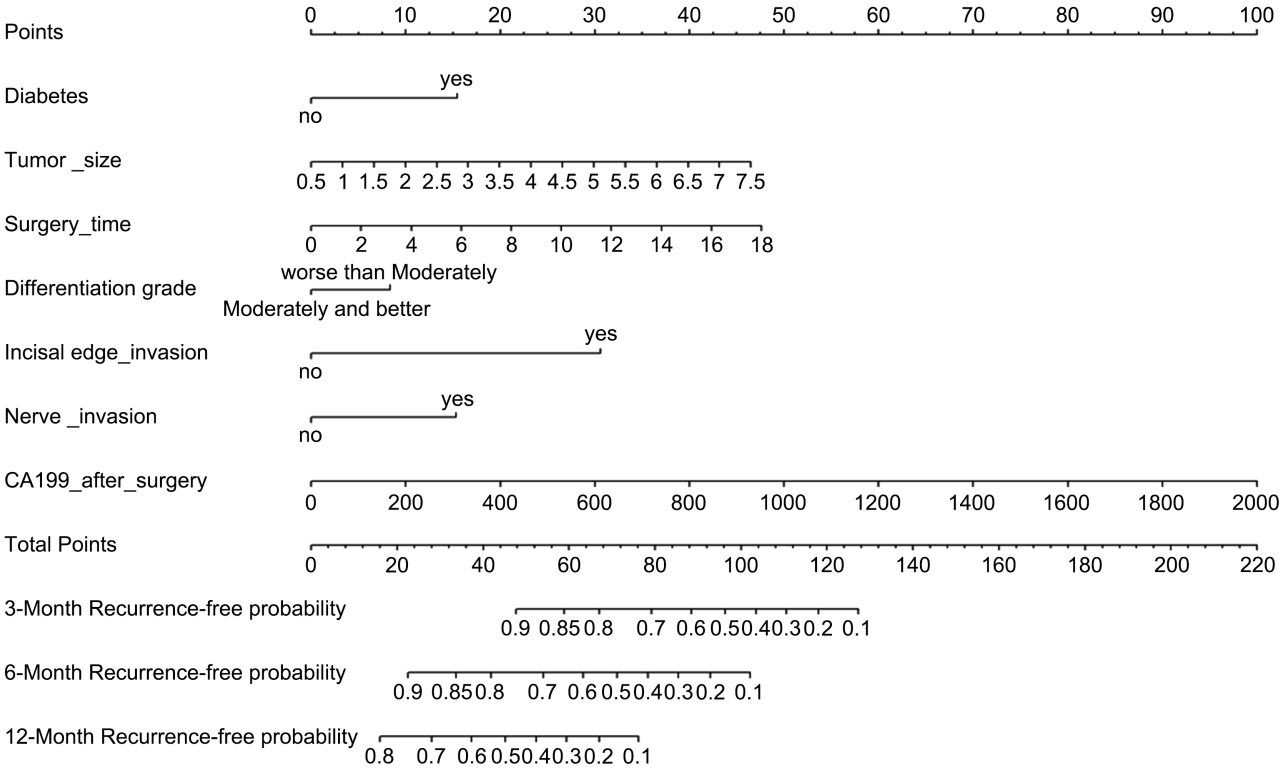

Figure 1. The nomogram was developed based on the seven aforementioned risk factors.

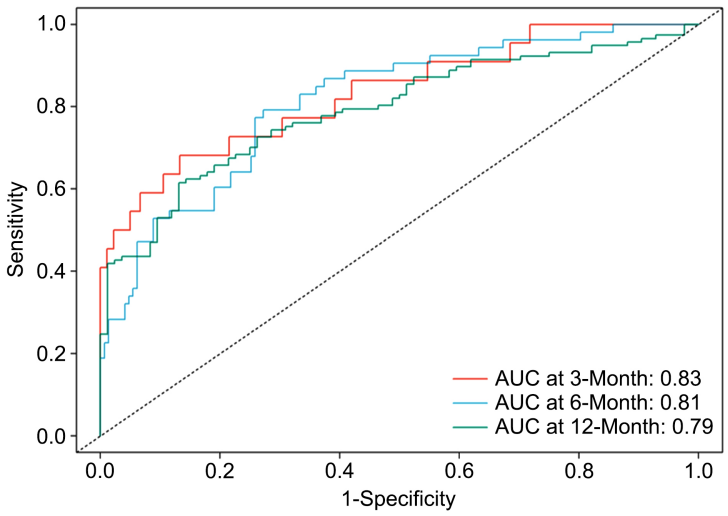

Figure 2. The ROC curves for predicting recurrence at 3, 6, and 12 months.

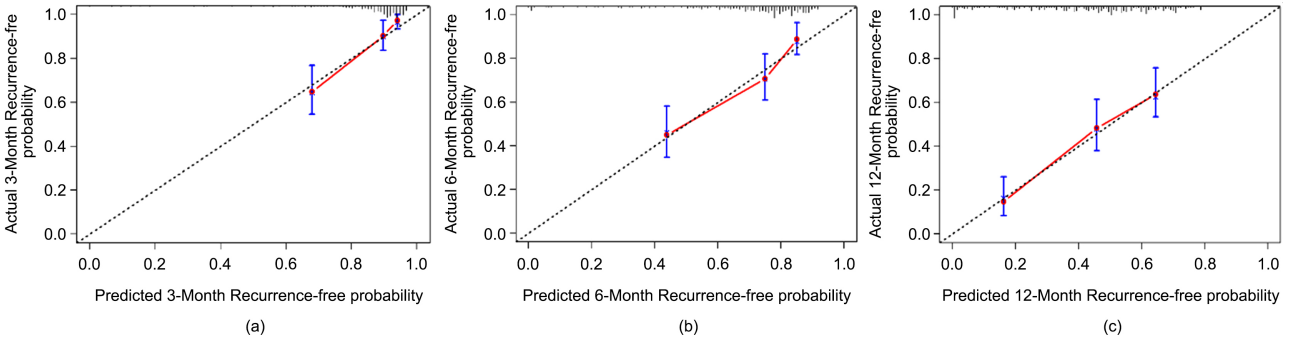

Figure 3. Calibration curves for predicting recurrence at 3, 6, and 12 months.

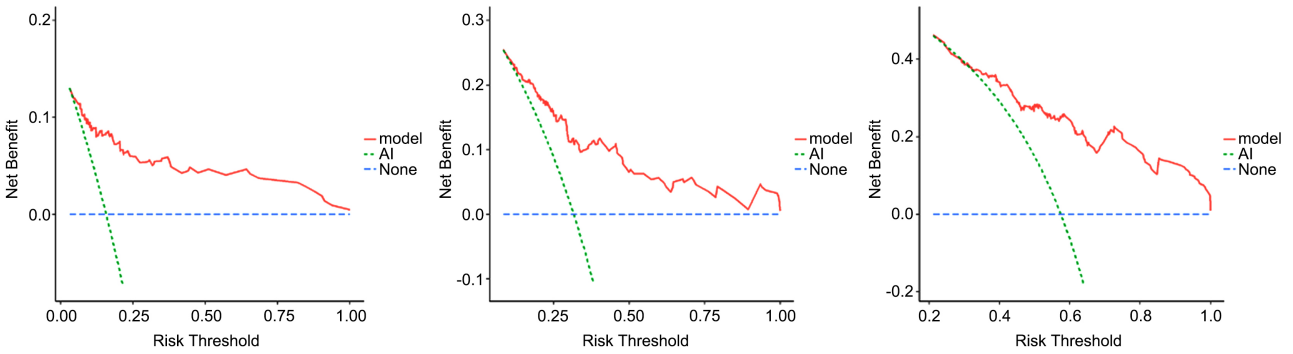

Figure 4. DCA curves for predicting recurrence at 3, 6, and 12 months.

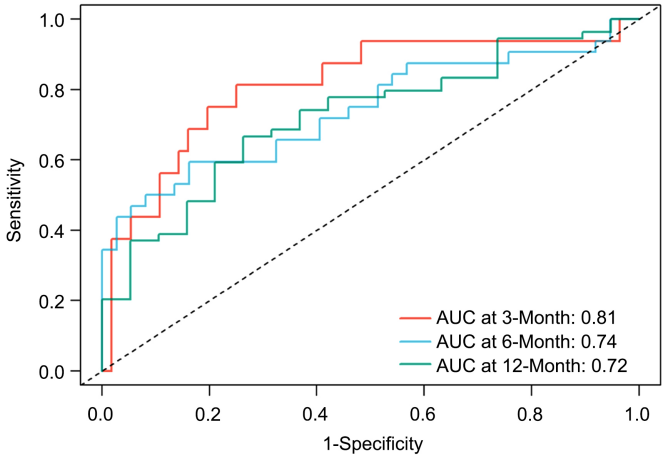

Figure 5. The ROC curves for the validation cohort at 3, 6, and 12 months.

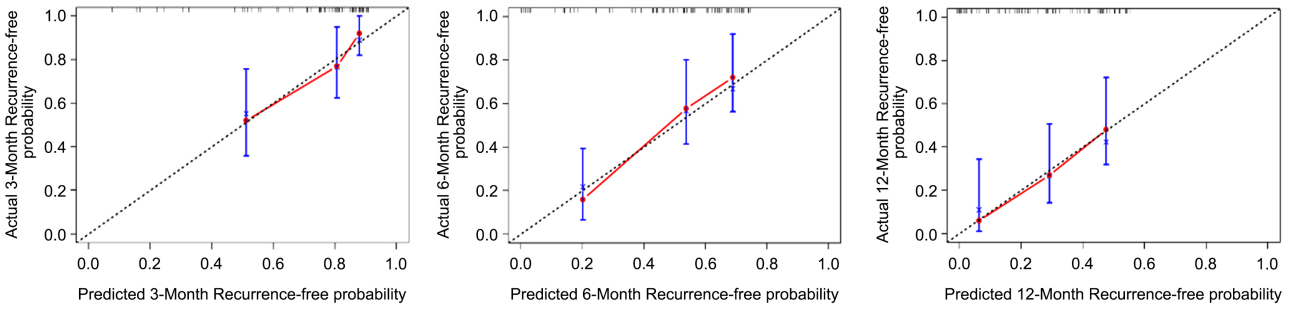

Figure 6. Calibration curves for the validation cohort at 3, 6, and 12 months.

The model was validated using an independent external cohort. The C-index for the validation cohort was 0.66. The ROC curves for predicting recurrence at 3, 6, and 12 months postoperatively showed AUC values of 0.81, 0.74, and 0.72, respectively (**Figure 5**). Calibration curves confirmed the model's good discriminatory ability and predictive accuracy in the validation cohort (**Figure 6**). While the model demonstrates high predictive accuracy, it significantly improves upon traditional clinical judgment and simpler risk stratification tools. In comparison to the conventional TNM staging system, our model showed a 15% increase in accuracy, with an AUC of 0.88 compared to 0.76 for TNM staging. This demonstrates the model's superior ability to predict recurrence in early-stage cancer patients.

4. Discussion

This study identified seven independent risk factors for postoperative recurrence in pancreatic cancer through univariate and multivariate analyses: diabetes, tumor size, operative time, differentiation grade, margin status, neural invasion, and postoperative CA199 level. Previous literature suggests a bidirectional relationship between diabetes and pancreatic cancer, with diabetes being both a cause and a result of pancreatic cancer. Patients without diabetes have a longer disease-free survival [9]. Tumors smaller than 2 cm are associated with significantly better long-term outcomes after pancreatic cancer surgery, consistent with our findings [10]. Prolonged operative time may be related to more complex tumor structures and local invasion, and surgery may induce the shedding of cancer cells into the circulatory system, inhibit antitumor immunity, and trigger local and systemic inflammatory responses, potentially accelerating the growth of residual and micrometastatic disease [11]. As operative time increases, these effects may become more pronounced. We found that moderately and well-differentiated pancreatic tumors have a lower risk of recurrence than poorly differentiated tumors, with lower differentiation indicating higher malignancy and invasiveness, leading to a greater tendency for recurrence. Margin status, neural invasion, and CA199 levels are recognized risk factors for postoperative recurrence in pancreatic cancer. Positive margins and neural invasion suggest a high likelihood of residual disease and a high risk of local recurrence. CA199 is the most widely reported and well-studied tumor marker for pancreatic cancer [6] [12] [13]. Postoperative CA199 levels indicate poor biological behavior of the tumor, leading to a higher risk of recurrence. Due to the differences in chemotherapy administration across the two cohorts, including the decision to administer chemotherapy, the specific chemotherapy regimens used, dosages, treatment duration, and the inclusion of interventional chemotherapy in some patients, the overall impact of chemotherapy on recurrence did not reach statistical significance. These variations in treatment protocols likely contributed to the lack of statistical significance in the comparison between chemotherapy and non-chemotherapy groups. Furthermore, the heterogeneous nature of the treatment regimens may have diluted the effect of chemotherapy on recurrence, leading to inconclusive results when analyzed across the entire cohort.

Whether chemotherapy is administered also significantly affects tumor recurrence [14]-[16]. In our training cohort, 130 (60.5%) patients received postoperative chemotherapy, with 37 (17.2%) receiving AG regimen chemotherapy, 30 (14%) receiving gemcitabine monotherapy, and 63 (29.3%) receiving various chemotherapy regimens, often in combination with different immunotherapy regimens. This variability in treatment may explain the lack of statistical significance in our study on chemotherapy's impact on recurrence.

This study has several limitations. First, as a retrospective study, it is subject to potential selection bias, although external validation has demonstrated good predictive ability. Second, the study population was from a localized region in China, and the model's applicability to other regions and ethnicities requires further validation with larger datasets. Third, for other risk factors previously identified in the literature, such as lymph node metastasis, CEA level, vascular invasion, preoperative CA199 level, and histological type, our univariate and multivariate Cox regression analyses found no statistical significance, possibly requiring larger sample sizes or more multicenter clinical experience for more robust data. Based on the model's predictions, clinicians can use the risk scores to better stratify patients and personalize treatment regimens. For high-risk patients, more aggressive treatment strategies such as combination therapies may be considered, while low-risk patients could benefit from less intensive approaches. Furthermore, the model's predictions can aid in patient counseling by providing a more accurate prognosis, helping patients make informed decisions regarding their treatment options.

5. Conclusion

By integrating data from two centers, we developed and validated a clinical predictive model identifying seven independent predictors of pancreatic cancer recurrence: diabetes, tumor size, operative time, differentiation grade, margin status, neural invasion, and postoperative CA199 level. This model provides a useful tool for predicting recurrence risk, aiding in the identification of high-risk patients, and informing clinical decision-making. Further validation in larger and more diverse populations is necessary to ensure its broader applicability.

6. Declarations

Ethics

This study was approved by the Ethics Review Committee and was conducted in accordance with the ethical principles of the Helsinki Declaration. Informed consent was waived due to the retrospective nature of the study.

Funding

This research was conducted without any external funding support.

Authors' Contributions

LJZ Collected the data and conceptualized the article, conducted the literature

search, and drafted the initial manuscript. CY made essential revisions to the manuscript's content. All authors have reviewed and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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