

Establishment and validation of a diagnostic model for evaluating synchronous liver metastasis in pancreatic cancer using comprehensive blood biochemical indicators

YIYI JIANG^{1*}, GAOYAO PENG^{1,2*}, SONGQING HE³⁻⁵ and JIANGFA LI^{1,3,4}

¹Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital of Guilin Medical University, Guilin, Guangxi 541001, P.R. China; ²Department of Breast Surgery, Guilin Women's and Children's Hospital, Guilin, Guangxi 541001, P.R. China; ³Key Laboratory of Early Prevention and Treatment for Regional High Frequency Tumor (Guangxi Medical University), Ministry of Education, Nanning, Guangxi 530021, P.R. China; ⁴Guangxi Key Laboratory of Immunology and Metabolism for Liver Diseases, Nanning, Guangxi 530021, P.R. China; ⁵Division of Hepatobiliary Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi 530021, P.R. China

Received December 15, 2025; Accepted March 13, 2026

DOI: 10.3892/ol.2026.15591

Abstract. The liver is the most common metastatic target organ of pancreatic cancer (PC). Currently, imaging examination is effective for detecting liver metastases (LM) of PC, but some small metastases are difficult to detect, making it necessary to establish a comprehensive diagnostic model with which to predict LM. A total of 59 patients with PC were enrolled as the training cohort and 16 patients with PC were included as the external validation cohort. The 59 patients in the training cohort were divided into LM and No-LM groups. Univariate and multivariate logistic regression analyses were performed to identify independent risk factors for synchronous liver metastasis (SLM) in PC. Based on these findings, a diagnostic model was constructed and a nomogram was developed to facilitate practical application. The accuracy and reliability of this diagnostic model were then evaluated using the area under the receiver operating characteristic curve (AUC), Hosmer-Lemeshow (HL) curves and decision curve analysis (DCA). Multivariate analysis identified CEA [odds ratio (OR)=1.05, 95% CI: 1.01-1.08], CA153 (OR=1.18,

95% CI: 1.06-1.31), white blood cells (WBC; OR=1.71, 95% CI: 1.08-2.72) and platelets (PLT; OR=1.01, 95% CI: 1.00-1.03) as independent risk factors. In the training and external validation cohorts, the diagnostic efficacy of the model's AUC was 0.92 and 0.90, respectively, with sensitivities of 0.96 and 0.83, and specificities of 0.86 and 0.75, respectively. The HL and DCA curves indicate the excellent calibration and clinical net benefit of the model. In conclusion, the diagnostic model integrating CEA, CA153, WBC and PLTs shows high predictive performance for identifying SLM in patients with PC.

Introduction

Pancreatic cancer (PC) accounts for >80% of pancreatic tumors and is one of the deadliest malignancies worldwide, with a 5-year survival rate of ~8% (1). Complete surgical resection is currently the only potentially curative option for PC. However, recurrence rates are high despite this intervention and long-term survival rates remain low (2). Unfortunately, nearly 80% of patients present with distant metastases and are diagnosed with advanced PC, thereby missing the opportunity for surgical intervention. Only the remaining 20% of patients may be eligible for surgery, which remains the sole treatment modality with curative potential (3). However, even following successful surgery, patients face a high risk of postoperative local recurrence or distant metastases. The liver represents the most common site of metastasis, followed by the lungs and the peritoneum (4,5). PC is the second most common primary lesion leading to liver metastasis (LM) (6). Notably, ~85% of patients with metastatic PC eventually develop LM (7), which is strongly associated with poor prognosis. Patients diagnosed with LM, whether treated with resection or palliative care, have an average survival of <6 months (8-10). A study by Takada *et al* (10) revealed that even aggressive combined surgical resection of both the primary tumor and LM failed to significantly improve the prognosis of such patients. Furthermore, a high proportion of patients developed new intrahepatic multilobar lesions within one year.

Correspondence to: Dr Songqing He, Division of Hepatobiliary Surgery, The First Affiliated Hospital of Guangxi Medical University, 6 Shuangyong Road, Nanning, Guangxi 530021, P.R. China

E-mail: dr_hesongqing@163.com

Dr Jiangfa Li, Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital of Guilin Medical University, 15 Lequn Road, Guilin, Guangxi 541001, P.R. China

E-mail: 247546160@qq.com

*Contributed equally

Key words: biochemical indicators, pancreatic cancer, liver metastases, diagnosis

Among patients with PC without distant metastases who undergo surgical resection, ~35-50% experience early recurrence within 12 months after surgery and nearly 25% of these recurrences involve only LM (11,12). Despite advances in understanding the metastatic mechanisms of PC, diagnostic techniques for synchronous liver metastasis (SLM) have not advanced significantly, particularly in improving diagnostic precision. Given the high incidence of LM and their potential for early presentation, accurate preoperative identification of LM is paramount for optimizing patient treatment and prognosis. Misdiagnosis or overdiagnosis can lead to unnecessary surgical interventions or missed opportunities for radical resection.

As early as 1863, Virchow proposed the association between malignant tumors and inflammation, noting the phenomenon of leukocyte infiltration in tumor tissues. He speculated that the inflammatory area might be the origin of the tumor (13). Current studies have confirmed that tumor-associated inflammatory states affect tumor cell survival, proliferation, metastasis, neovascularization and responsiveness to therapy. The white blood cell (WBC) count is closely related to metastasis, prognosis and diagnosis in pancreatic malignancies (14-16). Additionally, tumor markers have an essential role in the diagnosis of PC with SLM. Among these, carbohydrate antigen 19-9 (CA199) is one of the most widely used markers in PC. CA199 is not only helpful in evaluating prognosis but is also valuable in diagnosing PC with SLM (17). Meanwhile, several tumor markers, such as carcinoembryonic antigen (CEA), CA199, carbohydrate antigen 125 (CA125) and alpha-fetoprotein (AFP), are closely associated with LM in PC (18).

This study aims to establish a diagnostic model for the simple, fast and effective identification of SLM in patients with PC using multicenter integrated biochemical indices and evaluate the diagnostic value of blood biochemical indices.

Subjects and methods

Study population. According to the inclusion and exclusion criteria, 59 patients with PC treated at the Department of Hepatobiliary and Pancreatic Surgery of the Affiliated Hospital of Guilin Medical University (Guilin, China), including 28 males and 31 females with a median age of 58 years (range, 33-86 years), were continuously included in the training cohort between June 2018 and January 2023. Additionally, 16 patients with PC treated at the Department of Hepatobiliary and Pancreatic Surgery of the First Affiliated Hospital of Guangxi Medical University (Nanning, China) between January 2016 and June 2020, comprising 8 males and 8 females with a median age of 61.5 years (range, 39-71 years), who met the inclusion and exclusion criteria, were included in the external validation cohort (Fig. 1). There were no significant differences in terms of age and gender distribution between the training group and the validation group. All of the cases were recruited as consecutive cases based on the inclusion and exclusion criteria. PC was diagnosed based on tumor pathology and LM was finally diagnosed by imaging tests, pathological findings and follow-up results.

The inclusion criteria were as follows: i) First diagnosis of PC by pathology and LM confirmed by imaging or pathology; ii) in patients without LM at initial diagnosis, the follow-up

duration should be >6 months if there was no intrahepatic metastasis during the follow-up period; and iii) patients with pathologically confirmed PC and preoperative imaging and blood biochemistry indicators. The following exclusion criteria were applied: i) The nature of intrahepatic lesions is unclear; ii) lack of follow-up data; iii) incomplete information in patient clinical case data; iv) patients with metastases in other organs besides LM; v) patients with other malignant tumors in combination; and vi) patients with infectious diseases or autoimmune diseases. This study was approved by the ethics committees of both hospitals (ethics approval nos. 2022YJSL-03 and 2024-E717-01) and was prospectively registered in the Chinese Clinical Trial Registry (registration ID: ChiCTR2200066901).

Methods

Methods of testing blood biochemical indicators. All patients included in the study received serologic and imaging examinations one week before surgery. Each study subject provided 5 ml of fasting superficial venous blood, which was centrifuged at a constant temperature of 4°C at 4,975 x g for 15 min. The serum was retained for testing. The detection methods used to ascertain each index were as follows: WBC, platelets (PLTs), neutrophils (NEUT), lymphocytes (LYMPH) and LYMPH% were measured using an automated hematology analyzer (XN-9000; Sysmex Corp.). CEA, AFP, CA125, CA153 and CA19-9 levels were measured using an automated chemiluminescent immunoassay analyzer (Cobas e 801; Roche Diagnostics). Total bilirubin (TBIL), direct bilirubin (DBIL), total protein (TP), albumin (ALB), prealbumin, alkaline phosphatase, alanine aminotransferase, aspartate transaminase and gamma-glutamyltranspeptidase were also assayed.

Establishment and validation of the diagnostic model. The 59 patients in the training cohort were divided into the LM and non-liver metastasis (No-LM) groups based on the presence or absence of LM. Comparative analysis was adopted to screen for differences in clinical data between these groups. Univariate logistic regression analysis was conducted to identify the risk factors for SLM in patients with PC. Then, a Cox proportional hazards model was used in the multivariate logistic regression analysis to determine the independent risk factors for concurrent LM. The independent risk factors identified through multivariate analysis were integrated to construct a diagnostic model based on blood biochemical indices. Continuous variables were included as linear terms after assessing linearity with the log-odds of the outcome using restricted cubic splines. Multicollinearity among candidate variables was assessed using the variance inflation factor (VIF). A VIF value <5 indicates that there is no significant multicollinearity.

The performance of the model was evaluated by plotting the receiver operating characteristic (ROC) curve and calculating the area under the curve (AUC) and 95% confidence intervals for each ROC curve. A nomogram was constructed to visualize each indicator and the overall model to display the model more intuitively and show the weights of each independent risk factor and its influence on the diagnostic results. To further evaluate the performance of the model, the Hosmer-Lemeshow (HL) goodness-of-fit test was used. The model was refitted 1,000 times using bootstrap sampling and

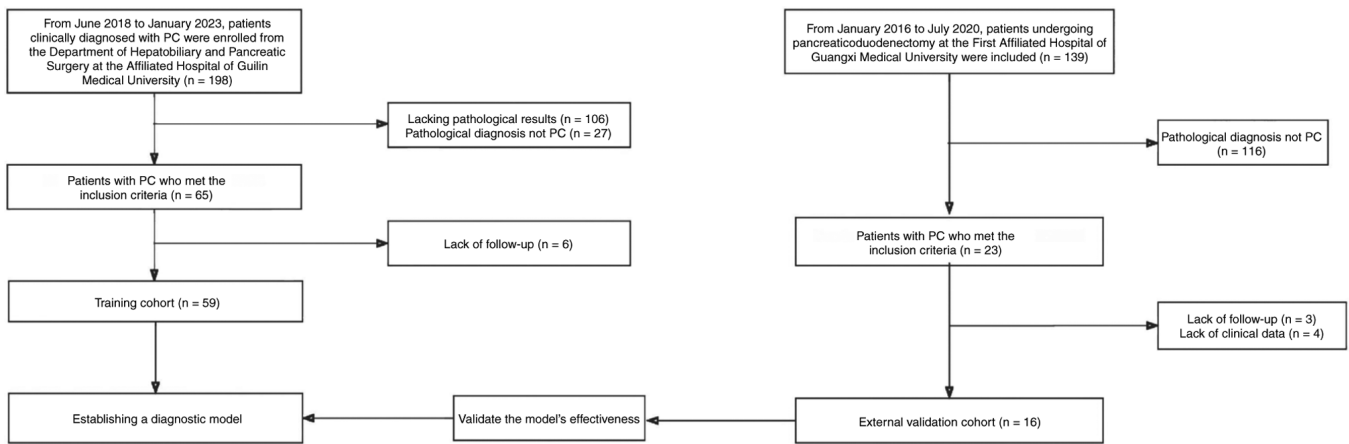


Figure 1. Flow chart outlining the process of patient selection and the inclusion criteria for the study. PC, pancreatic cancer.

its performance was assessed on the original complete dataset to calculate the average diagnostic performance and validate the model's reliability. Calibration curves were generated to ensure that the predicted probabilities match the actual observed rates, confirming the accuracy of the model. Finally, decision curve analysis (DCA) was conducted to assess the model's strengths and practical utility in clinical settings. The validity of the model was further verified using data from the external validation cohort.

Statistical analysis. Continuous variables were expressed as mean ± standard deviation or median, while categorical variables were expressed as frequencies and percentages. The independent t-test and the Mann-Whitney U-test were employed to compare continuous variables. The Chi-squared or Fisher's exact test was used to analyze categorical variables. All-important variable screening, model building and model comparison were statistically performed using SPSS 26.0 (IBM Corp.) and R software. All statistical tests were two-sided and $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. The general baseline information pertaining to the training cohort and the external validation cohort is displayed in Table I. There was a significant difference in the levels of ALB between the training cohort and the external validation cohort, while no significant differences were observed for the remaining indicators.

Risk factors for SLM of PC. In this study, 59 patients with PC were included in the training cohort, comprising 12 patients in the LM group and 47 patients in the No-LM group. To avoid omitting risk factors associated with SLM in PC, indicators with $P < 0.1$ in the univariate logistic regression analysis were included in the multivariate logistic regression analysis. Univariate logistic regression analysis identified the following indicators with $P < 0.1$: CEA, CA125, CA199, CA153, TBIL, DBIL, TP, WBC, NEUT, LYMPH%, PLT, SII and NLR (Table II). Multivariate logistic regression analysis suggested that WBC, PLT, CEA and CA153 were independent risk factors for SLM in patients with PC (Table III). CA19-9 and CA125,

though significant in the univariate analysis, were not retained in the final multivariate model. There was a strong correlation among the liver function indicators and inflammation-related indicators. The analysis indicates that there is little correlation between CA19-9 and other liver function indicators as well as inflammatory markers, while there is a certain correlation between CA125 and inflammatory markers (Fig. S1). Therefore, their predictive information may be covered by other included variables in this specific cohort, or be affected by the limited sample size.

Development and validation of the diagnostic model. Based on the results of the multivariate logistic regression analysis, a diagnostic model integrating four blood biochemical indicators for diagnosing SLM in patients with PC was established as follows: $\text{Logit}(P) = 0.05 \times (\text{CEA, ng/ml}) + 0.17 \times (\text{CA153, U/ml}) + 0.54 \times (\text{WBC, } \times 10^9/\text{l}) + 0.01 \times (\text{PLT, } \times 10^9/\text{l}) - 12.07$. In the training cohort, the AUC of the model was 0.92 (95% CI: 0.82-1.00), and sensitivity and specificity were 0.96 and 0.86, respectively. The AUC of the model was 0.90 (95% CI: 0.68-1.00), and the sensitivity and specificities were 0.83 and 0.75, respectively, in the external validation cohort. These results are summarized in Fig. 2 and Table IV. The optimal cut-off value for the diagnostic score was determined using the Youden index.

Nomogram. To ascertain the value of these factors more intuitively and understand the significance of these independent risk factors more quickly and easily in clinical practice, a nomogram for LM in patients with PC was constructed using R software (Fig. 3). This nomogram provides a visual tool to facilitate the practical application of the diagnostic model, allowing clinicians to estimate the probability of LM based on the CEA values, CA153, WBC and PLT. For instance, a patient with CEA=7.3 ng/ml, CA153=15.6 U/ml, WBC=9.4x10⁹/l and PLT=623x10⁹/l would have a total point score of ~2.253, corresponding to a predicted probability of LM of ~0.927.

Model fitting. The model's goodness of fit was evaluated using the HL test, which yielded a P-value of 0.017. Given the relatively small sample size, the calibration was also assessed using bootstrap resampling (1,000 replicates). The calibration

Table I. Clinical characteristics compared between the training and the external validation cohort.

Indexes	Training cohort (n=59)	Validation cohort (n=16)	P-value
Sex			0.857
Male	28 (47.46)	8 (50.00)	
Female	31 (52.54)	8 (50.00)	
Age, years	58.97±9.15	59.13±9.89	0.953
CEA, ng/ml	3.18 (1.58, 6.77)	3.85 (2.27, 8.04)	0.821
AFP, ng/ml	2.44 (1.63, 3.44)	2.04 (1.71, 2.39)	0.292
CA125, U/ml	19.45 (12.89, 29.44)	17.30 (9.50, 34.80)	0.628
CA199, U/ml	194.00 (22.18, 486.30)	493.78 (51.28, 1258.04)	0.382
CA153, U/ml	10.66 (5.99, 18.80)	17.40 (10.00, 22.90)	0.115
TBIL, μ mol/l	73.70 (10.10, 171.20)	128.70 (42.10, 185.30)	0.339
DBIL, μ mol/l	69.70 (4.30, 152.80)	87.60 (36.90, 126.20)	0.732
TP, g/l	68.14±5.24	67.43±7.36	0.664
ALB, g/l	38.17±3.87	35.69±3.92	0.028
G-GT, U/l	186.00 (22.00, 518.95)	198.90 (94.00, 248.00)	0.578
AST, U/l	45.30 (18.40, 91.50)	49.00 (25.00, 83.00)	0.923
ALT, U/l	49.70 (17.00, 131.70)	45.00 (25.00, 128.00)	0.974
ALP, U/l	177.00 (82.00, 339.00)	240.00 (172.00, 279.00)	0.157
PA, mg/l	199.17 (146.90, 230.65)	179.40 (133.80, 194.10)	0.129
WBC, $\times 10^9/l$	6.22 (4.85, 8.40)	6.69 (6.27, 7.95)	0.289
NEUT, $\times 10^9/l$	3.788 (2.87, 5.31)	4.48 (3.90, 4.95)	0.258
NEUT%	0.63±0.10	0.66±0.07	0.441
LYMPH, $\times 10^9/l$	1.32 (1.14, 1.75)	1.63 (1.03, 1.79)	0.776
LYMPH%	0.25 (0.18, 0.30)	0.22 (0.19, 0.26)	0.514
PLT, $\times 10^9/l$	271.00 (214.00, 313.00)	251.00 (208.90, 269.90)	0.453
LDH, U/l	181.35 (156.00, 231.00)	150.00 (145.00, 212.00)	0.252
FIB, g/l	3.68 (3.05, 4.34)	4.17 (3.38, 4.86)	0.247
INR	1.00 (0.93, 1.11)	1.02 (0.93, 1.11)	0.964
SII, $\times 10^9/l$	107.50 (82.06, 162.39)	131.98 (81.33, 175.12)	0.995
NLR	2.58 (2.04, 3.84)	3.00 (2.26, 4.35)	0.348
PLR	177.96 (144.74, 237.35)	196.99 (134.94, 248.32)	0.933
APRI	0.43 (0.22, 0.88)	0.50 (0.27, 0.94)	0.872
AAR	0.971 (0.63, 1.31)	0.92 (0.77, 1.44)	0.887
SLM			0.916
No-LM	45 (76.27)	12 (75.00)	
LM	14 (23.73)	4 (25.00)	

Values are expressed as n (%), mean \pm standard deviation or the median (interquartile range). ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; ALB, albumin; APRI, AST to platelet ratio index; AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; CA125, carbohydrate antigen 125; CA153, carbohydrate antigen 15-3; CA199, carbohydrate antigen 19-9; DBIL, direct bilirubin; FIB, fibrinogen; G-GT, gamma-glutamyltranspeptidase; INR, international normalized ratio; LYMPH, lymphocytes; LDH, lactate dehydrogenase; NEUT, neutrophils; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PLT, platelets; PA, prealbumin; SLM, synchronous liver metastasis; SII, systemic immune-inflammation index; TBIL, total bilirubin; TP, total protein.

curve (Fig. 4A) shows a good agreement between predicted and observed probabilities, with a mean absolute error of 0.067, indicating acceptable calibration.

DCA curve. DCA was performed to determine the net benefit of the diagnostic model, thereby evaluating its clinical applicability. As shown in Fig. 4B, when the threshold surpasses 0.06, the DCA curve is above the 'None' and 'All' curves, indicating that the model has a better clinical net benefit in this range.

These evaluations prove that the diagnostic model is not only statistically robust but also clinically applicable, offering a valuable tool for the early identification of SLM in patients with PC.

Discussion

PC is a highly lethal malignancy with significant metastatic potential. Even small PCs (<20 mm in diameter) can

Table II. Univariate logistic regression analysis in the training cohort.

Indexes	β	S.E.	Z	P-value	OR (95% CI)
CEA, ng/ml	0.02	0.01	1.75	0.080	1.02 (1.00-1.05)
AFP, ng/ml	-0.02	0.04	-0.45	0.650	0.98 (0.91-1.06)
CA125, U/ml	0.02	0.01	2.39	0.017	1.02 (1.01-1.03)
CA199, U/ml	0.00	0.00	1.83	0.067	1.00 (1.00-1.00)
CA153, U/ml	0.11	0.04	2.75	0.006	1.11 (1.03-1.20)
TBIL, μ mol/l	-0.01	0.00	-2.05	0.040	0.99 (0.98-0.99)
DBIL, μ mol/l	-0.01	0.00	-2.15	0.032	0.99 (0.98-0.99)
TP, g/l	0.13	0.07	1.97	0.049	1.14 (1.01-1.29)
ALB, g/l	0.07	0.08	0.82	0.413	1.07 (0.91-1.25)
GGT, U/l	0.00	0.00	0.21	0.836	1.00 (1.00-1.00)
AST, U/l	-0.00	0.00	-0.70	0.484	1.00 (0.99-1.01)
ALT, U/l	-0.00	0.00	-0.83	0.405	1.00 (0.99-1.00)
ALP, U/l	0.00	0.00	0.47	0.636	1.00 (1.00-1.00)
PA, mg/l	0.00	0.00	1.10	0.272	1.00 (1.00-1.00)
WBC, $\times 10^9/l$	0.37	0.15	2.53	0.012	1.45 (1.09-1.94)
NEUT, $\times 10^9/l$	0.44	0.16	2.73	0.006	1.55 (1.13-2.12)
LYMPH, $\times 10^9/l$	-0.39	0.66	-0.60	0.550	0.67 (0.19-2.46)
LYMPH%	-8.69	4.19	-2.07	0.038	0.00 (0.00-0.62)
PLT, $\times 10^9/l$	0.01	0.00	2.25	0.025	1.01 (1.01-1.02)
LDH, $\times 10^9/l$	0.00	0.00	1.09	0.274	1.00 (1.00-1.01)
FIB, g/l	-0.02	0.04	-0.57	0.566	0.98 (0.91-1.06)
INR	-1.35	1.50	-0.90	0.366	0.26 (0.01-4.87)
SII, $\times 10^9/l$	0.01	0.00	1.85	0.064	1.01 (1.00-1.02)
NLR	0.32	0.13	2.38	0.017	1.38 (1.06-1.79)
PLR	0.01	0.00	1.73	0.084	1.01 (1.00-1.01)
APRI	-0.54	0.52	-1.05	0.292	0.58 (0.21-1.60)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; ALB, albumin; APRI, AST to platelet ratio index; AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; CA125, carbohydrate antigen 125; CA153, carbohydrate antigen 15-3; CA199, carbohydrate antigen 19-9; CI, confidence interval; DBIL, direct bilirubin; FIB, fibrinogen; G-GT, gamma-glutamyltranspeptidase; INR, international normalized ratio; LYMPH, lymphocytes; LDH, lactate dehydrogenase; NEUT, neutrophils; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PLR, platelet-to-lymphocyte ratio; PLT, platelets; PA, prealbumin; SLM, synchronous liver metastasis; SII, systemic immune-inflammation index; S.E., standard error; TBIL, total bilirubin; TP, total protein; WBC, white blood cell count; Z, Z-score; β , regression coefficient.

Table III. Multivariate logistic regression analysis in the training cohort.

Indexes	β	S.E.	Z	P-value	OR (95%CI)
Intercept	-12.07	3.34	-3.61	<0.001	0.00 (0.00-0.00)
CA153, U/ml	0.17	0.05	3.08	0.002	1.18 (1.06-1.31)
WBC, $\times 10^9/l$	0.54	0.24	2.27	0.023	1.71 (1.08-2.72)
CEA, U/ml	0.05	0.02	2.66	0.008	1.05 (1.01-1.08)
PLT, $\times 10^9/l$	0.01	0.01	2.00	0.045	1.01 (1.01-1.03)

CI, confidence interval; CEA, carcinoembryonic antigen; CA153, carbohydrate antigen 15-3; OR, odds ratio; PLT, platelets; S.E., standard error; WBC, white blood cell count; Z, Z-score; β , regression coefficient.

metastasize and ultimately lead to death (19,20). Radical pancreatectomy is the only potentially curative treatment, but occult metastases often diminish its efficacy (21). Although

substantial progress has been made in the diagnosis of LM through advances in imaging techniques, minimally invasive surgery and biomarker research, the accurate preoperative

Table IV. Performance of the model.

Dataset	AUC	Accuracy	Sensitivity	Specificity	PPV	NPV	Cut-off point
Training cohort	0.92	0.93	0.96	0.86	0.96	0.86	0.457
Validation cohort	0.90	0.81	0.83	0.75	0.91	0.60	0.457

AUC, area under the receiver operating characteristic curve; NPV, negative predictive value; PPV, positive predictive value; Sensitivity, true positive rate; Specificity, true negative rate.

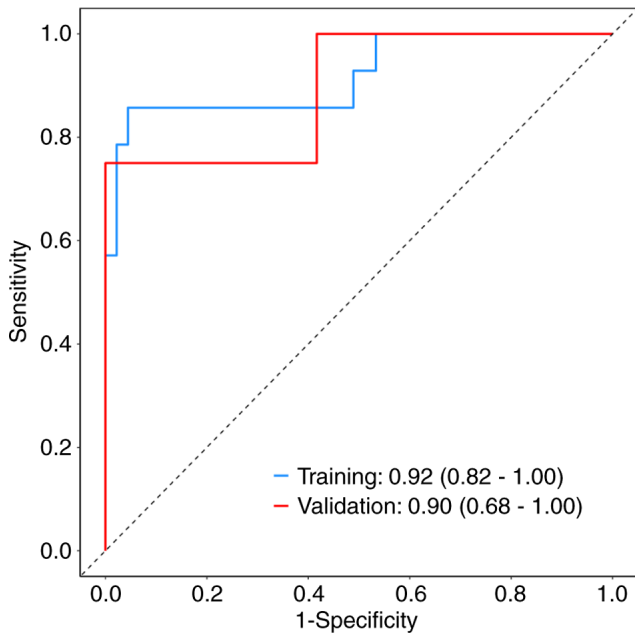


Figure 2. Receiver operating characteristic curve of the diagnostic model. Training, training cohort; Validation, external validation cohort.

diagnosis of LM in patients with PC remains a significant challenge. Currently, no biomarkers with both high specificity and high sensitivity are available for the diagnosis of LM from PC. Therefore, the exploration of effective biomarkers is critical to improving early diagnostic accuracy for LM and guiding individualized treatment strategies. This study revealed significant differences in CA153, CEA, WBC and PLT levels between the patient groups of LM and non-LM. CA153, although traditionally used for breast cancer (22), has shown potential value as the soluble form of mucin (MUC)-1 in PC (23). Notably, in the multivariate analysis of this study, CA153 emerged as an independent predictor of LM, while CA199 and CA125 were excluded from the final model. Statistically, in our multivariate analysis, CA153 remained an independent predictor of liver metastasis, while CA199 and CA125 did not, suggesting it provides unique information relevant to metastasis in the present cohort. This may be because CA153 (MUC-1) reflects unique biological processes related to tumor invasion and metastasis. Previous studies confirmed that the abnormal expression and glycosylation changes of MUC-1 in PC are directly associated with the occurrence and development of LM (24). Therefore, CA153 may serve as a supplementary biomarker, providing additional predictive information

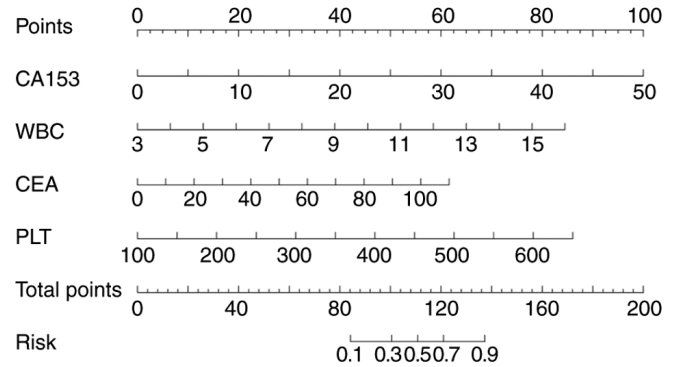


Figure 3. Nomogram of diagnostic model. CEA, carcinoembryonic antigen; CA153, carbohydrate antigen 153; WBC, white blood cell count; PLT, platelet count.

that is different from traditional markers for this diagnostic model. This finding may be interpreted as CA153 potentially adding complementary value in assessing metastatic risk, not as a replacement for conventional markers. Its clinical utility requires validation in larger, prospective studies. CEA is elevated in various malignant tumors, including PC (25). Currently, CEA is the second most common serum biomarker used clinically for detecting PC, with upregulated levels observed in 30-60% of patients with PC, and it is associated with PC survival (26). Studies have shown that abnormally high levels of CEA in patients with PC correlate with tumor progression, poor prognosis and the incidence of distant metastasis (27,28). Continuous monitoring of the changes of CEA levels in patients with PC can aid in assessing the treatment efficacy, predicting recurrence and guiding the selection of subsequent treatment strategies (29,30). This enables the optimization of therapeutic plans and disease progression monitoring.

The WBC count is a common indicator used to assess the body's inflammatory response, infection status and certain hematological diseases, which significantly inhibits tumor development (31,32). A previous study found that tumor-secreted factors trigger inflammatory responses within the liver microenvironment, promoting LM of PC (33). WBCs can be transformed by tumor cells and stromal cells into tumor-associated cells, which secrete multiple cytokines and chemokines that enhance immunosuppression in the tumor microenvironment, thereby facilitating the proliferation and migration of tumor cells (34). However, the specific phenotype, function and regulatory mechanisms of WBCs in the context of LM remain elusive in PC (35). In the present study,

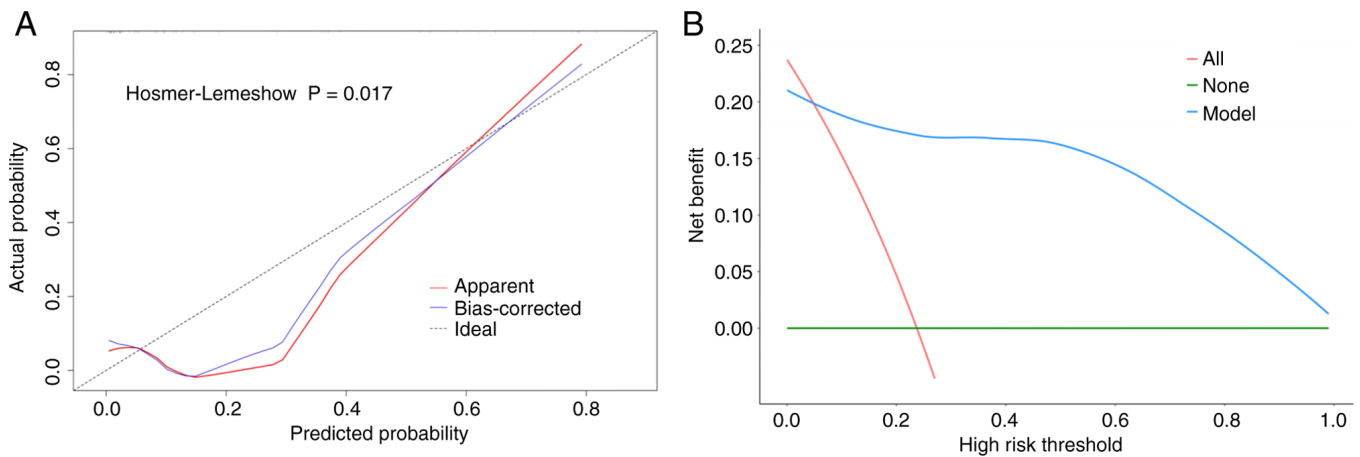


Figure 4. Decision curve analysis and Hosmer-Lemeshow curves of the diagnostic model. (A) Hosmer-Lemeshow curves. (B) Decision curve analysis.

the WBC count was identified as an independent risk factor for SLM in patients with PC. It has an auxiliary role in diagnosing SLM of PC and has the potential to improve the accuracy of such diagnoses.

A substantial amount of clinical and experimental data indicates that the interaction between PLTs and tumor cells is critical for tumor metastasis (36). PLTs contribute to the pre-metastatic microenvironment by forming microthrombi that trap circulating tumor cells, releasing growth factors (e.g., TGF- β , VEGF), and promoting the endothelial permeability and immune evasion in the liver (33,35,37). Multiple studies have shown that thrombocytosis (elevated PLT counts) is a predictor of poor prognosis in PC (38-40). The present study demonstrates a significant difference in PLT counts between the metastatic and non-metastatic groups.

In this study, a diagnostic model integrating CA153, CEA, WBC and PLT was established. This model exhibited high performance in identifying LM in patients with PC and outperformed single biochemical indices used in other studies (41-43). CA125 and CA199 are of certain value in diagnosing PC and its LM (41,43-45). The results of the present study also suggested that CA125 and CA199 were significantly different between the LM and Non-LM groups. However, in the multivariate logistic regression analysis, CA199 and CA125 were not included in the diagnostic model, which may be related to the sample size. Although the HL test suggested certain deviations between predicted and observed outcomes ($P < 0.05$), bootstrap calibration and visual inspection of the calibration curve showed a good model fit. This discrepancy may reflect the sensitivity of the HL test to limited sample sizes rather than poor model calibration performance.

Of note, the present study had certain limitations. First, the main limitation of this study is the relatively small sample size, particularly the limited number of patients with SLM ($n=14$ in the training cohort). This may affect the stability of the multivariate logistic regression model and increase the risk of overfitting. Therefore, the present results should be interpreted with caution, and further validation in larger, multicenter prospective studies is warranted. Second, the external validation cohort was small ($n=16$), which limits the strength of conclusions regarding

the model's generalizability. Future studies with larger, independent cohorts are needed to confirm the robustness and transportability of the model. In addition, the number of events (SLM cases) per predictor variable was below the recommended threshold of 10 events per variable for logistic regression (46), which may elevate the risk of overfitting. Although bootstrap validation confirmed reasonable stability, future studies with larger samples should consider penalized regression approaches to enhance the model's robustness. Finally, differences in the indicator detection methods between different medical institutions may affect the consistency of data collection and analysis.

In conclusion, CEA, CA153, WBC and PLT are important independent risk factors for SLM in patients with PC. The diagnostic model integrating these blood biochemical indices exhibits good diagnostic efficacy in identifying SLM in patients with PC and demonstrates strong clinical applicability.

Acknowledgements

Not applicable.

Funding

This study was supported by the Affiliated Hospital of Guilin Medical University, PhD Start-up Fund (grant no. KY1303) and Guangxi Key Laboratory of Immunology and Metabolism for Liver Diseases (grant no. GKE-KF202505).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YJ, GP, SH and JL conceived and designed the study. YJ, GP and JL analyzed the data. YJ, GP and JL wrote the manuscript. YJ and GP collected the data. SH and JL conceptualized and developed an outline for the manuscript and revised it. JY and JL confirm the authenticity of the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The retrospective study was approved by the Ethics Committee of the Affiliated Hospital of Guilin Medical University (grant no. 2022YJSL-03) and the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (grant no. 2024-E717-01). All patients signed informed consent forms allowing their case and imaging data to be used anonymously for research.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

- Rawla P, Sunkara T and Gaduputi V: Epidemiology of pancreatic cancer: Global trends, etiology and risk factors. *World J Oncol* 10: 10-27, 2019.
- McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG and McCain RS: Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. *World J Gastroenterol* 24: 4846-4861, 2018.
- Ducieux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goéré D, Seufferlein T, Haustermans K, Van Laethem JL, Conroy T, *et al*: Cancer of the pancreas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 26 (Suppl 5): v56-v68, 2015.
- Zhang XP, Gao YX, Xu S, Zhao GD, Hu MG, Tan XL, Zhao ZM and Liu R: A novel online calculator to predict early recurrence and long-term survival of patients with resectable pancreatic ductal adenocarcinoma after pancreaticoduodenectomy: A multicenter study. *Int J Surg* 106: 106891, 2022.
- Kolbeinsson H, Hoppe A, Bayat A, Kogelschatz B, Mbanugo C, Chung M, Wolf A, Assifi MM and Wright GP: Recurrence patterns and postrecurrence survival after curative intent resection for pancreatic ductal adenocarcinoma. *Surgery* 169: 649-654, 2021.
- de Ridder J, de Wilt JH, Simmer F, Overbeek L, Lemmens V and Nagtegaal I: Incidence and origin of histologically confirmed liver metastases: An explorative case-study of 23,154 patients. *Oncotarget* 7: 55368-55376, 2016.
- Hess KR, Varadhachary GR, Taylor SH, Wei W, Raber MN, Lenzi R and Abbruzzese JL: Metastatic patterns in adenocarcinoma. *Cancer* 106: 1624-1633, 2006.
- Ouyang HH, Pan ZY, Ma WD, Zhao LJ, Zhang T, Liu F and Quan MM: Multidisciplinary treatment and survival analysis for 497 cases of pancreatic cancer with liver metastases. *Zhonghua Yi Xue Za Zhi* 96: 425-430, 2016 (In Chinese).
- Ouyang H, Ma W, Liu F, Yue Z, Fang M, Quan M and Pan Z: Factors influencing survival of patients with pancreatic adenocarcinoma and synchronous liver metastases receiving palliative care. *Pancreatol* 17: 773-781, 2017.
- Takada T, Yasuda H, Amano H, Yoshida M and Uchida T: Simultaneous hepatic resection with pancreato-duodenectomy for metastatic pancreatic head carcinoma: Does it improve survival? *Hepatogastroenterology* 44: 567-573, 1997.
- Murakawa M, Kawahara S, Takahashi D, Kamioka Y, Yamamoto N, Kobayashi S, Ueno M, Morimoto M, Sawazaki S, Tamagawa H, *et al*: Risk factors for early recurrence in patients with pancreatic ductal adenocarcinoma who underwent curative resection. *World J Surg Oncol* 21: 263, 2023.
- Huang Y, Zhou S, Luo Y, Zou J, Li Y, Chen S, Gao M, Huang K and Lian G: Development and validation of a radiomics model of magnetic resonance for predicting liver metastasis in resectable pancreatic ductal adenocarcinoma patients. *Radiat Oncol* 18: 79, 2023.
- Balkwill F and Mantovani A: Inflammation and cancer: Back to virchow? *Lancet* 357: 539-545, 2001.
- Wang DS, Luo HY, Qiu MZ, Wang ZQ, Zhang DS, Wang FH, Li YH and Xu RH: Comparison of the prognostic values of various inflammation based factors in patients with pancreatic cancer. *Med Oncol* 29: 3092-3100, 2012.
- Smith RA, Bosonnet L, Ratary M, Sutton R, Neoptolemos JP, Campbell F and Ghaneh P: Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. *Am J Surg* 197: 466-472, 2009.
- Xue P, Kanai M, Mori Y, Nishimura T, Uza N, Kodama Y, Kawaguchi Y, Takaori K, Matsumoto S, Uemoto S and Chiba T: Neutrophil-to-lymphocyte ratio for predicting palliative chemotherapy outcomes in advanced pancreatic cancer patients. *Cancer Med* 3: 406-415, 2014.
- Raza SS, Khan H, Hajibandeh S, Hajibandeh S, Bartlett D, Chatzizacharias N, Roberts K, Marudanayagam R and Sutcliffe RP: Can preoperative carbohydrate antigen 19-9 predict metastatic pancreatic cancer? Results of a systematic review and meta-analysis. *HPB (Oxford)* 26: 630-638, 2024.
- Liu L, Xu H, Wang W, Wu C, Chen Y, Yang J, Cen P, Xu J, Liu C, Long J, *et al*: A preoperative serum signature of CEA+/CA125+/CA19-9 $\geq 1,000$ U/ml indicates poor outcome to pancreatectomy for pancreatic cancer. *Int J Cancer* 136: 2216-2227, 2015.
- Hidalgo M: Pancreatic cancer. *N Engl J Med* 362: 1605-1617, 2010.
- Vincent A, Herman J, Schulick R, Hruban RH and Goggins M: Pancreatic cancer. *Lancet* 378: 607-620, 2011.
- Hartwig W, Werner J, Jäger D, Debus J and Büchler MW: Improvement of surgical results for pancreatic cancer. *Lancet Oncol* 14: e476-e485, 2013.
- Ren Z, Yang J, Liang J, Xu Y, Lu G, Han Y, Zhu J, Tan H, Xu T and Ren M: Monitoring of postoperative neutrophil-to-lymphocyte ratio, D-dimer, and CA153 in: Diagnostic value for recurrent and metastatic breast cancer. *Front Surg* 9: 927491, 2023.
- Beatty P, Hanisch FG, Stolz DB, Finn OJ and Ciborowski P: Biochemical characterization of the soluble form of tumor antigen MUC1 isolated from sera and ascites fluid of breast and pancreatic cancer patients. *Clin Cancer Res* 7 (Suppl 3): 781s-787s, 2001.
- Remmers N, Anderson JM, Linde EM, DiMaio DJ, Lazenby AJ, Wandall HH, Mandel U, Clausen H, Yu F and Hollingsworth MA: Aberrant expression of mucin core proteins and o-linked glycans associated with progression of pancreatic cancer. *Clin Cancer Res* 19: 1981-1993, 2013.
- Diehl SJ, Lehmann KJ, Sadick M, Lachmann R and Georgi M: Pancreatic cancer: Value of dual-phase helical CT in assessing resectability. *Radiology* 206: 373-378, 1998.
- Swords DS, Firpo MA, Scaife CL and Mulvihill SJ: Biomarkers in pancreatic adenocarcinoma: Current perspectives. *Onco Targets Ther* 9: 7459-7467, 2016.
- Basso D, Fabris C, Del Favero G, Angonese C, Meggiato T, Infantino A, Plebani M, Piccoli A, Leandro G, Burlina A, *et al*: Serum carcinoembryonic antigen in the differential diagnosis of pancreatic cancer: Influence of tumour spread, liver impairment, and age. *Dis Markers* 6: 203-207, 1988.
- Chen Y, Gao SG, Chen JM, Wang GP, Wang ZF, Zhou B, Jin CH, Yang YT and Feng XS: Serum CA242, CA199, CA125, CEA, and TSGF are biomarkers for the efficacy and prognosis of cryo-ablation in pancreatic cancer patients. *Cell Biochem Biophys* 71: 1287-1291, 2015.
- Lee KJ, Yi SW, Chung MJ, Park SW, Song SY, Chung JB and Park JY: Serum CA 19-9 and CEA levels as a prognostic factor in pancreatic adenocarcinoma. *Yonsei Med J* 54: 643-649, 2013.
- Wu L, Huang P, Wang F, Li D, Xie E, Zhang Y and Pan S: Relationship between serum CA19-9 and CEA levels and prognosis of pancreatic cancer. *Ann Transl Med* 3: 328, 2015.
- Singel KL and Segal BH: Neutrophils in the tumor microenvironment: Trying to heal the wound that cannot heal. *Immunol Rev* 273: 329-343, 2016.
- Yan J, Kloecker G, Fleming C, Bousamra M II, Hansen R, Hu X, Ding C, Cai Y, Xiang D, Donninger H, *et al*: Human polymorphonuclear neutrophils specifically recognize and kill cancerous cells. *Oncoimmunology* 3: e950163, 2014.
- Costa-Silva B, Aiello NM, Ocean AJ, Singh S, Zhang H, Thakur BK, Becker A, Hoshino A, Mark MT, Molina H, *et al*: Pancreatic cancer exosomes initiate pre-metastatic niche formation in the liver. *Nat Cell Biol* 17: 816-826, 2015.

34. Caldeira PC, Vieira ÉLM, Sousa AA, Teixeira AL and Aguiar MCF: Immunophenotype of neutrophils in oral squamous cell carcinoma patients. *J Oral Pathol Med* 46: 703-709, 2017.
35. Wang X, Hu LP, Qin WT, Yang Q, Chen DY, Li Q, Zhou KX, Huang PQ, Xu CJ, Li J, *et al*: Identification of a subset of immunosuppressive P2RX1-negative neutrophils in pancreatic cancer liver metastasis. *Nat Commun* 12: 174, 2021.
36. Shi Q, Ji T, Tang X and Guo W: The role of tumor-platelet interplay and micro tumor thrombi during hematogenous tumor metastasis. *Cell Oncol (Dordr)* 46: 521-532, 2023.
37. Schlesinger M: Role of platelets and platelet receptors in cancer metastasis. *J Hematol Oncol* 11: 125, 2018.
38. Shirai Y, Shiba H, Sakamoto T, Horiuchi T, Haruki K, Fujiwara Y, Futagawa Y, Ohashi T and Yanaga K: Preoperative platelet to lymphocyte ratio predicts outcome of patients with pancreatic ductal adenocarcinoma after pancreatic resection. *Surgery* 158: 360-365, 2015.
39. Zhang SR, Yao L, Wang WQ, Xu JZ, Xu HX, Jin W, Gao HL, Wu CT, Qi ZH, Li H, *et al*: Tumor-infiltrating platelets predict postsurgical survival in patients with pancreatic ductal adenocarcinoma. *Ann Surg Oncol* 25: 3984-3993, 2018.
40. Saito R, Kawaida H, Hosomura N, Amemiya H, Itakura J, Yamamoto A, Takiguchi K, Maruyama S, Shoda K, Furuya S, *et al*: Exposure to blood components and inflammation contribute to pancreatic cancer progression. *Ann Surg Oncol* 28: 8263-8272, 2021.
41. Haridas D, Chakraborty S, Ponnusamy MP, Lakshmanan I, Rachagani S, Cruz E, Kumar S, Das S, Lele SM, Anderson JM, *et al*: Pathobiological implications of MUC16 expression in pancreatic cancer. *PLoS One* 6: e26839, 2011.
42. Shi HJ, Jin C and Fu DL: Preoperative evaluation of pancreatic ductal adenocarcinoma with synchronous liver metastasis: Diagnosis and assessment of unresectability. *World J Gastroenterol* 22: 10024-10037, 2016.
43. Yuan Z, Shu Z, Peng J, Wang W, Hou J, Han L, Zheng G, Wei Y and Zhong J: Prediction of postoperative liver metastasis in pancreatic ductal adenocarcinoma based on multiparametric magnetic resonance radiomics combined with serological markers: A cohort study of machine learning. *Abdom Radiol (NY)* 49: 117-130, 2024.
44. Zhang T, Dong X, Zhou Y, Liu M, Hang J and Wu L: Development and validation of a radiomics nomogram to discriminate advanced pancreatic cancer with liver metastases or other metastatic patterns. *Cancer Biomark* 32: 541-550, 2021.
45. Liu L, Xu HX, Wang WQ, Wu CT, Xiang JF, Liu C, Long J, Xu J, Fu de L, Ni QX, *et al*: Serum CA125 is a novel predictive marker for pancreatic cancer metastasis and correlates with the metastasis-associated burden. *Oncotarget* 7: 5943-5956, 2016.
46. Peduzzi P, Concato J, Kemper E, Holford TR and Feinstein AR: A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol* 49: 1373-1379, 1996.