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Original Article

A risk prediction model for metachronous peritoneal metastasis after radical gastrectomy in gastric cancer based on peripheral blood inflammatory markers and tumor pathological features

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Abstract: Purpose: To develop a prognostic scoring system for metachronous peritoneal dissemination (MPM) in gastric cancer patients following radical gastrectomy, based on preoperative peripheral blood inflammatory markers and postoperative tumor histological features. Methodology: A total of 522 gastric cancer patients who underwent radical gastrectomy were retrospectively analyzed, including 364 patients without MPM and 158 patients with MPM. Peripheral blood samples were collected within 7 days before surgery to measure neutrophil and lymphocyte counts, platelets, C-reactive protein (CRP), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and CA125. Four inflammatory indices were calculated: neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI). Histopathological features of the excised tissue were assessed postoperatively. Result: Compared with the non-MPM group, patients in the MPM group exhibited significantly larger tumors, a higher prevalence of diffuse-type Lauren patterns, poorly differentiated histology, deeper tumor invasion, more frequent lymph node metastasis, and elevated rates of perineural and lymphovascular infiltration (all $P < 0.05$). Neutrophil count, platelet count, CRP, NLR, PLR, SII, SIRI, CEA, CA19-9 and CA125 were all increased, whereas lymphocyte counts were reduced in the MPM group (all $P < 0.05$). Multivariate logistic regression analysis identified tumor size (OR=1.475), depth of invasion (OR=2.602), lymph node metastasis (OR=3.536), NLR (OR=2.457), PLR (OR=1.009), CA19-9 (OR=1.079), and CA125 (OR=1.156) as independent risk factors for MPM. A combined predictive model incorporating these seven parameters demonstrated an area under the receiver operating characteristic curve (AUC) of 0.952. Conclusion: A prognostic model integrating preoperative peripheral blood inflammatory indices and postoperative tumor histopathology can accurately predict the risk of metachronous peritoneal metastases in gastric cancer patients after radical gastrectomy.

Keywords: Gastric cancer, metachronous peritoneal metastasis, inflammatory markers, pathological features, prediction model

Introduction

Gastric cancer remains one of the leading causes of cancer-related mortality worldwide, with particularly high incidence in Eastern Asia [1, 2]. Despite progress in diagnostic techniques and therapeutic approaches, the prognosis of patients with advanced gastric cancer remains poor [3, 4]. Early detection and accurate risk stratification are critical for improving survival outcomes and optimizing treatment strategies. Metachronous peritoneal metastasis (MPM) refers to the dissemination of tumor cells from the primary gastric lesion to the peritoneal surface after radical gastrectomy, leading to extensive abdominal spread during follow-up. As the most common pattern of recurrence following curative resection, MPM is associated with a significantly impaired life quality and reduced overall survival [5, 6].

MPM represents a significant clinical challenge, as it is often diagnosed at an advanced stage when therapeutic options are limited. The

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development of MPM is influenced by multiple factors, including tumor biological characteristics, host immune status, and systemic inflammatory responses. Early identification of individuals at high risk for postoperative MPM could facilitate timely implementation of individualized surveillance and prophylactic therapeutic strategies, potentially improving outcomes [7-9]. However, currently available diagnostic methods, including imaging techniques and serum tumor markers, exhibit suboptimal sensitivity and specificity for the early detection of MPM [10, 11]. Therefore, there is an urgent need for developing reliable and non-invasive tools for risk assessment of MPM in gastric cancer patients. Peripheral blood inflammatory markers and tumor pathological features may offer valuable insights into disease progression and metastatic potential, providing a basis for developing predictive models.

Chronic inflammatory process plays a pivotal role in tumor initiation, progression, angiogenesis, immune escape, and metastatic dissemination. Elevated levels of inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP) have been associated with unfavorable prognosis in various malignancies, including gastric cancer [12, 13]. These markers reflect systemic inflammation status and immune dysregulation, both of which can promote tumor growth and metastasis. In addition, tumor pathological features such as histological subtype, differentiation grade, extent of tumor invasion, and lymph node involvement are well-established prognostic factors in gastric cancer. Poorly differentiated tumors generally exhibit more aggressive biological behavior and a higher metastatic potential compared to well-differentiated tumors. Advanced tumor invasion and extensive lymph node involvement are strongly associated with an increased risk of peritoneal dissemination. Combining these tumor pathological features with peripheral blood inflammatory markers offers a comprehensive and robust approach to predicting the risk of MPM.

The development of a predictive model incorporating both peripheral blood inflammatory markers and postoperative pathological features may substantially improve postoperative risk stratification and management of MPM in gastric cancer. By integrating these parameters, such a model may facilitate the identification of high-risk patients who may benefit from more intensive surveillance and targeted prophylactic interventions. Unlike previous studies that focused on overall recurrence or synchronous metastasis, our study specifically investigated metachronous peritoneal metastasis after radical gastrectomy. Furthermore, a clinically applicable prognostic model, incorporating seven independent predictive factors, was developed, with its predictive performance validated. Through systematic evaluation and refinement, we aim to establish an accurate and practical tool for predicting MPM and ultimately improve the long-term prognosis of patients with gastric cancer.

Materials and methods

Research framework and participant cohort

This retrospective cohort study was conducted at Suzhou Municipal Hospital. Consecutive patients who underwent surgery for histologically confirmed gastric cancer between January 2020 and December 2024 were screened for eligibility.

Inclusion criteria: (1) age ≥ 18 years; (2) histological confirmation of primary gastric cancer according to the WHO classification criteria; (3) underwent radical gastrectomy; (4) availability of complete preoperative peripheral blood laboratory data and clinicopathological records; (5) no history of neoadjuvant chemotherapy or radiotherapy before surgery; (6) absence of macroscopic peritoneal metastasis confirmed intraoperatively [14].

Exclusion criteria: (1) a history of other malignant tumors in the past five years; (2) active infectious or inflammatory disease at the time of blood sample collection; (3) autoimmune diseases; (4) hematological disorders; (5) receipt of blood transfusion within two weeks before preoperative blood collection; (6) concomitant extra-abdominal distant metastases.

A total of 522 patients meeting the inclusion criteria were ultimately included in this study. Based on the occurrence of MPM during postoperative follow-up, patients were divided into the MPM group (n=158) and the non-MPM group (n=364). This study was approved by the Ethics Committee of Suzhou Municipal Hospital

(No. KL-2025-086-K01) and was conducted in accordance with the principles of the Declaration of Helsinki. Given the retrospective nature of the study, the requirement for written informed consent was waived by the Ethics Committee.

Data collection

Demographic and clinical data: Demographic and clinical data were extracted from the electronic health record system. The collected variables included age (years), sex (male/female), body mass index (BMI, kg/m^2), smoking status, alcohol consumption, comorbidities, hypertension, diabetes mellitus, cardiovascular diseases (e.g., coronary artery disease with or without chronic heart failure), and genetic susceptibility to gastric cancer.

Laboratory measurements: Complete blood count (CBC) parameters were measured using an automated hematology analyzer (BC-6800 Plus, Shenzhen Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China). The CBC parameters included neutrophil count, lymphocyte count, and platelet count. Based on the above measured CBC parameters, the following inflammatory indices were calculated: Neutrophil-to-lymphocyte ratio (NLR) = neutrophil count/lymphocyte count; Platelet-to-lymphocyte ratio (PLR) = platelet count/lymphocyte count; Systemic immune-inflammation index (SII) = platelet count × neutrophil count/lymphocyte count; Systemic inflammation response index (SIRI) = neutrophil count × monocyte count/lymphocyte count.

Serum CRP levels was determined using immunoturbidimetric assay on a high-end semi-automated biochemical analyzer (Beckman Coulter AU5800, Beckman Coulter, Inc., Brea, CA, USA). Serum tumor markers, including CEA, CA19-9, and CA125, were measured using electrochemiluminescence immunoassays on a cobas e601 immunoassay analyzer (Roche Diagnostics, Basel, Switzerland). These tumor markers were routinely measured preoperatively and were included in this study.

High-throughput biochemical analysis of blood serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin, albumin, blood urea nitrogen (BUN), and creatinine was performed on a Beckman Coulter AU5800 high-throughput biochemical analyzer (Beckman Coulter, Inc., Brea, CA, USA). All laboratory procedures were performed in accordance with the manufacturers' instructions and institutional quality-control standards.

Pathological assessment: Resected specimens were independently examined by two experienced gastrointestinal pathologists who were blinded to patients' clinical characteristics and outcomes. Any discrepancies were resolved through joint review and consensus using multiheaded microscopy. Histopathological evaluation was performed according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system for gastric tumors [15]. The evaluated pathological variables included tumor size (maximum diameter of the main lesion measured on gross observation, cm), tumor location (upper, middle, or lower third of the stomach), Lauren's histological classification (intestinal, diffuse, or mixed type), histological differentiation grade (well, moderately, or poorly differentiated; poorly differentiated was further classified as primarily solid growth without glandular formation), depth of invasion (pT1, pT2, pT3, or pT4), lymph node metastasis (present or absent), perineural invasion (present or absent), and lymphovascular invasion (present or absent). Perineural invasion was defined as the presence of tumor cells within, surrounding, or invading the perineural space of a nerve. Lymphovascular invasion was defined as the presence of tumor emboli within endothelial-lined lymphatic or blood vessels.

The primary outcome of this study was MPM. MPM was defined as newly diagnosed peritoneal tumor metastasis detected by contrast-enhanced computed tomography (CT), laparoscopic exploration, or both, during postoperative follow-up, with histological verification obtained if possible. Subjects with synchronous peritoneal metastases identified at the time of initial surgery were excluded from the study.

Statistical analysis

All statistical analyses were performed using R software (version 4.0.0; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are expressed as mean ± standard deviation (SD). The normality of continuous variables was assessed using the

Shapiro-Wilk test. Variables conforming to normal distribution were compared between groups using the independent-samples t-tests. Categorical data were presented as counts (n) and percentages (%) and were compared using the Chi-square test. All statistical tests were two-tailed, and a *P* value < 0.05 were considered statistically significant.

Univariate logistic regression analysis was initially performed to screen factors associated with MPM. To reduce the risk of overfitting and address potential multicollinearity among candidate variables, least absolute shrinkage and selection operator (LASSO) logistic regression was subsequently conducted. Variables with statistical significance in the univariate analysis were entered into the LASSO model. Ten-fold cross-validation was used to determine the optimal penalty parameter (λ), and then the λ value corresponding to the minimum binomial deviance was selected. Variables with a non-zero regression coefficient at the optimal λ were retained as potential predictors and subsequently included in the multivariable logistic regression model. The results are reported as odds ratios (ORs) and corresponding 95% confidence intervals (CIs).

Receiver operating characteristic (ROC) curves analysis was employed to evaluate the predictive performance of the identified risk factors and the combined prognostic model. The area under the ROC curve (AUC) was calculated to assess discrimination ability. The optimal cut-off value for each predictor was determined using the Youden Index. Sensitivity, specificity, Youden Index, and F1 score were calculated. All ROC analyses and logistic regression analyses were performed using the pROC package (version 1.18.0) in R software.

External validation cohort

To evaluate the generalizability of the proposed prognostic model, an independent temporal validation set was employed. Consecutive patients with histologically confirmed gastric cancer who received radical gastrectomy at Suzhou Municipal Hospital between January 2025 to August 2025 were selected according to the same inclusion and exclusion criteria. A total of 156 eligible patients were included in the external validation group, comprising 46 patients who developed MPM and 110 who did not. Demographic, clinicopathological, and laboratory data were collected using the same procedures for the derivation group. The previously established multivariable logistic regression equation was applied to the validation cohort to calculate their predicted probability of MPM for each patient. The predictive performance of the model in the validation cohort was also assessed using ROC curve analysis.

Results

Patient characteristics

No significant differences were found between the MPM and non-MPM groups in terms of age, sex, BMI, smoking status, alcohol consumption, hypertension, diabetes mellitus, cardiovascular disease, or family history of gastric cancer (all P > 0.05, **Table 1**).

Clinicopathological characteristics

As shown in **Table 2**, compared with the non-MPM group, patients in the MPM group exhibited more aggressive clinicopathological features, including larger tumor size (5.26 ± 1.99 vs. 4.12 ± 1.63 cm, P < 0.001), higher proportion of diffuse-type Lauren subtyping (42.41% vs. 26.65%, P=0.002), higher frequency of poorly differentiated histology (43.67% vs. 29.40%, P=0.002), deeper tumor infiltration (pT3-pT4: 71.0% vs. 43.4%, P < 0.001), and higher rates of lymph node metastasis (79.11% vs. 46.15%, P < 0.001), perineural invasion (38.61% vs. 26.37%, P=0.005), and lymphovascular invasion (36.08% vs. 23.08%, P= 0.002). Tumor location did not differ significantly between the groups (P=0.158).

Peripheral blood inflammatory markers

Preoperative neutrophil counts were significantly higher in the MPM group compared with the non-MPM group [(4.57 ± 2.13) $\times 10^9$/L vs. (3.72 ± 1.56) $\times 10^9$/L, P < 0.001], whereas lymphocyte counts were lower [(1.73 ± 0.72) $\times 10^9$/L vs. (1.95 ± 0.81) $\times 10^9$/L, P=0.003]. In addition, platelet counts were elevated [(255.42 ± 89.36) $\times 10^9$/L vs. (238.15 ± 75.24) $\times 10^9$/L, P=0.035], and serum CRP levels [(10.46 ± 5.85) mg/L vs. (7.23 ± 3.57) mg/L, P < 0.001] were significantly higher in the MPM group (**Table 3**).

All composite inflammatory markers were significantly elevated in the MPM group: NLR (2.87

Table 1. Comparison of baseline characteristics between the MPM and non-MPM groups

Parameter	Non-MPM Group (n=364)	MPM Group (n=158)	t	χ^2	P
Age (years)	61.23 ± 11.02	60.54 ± 10.67	0.660		0.509
Sex (Male/Female)				0.035	0.852
Male	218 (59.89%)	96 (60.76%)			
Female	146 (40.11%)	62 (39.24%)			
BMI (kg/m^2)	22.58 ± 3.42	22.31 ± 2.31	1.056		0.291
Smoking history, n (%)	126 (34.62%)	52 (32.91%)		0.142	0.706
Alcohol consumption, n (%)	108 (29.67%)	44 (27.85%)		0.177	0.674
Hypertension, n (%)	159 (43.68%)	71 (44.94%)		0.070	0.791
Diabetes mellitus, n (%)	73 (20.05%)	29 (18.35%)		0.203	0.653
Cardiac comorbidities, n (%)	55 (15.11%)	24 (15.19%)		0.001	0.981
Family history of gastric cancer, n (%)	46 (12.64%)	21 (13.29%)		0.042	0.837

MPM: Metachronous peritoneal metastasis; BMI: Body mass index.

Table 2. Comparison of clinicopathological features between the MPM and non-MPM groups

Parameter	Non-MPM Group (n=364)	MPM Group (n=158)	t	χ^2	P
Tumor size (cm)	4.12 ± 1.63	5.26 ± 1.99	6.324		< 0.001
Tumor location, n (%)				3.688	0.158
Proximal third	84 (23.08%)	45 (28.48%)			
Middle third	126 (34.62%)	42 (26.58%)			
Distal third	154 (42.31%)	71 (44.94%)			
Lauren classification, n (%)				12.779	0.002
Intestinal type	172 (47.25%)	57 (36.08%)			
Diffuse type	97 (26.65%)	67 (42.41%)			
Mixed type	95 (26.1%)	34 (21.52%)			
Differentiation grade, n (%)				12.247	0.002
Well	64 (17.58%)	15 (9.49%)			
Moderate	193 (53.02%)	74 (46.84%)			
Poor	107 (29.4%)	69 (43.67%)			
Depth of invasion (pT), n (%)				46.547	< 0.001
pT1	68 (18.68%)	8 (5.06%)			
pT2	138 (37.91%)	38 (24.05%)			
pT3	98 (26.92%)	49 (31.01%)			
pT4	60 (16.48%)	63 (39.87%)			
Lymph node metastasis, n (%)	168 (46.15%)	125 (79.11%)		48.607	< 0.001
Perineural invasion, n (%)	96 (26.37%)	61 (38.61%)		7.841	0.005
Lymphovascular invasion, n (%)	84 (23.08%)	57 (36.08%)		9.443	0.002

MPM: metachronous peritoneal metastases.

± 1.62 vs. 1.78 ± 0.86, P < 0.001), PLR (155.56 ± 72.43 vs. 126.34 ± 60.82, P < 0.001), SII (734.23 ± 372.47 vs. 456.78 ± 224.35, P < 0.001), and SIRI (1.41 ± 0.67 vs. 0.72 ± 0.35, P < 0.001) (**Figure 1**).

Serum tumor markers

Compared with the non-MPM group, the MPM group demonstrated significantly higher concentration of serum CEA (4.54 vs. 3.88, P= 0.002), CA19-9 (35.36 vs. 20.42, P < 0.001) and CA125 (38.67 vs. 16.83, P < 0.001) (**Table 4**).

Hepatic and renal function parameters

No significant differences were observed between the MPM and non-MPM groups in terms of hepatic or renal functional indices, including

Table 3. Comparison of peripheral blood cell counts and CRP between the MPM and non-MPM groups

Parameter	Non-MPM Group (n=364)	MPM Group (n=158)	t	P
Neutrophil count (×10^9/L)	3.72 ± 1.56	4.57 ± 2.13	4.535	< 0.001
Lymphocyte count (×10^9/L)	1.95 ± 0.81	1.73 ± 0.72	2.941	0.003
Platelet count (×10^9/L)	238.15 ± 75.24	255.42 ± 89.36	2.125	0.035
CRP (mg/L)	7.23 ± 3.57	10.46 ± 5.85	6.438	< 0.001

MPM: metachronous peritoneal metastases; CRP: C-reactive protein.

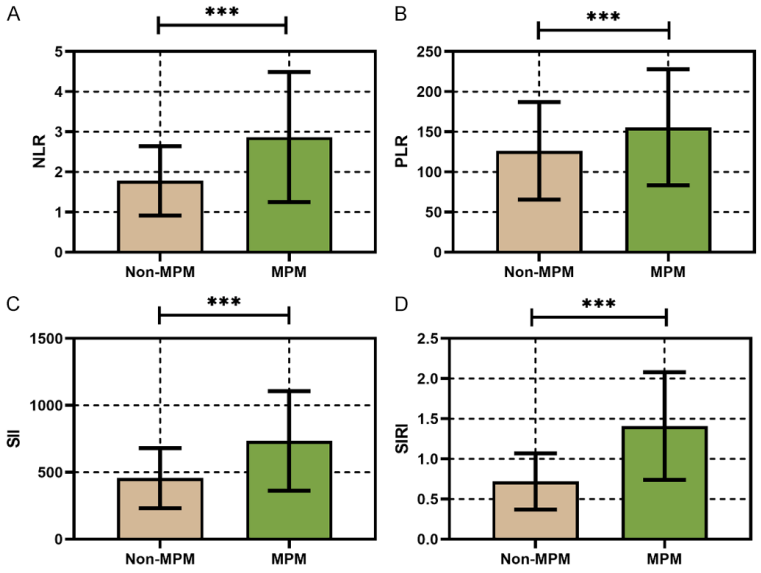

Figure 1. Comparison of integrated pro-inflammatory markers between the two groups. A. NLR; B. PLR; C. SII; D. SIRI. ***: P < 0.001. Notes: MPM: Metachronous peritoneal spread; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index; SIRI: Systemic inflammation response index.

ALT, AST, ALP, GGT, total bilirubin, albumin, BUN, and creatinine (all P > 0.05, **Table 5**).

Logistic regression analysis

Univariate logistic regression analysis shows that primary tumor size, histological differentiation grade, depth of invasion, lymph node metastasis, perineural invasion, lymphovascular invasion, neutrophil count, lymphocyte count, platelet count, CRP, NLR, PLR, SII, SIRI, CEA, CA19-9 and CA125 were associated with MPM (all P < 0.05). Lauren classification was not significantly associated with MPM in univariate analysis (P=0.390) (**Table 6**).

To reduce multicollinearity and select a smaller set of predictors, LASSO regression was performed (**Figure 2**). Nine variables had non-zero coefficients at the λ value that minimized the binomial deviance, as determined by ten-fold cross-validation. These nine indicators - tumor size, histological differentiation degree, depth of invasion, lymph node metastasis, NLR, PLR, CEA, CA19-9, and CA125 - were retained as candidate predictors for multivariate logistic regression model. Although differentiation grade was retained by LASSO, it did not achieve statistical significance in the multivariate analysis, likely due to collinearity with other retained pathological variables such as depth of invasion and lymph node metastasis.

Multivariate logistic regression identified that tumor size (OR=1.475, P < 0.001), depth of invasion (OR=2.602, P=0.014), lymph node metastasis (OR=3.536, P < 0.001), NLR (OR=2.457, P < 0.001), PLR (OR=1.009, P=0.003), CA19-9 (OR=1.079, P < 0.001), and CA125 (OR=1.156, P < 0.001) were all independent risk factors for MPM. However, histological differentiation (P=0.101) and CEA (P=0.135) were not independent predictors (**Table 7**).

ROC analysis

The discriminative ability of each predictor for MPM was evaluated using ROC curves. CA125 showed the highest prognostic performance (AUC=0.794; sensitivity 0.778, specificity 0.863), followed by CA19-9 (AUC=0.749), NLR (AUC=0.711), and tumor size (AUC=0.669). The optimal cutoff value for CA125 was 24.82 U/mL, determined by the Youden index, which maximizes the sum of sensitivity and specificity. This value is lower than the conventional upper normal limit (35 U/mL) because it is opti-

Table 4. Comparison of tumor marker levels between the MPM and non-MPM groups

Parameter	Non-MPM Group (n=364)	MPM Group (n=158)	t	P
CEA (ng/mL)	3.88 ± 1.84	4.54 ± 2.32	3.172	0.002
CA19-9 (U/mL)	20.42 ± 8.68	35.36 ± 18.75	9.585	< 0.001
CA125 (U/mL)	16.83 ± 7.52	38.67 ± 18.34	14.447	< 0.001

MPM: Metachronous peritoneal spread; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; CA125: Carbohydrate antigen 125.

Table 5. Comparison of hepatic and renal function parameters between the MPM and non-MPM groups

Parameter	Non-MPM Group (n=364)	MPM Group (n=158)	t	P
ALT (U/L)	23.86 ± 11.93	24.53 ± 12.47	0.583	0.560
AST (U/L)	25.47 ± 12.65	26.18 ± 13.22	0.584	0.560
ALP (U/L)	76.92 ± 24.87	78.56 ± 25.43	0.685	0.494
GGT (U/L)	32.85 ± 15.94	34.27 ± 16.56	0.928	0.354
Total bilirubin (μmol/L)	11.02 ± 4.65	11.34 ± 4.87	0.721	0.471
Albumin (g/L)	39.15 ± 5.12	38.42 ± 5.33	1.469	0.142
BUN (mmol/L)	5.13 ± 1.58	5.24 ± 1.67	0.692	0.489
Creatinine (μmol/L)	71.28 ± 15.93	72.35 ± 18.46	0.633	0.527

MPM: simultaneous peritoneal spread; ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; BUN: blood urea nitrogen.

Table 6. Univariate logistic regression analysis of risk factors for MPM in gastric cancer patients

Variable	Coefficient	Std_Error	Wald_Stat	*P*_Value	OR	OR_CI_Lower	OR_CI_Upper
Tumor size	0.369	0.059	6.276	< 0.001	1.446	1.292	1.627
Lauren classification	0.101	0.118	0.859	0.390	1.106	0.878	1.393
Differentiation grade	0.511	0.148	3.451	< 0.001	1.666	1.251	2.236
Depth of invasion	0.694	0.106	6.535	< 0.001	2.002	1.632	2.476
Lymph node metastasis	1.486	0.222	6.689	< 0.001	4.419	2.888	6.915
Perineural invasion	0.563	0.202	2.785	0.005	1.756	1.179	2.607
Lymphovascular invasion	0.632	0.207	3.050	0.002	1.881	1.251	2.822
Neutrophil count ($\times 10^9$/L)	0.277	0.057	4.870	< 0.001	1.319	1.182	1.478
Lymphocyte count ($\times 10^9$/L)	-0.359	0.124	2.900	0.004	0.698	0.546	0.888
Platelet count ($\times 10^9$/L)	0.003	0.001	2.256	0.024	1.003	1.000	1.005
CRP (mg/L)	0.160	0.023	6.836	< 0.001	1.174	1.122	1.230
NLR	0.777	0.096	8.131	< 0.001	2.176	1.815	2.642
PLR	0.007	0.002	4.551	< 0.001	1.007	1.004	1.010
SII	0.003	0.000	8.434	< 0.001	1.003	1.003	1.004
SIRI	2.820	0.277	10.177	< 0.001	16.772	9.997	29.681
CEA (ng/mL)	0.154	0.047	3.308	< 0.001	1.166	1.066	1.279
CA19-9 (U/mL)	0.124	0.012	10.715	< 0.001	1.132	1.108	1.159
CA125 (U/mL)	0.143	0.014	10.552	< 0.001	1.153	1.125	1.186

MPM: synchronous peritoneal dissemination; OR: odds ratio; CI: confidence interval; CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; CA125: carbohydrate antigen 125.

mized for predicting postoperative peritoneal metastasis rather than general screening. The AUC values for depth of invasion (dichotomized as pT3-pT4 vs. pT1-pT2), lymph node metastasis (positive vs. negative) and PLR were 0.678, 0.665, and 0.618, respectively (**Table 8**).

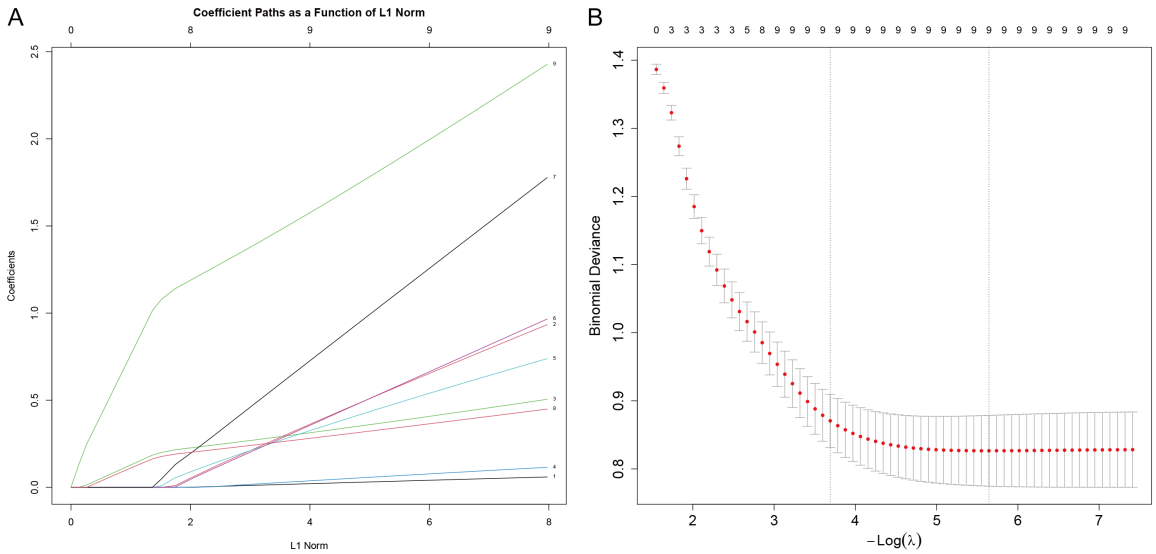

Figure 2. Feature extraction via LASSO modelling for MPM forecasting in gastric cancer. A. Profile trajectories of potential predictors across the L1 penalty range; B. Optimal λ selection through cross-validation techniques. Notes: LASSO: Least Absolute Shrinkage and Selection Operator; MPM: Metachronous peritoneal metastasis.

Table 7. Multivariate logistic regression analysis of independent risk factors for MPM

Variable	Coefficient	Std_Error	Wald_Stat	*P*_Value	OR	OR_CI_Lower	OR_CI_Upper
Tumor size	0.389	0.116	3.341	< 0.001	1.475	1.174	1.853
Differentiation grade	0.945	0.576	1.642	0.101	1.089	0.126	1.201
Depth of invasion	0.956	0.388	2.462	0.014	2.602	1.215	5.570
Lymph node metastasis	1.263	0.382	3.308	< 0.001	3.536	1.673	7.472
NLR	0.899	0.163	5.516	< 0.001	2.457	1.785	3.381
PLR	0.008	0.003	3.011	0.003	1.009	1.003	1.014
CEA (ng/mL)	0.130	0.087	1.496	0.135	1.138	0.961	1.349
CA19-9 (U/mL)	0.076	0.015	5.248	< 0.001	1.079	1.049	1.111
CA125 (U/mL)	0.145	0.018	8.155	< 0.001	1.156	1.117	1.197

MPM: multiple peritoneal dissemination; OR: odds ratio; CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; CA125: carbohydrate antigen 125.

Table 8. Predictive performance of individual predictors and their combined model for MPM

Parameters	Best_threshold	Sensitivities	Specificities	AUC	Youden_index	F1_score
Tumor size	5.675	0.437	0.849	0.669	0.286	0.489
Depth of invasion	/	0.709	0.566	0.678	0.275	0.523
Lymph node metastasis	/	0.791	0.538	0.665	0.329	0.554
NLR	2.685	0.570	0.835	0.711	0.405	0.584
PLR	134.51	0.633	0.571	0.618	0.204	0.483
CA19-9	32.690	0.589	0.920	0.749	0.509	0.664
CA125	24.820	0.778	0.863	0.794	0.641	0.743

MPM: synchronous peritoneal metastasis; AUC: area under the curve; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; CA125: carbohydrate antigen 125. Optimal cutoff values were determined using the Youden index. For depth of invasion, the threshold corresponds to dichotomization as pT3-pT4 (positive) vs. pT1-pT2 (negative); for lymph node metastasis, a positive result indicates the presence of pathological lymph node metastasis. The optimal cutoff value for CA125 was 24.82 U/mL, corresponding to the maximum Youden index (sensitivity + specificity - 1=0.641) on the ROC curve.

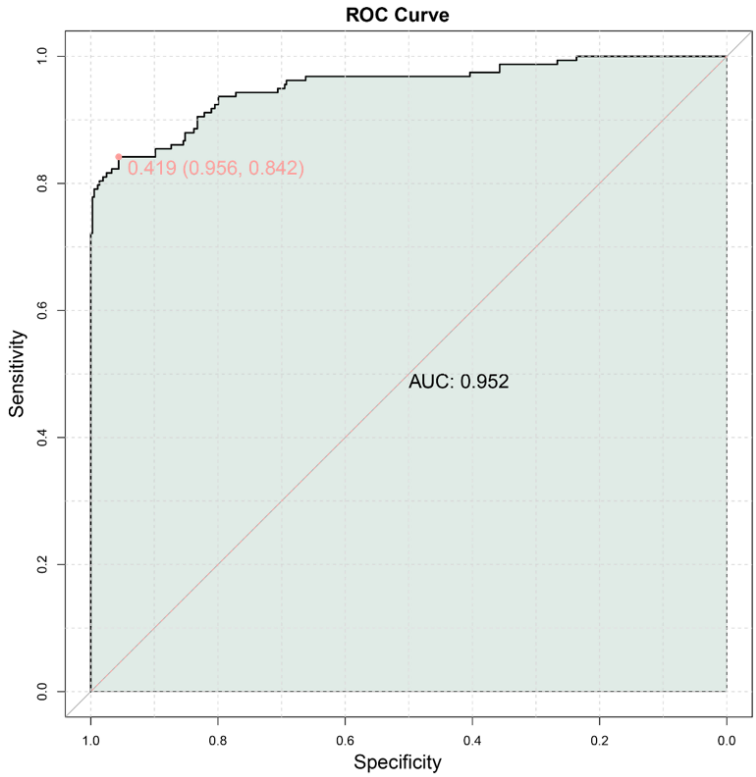

Figure 3. ROC curve analysis of the predictive model for MPM. Notes: ROC: Receiver Operating Characteristic; AUC: Area Under the Curve; MPM: metachronous peritoneal metastasis.

In addition, a combined prognostic model integrating tumor size, depth of invasion, lymph node metastasis, NLR, PLR, CA19-9 and CA125 showed excellent predictive performance, with an AUC of 0.952 (**Figure 3**).

External validation

An external validation cohort comprising 156 patients were established to verify the predictive performance of the predictive model. Baseline characteristics and primary predictive factors were compared between the MPM and non-MPM groups in the external validation cohort (**Table 9**). Each of the seven selected predictors - tumor size, depth of invasion, lymph node metastasis, NLR, PLR, CA19-9, and CA125 - remained significantly higher in the MPM group (all $P < 0.05$). The AUC of the integrated prognostic model in the validation set was 0.970 (95% CI: 0.913-0.989), demonstrating excellent discrimination (**Figure 4**).

Discussion

Patients who developed MPM after radical gastrectomy exhibited larger tumor sizes compared to those who did not. Larger tumor size is associated with increased risk of metastasis due to a greater potential for local invasion and dissemination. Additionally, the proportion of diffuse-type Lauren classification was higher in the MPM group, which suggests that this subtype is more prone to peritoneal spread. Diffuse-type gastric cancers are characterized by poor differentiation and aggressive behavior, which facilitates early and extensive metastasis [16-18]. Correspondingly, poorly differentiated tumors were more prevalent in the MPM group, indicating a higher propensity for invasive growth and metastasis [19]. Depth of tumor invasion was also greater in the MPM group, suggesting that advanced-stage tumors are more likely to result in MPM. Deeper tumor invasion increases the likelihood of direct extension into the peritoneum, facilitating metastatic spread [20-22]. Lymph node metastasis was more frequent in the MPM group, implying that lymphatic channels may serve as pathways for peritoneal dissemination. Perineural and lymphovascular invasions were more common in the MPM group, indicating that these pathways play important roles in facilitating metastasis. Collectively, these findings suggest that multiple factors contribute to the development of MPM.

Systemic inflammatory responses also play a critical role in cancer progression and metastasis. Patients in the MPM group had higher neutrophil counts and lower lymphocyte counts compared to those in the non-MPM group. Neutrophils can promote tumor growth and metastasis by releasing various pro-inflammatory cytokines and chemokines, which create a favorable microenvironment for tumor cells. Specifically, neutrophil-derived MMP-9 and VEGF promote peritoneal angiogenesis and mesothelial-to-mesenchymal transition (EMT), facilitating tumor cell implantation. Conversely, lymphocytes, particularly T cells, are essential for immune surveillance and tumor elimination.

Table 9. Comparison of baseline characteristics between the MPM and non-MPM groups in the validation cohort

Parameter	Non-MPM Group (n=110)	MPM Group (n=46)	t	χ^2	P
Age (years)	61.05 ± 11.28	60.22 ± 10.95	0.426		0.671
Sex (Male/Female)				0.097	0.756
Male	64 (58.18%)	28 (60.87%)			
Female	46 (41.82%)	18 (39.13%)			
BMI (kg/m^2)	22.63 ± 3.51	22.18 ± 2.48	0.916		0.362
Smoking history, n (%)	38 (34.55%)	15 (32.61%)		0.054	0.816
Alcohol consumption, n (%)	31 (28.18%)	12 (26.09%)		0.071	0.789
Hypertension, n (%)	48 (43.64%)	21 (45.65%)		0.053	0.817
Diabetes mellitus, n (%)	22 (20%)	8 (17.39%)		0.142	0.706
Cardiac comorbidities, n (%)	16 (14.55%)	7 (15.22%)		0.012	0.914
Family history of gastric cancer, n (%)	13 (11.82%)	6 (13.04%)		0.046	0.831
Tumor size (cm)	4.18 ± 1.72	5.41 ± 2.11	3.800		< 0.001
Depth of invasion, n (%)				14.231	0.003
pT1	20 (18.18%)	2 (4.35%)			
pT2	42 (38.18%)	11 (23.91%)			
pT3	29 (26.36%)	14 (30.43%)			
pT4	19 (17.27%)	19 (41.3%)			
Lymph node metastasis, n (%)	52 (47.27%)	37 (80.43%)		14.558	< 0.001
NLR	1.85 ± 0.92	3.02 ± 1.78	4.221		< 0.001
PLR	129.63 ± 63.49	162.35 ± 78.52	2.732		0.007
CA19-9 (U/mL)	21.34 ± 9.44	37.26 ± 20.18	5.120		< 0.001
CA125 (U/mL)	17.51 ± 7.26	40.13 ± 17.64	8.407		< 0.001

MPM: multiple peritoneal metastases; BMI: body mass index; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; CA19-9: carbohydrate antigen 19-9; CA125: carbohydrate antigen 125.

Therefore, an elevated NLR indicates an immune imbalance that favors tumor progression [23, 24].

Platelet counts were also higher in the MPM group. Platelets may promote metastasis by supporting tumor cell adhesion and dissemination, partly through the release of TGF-β and platelet-derived growth factor (PDGF), which enhance EMT in gastric cancer cells. Elevated CRP in the MPM group suggests widespread inflammation that may promote the growth and metastasis of tumors via several routes, such as new blood vessel formation and suppression of the anti-cancer immune response. CRP can also activate the complement system and interact with Fc receptors on immune cells, creating a pro-metastatic peritoneal microenvironment. Furthermore, composite inflammatory markers such as NLR, PLR, SII, and SIRI were all significantly elevated in the MPM group, reinforcing the pivotal role of systemic inflammation in driving MPM. Such biomarkers mirror the intricate crosstalk between tumor cells and host immune mechanisms [25-27].

Serum tumor markers were significantly elevated in the MPM group. CEA is a glycoprotein involved in cellular attachment and has been associated with multiple malignancies, such as gastric cancer. CA19-9 is a sialylated Lewis antigen expressed on epithelial surfaces, commonly used as a marker for pancreatic and biliary tract cancers, but it also correlates with gastric cancer progression. CA125, primarily used as a marker for ovarian cancer, has been reported to be elevated in several other malignancies [28, 29]. These markers likely reflect tumor burden and the extent of peritoneal involvement. Elevated levels of these markers may indicate increased tumor shedding and secretion of these antigens into the bloodstream, providing a basis for their use in predicting MPM [30, 31]. The optimal CA125 cutoff (24.82 U/mL) determined by the Youden index is lower than the conventional upper nor-

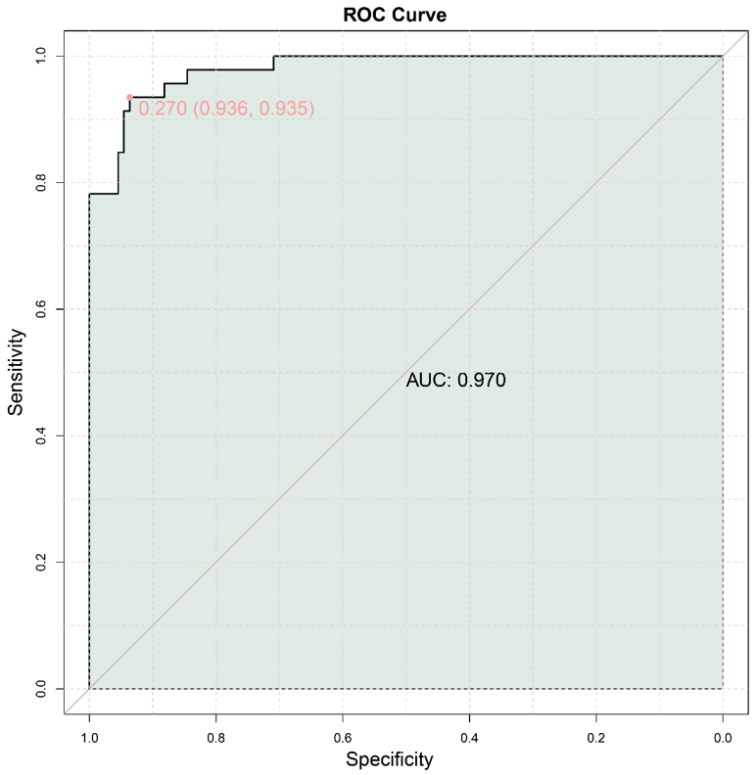

Figure 4. ROC curve analysis of the predictive model for MPM in the external validation cohort. Notes: ROC: Receiver Operating Characteristic; AUC: Area Under the Curve.

mal limit (35 U/mL). This may be because a risk prediction model for metastasis requires higher sensitivity, even at the cost of a lower threshold; this cutoff corresponds to the upper-left region of the ROC curve, where sensitivity and specificity are optimally balanced.

Multivariate logistic regression analysis identified tumor size, depth of invasion, lymph node metastasis, NLR, PLR, CA19-9, and CA125 as independent risk factors for MPM. These findings underscore the importance of integrating both tumor characteristics and systemic inflammatory markers for accurate risk stratification. Tumor size and depth of invasion directly correlate with the likelihood of local invasion and subsequent metastasis. Lymph node metastasis serves as a surrogate for tumor aggressiveness and the extent of disease spread. Systemic inflammatory markers provide insight into the host immune response, which plays a critical role in modulating metastatic potential. Serum tumor markers, including CA19-9 and CA125, provide additional information on tumor biology and burden, thereby enhancing the predictive power of the prognostic model.

The combined predictive model outperformed any individual factor in distinguishing MPM. The predictive model achieved an AUC of 0.952 in the derivation cohort and 0.970 in the external validation set. By comparison, a recently reported model for peritoneal metastasis in gastric cancer by Zhong et al. [32], which incorporated tumor-stroma ratio, CA125, CA724, and Borrmann type, yielded AUCs of 0.85 in the training cohort, 0.73 in external validation, and only 0.72 for predicting metachronous peritoneal metastasis. The superior discriminative performance of our model, particularly in the metachronous setting and external validation, may be attributed to the integration of multiple inflammatory markers with both pathological factors and serum tumor markers, as well as its exclusive focus on metachronous peritoneal metastasis after radical gastrectomy. The robustness of the model in distinguishing patients with and without MPM supports its utility in guiding therapeutic decisions, such as determining the need for intensified imaging, surgical exploration, or other preventive interventions. Ultimately, this approach facilitates individualized therapy via tailoring interventions to patient-specific risk profiles, potentially improving outcomes and survival for gastric cancer patients [33, 34].

Despite these promising findings, several limitations of this work must be acknowledged. The retrospective design may have introduced potential biases, including selection bias and residual confounding, which may affect the generalizability of the results. Serum CA125 levels can be elevated in benign conditions such as ascites, liver disease, or gynecological disorders. In our cohort, patients with active liver disease, pelvic inflammatory disease, or gynecologic malignancies were excluded at enrollment; also, the prevalence of ascites did

not differ significantly between the MPM and non-MPM groups (data not shown). Nevertheless, residual confounding cannot be completely excluded. Prospective investigations employing larger cohorts are warranted to validate these observations and to evaluate the long-term clinical implications of the predictive model. While our model integrates both tumor characteristics and systemic inflammatory markers, it does not account for other potential factors, such as genetic mutations and epigenetic alterations, which may also influence MPM. Future research should aim to incorporate these additional factors to enhance the predictive accuracy and clinical utility of the model. Through systematic evaluation and refinement of current predictive strategies, it is possible to advance personalized treatment for gastric cancer patients at high risk for MPM. Future studies should focus on identifying novel biomarkers and refining existing models to optimize personalized treatment strategies and improve patient care.

Conclusion

In this study, we developed a prognostic model for MPM in gastric cancer by integrating preoperative peripheral blood inflammatory markers with postoperative histopathological features. The combined model demonstrated superior predictive performance compared with individual factors, allowing timely identification of high-risk patients who may benefit from enhanced surveillance or tailored therapeutic strategies, therefore improving treatment outcome.

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Disclosure of conflict of interest

None.

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