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Prognostic value of neutrophil-to-lymphocyte ratio and CA 19–9 in overall survival of patients with peritoneal carcinomatosis of colorectal cancer undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

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Abstract

Background The neutrophil-to-lymphocyte ratio and other inflammatory factors have been used as prognostic indicators in several cancers. This study aims to evaluate the prognostic value of inflammatory factors and tumor markers in patients with peritoneal metastasis of colorectal cancer (CRC) after undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

Methods We collected data from 116 patients who underwent CRS and HIPEC for peritoneal carcinomatosis of colorectal origin between August 2015 and December 2018 at Hubei Cancer Hospital. Kaplan–Meier analysis was used to calculate overall survival (OS) and Progression-Free-Survival (PFS). Univariate and multivariate Cox regression analyses were conducted to evaluate the influence of inflammatory factors and tumor markers on OS and PFS.

Results The median OS was 52.63 months (95% CI 46.02–59.25), and the median PFS was 27.03 months(95% CI 23.35–30.72). Significant differences in OS and PFS were observed between patients with NLR < 2.33 and those with NLR ≥ 2.33(65.38 vs. 44.20, $p = 0.005$, 35.49 vs. 21.90, $p < 0.001$). Patients with CA 19–9 > 36.65 also showed significantly poorer OS and PFS compared to patients with CA 19–9 ≤ 36.65(34.86 vs. 65.68, $p < 0.001$, 17.80 vs. 34.00, $p < 0.001$). Multivariate analyses suggested that NLR < 2.33, PCI < 10, and CA 19–9 ≤ 36.65 were independent predictive factors for better OS and PFS.

Conclusions Preoperative NLR and CA 19–9 may serve as prognostic markers in patients with peritoneal metastasis of CRC undergoing CRS and HIPEC. These markers may have potential value as selection tools for determining the suitability for CRS + HIPEC in these patients.

Keywords Peritoneal carcinomatosis, Colorectal cancer, CRS, HIPEC, PCI

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Introduction

The peritoneum is a common site of metastasis in patients with colorectal carcinoma (CRC) and appendiceal adenocarcinoma (AC). Traditionally, peritoneal carcinomatosis (PC) is associated with a relatively poor prognosis among all metastatic sites, with a median survival of less than six months [1]. Metachronous peritoneal metastases are observed in 4% to 19% of cases, with synchronous disease occurring in 5% to 7% of CRC cases [2, 3]. In recent years, with advances in chemotherapy drugs and biological agents, the median survival of patients with PC has improved to 16 months [1]. However, this outcome is still the worst among all sites of metastases.

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have recently provided the highest chance of long-term survival for carefully selected patients with peritoneal metastatic disease of appendiceal and colorectal origin, with acceptable morbidity and mortality [4, 5]. Numerous studies have suggested that CRS and HIPEC can be effective therapies for PC of appendiceal and colorectal origin, resulting in a median overall survival of 22–63 months and a 19% to 51% rate of 5-year survival in selected patients [6–11]. Thus, it is necessary to optimize patient selection for those most likely to benefit from CRS and HIPEC treatments.

Previous studies have indicated that many factors may affect the prognosis of patients with PC of appendiceal and colorectal origin, such as tumor size, grade, and lymph node (LN)involvement [12, 13]. The peritoneal cancer index (PCI) and completeness of cytoreduction (CC) score have also been shown to be important factors for predicting treatment outcomes and disease progression for patients with PC of CRC [14, 15]. However, solely relying on PCI to decide whether to undergo CRS ± HIPEC treatment may not be the most accurate approach. Therefore, there is a need to explore new prognostic factors that can guide personalized treatment decisions, considering the risk–benefit ratio for patients with CRC-related PC.

In recent years, an increasing number of studies have reported the prognostic significance of inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) in solid tumors [16–18]. These inflammation-related markers are simple yet effective laboratory parameters that can be easily obtained through routine blood tests. This idea has led many researchers to explore the most cost-effective prognostic biomarkers. While some studies have examined the prognostic value of these inflammatory markers in patients with CRC after surgery, few studies have focused on metastatic CRC [19, 20]. Notably, previous reports have confirmed that the NLR and PLR serve as independent prognostic markers for postoperative patients with CRC and those with advanced CRC undergoing chemotherapy [21]. Regrettably, research on these indicators in peritoneal metastasis of CRC remains scarce. Inflammatory markers were regarded as host-related factors owing to their association with delayed wound healing, immune-related dysfunction, infection, and postoperative complications, all of which can subsequently affect the survival time of patients with cancer. In addition, inflammation has been linked to tumorigenesis, with some studies identifying the molecular pathways connecting inflammation and tumor development. The PCI is used to assess abdominal tumor burden in patients with peritoneal metastasis. We hypothesize that the inflammatory immune status of patients might affect their tumor burden, thereby affecting their prognosis.

To test this hypothesis, we investigated the prognostic impact of inflammatory markers. In addition, we attempted to integrate the PCI with an inflammation biomarker-based immunoscore to investigate its predictive ability for clinical outcomes in patients with PC of CRC.

Materials and methods

Study design and patients

This was a single-center retrospective study. Data were prospectively collected from the peritoneal disease database and analyzed retrospectively. A waiver of the Health Insurance Portability and Accountability Act was obtained for the study. All methods were performed in accordance with the relevant guidelines and regulations. The informed consent of this study has been obtained from patients or their legal guardians. Specifically, we clarify that this study included a patient under the age of 16, and we had obtained informed consent from the patient's parents before conducting the retrospective analysis. The study cohort comprised patients who underwent cytoreductive surgery and HIPEC for PC originating from appendiceal cancer and CRC at the Department of Gastrointestinal Surgery of Hubei Cancer Hospital from August 2015 to December 2018. Inclusion criteria were the following: (1) histopathologic or cytologic confirmation of PC; (2) Patients who underwent CRS + HIPEC; (3) Availability of complete preoperative hematological and follow-up data; (4) absence of hematogenous metastasis except liver metastasis of less than 3 and absence of remote lymph node metastasis. Exclusion criteria included: (1) extra-abdominal disease, involvement of retroperitoneal lymph nodes,; (2) multiple hepatic metastasis; (3) Patients with other concurrent malignancies; (4) Missing follow-up data. Clinical variables were recorded, including patient age, sex, primary

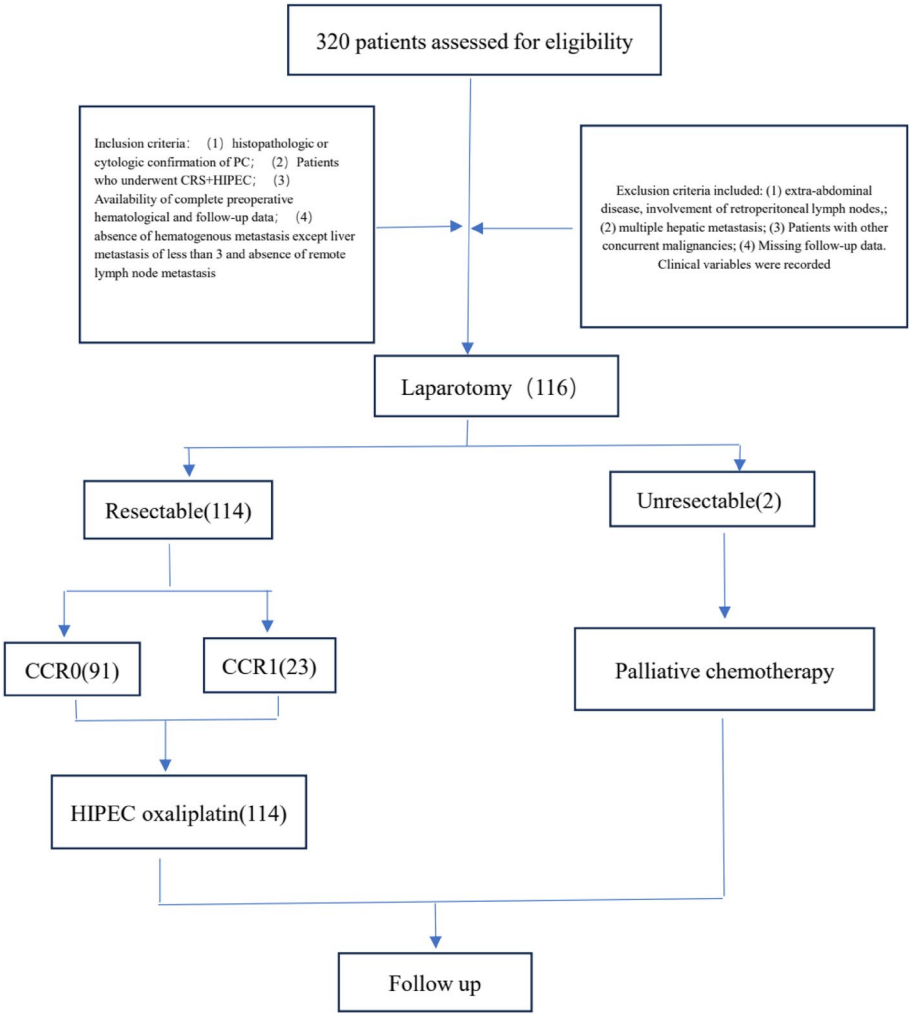

Fig. 1 Schematic of study design

tumor location, histopathological details, tumor differentiation, PCI, CC score, number of HIPEC sessions, and number of positive lymph nodes.

The extent of PC was assessed in accordance with the PCI, adhering to the established guidelines [22] during the surgery. After cytoreduction, the CC score was used, with the following classifications: CC-0, no visible residual disease; CC-1, residual tumor nodules up to 2.5 mm; CC-2, residual nodules up to 2.5 cm; and CC-3, residual nodules >2.5 cm [23]. Typically, HIPEC was administered 1–3 times. All visible disease was removed through resection of affected organs, resection of carcinomatosis deposits, fulguration of smaller carcinomatosis nodules, and omentectomy to achieve a complete cytoreduction score of 0 (CCR0) or 1 (CCR1, all remaining disease is less than 2.5 mm in size). The choice of intraperitoneal chemotherapy involved either a single instance of oxaliplatin (400 mg/m2) or multiple administrations of oxaliplatin (200 mg/m2), based on the clinician's preference, at 42–43 °C for 90 min. The details of schematic of study design are presented in Fig. 1. The survival outcomes were defined as follows. Overall survival (OS) was defined as the duration from the date of the operation to the date of death for many cause, whereas PFS was determined as the time interval from the date of diagnosis to the date of clinically proven disease progression.

Data collection

Inflammatory factors and tumor markers before the surgery were collected, including neutrophils (N), lymphocytes (L), platelets(P), and monocytes (M), as well as CEA and CA 19–9. From these data, various ratios were calculated, namely the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR),

monocyte-to-lymphocyte ratio (MLR), and (lymphocyte-to-monocyte ratio (LMR).

Statistics

Continuous variables were expressed as median and range, and categorical variables were summarized as total number and percentage relative to the entire group. The association between continuous variables and primary tumor sidedness was assessed using non-parametric tests (Wilcoxon rank–sum), whereas categorical variables were analyzed using the chi-square or Fisher's exact test, as appropriate. The cut-off value for each indicator was determined through ROC curve analysis. OS and PFS were estimated using the Kaplan–Meier method and compared using the log-rank test. Univariate Cox proportional hazards regression was utilized to evaluate associations between individual factors and OS. A multivariate analysis was performed to identify predictors of survival by constructing stepwise Cox proportional hazard regression models incorporating the variables selected based on the results of the univariate analysis. *P*-values less than 0.05 were considered statistically significant. Statistical analyses were conducted using R software and SPSS software version 24.0 (IBM Corporation, Armonk, NY, USA).

Results

Patient characteristics

A total of 116 patients who underwent CRS or HIPEC for CRC were enrolled in the study. The patient flow diagram is shown in Fig. 1. Of these patients, 35 (30.17%) had primary tumors on the right side, 42 (36.21%) had left-sided primary tumors, and 39 (33.62%) had primary tumors originating from the appendix. The median age was 51 (range, 13–74) years for patients with right-sided tumors, 51 (range, 28–80) years for patients with left-sided tumors, and 54 (range, 33–75) years for patients with primary tumors originating from the appendix, with no significant differences observed between the groups in terms of age. A total of 32 (82.05%) patients with primary tumors originating from the appendix had mucinous adenocarcinoma histology, whereas most of the patients with right and left primary tumors were more likely to have non-mucinous adenocarcinoma histology. This difference was statistically significant ($p < 0.05$). In addition, among patients with primary tumors originating from the appendix, 21 (53.84%) had poorly differentiated tumors, while more than half of the patients with right and left primary tumors had well to moderately differentiated tumors. This difference was also statistically significant ($p < 0.05$). The majority (> 50%) of patients had synchronous peritoneal metastasis among the three groups. CC-0 was achieved in 78.45% of all patients, and CC-1 cytoreduction was achieved in 19.83% of patients. Only two (1.72%) patients had residual gross disease (CC-2). With regard to HIPEC, a total of 73 (62.93%) patients underwent it once, with only a few undergoing multiple HIPEC sessions. The majority (92.24%) of the patients did not receive chemotherapy before surgery. A total of 49 (42.24%) patients underwent more than three rounds of postoperative chemotherapy. A total of 14 (12.06%) patients developed postoperative severe complications. There was one case of postoperative massive hemorrhage, one case of septic shock, four cases of enteric fistula, three cases of intra-abdominal infection, two cases of urinary leakage, and two cases of wound infection. The two patients who suffered from postoperative massive hemorrhage and septic shock both died as a result, while the remaining patients with complications achieved complete recovery following secondary surgical intervention or appropriate symptomatic management. The baseline clinical data are shown in Table 1.

ROC curve analysis of inflammatory indices

Optimal cut-off values for NLR, PLR, MLR, CEA, and CA 19–9 were determined using an ROC curve analysis with the Youden index. The results showed that patients with NLR ≥ 2.33, PLR > 156, MLR > 0.38, CEA > 9.5, and CA199 > 36.65 were considered high-risk groups based on the derived cut-off values (Fig. 2A).

Overall survival

The median OS for all patients was 52.63 months (95% CI 46.02–59.25), and the median PFS was 27.03 months (95% CI 23.35–30.72). Among all the clinicopathological factors analyzed, NLR, MLR, PCI, CA 19–9, and CC score were found to have a significant prognostic impact on both OS and PFS. Patients with a PCI < 10 showed significantly longer median survival compared to patients with PCI ≥ 10. In addition, significant differences in both OS and PFS were observed between patients with NLR < 2.33 and those with NLR ≥ 2.33 (OS: 65.38 vs. 44.20, $p = 0.005$, PFS: 35.49 vs. 21.90, $p < 0.001$; Fig. 3A and C). The median OS for patients with MLR > 0.38 was 41.74 months and that for patients with MLR ≤ 0.38 was 58.14 months. There was a statistically significant difference in OS between these two groups ($p = 0.024$), although no difference in PFS was observed. Elevated CEA and CA 19 9 levels were also linked to a significant impact on OS, but CEA levels had no impact on PFS. Patients with CEA level > 9.5 had a significantly poorer OS compared to patients with CEA level ≤ 9.5 (43.40 vs 58.56, $p = 0.031$). Patients with CA 19–9 > 36.65 also had significantly poorer OS and PFS compared to patients with CA 19–9 ≤ 36.65 (OS: 34.86 vs.65.68, $p < 0.001$, PFS: 17.80 vs. 34.00, $p < 0.001$; Fig. 3B and D). Except for the

Table 1 Characteristics of patients ($n = 116$)

Variable	N	Non-appendix (77)	Appendix(39)	*P*-value
Age, years [median (range)]	116	51(13–80)	54(33–75)	0.196
Gender				0.476
Female sex	62	43	19(48%)	
Male	54	34	20	
Histopathology				**< 0.001**
Mucinous adenocarcinoma	52	20	32	
Non- mucinous adenocarcinoma	64	57	7	
Differentiation				**0.002**
Well	49	36	13	
moderate	37	32	5	
poor	30	9	21	
Synchronous diagnosis of PC	76	47	29	0.142
Lymph node status				**0.004**
N0	60	36	24	
N1	18	15	3	
N2	27	23	4	
Nx	11	3	8	
NLR				**0.002**
< 2.33	43	25	18	
≥ 2.33	73	52	21	
PLR				0.162
> 156	76	53	23	
≤ 156	40	24	16	
MLR				0.216
> 0.38	40	29	11	
≤ 0.38	76	48	28	
CEA				0.135
> 9.5	50	31	19	
≤ 9.5	66	46	20	
CA 19–9				0.312
> 36.65	51	30	21	
≤ 36.65	65	47	18	
PCI in surgery				0.232
< 10	65	46	19	
≥ 10	51	31	20	
CC score				0.873
0	91	61	30	
≥ 1	25	16	9	
HIPEC times				0.317
1	73	46	27	
> 1	43	31	12	
Preoperative chemotherapy				0.037
Yes	9	9	0	
No	107	68	39	
Post-CRS/HIPEC chemotherapy				**< 0.001**
0	35	14	21	
1–3 times	14	11	3	
≥ 3	56	46	10	
Missing data	11	6	5	

Table 1 (continued)

Variable	N	Non-appendix (77)	Appendix(39)	*P*-value
Complications				
Postoperative massive hemorrhage	1	1	0	
Septic shock	1	1	0	
Intestinal fistula	4	4	0	
Intra-abdominal infection	3	3	0	
Urinary leakage	2	2	0	
Wound infection	3	3	0	

above indicators, the remaining indicators had no impact on survival. For patients with primary tumors originating from the appendix, the median OS was 42.66 months (95% CI 33.19–52.14), whereas those with primary tumors not originating from the appendix had a median OS of 57.17 months (95% CI 48.87–65.49). The difference between the groups was not statistically significant ($p=$ 0.062). Moreover, there were no differences in survival based on the presence of mucinous adenocarcinoma and non-mucinous adenocarcinoma (57.09 vs. 47.68 months, $p=$ 0.225). Patients undergoing CC-0 surgery showed better survival compared to those undergoing CC-1 or CC-2 procedures (55.83 vs. 34.58 months, $p=$ 0.001). Interestingly, no significant difference in survival was found between patients undergoing one HIPEC session versus multiple sessions (56.00 vs. 45.80, $p=$ 0.214). Further details are shown in Table 2.

To further predict the survival of patients with PC of CRC undergoing CRS ± HIPEC treatment, all the significant independent risk prognostic factors were integrated into anomogram. The nomogram was developed based on the current cohort without external validation. Its clinical applicability should be interpreted with caution until further validated in independent populations. This nomogram was developed to predict the 2-, 5-, and 10-year survival probabilities based on a multivariate Cox regression model analysis (Fig. 2B).

Univariate and multivariate analysis for OS and PFS by Cox regression model

In univariate analyses, age, gender, and PLR did not show a significant correlation with OS and PFS. However, a more favorable trend in terms of OS and PFS was observed for patients with primary tumors originating from the appendix. Factors such as CC0 status, PCI < 10, low NLR, low MLR, low CEA, and low CA 19–9 were associated with improved OS; however, there was no observed relationship between MLR, CEA, and PFS (Table 3). When significant factors in the univariate analysis were included in an adjusted analysis using a multivariate Cox regression model, we found that low NLR, low CA199 and PCI < 10 were independent factors associated with better OS and PFS. (Table 4).

Discussion

PC originating from CRC was once considered a stage IV condition with limited survival prospects, often associated with a very poor prognosis compared to metastases at other sites. In recent years, CRS with or without HIPEC has emerged as a promising approach for achieving long-term survival among patients with peritoneal metastatic disease. Nonetheless, the outcomes of recent randomized trials, such as Prodige-7, have failed to demonstrate survival benefits from CRS with or without HIPEC [5], necessitating a careful selection of the patient population that will benefit from these treatments [24]. Identifying prognostic factors is important for refining patient selection. For example, primary tumor location is now considered a stratification factor for survival [25]. In addition, PC arising from appendiceal cancer is known to differ from CRC in terms of distinct clinical and biological behavior [26]. However, there is a controversy in the literature regarding the impact of tumor location on prognosis.

Both PCI and CC scores have been shown to influence survival following CRS and HIPEC in multiple studies [27, 28]. Among them, PCI is by far the most important prognostic factor [28]. Researchers often use the PCI score to decide whether CRS and HIPEC are appropriate treatment options. However, these scores require intraoperative exploration or preoperative imaging examinations, and sometimes, the scores obtained through preoperative imaging examinations may not be consistent with intraoperative scores, thus negating the potential benefits of PCI score as a preoperative basis for selecting CRS + HIPEC treatment.

Serological markers possess the advantages of convenience and cost-effectiveness. However, many uncertainties

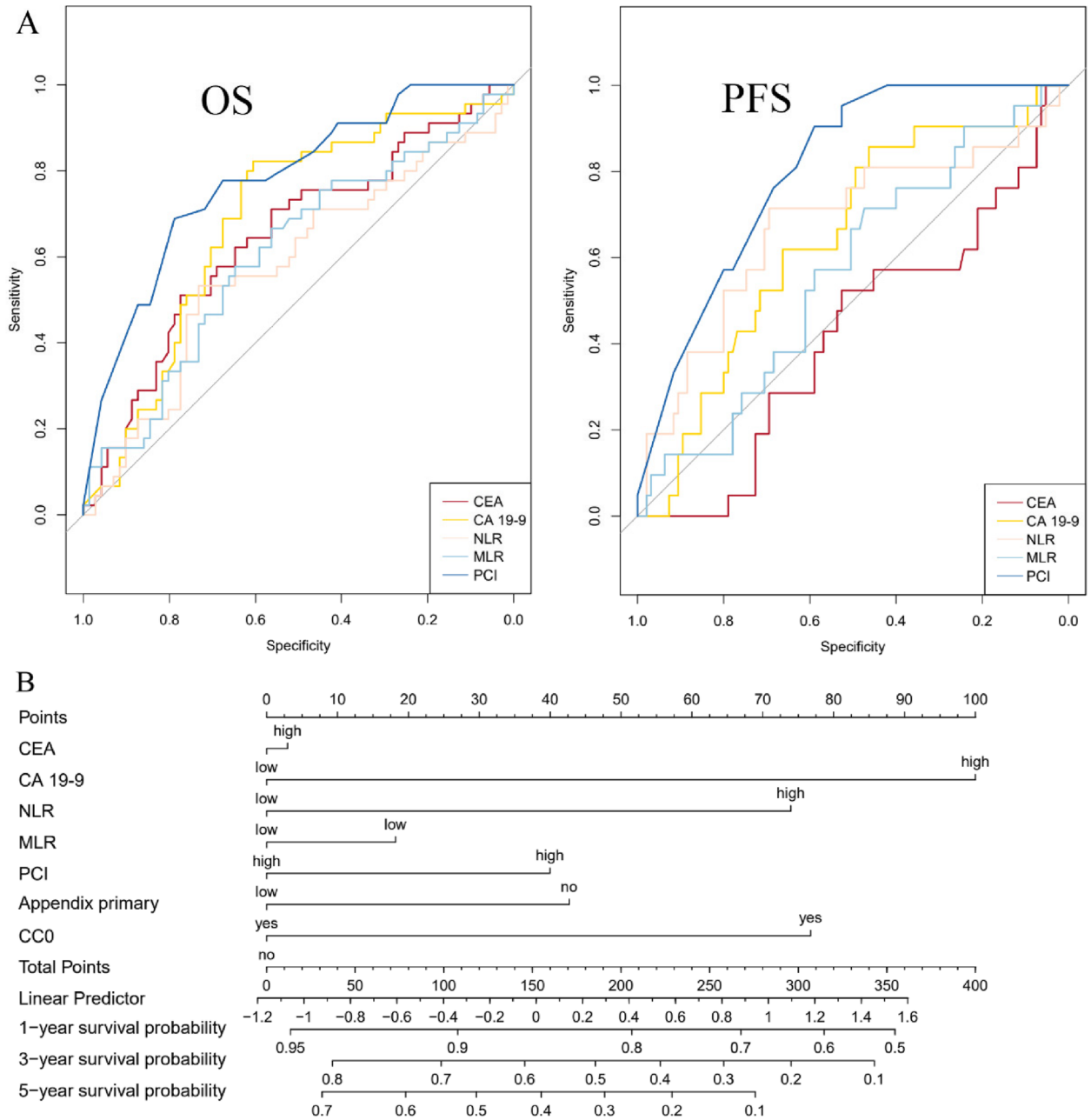

Fig. 2 **A** ROC curves of the probability of neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, peritoneal cancer index, carcinoembryonic antigen, and CA 19–9 on overall survival and progression-free survival; **B** Nomogram to predict 1-, 3-, and 5-year overall survival and using the training set

persist regarding their use in predicting the prognosis of patients with PC of CRC. In this study, we evaluated the prognostic impact of serological markers based on our center's experience. Furthermore, we compared the impact of serological markers with PCI scores on the prognosis of patients with PC of colorectal cancer.

The relationship between inflammation and tumors has always been a captivating research area, and previous studies have shown that systemic inflammatory response plays a crucial role in the development and metastasis of tumors [29]. Owing to the crucial role of neutrophils, lymphocytes, monocytes, and platelets in tumor induced systemic inflammatory response, these markers have the potential to reflect the broader systemic inflammatory response in patients with cancer [30]. NLR, PLR, and MLR are the most commonly used predictors of all

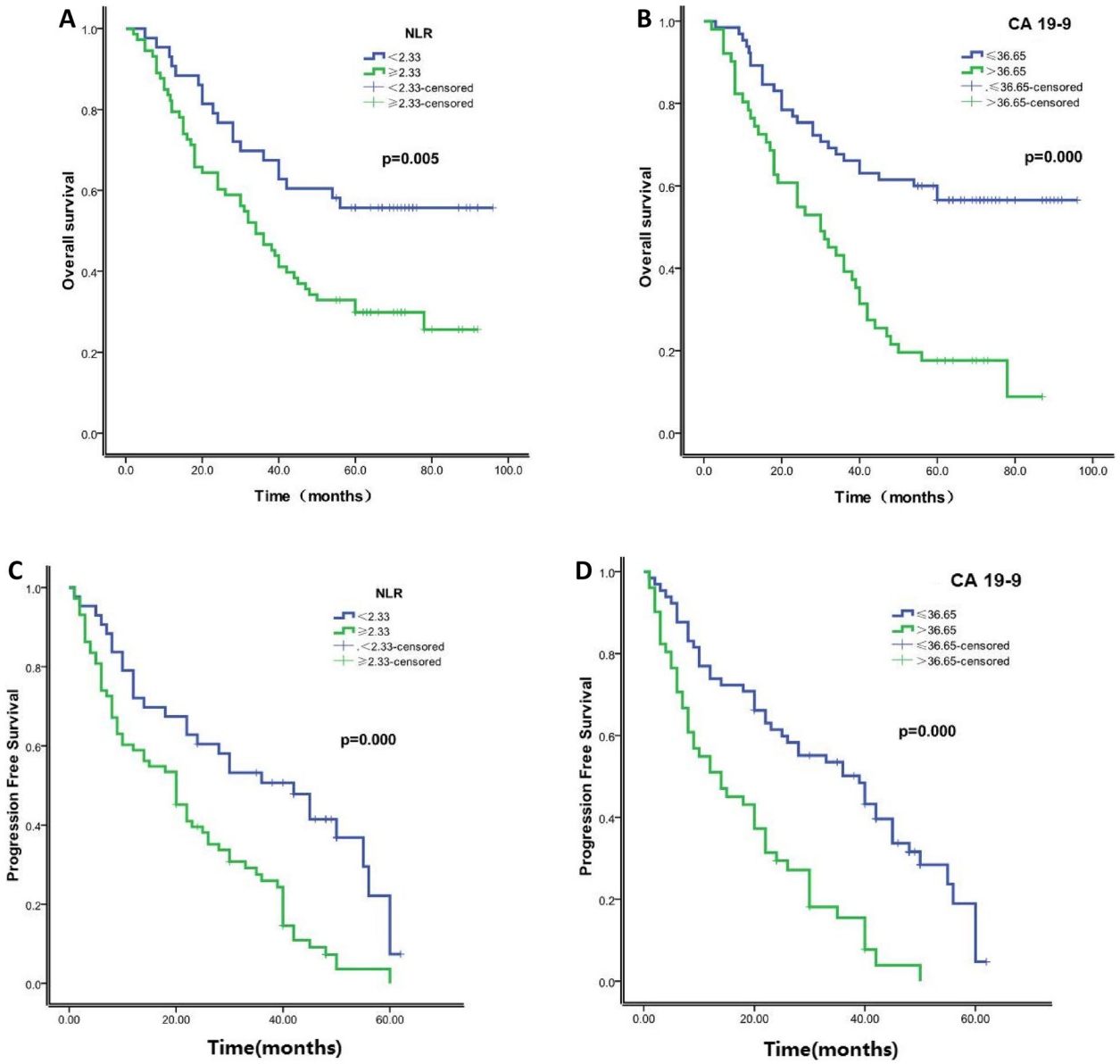

Fig. 3 Overall survival and progression-free survival stratified by neutrophil-to-lymphocyte ratio (NLR) and CA 19–9 (**A**) overall survival curve stratified by NLR; (**B**) overall survival curve stratified by CA 19–9; (**C**) progression-free survival stratified by NLR; and (**D**) progression-free survival stratified by CA 19–9

systemic inflammatory indicators. These indicators have been reported in many tumors, including lung cancer, cervical cancer, breast cancer, and CRC [31–34]. Previous studies have identified correlations between NLR, PLR, and factors such as tumor size, staging, and lymph node metastasis, establishing their utility for early diagnosis and prognosis evaluation of patients with CRC [35]. Additionally, MLR levels in postoperative peripheral blood have emerged as independent prognostic factors in conditions such as colon cancer [36] and other tumor types. These indicators reflect the inflammatory response during the cancer process and the interaction between cancer cells and immune system components [29]. However, there has been little research on the role of these inflammatory factors in patients with peritoneal metastasis of CRC.

For many years, PC was synonymous with an incurable disease. However, advances in CRS and HIPEC changed the prognosis of PC, with the median survival extending from 13 to 63 months [37]. Our study contributes to this

Table 2 Analysis of overall survival in patients by kaplan–Meier method

Variables	Median value	OS		PFS	
		Median OS (months)	Log-rank *p*	Median PFS (months)	Log-rank *p*
Appendix primary	Yes	42.66	0.062	22.43	0.058
	No	57.17		29.29	
CC score	0	55.83	**0.001**	29.12	**0.023**
	≥ 1	34.58		19.40	
Mucinous histology	Yes	57.09	0.225	27.58	0.908
	No	47.68		26.76	
HIPEC times	1	56.00	0.214	28.34	0.482
	> 1	45.80		24.87	
PCI	< 10	62.97	**< 0.001**	33.08	**< 0.001**
	≥ 10	38.87		19.85	
NLR	< 2.33	65.38	**0.005**	35.49	**< 0.001**
	≥ 2.33	44.20		21.90	
PLR	> 156	50.04	0.634	26.10	0.424
	≤ 156	54.96		28.64	
MLR	> 0.38	41.74	**0.024**	23.11	0.148
	≤ 0.38	58.144		29.08	
CEA	> 9.5	43.40	**0.031**	23.83	0.154
	≤ 9.5	58.56		29.2	
CA 19–9	> 36.65	34.86	**< 0.001**	17.80	**< 0.001**
	≤ 36.65	65.68		34.00	

improvement by showing a median OS of 52.63 months and a median PFS of 27.03 months. Importantly, both the PCI score and CC score continue to be prognostic indicators for patients with peritoneal metastasis of CRC, which is consistent with previous studies.

In addition to these traditional discoveries, our study found that some inflammatory markers and tumor markers are also associated with the prognosis of patients with peritoneal metastatic cancer. Notably, Kaplan–Meier survival analysis underscored the significance of NLR, PCI, and CA 19–9 for both OS and PFS. Meanwhile, MLR and CEA only showed an association with OS. However, PLR did not show any significant association with survival. The results of univariate Cox regression analysis were consistent with these findings. In the multivariate analysis, NLR, PCI, and CA 19–9 emerged as significant prognostic markers in terms of both OS and PFS. Similar observations have been reported by Ihemelandu et al., where PLR and CA 19–9 were identified as significant prognostic indicators of survival [38]. Rangarajan et al. found that patients with high NLR have poorer survival and proposed NLR as a reliable tool for predicting the outcomes of CRS and HIPEC for pseudomxyoma peritonei of appendiceal origin [36]. Another study indicated that preoperative PLR and CEA are associated with OS in patients with PC or CRC undergoing CRS and HIPEC [39]. Zager et al. reported that patients with higher NLR and lower LMR have worse overall survival after CRS + HIPEC, highlighting the potential of LMR in selecting patients who can benefit from this treatment [20]. A recent study focusing on patients undergoing CRS for CRC peritoneal metastases suggests that a higher NLR is associated with poorer OS, whereas a higher PLR predicts favorable DFS [40].

The exact mechanism by which these inflammatory factors exert their predictive effect on the prognosis of certain tumors is still unclear. Currently, it is widely recognized that inflammation plays a crucial role in the formation and development of tumors [41]. Nonetheless, there is still disagreement on which inflammatory indicators can provide the most effective prediction for clinical practice. Further exploration is needed to determine how these biomarkers should be synergistically employed for prognostication and to identify their optimal cutoff values [29].

In addition, this study included traditional predictive factors, revealing that, in multivariate analysis, PCI, CA 19–9, and CC0 status were independent prognostic factors. However, the prognostic role of CEA appeared relatively weak. There have been some reports on the predictive value of CEA and CA 19–9 in early-stage peritoneal metastatic cancer. For instance, Aziz et al. found that

Table 3 Univariate Cox-regression analysis for OS and PFS of PCI and serological biomarkers for all the patients

Variables		OS			PFS		
	N	HR(95%CI)	HR	*P* value	HR(95%CI)	HR	*P*-value
Appendix primary				0.067			0.066
Yes	39	1			1		
No	77	1.559	0.970–2.506		1.489	0.974–2.275	
PCI				**< 0.001**			**< 0.001**
< 10	65	1			**1**		
≥ 10	51	1.425–3.677	2.829		1.533–3.577	2.335	
NLR				**0.007**			
< 2.33	43	1			1		**< 0.001**
≥ 2.33	73	1.224–3.508	2.072		1.465–3.617	2.302	
MLR				**0.027**			0.165
> 0.38	40	1			1		
≤ 0.38	76	1.063–2.729	1.703		0.885–2.046	1.346	
CEA				**0.035**			0.169
> 9.5	50	1.037–2.640	1.654		0.885–2.009	1.334	
≤ 9.5	66	1			1		
CA 19–9				**< 0.001**			**< 0.001**
> 36.65	51	1.891–4.697	2.900		1.743–4.153	2.690	
≤ 36.65	65	1					
CC score				**0.002**			**0.031**
0	71	1			1		
≥ 1	45	1.332–3.663	2.209		1.049–2.676	1.675	

CEA < 6 is associated with significantly higher OS and DFS in patients with peritoneal metastasis originating from the appendix undergoing CRS and HIPEC, whereas CA 19–9 < 38 is not associated with OS or DFS [42]. Another study reported that CA 19–9 > 500 is associated with a poorer OS in patients with peritoneal metastasis originating from colonic sites [38]. In our study, patients with CA 19–9 > 36.65 had significantly poorer OS and PFS. The results of ROC curve analysis showed that the PCI continues to be the most robust prognostic indicator. Meanwhile, CA 19–9 is also a valuable prognostic factor for both OS and PFS, with NLR showing certain advantages in predicting PFS. There are different reports on the predictive value of CEA and CA 19–9, along with different cut-off values of these biomarkers, which accentuates the need for further clarity. In addition, whether patients with appendiceal origin should be studied as a separate subgroup warrants further exploration.

This study has several limitations that should be acknowledged. Firstly, this was a retrospective single-center study with a small sample size, which may have resulted in insufficient statistical power. Secondly, some patients underwent chemotherapy or targeted drug therapy in other centers after undergoing CRS + HIPEC, and we do not have complete data in this regard. Thirdly, owing to the small sample size, this study did not separate patients based on whether the peritoneal metastasis originated from the appendix or

Table 4 Multivariate analysis of factors associated with OS by COX model

Variables	0S			PFS		
	HR	95%CI	*p*-value	HR	95%CI	*p*-value
NLR < 2.33	0.578	0.338–0.987	**0.045**	0.445	0.685–1.765	**0.002**
MLR ≤ 0.38	1.058	0.615–1.818	0.839	1.430	0.890–2.298	0.139
CEA ≤ 9.5	0.996	0.583–1.703	0.989	1.099	0.685–1.765	0.695
CA 19–9 ≤ 36.65	0.345	0.213–0.558	**0.005**	0.489	0.293–0.816	**0.006**
PCI ≥ 10	1.633	0.980–2.723	**0.006**	1.922	1.211–3.051	**0.006**

non-appendix sources for analysis. Tumors of appendiceal origin and non-appendiceal origin exhibit differences in prognosis. However, due to the limited sample size in this study, we were unable to perform separate analyses for these two groups, which may introduce potential bias to the conclusions. We are continuing to collect cases of peritoneal metastatic carcinomas and plan to conduct subgroup analyses based on tumor origin in future studies. Fourth, although all procedures were performed by the same specialized surgical team to minimize variability, differences in individual patient conditions (e.g., disease burden) may still influence outcomes. In summary, our research findings underscore the independent prognostic significance of NLR, PCI, and CA 19–9 in patients undergoing CRS + HIPEC for peritoneal metastasis of CRC. However, these findings should be further validated through large multicenter studies to strengthen their clinical implications.

Conclusions

In conclusion, identifying patients with PC originating from CRC who will benefit from CRS and HIPEC, as well as those who may require additional treatments, is essential for the management of this disease. Our study found that NLR and CA 19–9 could potentially be valuable prognostic markers in patients with peritoneal metastasis of CRC undergoing CRS and HIPEC, though their utility needs to be further verified in larger prospective cohort studies. The potential integration of these two markers with other traditional indicators might enhance the screening of patients who could optimally benefit from CRS and HIPEC treatment. These findings provide a theoretical basis for more individualized treatment and patient screening, offering a promising avenue for improved clinical decision-making.

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Disclosure statement
We declare that this paper is being submitted for consideration for publication. The contents in this manuscript have not been published or submitted for publication elsewhere.

Statements and declarations
The authors declare that there are no financial interests that are directly or indirectly related to the work submitted for publication.

Authors' contributions
Y.N. and S.Y. conceived and designed the study. S.L. and H.Y. collected the patient data, Y.N., F. G. and X. J. analyzed the data, Y. N. wrote the paper, S.Y. reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study has been approved by the ethics committee of Hubei cancer hospital.

Consent for publication
The informed consent of this study has been obtained from patients.

Competing interests
The authors declare no competing interests.

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