Diagnostic Accuracy Study

Medicine®

OPEN

Do inflammatory markers predict prognosis in patients with synchronous colorectal cancer?

Wanbin He, MD[a], Mingtian Wei, MD[a,b], Xuyang Yang, MD[a], Bingchen Chen, MD[a], Qingbin Wu, MD[a], Erliang Zheng, MD[a], XiangBing Deng, MD[a,*], Ziqiang Wang, MD, PhD[a,*]

Abstract

Systematic inflammatory response markers are considered as the most informative prognostic factors in many types of cancer. However, in synchronous colorectal cancer (synCRC), the prognostic value of inflammatory markers, including prognostic nutritional index (PNI), neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio (d-NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), had rarely been evaluated. Thus, this present study reviewed our consecutive patients with synCRC to investigate the prognostic value of those factors.

The primary endpoint was overall survival (OS), and disease-free survival (DFS) was considered as the secondary endpoint. Receiver-operating characteristic curve analysis was conducted to determine optimal cutoff levels for the 5 markers. Kaplan–Meier survival curves and Cox proportional hazards models were applied to assess the relationship between OS, DFS, and inflammatory markers.

In total, 114 patients with pathologically confirmed synCRC at initial diagnosis were identified among 5742 patients who underwent surgery for colorectal cancer from October 2009 to May 2013. In the multivariate analysis, elevated postoperative NLR (≥10.50) was confirmed as an independent prognostic factor for 3-year OS ($P = .001$; hazard ratio [HR] 4.123, 95% confidence interval [CI] 1.750–9.567) and DFS ($P = .001$; HR 3.342, 95% CI 1.619–6.898). In addition, for 3-year OS, both tumor grade and pN stage were confirmed as independent prognostic factors. And pN stage was confirmed as an independent prognostic factor for 3-year DFS.

In conclusion, this study identified elevated postoperative NLR is associated with a poor prognosis in patients with synCRC underwent surgery resection, and the NLR provides improved accuracy for predicting clinical outcomes to stratify patients into different risk categories.

Abbreviations: CEA = carcinoembryonic antigen, CI = confidence interval, DFS = disease-free survival, d-NLR = derived neutrophil-to-lymphocyte ratio (neutrophil count/(leucocyte count–neutrophil count), HR = hazard ratio, LMR = lymphocyte-to-monocyte ratio, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival, PLR = platelet-to-lymphocyte ratio, PNI = prognostic nutritional index (Albumin + 5 × total lymphocyte count), synCRC = synchronous colorectal cancer, WBC = white blood cell.

Keywords: inflammatory markers, prognosis, survival, synchronous colorectal cancer

1. Introduction

In the diagnosis of colorectal cancers, 5% to 10% patients with colorectal cancer have a probability [1,2] of being detected with multiple primary colorectal cancers (defined as two or more cancers detected in the same or other organs synchronously or metachronously, with histological type being identical or different). Among them, 3.1% to 3.9% patients with more than 1 tumor is diagnosed at the same time or within 6 months after initial operation,[3,4] which is called synchronous colorectal cancer (synCRC). In consistent with the usage of predictors for survival outcomes in solitary tumor, the oncological factors such as pTNM stage, tumor grade, and tumor classification are under accuracy and more novel objective predictors are emergent to be reported in synCRC. Therefore, it is indispensable that identifying prognostic factors as complementary tools to predict the prognosis and selecting high-risk patients with synCRC underwent curative resection to recommend individualized treatment.

Systematic inflammation is an important component of the tumor microenvironment, and cancer-related inflammation affects many aspects of malignancy.[5] The changes of peripheral blood cells with inflammatory response have been shown to have prognostic significance in malignancy.[6] Emerging evidence suggests that the inflammatory markers have significant correlations with the poor prognosis in colorectal cancer. The preoperative elevated NLR was an independent marker and predicted of a poor prognosis in colorectal cancer patients underwent surgery resection.[7–9] In addition, the neutrophil-to-lymphocyte ratio (d-NLR), lymphocyte-to-monocyte ratio

Editor: Jae-Ho Lee.

WBH and MTW are senior co-authors.

Grant Support: This study was supported by two grants from the National Natural Science Foundation of China (No. 81172373) and Department of Science and Technology of Sichuan Province (No. 2012FZ0005).

The authors declare no actual or potential conflicts of interest

[a] Department of Gastrointestinal Surgery, [b] State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, Sichuan, China.

[*] Correspondence: Ziqiang Wang, Department of Gastrointestinal Surgery, West China Hospital, Sichuan University, 37 Guoxue Street, Chengdu [610041], China (e-mail: wangzqzyh@163.com); XiangBing Deng, Department of Gastrointestinal Surgery, West China Hospital, Sichuan University,37 Guoxue Street, Chengdu [610041], China (e-mail: 247940362@qq.com).

Medicine (2017) 96:17(e6607)

Received: 28 September 2016 / Received in final form: 12 February 2017 / Accepted: 23 March 2017

http://dx.doi.org/10.1097/MD.0000000000006607

(LMR), platelet-to-lymphocyte ratio (PLR), and prognostic nutritional index (PNI) were found as a prognostic factor of colorectal cancer.[10–13] Of note, however, is that the influence of inflammatory markers on the prognosis of synCRC has been not reported, and the majority of studies have only explored single inflammatory markers (without comparisons of other inflammatory variables) and some have scarcely examined the preoperative inflammatory state as a predictor in cancer, and ignored that the postoperative systematic inflammation also contributing to cancer prognosis.

We aim, therefore, to validate the prognostic value of multiple inflammatory variables in the patients with synCRC, including the NLR, d-NLR, LMR, PLR, and PNI. Additionally, not only the effects of the preoperative inflammatory state, but also the effects of the early postoperative inflammatory state on cancer prognosis were examined.

2. Materials and methods

2.1. Patients

This study was approved by the Ethics Committee of West China Hospital of Sichuan University, and the need to obtain informed consent was waived. A retrospective review of the database at the Department of Gastrointestinal Surgery of West China Hospital of Sichuan University identified 5742 consecutive patients who underwent surgery for colorectal cancer between October 2009 and May 2013.

2.2. Inclusion and exclusion criteria

The inclusion criteria included: all patients who were diagnosed with pathologically confirmed synCRC at the initial operation; treated without preoperative neoadjuvant therapy; receiving curative resection. Exclusion criteria were as follows: patients who underwent enterostomy without tumor resection (owing to neoplastic cells having invaded the surrounding tissue); patients with the type of synCRC that was diagnosed within 6 months after the initial operation; the cancer has local excision; poor data integrity; loss to follow up within 6 months after curative resection.

2.3. Data collection

Pathological data were collected from the pathological report and the cancer stage classified by the highest cancer, and the N-stage determined by totaling all lymph nodes. The pathologic stage was determined according to the seventh edition of the American Joint Committee on Cancer (AJCC) staging manual.[14] Clinicopathological data were collected from patients' medical records held in the Hospital Information System. Laboratory data, including carcinoembryonic antigen levels and absolute albumin, basophilic granulocyte, eosinophilic granulocyte, leukocyte, lymphocyte, monocyte, neutrophil, and platelet counts, were collected from the Laboratory Information Management System. Preoperative and postoperative data were obtained within 3 days prior to or following surgery. At the time of sampling, the patients had no clinical signs of infection or other inflammatory conditions.

2.4. Follow-up

After the operation, patients were followed-up every 6 months for the first 3 years and every 12 months thereafter. Clinical evaluations included a complete blood count, liver and kidney function test, analysis of serum carcinoembryonic antigen and carbohydrate antigen 19 to 9 levels, physical examination (conducted at each visit), computed tomography scan of the abdomen, chest, and pelvis (conducted every 6 months), and colonoscopy (conducted every 12 months). In addition, magnetic resonance imaging of the upper abdomen was performed in patients with suspected liver metastases.

2.5. Statistical analysis

The primary endpoint was overall survival (OS), which was defined as the time period from the date of surgery to the date of death from any cause. Disease-free survival (DFS) was considered as the secondary end point, which was defined as the time period from the date of surgery to the date of tumor recurrence and/or distant metastasis. Optimal cutoff levels for the NLR, d-NLR, LMR, PLR, and PNI markers were determined by applying receiver-operating characteristic (ROC) curve analysis.[15] Youden's index was used to filter the optimal cutoff levels. The relationships between the NLR, d-NLR, LMR, PLR, PNI markers, and the clinicopathological parameters of the patients were assessed using a nonparametric chi-squared or Fisher exact test. Means were compared using Student *t* tests. Survival curves were calculated using the Kaplan–Meier method and statistical significance was determined by a log-rank test. Univariate and multivariate analysis were conducted using Cox proportional hazards models with all possible clinicopathological parameters included in the analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were used as common measures to assess relative risk. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) for Windows, Software Version 22.0 (IBM Corp., Armonk, NY). A probability (*P*)-value below 0.05 was considered statistically significant.

3. Results

Based on our inclusion and exclusion criteria, a total of 114 (2.0%) patients who were diagnosed synCRC were eligible for our analysis. The male to female ratio of synCRC patients included was 2:1 (Table 1). The median age at diagnosis was 60 years (range, 20–85 years). In total, 72 patients (63.2%) were diagnosed ≥60 years of age. For all the patients with synCRC, tumor size, cancer grade, depth of tumor invasion, and tumor location of pathological specimen were listed in Table 1. Index lesions were larger in size, more deeply penetrated, more frequently lymphatic invasion than in concurrent lesions.[16] There are 13 patients (11.4%) have more than 2 tumors (the date of tumor size, cancer grade, depth of tumor invasion, and tumor location were not shown). The number of highest cancer stage I, II, and III were 18 (15.8%), 41 (40.0%), and 52 (45.6%), respectively. There are 68 patients (59.6%) accepted adjuvant chemotherapy and/or radiotherapy after operation. Until the deadline of following-up, 31 patients (27.2%) were cancer-related death and 41 patients (36.0%) were identified as local recurrence or distal metastasis. The median follow-up period for all the patients was 39 months (range 1–73 months), and the median follow-up period for the OS was 47 months (range 1–73 months, 95% CI 44.6–49.4 months), and the median follow-up period for the DFS was 48 months (range 1–73 months, 95% CI 45.5–50.5 months).

3.1. Sensitivity and specificity

ROC analyses regarding the prognostic value of investigated parameters relate to overall survival. The optimal cutoff values

Table 1

Clinicopathological parameter.

Clinicopathological parameter (n = 114)	Index lesion	Concurrent lesion
Pathological parameter		
Tumor size, mean ± SD, cm	4.17 ± 2.22	2.79 ± 1.73
Cancer grade (G), n (%)		
G1	5 (4.4)	28 (24.6)
G2	69 (60.5)	74 (64.9)
G3	31 (27.2)	9 (7.9)
G4	9 (7.9)	3 (2.6)
Depth of tumor invasion (T stage), n (%)		
Tis	2 (1.8)	24 (21.1)
T1	4 (3.5)	32 (28.1)
T2	19 (16.7)	30 (26.3)
T3	68 (59.6)	20 (17.5)
T4	21 (18.4)	8 (7.0)
Tumor location, n (%)		
Right side	34 (29.8)	15 (13.1)
Left side	28 (24.6)	41 (36.0)
Rectum	52 (45.6)	58 (50.9)
Regional lymph node status (N stage), n (%)		
N0	59 (51.8)	
N1	31 (27.2)	
N2	21 (18.4)	
Unknown	3 (2.6)	
Cancer stage, n (%)		
I	18 (15.8)	
II	41 (40.0)	
III	52 (45.6)	
Unknown	3 (2.6)	
Location of the synchronous tumor, n (%)		
Rectum	36 (31.6)	
Colon	41 (36.0)	
Both	37 (32.4)	
Mucinous adenocarcinoma and/or signet-ring cell carcinoma, n (%), (yes/no)	48 (42.1)/66 (57.9)	
No. tumor per case, n (%), (2 synCRC/>2 synCRC)	101 (88.6)/13 (11.4)	
No. LN samples, n (%), (≥12/<12)	74 (64.9)/40 (35.1)	
Polypus, n (%), (yes/no)	51 (44.7)/63 (55.3)	
Tumor deposit, n (%), (yes/no)	24 (21.1)/90 (78.9)	
Cancer embolus, n (%), (yes/no)	8 (7.0)/106 (93.0)	
Perineural invasion, n (%), (yes/no)	5 (4.4)/109 (95.6)	
Patients characteristics		
Sex, n (%) (Male/Female)	76 (66.7)/38 (33.3)	
Age of operation, n (%) (<60 y/≥60 y)	42 (36.8)/ 72 (63.2)	
Preoperative CEA levels, n (%)		
Normal	53 (46.5)	
Elevated	53 (46.5)	
Unknown	8 (7.0)	
Adjuvant chemotherapy and/or radiotherapy after operation, n (%), (yes/no)	68 (59.6)/46 (40.1)	
Operative approach, n (%), (conventional/laparoscopic)	96 (84.2)/18 (15.8)	
Postoperative complications, n (%), (yes/no)	23 (20.2)/91 (79.8)	
Preoperative LMR, n (%), (high/low)	80 (70.2)/34 (29.8)	
Preoperative PNI, n (%), (high/low)	84 (73.7)/30 (26.3)	
Postoperative NLR, n (%), (high/low)	49 (43.0)/65 (57.0)	
Postoperative d-NLR, n (%), (high/low)	56 (49.1)/58 (50.9)	
Postoperative PLR, n (%), (high/low)	68 (59.6)/46 (40.4)	

CEA = carcinoembryonic antigen, d-NLR = derived neutrophil-to-lymphocyte ratio, LMR = lymphocyte-to-monocyte ratio, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, PNI = prognostic nutritional index, SD = standard deviation, synCRC = synchronous colorectal cancer.

and ROC curves of the preoperative NLR, PLR, d-NLR, LMR, and PNI markers are presented in Fig. 1. Curves for the preoperative NLR, PLR, and d-NLR were below the reference line, and areas under the curve were <0.500. In contrast, areas under the curve for the preoperative LMR and PNI were 0.635 and 0.621, respectively, with optimal cutoff values of 3.40 (sensitivity 77.1%, specificity 48.4%) and 44.03 (sensitivity 81.9%, specificity 48.4%).

The optimal cutoff values and ROC curves of the postoperative NLR, PLR, d-NLR, LMR, and PNI markers are presented in Fig. 2. The curve for the postoperative PNI was below the reference line, with an area under the curve of 0.409. In contrast,

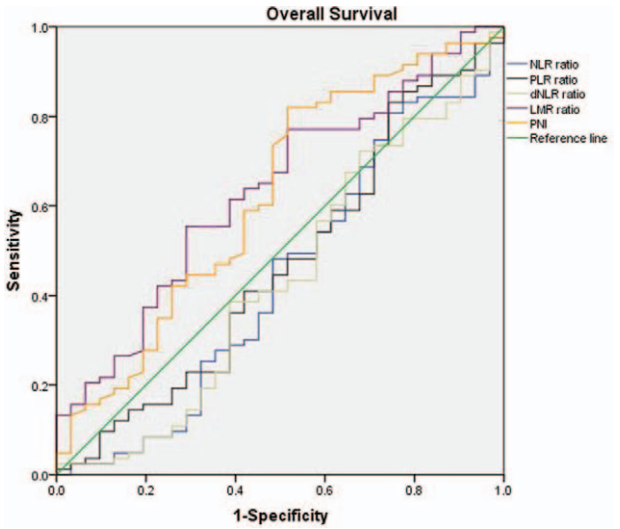

Figure 1. Receiver-operating characteristic curves for overall survival to determine optimal cutoff points of the preoperative neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), derived NLR (d-NLR), lymphocyte-to-monocyte ratio (LMR), and prognostic nutritional index (PNI).

areas under the curve for the postoperative NLR, PLR, d-NLR, and LMR were 0.585, 0.574, 0.618, and 0.565, respectively, with optimal cutoff values of 10.50 (sensitivity 63.3%, specificity 64.0%), 193.94 (sensitivity 76.7%, specificity 48.4%), 6.18 (sensitivity 63.3%, specificity 58.5%), and 1.62 (sensitivity 70.0%, specificity 43.9%).

3.2. Correlations with clinicopathological parameters

Correlations between the preoperative LMR, PNI, postoperative NLR, d-NLR, PLR markers, and the clinicopathological parameters of synCRC patients are displayed in Table 2. Patients were stratified into high and low groups according to the cutoff values derived from the ROC curve analysis. In relation to the preoperative LMR and PNI levels, 70.2% (n = 80) and 73.7% (n = 84) of patients were distributed in the high group (LMR ≥ 3.40, PNI ≥ 44.02), and in relation to the postoperative NLR, PLR, and d-NLR levels, 43.0% (n = 49), 49.1% (n = 56), and 59.6% (n = 68) of patients were distributed in the high group (NLR ≥ 10.50, PLR ≥ 193.94, and d-NLR ≥ 6.18, Table 2). The results indicated that pN stage and cancer stage were significantly associated with postoperative PLR ($P = .019$; $P = .006$, respectively) and location of the synchronous tumor has correlation with the preoperative LMR ($P = .007$) and PNI ($P = .007$). The distributions of preoperative WBC counts were significant difference in preoperative LMR ($P = .034$) and PNI ($P = .001$). Simultaneously, the distributions of postoperative WBC counts were significant difference in postoperative NLR ($P = .001$) and d-NLR ($P = .003$). No associations were observed between the clinicopathological parameters of synCRC patients and the remaining inflammatory markers.

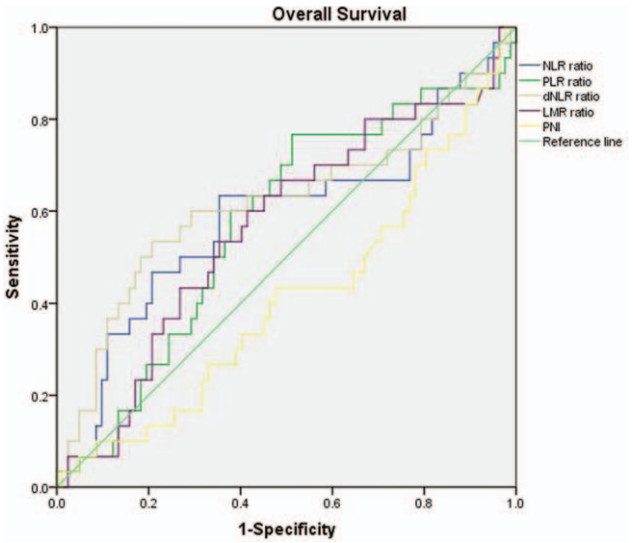

Figure 2. Receiver-operating characteristic curves for overall survival to determine optimal cutoff points of the postoperative neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), derived NLR (d-NLR), lymphocyte-to-monocyte ratio (LMR), and prognostic nutritional index (PNI).

3.3. Prognostic factor for OS and DFS

Kaplan–Meier curve, analyzing the preoperative data, indicated that, the 3 years OS and DFS rates in patients in the low (<3.40) and high (≥3.40) preoperative LMR groups were 55.9%, 80.0%, and 50.0%, 72.5%, respectively. This suggests that the 3 years OS and DFS rates of the high LMR group were significantly better than that of the low LMR group ($P = .013$; Fig. 3A, $P = .025$; Fig. 4A). And the 3 years OS and DFS rates in the low (<40.02) and high (≥40.02) preoperative PNI groups were 50.0%, 81.0% and 46.7%, 72.6%, respectively. The 3 years OS and DFS rates of the high PNI group were significantly better than that of the low PNI group ($P = .001$; Fig. 3B, $P = .005$; Fig. 4B). Kaplan–Meier curve analysis for the postoperative data also indicated that the 3 years OS and DFS rates in the low (<10.50) and high (≥10.50) postoperative NLR groups were 83.1%, 59.2% and 76.9%, 51.0%, respectively. The 3 years OS and DFS rates of the high NLR group were significantly poorer than that of the low NLR group ($P = .001$; Fig. 3C, $P = .001$; Fig. 4C). Moreover, the 3 years OS and DFS rates in the low (<193.94) and high (≥193.94) postoperative PLR groups were 84.8%, 64.7% and 80.4%, 55.9%, respectively, and the 3 years OS and DFS rates in the low (<6.18) and high (≥6.18) postoperative d-NLR groups were 81.0%, 64.3% and 74.1%, 57.1%, respectively. The 3 years OS and DFS rates of the high PLR and d-NLR groups were significantly poorer than those of the low PLR ($P = .028$; Fig. 3D, $P = .012$; Fig. 4D) and d-NLR groups ($P = .018$; Fig. 3E, $P = .030$; Fig. 4E). The OS and DFS of postoperative LMR had no significant difference (date was not shown).

In the univariate analysis, decreased preoperative LMR ($P = .016$; HR 2.238, 95% CI 1.175–4.838) and PNI ($P = .002$; HR 3.126, 95% CI 1.526–6.043), elevated postoperative NLR ($P = .002$; HR 3.180, 95% CI 1.511–6.695), and PLR ($P = .034$; HR 2.488, 95% CI 1.069–5.790), and d-NLR ($P = .022$; HR 2.369, 95% CI 1.130–4.965) were significantly associated with worse 3 years OS. Regarding DFS, decreased preoperative LMR ($P = .030$; HR 2.028, 95% CI 1.072–3.836) and PNI ($P = .007$; HR 2.452, 95% CI 1.281–4.695), elevated postoperative NLR ($P = .002$; HR 2.813, 95% CI 1.465–5.402) and PLR ($P = .017$; HR 2.495, 95% CI 1.180–5.272) and d-NLR ($P = .034$; HR 2.011, 95% CI 1.052–3.841) were significantly associated with worse 3 years DFS. In addition, cancer grade (G2: $P = .001$; HR 0.162, 95% CI 0.056–0.468) and pN stage (Unknown: $P = .030$; HR 5.731, 95% CI 1.188–27.638, N1: $P = .003$: HR 4.159, 95%

Table 2

Correlations between the preoperative lymphocyte-to-monocyte ratio (LMR), prognostic nutritional index (PNI), postoperative neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio (d-NLR), platelet-to-lymphocyte ratio (PLR), and clinicopathological parameters of patients ($n=114$) with synchronous colorectal cancer.

Parameter	Patients (n = 114)	LMR		PNI		NLR		d-NLR		PLR	
		High/Low	*P* value	High/Low	*P* value	High/Low	*P* value	High/Low	*P* value	High/Low	*P* value
Age of operation, n (%)											
<60 y	42 (36.8)	28 (35.0)/14 (41.2)	.53	31 (36.9)/11 (36.7)	.98	17 (34.7)/25 (38.5)	.68	19 (33.9)/23 (39.7)	.53	28 (41.2)/14 (30.4)	.24
≥60 y	72 (63.2)	52 (65.0)/20 (58.8)		53 (63.1)/19 (63.3)		32 (65.3)/40 (61.5)		37 (66.1)/35 (60.3)		40 (58.8)/32 (69.6)	
Sex, n (%)											
Male	76 (66.7)	49 (61.2)/27 (79.4)	.60	56 (66.7)/20 (66.7)	1.00	34 (69.4)/42 (64.6)	.59	39 (69.6)/37 (63.8)	.15	48 (70.6)/28 (60.9)	.28
Female	38 (33.3)	31 (38.8)/7 (20.6)		28 (33.3)/10 (33.3)		15 (30.6)/23 (35.4)		17 (30.4)/21 (36.2)		20 (29.4)/18 (39.1)	
Cancer grade (G), n (%)											
G1	5 (4.4)	4 (5.0)/1 (3.0)	.39	5 (6.0)/0 (0)	.14	2 (4.1)/3 (4.6)	1.00	2 (3.6)/3 (5.2)	.70	3 (4.4)/2 (4.3)	.57
G2	69 (60.5)	50 (62.5)/19 (55.9)		51 (60.7)/18 (60.0)		30 (61.2)/39 (60.0)		32 (57.1)/37 (63.8)		38 (55.9)/31 (67.4)	
G3	31 (27.2)	22 (27.5)/9 (26.5)		24 (28.6)/7 (23.3)		13 (26.5)/18 (27.7)		16 (28.6)/15 (25.9)		20 (29.4)/11 (23.9)	
G4	9 (7.9)	4 (5.0)/5 (14.7)		4 (4.8)/5 (16.7)		4 (8.2)/5 (7.7)		6 (10.7)/3 (5.2)		7 (10.3)/2 (4.3)	
Depth of tumor invasion (pT stage), n (%)											
Tis	2 (1.8)	2 (2.5)/0 (0)	.50	2 (2.4)/0 (0)	.38	0 (0)/2 (3.1)	.50	0 (0)/2 (3.4)	.73	0 (0)/2 (4.3)	.13
T1	4 (3.5)	3 (3.8)/1 (2.9)		4 (4.8)/0 (0)		1 (2.0)/3 (4.6)		2 (3.6)/2 (3.4)		3 (4.4)/1 (2.2)	
T2	19 (16.7)	16 (20.0)/3 (8.8)		16 (19.0)/3 (10.0)		8 (16.3)/11 (17.0)		8 (14.3)/11 (19.0)		8 (11.8)/11 (23.9)	
T3	68 (59.6)	46 (57.5)/22 (64.7)		49 (58.3)/19 (63.3)		28 (57.1)/40 (61.5)		35 (62.5)/33 (57.0)		42 (61.8)/26 (56.5)	
T4	21 (18.4)	13 (16.3)/8 (23.5)		13 (15.5)/8 (26.7)		12 (24.5)/9 (13.8)		11 (19.6)/10 (17.2)		15 (22.1)/6 (13.0)	
Regional lymph node status (pN stage), n (%)											
N0	59 (51.8)	43 (53.8)/16 (47.1)	.21	45 (53.6)/14 (46.7)	.79	22 (44.9)/37 (57.0)	.44	29 (51.8)/30 (51.7)	.94	27 (39.7)/32 (69.6)	.019*
N1	31 (27.2)	23 (28.8)/8 (23.5)		23 (27.4)/8 (26.7)		14 (28.6)/17 (26.1)		15 (26.7)/16 (27.6)		23 (33.8)/8 (17.4)	
N2	21 (18.4)	11 (13.8)/10 (29.4)		14 (16.7)/7 (23.3)		12 (24.5)/9 (13.8)		11 (19.6)/10 (17.2)		16 (23.5)/5 (10.9)	
Unknown	3 (2.6)	3 (3.8)/0 (0)		2 (2.4)/1 (3.3)		1 (2.0)/2 (3.1)		1 (1.8)/2 (3.4)		2 (2.9)/1 (2.2)	
Cancer stage, n (%)											
I	18 (15.8)	15 (18.7)/3 (8.8)	.38	17 (20.2)/1 (3.3)	.12	6 (12.2)/12 (18.5)	.58	7 (12.5)/11 (18.9)	0.71	6 (8.8)/12 (26.1)	.006*
II	41 (40.0)	28 (35.0)/13 (38.2)		28 (33.3)/13 (43.3)		16 (32.7)/25 (38.5)		22 (39.3)/19 (32.8)		21 (30.9)/20 (43.5)	
III	52 (45.6)	34 (42.5)/18 (52.9)		37 (44.0)/15 (50.0)		26 (53.1)/26 (40.0)		26 (46.4)/26 (44.9)		39 (57.4)/13 (28.3)	
Unknown	3 (2.6)	3 (3.8)/0 (0)		2 (2.4)/1 (3.3)		1 (2.0)/2 (3.1)		1 (1.8)/2 (3.4)		2 (2.9)/1 (2.2)	
Location of the synchronous tumor, n (%)											
Rectum	36 (31.6)	32 (40.0)/4 (11.7)	.007*	29 (34.5)/7 (23.3)	.007*	11 (22.4)/25 (38.4)	.17	13 (23.2)/23 (39.7)	.09	18 (26.5)/18 (39.1)	.16
Colon	41 (36.0)	24 (30.0)/17 (50.0)		23 (27.4)/18 (60.0)		21 (42.9)/20 (30.8)		25 (44.6)/16 (27.6)		29 (42.6)/12 (26.1)	
Both	37 (32.4)	24 (30.0)/13 (38.2)		32 (38.1)/5 (16.7)		17 (34.7)/20 (30.8)		18 (32.1)/19 (32.7)		21 (30.9)/16 (34.8)	
Preoperative CEA levels, n (%)											
Normal	53 (46.5)	41 (51.2)/12 (35.3)	.28	44 (52.4)/9 (30.0)	.10	20 (40.8)/33 (50.8)	.44	24 (42.9)/29 (50.0)	.81	30 (44.1)/23 (50.0)	.28
Elevated	53 (46.5)	34 (42.5)/19 (55.9)		35 (41.7)/18 (60.0)		26 (53.1)/27 (41.5)		28 (50.0)/25 (43.1)		35 (51.5)/18 (39.1)	
Unknown	8 (7.0)	5 (6.3)/3 (8.8)		5 (5.9)/3 (10.0)		3 (6.1)/5 (7.7)		4 (7.1)/4 (6.9)		3 (4.4)/5 (10.9)	
Mucinous adenocarcinoma and/or signet-ring cell carcinoma, n (%)											
Yes	48 (42.1)	31 (38.8)/17 (50.0)	.30	32 (38.1)/16 (53.3)	.20	23 (46.9)/25 (38.5)	.44	26 (46.4)/22 (37.9)	.45	32 (47.1)/16 (34.9)	.25
No	66 (57.9)	49 (61.3)/17 (50.0)		52 (61.9)/14 (46.7)		26 (53.1)/40 (61.5)		30 (53.6)/36 (62.1)		36 (52.9)/30 (65.2)	
Polypus, n (%)											
Yes	51 (44.7)	36 (45.0)/15 (44.1)	1.00	38 (45.2)/13 (43.3)	1.00	20 (40.8)/31 (47.7)	.57	25 (44.6)/26 (44.8)	.98	30 (44.1)/21 (45.7)	1.00
No	63 (55.3)	44 (55.0)/19 (55.9)		46 (54.8)/17 (56.7)		29 (59.2)/34 (52.3)		31 (55.4)/32 (55.2)		38 (55.9)/25 (54.3)	
Tumor deposit, n (%)											
Yes	24 (21.1)	16 (20.0)/8 (23.5)	.80	16 (19.0)/8 (26.7)	.44	14 (28.6)/10 (15.4)	.11	15 (26.8)/9 (15.5)	.17	16 (23.5)/8 (17.4)	.49
No	90 (78.9)	64 (80.0)/26 (76.5)		68 (81.0)/22 (73.3)		35 (71.4)/55 (84.6)		41 (73.2)/49 (84.5)		52 (76.5)/38 (82.6)	
Preoperative WBC count ($\times 10^9$)											
<3.5	6 (5.3)	5 (6.3)/1 (2.9)	.034*	1 (1.2)/5 (16.7)	.001*	3 (6.1)/3 (4.6)	.65	2 (3.6)/4 (6.9)	.76	4 (5.9)/2 (6.4)	.51
3.5–9.5	105 (92.1)	75 (93.8)/30 (88.2)		82 (97.6)/23 (76.7)		44 (89.8)/61 (93.8)		52 (92.9)/53 (91.4)		61 (89.7)/44 (93.6)	
>9.5	3 (2.6)	0 (0)/3 (8.8)		1 (1.2)/2 (6.7)		2 (4.1)/1 (1.5)		2 (3.6)/1 (1.7)		3 (4.4)/0 (0)	
Postoperative WBC count ($\times 10^9$)											
<3.5	0 (0)	0 (0)/0 (0)	.75	0 (0)/0 (0)	.21	0 (0)/0 (0)	.001*	0 (0)/0 (0)	.003*	0 (0)/0 (0)	.88
3.5–9.5	61 (53.5)	45 (56.3)/18 (52.9)		42 (50.0)/19 (63.7)		17 (34.7)/44 (67.7)		22 (39.3)/39 (67.2)		36 (52.9)/25 (54.3)	
>9.5	53 (46.5)	35 (43.8)/16 (47.1)		42 (50.0)/11 (36.3)		32 (65.3)/21 (32.3)		34 (60.7)/19 (32.8)		32 (47.1)/21 (45.7)	

CEA = carcinoembryonic antigen, d-NLR = derived neutrophil-to-lymphocyte ratio, LMR = lymphocyte-to-monocyte ratio, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, PNI = prognostic nutritional index, WBC = white blood cell.

* Indicates values which are statistically significant ($P < .05$).

CI 1.609–10.751, N2: $P < .001$; HR 8.093, 95% CI 3.101–21.123) and pTNM stage (stage I: $P = .013$; HR 0.160, 95% CI 0.037–0.683, stage II: $P = .001$; HR 0.195, 95% CI 0.073–0.515) and tumor deposit ($P < .001$; HR 0.224, 95% CI 0.105–0.479) were also found to be a significant prognostic factor for 3 years OS. The cancer grade (G2: $P = .008$; HR 0.260, 95% CI 0.095–0.708) and pN stage (N1: $P = .001$; HR 4.055, 95% CI 1.818–9.047, N2: $P < .001$; HR 6.445, 95% CI

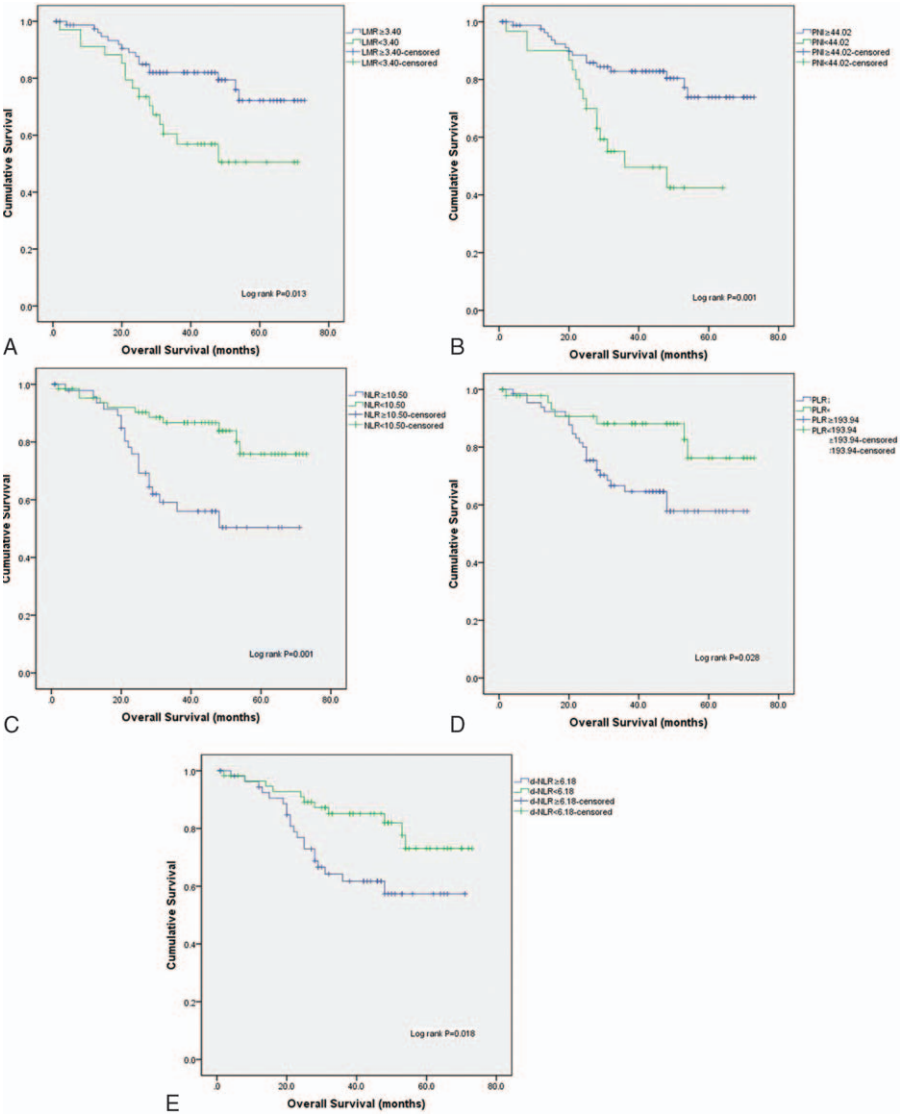

Figure 3. Kaplan–Meier curves of overall survival (OS) for synchronous colorectal cancer patients according to the preoperative lymphocyte-to-monocyte ratio (LMR) (A), preoperative prognostic nutritional index (PNI) (B), postoperative neutrophil-to-lymphocyte ratio (NLR) (C), postoperative platelet-to-lymphocyte ratio (PLR) (D), postoperative derived neutrophil-to-lymphocyte ratio (d-NLR) (E).

2.730–15.215) and pTNM stage (stage I: $P=.006$; HR 0.185, 95% CI 0.056–0.614, stage II: $P<.001$; HR 0.219, 95% CI 0.095–0.505) and tumor deposit ($P<.001$; HR 0.257, 95% CI 0.127–0.520) and operative approach ($P<.031$; HR 4.806, 95% CI 1.157–19.967) were also found to be a significant prognostic factor for 3 years DFS (Table 3).

In the multivariate analysis, elevated postoperative NLR were confirmed as independent prognostic factor for 3 years OS ($P=.001$; HR 4.123, 95% CI 1.750–9.567) and DFS ($P=.001$; HR 3.342, 95% CI 1.619–6.898). The cancer grade (G1: $P=.004$; HR 0.023, 95% CI 0.002–0.351, G2: $P=.015$; HR 0.236, 95% CI 0.073–0.759) and pN stage (Unknown: $P=.004$; HR 17.041, 95% CI 2.531–114.72, N1: $P=.002$, HR 4.605, 95% CI 1.768–11.998, N2: $P<.001$; HR 7.705, 95% CI 2.607–19.199) also were confirmed as independent prognostic factors for 3 years OS. And pN stage (Unknown: $P=.030$; HR 12.115, 95% CI 1.285–114.21, N0: $P<.001$; HR 4.432, 95% CI 1.973–9.959, N1: $P<.001$; HR 5.220, 95% CI 2.105–12.944) was confirmed as independent prognostic factor for 3 years the DFS (Table 3).

4. Discussion

The synCRC is a rare type of colorectal cancers, and the prevalence of synCRC was 2.0% in the present study. The main finding of this study is that elevated postoperative NLR was confirmed as an independent prognostic factor for worse 3 years OS and DFS in patients with synCRC underwent surgery resection. Furthermore, the cancer grade and regional lymph node involvement (pN stage) was an independent clinical prognostic factors for 3 years OS and DFS.

The association between cancer and inflammation was first recognized on the basis of observations that tumors frequently arise at sites of chronic inflammation and that inflammatory cells are present in tumor biopsy samples,[17] suggesting that the "lymphoreticular infiltrate" at sites of chronic inflammation

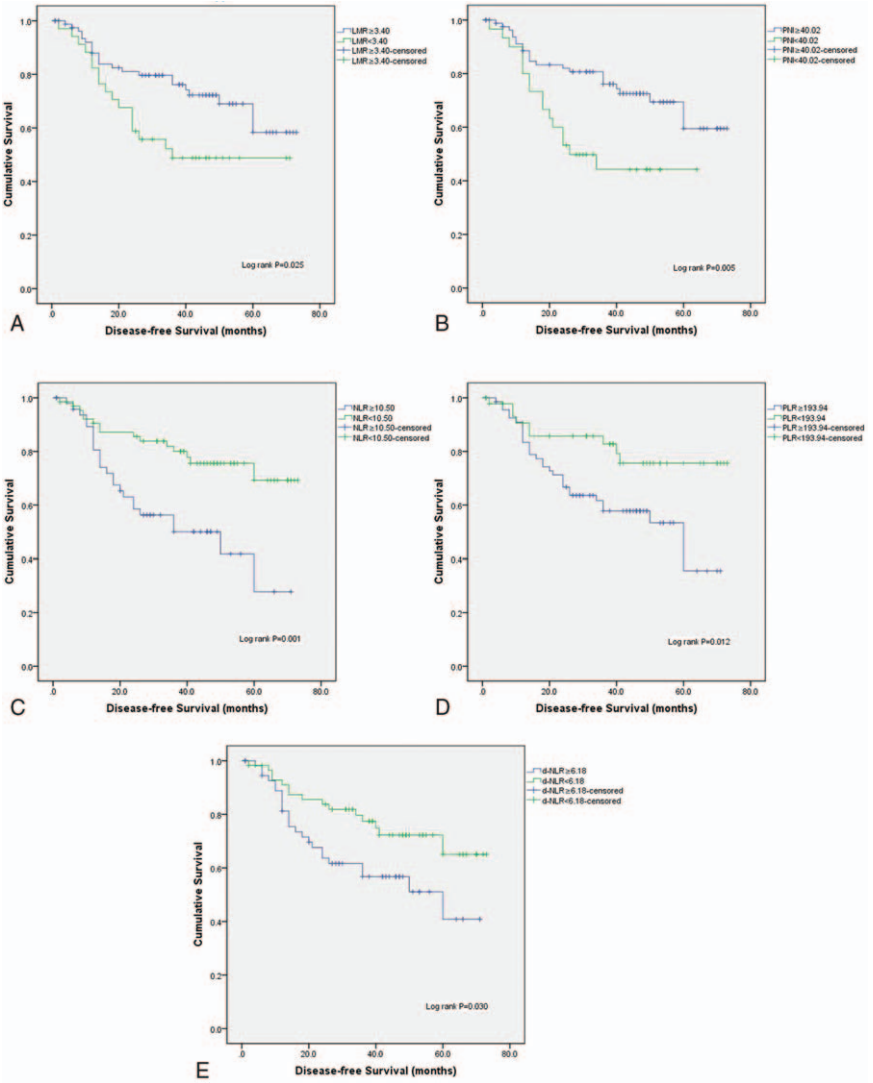

Figure 4. Kaplan–Meier curves of disease-free survival (DFS) for synchronous colorectal cancer patients according to the preoperative lymphocyte-to-monocyte ratio (LMR) (A), preoperative prognostic nutritional index (PNI) (B), postoperative neutrophil-to-lymphocyte ratio (NLR) (C), postoperative platelet-to-lymphocyte ratio (PLR) (D), postoperative derived neutrophil-to-lymphocyte ratio (d-NLR) (E).

reflects the origins of cancer. Epidemiological studies suggested chronic inflammation may cause a variety of malignancies.[5] Moreover, many triggers of chronic inflammation increase the risk of developing cancer. Peripheral inflammatory cells (leukocytes, lymphocytes, monocytes, neutrophils, platelets) and albumin were associated with the progression and prognosis of various types of malignancies.[18] Thus, NLR, d-NLR, PLR, LMR, and PNI that represent systematic inflammatory response have potential value as prognostic factors for synCRC.

In our study, low preoperative LMR and PNI were associated with poor OS and DFS. Furthermore, we also demonstrated a significant correlation between postoperative NLR, d-NLR, PLR, and OS as well as DFS, which suggested that high NLR, d-NLR, and PLR were associated with poor outcome. Those findings are consistent with previous studies on the relationship of NLR, PLR, LMR, PNI, and prognosis of colorectal cancer.[7,8,12,13] Moreover, only the elevated postoperative NLR was considered as an independent indicator for OS and DFS by multivariate analysis. The association between elevated NLR and poor survival is likely complex. There are significant data demonstrating an association between elevated neutrophil count and poor outcome in patients with cancer.[19] And neutrophils, as a major component of leukocyte population, was activated and migrated from venous system to tumor cells.[8] Lymphocytes, responsible for the antitumor immune response of the host, play a considerable role in tumor suppression,[20] including cytotoxic cell death and the inhibition of tumor cell proliferation and migration.[21] A decreased lymphocytes count is considered to be relating to insufficient immunologic reaction to the tumor, promoting tumor progression and metastasis.[11] Thus, the NLR reflects both the immune status of the host and the degree of tumor progression. Simultaneously, the results of our study confirmed that a postoperative inflammatory responses could also be a contributory factors to the cancer[22] and postoperative systemic inflammatory responses are associated with oncologic outcomes of the colorectal cancer, which is independent of tumor stage.[23] In this study, elevated postoperative NLR, PLR, and d-NLR had a correlations with the poor survival in univariate analysis, which

Table 3

Univariate analysis and multivariate analysis of clinicopathological parameters for the prediction of overall survival (OS) and disease-free survival (DFS) in patients (n = 114) with synchronous colorectal cancer.

Clinicopathological	OS			DFS		
parameter	HR	95% CI	*P* value	HR	95% CI	*P* value
Univariate analysis						
Age of operation, n (%)						
≥60 y	1.135	0.534–2.410	.74	0.674	0.358–1.270	.22
<60 y	Reference			Reference		
Sex, n (%)						
Male	0.731	0.355–1.506	.40	0.831	0.432–1.601	.58
Female	Reference			Reference		
Cancer grade (G), n (%)						
G1	0.146	0.017–1.276	.08	0.340	0.065–1.773	.20
G2	0.162	0.056–0.468	.001*	0.260	0.095–0.708	.008*
G3	0.463	0.161–1.330	.15	0.551	0.195–1.558	.26
G4	Reference			Reference		
Depth of tumor invasion (pT stage), n (%)						
Tis	0	—	.99	0	—	.98
T1	0	—	.98	0	—	.98
T2	0.409	0.137–1.217	.11	0.534	0.213–1.340	.18
T3	0.450	0.204–0.991	.05	0.561	0.278–1.129	.11
T4	Reference			Reference		
Regional lymph node status (pN stage), n (%)						
Unknown	5.731	1.188–27.638	.030*	4.194	0.915–19.226	.65
N1	4.159	1.609–10.751	.003*	4.055	1.818–9.047	.001*
N2	8.093	3.101–21.123	<.001*	6.445	2.730–15.215	<.001*
N0	Reference			Reference		
Cancer stage						
Unknown	1.051	0.246–4.488	.95	0.875	0.206–3.715	.86
I	0.160	0.037–0.683	.013*	0.185	0.056–0.614	.006*
II	0.195	0.073–0.515	.001*	0.219	0.095–0.505	<.001*
III	Reference			Reference		
Location of the synchronous tumor, n (%)						
Rectum	0.659	0.255–1.705	.39	0.681	0.295–1.575	.37
Colon	1.381	0.615–3.103	.43	1.325	0.646–2.717	.44
Both	Reference			Reference		
Preoperative CEA levels, n (%)						
Unknown	0.986	0.283–3.429	.98	1.054	0.358–3.109	.92
Normal	0.597	0.281–1.269	.18	0.610	0.311–1.198	.15
Elevated	Reference			Reference		
Mucinous adenocarcinoma and/or signet-ring cell carcinoma, n (%)						
No	1.352	0.635–2.879	.44	1.223	0.635–2.356	.55
Yes	Reference			Reference		
No. LN samples, n (%)						
≥12	0.710	0.350–1.442	.34	0.725	0.385–1.365	.32
<12	Reference			Reference		
Polypus, n (%)						
No	0.936	0.463–1.894	.86	0.946	0.505–1.772	.86
Yes	Reference			Reference		
Tumor deposit, n (%)						
No	0.224	0.105–0.479	<.001*	0.257	0.127–0.520	<.001*
Yes	Reference			Reference		
Cancer embolus, n (%)						
No	1.630	0.222–11.981	.63	2.209	0.302–16.129	.44
Yes	Reference			Reference		
Perineural invasion, n (%)						
No	0.334	0.079–1.421	.14	0.332	0.101–1.088	.07
Yes	Reference			Reference		
Adjuvant chemotherapy and/or radiotherapy after operation, n (%)						
No	0.749	0.352–1.591	.45	0.643	0.325–1.269	.20
Yes	Reference			Reference		
Operative approach, n (%)						
Conventional	0.274	0.065–1.149	.08	4.806	1.157–19.967	.031*
Laparoscopic	Reference			Reference		
Postoperative complications, n (%)						

(*continued*)

Table 3

(continued).

Clinicopathological parameter	OS			DFS		
	HR	95% CI	*P* value	HR	95% CI	*P* value
No	0.878	0.360–2.142	.77	0.921	0.436–1.944	.83
Yes	Reference			Reference		
Preoperative WBC count ($\times 10^9$)						
<3.5	0.399	0.056–2.853	.36	0.245	0.041–1.482	.13
3.5–9.5	0.320	0.075–1.359	.12	0.243	0.073–0.807	.021*
>9.5	Reference			Reference		
Preoperative WBC count ($\times 10^9$)						
<3.5	–	–	–	–	–	–
3.5–9.5	0.854	0.422–1.730	.66	0.881	0.469–1.653	.69
>9.5	Reference			Reference		
Preoperative LMR, n (%)						
Low	2.238	1.175–4.838	.016*	2.028	1.072–3.836	.030*
High	Reference			Reference		
Preoperative PNI, n (%)						
Low	3.126	1.526–6.043	.002*	2.452	1.281–4.695	.007*
High	Reference			Reference		
Postoperative NLR, n (%)						
High	3.180	1.511–6.695	.002*	2.813	1.465–5.402	.002*
Low	Reference			Reference		
Postoperative PLR, n (%)						
High	2.488	1.069–5.790	.034*	2.495	1.180–5.272	.017*
Low	Reference			Reference		
Postoperative d-NLR, n (%)						
High	2.369	1.130–4.965	.022*	2.011	1.052–3.841	.034*
Low	Reference			Reference		
Multivariate analysis						
Cancer grade (G), n (%)						
G1	0.023	0.002–0.351	.004*	0.142	0.014–1.431	.10
G2	0.236	0.073–0.759	.015*	0.397	0.135–1.153	.09
G3	0.664	0.216–2.043	.48	0.968	0.318–2.948	.95
G4	Reference			Reference		
Regional lymph node status (N stage), n (%)						
Unknown	17.041	2.531–114.72	.004*	12.115	1.285–114.21	.030*
N1	4.605	1.768–11.998	.002*	4.432	1.973–9.959	<.001*
N2	7.705	2.607–19.199	<.001*	5.220	2.105–12.944	<.001*
N0	Reference			Reference		
Postoperative NLR, n (%)						
High	4.123	1.750–9.567	.001*	3.342	1.619–6.898	.001*
Low	Reference			Reference		

CEA = carcinoembryonic antigen, CI = confidence interval, DFS = disease-free survival, d-NLR = derived neutrophil-to-lymphocyte ratio, HR = hazard ratio, LMR = lymphocyte-to-monocyte ratio, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival, PLR = platelet-to-lymphocyte ratio, PNI = prognostic nutritional index, WBC = white blood cell.

* Indicates values which are statistically significant ($P < .05$).

indicated not only focusing on one point of time to analyze the inflammatory response, but also on a certain period of an inflammatory condition. In multivariate analysis, NLR, cancer grade, and pN stage were an independent prognostic factor in patients with synCRC.

Although the applicable thresholds of LMR, PNI, NLR, d-NLR, and PLR were observed by the ROC curves, the optimal thresholds of NLR and d-NLR were not consistent with other studies.[9,10] The optimal thresholds of LMR, PNI, and PLR were close to the range of previous reports.[12,13,24] The exact mechanisms underlying these relationships are unclear. The differences include that number of patient from a different geographic region and race and different survival end point may be the most important factors that contribute to the phenomenon.[8] Moreover, the potential explanation is that synCRC is a different from other cancer. We also examined the correlations between inflammatory markers and DFS. While, optimal thresholds calculated by OS were also fit for the DFS, which indicated that the cut-off values were used commonly for the type of cancer to evaluate the outcome.

While other systemic inflammation indicators such as CRP, IL-6, and IL-11 had correlations with the development of cancer.[25] However, the levels of those inflammation indicators are not always examined in the hospital. Peripheral blood test is routinely performed without need for additional expenses in all patients with cancer during in the follow-up and NLR is simply obtained by routine postoperative examination. On the other hand, the anatomic extent of tumor (pTNM classification) is regarded as the most relevant prognostic factor in colorectal cancer.[26] However, the 10% to 25% colorectal patients with low stage have no received any adjuvant therapies, which developed unexpectedly progress during in the follow-up, and the advanced stage may show heterogeneous clinical outcome.[27] Both the pTNM stage and histological characteristics mirror the anatomi-

cal extent and biological characteristics of the tumor. Thus, the NLR, independently from pTNM stage and histological characteristics, acted as prognostic parameter and reflected biological properties of organism to select high-risk patients.

Several limitations of our study require consideration: first, its retrospective design and small sample sizes and single-center experience, which could not be representative of all synCRC patients in general and might weaken the meaning of our findings; second, underlying blood conditions (e.g., ischemia, coronary/metabolic syndrome, diabetes mellitus, and renal/hepatic dysfunction) were not taken into consideration. Furthermore, anti-inflammatory medicine was regularly used after surgery, which also interfered the postoperative results; third, despite the determining values based on ROC curve analysis, markers sensitivity and specificity was lower, which may introduce bias into the predictions of prognosis. Thus, combining other clinical parameter with those markers may improve accuracy selecting the high risk patients with synCRC.

On the other hand, previous study reported postoperative NLR decreased after surgery,[28] simultaneously, chemoradiotherapy has effect on peripheral blood as well. Therefore, an appropriate timing for the evaluation of the postoperative systemic inflammatory response to predict the survival was unknown.[28,29] Further investigation with larger scale and long-term follow-up is required to confirm the appropriate evaluating time and prognostic role of it.

5. Conclusion

Postoperative NLR, cancer grade, and pN stage were confirmed as an independent prognostic factors for 3 years OS and DFS for the patients who were diagnosed synCRC and underwent surgery resection. Integrating postoperative NLR and pTNM stage and histological characteristics may allow stratifying patient into different risk categories and offer appropriate personal therapeutic strategy. Large-scale, multi-institutional studies are required to validate these findings and to further clarify the role of inflammatory markers in synCRC.

Acknowledgments

The authors thank all the patients who participated in this study and provided the follow-up data for our study.

References

[1] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
[2] Pajares JA, Perea J. Multiple primary colorectal cancer: Individual or familial predisposition? World J Gastrointest Oncol 2015;7:434–44.
[3] Kaibara N, Koga S, Jinnai D. Synchronous and metachronous malignancies of the colon and rectum in Japan with special reference to a coexisting early cancer. Cancer 1984;54:1870–4.
[4] Mulder SA, Kranse R, Damhuis RA, et al. Prevalence and prognosis of synchronous colorectal cancer: a Dutch population-based study. Cancer Epidemiol 2011;35:442–7.
[5] Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. Nature 2008;454:436–44.
[6] Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncol 2010;6:149–63.
[7] Shibutani M, Maeda K, Nagahara H, et al. A high preoperative neutrophil-to-lymphocyte ratio is associated with poor survival in patients with colorectal cancer. Anticancer Res 2013;33:3291–4.
[8] Ying HQ, Deng QW, He BS, et al. The prognostic value of preoperative NLR, d-NLR, PLR and LMR for predicting clinical outcome in surgical colorectal cancer patients. Med Oncol 2014;31:305.
[9] Malietzis G, Giacometti M, Kennedy RH, et al. The emerging role of neutrophil to lymphocyte ratio in determining colorectal cancer treatment outcomes: a systematic review and meta-analysis. Ann Surg Oncol 2014;21:3938–46.
[10] Absenger G, Szkandera J, Pichler M, et al. A derived neutrophil to lymphocyte ratio predicts clinical outcome in stage II and III colon cancer patients. Br J Cancer 2013;109:395–400.
[11] Stotz M, Pichler M, Absenger G, et al. The preoperative lymphocyte to monocyte ratio predicts clinical outcome in patients with stage III colon cancer. Br J Cancer 2014;110:435–40.
[12] Zhou X, Du Y, Huang Z, et al. Prognostic value of PLR in various cancers: a meta-analysis. PLoS One 2014;9:e101119.
[13] Sun K, Chen S, Xu J, et al. The prognostic significance of the prognostic nutritional index in cancer: a systematic review and meta-analysis. J Cancer Res Clin Oncol 2014;140:1537–49.
[14] Edge S, Byrd D, Compton C. AJCC (American Joint Committee On Cancer). Cancer Staging Manual. 2010.
[15] Greiner M, Pfeiffer D, Smith RD. Principles and practical application of the receiver-operating characteristic analysis for diagnostic tests. Prev Vet Med 2000;45:23–41.
[16] Oya M, Takahashi S, Okuyama T, et al. Synchronous colorectal carcinoma: clinico-pathological features and prognosis. Jpn J Clin Oncol 2003;33:38–43.
[17] Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001;357:539–45.
[18] Xiao WW, Zhang LN, You KY, et al. A low lymphocyte-to-monocyte ratio predicts unfavorable prognosis in pathological T3N0 rectal cancer patients following total mesorectal excision. J Cancer 2015;6:616–22.
[19] Neal CP, Cairns V, Jones MJ, et al. Prognostic performance of inflammation-based prognostic indices in patients with resectable colorectal liver metastases. Med Oncol 2015;32:144.
[20] Smith RA, Bosonnet L, Raraty M, et al. Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. Am J Surg 2009;197:466–72.
[21] Shibutani M, Maeda K, Nagahara H, et al. Prognostic significance of the lymphocyte-to-monocyte ratio in patients with metastatic colorectal cancer. World J Gastroenterol 2015;21:9966–73.
[22] Paik KY, Lee IK, Lee YS, et al. Clinical implications of systemic inflammatory response markers as independent prognostic factors in colorectal cancer patients. Cancer Res Treat 2014;46:65–73.
[23] McSorley ST, Watt DG, Horgan PG, et al. Postoperative systemic inflammatory response, complication severity and survival following surgery for colorectal cancer. Ann Surg Oncol 2016;23:2832–40.
[24] Nishijima TF, Muss HB, Shachar SS, et al. Prognostic value of lymphocyte-to-monocyte ratio in patients with solid tumors: A systematic review and meta-analysis. Cancer Treat Rev 2015;41:971–8.
[25] Taniguchi K, Karin M. IL-6 and related cytokines as the critical lynchpins between inflammation and cancer. Semin Immunol 2014;26:54–74.
[26] Mlecnik B, Bindea G, Pagès F, et al. Tumor immunosurveillance in human cancers. Cancer Metastasis Rev 2011;30:5–12.
[27] Barresi V, Reggiani Bonetti L, Ieni A, et al. Poorly differentiated clusters: clinical impact in colorectal cancer. Clin Colorectal Cancer 2017;16:9–15.
[28] Forget P, Dinant V, De Kock M. Is the Neutrophil-to-Lymphocyte ratio more correlated than C-reactive protein with postoperative complications after major abdominal surgery? PeerJ 2015;3:e713.
[29] Shibutani M, Maeda K, Nagahara H, et al. The prognostic significance of a postoperative systemic inflammatory response in patients with colorectal cancer. World J Surg Oncol 2015;13:194.