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Predictive Values of Postoperative and Dynamic Changes of Inflammation Indexes in Survival of Patients with Resected Colorectal Cancer*

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Summary: The aim of the present study was to evaluate the prognostic potential of postoperative scores of inflammation indexes and the dynamic changes of scores before and after tumor resection in colorectal cancer patients. The study included 516 colorectal cancer patients with primary colorectal tumor resection. Cox regression was applied to estimate the associations of postoperative and dynamic changes of inflammation indexes with progression-free survival and overall survival. As results, we found that higher postoperative neutrophil to lymphocyte ratio (NLR), neutrophil and monocyte to lymphocyte ratio (NMLR), platelet to lymphocyte ratio (PLR) and systemic immune inflammation index (SII) were associated with shorter progression-free survival. The increased NLR, NMLR, PLR, SII and C-reaction protein (CRP) to albumin (ALB) ratio (CAR) were associated with poor progression-free survival, with HRs (95% CIs) of 1.92 (1.27–2.90), 1.46 (1.11–2.09), 2.10 (1.34–3.30), 1.81 (1.22–2.70) and 1.65 (1.03–2.67), respectively. Postoperative NMLR, SII, CAR, and their dynamic changes were also significantly correlated with overall survival, with the HRs (95% CIs) of 2.63 (1.30–3.97), 2.44 (1.43–4.17), 2.74 (1.31–5.74), 2.08 (1.21–3.60), 1.97 (1.12–3.45) and 2.55 (1.21–5.38) respectively. In conclusion, postoperative inflammation indexes and their dynamic changes, particularly for NMLR, SII and CAR are promising prognostic predictors of CRC patients.
Key words: colorectal cancer; postoperative inflammation index; dynamic change; prognosis

Colorectal cancer (CRC) is the third most common cancer worldwide, with an estimate of over 1.4 million new cases and 694 thousand deaths every year recently[1]. More than 60% of colorectal cancer patients develop regional and/or distant metastasis at the time of diagnosis. Although the prognosis improved during the past decade, the 5-year survival rates of patients with local metastasis and patients with distant metastasis are 69.2% and 11.7%, respectively[2, 3]. Therefore, prognostic studies are needed for better strategies of clinical therapies. Traditional prognostic prediction mainly relies upon clinicopathological characteristics, such as TNM stage. However, even on the same stage, the clinical processes of CRC patients are not exactly the same. Thus, novel prognostic markers are still warranted[4, 5].

Systemic inflammation has been linked to poor prognosis of colorectal cancer[6]. Recently, preoperative systemic inflammation indexes are considered as promising prognostic predictors which give the easy accessibility and convenient application[7]. Generally, there are two kinds of inflammation indexes. The first

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one is derived from the combination of C-reaction protein (CRP) and albumin (ALB), including the Glasgow prognostic score (GPS), modified Glasgow prognostic score (MGPS), and CRP to ALB ratio (CAR). GPS and MGPS have been indicated as short-term and long-term prognostic predictors for CRC patients receiving radical operation[8]. CAR has been reported for its correlation with side effects of adjuvant chemotherapy[9]. The other kind is leukocyte-related inflammation scores, including prognostic index (PI), prognostic nutritional index (PNI), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), neutrophil and monocyte to lymphocyte ratio (NMLR) and systemic immune-inflammation index (SII). PI has been reported as a predictor of tumor recurrence in patients with curatively resected hepatocellular carcinoma[10]. Elevated NLR and PLR have been associated with poor survival of colorectal cancer[11]. Whereas, decreased LMR and PNI have presented significant associations with poor survival of CRC[12, 13]. NMLR, a new index derived from the counts of neutrophils, monocytes and lymphocytes, has been reported as an indicator for poor prognosis of liver cancer[14]. In addition, SII, a combination of PLR and NLR, has presented useful values for prognostic evaluation of small cell lung cancer[15].

Although a couple of inflammation indexes are developed, to date, most studies have focused on the prognostic values of preoperative inflammation indexes. Here, we designed this study to evaluate the prognostic potential of postoperative scores of inflammation indexes and the dynamic changes of scores before and after tumor resection in CRC patients.

1 MATERIALS AND METHODS

1.1 Patients

Primary colorectal cancer patients who underwent tumor resection at Hubei Cancer Hospital from January 2007 to December 2015 were recruited. Patients satisfying the following criteria were included in the final analysis: (1) no infectious disease or other disease that caused systemic inflammation before surgery; (2) no previous or concurrent malignancies.

1.2 Evaluation of Clinicopathological Features

The clinicopathological features of all colorectal cancer patients, including age at diagnosis, sex, tumor location (colon, rectum or both of them), tumor size (maximum diameter), tumor stage, histological type, tumor differentiation, surgical margin infiltration, vascular/lymphatic and perineural invasion, surgery complications, and adjuvant therapies, were recorded through review of medical records. Tumor stage was estimated according to Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) TNM Stage (version 7). Histological type contained non-mucinous (tubular or papillary), mucinous and hybrid adenocarcinomas. Differentiation of non-mucinous adenocarcinoma was graded as well, moderate or poor-differentiated according to the proportion of glandular cells. Mucinous and hybrid adenocarcinomas were considered as poorly differentiated[16]. Surgical margin infiltration was defined as tumor extension within 1 mm of the surgical margin[17]. Vessel invasion included blood-vessel and lymph-vessel invasion of tumor. The counts of peripheral white blood cell (WBC), neutrophil (NEU), lymphocyte (LYM), monocyte (MON) and platelet (PLT), and the concentrations of CRP and ALB were detected before and one month after the tumor resection, respectively. Dynamic monitoring of computed tomography and magnetic resonance imaging were used for detecting tumor recurrence and metastasis. Patients were followed up via telephone interview and review of medical records until April 30th, 2017.

1.3 Assessment of Inflammation Indexes

Inflammation indexes in this study included LMR, NLR, NMLR, PLR, SII, PNI, CAR, GPS, MGPS and PI. The differences of these indexes before and one month after the tumor resection was calculated as their dynamic changes (marked with prefix "Δ"). The dynamic changes of LMR, NLR, NMLR, PLR, SII, PNI and CAR are defined as their postoperative values minus preoperative values, respectively[18]. LMR, NLR, NMLR, PLR, SII, PNI, CAR and their corresponding dynamic changes (ΔLMR, ΔNLR, ΔNMLR, ΔPLR, ΔSII, ΔPNI and ΔCAR) were dichotomized by the optimal cut-off points with the highest Youden Indices (specificity + sensitivity − 1) derived from the receiver operating characteristic (ROC) curves. The corresponding cut-off points are shown in the table 1. The scores assignments of dynamic changes of GPS, MGPS and PI (ΔGPS, ΔMGPS and ΔPI) based on postoperative scores of GPS, MGPS, PI minus their preoperative scores. ΔGPS, ΔMGPS and ΔPI are allocated scores of 0 if postoperative scores of GPS, MGPS, PI decreased or remained at 0; ΔGPS, ΔMGPS and ΔPI were allocated the score of 1 if postoperative scores of GPS, MGPS, PI increased or remained at 1 or 2[19]. Table 2 and 3 show the score assignments of the inflammation indexes and dynamic changes of the inflammation indexes, respectively.

1.4 Statistical Analysis

Chi-square test or Fisher's exact test was used to compare the clinicopathological characteristics of patients with different survival outcomes. The primary study outcome was progression-free survival (PFS), followed by overall survival (OS) as the secondary outcome. PFS was defined as the time interval from date of tumor resection to recurrence, metastasis, death

Table 1 The cut-off points of inflammation indexes

Index	Pre-operation	Post-operation	Δ[a]	Clinical outcomes
	Cut-off	Cut-off	Cut-off	
LMR	3.76	4.76	0.24	PFS
	3.16	3.43	1.37	OS
NLR	1.69	2.39	–0.62	PFS
	1.71	2.41	0.04	OS
NMLR	0.62	0.78	0.11	PFS
	0.67	0.88	0.50	OS
PLR	177.78	163.40	−28.80	PFS
	178.85	249.12	−25.25	OS
SII	531.27	568.69	−69.99	PFS
	385.91	503.46	−69.99	OS
PNI	50.65	49.15	4.90	PFS
	47.95	49.95	0.10	OS
CAR	0.08	0.09	0.02	PFS
	0.07	0.09	0.02	OS

LMR: lymphocyte to monocyte ratio; NLR: neutrophil to lymphocyte ratio; NMLR: neutrophil and monocyte to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SII: systemic immune inflammation index; PNI: prognostic nutritional index; CAR: C-reactive protein to albumin ratio; [a]ΔLMR, ΔNLR, ΔNMLR, ΔPLR, ΔSII, ΔPNI and ΔCAR represent the postoperative dynamic changes of LMR, NLR, NMLR, PLR, SII, PNI and CAR, respectively. The dynamic change is defined as postoperative values of the indexes minus corresponding preoperative values. PFS: progression-free survival; OS: overall survival

from colorectal cancer, or the end of the follow-up, whichever came first. OS was defined as the interval from the date of tumor resection to the date of death or to the end of the follow-up, whichever came first. The cumulative PFS and OS were quantified using life-table method. The PFS and OS curves were constructed by Kaplan-Meier method and compared by log-rank test. The Cox proportional hazards regression was applied to compute the hazard ratios (HRs) and 95% confidence intervals (CIs) for PFS and OS, and Harrel's concordance index (C-index) was used to evaluate the predictive accuracy of multivariate Cox regression[20]. All statistical tests were two-sided, and $P<0.05$ was considered as statistically significant. All statistical analyses were performed using the SAS Statistics software 9.4 (SAS Institute, USA).

1.5 Ethics

Ethical committee of Tongji Medical College of Huazhong University of Science and Technology approved this study. Written informed consent was obtained from all patients before this study.

2 RESULTS

2.1 Baseline Clinicopathological Characteristics of Patients with Colorectal Cancer

A total of 516 patients were finally included in the current study, including 331 (64.14 %) males and 185 (35.85 %) females. The age at diagnosis ranged from 16 to 87 years. Tumors of stage I, II, III and IV fell in 69 (13.37%), 164 (31.78%), 201 (38.95%) and 82 (15.89%) patients, respectively. Eighty-one (15.69%) patients died and 166 (32.42%) patients had cancer progression (tumor recurrence, metastasis and death from colorectal cancer), among a median follow-up time of 21.72 months (range: 2.11 to 118.72 months) through the end of follow-up (April 30th, 2017). Cumulative 3-year PFS rate was 57.22%. Cumulative 3-year OS rate was 77.78%. We observed differential distribution of TNM stage ($P<0.0001$), differentiation ($P=0.0009$) and perineural invasion ($P=0.02$) between CRC patients with different disease progression status. Besides, tumor TNM stage ($P<0.0001$), histological type ($P=0.002$), differentiation ($P=0.007$) and tumor involvement of circumferential resection margin ($P=0.004$) were different between alive and dead patients with colorectal cancer (table 4).

2.2 Inflammation Indexes and PFS of Colorectal Cancer Patients

The Kaplan-Meier curves of PFS distribution by dichotomized postoperative NLR, NMLR, PLR and SII are shown in fig. 1. PFS curves of ΔNLR, ΔNMLR, ΔPLR and ΔSII are shown in fig. 2. Sex, age at diagnosis, TNM stage, tumor differentiation, circumferential resection margin status, perineural invasion, neoadjuvant therapy and postoperative adjunctive therapy were further adjusted in multivariable analyses. The scores of pre-operative inflammation indexes were also considered as adjusted variables for corresponding dynamic changes of inflammation scores. Higher postoperative NLR, NMLR, PLR and SII were associated with shorter PFS, with HRs (95% CIs) of 1.77 (1.24–2.52), 1.65 (1.13–2.05), 1.57 (1.10–2.24) and 1.75 (1.23–2.49), respectively. Furthermore, the increased NLR, NMLR, PLR and SII (ΔNLR, ΔNMLR, ΔPLR and ΔSII) were associated with poor PFS, with HRs (95% CIs) of 1.92 (1.27–2.90), 1.46 (1.11–2.09), 2.10 (1.34–3.30), and 1.81 (1.22–2.70), respectively (table 5). C-index of postoperative NLR, NMLR, PLR and SII in multivariable Cox proportional hazards regression was 0.72, 0.71, 0.72 and 0.72, respectively and C-index of dynamic changes of relevant inflammation indexes in multivariable Cox proportional hazards regression was 0.72, 0.71, 0.72, 0.72, respectively.

2.3 Inflammation Indexes and OS of Patients with Colorectal Cancer

Preoperative NLR, NMLR, PLR, SII, PNI and CAR presented significant associations with OS of CRC patients in univariate analyses. After adjustment for sex, age at diagnosis, TNM stage, tumor differentiation, histological type, circumferential resection margin status, neoadjuvant therapy and postoperative adjunctive therapy, PNI was the

Table 2 The assignment of inflammation scores

Inflammation index	Score
LMR	
Lymphocyte count/monocyte count≥cut-off	0
Lymphocyte count/monocyte count<cut-off	1
NLR	
Neutrophil count/lymphocyte count<cut-off	0
Neutrophil count/lymphocyte count≥cut-off	1
NMLR	
Neutrophil count×monocyte count/lymphocyte count<cut-off	0
Neutrophil count×monocyte count/lymphocyte count≥cut-off	1
PLR	
Platelet count/lymphocyte count<cut-off	0
Platelet count/lymphocyte count≥cut-off	1
SII	
Neutrophil count × platelet count / lymphocyte count<cut-off	0
Neutrophil count × platelet count / lymphocyte count≥cut-off	1
PNI	
ALB(g/L)+5×total lymphocyte count (10^9/L)≥cut-off	0
ALB(g/L)+5×total lymphocyte count (10^9/L)<cut-off	1
CAR	
CRP/ALB<cut-off	0
CRP/ALB≥cut-off	1
GPS	
CRP<10 mg/L with ALB≥35 g/L	0
CRP<10 mg/L with ALB<35 g/L	1
CRP≥10 mg/L with ALB≥35 g/L	1
CRP≥10 mg/L with ALB<35 g/L	2
MGPS	
CRP<10 mg/L	0
CRP≥10 mg/L with ALB≥35 g/L	1
CRP≥10 mg/L with ALB<35 g/L	2
PI	
CRP<10 mg/L with WBC<11×10^9/L	0
CRP<10 mg/L with WBC≥11×10^9/L	1
CRP≥10 mg/L with WBC<11×10^9/L	1
CRP≥10 mg/L with WBC≥11×10^9/L	2

LMR: lymphocyte to monocyte ratio; NLR: neutrophil to lymphocyte ratio; NMLR: neutrophil and monocyte to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SII: systemic immune inflammation index; PNI: prognostic nutritional index; CAR: C-reactive protein to albumin ratio; GPS: Glasgow prognostic score; MGPS: modified Glasgow prognostic score; PI: prognostic index

Table 3 The assignment of dynamic changes of inflammation scores

Dynamic changes of inflammation index	Score
ΔNLR, ΔNMLR, ΔPLR, ΔSII, ΔCAR[a]	
Value<cut-off	0
Value≥cut-off	1
ΔLMR, ΔPNI[a]	
Value<cut-off	0
Value≥cut-off	1
ΔGPS, Δ MGPS, ΔPI[b]	
Postoperative score decreased or remained at 0	0
Postoperative score increased, or remained at 1 or 2	1

LMR: lymphocyte to monocyte ratio; NLR: neutrophil to lymphocyte ratio; NMLR: neutrophil and monocyte to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SII: systemic immune inflammation index; PNI: prognostic nutritional index; CAR: C-reactive protein to albumin ratio; GPS: Glasgow prognostic score; MGPS: modified Glasgow prognostic score; PI: prognostic index.

[a]ΔLMR, ΔNLR, ΔNMLR, ΔPLR, ΔSII, ΔPNI and ΔCAR are the postoperative dynamic changes of LMR, NLR, NMLR, PLR, SII, PNI and CAR, respectively. The dynamic change is defined as postoperative values of the indexes minus corresponding preoperative values. [b]ΔGPS, Δ MGPS, ΔPI are the postoperative dynamic changes of GPS, MGPS and PI, respectively. Score assignments of dynamic changes of ΔGPS, ΔMGPS and ΔPI are based on postoperative scores of GPS, MGPS and PI comparing with their preoperative scores.

Table 4 Baseline clinicopathological characteristics of 516 colorectal cancer patients [*n* (%)]

Variables	Cancer progression[a]		*P*	Survival[b]		*P*
	No (*n*=350)	Yes (*n*=166)		Alive (*n*=435)	Dead (*n*=81)	
Age at diagnosis (year)[c]			0.81			0.29
≤65	241 (68.86)	116 (69.88)		305 (70.11)	52 (64.20)	
>65	109 (31.14)	50 (30.12)		130 (29.89)	29 (35.80)	
Sex			0.62			0.81
Male	222 (63.43)	109 (65.66)		280 (64.40)	51 (63.00)	
Female	128 (36.57)	57 (34.34)		155 (35.60)	30 (37.00)	
TNM stage			<0.0001			<0.0001
I or II	197 (56.29)	36 (21.69)		225 (51.72)	8 (9.88)	
III or IV	153 (43.71)	130 (78.31)		210 (48.28)	73 (90.12)	
Histological type[d]			0.26			0.002
Non-MAC	302 (86.29)	137 (82.53)		337 (86.67)	62(76.54)	
Others	48 (13.71)	29 (17.47)		58 (13.33)	19(23.46)	
Differentiation			0.0009			0.007
Well	53 (15.14)	17 (10.24)		59 (13.56)	11(13.58)	
Moderate	253 (72.29)	107 (64.46)		313 (71.95)	47(58.02)	
Poor	44 (12.57)	42 (25.30)		63 (14.48)	23(28.40)	
Tumor size (cm, maximum diameter)			0.71			0.23
≤ 4	202 (58.72)	98 (60.87)		259 (60.51)	41(53.25)	
> 4	142 (41.28)	63 (39.13)		169 (39.49)	36(46.75)	
Unknown	6 (1.16)	5 (0.97)		7 (1.36)	4 (0.77)	
Vessel invasion			0.10			0.44
Absent	270 (77.14)	117 (70.48)		329 (75.63)	58 (71.60)	
Present	80 (22.86)	49 (29.52)		106 (24.37)	23 (28.40)	
Perineural invasion			0.02			0.92
Absent	304 (86.86)	131 (78.92)		367 (84.37)	68 (83.95)	
Present	46 (13.14)	35 (21.08)		68 (15.63)	13 (16.05)	
CRM[e] invasion			0.09			0.004
Negative	343 (98.00)	158 (95.18)		427 (98.16)	74 (91.36)	
Positive	7 (2.00)	8 (4.82)		8 (1.84)	7 (8.64)	
Tumor location			0.71			0.51[f]
Colon	122 (34.86)	64 (38.55)		153 (35.17)	33 (40.74)	
Rectum	222 (63.43)	99 (59.64)		275 (63.22)	46 (56.79)	
Both	6 (1.71)	3 (1.81)		7 (1.61)	2 (2.47)	
Complication[g]			0.15			0.35
Absent	329 (94.00)	150 (90.36)		406 (93.33)	73 (90.12)	
Present	21 (6.00)	16 (9.64)		29 (6.67)	8 (9.88)	
Neoadjuvant therapy			0.13			0.43
No	334 (95.43)	153 (92.17)		412 (94.71)	75 (92.59)	
Yes	16 (4.57)	13 (7.83)		23 (5.29)	6 (7.41)	
Adjuvant therapy (after surgery)			0.09			0.55
No	55 (15.70)	17 (10.20)		59 (13.60)	13 (16.00)	
Yes	295 (84.30)	149 (89.80)		376 (86.40)	68 (84.00)	

[a]Tumor recurrence, metastasis and death of diagnosis were considered as cancer progression. [b]Cause of death of the 81 patients was colorectal cancer. [c]Mean age (standard deviation) at diagnosis was 58.40 (11.77). [d]Non-MAC: non-mucinous adenocarcinoma (tubular or papillary); others histological categories contained mucinous adenocarcinoma and mixed adenocarcinoma. [e]Circumferential resection margin. [f]Fisher exact test. [g]Including 30 (5.81%) patients with postoperative infections and 10 (1.94%) patients with anastomotic fistulas.

only preoperative inflammation index that showed significant association with OS, with an HR of 1.63 (95%CI, 1.01–2.64). Postoperative NLR, NMLR, SII, CAR and MGPS were significant predictors for the death of CRC patients in multivariable analyses, with HRs (95% CIs) of 2.08 (1.23–3.52), 2.63 (1.30–3.97), 2.44 (1.43–4.17), 2.74 (1.31–5.74) and 1.76 (1.05–2.95), respectively. OS curves of postoperative NMLR, SII, CAR and MGPS are shown in fig. 3. In addition, the dynamic changes of NMLR, SII, CAR and MGPS (ΔNMLR, ΔSII, ΔCAR and ΔMGPS) were significantly correlated with OS, with HRs (95% CIs) of 2.08 (1.21–3.60), 1.97 (1.12–3.45), 2.55 (1.21–5.38) and 2.33 (1.01–5.38), respectively

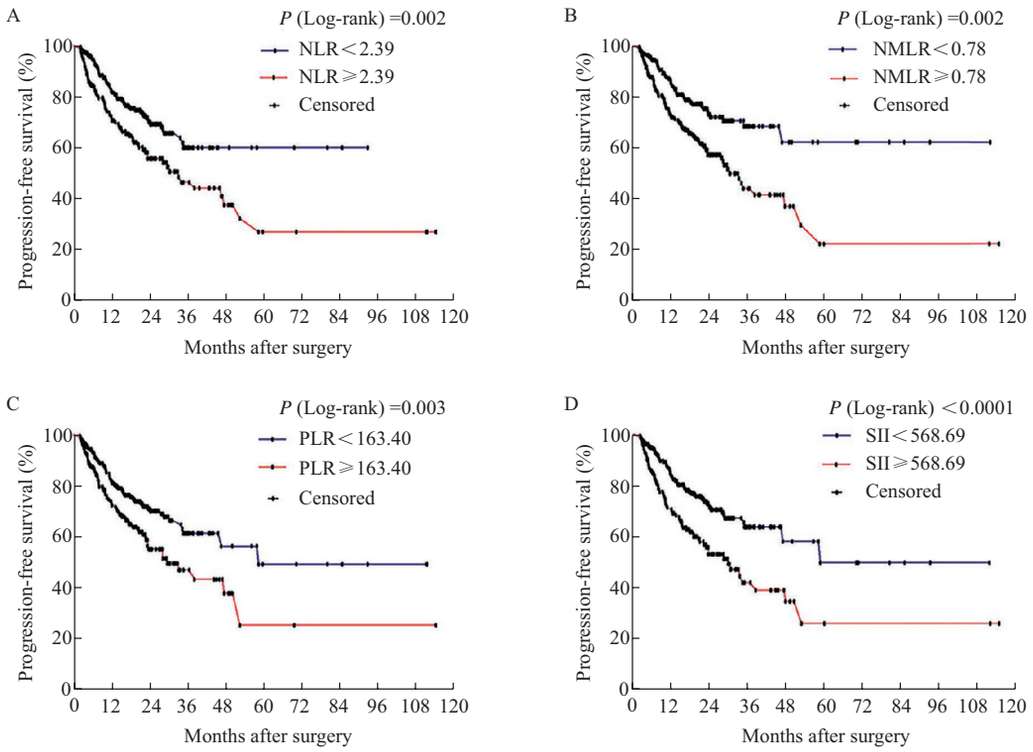

Fig. 1 Kaplan-Meier curves of PFS for patients with CRC stratified by postoperative inflammation indexes
A: neutrophil to lymphocyte ratio (NLR); B: neutrophil and monocyte to lymphocyte ratio (NMLR); c: platelet to lymphocyte ratio (PLR); D: systemic immune inflammation index (SII)

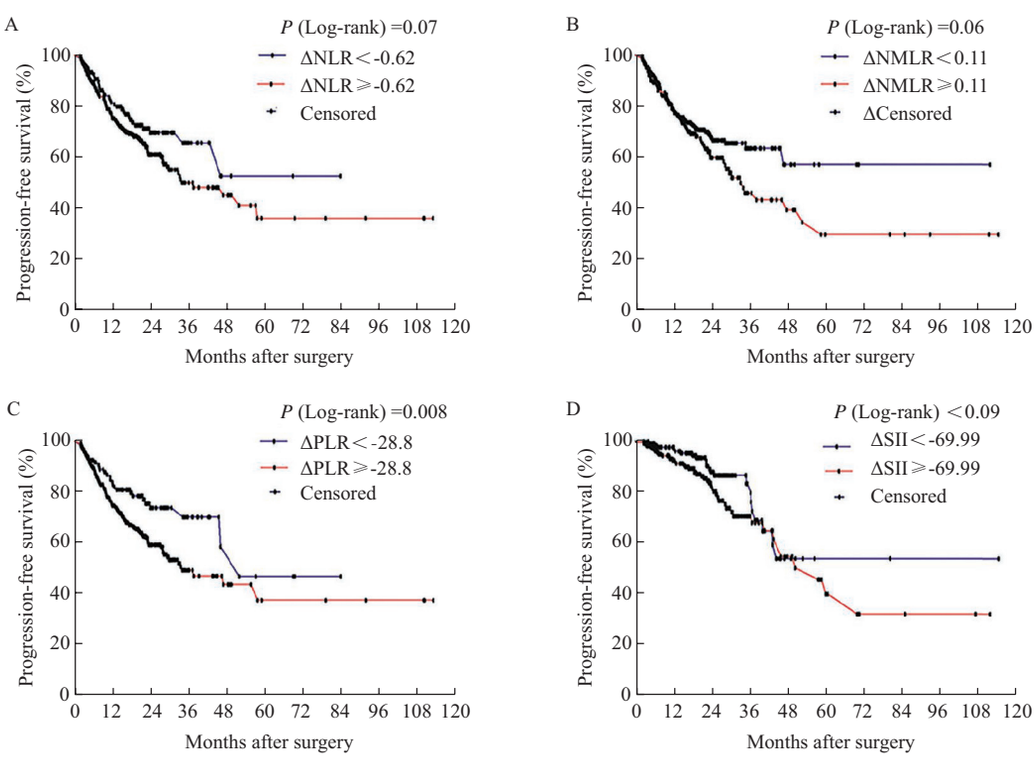

Fig. 2 Kaplan-Meier curves of PFS for patients with CRC stratified by postoperative dynamic changes of inflammation indexes
A: dynamic change of neutrophil to lymphocyte ratio (ΔNLR); B: dynamic change of neutrophil and monocyte to lymphocyte ratio (ΔNMLR); C: dynamic change of platelet to lymphocyte ratio (ΔPLR); D: dynamic change of systemic immune inflammation index (ΔSII)
The dynamic changes of NLR, NMLR, PLR and SII are described as postoperative values of the index minus the corresponding preoperative values.

Table 5 Association between inflammation indexes and PFS of patients with colorectal cancer

Index	Crude HR (95% CI)			Multi-variable HR (95% CI)[a]		
	Pre-operation	Post-operation		Pre-operation	Post-operation	
		1 month	Dynamic change[b]		1 month	Dynamic change[b]
LMR	1.55 (1.13–2.14)	1.86 (1.17–2.93)	1.13 (0.79–1.60)	1.21 (0.87–1.69)	1.40 (0.87–2.24)	1.25 (0.85–1.83)
NLR	1.79 (1.15–2.81)	1.76 (1.23–2.43)	1.43 (0.97–2.11)	1.44 (0.91–2.30)	1.77 (1.24–2.52)	1.92 (1.27–2.90)
NMLR	1.89 (1.26–2.84)	1.91 (1.33–2.75)	1.34 (0.95–1.89)	1.38 (0.90–2.11)	1.65 (1.13–2.05)	1.46 (1.11–2.09)
PLR	1.27 (0.94–1.79)	1.67 (1.18–2.34)	1.71 (1.13–2.58)	1.00 (0.73–1.37)	1.57 (1.10–2.24)	2.10 (1.34–3.30)
SII	1.12 (0.83–1.51)	1.90 (1.35–2.67)	1.57 (1.09–2.24)	1.71 (0.95–3.07)	1.75 (1.23–2.49)	1.81 (1.22–2.70)
PNI	1.62 (1.18–2.23)	1.55 (1.09–2.22)	1.28 (0.73–2.23)	1.34 (0.99–1.94)	1.51 (1.03–2.19)	1.55 (0.86–2.87)
CAR	1.43 (0.99–2.07)	2.13 (1.36–3.35)	1.95 (1.25–3.03)	1.05 (0.71–1.56)	1.38 (0.85–2.24)	1.65 (1.03–2.67)
GPS	1.16 (0.83–1.61)	1.53 (1.09–2.15)	1.88 (1.17–3.02)	0.94 (0.66–1.32)	1.21 (0.83–1.77)	1.63 (0.96–2.75)
MGPS	1.17 (0.84–1.63)	1.51 (1.07–2.13)	1.85 (1.14–3.00)	0.93 (0.66–1.32)	1.16 (0.79–1.71)	1.56 (0.90–2.96)
PI	1.17 (0.81–1.70)	1.80 (1.17–2.77)	1.82 (1.12–2.96)	0.70 (0.61–1.32)	1.18 (0.73–2.21)	1.49 (0.87–2.58)

HR: hazard ratio; CI: confidence interval; LMR: lymphocyte to monocyte ratio; NLR: neutrophil to lymphocyte ratio; NMLR: neutrophil and monocyte to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SII: systemic immune inflammation index; PNI: prognostic nutritional index; CAR: C-reactive protein to albumin ratio; GPS: Glasgow prognostic score; MGPS: modified Glasgow prognostic score; PI: prognostic index

[a]Adjusted for sex, age at diagnosis, TNM stage, differentiation, circumferential resection margin status, perineural invasion, neoadjuvant therapy and postoperative adjunctive therapy. The preoperative inflammation indexes were also adjusted for corresponding dynamic changes of inflammation indexes. [b]Dynamic changes of LMR, NLR, NMLR, PLR, SII, PNI and CAR represented postoperative values of the indexes minus corresponding preoperative values. Score assignments of dynamic changes of GPS, MGPS and PI were based on postoperative scores of GPS, MGPS and PI comparing with their preoperative scores.

(table 6). OS curves of ΔNMLR, ΔSII, ΔCAR and ΔMGPS are shown in fig. 4. C-index of postoperative NLR, NMLR, SII, CAR, MGPS in multivariable Cox proportional hazards regression was 0.82, 0.82, 0.82, 0.87 and 0.85, respectively and C-index of dynamic changes of NMLR, PLR, SII, CAR, GPS and MGPS in multivariable Cox proportional hazards regression were 0.82, 0.81, 0.81, 0.85, 0.85 and 0.85, respectively.

3 DISCUSSION

Recent evidence has indicated the predictive potential of some preoperative systemic inflammation indexes, including GPS, MGPS, CAR, NLR, PLR, LMR and PNI in the survival of patients with CRC[8, 9, 11–13]. To the best of our knowledge, previous studies merely focused on the association between

Table 6 Association between inflammation indexes and OS of patients with colorectal cancer

Index	Crude HR (95% CI)			Multi-variable HR (95% CI)[a]		
	Pre-operation	Post-operation		Pre-operation	Post-operation	
		1 month	Dynamic change[b]		1 month	Dynamic change[b]
LMR	1.50 (0.97–2.33)	1.68 (1.02–2.75)	1.68 (0.85–3.28)	1.11 (0.70–1.74)	1.25 (0.74–2.12)	1.33 (0.66–2.69)
NLR	2.01 (1.23–3.28)	2.01 (1.23–3.28)	1.22 (0.75–1.99)	1.31 (0.64–2.68)	2.08 (1.23–3.52)	1.65 (0.98–2.78)
NMLR	2.06 (1.11–3.80)	2.54 (1.50–4.29)	1.89 (1.13–3.16)	1.12 (0.58–2.16)	2.63 (1.30–3.97)	2.08 (1.21–3.60)
PLR	1.62 (1.04–2.50)	1.97 (1.12–3.48)	1.74 (0.98–3.09)	1.11 (0.70–1.76)	1.50 (0.84–2.67)	2.16 (1.19–3.95)
SII	1.77 (1.02–3.05)	2.49 (1.49–4.15)	1.50 (0.90–2.50)	1.16 (0.66–2.06)	2.44 (1.43–4.17)	1.97 (1.12–3.45)
PNI	2.43 (1.56–3.78)	2.29 (1.28–4.10)	1.33 (0.78–2.28)	1.63 (1.01–2.64)	1.58 (0.86–2.90)	1.26 (0.72–2.19)
CAR	2.51 (1.05–4.46)	4.89 (2.45–9.73)	2.85 (1.46–5.54)	1.59 (0.86–2.91)	2.74 (1.31–5.74)	2.55 (1.21–5.38)
GPS	1.45 (0.92–2.29)	2.05 (1.31–3.22)	2.53 (1.28–4.99)	1.07 (0.66–1.74)	1.66 (0.98–2.80)	2.70 (1.19–6.11)
MGPS	1.45 (0.97–2.30)	2.11 (1.29–3.16)	2.48 (1.22–4.94)	1.07 (0.66–1.74)	1.76 (1.05–2.95)	2.33 (1.01–5.38)
PI	1.50 (0.89–2.58)	2.76 (1.48–4.84)	2.46 (1.24–4.90)	1.02 (0.59–1.78)	1.96 (0.96–4.01)	2.23 (0.96–5.18)

HR: hazard ratio; CI: confidence interval; LMR: lymphocyte to monocyte ratio; NLR: neutrophil to lymphocyte ratio; NMLR: neutrophil and monocyte to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SII: systemic immune inflammation index; PNI: prognostic nutritional index; CAR: C-reactive protein to albumin Ratio; GPS: Glasgow prognostic score; MGPS: modified Glasgow prognostic score; PI: prognostic index

[a]Adjusted for sex, age at diagnosis, TNM stage, differentiation, histological type, circumferential resection margin status, neoadjuvant therapy and postoperative adjunctive therapy. The preoperative inflammation indexes were also adjusted for corresponding dynamic changes of inflammation indexes. [b]Dynamic changes of LMR, NLR, NMLR, PLR, SII, PNI and CAR represented postoperative values of the indexes minus corresponding preoperative values. Score assignments of dynamic changes of GPS, MGPS and PI were based on postoperative scores of GPS, MGPS and PI comparing with their preoperative scores.

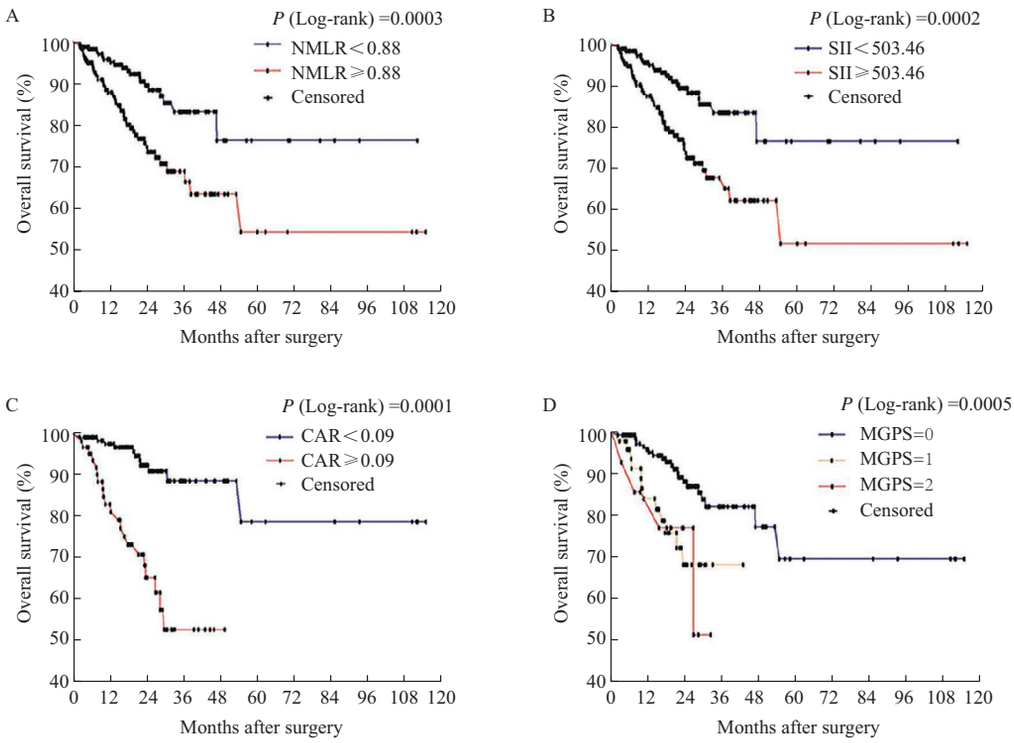

Fig. 3 Kaplan-Meier curves of OS for patients with CRC stratified by postoperative inflammation indexes
A: neutrophil and monocyte to lymphocyte ratio (NMLR); B: systemic immune inflammation index (SII); C: C-reactive protein to albumin ratio (CAR); D: modified Glasgow prognostic score (MGPS)

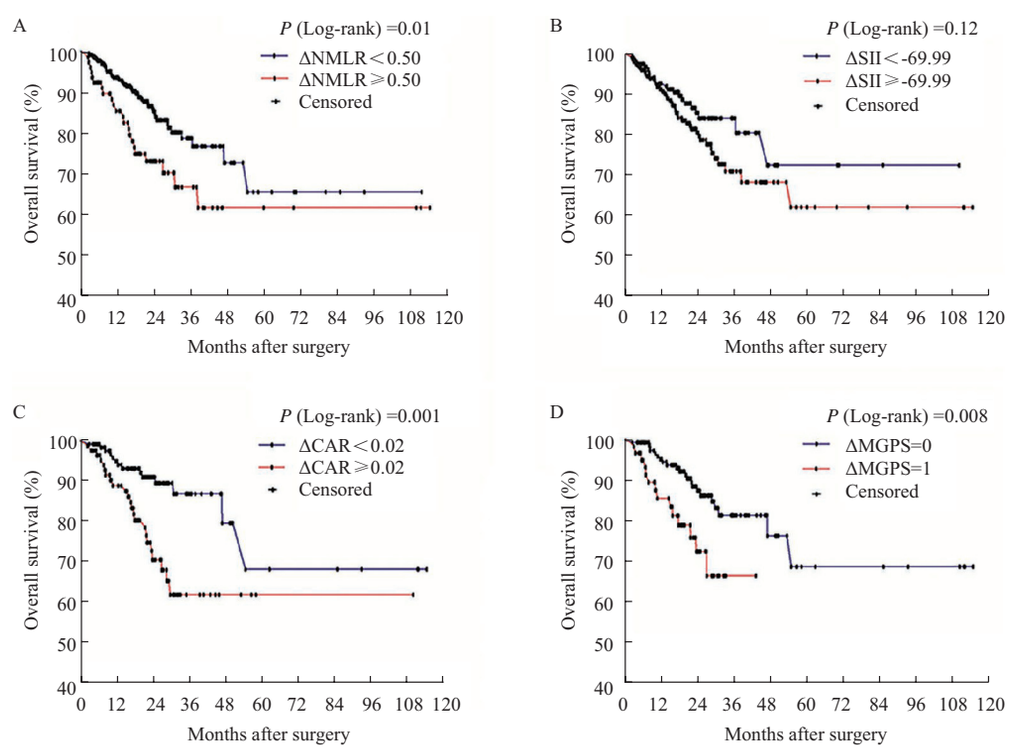

Fig. 4 Kaplan-Meier curves of OS for patients with CRC stratified by postoperative dynamic changes of inflammation indexes
A: dynamic change of neutrophil and monocyte to lymphocyte ratio (ΔNMLR); B: dynamic change of systemic immune inflammation index (ΔSII); C: dynamic change of C-reactive protein to albumin ratio (ΔCAR); D: dynamic change of modified Glasgow prognostic score (ΔMGPS). The dynamic changes of NMLR, SII and CAR are calculated by postoperative values of the index minus the corresponding preoperative values. The dynamic change of MGPS bases on the comparison between postoperative score and preoperative score. If postoperative score decreased or remained at 0, ΔMGPS was allocated the score of 0; otherwise, if postoperative scores increased, or remained at 1 or 2, ΔMGPS was allocated the score of 1.

postoperative dynamic changes of inflammation indexes and survival of colorectal cancer. Our study first extended the research by widely assessing the prognostic values of postoperative and dynamic changes of systemic inflammation scores, including LMR, NLR, NMLR, PLR, SII, PNI, CAR, GPS, MGPS and PI in CRC patients. There has been no universal standard regarding the appropriate timing for measurement of inflammation indexes after surgery. It has been reported that inflammation due to the surgical wound healing process ceased one month after the operation[21], thus we chose the postoperative measurements performed one month after surgery to minimize the surgery-related disturbances. Based on our study, we demonstrated that postoperative NMLR and SII, and their dynamic changes (ΔNMLR, ΔSII) were significant predictors for both PFS and OS in CRC patients. Besides, our study also suggested the prognostic potential of postoperative NLR and PLR, and their dynamic changes for PFS, and postoperative MGPS, CAR, and their dynamic changes for OS of CRC patients.

Our study demonstrated that elevated NLR and ΔNLR were independent predictors for shorter PFS, and higher levels of NMLR and ΔNMLR after surgery were independently associated with both shorter PFS and OS. The critical roles of lymphocytes in tumor immune surveillance and immunoediting have been widely studied[22]. Lymphocytes can eliminate tumor cells through the cytotoxic effects[23]. On the contrary, neutrophils and monocytes may contribute to the tumor progression. Neutrophils release prostaglandin E2 (PGE2) to amplify inflammation and create tumor microenvironment, which can promote colon tumorigenesis, suppress activities of natural killer cells and increase exudation of tumor cells through secretion of interleukin-1β (IL-1β) and matrix metalloproteinases (MMP)[24]. Besides, neutrophils can release neutrophil extracellular traps (NETs) to promote hepatic metastasis of CRC by trapping tumor cells[25]. Thereby, NLR is an integrated indicator for the pro-tumor effect of NEU and anti-tumor immunity of lymphocytes. Besides, monocytes also act as a tumor promoter. Circulating monocytes can differentiate into tumor-associated macrophages (TMAs). As a part of the aggressive tumor microenvironment, mobilization of TMAs in tumor tissues promotes cancer progression[26]. NMLR can be considered as NLR multiplying by monocyte counts, which can act as a more comprehensive integrated inflammatory indicator to reflect the balance between pro-tumor inflammation and anti-tumor immunity. After tumor resection, sustaining high level of NMLR represents persistent pro-tumor inflammation and low level of anti-tumor immunity, which facilitate the regeneration and progression of tumor lesions, especially under the existence of residual malignant cells (micro-metastatic tumor). SII and ΔSII also presented prognostic values for PFS and OS in CRC patients. Besides, PLR and ΔPLR showed prognostic potential for PFS but not for OS. It has been demonstrated that high levels of platelets are capable of promoting cancer progression by increasing angiogenesis through the production of vascular endothelial growth factor (VEGF), overexpression of which has been associated with disease progression and metastasis in patients with CRC[27, 28]. Therefore, continuously elevated postoperative platelet counts probably signify an organic microenvironment conducive to tumor growth. PLR can reflect the balance between cancer promotion capacity of platelet and anti-tumor immunity of lymphocyte. As an index that is defined as PLR multiplying by NEU counts, SII reflects the tumor enhancement effects of platelet and neutrophil, and anti-tumor effect of lymphocyte, and therefore it could also be considered as an integrated inflammation index to predict the prognosis of CRC patients.

Moreover, our study revealed associations of postoperative MGPS, ΔMGPS, CAR and ΔCAR with OS of CRC patients. Previous research has demonstrated that tumor growth could release chemokines, and thus promote inflammatory cells to infiltrate into tumor and surrounding microenvironment, which may cause CRP elevation[29–31]. As a biomarker of chronic inflammation, CRP is capable to promote cancer progression by increasing the expression of oncogenes, causing DNA injury and impairing immune functions[32]. Inflammatory mediators, including interleukin 1 (IL-1), IL-6 and tumor necrosis factor (TNF), can promote the synthesis of CRP but suppress the production of ALB in hepatocytes[33]. Besides, ALB has been used to evaluate the long-term nutritional status. Low level of ALB may reduce the tolerance of postoperative anticancer therapy and cause poor survival[34]. Therefore, persistent high level of CRP and low level of ALB after surgery could be signs of poor survival in CRC patients. Our findings are supported by previous study from Watt *et al*, which demonstrated that elevated postoperative MGPS was associated with increased complication rates and OS of patients with CRC[8]. Besides, we further revealed the prognostic values of dynamic changes of MGPS and CAR. Dynamic change of CAR had higher level of C-index than postoperative and dynamic changes of blood cell related inflammation indexes (NLR, NMLR, PLR, SII). And for OS, MGPS also had higher C-index than blood cell related inflammation indexes. Higher levels of C-index indicates better prediction accuracy[20].

Although lines of studies have evaluated the predictive values of inflammation indexes on the prognosis of CRC patients, most of them focused on preoperative measurements[8, 9, 11–13]. However,

once tumor has been removed, the balance between the systemic inflammation and immune responses changed. Postoperative scores of inflammation indexes can reflect the pro-tumor and anti-tumor balance that differed from preoperative status[35]. Persistent elevated inflammation scores after surgery usually indicate high levels of pro-tumor factors and low levels of anti-tumor factors as mentioned above. Patients who have elevated postoperative inflammation scores may have higher probability of cancer progression, lower immune functions or poorer nutrition status, which can lead to poor clinical outcomes and weak tolerance to postoperative anticancer therapies[23–27, 34]. Therefore, postoperative monitoring of inflammation indexes is important and practical. The present study suggested that postoperative NMLR, SII, ΔNMLR and ΔSII are integrative indexes, and ΔCAR had better prediction accuracy for CRC prognosis. High level of these inflammation indexes had impacts on the survival of patients and multivariate Cox regressions showed that these impacts were independent of clinicopathological prognostic factors such as TNM stages, tumor differentiation, clinical therapy (neoadjuvant/adjuvant therapy). Clinicians can distinguish high risk patients through estimation of postoperative and dynamic changes of these indexes, and formulate pertinent treatments and follow-up monitoring accordingly.

Here, we revealed the prognostic values of postoperative inflammation scores and their dynamic changes from preoperative measurements in CRC patients, which was consistent with our previous finding about the predictive roles of postoperative inflammation scores in the survival of patients with primary hepatic carcinoma[21]. The present study widely covered the inflammation indexes, and highlighted the prognostic potential of postoperative inflammation indexes on CRC patients. In addition, this study provided a novel approach of prognostic prediction by monitoring the changes of inflammation indexes. There are also several limitations in this study. First, since the follow-up was conducted by telephone interview and review of medical records, the recall bias inevitably exists. Second, the cut-off points of inflammation indexes were study-specific. Third, it was a single center based study with limited sample size. It is not powerful enough to estimate the prognosis potential of inflammation indexes in patients with different clinicopathological features. To deal with this limitation, further studies (systematic review, meta-analysis and multicenter clinical studies with large sample size) are warranted to optimize the cut-off points and verify the reported findings.

In conclusion, our study suggests that the postoperative and dynamic changes of NMLR and SII are associated with the PFS and OS of patients with CRC, and dynamic changes of CAR are also good predictor for survival. Although our findings still need further validation, the current study implies the clinical potential of postoperative inflammation indexes and their dynamic changes in prognostic prediction of colorectal cancer.

Conflict of Interest Statement

The authors declare that there is no conflict of interest with any financial organization or corporation or individual that can inappropriately influence this work.

REFERENCES

1 Ferlay J, Soerjomataram I, Dikshit R, *et al*. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer, 2015,136(5):E359-386

2 Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet, 2014,383(9927):1490-1502

3 Siegel R, DeSantis C, Virgo K, *et al*. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin, 2012,62(4):220-241

4 Hu H, Krasinskas A, Willis J. Perspectives on current tumor-node-metastasis (TNM) staging of cancers of the colon and rectum. Semin Oncol, 2011,38(4):500-510

5 Stintzing S, Stremitzer S, Sebio A, *et al*. Predictive and prognostic markers in the treatment of metastatic colorectal cancer (mCRC): personalized medicine at work. Hematol Oncol Clin North Am, 2015,29 (1):43-60

6 Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncol, 2010,6(1):149-163

7 Park JH, Watt DG, Roxburgh CS, *et al*. Colorectal Cancer, Systemic Inflammation, and Outcome: Staging the Tumor and Staging the Host. Ann Surg, 2016,263(2):326-336

8 Watt DG, McSorley ST, Park JH, *et al*. A Postoperative Systemic Inflammation Score Predicts Short- and Long-Term Outcomes in Patients Undergoing Surgery for Colorectal Cancer. Ann Surg Oncol, 2017,24 (4):1100-1109

9 Tominaga T, Nonaka T, Sumida Y, *et al*. The C-Reactive Protein to Albumin Ratio as a Predictor of Severe Side Effects of Adjuvant Chemotherapy in Stage III Colorectal Cancer Patients. PLoS One, 2016,11(12):e0167967

10 Yamamura K, Sugimoto H, Kanda M, *et al*. Comparison of inflammation-based prognostic scores as predictors of tumor recurrence in patients with hepatocellular carcinoma after curative resection. J Hepatobiliary Pancreat Sci, 2014,21(9):682-688

11 Zou ZY, Liu HL, Ning N, *et al*. Clinical significance of pre-operative neutrophil lymphocyte ratio and platelet lymphocyte ratio as prognostic factors for patients with colorectal cancer. Oncol Lett,

2016,11(3):2241-2248
12 Song W, Wang K, Zhang RJ, *et al*. Prognostic value of the lymphocyte monocyte ratio in patients with colorectal cancer: A meta-analysis. Medicine, 2016,95(49):e5540
13 Yang Y, Gao P, Chen X, *et al*. Prognostic significance of preoperative prognostic nutritional index in colorectal cancer: results from a retrospective cohort study and a meta-analysis. Oncotarget, 2016,7(36):58543-58552
14 Liao R, Jiang N, Tang ZW, *et al*. Systemic and intratumoral balances between monocytes/ macrophages and lymphocytes predict prognosis in hepatocellular carcinoma patients after surgery. Oncotarget, 2016,7(21):30951-30961
15 Hong X, Cui B, Wang M, *et al*. Systemic Immune-inflammation Index, Based on Platelet Counts and Neutrophil-Lymphocyte Ratio, Is Useful for Predicting Prognosis in Small Cell Lung Cancer. Tohoku J Exp Med, 2015,236(4):297-304
16 Hamilton, Stanley R, Lauri A, *et al*. Pathology and genetics of tumours of the digestive system. Histopathology, 2010,38(6):585-585
17 Brown G, Radcliffe AG, Newcombe RG, *et al*. Preoperative assessment of prognostic factors in rectal cancer using high-resolution magnetic resonance imaging. Br J Surg, 2003,90(3):355-364
18 Jin F, Han A, Shi F, *et al*. The postoperative neutrophil-to-lymphocyte ratio and changes in this ratio predict survival after the complete resection of stage I non-small cell lung cancer. Onco Targets Ther, 2016,9:6529-6537
19 Pang S, Zhou Z, Yu X, *et al*. The predictive value of integrated inflammation scores in the survival of patients with resected hepatocellular carcinoma: A Retrospective Cohort Study. Int J Surg, 2017,42:170-177
20 Harrell FE Jr, Califf RM, Pryor DB, *et al*. Evaluating the yield of medical tests. JAMA, 1982,247:2543-2546
21 Josa V, Krzystanek M, Eklund AC, *et al*. Relationship of postoperative thrombocytosis and survival of patients with colorectal cancer. Int J Surg, 2015,18:1-6
22 Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. Immunity, 2004, 21 (2): 137-148
23 Titu LV, Monson JR, Greenman J. The role of CD8(+) T cells in immune responses to colorectal cancer. Cancer Immunol Immunother, 2002,51(5):235-247
24 Spiegel A, Brooks MW, Houshyar S, *et al*. Neutrophils Suppress Intraluminal NK Cell-Mediated Tumor Cell Clearance and Enhance Extravasation of Disseminated Carcinoma Cells. Cancer Discov, 2016,6(6):630-649
25 Cools-Lartigue J, Spicer J, Mcdonald B, *et al*. Neutrophil extracellular traps sequester circulating tumor cells and promote metastasis. J Clin Invest, 2013,123(8):3446-3458
26 Chanmee T, Ontong P, Konno K, *et al*. Tumor-associated macrophages as major players in the tumor microenvironment. Cancers, 2014,6(3):1670-1690
27 Gay LJ, Felding-Habermann B. Contribution of platelets to tumour metastasis. Nat Rev Cancer, 2011,11(2):123-134
28 Palumbo JS, Talmage KE, Massari JV, *et al*. Platelets and fibrin(ogen) increase metastatic potential by impeding natural killer cell-mediated elimination of tumor cells. Blood, 2005,105(1):178-185
29 Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet, 2001,357(9255):539-545
30 Hara M, Yonei A, Ayabe T, *et al*. Postoperative serum C-reactive protein levels in non-small cell lung cancer patients. Ann Thorac Cardiovasc Surg, 2010,16(2):85-90
31 Heikkila K, Ebrahim S, Lawlor DA. A systematic review of the association between circulating concentrations of C reactive protein and cancer. J Epidemiol Community Health, 2007,61(9):824-833
32 Coussens LM, Werb Z. Inflammation and cancer. Nature, 2002,420(6917):860-867
33 Nazha B, Moussaly E, Zaarour M, *et al*. Hypoalbuminemia in colorectal cancer prognosis: Nutritional marker or inflammatory surrogate? World J Gastrointest Surg, 2015,7(12):370-377
34 Li G, Gao J, Liu ZG, *et al*. Influence of pretreatment ideal body weight percentile and albumin on prognosis of nasopharyngeal carcinoma: Long-term outcomes of 512 patients from a single institution. Head Neck, 2014,36(5):660-666
35 Dan J, Zhang Y, Peng Z, *et al*. Postoperative neutrophil-to-lymphocyte ratio change predicts survival of patients with small hepatocellular carcinoma undergoing radiofrequency ablation. PLoS One, 2013,8(3):e58184

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