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ORIGINAL RESEARCH

Chronic Inflammation Index-Based Tumor Subsite Classification Correlated with Chemotherapy Benefit and Survival Outcomes in Stage II-III Colorectal Cancer

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Purpose: This study aimed to develop and validate an integrated inflammatory prognostic index and to investigate associations between primary tumor location, chronic inflammatory status, adjuvant chemotherapy response, and survival outcomes in stage II–III colorectal cancer (CRC).

Patients and Methods: A total of 1413 stage II–III CRC patients who underwent radical resection were enrolled and divided into discovery and validation cohorts. Preoperative systemic inflammatory biomarkers were quantified, and patients were followed for 3 years to establish an optimal chronic inflammatory index (CII) and evaluate its association with survival and chemotherapy efficacy across primary tumor locations.

Results: The comprehensive CII was the top-performing prognostic biomarker, with time-dependent AUCs of 0.71(95% CI: 0.68–0.74) for 36-month RFS and 0.74(95% CI: 0.70–0.77) for OS. Furthermore, the 3C (CII, CEA and CA19-9) combined score demonstrated prognostic predictive AUCs of 0.74(95% CI: 0.71–0.77) for RFS and 0.76(95% CI: 0.72–0.79) for OS in the overall population. The splenic flexure and ascending colon showed significantly elevated CII levels versus other subsites, and the disease was divided into the proximal colon, transverse colon, distal colon and rectum. A significant CII gradient emerged across subsites (proximal > transverse > distal > rectal), with corresponding survival decrements (log-rank $p < 0.001$). Proximal CRC exhibited marked worse survival outcomes ($p = 0.002$ for RFS and $p = 0.001$ for OS) and inferior chemotherapy efficacy ($p < 0.001$ for RFS and OS) versus rectal cancer, with no significant differences between adjacent subsites (all $p > 0.05$).

Conclusion: The validated CII represents a biologically relevant, subsite-specific prognostic biomarker in CRC. The chronic inflammation-based tumor subsite classification correlated with chemotherapy efficacy and clinical outcomes, highlighting its potential for personalized treatment strategies.

Keywords: colorectal cancer, systemic inflammation, location-based therapy, precision medicine

Introduction

Colorectal cancer (CRC) is highly heterogeneous, and various factors, including chronic inflammation, the microbiome, and epigenetic modifications, may influence its biological diversity.[1–5] Primary tumor sidedness has gained widespread attention as a key prognostic factor for the prediction of survival outcomes in CRC patients.[6–8] Typically, tumors located on the right side are associated with worse survival outcomes than those located on the left side;[9,10] however, several

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studies have reported opposite findings.[8,11] Interestingly, in recent years, numerous studies have demonstrated that detailed tumor primary sites (rather than the traditional two-stage classification at the splenic flexure) can characterize more specific and accurate prognostic information and molecular characteristics.[12–15] These findings suggest that the simplistic approach of dividing the colon into two segments (proximal and distal colon) is not advisable.

CRC is closely associated with inflammation.[16,17] Cancer-associated inflammation impairs the effectiveness of chemotherapy and drives CRC progression and metastasis, serving as a robust prognostic indicator in CRC.[18–20] Furthermore, our previous study demonstrated significant heterogeneity in chronic inflammation across primary tumor sites, with a higher chronic inflammation observed in the right colon than in the left colon. Severe inflammation may contribute to an unsatisfactory prognosis for patients with right-sided colon cancer.[20] However, the heterogeneity of chronic inflammation based on detailed primary tumor locations and its relationship with patient prognosis and chemotherapy efficacy have not been reported.

In this study, we aimed to comprehensively analyze the correlations among chronic inflammation status, primary tumor location, and the prognosis of CRC patients. We first evaluated multiple biomarkers of chronic inflammation to identify the optimal biomarker for predicting patient prognosis and to determine the best classification of tumor location based on chronic inflammation. Furthermore, we investigated the relationships between chronic inflammation, survival outcomes, and chemotherapy efficacy according to specific tumor sites. We aimed to provide a holistic perspective to elucidate the changes in patient prognosis and chemotherapy efficacy based on particular tumor location and chronic inflammatory status.

Materials and Methods

Population

In this study, 1413 patients with stage II–III CRC who presented at the Second Affiliated Hospital of Nanchang University between June 2011 and February 2021 were prospectively enrolled. These patients were divided into two cohorts: a discovery cohort comprising those diagnosed before 2017 and a validation cohort comprising those diagnosed after 2017. Patients were included based on the following inclusion and exclusion criteria. The inclusion criteria were as follows: 1) patients who were clinically and pathologically diagnosed with stage II–III CRC following the Chinese Protocol of Diagnosis and Treatment of Colorectal Cancer;[21] 2) patients who underwent radical resection; and 3) patients who volunteered to participate and provided informed consent. The exclusion criteria were as follows: 1) patients with concurrent malignancies, haematologic diseases, autoimmune diseases, benign chronic inflammatory bowel disease, or recent infections or injuries; 2) those under 18 years of age; and 3) non-first clinical diagnosis or prior clinical intervention before diagnosis; 4) patients receiving preoperative chemoradiotherapy. This study was approved by the Ethics Committee of the participating hospitals.

Data Collection

The clinical and pathological characteristics of patients, obtained from the electronic medical record system of the participating hospital, included gender, age, smoking status, alcohol consumption, diabetes, hypertension, cellular differentiation, tumor size, depth of tumor invasion, lymph node involvement, distant metastasis, primary tumor location, and treatment.

Sample Collection and Clinical Laboratory Detection

The sample collection and laboratory detection methods have been previously described.[19] In brief, 5 mL of peripheral blood was collected one week before radical resection and analyzed through routine laboratory measurements. The coefficients of variance for both inter- and intra-assay precision remained below 10%. Based on the detection results, we constructed six inflammatory biomarkers, NFAR, NFPR, MFAR, MFPR, PFAR, and PFPR, using corresponding calculation formulas. Furthermore, six inflammatory scores (NFAS, NFPS, MFAS, MFPS, PFAS, and PFPS) were established based on the specified cut-off values for each parameter, with scores assigned as zero, one, or two. Supplementary Table S1 provides details of the calculation formulas and scoring criteria.

Follow-Up

Over three years, we followed up each qualified patient every three months during the first two years and biannually during the third year. These follow-ups were performed via clinical appointments, phone calls, e-mails, and by reviewing the medical records. Clinical imaging examinations were utilized to determine whether patients experienced recurrence or distant metastasis. The primary follow-up endpoints were recurrence-free survival (RFS) and overall survival (OS). The follow-up period ended on 31 December 2023. RFS and OS were determined as the intervals from surgery until the first occurrence of recurrence or metastasis and until death or the endpoint of follow-up, respectively.

Statistics

Appropriate cut-off values were determined according to the RFS and OS using X-tile software (Yale University, New Haven, CT) for each inflammatory biomarker and inflammation-based ratio, as detailed in Supplementary Table S1. Categorical variables are presented as counts and proportions, and group differences were analyzed via the chi-square test or Fisher's exact test, as appropriate. Continuous values are displayed as the means ± SD, and differences between groups were assessed with the Student's *t*-test. Survival analyses were performed via Kaplan-Meier curves (Log rank test), and univariate and multivariate Cox regression models were used to investigate independent prognostic factors for RFS and OS, and the strength was evaluated by hazard ratios (HRs) and 95% confidence intervals (CIs). A post-hoc power analysis using Gpower confirmed that the total sample size of 1413 yielded a statistical power of 0.9999 for detecting significant differences in RFS and OS, based on event rates and the proportion of high-risk groups, with a significance level of $\alpha = 0.05$. The predictive performance of these indicators was evaluated with time-dependent receiver operating characteristic (ROC) curves. Statistical analyses were performed with SPSS version 27.0 (IBM Corp., Armonk, NY, USA), R version 4.3.3 (Institute for Statistics and Mathematics, Vienna, Austria), and GraphPad Prism version 10 (GraphPad Software Inc., San Diego, CA, USA).

Results

Characteristics of the Enrolled Patients

This study ultimately included 1413 CRC patients, and of these, 981 patients were allocated to the discovery cohort, and 432 to the validation cohort. Table 1 displays the demographics, treatments, 12 biomarkers of inflammation (NFAR, NFAS, NFPR, NFPS, MFAR, MFAS, MFPR, MFPS, PFAR, PFAS, PFPR, PFPS), and data on recurrence and mortality. In both cohorts, approximately 60% of the participants were male, and most were older than 60. All recipients underwent radical treatment, and more than 80% of the patients received postoperative chemotherapy, with most of them receiving fluoropyrimidine-based regimens (eg, FOLFOX or CapeOX). After three years of follow-up, recurrence and mortality rates were 28.6% and 17.1% in the discovery cohort, and 22.7% and 12.0% in the validation cohort.

Independent Prognostic Biomarkers in the Discovery and Validation Cohort

In the discovery cohort, Kaplan-Meier curve, multivariable Cox analysis adjusting for confounding factors including gender, age, smoking, drinking, hypertension, T stage, lymph node (LN) status, differentiation, tumor size, and postoperative chemotherapy and radiotherapy, identified that CA19-9 and 12 inflammation biomarkers (NFAR, NFAS, NFPR, NFPS, MFAR, MFAS, MFPR, MFPS, PFAR, PFAS, PFPR, PFPS) were significantly correlated to patient clinical outcomes (Figure 1A and B, Supplementary Table S2). Additionally, multivariable analysis in the validation cohort revealed that CEA, CA19-9, and 10 of the 12 biomarkers (except for PFAR and PFAS) were significantly correlated with patient clinical outcomes (Figure 1C and D, Supplementary Table S3).

Development and Validation of the Chronic Inflammation Index (CII)

Since the predictive performance of the above inflammatory markers was relatively similar, identifying the best predictor of CRC prognosis was challenging (Figure 1E and F, Supplementary Table S4). To address this, we incorporated these markers into a multivariate Cox regression analysis and developed a new chronic inflammation index (CII) (see Table 2 for the definition of the CII). As shown in Figure 2A–D, a high CII was associated with worse survival outcomes in both

Table 1 Baseline Clinical Characteristics of the Eligible Patients in Two Cohorts

Parameters	Discovery Cohort N=981, N (%)	Validation Cohort N=432, N (%)	*p*-value
Gender (male)	597(60.90)	252(58.30)	0.372
Age (≥60 year)	483(49.20)	232(53.70)	0.122
Smoking (yes)	187(19.10)	52(12.00)	0.001
Drinking (yes)	129(13.10)	38(8.80)	0.02
Diabetes (yes)	79(8.10)	29(6.70)	0.382
Hypertension (yes)	164(16.70)	80(18.50)	0.409
Radical operation (yes)	981(100)	432(100)	
Chemotherapy (yes)	799(81.40)	359(83.10)	0.456
Radiotherapy (yes)	88(9.00)	18(4.20)	0.002
T stage (T3-4)	937(95.50)	344(79.60)	<0.001
LN status (N1)	468(47.70)	252(58.30)	<0.001
Tumor size (≥5cm)	409(42.40)	188(44.00)	0.578
Differentiation (G2)	98(10.40)	52(12.70)	0.218
Right hemicolon	230(23.40)	130(30.10)	0.008
Adenocarcinoma	981(100.00)	432(100.00)	
CEA (>2.8 ng/mL)	492(50.20)	224(51.90)	0.556
CA199 (>21.5 U/mL)	344(35.10)	160(37.0)	0.476
NFAR (>33.2)	369(37.60)	193(44.70)	0.012
High NFAS	367(67)	181(33)	0.111
NFPR (>61.6)	384(39.10)	211(48.80)	0.001
High NFPS	252(64.9)	136(35.1)	0.025
MFAR (>2.4)	559(57.00)	223(51.60)	0.062
High MFAS	323(69)	145(31)	0.814
MFPR (>5.3)	453(46.20)	194(44.90)	0.659
High MFPS	226(67.3)	110(32.7)	0.324
PFAR (>17.4)	431(43.90)	225(52.10)	0.005
High PFAS	304(65.2)	162(34.8)	0.017
PFPR (>38.5)	340(34.70)	199(46.10)	<0.001
High PFPS	221(64.4)	122(35.6)	0.021
Recurrence	281(28.60)	98(22.70)	0.02
Mortality	168(17.10)	52(12.00)	0.015

Abbreviations: LN, lymph node; NFAR, neutrophil to fibrinogen to Alb ratio; NFAS, NFAR score; NFPR, neutrophil to fibrinogen to pAlb ratio; NFPS, NFPR score; MFAR, monocyte to fibrinogen to Alb ratio; MFAS, MFAR score; MFPR, monocyte to fibrinogen to pAlb ratio; MFPS, MFPR score; PFAR, platelet to fibrinogen to Alb ratio; PFAS, PFAR score; PFPR, platelet to fibrinogen to pAlb ratio; PFPS, PFPR score.

discovery (adjusted HR = 3.71, 95% CI = 2.88–4.76 for RFS; adjusted HR = 4.42, 95% CI = 3.20–6.12 for OS) and validation (adjusted HR = 4.84, 95% CI = 3.13–7.49 for RFS; adjusted HR = 5.78, 95% CI = 3.06–10.92 for OS) cohorts. Furthermore, the multivariate Cox analysis demonstrated that the CII was significantly correlated with patient clinical outcomes in stage II (adjusted HR = 5.54, 95% CI = 3.71–8.26 for RFS; adjusted HR = 6.19, 95% CI = 3.66–10.46 for OS) and III (adjusted HR = 3.43, 95% CI = 2.66–4.43 for RFS; adjusted HR = 3.98, 95% CI = 2.82–5.61 for OS) subgroups (Supplementary Table S5).

Notably, the multivariate analysis identified the CII as an independent prognostic factor for CRC patients, regardless of whether it was considered a continuous or a categorical variable in the overall population. Further analysis and the division of CII into four categories revealed a progressive increase in the risk of poor prognosis across groups Q2, Q3, and Q4 compared with Q1, with HRs (95% CI) of 1.49 (0.72–3.08), 2.63 (1.27–5.46), and 6.90 (3.39–14.04) for RFS and 1.44 (0.51–4.06), 3.39 (1.22–9.43), and 8.83 (3.25–23.96) for OS, respectively (Table 2). Multivariate restricted cubic spline (RCS) analysis further demonstrated a linear correlation between the CII and poor survival outcomes in CRC

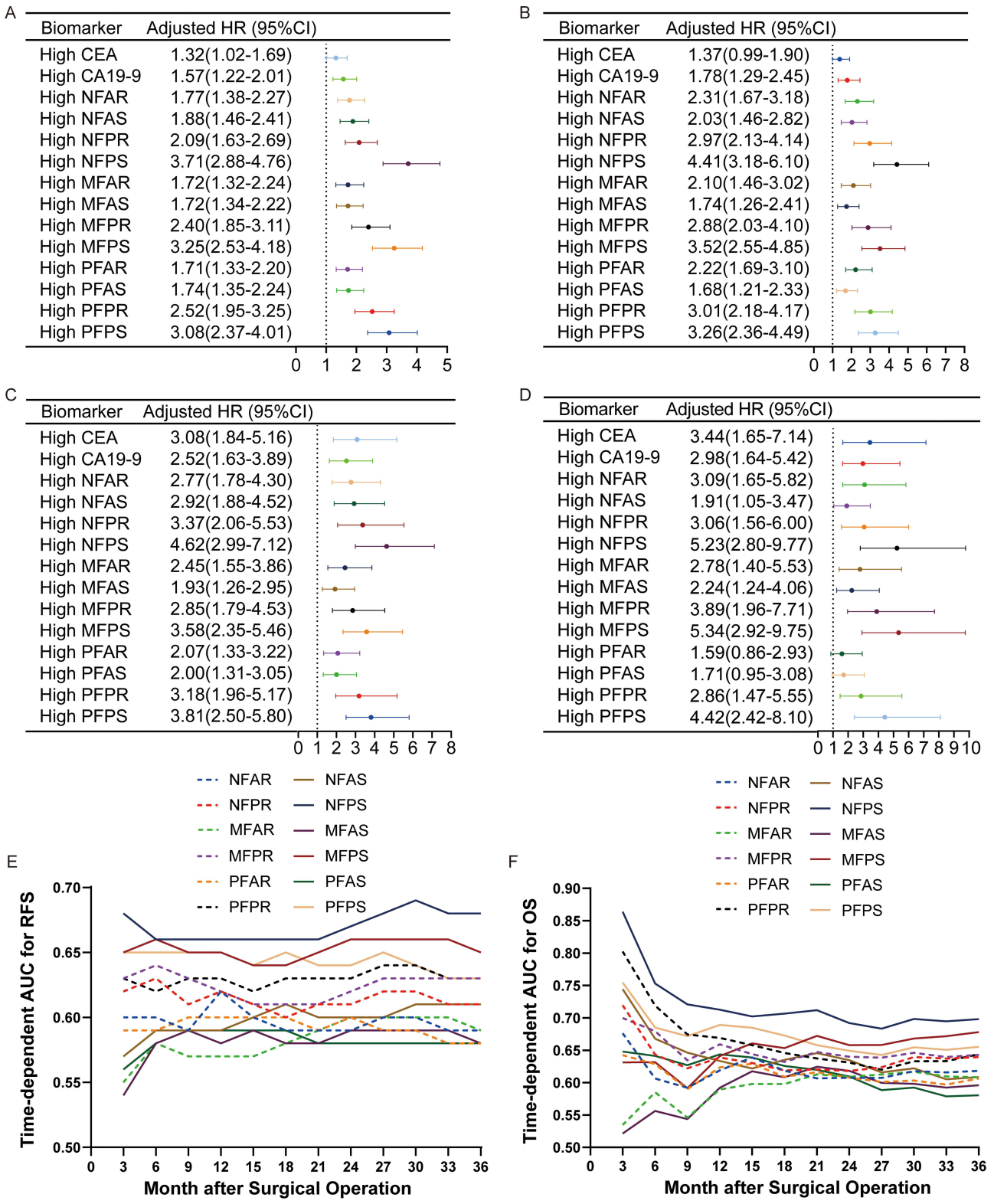

Figure 1 Prognostic forest plots and the areas under the time-dependent ROC curve (AUROC) of biomarkers. (**A** and **B**) Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of biomarkers for recurrence-free survival (RFS) (**A**) and overall survival (OS) (**B**) in the discovery cohort; (**C** and **D**) Adjusted HRs with 95% CIs of biomarkers for RFS (**C**) and OS (**D**) in the validation cohort; (**E** and **F**) AUROC of 12 biomarkers of inflammation biomarkers for RFS (**E**) and OS (**F**) in the overall population.

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Table 2 Cox Regression Analysis for RFS and OS

CII	Recurrence-Free Survival				Overall Survival			
	Model a	*p*-value	Model b	*p*-value	Model a	*p*-value	Model b	*p*-value
As continuous (per SD)	2.36(2.09–2.67)	<0.001	2.35(2.07–2.67)	<0.001	2.73(2.32–3.21)	<0.001	2.62(2.21–3.12)	<0.001
By CII cut-off								
Low (<0.79)	Ref		Ref		Ref		Ref	
High (≥0.79)	3.93(3.21–4.81)	<0.001	3.96(3.19–4.90)	<0.001	4.85(3.70–6.35)	<0.001	4.54(3.40–6.05)	<0.001
Quartiles								
Q1(≤-0.05)	Ref		Ref		Ref		Ref	
Q2 (−0.05–0.01)	1.58(0.77–3.24)	0.215	1.49(0.72–3.08)	0.283	1.38(0.50–3.83)	0.54	1.44(0.51–4.06)	0.489
Q3 (0.01–1.11)	2.52(1.22–5.20)	0.012	2.63(1.27–5.46)	0.009	2.84(1.02–7.85)	0.045	3.39(1.22–9.43)	0.019
Q4 (>1.11)	7.14(3.52–14.50)	<0.001	6.90(3.39–14.04)	<0.001	8.75(3.23–23.69)	<0.001	8.83(3.25–23.96)	<0.001

Notes: Model a: no adjusted; Model b: multivariate cox regression was adjusted by gender, age, smoking, drinking, hypertension, T stage, lymph node status, differentiation, tumor size, chemotherapy, radiotherapy. CII = 2.816*NFPS + 0.659*MFAS +2.180*MFPS +1.538*NFAR.
Abbreviations: SD, standard deviation; Ref, reference; CII, chronic inflammation index;

patients (p for non-linearity = 0.21 for RFS and 0.16 for OS) (Figure 2E and F). The time-dependent ROC analysis showed that the CII achieved a high AUC for predicting survival at 12 months (AUC = 0.70 for RFS, 0.73 for OS), 24 months (AUC = 0.70 for RFS, 0.72 for OS) and 36 months (AUC = 0.71 for RFS, 0.74 for OS) within the total population (Figure 2G and H). We calculated Harrell's C-index to strengthen the finding, which yielded 0.68 (95% CI = 0.65–0.71) for RFS and 0.72 (95% CI = 0.68–0.75) for OS.

Furthermore, we developed a new combined indicator, 3C, which integrates the CII, CEA, and CA19-9 (3C = 3.646×CII + 1.455×CEA + 1.673×CA19-9). Survival analysis indicated that high levels of 3C were significantly associated with poorer RFS and OS, with recurrence and mortality rates of 38.9% and 24.8%, respectively, in the 3C-high subgroup and 13.2% and 5.2%, respectively, in the 3C-low subgroup (Supplementary Figure S1A and B). Notably, 3C outperformed any indicator (CII, CEA, or CA19-9) in predicting CRC prognosis at all observed time points (Supplementary Figure S1C and D). Time-dependent ROC analysis confirmed the superior predictive performance of 3C for 36-month survival in the overall population, with AUCs of 0.74 for RFS and 0.76 for OS (Supplementary Figure S1E and F). Moreover, prognostic predicted AUCs of 3C were 0.73 for RFS and 0.75 for OS in the discovery cohort; 0.77 and 0.80 for RFS and OS in the validation cohort, respectively (Supplementary Figure S1G–J).

CII, Clinical Characteristics, and Primary Tumor Location

Compared to low CII patients, those with high CII exhibited significantly higher frequencies of advanced T stages (T3-4) ($p = 0.02$), large tumor burden (≥ 5 cm) ($p < 0.001$), and poorly differentiated histology ($p = 0.001$), while no distribution differences of LN status ($p = 0.74$) was observed between them (Figure 3A–C and Supplementary Table S6). The primary tumor sites were stratified into eight anatomical subsites from distal to proximal: rectum, sigmoid, descending, splenic flexure, transverse, hepatic flexure, ascending, and cecum. Both absolute CII values and the proportion of high CII cases tended to progressively elevate from the rectum to cecum subsites ($p < 0.001$) (Figure 3D and E). The CII gradient reached its first zenith at the splenic flexure after gradually increasing from the rectum. It declined transiently at the transverse colon and ascended through the hepatic to the cecum. Similar trends were also observed for recurrence and mortality from the rectum to the cecum, with a first peak at the splenic flexure and one trough each in the adjacent descending and transverse colon (Supplementary Table S7). Conversely, RFS and OS displayed increased deterioration from rectum to cecum subsites (Supplementary Table S8).

Due to the changing trend of CII in the eight anatomical subsites, we further divided them into the following four subsites: the rectum, distal colon (including the sigmoid and descending colon), transverse (including the hepatic flexure, transverse colon, and splenic flexure), and proximal colon (including the ascending colon and cecum). From the rectum to the proximal colon, both absolute CII values and the proportion of high CII cases were gradually increased ($p < 0.001$) (Figure 3F and G). More interestingly, similar trends were observed for recurrence and mortality (Figure 3H and I). RFS and OS progressively deteriorated from the rectum to the proximal colon, and significant prognostic differences were

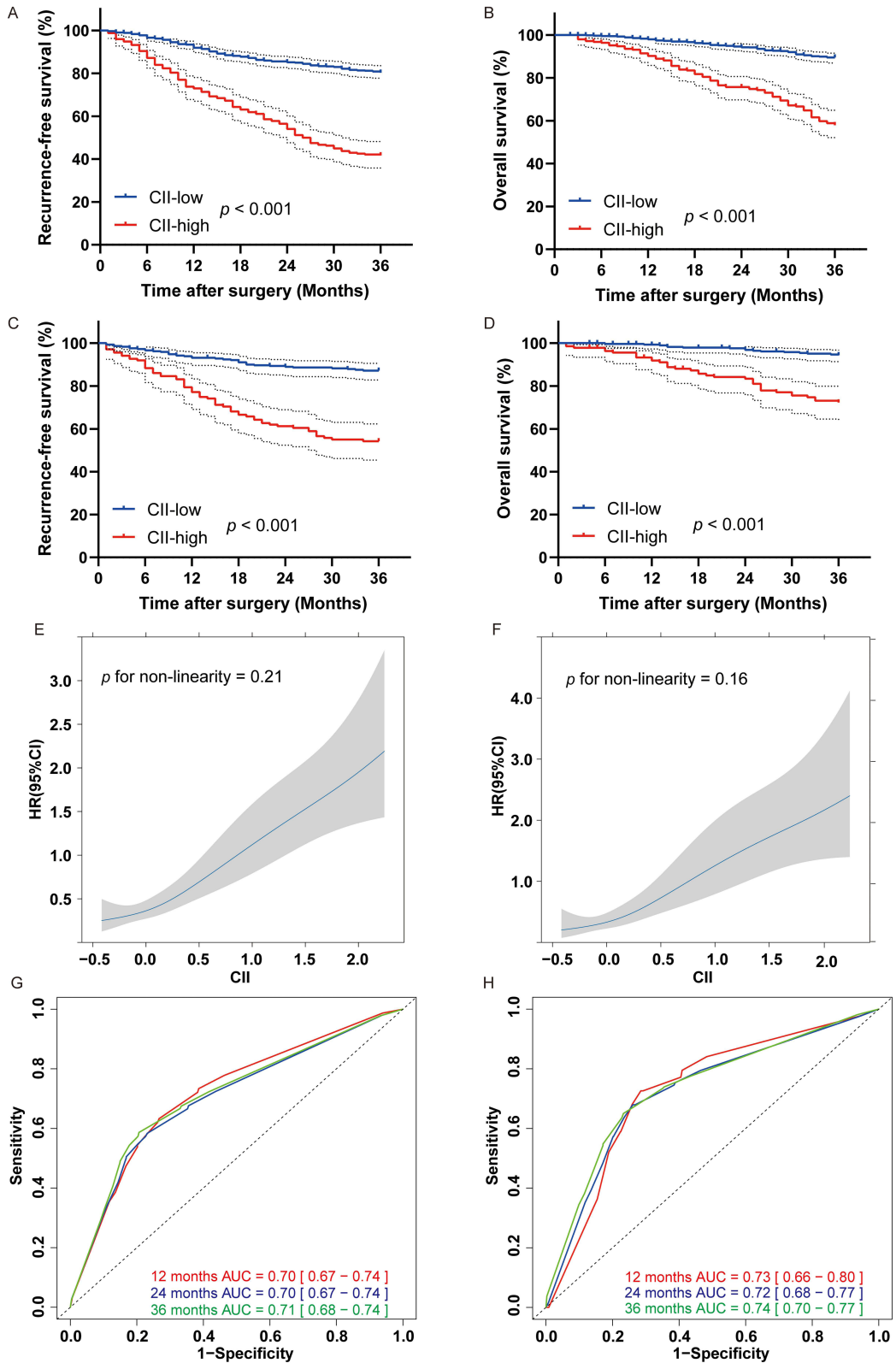

Figure 2 The predictive performance of the preoperative CII as a prognostic indicator of CRC. (**A** and **B**) Kaplan-Meier (KM) curves of the CII for RFS (**A**) and OS (**B**) in the discovery cohort; (**C** and **D**) KM-plot of the CII for RFS (**C**) and OS (**D**) in the validation cohort; (**E** and **F**) The restricted cubic spline (RCS) plot of the CII for RFS (**E**) and OS (**F**) in the overall population; (**G** and **H**) AUROC curves of the CII for RFS (**G**) and OS (**H**) in the overall population.

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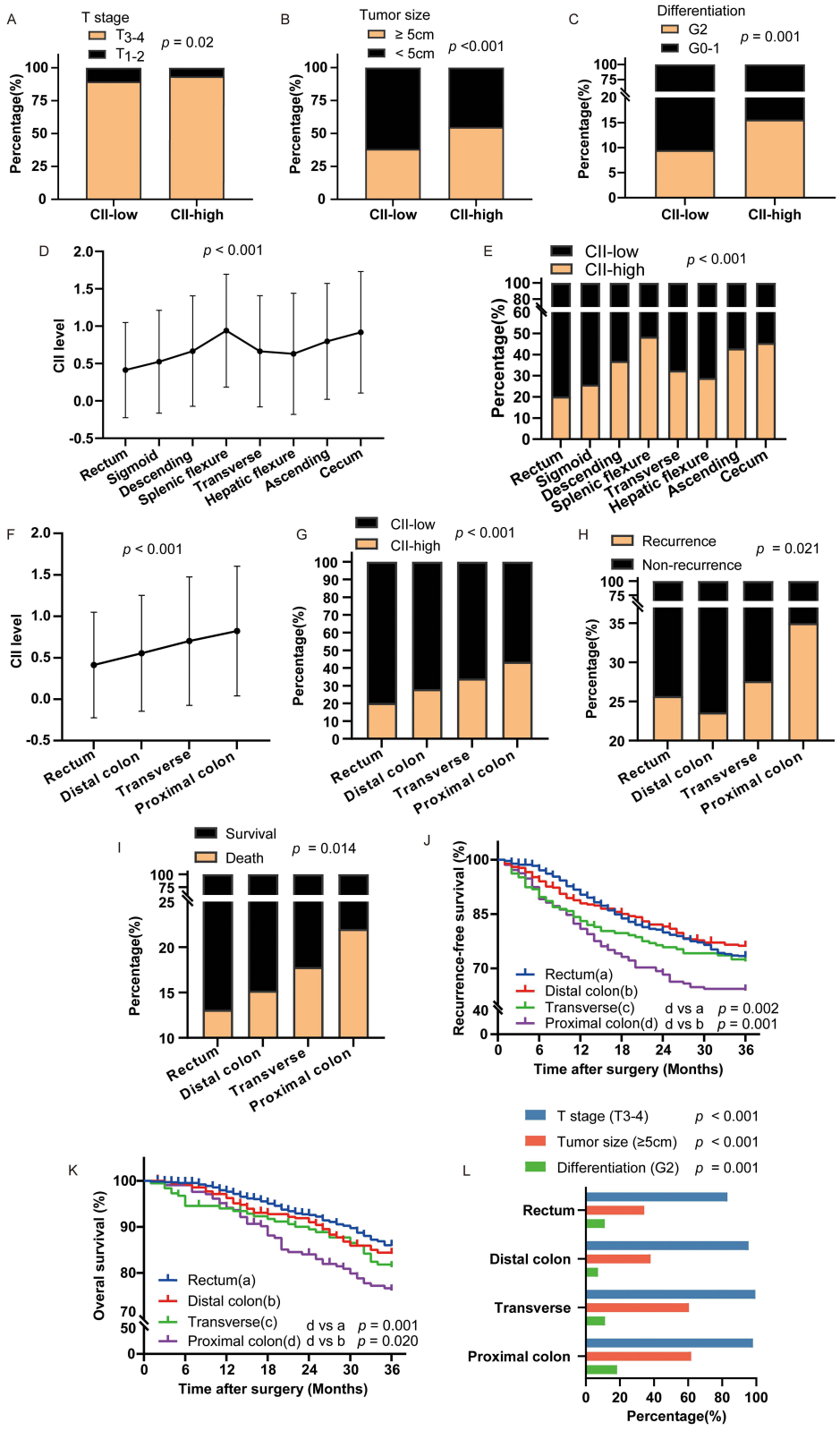

Figure 3 Relationships between preoperative CII levels, primary tumor location, and clinical tumor parameters. (**A**–**C**) CII and T stage (**A**), tumor size (**B**) and cell differentiation (**C**); (**D** and **E**) CII-average (**D**) and CII-high distribution (**E**) across eight tumor locations; (**F** and **G**) CII-average (**F**) and CII-high distribution (**G**) across four tumor locations; (**H** and **I**) Recurrence (**H**) and mortality (**I**) in four tumor locations; (**J** and **K**) KM-plot for RFS (**J**) and OS (**K**) in four tumor locations; (**L**) Distribution of T stage, tumor size and cell differentiation across four tumor locations.

observed in the proximal colon versus the rectum ($p = 0.002$ for RFS; $p = 0.001$ for OS) or the distal colon ($p = 0.001$ for RFS; $p = 0.020$ for OS) (Figure 3J and K, Supplementary Table S9). Notably, a progressively increased trend was observed in the tumor burden from the rectum to the proximal colon ($p < 0.001$). Similar trends were observed in the proportions of T3-4 stage tumors ($p < 0.001$) and poorly differentiated histology ($p = 0.001$) (Figure 3L).

A stratified analysis by tumor location showed that RFS (Figure 4A, C, E and G) and OS (Figure 4B, D, F and H), as well as recurrence (Figure 4I) and mortality (Figure 4J), were significantly worse in the CII-high population than in the CII-low population across all primary tumor locations. Multivariate Cox analysis confirmed that the CII was an independent factor for both RFS and OS in a tumor location-stratified analysis. The specific HRs with 95% CIs were 3.53(2.54–4.90) for RFS and 4.95(3.15–7.78) for OS in the rectum, 2.87(1.82–4.51) for RFS and 3.59(2.02–6.39) for OS in the distal colon, 4.50(2.50–8.11) for RFS and 4.24(2.02–8.89) for OS in the transverse colon, and 7.51(3.99–14.12) for RFS and 4.92(2.41–10.06) for OS in the proximal colon (Supplementary Table S10).

The CII and Adjuvant Chemotherapy in Four Tumor Subsites

In patients with low CII, no RFS or OS differences were observed in comparison of those with or without adjuvant chemotherapy treatment. Conversely, high CII patients who received chemotherapy harbored more prolonged RFS and OS than those without the treatment ($p = 0.017$ for RFS and $p < 0.001$ for OS) (Figure 5A and B). Of those treated with chemotherapy, the RFS and OS of patients in the highest CII quartile (CII-Q4) were significantly worse than those with CII-Q1, -Q2, or -Q3 ($p < 0.001$); however, the prognosis was better than those without chemotherapy (CII-Q4) ($p = 0.001$ for RFS and $p <0.001$ for OS) (Figure 5C and D). Patients were further stratified into high and low groups according to the median CII values specific to each tumor subsite. In the chemotherapy-treated CII-high subgroup, RFS and OS progressively worsened from the rectum to the proximal colon (Figure 5E and F). Significant RFS and OS differences were observed only between the proximal colon and rectum ($p < 0.001$ for RFS and OS). Adjuvant chemotherapy-treated high-CII patients with proximal colon cancer showed improved survival outcomes compared to those without the treatment; however, the statistical differences did not reach significance ($p = 0.155$ for RFS and $p = 0.076$ for OS). Furthermore, linear negative correlations of quantitative CII with RFS and OS were observed in the adjuvant chemotherapy-treated patients (p for non-linearity = 0.30 for RFS and 0.68 for OS) (Figure 5G and H).

Discussion

CRC displays significant heterogeneity and exhibits complex interactions with various components of the tumor microenvironment.[22] Studies have revealed distinct molecular characteristics across primary tumor locations that partially explain the heterogeneity observed in CRC.[13,14] However, whether chronic inflammation contributes to the heterogeneity associated with primary tumor location remains an unresolved question that warrants further investigation. This study investigated the influence of chronic inflammation and the specific anatomic location (rectum, distal colon, transverse, or proximal colon) of the primary tumor on survival outcomes in patients with stage II–III CRC. From the rectum to the cecum, a significant trend towards increased chronic inflammation was observed, along with decreased survival and reduced response sensitivity to chemotherapy. The proximal colon exhibited the worst response to chemotherapy, and a significant survival difference was observed only between the proximal colon and rectum.

Cancer-elicited chronic inflammation is a crucial factor influencing tumor development and treatment response. Tumors with chronic inflammatory microenvironments, commonly called “cold tumors”, are characterized by a lack of active immune cell infiltration, particularly the absence of T cells. This cold tumor environment facilitates tumor immune escape.[23,24] Studies have shown that inflammatory factors in the tumor microenvironment, such as cytokines and chemokines, can regulate immune cell function. For example, tumor-associated macrophages undergo polarization in the chronic inflammatory microenvironment, altering their functions and thereby promoting tumor growth and metastasis.[25] Myeloid-derived suppressor cells (MDSCs) and T regulatory (Treg) cells are key immunosuppressive elements within the tumor microenvironment. These cells contribute to immune evasion by releasing reactive oxygen species, which inhibit the response of natural killer cells.[26] In recent years, numerous studies have focused on identifying inflammation-based biomarkers, such as C-reactive protein-albumin-lymphocyte index, lymphocyte to CRP ratio, CRP to albumin ratio, FPR, neutrophil-to-lymphocyte ratio to predict CRC prognosis and to guide treatment decisions.[27–30]

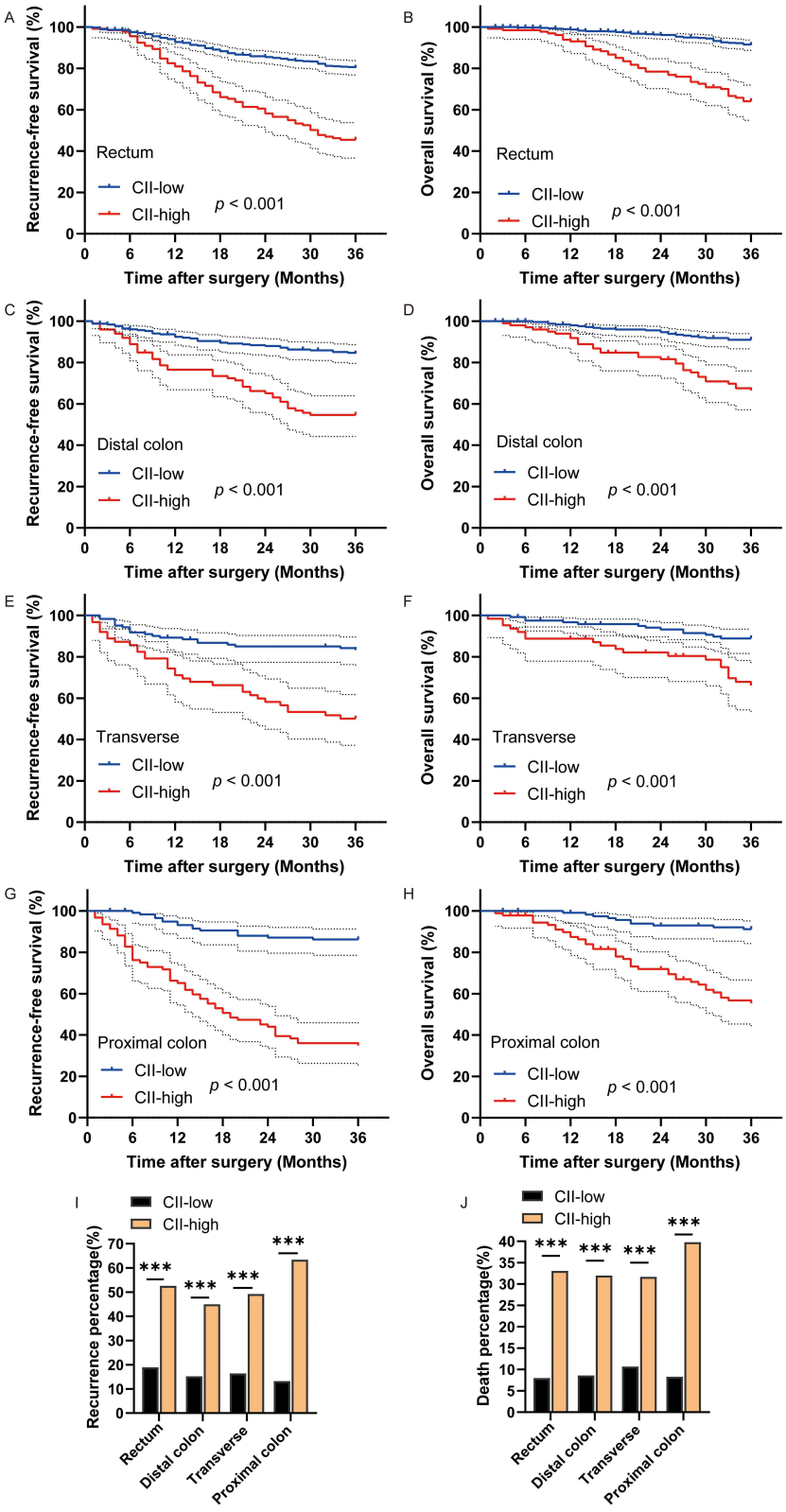

Figure 4 Prognostic effect of the preoperative CII across four tumor locations. (**A, C, E, G**) KM-plot of the CII for RFS in patients with tumors located in the rectum (**A**), distal colon (**C**), transverse (**E**) and proximal colon (**G**); (**B, D, F, H**) KM-plot of the CII for OS in patients with tumors located in the rectum (**B**), distal colon (**D**), transverse (**F**) and proximal colon (**H**); (**I** and **J**) Recurrence (**I**) and mortality (**J**) comparisons between the CII-low and CII-high groups across the four tumor locations. ***$p < 0.001$.

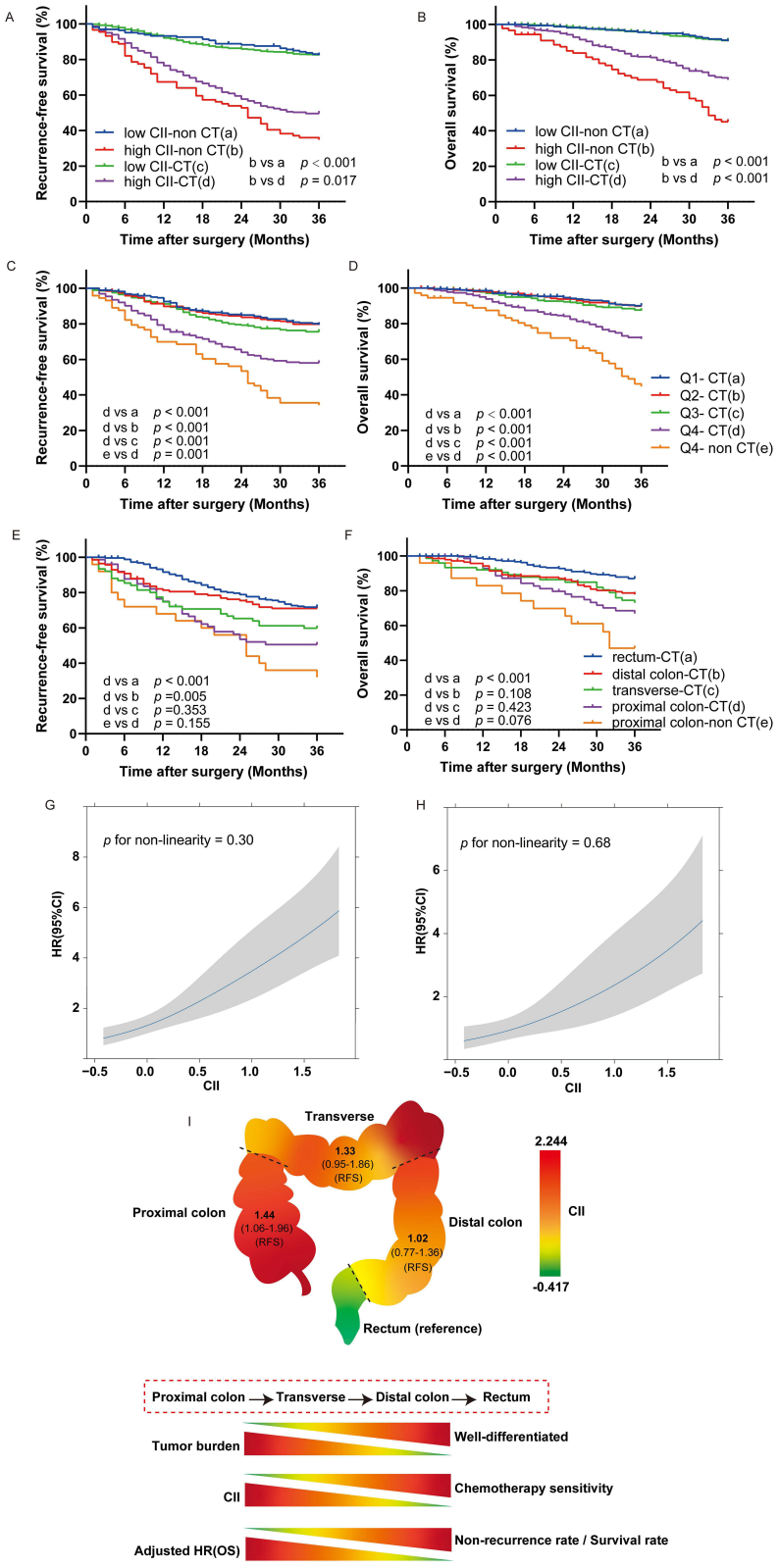

Figure 5 The CII and chemotherapy effectiveness. (**A** and **B)** KM-plot for RFS (**A**) and OS (**B**) in CII-high and CII-low populations with or without chemotherapy (CT), a: low CII patients without CT, b: high CII patients without CT, c: low CII patients with CT, d: high CII patients with CT; (**C** and **D**) KM-plot for RFS (**C**) and OS (**D**) in different CII groups (Q1-Q4) with chemotherapy or the Q4 population not treated with chemotherapy, a: Q1 patients with chemotherapy, b: Q2 patients with chemotherapy, c: Q3 patients with chemotherapy, d: Q4 patients with chemotherapy, e: Q4 patients without chemotherapy; (**E** and **F**) KM-plot for RFS (**E**) and OS (**F**) in CII-high groups with or without chemotherapy across four tumor locations, a: high CII populations with CT in rectum, b: high CII populations with CT in distal colon, c: high CII populations with CT in transverse, d: high CII populations with CT in proximal colon, e: high CII populations without CT in proximal colon; (**G** and **H**) RCS plot of CII for RFS (**G**) and OS (**H**) in patients with chemotherapy; (**I)** Characteristics of chronic inflammation, clinicopathological characteristics and clinical outcomes across tumor locations.

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However, these reported inflammatory biomarkers have focused on a limited set of parameters,[31–33] and all of them did not reach a satisfactory predicted efficacy for the disease.

In this study, we developed and validated a new chronic inflammatory index, CII. This index combines neutrophils, monocytes, Fib, albumin, and prealbumin, which enables a more comprehensive reflection of chronic inflammation status. We identified the CII as the optimal prognostic predictor in both the discovery and validation cohorts of stage II–III CRC patients, for predicted AUCs of the CII for 36-month RFS and OS were 0.71 and 0.74 in the overall population, respectively. Furthermore, we combined the CII with CEA and CA19-9 to form a 3C score, which further improved the predictive performance, as the AUCs for 36-month RFS and OS reached 0.74 and 0.76, respectively. Recent strategies for predicting treatment response and prognosis in CRC, including molecular subtyping,[34] circulating tumor DNA,[35] and radiomics,[36] have shown great promise. However, these approaches often rely on high-cost platforms or complex analytical procedures, which may limit their broad applicability. In contrast, the CII and 3C are simple, low-cost, and readily accessible biomarkers derived from routine laboratory tests, offering practical utility in real-world clinical settings.

Recently, substantial attention has been given to primary tumor location as a potential prognostic indicator in CRC.[7,9,10,37] However, most reported studies have relied on a binary classification design (proximal colon vs distal colon) instead of analyzing the precise subsites of the colon. In this study, we classified primary tumor locations into the rectum, distal colon, transverse, and proximal colon based on chronic inflammation status. Significant trends for worse RFS and OS were observed from the rectum to the proximal colon, with significant prognostic differences observed only in the proximal colon versus the rectum or the distal colon, suggesting a continuous decline in patient survival from the rectum to the proximal colon rather than a sudden change. The lack of significant survival differences between patients with tumors in the transverse colon and those with tumors in adjacent regions further highlights the inappropriateness of the traditional method of dividing the colon into left and right sides at the splenic flexure.[9,38,39]

Chronic inflammation, recognized as a key factor in cancer development, is associated with clinical pathological characteristics, such as malignancy grade, differentiation status, and tumor burden in CRC.[40,41] In our study, CII level gradually increased along the rectum to the proximal colon, and T3-4 stage, poor cellular differentiation, and large tumor size showed an upward trend in the four subsites, indicating that the diseases with proximal colon and rectum harbored the worst and best malignant characteristics. Moreover, patients with high CII had higher T-staging, poorer cellular differentiation, and a greater tumor burden than those with low CII, demonstrating that the malignant characteristics of CRC determined high CII, high CII contributed to its designation as a “cold tumor”. Additionally, the CII-high group exhibited reduced clinical response to adjuvant chemotherapy. The proximal colon, with its higher CII levels, exhibited significantly short survival compared to the rectum, and improved outcomes within chemotherapy-treated patients compared to those without the treatment, revealing that the grade of cancer-derived inflammation attenuated chemotherapy sensitivity. These findings illustrated that proximal colon cancer harbored the highest CII level, the most aggressive clinicopathological features, the highest recurrence and mortality rates, the poorest RFS and OS, and the lowest sensitivity to chemotherapy (Figure 5I).

This study is the first to elucidate the role of chronic inflammation in CRC heterogeneity according to primary tumor location, which clarifies the potential mechanisms underlying reduced chemotherapy sensitivity. Nevertheless, this study has several limitations. Firstly, except for rectal and sigmoid colon cancers, this study has a small sample size for the other primary tumor locations, which may limit its statistical power. Secondly, the biomarkers of chronic inflammation defined in this study currently lack established and widely accepted cut-off values. Therefore, establishing optimal cut-off values for these biomarkers when applied to other research cohorts is essential. Thirdly, a limitation of the CII is its potential susceptibility to confounding from undetected systemic inflammatory conditions not captured by our exclusion criteria (eg, subclinical infections). Finally, microsatellite instability-high (MSI-H) status is a predictive factor for postoperative chemotherapy benefit in stage III CRC.[42] Meanwhile, large meta-analyses of randomized trials have shown that *KRAS*- or *BRAF*-mutant stage II–III cancers have significantly higher recurrence rates and worse survival despite adjuvant FOLFOX/CAPOX regimens compared to wild-type.[43] Since we could not obtain data on *RAS* and *BRAF* mutations, and microsatellite instability status for the enrolled patients, we did not explore the relationships among these molecular characteristics, chronic inflammation status, and survival outcomes of patients with tumors in various locations.

Conclusions

This study identified CII and 3C score as robust and independent prognostic indicators for patients with stage II–III CRC. We developed a four-category classification of primary tumor locations based on chronic inflammation status and provided a holistic view of chronic inflammation, recurrence, mortality, survival outcomes, and chemotherapy response trends across the rectum, distal colon, transverse, and proximal colon. More accurate prognosis and treatment guidance may be achieved by considering chronic inflammation and detailed tumor subsite classifications rather than relying on the traditional binary classification.

Abbreviations

AUC, Area under the curve; CII, Chronic inflammation index; CIs, Confidence intervals; CRC, Colorectal cancer; CT, Chemotherapy; HRs, Hazard ratios; LN, lymph node; MFAR, Monocyte to fibrinogen to Alb ratio; MFAS, MFAR score; MFPR, Monocyte to fibrinogen to pAlb ratio; MFPS, MFPR score; NFAR, Neutrophil to fibrinogen to Alb ratio; NFAS, NFAR score;; NFPR, Neutrophil to fibrinogen to pAlb ratio; NFPS, NFPR score; PFAR, Platelet to fibrinogen to Alb ratio; PFAS, PFAR score; PFPR, Platelet to fibrinogen to pAlb ratio; PFPS, PFPR score; RCS, Restricted cubic spline; RFS, Recurrence-free survival; ROC, Receiver operating characteristic; OS, Overall survival.

Data Sharing Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study was performed in compliance with the Declaration of Helsinki and approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University.

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Disclosure

The authors declare no competing interests in this work.

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