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A Novel Chronic Inflammatory Signature Guides Personalized Adjuvant Chemotherapy Selection in Early-Stage Colorectal Cancer: Superior Outcomes with De-escalated Regimens

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ABSTRACT

Tailored administration of adjuvant chemotherapy (ACT) enhances treatment efficiency and postoperative well-being in individuals with stage II–III colorectal cancer (CRC). Nonetheless, reliable biomarkers capable of forecasting responses to 5-fluorouracil (5-FU) and oxaliplatin remain insufficient. Three separate cohorts comprising 1676 stage II–III surgical cases were assessed to determine the prognostic value of 12 inflammatory markers. Using multivariable Cox modeling, we generated a novel Chronic Inflammatory Comprehensive Signature (CICS). We compared 3-year recurrence-free survival (RFS) and overall survival (OS) between CICS-based groups (CICS-L vs CICS-H) treated with either 5-FU– or oxaliplatin-based ACT. Two new inflammatory ratios (FPSIIR, FPSIRIR) along with six combined indices (FPSIIS, FPSIRIS, FPSIRS, FASIIS, FASIRS, FASIRIS) consistently predicted outcomes across all cohorts (all plog-rank < 0.05). CICS reached an AUC of 0.690, which increased to 0.724 when integrated with CEA-CA19-9. Individuals categorized as CICS-H showed diminished responsiveness to both drugs, with evident therapeutic benefit mainly in the CICS-L group. For stage II patients within the CICS-L category, similar favorable RFS was found in those receiving 5-FU alone or oxaliplatin-based ACT, compared with non-ACT management (97.73% vs 91.02% vs 91.46%, plog-rank = 0.33). In contrast, stage II CICS-H patients had better survival and fewer recurrences when treated with 5-FU rather than oxaliplatin-based regimens. In stage III cases, both CICS-H and CICS-L subgroups demonstrated clearer benefit from oxaliplatin relative to 5-FU. Optimal ACT choices differed between CICS-L and CICS-H across stages. A CICS-driven approach improved regimen selection (RR = 0.47, 95% CI = 0.35–0.62, p < 0.01) and increased therapeutic performance (HR = 0.70, 95% CI = 0.53–0.92 for RFS; HR = 0.70, 95% CI = 0.47–0.97 for OS in stage III CRC). Higher CICS-defined inflammation corresponds to reduced sensitivity to 5-FU/oxaliplatin. Employing CICS to guide ACT enables precise de-escalation while still maximizing clinical benefit, thereby supporting a biomarker-oriented model for individualized postoperative CRC care.

Keywords: Chronic inflammatory comprehensive signature, CEA-CA19-9-CICS score, Oxaliplatin, 5-fluorouracil, Colorectal cancer

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Introduction

Adjuvant chemotherapy (ACT) following radical tumor removal is the recommended treatment modality for high-risk stage II and III colorectal cancer (CRC), intended to lower the likelihood of relapse and distant spread [1, 2]. Beyond single-agent fluorouracil (FU) and its analogs (5-FU, capecitabine, tegafur), combination therapies such as capecitabine plus oxaliplatin (XELOX) and oxaliplatin/5-FU/leucovorin (FOLFOX) have been progressively adopted as standard ACT regimens [3–6]. Oxaliplatin contributes roughly a 5%–6% reduction in disease progression [7]. Despite these advantages, 8%–12% of surgically treated patients still relapse within the first six months [8], indicating that intrinsic drug resistance exists in part of the population.

Extensive evidence also documents the toxic burden associated with 5-FU and oxaliplatin. Common adverse reactions to 5-FU include diarrhea and vomiting [9]. Oxaliplatin is particularly known for causing severe acute and chronic neurotoxicity [7, 10]. Findings from the CALGB/SWOG 80702 trials indicate that 85–93% of patients exposed to oxaliplatin develop acute chemotherapy-induced peripheral neuropathy, about half of whom eventually experience chronic forms. These toxicities not only impair life quality but also lead to unwarranted economic strain on healthcare systems [10]. Consequently, the development of efficacy-based biomarkers to determine which CRC patients truly derive benefit from ACT is essential for preventing avoidable toxicity.

A variety of innovative biomarkers have been explored to distinguish low-risk postoperative cases, evaluate therapeutic effectiveness, and estimate clinical outcomes [11]. Circulating tumor DNA (ctDNA) and consensus molecular subtype (CMS) categorization have shown potential in identifying groups with elevated recurrence likelihood [12–15]. However, their reliance on next-generation sequencing poses limitations due to high cost and shortages of skilled staff, restricting widespread uptake, especially in resource-limited medical facilities. Additionally, ctDNA and CMS do not reliably pinpoint which patients benefit from oxaliplatin, 5-FU, or related compounds [16, 17]. The T1-3 and N1 classifications have been noted as useful indicators for selecting individuals who can safely limit cumulative ACT exposure, since three months of ACT can achieve non-inferiority relative to six months [7]. Thus, there remains a strong need for predictive biomarkers that accurately forecast the therapeutic value of oxaliplatin and 5-FU.

Emerging research highlights the critical influence of the tumor microenvironment (TME) and metabolic shifts in the development and progression of colorectal cancer (CRC) [16, 18]. Specifically, alterations in amino acid metabolism, particularly serine and glycine, fuel CRC cell growth, metastasis, and resistance to adjuvant chemotherapy (ACT) by fulfilling anabolic requirements and creating a pro-inflammatory TME [16, 19]. Consequently, inflammation driven by cancer has gained recognition as a defining feature of CRC [20]. Among chronic inflammatory indicators, the fibrinogen-to-pre-albumin ratio (FPR), systemic inflammation ratio/index (SIR/SII), and systemic inflammation response index (SIRI) have been validated as independent prognostic markers [21–23]. While FPR has been suggested to perform better than SIR/SII or SIRI in outcome prediction [24], its predictive accuracy is still limited and requires refinement. Prior work indicates that tumor-induced inflammation can lower ACT effectiveness or trigger drug resistance, particularly in metastatic CRC cases [21, 25, 26]. However, how varying levels of chronic inflammation affect clinical responses to oxaliplatin or 5-FU and related agents in surgically treated patients remains unclear, underlining the need for more robust predictive biomarkers.

In this study, we introduce and evaluate a chronic inflammatory comprehensive signature (CICS) along with the CEA-CA19-9-CICS (3C) score, designed to estimate the effectiveness of 5-FU and oxaliplatin-based treatments by integrating inflammatory indices. Assuming that chronic inflammation reflects both tumor biology and TME features relevant to chemotherapy response, we applied Cox regression modeling to uncover patterns indicative of therapeutic benefit. The predictive performance of CICS and the 3C score was assessed across three cohorts—discovery, internal validation, and external validation—comprising 1,676 stage II–III CRC patients from three institutions. Results showed that both CICS and the 3C score reliably forecasted treatment benefit for oxaliplatin and 5-FU regimens.

Materials and Methods

Study design and population

The CRC chronic inflammation cohort consisted of 1,706 patients with stage II–III CRC who underwent radical surgery followed by ACT between June 2011 and January 2017. Inclusion criteria required that patients had no concurrent cancers, hematologic or autoimmune disorders, benign chronic inflammatory bowel disease, or recent infections/trauma. Participants were randomly assigned to discovery, internal validation, and external validation cohorts. Evidence showing similar efficacy among 5-FU, capecitabine, and tegafur [27] allowed grouping these as a single 5-FU cohort. Likewise, given the comparable effectiveness of XELOX and FOLFOX [28, 29], patients on these regimens were combined as the oxaliplatin-treated (OXA) cohort. Written informed consent was obtained from all patients, and the study was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University (O-MedResEthicsRev [2025] No. 54).

Sample collection and laboratory analysis

Baseline data included age, sex, smoking and alcohol habits, diabetes, hypertension, along with pathological variables such as tumor differentiation, size, depth of invasion, lymph node status, tumor location, and treatment type. Laboratory biomarkers were collected and measured following protocols from previous studies [25, 26]. Inter-assay and intra-assay variability were <10%.

CICS and 3C model construction

We postulated that variability in CRC response to oxaliplatin and 5-FU might be linked to differences in tumor-associated inflammation. To test this, multivariable Cox regression identified the independent prognostic significance of the 12 biomarkers. These independent inflammatory factors were then used to construct the CICS, reflecting the overall inflammatory status. Because CICS measures only inflammation, while traditional tumor markers capture tumor-specific properties [30], we created the 3C score, combining CEA, CA19-9, and CICS. Each marker was stratified as abnormal or normal, generating scores from 0 to 3:

- 3 points: all three markers abnormal (CICS ≥0.75, CEA ≥5.00 ng/mL, CA19-9 ≥37.00 U/mL)
- 2 points: any two markers abnormal
- 1 point: one marker abnormal
- 0 points: none abnormal (CICS <0.75, CEA <5.00 ng/mL, CA19-9 <37.00 U/mL)

Follow-up

Patients were observed over a three-year period, with evaluations scheduled every three months for the first two years and every six months during the third year. The primary outcome of interest was recurrence-free survival (RFS), while overall survival (OS) was considered a secondary outcome. The final follow-up date was January 1, 2020. To detect tumor recurrence or distant metastasis, both tumor biomarkers (CEA and CA19-9) and imaging techniques—including CT, MRI, and SPECT—were utilized. RFS was defined as the interval from surgery until recurrence, metastasis, or the end of follow-up without events. Similarly, OS was calculated from surgery to death or until the follow-up endpoint if the patient remained alive.

Statistical analysis

The study followed a double-blind approach, where the laboratory personnel performing biomarker measurements were unaware of clinical outcomes, and the clinical evaluators did not know the assay procedures or results. Two main objectives guided the analyses:

1. To assess the prognostic performance of CICS and the 3C score in the discovery, internal validation, and external validation cohorts among patients receiving ACT.
2. To evaluate whether CICS-H and CICS-L patients responded differently to oxaliplatin or 5-FU treatment.

Categorical variables were compared using Chi-square or Fisher's exact tests, reported as counts and percentages. Continuous variables were summarized as median (25th–75th percentile) and mean ± SD, with group differences tested via Wilcoxon or t-tests. The optimal cutoffs for continuous inflammatory biomarkers relative to RFS were established using X-tile software (Yale University, New Haven, CT), allowing patient stratification into high and low biomarker groups.

Survival associations were evaluated using Kaplan–Meier curves with log-rank tests, along with univariate and multivariate Cox regression models employing backward likelihood ratio selection, and restricted cubic splines (RCS) to model non-linear effects. Hazard ratios (HRs) with 95% confidence intervals (CIs) quantified association strength. Time-dependent AUC analysis was performed to assess predictive performance. Analyses were conducted using SPSS 27.0 (IBM, Armonk, NY, USA), R 4.4.2 (Vienna, Austria), and GraphPad Prism 10 (San Diego, CA, USA).

Results and Discussion

Baseline characteristics

A total of 1,676 patients met the inclusion criteria (discovery cohort: 490; validation cohort: 1,186). No significant differences were noted between the discovery and internal validation cohorts. However, the external validation cohort had a higher proportion of older patients, non-smokers, and right-sided tumors compared with the other two cohorts.

Inflammatory biomarkers and clinical outcomes

Survival analyses across the three cohorts showed that in the discovery cohort, elevated levels of FPSIIR, FPSIIS, FPSIRR, FPSIRS, FPSIRIR, FPSIRIS, FASIIR, FASIIS, FASIRR, FASIRS, FASIRIR, FASIRIS (all $p<0.05$) were significantly associated with reduced RFS and OS. Multivariate Cox models, adjusted for age, sex, smoking, alcohol use, hypertension, and diabetes, confirmed these markers as independent predictors of outcomes.

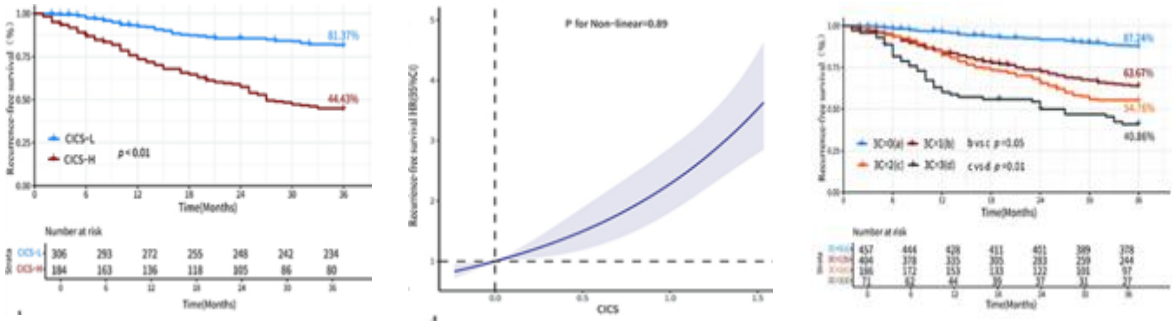
In the internal validation cohort, FPSIIR, FPSIIS, FPSIRR, FPSIRS, FPSIRIR, FPSIRIS, FASIIS, FASIRS, FASIRIR, FASIRIS (all $p<0.05$) were again validated as significantly linked to both RFS and OS. In the external validation cohort, FPSIIR, FPSIIS, FPSIRR, FPSIRS, FPSIRIR, FPSIRIS, FASIIS, FASIRS, FASIRIR, FASIRIS (all $p<0.05$) remained significantly associated with RFS, while for OS, the significant associations were observed with FPSIIR, FPSIIS, FPSIRS, FPSIRIR, FPSIRIS, FASIIS, FASIRS, FASIRIS (all $p<0.05$) only.

In this analysis, eight novel inflammatory markers—FPSIIR, FPSIIS, FPSIRS, FPSIRIR, FPSIRIS, FASIIS, FASIRS, and FASIRIS—consistently demonstrated negative correlations with clinical outcomes in stage II–III CRC patients across the three cohorts. To integrate their prognostic value, these biomarkers were incorporated into a Cox regression model to generate a chronic inflammatory comprehensive signature (CICS). The CICS formula is expressed as:

$$CICS = 0.592 \times FPSIRIR + 1.174 \times FPSIRS + 0.567 \times FASIRIS - 0.799 \times FASIRS. \quad (1)$$

Using X-tile software, the optimal threshold was defined as 0.75, stratifying patients into CICS-H (n=885) and CICS-L (n=569) groups. High CICS scores were strongly linked to advanced tumor stage (T3-4, $p<0.01$), poor differentiation (G3, $p<0.01$), larger tumor size ($p<0.01$), right-sided tumors ($p<0.01$), as well as increased recurrence and mortality (all $p<0.01$). Across the three cohorts, patients in the CICS-H group experienced significantly shorter RFS and OS compared with those in CICS-L **(Figures 1a and 1b)**.

After controlling for confounding factors, multivariate Cox regression confirmed that CICS-H independently predicted adverse outcomes in CRC (RFS: adjusted HR=3.42, 95% CI=2.68–4.44; OS: adjusted HR=4.25, 95% CI=3.04–5.94; plog-rank<0.01). When analyzed as a continuous variable, higher CICS values remained associated with poor prognosis (RFS: HR=1.83, 95% CI=1.62–2.07; OS: HR=2.03, 95% CI=1.72–2.39, plog-rank<0.01). Each 1 SD increase in CICS corresponded to an 83% higher risk for recurrence and a 103% higher risk of death. The associations between CICS and outcomes were predominantly linear (p for nonlinearity = 0.89 for RFS; 0.72 for OS), and higher CICS values consistently predicted greater HRs for recurrence and mortality, independent of other covariates **(Figures 1c and 1d)**. Time-dependent ROC analysis revealed that CICS outperformed the individual inflammatory biomarkers, with AUROCs for 1-, 2-, and 3-year RFS and OS of 0.708 & 0.705, 0.687 & 0.693, 0.683 & 0.690, respectively.



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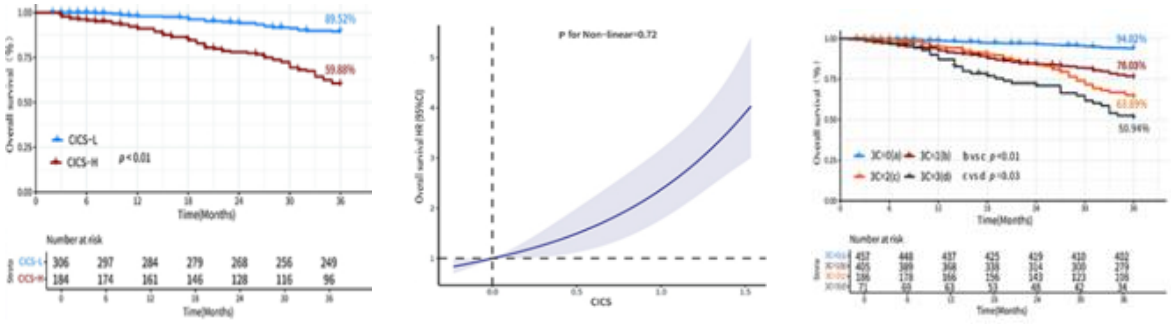

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Figure 1. CICS, 3C Score, and Survival in Stage II–III CRC Patients.
(a–b) Kaplan–Meier (KM) survival curves for patients in the discovery cohort;
(c–d) Restricted cubic spline (RCS) plots showing the relationship between CICS and survival in the overall population;
(e–f) KM curves illustrating survival outcomes according to the 3C score.

CEA and CA19-9, as established tumor markers in CRC, were also associated with worse survival outcomes. Their AUROCs for RFS and OS were 0.604 & 0.596 and 0.636 & 0.641, respectively. Integrating these with CICS, we constructed a CEA-CA19-9-CICS (3C) score. Compared with patients scoring zero, higher 3C scores were progressively linked to poorer outcomes:

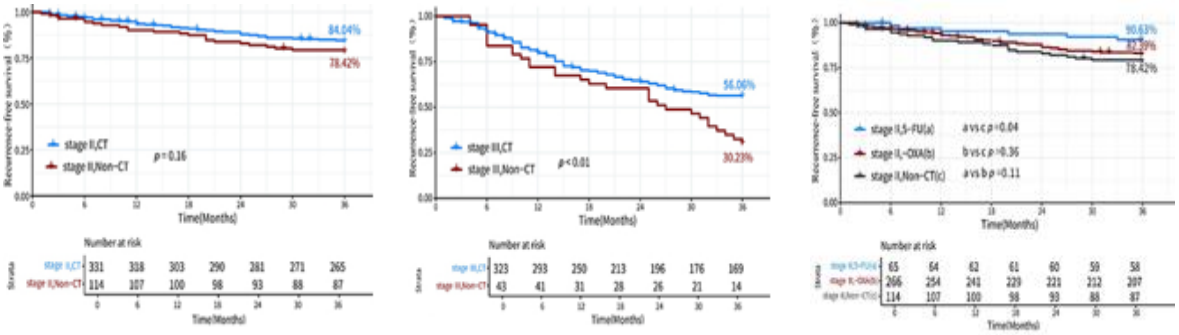
- RFS: 1 vs 0: HR=3.34 (95% CI=2.44–4.56); 2 vs 0: HR=4.43 (95% CI=3.14–6.25); 3 vs 0: HR=6.97 (95% CI=4.62–10.51)
- OS: 1 vs 0: HR=4.37 (95% CI=2.82–6.77); 2 vs 0: HR=6.56 (95% CI=4.13–10.42); 3 vs 0: HR=10.08 (95% CI=5.98–17.00)

(Figures 1e and 1f). The 3-year time-dependent AUROCs for predicting RFS and OS using 3C were 0.698 and 0.724, exceeding the predictive capacity of CICS alone.

CICS and chemotherapy response

We next evaluated the effect of 5-FU and oxaliplatin (OXA) in postoperative stage II–III patients. Among stage II patients, differences in survival between those receiving ACT or not were marginal (RFS $p_{log\text{-}rank}$ =0.16; OS $p_{log\text{-}rank}$ =0.05). Patients treated with 5-FU alone showed improved outcomes versus untreated patients (RFS: 90.63% vs 78.42%, $p_{log\text{-}rank}$ =0.04; OS: 92.06% vs 84.53%, $p_{log\text{-}rank}$ =0.14). Adding OXA to 5-FU did not substantially change RFS (90.63% vs 82.39%) or OS (92.06% vs 90.76%) **(Figures 2a–2c)**.

In stage III patients, ACT produced clear survival advantages (all $p_{log\text{-}rank}$ <0.01 for RFS and OS) **(Figure 2b)**. Within this cohort, OXA-containing regimens conferred superior survival compared with 5-FU alone (RFS $p_{log\text{-}rank}$ =0.06; OS $p_{log\text{-}rank}$ =0.05), with the effect most pronounced in the XELOX subgroup ($p_{log\text{-}rank}$ =0.01; OS $p_{log\text{-}rank}$ =0.02) **(Figures 2d–2f)**.



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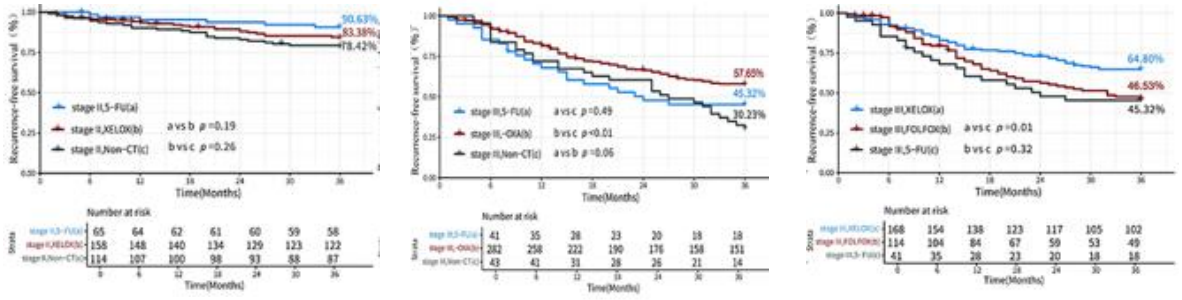
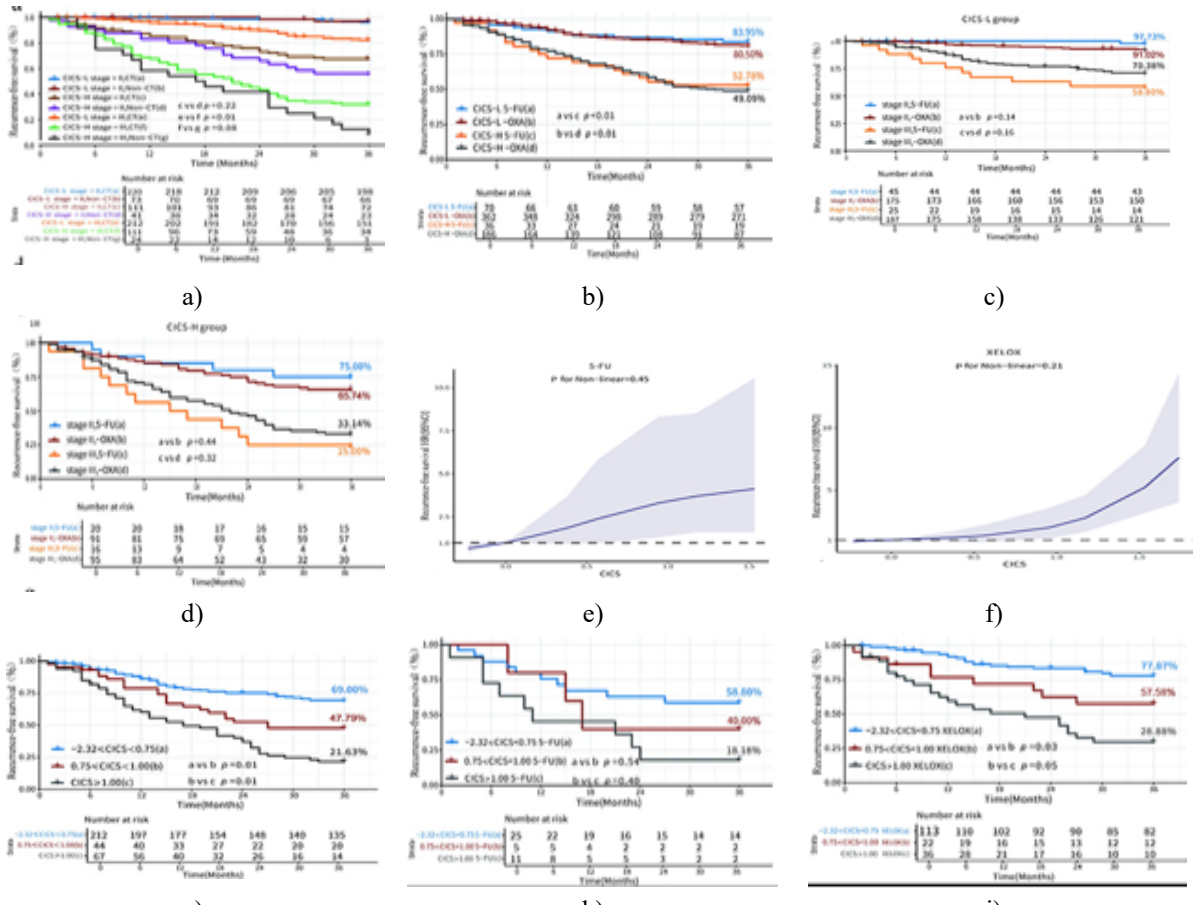


d) e) f)

Figure 2. Comparison of survival in stage II–III CRC patients receiving or not receiving adjuvant chemotherapy (ACT).

(a) Kaplan-Meier (KM) survival curves for stage II CRC patients with or without chemotherapy; (b) KM curves for stage III patients with or without chemotherapy; (c) KM curves for stage II patients treated with 5-FU, OXA, or no chemotherapy; (d) KM curves for stage II patients receiving 5-FU, XELOX, or no chemotherapy; (e) KM curves for stage III patients treated with 5-FU, XELOX, or no chemotherapy; (f) KM curves for stage III patients receiving XELOX, FOLFOX, or no chemotherapy.

We next evaluated how CICS stratification affected responses to 5-FU and oxaliplatin in the entire cohort, focusing separately on stage II and III CRC. For stage II patients with low CICS (CICS-L), survival was consistently favorable, independent of chemotherapy. In contrast, stage II patients with high CICS (CICS-H) derived clear survival benefits when undergoing ACT. Among stage III patients, chemotherapy improved outcomes regardless of CICS classification **(Figure 3a)**.



a) b) c)

d) e) f)

g) h) i)

Figure 3. Effects of adjuvant therapy stratified by CICS in stage II–III CRC.

(a) KM curves showing survival of stage II/III patients with CICS-L or CICS-H receiving or not receiving chemotherapy; (b) KM curves for CICS-L and CICS-H patients receiving 5-FU or OXA; (c,d) KM curves of

stage II/III CICS-L and CICS-H patients receiving 5-FU or OXA; (e,f) restricted cubic spline (RCS) analyses for CICS vs RFS in 5-FU or XELOX-treated patients; (g–i) KM curves for stage III patients treated with chemotherapy, 5-FU, or XELOX stratified by CICS tertiles.

For patients on the OXA regimen, 3-year RFS and OS were 80.50% and 90.08% in CICS-L, compared with 49.09% and 68.40% in CICS-H. In the 5-FU and XELOX groups, CICS-L patients exhibited superior survival:

- RFS: 5-FU: 83.95% vs 52.78%, plog-rank<0.01; XELOX: 84.10% vs 56.57%, plog-rank<0.01
- OS: 5-FU: 86.80% vs 65.26%, plog-rank=0.02; XELOX: 92.80% vs 68.99%, plog-rank<0.01

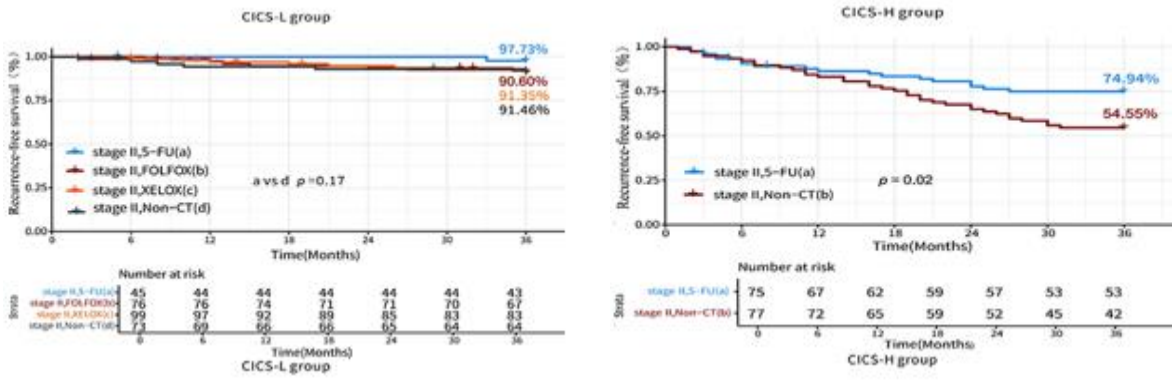
Among CICS-H patients, 3-year RFS was similar for XELOX vs 5-FU (56.57% vs 52.78%) without significant difference **(Figure 3b)**.

For stage II CICS-L patients, 5-FU and OXA yielded comparable outcomes: RFS 97.73% vs 91.02% (plog-rank=0.14) and OS 97.73% vs 95.77% (plog-rank=0.54). Stage II CICS-H patients showed no meaningful differences (RFS 75.00% vs 65.74%, plog-rank=0.44; OS 78.95% vs 80.78%, plog-rank=0.95). In stage III CICS-H patients, OXA-treated cases had slightly higher RFS and OS than 5-FU (RFS 33.14% vs 25.00%, plog-rank=0.32; OS 55.55% vs 44.14%, plog-rank=0.68), but differences were not statistically significant. CICS-L stage III patients tended to benefit more from OXA than 5-FU (RFS 70.38% vs 58.80%, plog-rank=0.16; OS 84.42% vs 66.78%, plog-rank=0.03), indicating borderline statistical significance **(Figures 3c and 3d)**.

Restricted cubic spline analyses revealed that higher CICS values corresponded to increasing HRs for RFS, with a similar trend for OS in 5-FU or XELOX recipients **(Figures 3e and 3f)**. Stage III patients were further divided into CICS-L (−2.32≤CICS<0.75), CICS-H (0.75≤CICS<1.00), and super CICS-H (CICS≥1.00). Their 3-year RFS rates were 69.00%, 47.79%, and 21.63%, and OS rates were 82.22%, 67.65%, and 45.61%, showing significant differences across subgroups, consistent across 5-FU and XELOX groups **(Figures 3g–3i)**. Within CICS-L, XELOX had higher RFS than 5-FU (77.87% vs 58.80%, plog-rank=0.02). For CICS-H (5-FU: n=5, XELOX: n=22) and super CICS-H (5-FU: n=11, XELOX: n=37), no significant differences were noted (CICS-H: 57.58% vs 40.00%, plog-rank=0.49; CICS-SH: 28.88% vs 18.18%, plog-rank=0.34).

CICS as a guide for adjuvant therapy

We then assessed whether CICS could help tailor ACT regimens. In stage II CICS-L patients, outcomes with 5-FU were comparable to those receiving FOLFOX, XELOX, or no chemotherapy, with RFS and OS above 97.73%, suggesting that ACT may not be required. CICS-H patients receiving 5-FU experienced significantly better RFS than untreated patients (74.94% vs 54.55%, plog-rank=0.02; HR=0.51, 95% CI=0.29–0.90). There was no significant difference in RFS between OXA-treated and untreated CICS-H patients, indicating that 5-FU is likely the optimal adjuvant therapy in this group **(Figures 4a and 4b)**.



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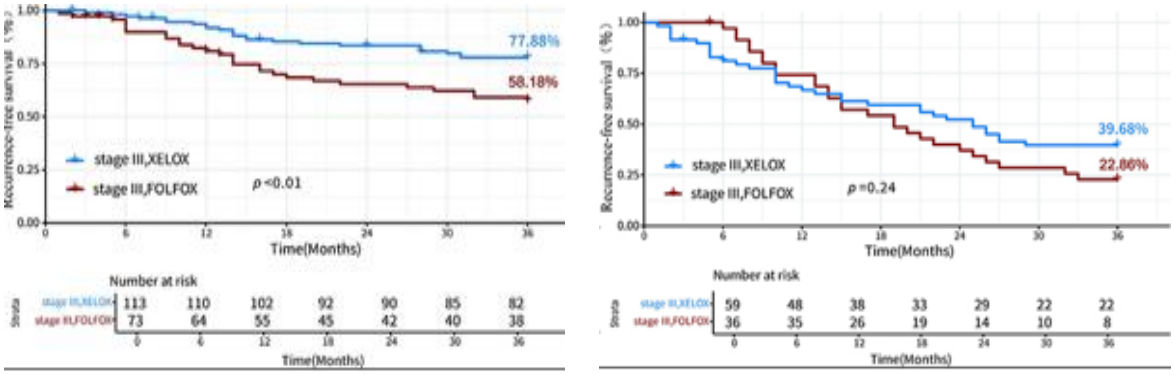

c) d)

Figure 4. Adjuvant chemotherapy optimization based on CICS in stage II–III CRC.
(a) KM curves depicting CICS-L stage II patients receiving 5-FU, XELOX, FOLFOX, or no chemotherapy; (b) KM curves for CICS-H stage II patients receiving 5-FU or no treatment; (c, d) KM curves for CICS-L and CICS-H stage III patients treated with XELOX or FOLFOX regimens.

In stage III patients classified as CICS-L, those who received XELOX had notably higher recurrence-free survival (RFS) than those treated with FOLFOX (77.88% vs 58.18%, plog-rank <0.01, HR=0.46, 95% CI=0.27–0.79), and overall survival (OS) was also superior (89.40% vs 76.05%, plog-rank=0.02, HR=0.40, 95% CI=0.18–0.86). Among CICS-H patients, RFS was higher for those on XELOX (39.68% vs 22.86%) with a slightly increased OS (56.51% vs 52.93%) compared to FOLFOX, but these differences were not statistically significant **(Figures 4c and 4d)**.

Impact of CICS-guided therapy

We evaluated how a CICS-based strategy could influence chemotherapy administration and clinical outcomes. Across the cohort, 158 patients did not undergo ACT. Using CICS guidance, 65.92% of stage II CICS-L patients achieved favorable outcomes without chemotherapy. Limiting ACT to only CICS-H patients reduced the proportion of treated patients while preserving clinical efficacy. Overall, ACT administration decreased from 80.54% to 63.79% (p<0.01, RR=0.43, 95% CI=0.34–0.53), with a shift toward single-agent 5-FU and a reduction in OXA-containing regimens (p<0.01, RR=0.47, 95% CI=0.35–0.62). No significant differences were seen in 3-year recurrence or mortality rates.

For stage II, the CICS strategy lowered ACT use from 74.22% to 34.08% (p<0.01, RR=0.18, 95% CI=0.13–0.24) and increased single-agent 5-FU while removing OXA doublets (p<0.01), without affecting survival. Among stage III patients, XELOX utilization rose, other regimens decreased (p<0.01), and 3-year RFS (plog-rank=0.02, RR=0.70, 95% CI=0.53–0.92) and OS (plog-rank=0.05, RR=0.70, 95% CI=0.47–0.97) improved compared to traditional treatment **(Table 1)**.

Table 1. Comparing Clinical Benefit: Conventional vs CICS-Guided ACT in Stage II–III CRC

Population	Treatment Parameter	Traditional Approach (%)	CICS-Guided Approach (%)	Absolute Change (%)	P-value	RR / HR (95% CI)
Overall population						
	Adjuvant chemotherapy (ACT) administered					
	No	19.46	36.21	–	–	–
	Yes	80.54	63.79	−16.75	0.01*	0.43 (0.34–0.53)
	Type of ACT regimen					
	Single-agent 5-FU	16.21	29.34	–	–	–
	Oxaliplatin-based doublet	83.79	70.66	−13.13	0.01*	0.47 (0.35–0.62)
	3-year recurrence rate	29.56	25.94	−3.62	0.30	0.87 (0.67–1.13)

	3-year mortality rate	17.86	15.41	−2.45	0.35	0.85 (0.61–1.18)
Stage II subgroup						
	Adjuvant chemotherapy (ACT) administered					
	No	25.78	65.92	–	–	–
	Yes	74.22	34.08	−40.14	0.01*	0.18 (0.13–0.24)
	Type of ACT regimen					
	Single-agent 5-FU	19.64	34.08	+14.44	–	–
	Oxaliplatin-based doublet	80.36	0	−80.36	0.01*	–
	3-year recurrence rate	16.82	11.70	−5.12	0.24	0.69 (0.39–1.20)
	3-year mortality rate	10.31	7.45	−2.86	0.39	0.71 (0.35–1.43)
Stage III subgroup						
	Preferred ACT regimen					
	XELOX	53.25	100	–	0.01*	–
	Other regimens	46.75	0	−46.75	0.01*	–
	3-year recurrence rate	45.08	33.72	−11.36	0.02	0.70 (0.53–0.92)
	3-year mortality rate	27.05	19.77	−7.28	0.05	0.70 (0.47–0.97)

*Notes: p<0.01; Traditional regimens include 5-FU, XELOX, and FOLFOX.
Abbreviations: 5-FU, 5-fluorouracil; ACT, adjuvant chemotherapy; CICS, chronic inflammation signature; RR, relative risk; HR, hazard ratio; XELOX, capecitabine plus oxaliplatin.

Precision chemotherapy aims to maximize benefit while minimizing unnecessary toxicity. We developed a novel inflammatory marker (CICS) and evaluated its ability to predict survival, sensitivity to 5-FU or oxaliplatin, and guide ACT regimens across three independent cohorts under a double-blind design. Both CICS and 3C scores were independent prognostic markers in stage II–III patients, with 3C achieving an AUROC of 0.724.

Patients with high CICS (CICS-H) had lower responses to 5-FU and oxaliplatin, identifying a subset with poorer outcomes on 5-FU alone. Adding oxaliplatin improved their survival. Stage II CICS-L patients may safely skip ACT without harming outcomes, while CICS-H patients benefit from 5-FU. For stage III, XELOX was optimal for CICS-L, while CICS-H patients achieved similar outcomes with XELOX or FOLFOX. Overall, CICS reliably predicts who benefits from 5-FU and oxaliplatin, enabling personalized adjuvant chemotherapy for stage II–III CRC.

Tumor microenvironment, inflammation, and chemotherapy response in CRC

The tumor microenvironment (TME) in colorectal cancer (CRC) comprises interactions among cancer cells, stem-like cells, inflammatory immune cells, and stromal components, all of which contribute to chemoresistance and tumor progression [31]. Chronic inflammation induced by cancer serves as a hallmark that reflects TME dynamics [32]. Circulating inflammatory markers can provide insights into the responsiveness of CRC patients to chemotherapeutics, such as 5-fluorouracil (5-FU) and oxaliplatin, as well as overall prognosis following surgery. Recent indices, including FPR, SIR/SII, and SIRI, have shown predictive utility for survival in stage II–III CRC, with reported AUCROCs ranging from 0.50 to 0.65 [20–23].

In this investigation, we generated six new inflammatory ratios and six composite inflammatory scores derived from FPR, SIR/SII, and SIRI. Analyses in the discovery cohort demonstrated significant negative correlations between these markers and RFS or OS in stage II–III patients. Associations for FPSIIR, FPSIIS, FPSIRS, FPSIRIR, FPSIRIS, FASIIS, FASIRS, and FASIRIS were confirmed in both internal and external validation cohorts. Building upon these findings, we constructed a chronic inflammatory comprehensive signature (CICS) using independent contributors including FPSIRS, FPSIRIR, FASIRS, and FASIRIS. Patients with CICS-L showed substantially longer RFS and OS than CICS-H individuals, regardless of chemotherapy regimens or staging, while the predictive accuracy of CICS exceeded 0.69, outperforming each single biomarker and establishing it as a robust integrative prognostic tool.

CEA and CA19-9 are established tumor markers for survival prediction in CRC [33, 34], and their prognostic trends in this cohort were consistent with prior studies [26, 27]. Integrating CICS with CEA and CA19-9, we derived the 3C score, which strongly correlated with clinical outcomes. Its predictive capacity reached 0.724, indicating that combining these markers effectively stratifies patients by recurrence risk and improves prognostic precision for stage II–III CRC.

Chemotherapy and inflammation

Regimens containing 5-FU and oxaliplatin are widely used in gastrointestinal malignancies [35]. Both agents can activate NF-κB and MAPK signaling [36], leading to production of inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which drive systemic inflammation [37]. In our study, the clinical benefits of 5-FU- and oxaliplatin-based ACT were more prominent in CICS-L patients compared to CICS-H. In CICS-H patients, survival outcomes were similar between those treated with oxaliplatin or 5-FU alone. The degree of chronic inflammation correlated with CRC pathological features, increasing with tumor invasion depth [38]. Furthermore, stage III patients treated with these agents demonstrated worse survival compared to stage II, highlighting that high-grade cancer-related inflammation may reduce chemotherapeutic sensitivity.

Clinical decision-making and risk stratification

Precision adjuvant therapy in CRC depends on identifying patients most likely to benefit from treatment while limiting unnecessary toxicity [39]. Liquid biopsies, such as circulating tumor cells, exosomes, and ctDNA, offer potential for detecting high-risk individuals, aiding therapeutic decisions [40]. In our cohort, stage II CICS-L patients had recurrence and mortality rates of only 7.48% and 3.74%, respectively. Outcomes for these patients treated with 5-FU, XELOX, or FOLFOX were similar to those who underwent surgery alone. Thus, applying CICS-guided stratification could potentially spare approximately 65.92% of stage II CICS-L patients from unnecessary chemotherapy, reducing exposure to toxicity and healthcare costs.

For stage II CICS-H patients, survival with 5-FU alone was comparable to outcomes with XELOX or FOLFOX, indicating that oxaliplatin could be omitted to avoid adverse effects without compromising efficacy. In stage III disease, high-grade inflammation may attenuate responses to 5-FU or oxaliplatin, yet XELOX-treated patients consistently exhibited improved survival over 5-FU or FOLFOX across both CICS-H and CICS-L subgroups. Implementation of the CICS-guided strategy reduced recurrence and mortality rates and improved overall survival compared to conventional chemotherapy selection.

These findings suggest that CICS-L stage III patients derive particular benefit from oxaliplatin, supporting XELOX as the preferred regimen, while CICS also demonstrates high sensitivity and negative predictive value, confirming its utility for tailoring adjuvant chemotherapy in operable stage II–III CRC.

This research represents, as far as we are aware, the first effort to design a novel Chronic Inflammatory Comprehensive Signature (CICS) and explore how tumor-derived inflammation affects the clinical response to 5-FU and oxaliplatin. Our data indicate that CICS serves as a robust and innovative biomarker, capable of predicting survival outcomes, guiding chemotherapy choices, and evaluating the benefit of these two drugs. Compared with ctDNA or CMS, CICS offers a cost-efficient, practical, and scalable solution, which can be more readily implemented in diverse healthcare settings. In contrast, ctDNA assays face challenges with standardization and are largely used for detecting postoperative residual disease and assessing recurrence risk [41]. Likewise, while CMS profiling provides insights into tumor heterogeneity, its limited molecular coverage constrains clinical utility for chemotherapy guidance [42].

The findings suggest that a CICS-based strategy could be actively applied in clinical decision-making for personalized adjuvant chemotherapy (ACT). Specifically, it allows clinicians to withhold ACT in low-risk stage II patients without compromising outcomes, while optimizing regimen selection for high-risk stage II and stage III patients. Moreover, CICS could help identify patients who might benefit from avoiding oxaliplatin, especially those at risk of neuropathy or other toxicities, such as elderly patients or those with comorbidities. Considering the high incidence of CRC in China, adopting this strategy has the potential to lower healthcare costs while improving patient quality of life, offering a precision-based approach for a high-burden malignancy.

Several limitations should be acknowledged. First, the current CICS cutoff may lead to approximately 66% of stage II patients receiving unnecessary ACT and 34% being exposed to oxaliplatin unnecessarily. Therefore, further optimization of the threshold is needed to improve specificity. Second, due to the heterogeneity of CRC, not all patients may gain benefit from a CICS-guided approach with 5-FU and oxaliplatin. Combining CICS with

liquid biopsy techniques could enhance treatment precision and enable alternative strategies for non-responders. Finally, although the results are promising, they require confirmation through multicenter prospective studies with larger cohorts, and preclinical studies are necessary to elucidate the mechanistic link between inflammatory markers and chemotherapy sensitivity.

Conclusion

In summary, CICS provides a reliable tool to predict response to 5-FU and oxaliplatin in the adjuvant CRC setting. Applying a CICS-guided approach can help select the most appropriate chemotherapy regimen, reduce unnecessary ACT, and maintain clinical outcomes in stage II–III operable CRC patients.

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