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ORIGINAL RESEARCH

Chronic Inflammatory Comprehensive Signature Predicts Oxaliplatin and 5-Fluorouracil Benefit in Early Colorectal Cancer

Yue Peng[1,2], Rong Shang[1,2], Zhi-Jie Wang[1,2], Qiu-Ying Ye[3,4], Xiao-Yan Tang[1,2], Xue-Xin Cheng[1,2], Hou-Qun Ying[1,4,5]

[1]Jiangxi Province Key Laboratory of Immunology and Inflammation, Jiangxi Provincial Clinical Research Center for Laboratory Medicine, Department of Clinical Laboratory, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi, People's Republic of China; [2]School of Public Health, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi, People's Republic of China; [3]Department of Medical Technology, Jiangxi Medical College, Shangrao, Jiangxi, People's Republic of China; [4]Department of Laboratory Medicine, Central Hospital of Shangrao City, Shangrao, Jiangxi, People's Republic of China; [5]Shangrao Medical Center of The Second Affiliated Hospital of Nanchang University, Shangrao, Jiangxi, People's Republic of China

Correspondence: Hou-Qun Ying, Department of Clinical Laboratory, Immunity and Inflammation Key Laboratory of Jiangxi Province, The Second Affiliated Hospital of Nanchang University, No. 1 of Minde Road, Nanchang, 330006, People's Republic of China, Tel/Fax +86 0791-86297662, Email yinghouqun2013@163.com

Background: Precision delivery of adjuvant chemotherapy (ACT) improves healthcare efficiency and postoperative quality of life in stage II–III colorectal cancer (CRC). However, there remains an unmet need for identifying biomarkers that can predict therapeutic responses to 5-fluorouracil (5-FU) and oxaliplatin.

Methods: We analyzed three independent cohorts (1676 stage II–III surgical cases) to evaluate the prognostic role of 12 inflammatory indices. A novel Chronic Inflammatory Comprehensive Signature (CICS) was developed using multivariable Cox regression. Three-year recurrence-free survival (RFS) and overall survival (OS) were compared between CICS-stratified subgroups (CICS-L vs CICS-H) receiving 5-FU- or oxaliplatin-based ACT.

Results: Two novel inflammatory ratios (FPSIIR, FPSIRIR) and six composite scores (FPSIIS, FPSIRIS, FPSIRS, FASIIS, FASIRS, FASIRIS) independently predicted prognosis across all three cohorts (all $p_{\text{log-rank}}<0.05$). The CICS demonstrated an AUC of 0.690 for outcome prediction, increasing to 0.724 when combined with CEA-CA19-9. CICS-H patients exhibited reduced chemosensitivity to both agents, with therapeutic benefits primarily confined to the CICS-L subgroup. Comparable favorable RFS was observed in stage II CICS-L patients undergoing 5-FU monotherapy or oxaliplatin-based ACT versus non-ACT treatments (97.73% vs 91.02% vs 91.46%, $p_{\text{log-rank}}=0.33$). Superior survival outcomes and a lower recurrence rate were observed in stage II CICS-H patients receiving 5-FU compared to those receiving oxaliplatin-based ACT. Consistent oxaliplatin benefits were observed in CICS-H and CICS-L patients compared to 5-FU-treated cases in the stage III subgroup. Optimal ACT regimens for patients with CICS-L and CICS-H differ in different stages. The CICS strategy can help patients select a more optimal ACT regimen (RR=0.47, 95% CI=0.35–0.62, p<0.01) and enhance therapeutic efficacy (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).

Conclusion: CICS-quantified cancer-derived inflammation inversely correlates with the therapeutic responsiveness to 5-FU/oxaliplatin. A CICS-guided strategy maximizes survival outcomes while precision-deescalating chemotherapy use without compromising outcomes, establishing a biomarker-driven paradigm for personalized postoperative management of CRC.

Keywords: chronic inflammatory comprehensive signature, CEA-CA19-9-CICS score, oxaliplatin, 5-fluorouracil, colorectal cancer

Introduction

Postoperative adjuvant chemotherapy (ACT) is the standard therapeutic approach for high-risk stage II and III colorectal cancer (CRC) following radical resection, aimed at preventing recurrence and metastasis.[1,2] In addition to single fluorouracil (FU) and its derivatives such as 5-FU, capecitabine, and tegafur, combination regimens including capecitabine plus oxaliplatin (XELOX) and oxaliplatin/5-FU/ leucovorin (FOLFOX) have been sequentially established as first-line ACT regimens for these patients,[3–6] for which oxaliplatin yielded to an approximately 5%~6% reduction in disease progression.[7]

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Despite the significant clinical benefits associated with 5-FU and oxaliplatin, it has been reported that approximately 8% ~12% of surgical patients experience recurrence within six months following treatment.[8] This observation suggests that some individuals possess a natural resistance to these chemotherapeutic agents.

Accumulating evidence shows that 5-FU and oxaliplatin are associated with a variety of toxic adverse effects. Diarrhea and vomiting frequently occur in patients receiving 5-FU.[9] Oxaliplatin is linked to a high incidence of both acute and chronic disabling peripheral neurotoxicities.[7,10] The CALGB/SWOG 80702 clinical trials demonstrate that acute chemotherapy-induced peripheral neuropathy can be observed in more than 85–93% of patients treated with oxaliplatin, with an estimated half progressing to chronic peripheral neuropathies. These side effects may significantly impact the quality of life for patients and impose substantial unnecessary financial burdens on healthcare systems.[10] Therefore, there is an urgent need to develop efficacy biomarkers to identify CRC patients who may benefit from ACT, as this could help avoid or deescalate unnecessary side effects in clinical practice.

Numerous novel biomarkers have been developed to identify low-risk surgical patients, evaluate clinical efficacy, and predict patient outcomes.[11] Circulating tumor DNA (ctDNA) and consensus molecular subtype (CMS) classification have shown promise in stratifying high- or low-risk patients likely to experience recurrence.[12–15] However, these novel biomarkers rely on next-generation sequencing, which is hindered by high cost and a shortage of qualified personnel. This limitation restricts their widespread application in clinical settings, particularly in numerous basic medical units. Furthermore, circulating ctDNA and CMS classification may not effectively identify the high-risk subgroup that could benefit from oxaliplatin, 5-FU, and its derivatives.[16,17] The T1-3 and N1 classifications have been reported as valuable tools for identifying patients to limit the cumulative toxicities associated with ACT, for the patients can achieve non-inferiority after three months of ACT compared to a six-month duration.[7] Therefore, significant efforts are required to develop efficacy biomarkers that can accurately predict the benefits of oxaliplatin and 5-FU.

Emerging studies have demonstrated that tumor microenvironment (TME) and metabolic reprogramming play crucial role in tumorigenesis and progression of CRC.[16,18] The reprogramming of amino acids metabolism, particularly serine and glycine, supports the proliferation, metastasis, and resistance to ACT of CRC cells by contributing to their anabolic demands and fostering an unfavorable TME with high-grade inflammation.[16,19] Thus, cancer-derived inflammation has emerged as a critical hallmark of CRC.[20] Chronic inflammatory biomarkers such as fibrinogen-pre-albumin ratio (FPR), systematic inflammation ratio/index (SIR/SII), and systematic inflammation response index (SIRI) have been identified as independent prognostic indicators for CRC.[21–23] Although FPR has been reported to outperform SIR/SII or SIRI in predicting disease outcomes,[24] its predictive efficacy remains unsatisfactory and requires enhancement. Our previous studies suggest that cancer-elicited inflammation may diminish sensitivity to ACT or trigger resistance in CRC patients, particularly those with metastatic disease.[21,25,26] However, the clinical response to oxaliplatin or 5-FU and its derivatives in surgical CRC patients exhibiting varying degrees of chronic inflammation remains unknown. Therefore, an unmet need exists to develop optimal biomarkers with high clinical efficacy.

Here, we report the development and evaluation of a new chronic inflammatory comprehensive signature (CICS) and the CEA-CA19-9-CICS (3C) score, which predict the efficacy of 5-FU and oxaliplatin-based regimens by utilizing chronic inflammatory indices as input features. Based on the key assumption that chronic inflammation reflects cancer characteristics and its microenvironment, which are informative regarding drug responses, we employed Cox regression methods to identify such patterns and utilize them as features for assessing benefits from oxaliplatin or 5-FU treatment. We evaluated the capability of CICS and 3C score in predicting the benefits of oxaliplatin and 5-FU in stage II–III CRC adjuvant settings through three distinct cohorts: discovery, internal validation, and external validation cohorts, comprising a total of 1, 676 patients across three centers. Our findings support that CICS and 3C score were reliable predictors for determining benefits from oxaliplatin and 5-FU therapies.

Materials and Methods

Study Design and Population

The CRC chronic inflammation cohort randomly assigned 1706 patients with stage II–III CRC who underwent radical surgery followed by ACT June 2011 to January 2017 in the hospital. Eligible patients were initially diagnosed at the hospital and have no concurrent malignancies, haematologic diseases, autoimmune disorders, benign chronic

inflammatory bowel disease, or recent infections or injuries. We randomly divided the patients into discovery, internal validation, and external validation cohorts. Based on existing evidence indicating comparable efficacy among 5-FU, capecitabine, and tegafur,[27] we combined these patients into a single group treated with 5-FU (referred to as the 5-FU group). Similarly, given that XELOX and FOLFOX regimens demonstrate similar effectiveness in treating CRC,[28,29] these cases were classified as an oxaliplatin-treated group (collectively referred to as OXA) for subsequent analyses. All the enrolled patients have signed the inform consent, and this study was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University (O-MedResEthicsRev [2025] No. 54).

Sample Collection and Laboratory Detection

Baseline characteristics, including gender, age, smoking status, alcohol consumption, diabetes, hypertension, and pathological features such as cellular differentiation, tumor size, depth of tumor invasion, lymph node involvement, primary tumor location, and treatment modalities, were collected from each eligible patient. The collection and detection of laboratory biomarkers were conducted in accordance with our previous studies.[25,26] The coefficients of variation for both inter-assay and intra-assay precision were found to be less than 10%. Definitions for twelve new inflammatory biomarkers were presented in Table S1.

CICS and 3C Model Development

We hypothesized that the heterogeneous responses of CRC to oxaliplatin and 5-FU might be attributed to variations in cancer-related inflammation. To investigate the role of twelve new inflammatory biomarkers in predicting clinical outcomes, we employed multivariable Cox regression analysis to identify independent prognostic factors. Utilizing these independent inflammatory prognostic factors as input variables, we derived a new chronic inflammatory comprehensive signature (CICS) through Cox regression. However, CICS is a comprehensive index that solely represents inflammation status, whereas common tumor biomarkers reflect the characteristics specific to CRC.[30] Therefore, we developed a new prognostic score, the 3C score, comprising carcinoembryonic antigen (CEA), carbohydrate antigen 19–9 (CA19-9), and CICS. Among these markers, CICS, CEA, and CEA19-9 were stratified into subgroups based on their abnormal statuses: 0-, 1-, 2- or 3-score subgroups. A score of three points is assigned when all three indicators are abnormal, defined by the following thresholds: CICS $\geq$0.75, CEA$\geq$5.00 ng/mL, and CA19-9$\geq$37.00 U/mL. A score of two points is allocated if any two of these indicators are abnormal; one point is given when only one indicator is abnormal. A score of zero points is designated when none of the indicators meet the abnormal thresholds, specifically, CICS<0.75, CEA<5.00 ng/mL, and CEA19-9<37.00 U/mL.

Follow-Up

In the three-year follow-up period, we conducted follow-ups every three months during the first two years and every six months in the third year. The primary endpoint was recurrence-free survival (RFS), while overall survival (OS) served as a secondary endpoint, with a deadline established for January 1, 2020. Tumor biomarkers detection, including CEA and CA19-9, and imaging detection, such as computed tomography (CT), magnetic resonance imaging (MRI), and single-photon emission computed tomography, were utilized to identify recurrence or distant metastasis. RFS is defined as the time from surgery to either recurrence, distant metastasis or until the deadline without recurrence; OS is defined as the duration from surgery to death or until the deadline without death.

Statistics

The study was conducted in a double-blinded manner. The laboratory detection team was blinded to clinical outcome data, while the clinical evaluation team remained unaware of the methodology and detection results. Two primary objectives were prespecified for data analyses. The first objective was to evaluate the independent inflammatory biomarker, CICS, and 3C score across discovery, internal validation, and external validation cohorts when treated with ACT. The second objective aimed to determine whether the effects of oxaliplatin and 5-FU treatment differed between the CICS-H and CICS-L groups.

The Chi-square or Fisher's exact test was employed to analyze differences between categorical variables, which are presented as counts and percentages. Continuous variables are represented by median (25th ~75th percentiles) and means ± standard deviation (SD). Wilcoxon test or *t*-test was utilized to assess the differences between groups. Optimal cut-offs for each continuous inflammatory biomarker related to RFS were determined using X-tile software (Yale University, New Haven, CT). Based on these cut-offs, these biomarkers dichotomized patients into two subgroups labeled as high and low. Kaplan–Meier curves with Log rank tests, univariate and multivariate Cox regression models (backward likelihood ratio method), and restricted cubic spline (RCS) were selected to explore potential associations between biomarkers and clinical outcomes. Hazard ratios (HRs), along with 95% confidence intervals (CIs), were used to evaluate the strength of these associations. The area under the time-dependent receiver operating characteristic curve (AUC) was employed to assess the predicted efficacy of biomarkers. Statistical analyses were performed using SPSS version 27.0 (IBM Corp, Armonk, NY, USA), R version 4.4.2 (Institute for Statistics and Mathematics, Vienna, Austria), and GraphPad Prism version 10 (GraphPad Software Inc., San Diego, CA, USA).

Results

Baseline Characteristics

According to the established inclusion and exclusion criteria, 1676 eligible patients were enrolled in this study (discovery cohort: 490 patients; validation cohort: 1186 patients) (Figure S1). The demographics and clinical baseline characteristics of the discovery, internal validation, and external validation cohorts are described in Table S2. No statistically significant difference was observed among the discovery and internal validation cohorts regarding all the clinical characteristics. However, it was noted that age, non-smoking status, and right-location proportions within the external validation cohort were higher than those in the other two cohorts.

Inflammatory Biomarkers and Clinical Outcome

We conducted survival analyses of patients across the three cohorts. Kaplan-Meier curves and univariable Cox regression analyses indicated that elevated FPSIIR, FPSIIS, FPSIRR, FPSIRS, FPSIRIR, FPSIRIS, FASIIR, FASIIS, FASIRR, FASIRS, FASIRIR, FASIRIS (all $p<0.05$) were statistically associated with shorter RFS and OS in the discovery cohort. Multivariate analysis suggested that these novel inflammatory ratios and scores remained significantly associated with patient outcomes after adjusting for confounding variables such as age, gender, smoking, alcohol consumption, hypertension, and diabetes in the discovery cohort (Table S3). In the internal validation cohort, FPSIIR, FPSIIS, FPSIRR, FPSIRS, FPSIRIR, FPSIRIS, FASIIS, FASIRS, FASIRIR, FASIRIS (all $p<0.05$) were validated to be significantly associated with RFS and OS among patients. However, in the external validation cohort, significant associations were observed between FPSIIR, FPSIIS, FPSIRR, FPSIRS, FPSIRIR, FPSIRIS, FASIIS, FASIRS, FASIRIS (all $p<0.05$) and RFS of the patients. Interestingly, the same relationships between the inflammatory biomarkers and OS of the patients were only examined on FPSIIR, FPSIIS, FPSIRS, FPSIRIR, FPSIRIS, FASIIS, FASIRS, FASIRIS (all $p<0.05$). (Table S3).

CICS and 3C Score and Clinical Outcome

In our study, the eight novel inflammatory biomarkers-FPSIIR, FPSIIS, FPSIRS, FPSIRIR, FPSIRIS, FASIIS, FASIRS, FASIRIS were consistently found to be negatively associated with clinical outcomes in stage II–III patients across three independent cohorts. Consequently, all of these biomarkers were incorporated into a Cox regression analysis to develop a new chronic inflammatory comprehensive signature (CICS). The formula for calculating CICS is as follows: CICS=0.592×FPSIRIR+ 1.174×FPSIRS+0.567×FASIRIS-0.799×FASIRS. An optimal cut-off value of 0.75 was determined for this novel signature based on clinical outcomes using X-tile software. Patients were subsequently classified into two subgroups: CICS-H (n=885) and CICS-L (n=569). A high level of CICS was significantly associated with T3-4 stage ($p<0.01$), G3 differentiation ($p<0.01$), tumor size ($p<0.01$), right-sided location ($p<0.01$), recurrence rates, and death rates (all $p<0.01$), as detailed in Table S4. The cases with CICS-H exhibited inferior RFS and OS compared to those in the CICS-L across the three cohorts, respectively (Figure 1a and b, Figure S2a-d). After adjusting for

confounding variables, multivariate Cox proportional hazards regression analyses indicated that CICS-H serves as an independent biomarker for CRC ($p_{log\text{-}rank}$<0.01, adjusted HR=3.42, 95% CI=2.68–4.44 for RFS; $p_{log\text{-}rank}$<0.01, adjusted HR=4.25, 95% CI=3.04–5.94 for OS) within the overall population. When considering CICS as a continuous variable, it was consistently linked to unsatisfactory RFS ($p_{log\text{-}rank}$<0.01, adjusted HR=1.83, 95% CI=1.62–2.07) and OS ($p_{log\text{-}rank}$<0.01, adjusted HR=2.03, 95% CI=1.72–2.39). For every SD increase in the CICS score among CRC patients, there was an observed increase in risk of poor RFS by 83% ($p_{log\text{-}rank}$<0.01, adjusted HR=1.83, 95% CI=1.62–2.07) and poor OS by 103% ($p_{log\text{-}rank}$<0.01, adjusted HR=2.03, 95% CI=1.72–2.39), as summarized in Table S5. Furthermore, significant linear relationships were observed between the CICS and both RFS (*p*-value for nonlinearity=0.89) and OS (*p*-value for nonlinearity=0.72) among CRC patients. With an increasing CICS score, the HRs for patient recurrence and mortality significantly increased regardless of other confounding factors (Figure 1c and d). Time-dependent ROC demonstrated that the predictive efficacy of the CICS for survival exceeded that of individual inflammatory biomarkers (Figure S2e-f), with AUROCs predicting one, two, and three-year RFS and OS reaching values of 0.708 and 0.705, 0.687 and 0.693, 0.683 and 0.690, respectively.

CEA and CA19-9 are recognized as significant tumor biomarkers for predicting survival in CRC.[31] Elevated levels of both CEA and CA19-9 were negatively associated with patient outcomes within the overall population. The respective AUROCs for RFS and OS were recorded at 0.604 and 0.596, as well as 0.636 and 0.641, respectively. We developed a novel CEA-CA19-9-CICS score (3C score), as detailed in (Table S6). Compared to cases with a zero-score, RFS (score 1 vs 0: adjusted HR =3.34, 95% CI=2.44–4.56; score 2 vs 0: adjusted HR=4.43, 95% CI=3.14–6.25; score 3 vs 0: adjusted HR=6.97, 95% CI =4.62–10.51) and OS (score 1 vs 0: adjusted HR=4.37, 95%=2.82–6.77; score 2 vs 0: adjusted HR=6.56, 95%= 4.13–10.42; score 3 vs 0: adjusted HR=10.08, 95%=5.98–17.00) were significantly worsened with an increased 3C score (Figure 1e and f). The time-dependent AUROCs for the predictive capability regarding three-year RFS and OS using 3C were 0.698 and 0.724 across the overall population, demonstrating superiority over CICS (Figure S2g-h).

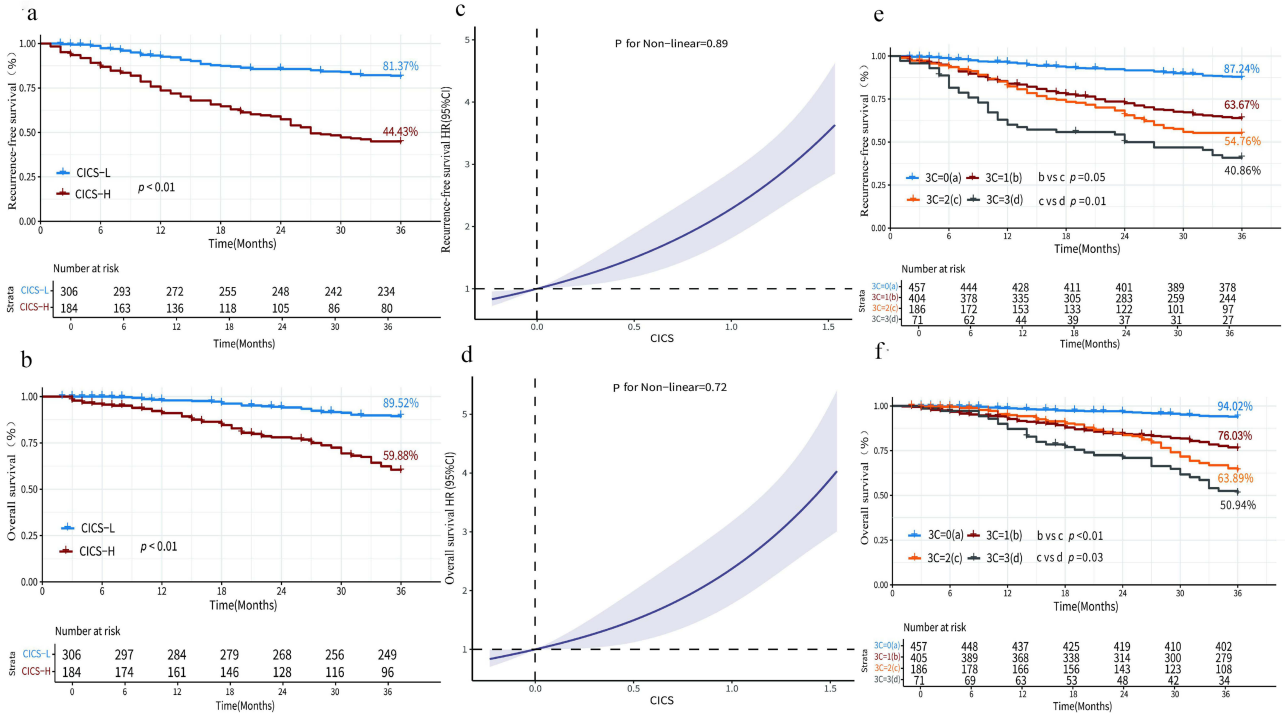

Figure 1 CICS, 3C score and survival outcomes in patients with stage II–III CRC. (**a** and **b**) Kaplan-Meier (KM) curve within the discovery cohort; (**c** and **d**) restricted cubic spline plot of CICS in the overall population; (**e** and **f**) KM curve of the 3C score.

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CICS and Sensitivity to Oxaliplatin and 5-Fluorouracil

The treatment effects of 5-FU and oxaliplatin were evaluated in postoperative patients with stage II–III CRC. A borderline significance in survival was noted among stage II surgical patients with or without CT ($p_{log\text{-}rank}$=0.16 and 0.05 for RFS and OS, respectively). Patients treated with 5-FU exhibited a significantly better prognosis compared to those who did not receive CT ($p_{log\text{-}rank}$=0.04, 90.63% vs 78.42% for RFS; $p_{log\text{-}rank}$=0.14, 92.06% vs 84.53% for OS). However, no significant differences were observed in RFS (90.63% vs 82.39%) and OS (92.06% vs 90.76%) between the groups receiving the combined treatment of 5-FU and OXA regimen (Figure 2a–c, Figure S3a-c). Stage III CRC surgical patients derived substantial benefits from ACT (all $p_{log\text{-}rank}$<0.01 for RFS and OS, respectively) (Figure 2b and Figure S3b). Furthermore, patients treated with the OXA regimen demonstrated a more favorable prognosis compared to those receiving only the standard treatment with 5-FU ($p_{log\text{-}rank}$=0.06 and 0.05 for RFS and OS, respectively), especially pronounced within the subgroup undergoing the XELOX regimen ($p_{log\text{-}rank}$=0.01 and 0.02 for RFS and OS, respectively) (Figure 2d-f, Figure S3d-f).

We subsequently assessed the impact of CISC classification on the effects of 5-FU and oxaliplatin in the overall population, specifically in stage II and III cases. A consistently favorable outcome was observed in stage II CICS-L patients with or without ACT. However, a significantly improved prognosis was observed among stage II CISC-H patients undergoing ACT compared to those who did not receive ACT. Patients with stage III CRC appeared to benefit from CT irrespective of their CICS status (Figure 3a and Figure S4a).

Among patients treated with the OXA regimen, the estimated 3-year RFS and OS rates were 80.50% and 90.08% for CICS-L group, 49.09% and 68.40% for CICS-H group, respectively. In patients receiving the 5-FU and XELOX regimens, RFS (5-FU group: 83.95% vs 52.78%, $p_{log\text{-}rank}$<0.01; XELOX group: 84.10% vs 56.57%, $p_{log\text{-}rank}$<0.01) and OS (5-FU group: 86.80% vs 65.26%, $p_{log\text{-}rank}$=0.02; XELOX group: 92.80% vs 68.99%, $p_{log\text{-}rank}$<0.01) of CICS-L patients were significantly superior to those of CICS-H cases. Among CICS-H patients, the estimated three-year RFS

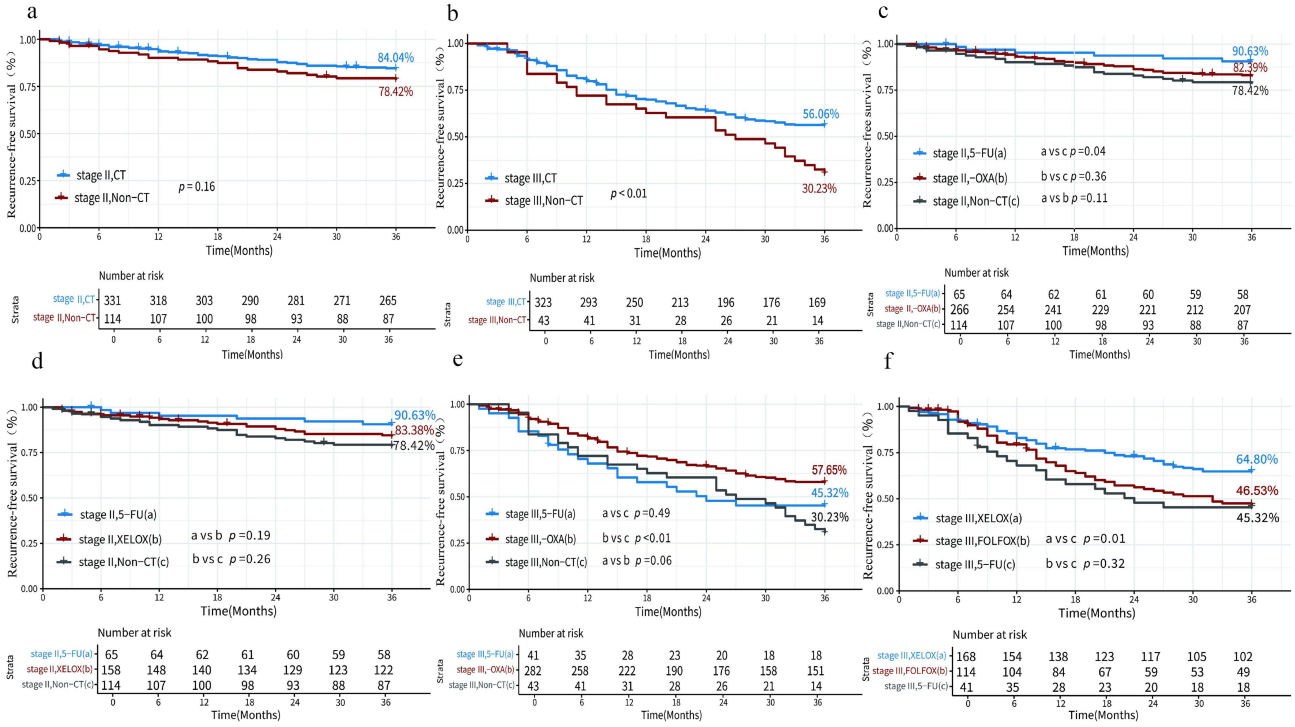

Figure 2 Survival comparison in patients with stage II–III CRC with or without ACT. (**a**) Kaplan-Meier (KM) curves for stage II CRC patients with or without CT; (**b**) KM curves for stage III CRC patients with or without CT; (**c**) KM curves for stage II colorectal cancer patients undergoing 5-FU, -OXA, or non-CT; (**d**) KM curves for stage II colorectal cancer patients receiving 5-FU, XELOX, or non-CT; (**e**) KM curves for stage III CRC patients receiving 5-FU, XELOX, or non-chemotherapy. (**f**) KM curves for stage III CRC patients receiving XELOX, FOLFOX, or non-CT.

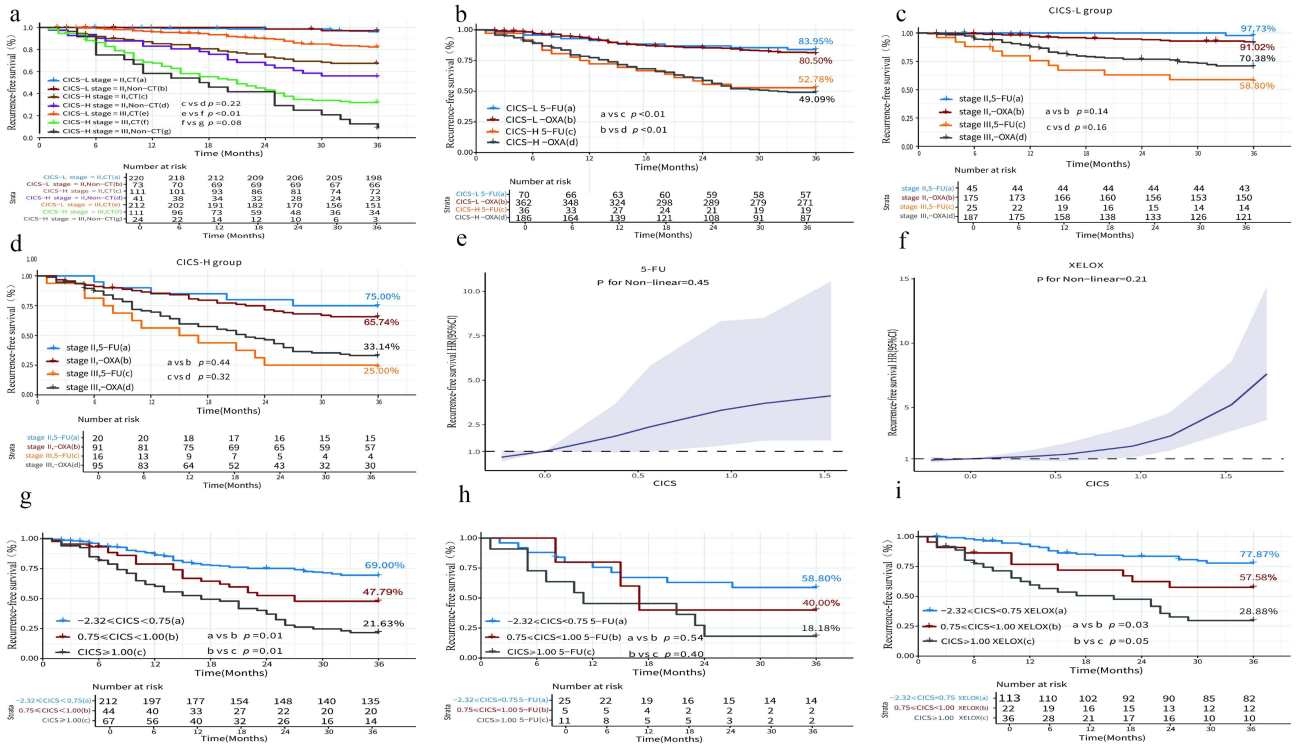

Figure 3 Treatment effects of ACT in stage II–III patients with different CICS status. (**a**) Kaplan-Meier (KM) curve for CICS-H and CICS-L stage II/III patients with or without CT; (**b**) KM curve for CICS-H and CICS-L patients with 5-FU or OXA regimen; (**c** and **d**) KM curve for CICS-L and CICS-H stage II/III patients with 5-FU or OXA regimen; (**e** and **f**) restricted cubic spline (RCS) plot between CICS and RFS in patients undergoing 5-FU and XELOX regimens; (**g–i**) KM curves for CT/5-FU/XELOX-treated stage III CRC patients stratified by tertiles of CICS.

rates for those treated with XELOX and 5-FU were 56.57% and 52.78%, respectively, with no significant differences observed (Figure 3b and Figure S4b-d).

A similar satisfactory outcome was observed in stage II cases treated with the 5-FU and OXA regimen within the CICS-L subgroup ($p_{\text{log-rank}}$ =0.14, 97.73% vs 91.02% for RFS; $p_{\text{log-rank}}$ =0.54, 97.73% vs 95.77% for OS), and no significant survival difference was observed between these groups in CICS-H patients ($p_{\text{log-rank}}$ =0.44, 75.00% vs 65.74% for RFS; $p_{\text{log-rank}}$=0.95, 78.95% vs 80.78% for OS). Although the three-year RFS (33.14% vs 25.00%, $p_{\text{log-rank}}$ =0.32) and OS rates (55.55% vs 44.14%, $p_{\text{log-rank}}$ =0.68) within OXA-treated cases were higher than those receiving the 5-FU, with non-survival difference between them in CICS-H patients with the stage III disease. CICS-L patients can benefit from OXA-regimen compared to 5-FU treatment (70.38%vs 58.80%, $p_{\text{log-rank}}$ =0.16 for RFS; 84.42% vs 66.78%, $p_{\text{log-rank}}$ =0.03 or OS), as a borderline statistical significance was observed between them (Figure 3c and d, Figure S4e-f).

We employed restricted cubic spline analysis to investigate the association of CICS with prognosis in the patients undergoing 5-FU or XELOX regimen. As illustrated in Figure 3e and f, the HRs for RFS significantly increased with higher levels of CICS, and a similar trend was observed for OS (Figure S4g-h). We stratified ACT-treated patients into three subgroups based on their CICS: CICS-L (−2.32≤CICS<0.75), CICS-H (0.75≤CICS<1.00), and super CICS-H (CISC-SH: CICS≥1.00) among stage III patients. The respective survival rates were 69.00%, 47.79%, and 21.63% for RFS and 82.22%, 67.65%, and 45.61% for OS, revealing significant differences in survival between these groups; the analogous outcome trends were identified within both the 5-FU and XELOX-treated groups (Figure 3g-i and Figure S4i-k). In comparisons between XELOX- and 5-FU-treated cases within the CICS-L group, oxaliplatin demonstrated superior RFS (77.87% vs 58.80%, $p_{\text{log-rank}}$ =0.02). Presumably, due to smaller sample sizes in 5-FU (CICS-H: 5; CICS-SH: 11) and XELOX (CISC-H: 22; CICS-SH: 37) groups, the survival comparison was not significant in the CICS-H cases (57.58% vs 40.00%, $p_{\text{log-rank}}$ =0.49), nor among the patients classified as CICS-SH (28.88% vs 18.18%, $p_{\text{log-rank}}$ =0.34) (Figure S4l).

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CICS and Adjuvant Therapeutic Regimen

We further explored the role of CICS in determining the optimal adjuvant therapeutic regimen for the patients. In individuals with stage II disease classified as CICS-L, those treated with the 5-FU exhibited comparable RFS and OS to patients receiving either the FOLFOX or XELOX regimen and those who did not undergo ACT. Notably, their recurrence and mortality rates were both less than 97.73%. These findings suggest that CICS-L patients may not receive ACT without compromising RFS and OS. Furthermore, CICS-H patients treated with 5-FU demonstrated significantly prolonged survival compared to cases that did not receive ACT (74.94% vs 54.55%, $p_{\text{log-rank}}$=0.02, HR=0.51, 95% CI=0.29–0.90 for RFS). No significant difference in RFS was observed between patients treated with the OXA regimen and those who did not receive ACT, indicating that 5-FU is the optimal adjuvant regimen for this group (Figure 4a and b, Figure S5a-b).

Among stage III patients in the CICS-L subgroup, those treated with the XELOX regimen demonstrated superior RFS compared to individuals receiving the FOLFOX regimen (77.88% vs 58.18%, $p_{\text{log-rank}}$ <0.01, HR=0.46, 95% CI=0.27–0.79). A significant difference in OS was also observed between patients undergoing XELOX and FOLFOX regimens (89.40% vs 76.05%, $p_{\text{log-rank}}$ =0.02, HR=0.40, 95% CI= 0.18–0.86). Furthermore, RFS for CICS-H patients treated with XELOX exceeded that of their counterparts receiving the FOLFOX regimen (39.68% vs 22.86%). The three-year OS for XELOX-treated patients was longer than those receiving FOLFOX treatments (56.51% vs 52.93%). However, no statistically significant difference in survival was observed between these cases (Figure 4c and d, Figure S5c-d).

Clinical Benefit of CICS-Guided Therapeutic Strategy

We investigated the impact of a chronic inflammation-based CICS strategy on the administration of ACT and survival outcomes in patients with stage II–III CRC. In the overall cohort, 158 patients did not receive ACT, while others underwent the treatment. According to the CICS-guided approach, 65.92% of patients classified as CICS-L with stage II CRC achieved satisfactory outcomes without necessitating ACT. By treating only those CICS-H patients with stage II and III CRC, we observed a reduction in the percentage of patients receiving ACT compared to traditional management

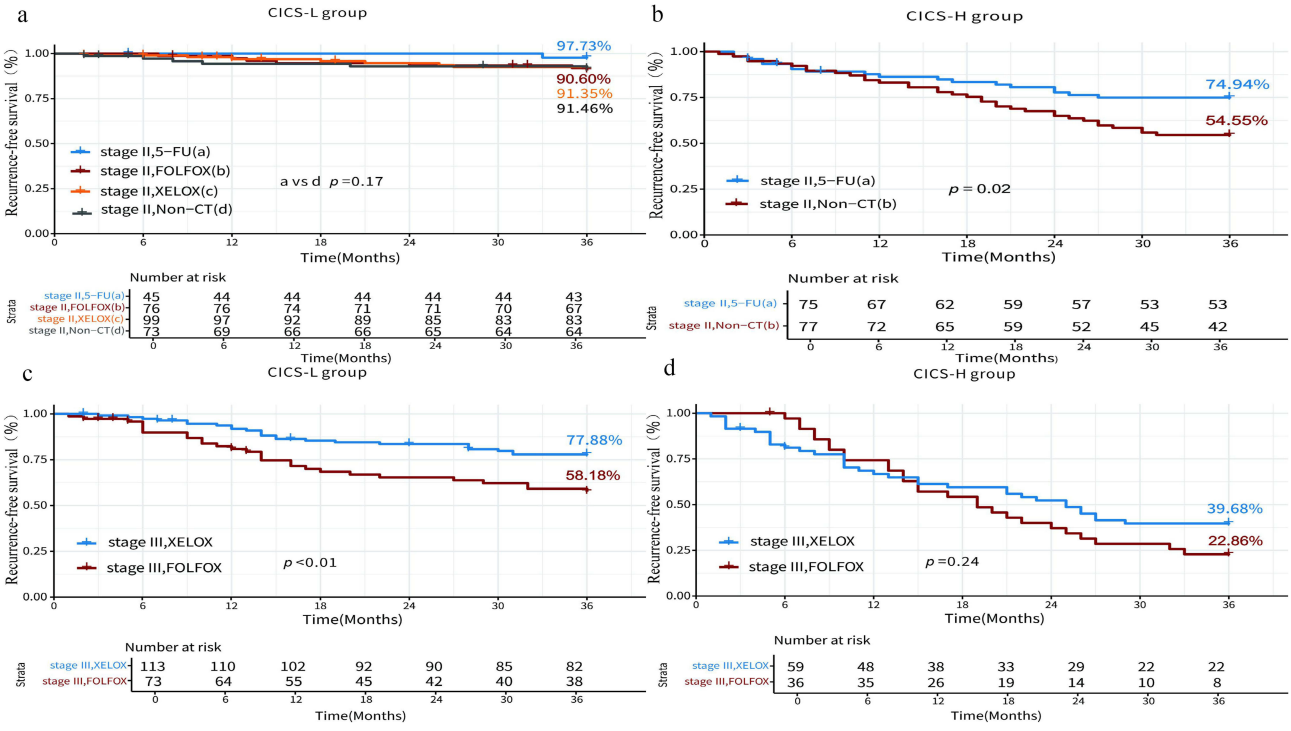

Figure 4 Optimal adjuvant chemotherapy regimen in stage II–III CRC patients with different CICS status. (**a**) Kaplan-Meier (KM) curves for CICS-L stage II CRC patients undergoing 5-FU, XELOX, FOLFOX, or non-CT; (**b**) KM curves for CICS-H stage II CRC patients undergoing 5-FU or non-CT; (**c** and **d**) KM curves for CICS-L and CICS-H stage III CRC patients undergoing XELOX or FOLFOX regimens.

without compromising clinical outcomes. For the overall cohort, implementation of the CICS strategy resulted in a decrease in ACT receipt from 80.54% to 63.79% ($p<0.01$, relative risk RR=0.43, 95% CI=0.34–0.53). Additionally, there was an increase in the utilization of single-agent 5-FU and a decrease in OXA-based doublet regimens ($p<0.01$, RR=0.47, 95% CI=0.35–0.62). Notably, differences in three-year recurrence and mortality rates were not statistically significant.

In stage II CRC, applying the CICS strategy led to a substantial reduction in ACT receipt from 74.22% to 34.08% ($p<0.01$, RR=0.18, 95% CI=0.13–0.24). This approach also influenced regimen selection by increasing the single-agent use of 5-FU while eliminating OXA-based doublets ($p<0.01$), with no significant differences observed regarding survival outcomes (Table 1). For stage III CRC cases, there was increased adoption of XELOX regimens alongside phasing out other ACT regimens ($p<0.01$), and three-year recurrence ($p_{log\text{-}rank}=0.02$, RR=0.70, 95% CI= 0.53–0.92) and mortality ($p_{log\text{-}rank}=0.05$, RR=0.70, 95% CI=0.47–0.97) rates were significantly decreased in comparison with the traditional management (Table 1).

Discussion

Successfully selecting a chemotherapy drug for radically resected patients to maximize clinical efficacy while minimizing unnecessary side effects represents a precision treatment approach for CRC. Here, we developed a novel inflammatory signature termed CICS and evaluated its predictive capability concerning prognosis, the benefits of oxaliplatin or 5-FU, and its role in guiding chemotherapy regimen selection through a double-blind study involving three independent cohorts. CICS and 3C emerged as independent prognostic biomarkers for patients with stage II–III disease, with the predictive efficacy of 3C reaching an impressive value of 0.724. Notably, high chronic inflammation represented by CICS-H conferred reduced sensitivity to 5-FU and oxaliplatin in the overall population, identifying a subgroup of CRC

Table 1 Clinical Benefit Comparison Between Traditional Strategy and CICS-Guided ACT in Stage II–III CRC

Population	Treatment Characteristics	Traditional Strategy	CICS Strategy	Changing Percentage (%)	*p*-value	RR/HR (95% CI)
Overall population	**ACT received-no. (%)**					
	No	19.46	36.21		-	-
	Yes	80.54	63.79	−16.75	0.01*	0.43(0.34–0.53)
	ACT regimen received-no. (%)					
	Single-agent 5-FU	16.21	29.34		-	-
	OXA-based doublet	83.79	70.66	−13.13	0.01*	0.47(0.35–0.62)
	3 years recurrence rate-no. (%)	29.56	25.94	−3.62	0.30	0.87(0.67–1.13)
	3-years death rate-no. (%)	17.86	15.41	−2.45	0.35	0.85(0.61–1.18)
Stage II population	**ACT received-no. (%)**					
	No	25.78	65.92		-	-
	Yes	74.22	34.08	−40.14	0.01*	0.18(0.13–0.24)
	ACT regimen received-no. (%)					
	Single-agent 5-FU	19.64	34.08	14.44	-	-
	OXA-based doublet	80.36	0	−80.36	0.01*	-
	3 years recurrence rate-no. (%)	16.82	11.70	−5.12	0.24	0.69(0.39–1.20)
	3-years death rate-no. (%)	10.31	7.45	−2.86	0.39	0.71(0.35–1.43)
Stage III population	**ACT regimen received-no. (%)**					
	XELOX regimen	53.25	100			
	Other ACT regimen	46.75	0	−46.75	0.01*	-
	3 years recurrence rate-no. (%)	45.08	33.72	−11.36	0.02	0.70(0.53–0.92)
	3-years death rate-no. (%)	27.05	19.77	−7.28	0.05	0.70(0.47–0.97)

Notes: *: $p<0.01$. Traditional strategy refers to the original chemotherapy regimens of 5-FU, capecitabine plus oxaliplatin (XELOX), leucovorin plus fluorouracil and oxaliplatin (FOLFOX) for patients with stage II–III colorectal cancer.

Abbreviations: 5-FU, 5-fluorouracil; ACT, adjuvant chemotherapy; CICS, chronic inflammation comprehensive signature; RR, relative risk; HR, hazard ratio; XELOX, capecitabine plus oxaliplatin.

adjuvant patients (CICS-H) who experience poorer survival outcomes when treated exclusively with 5-FU. Fortunately, incorporating oxaliplatin into the treatment regimen significantly enhances the outcomes of these patients. Further analysis indicates that stage II patients classified as CICS-L may not require any unnecessary ACT; conversely, administering 5-FU could improve survival rates among CICS-H patients. The XELOX regimen emerges as the optimal choice for stage III patients with CICS-L; meanwhile, CICS-H patients can derive comparable benefits from either XELOX or FOLFOX regimens. Therefore, CICS is an effective predictor of potential benefits from 5-FU and oxaliplatin in stage II–III CRC patients striving to achieve satisfactory survival outcomes.

Interactions between CRC cells and their stem cell, inflammatory immune cells, and stromal cells constitute the tumor microenvironment, which plays a significant role in drug resistance and promotes CRC progression.[32] Cancer-derived inflammation is a distinctive characteristic that comprehensively reflects the tumor microenvironment.[33] Circulating inflammatory biomarkers may predict sensitivity to chemotherapeutic agents such as 5-FU and oxaliplatin, and prognosis for operative patients. Emerging inflammatory scores and ratios, such as FPR, SIR/SII, and SIRI, have been shown to predict survival in stage II–III CRC patients.[21–23] Although their predicted AUCROCs range from 0.50 to 0.65, these four indexes are promising candidates for inflammatory biomarkers.[20] In this study, we established six novel inflammatory ratios and six newly inflammatory scores based on FPR, SIR/SII, and SIRI. Our discovery cohort identified significant negative corrections between these newly developed biomarkers and RFS or OS of the patients with stage II–III CRC. The considerable associations concerning FPSIIR, FPSIIS, FPSIRS, FPSIRIR, FPSIRIS, FASIIS, FASIRS, and FASIRIS were validated in both internal and external validation cohorts. Furthermore, we developed a novel CICS, relying on independent factors including FPSIRS, FPSIRIR, FASIRS, and FASIRIS. Our analysis revealed that patients with CICS-L exhibited long RFS and OS compared to those with CICS-H, both in the overall population and within stage II and III subgroups, even when stratified by different chemotherapy regimens. Additionally, the predictive efficacy of CICS exceeds 0.69, and it was significantly superior to its single index, illustrating that it represents a novel comprehensive signature reflecting chronic inflammation while serving as a robust prognostic factor among operative CRC patients. CEA and CA19-9 are recommended for monitoring and predicting patients' survival.[31,34] Our findings closely align with previous studies.[26,27] Consequently, the 3C score, which comprises CEA, CA19-9, and CICS, was significantly associated with clinical outcomes in these patients. Its predictive efficacy reached an impressive value of 0.724, suggesting that combining CICS with CEA and CA19-9 can effectively stratify the risk of recurrence and identify high-risk population, as well as substantially enhance prognostic prediction in patients with stage II–III CRC.

5-FU and oxaliplatin-containing regimens are extensively employed in treating malignancies, particularly gastric and colorectal cancers.[35] These two chemotherapeutic agents have been demonstrated to activate the NF-kB and MAPK pathway,[36] producing of inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which induce systematic inflammation.[37] Our study observed that the clinical benefits of 5-FU- and oxaliplatin-based ACT were more pronounced in patients with CICS-L than those with CICS-H. The survival outcomes of patients receiving oxaliplatin were comparable to those undergoing 5-FU-based chemotherapy in the CICS-H group. The degree of chronic inflammation was corrected with CRC pathological characteristics; it progressively increased alongside cancer invasion depth.[38] Moreover, we found that patients treated with these two chemotherapeutic agents at stage III CRC exhibited significantly poorer survival outcomes than those diagnosed with stage II disease. These findings illustrate that high-grade cancer-derived inflammation may diminish sensitivity to 5-FU and oxaliplatin treatments. Precision CRC adjuvant therapy relies on accurately identifying suitable patients for operative adjuvant therapy, and informed clinical decision-making regarding appropriate chemotherapeutic regimens. This approach aims to maximize clinical efficacy while minimizing toxic side effects.[39] Liquid biopsies, such as circulating tumor cells, exosomes, and ctDNA, show promise in identifying patients at high risk of cancer recurrence, thereby facilitating more informed decision-making.[40] Here, we found that recurrence and mortality rates within stage II CRC patients with CICS-L were only 7.48% and 3.74%, respectively. These patients treated with 5-FU, XELOX, and FOLFOX exhibited comparable outcomes to those of surgically managed patients who did not receive ACT, and as such, if a decision were made on the basis of the prediction by CICS, approximately 65.92% of patients with the stage II disease (CICS-L cases) may be spared unnecessary chemotherapy and its associated side effects. Decision marking is crucial for selecting an appropriate chemotherapeutic regimen for these patients.[41] Our findings indicate that when

treated solely with 5-FU, the CICS-H subgroup of stage II CRC demonstrates a relatively favorable prognosis comparable to that of patients receiving XELOX or FOLFOX regimens. Notably, adding oxaliplatin does not confer additional benefits; rather it exposes these patients to unnecessary side effects. Consequently, individuals within this group are potential candidates for omitting oxaliplatin in favor of treatment with 5-FU alone. This strategy would help prevent avoidable adverse effects and reduce costs associated with oxaliplatin-induced neurotoxicity. Although high-grade inflammation in stage III disease may attenuate sensitivity to 5-FU and oxaliplatin, XELOX-treated patients exhibited superior survival outcomes compared to those receiving 5-FU or FOLFOX in the CICS-H and -L subgroups, respectively. Moreover, the CICS therapeutic strategy significantly reduced recurrence and mortality rates while improving survival outcomes when compared to the traditional treatment approaches. The findings reveal that CICS-L cases can derive substantial benefit from oxaliplatin, positioning XELOX as the optimal choice for stage III patients. Furthermore, CICS exhibits a high sensitivity and negative predictive value, rendering it clinically applicable for selecting appropriate adjuvant chemotherapeutic regimens for operable stage II–III patients.

This study, to the best of our knowledge, represents the first effort to develop a novel CICS and to investigate the role of cancer-derived inflammation in clinical response to 5-FU and oxaliplatin. The findings support CICS as a robust and innovative biomarker for predicting survival, guiding chemotherapeutic decisions, and evaluating clinical benefits from 5-FU and oxaliplatin. Compared to ctDNA or CMS, CICS emerges as an efficient, cost-effective, and practical biomarker that can be easily popularized and implemented across abroad spectrum of basic medical units. To date, challenge remains in standardizing ctDNA testing, and its primary roles is as a prognostic biomarker for detecting post-surgical molecular residual disease and predicting recurrence risk.[42] While CMS detection provides deeper insights into the heterogeneity of CRC, the limited number of available molecular features constrains its utility in guiding the clinical treatment.[43] Our findings demonstrate that a CICS-guided strategy can be prospectively integrated into clinical decision-making to personalize ACT. This approach notably facilitates the avoidance of unnecessary ACT in low-risk stage II patients while optimizing regimen selection for those with high-risk II stage or III disease. Furthermore, CICS may be employed to proactively exclude oxaliplatin in patients at high risk of neuropathy or other toxicities, particularly in the elderly or those with comorbidities. Given the high incidence of CRC in China, optimizing ACT regimens guiding by the CISC strategy could potentially reduce healthcare costs while enhancing quality of life for a significant number of CRC patients, thereby providing a precise solution for this high-burden disease.

In order to comprehensively understand the role of CICS in the disease, s several limitations must be considered as follows. Firstly, the current cutoff threshold established by CICS may subject approximately 66% and 34% of patients with stage II CRC to unnecessary ACT and oxaliplatin treatment, respectively. Therefore, it is crucial that this cutoff threshold be further refined to enhance its specificity. Secondly, due to the heterogeneity of the disease, not all patients will likely benefit from the therapeutic strategy guided by CICS involving 5-FU and oxaliplatin. Consequently, integrating CICS with liquid biopsy may improve the precision of CRC therapy, allowing for alternative treatments to be administered to those non-benefiting patients. The last, although our findings are intriguing, they shall be validated by multi-center prospective trials with large sample size. Additionally, foundational studies will be conducted to investigate the potential biological mechanism underlying the relationship between these inflammatory indicators and chemotherapy sensitivity.

In conclusion, the CICS predicts the benefits of 5-FU and oxaliplatin in the adjuvant treatment setting for CRC. A CICS-guided strategy proved effectively in optimizing the selection of chemotherapeutic regimens and reducing ACT use without compromising outcomes for patients with stage II–III operable disease.

Data Sharing Statement

All data analyzed during the study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

All the enrolled patients signed the informed consent form. The study adhered to the ethical standards of the Helsinki Declaration and was approved by the Ethics Committee of The Second Affiliated Hospital of Nanchang University (O-MedResEthicsRev [2025] No. 54).

Consent for Publication

All authors have read and approved the final version of the manuscript and consent to its publication in *Drug Design Development and Therapy.*

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest in this work.

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