The Association of the Cancer Inflammation Prognostic Index with Microsatellite Instability, Tumor Budding and Prognosis in Colorectal Adenocarcinoma

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AIM: This study aimed to investigate the relationship between the Cancer Inflammation Prognostic Index (CIPI) and microsatellite instability (MSI), tumor budding, and prognosis in colorectal cancer cases.

METHODS: Patients with stage 1–3 colorectal cancer who underwent curative surgical treatment between May 2020 and January 2022 were included. Serum CIPI was calculated, a cut-off point was established using Receiver Operating Characteristic (ROC) analysis and Patients were divided into two groups according to their CIPI scores: Group 1 (low CIPI) consisted of 94 patients, and Group 2 (high CIPI) consisted of 95 patients.

RESULTS: A CIPI score >8.54 predicted mortality with 82.2% sensitivity and 59.7% specificity (area under the curve (AUC): 0.712). There were differences in tumor localization ($p = 0.01$). Group 2 had higher C-reactive protein (CRP) levels (4.2 vs 11.7, $p < 0.001$), lower albumin levels (4.1 vs 4, $p = 0.04$), higher neutrophil counts (3.76 vs 4.83, $p = 0.002$), and higher levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 19.9 (Ca 19.9) (2.08 vs 8.27, $p < 0.001$ and 8.85 vs 13.9, $p = 0.014$, respectively). Tumor diameter was larger in high CIPI group (3 vs 3.8 cm, $p = 0.001$) , disease-free survival (37.7 vs 27.6 months, $p < 0.001$) and overall survival (39.6 vs 30.6 months, $p < 0.001$) were lower in high CIPI group 2. In the multivariate Cox regression analysis, a high CIPI score remained a strong independent predictor of poor overall survival (hazard ratio (HR) = 3.383, 95% confidence interval (CI): 1.445–7.921, $p = 0.005$) disease-free survival, a high CIPI score again stood out as a critical prognostic factor (HR = 3.280, 95% CI: 1.695–6.347, $p < 0.001$).

CONCLUSIONS: A high CIPI score is associated with poor histopathological features and decreased survival. Closer monitoring or more aggressive treatment might improve prognosis for patients with high CIPI values.

Keywords: cancer; inflammation; tumor marker; prognosis; composite index

Introduction

According to Global Cancer Statistics (GLOBOCAN) 2024 data published by the International Agency for Research on Cancer (IARC), colorectal cancer (CRC) is the third most common cancer globally, ranking as the third most prevalent in women, the third in men, and one of the leading causes of cancer-related deaths worldwide [1].

Systemic inflammation represents one of the most pertinent illustrations of tumor-host interactions in cancer [2]. Links have been established between inflammatory factors within the tumor microenvironment and tumor size, growth rate, and metastatic potential [3,4].

The neutrophil-to-lymphocyte ratio (NLR) is acknowledged as both an indicator of inflammation and a prognostic factor for malignancies, contributing to the development of treatment strategies [4,5]. The most widely used tumor marker for colorectal cancer (CRC) is serum carcinoembryonic antigen (CEA) level, and raised levels are linked to a higher risk of recurrence and worse patient outcomes [5]. Theoretically, the level of CEA could provide additional information necessary for crafting treatment options tailored to individual prognoses. Thus, it is rational to propose the use of the Cancer Inflammation Prognostic Index (CIPI) as a concurrent carrier for tumor and immunity-related markers in CRC.

CRC is a heterogeneous disease. It is thought that the clinical stage, histological type, and molecular features dictate its course and prognosis. However, variations in outcomes and treatment responses even among patients at the same stage prompt clinicians to search for biomarkers that can predict these differences. Identifying practical, easily accessible, and preoperative biomarkers holds considerable clinical value in determining patients with a higher risk

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of poor outcomes. This is particularly pertinent for CRC, where the incidence is on the rise and absolute success in early diagnosis and treatment has yet to be achieved [6–9]. Recently, the prognostic importance of a new biomarker, the Combined Inflammatory and Prognostic Index (CIPI), which integrates neutrophil, lymphocyte, and CEA levels, has been emphasized in patients with colorectal and lung cancer [10–12]. However, there is a paucity of studies in the literature on this topic, and the relationship of this new prognostic composite index with prognostic factors such as microsatellite instability (MSI), status and tumor budding remains unclear.

The present study seeks to investigate the association "CIPI" with "MSI", tumor budding, and prognosis in cases of colorectal cancer.

Materials and Methods

Study Design

Following the approval from the local ethics committee dated 13 March 2024 with decision (Number 194). This study was designed as a single-center retrospective analysis. Patients who underwent surgical treatment for colorectal cancer between May 2020 and January 2022 were included. Those with non-adenocarcinoma pathology, initial metastatic presentation, Lynch syndrome, chronic inflammatory diseases, hematological disorders, corticosteroid usage, or inaccessible records were excluded. The data set was compiled through the hospital's digital data system, oncology follow-up cards made for each patient, pathology data, and population registry data.

CIPI was defined as the product of CEA concentration (mg/L) and neutrophil count (10^9/L) divided by lymphocyte count (10^9/L). The Receiver Operating Characteristic (ROC) curve was employed to assess the ability of CIPI to classify mortality status. The optimal cut-off value for CIPI in predicting mortality was determined through ROC curve analysis based on the Youden index. The cut-off value we found is representative of our cohort.

Patients were divided into two groups according to their CIPI scores: Group 1 with low CIPI scores and Group 2 with high CIPI scores. Demographic data, neoadjuvant treatment status, type of operation, tumor localization, histopathological diagnosis, tumor diameter, grade, depth of tumor invasion, presence of lymphovascular invasion, perineural invasion, peritumoral lymphocytic response, tumor budding, Crohn-like lymphocytic reaction, pathological stage, lymph node metastasis status, MSI status, disease-free survival, and overall survival times were compared between these groups.

Surgical indications for all patients were established through institutional multidisciplinary team discussions. Preoperative evaluations included colonoscopy imaging, thoracic, abdominal, and pelvic computed tomography (CT) scans for all patients, magnetic resonance imaging for rectal cancer cases, and positron emission tomography-computed tomography (PET-CT) scans when deemed necessary. Peripheral venous blood samples were collected from all patients upon hospital admission before surgery for complete blood count and tumor marker analysis. The pathological staging of the disease was conducted according to the 8th Edition of the Classification of Malignant Tumors (TNM) [13]. Pathology descriptions were made considering the recommendations from the 2018 College of American Pathologists (CAP) Colorectal Carcinoma Reporting Protocol [14]. The recommendations from the 2016 International Tumor Budding Consensus Conference (ITBCC) were used to determine tumor budding [15]. The presence of microsatellite instability was inferred from the complete loss (negative) of any of the four markers (MutL protein homolog 1 (*MLH1*), MutS homolog 2 (*MSH2*), MutS homolog 6 (*MSH6*), Postmeiotic segregation increased 2 (*PMS2*)) used in immunohistochemistry. The absence of expression loss in these four markers (nuclear staining in tumor cells) was interpreted as microsatellite stability (MSS).

Follow up

Postoperative follow-up for CRC patients was conducted every 3 months for the first 2 years and then every 6 months thereafter. Disease-free survival was defined as the time from radical resection to the first occurrence of recurrence, death, or the last follow-up. Overall survival (OS) was defined as the period between radical resection and the date of death or last follow-up.

The patient's informed consent has been obtained for this study and a statement that this study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

The statistical analysis of our study was conducted using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). The association between the CIPI and mortality was assessed using ROC analysis, from which a cut-off point was determined. Based on this cut-off value, patients were divided into groups with high and low CIPI scores. The normal distribution of numerical data was evaluated using the Shapiro-Wilk test. Numerical data conforming to normal distribution were presented as mean $\pm$ standard deviation, while those not conforming were expressed as median (minimum-maximum). Categorical data were presented as frequency and percentage.

For the comparison of numerical variables between groups, the Independent Samples *t*-test was applied for variables with normal distribution, and the Mann Whitney U Test was used for variables without normal distribution. The Chi-square test was employed for the comparison of categorical data. The survival times of the patients were analyzed using the Kaplan-Meier method, and the statistical significance of differences between groups was tested with the Log-Rank test. Multivariate Cox proportional hazards

regression analysis was conducted to identify independent predictors of overall and disease-free survival. Hazard ratios with 95% confidence intervals (CI) were calculated to quantify the strength and direction of associations between the covariates and survival outcomes. A *p*-value of <0.05 was considered statistically significant in all tests.

Results

ROC analysis was conducted to determine a cut-off point for the (CIPI) score, resulting in the creation of an ROC curve. The area under the ROC curve was 0.712. At this cut-off point, a CIPI score greater than 8.54 predicted mortality with a sensitivity of 82.2% and a specificity of 59.7%, as presented in Fig. 1 and Table 1.

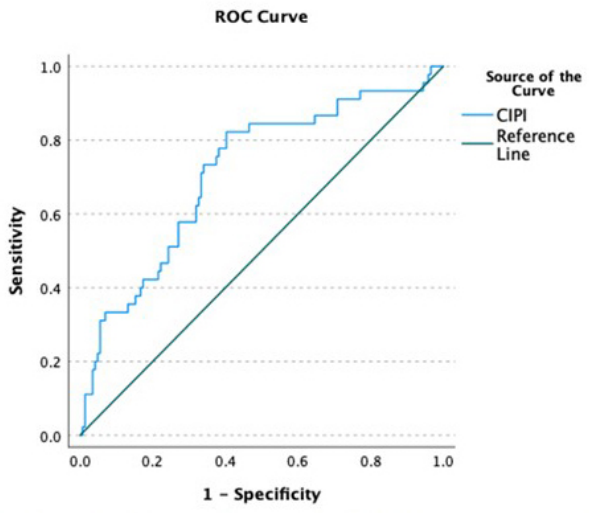

Fig. 1. Receiver operating characteristic curve analyses for overall survival. CIPI, Cancer Inflammation Prognostic Index; ROC, Receiver Operating Characteristic.

Demographic Results

When patients were divided into two groups based on the cut-off value of 8.54, Group 1 (low CIPI) consisted of 94 patients, and Group 2 (high CIPI) consisted of 95 patients. Demographic data such as age and gender were similar between the groups, but there were differences in tumor localization ($p = 0.01$). Group 2 had higher C-reactive protein (CRP) levels (4.2 vs 11.7, $p < 0.001$), lower albumin levels (4.1 vs 4, $p = 0.04$), higher neutrophil counts (3.76 vs 4.83, $p = 0.002$), lower levels Lymphocyte count (1.79 vs 1.39, $p < 0.001$) and higher levels of CEA and carbohydrate antigen 19.9 (Ca 19.9) (2.08 vs 8.27, $p < 0.001$ and 8.85 vs 13.9, $p = 0.014$, respectively), as shown in Table 2.

Operative Results

No significant differences were observed in the type of operation performed, surgical approach, or postoperative hospital stay, as indicated in Table 3.

Table 1. Proposed cut-off values for significant parameters in overall survival.

	CIPI
AUC	0.712
Cut-off	≤8.54
Specifity (%)	59.7
95% CI (%)	51.7–67.7
Sensitivity (%)	82.2
95% CI (%)	71.1–93.4
PPV	38.9
NPV	91.5
+LR	2.05
-LR	0.29
p	<0.05

CIPI, Cancer Inflammation Prognostic Index; AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; -LR, negative likelihood ratio.

Pathological Results

The presence of high MSI (8.5% vs 6.3%, $p = 0.565$), tumor budding (67.0% vs 77.9%, $p = 0.094$), and the degree of tumor budding ($p = 0.950$) in patients with this feature were similar between the groups. Group 2 had a higher incidence of T4 tumors ($p = 0.004$), lymphovascular invasion (57.4% vs 71.6%, $p = 0.042$), perineural invasion (33% vs 56.8%, $p < 0.001$), and tumor perforation rates (5.3% vs 18.9%, $p = 0.004$). Tumor diameter was larger in Group 2 (3 vs 3.8 cm, $p = 0.001$), and the median value for malignant lymph nodes was higher in Group 2 (0 vs 1, $p = 0.008$). Pathological data are presented in Table 4.

Oncologic Follow up

The average disease-free survival time (37.7 vs 27.6 months, $p < 0.001$) and overall survival time (39.6 vs 30.6 months, $p < 0.001$) were lower in Group 2, as illustrated in Figs. 2,3.

In the multivariate Cox regression analysis for overall survival, CIPI emerged as a particularly strong independent prognostic factor, with high CIPI scores linked to a marked increase in mortality risk (hazard ratio (HR) = 3.383, 95% CI: 1.445–7.921, $p = 0.005$) (Table 5). Alongside CIPI, age also reached statistical significance (HR = 1.035, 95% CI: 1.005–1.066, $p = 0.020$), indicating a modest but noteworthy rise in the hazard of death with increasing age. Notably, perineural invasion (HR = 0.389, 95% CI: 0.175–0.861, $p = 0.020$) and MSI status (HR = 0.206, 95% CI: 0.074–0.574, $p = 0.003$) both showed significant protective effects when absent—underscoring their importance in overall survival. Elevated Ca 19.9 levels remained a significant indicator of poorer prognosis (HR = 1.010, 95% CI: 1.004–1.016, $p =$

Table 2. Demographical and clinical data.

	Group 1 low CIPI (n = 94)	Group 2 high CIPI (n = 95)	*p*
Gender (n (%))			
Male	59 (62.8)	55 (57.9)	0.494[a]
Female	35 (37.2)	40 (42.1)	
Age (Mean ± SD)	59.5 ± 14.3	63.0 ± 13.7	0.083[b]
Neoadjuvant treatment (n (%))	17 (18.1)	15 (15.8)	0.674[a]
Admission (n (%))			
Emergency	5 (5.3)	8 (8.4)	0.400[a]
Elective	89 (94.7)	87 (91.6)	
Localization (n (%))			
Appendix	1 (1.1)	-	0.01*[a]
Caecum	3 (3.2)	11 (11.6)	
Ascending colon	16 (17.0)	9 (9.5)	
Hepatic flexure	0	5 (5.3)	
Descending colon	1 (1.1)	4 (4.2)	
Rektosigmoid	14 (14.9)	15 (15.8)	
Rectum	29 (30.9)	31 (32.6)	
Sigmoid colon	21 (22.3)	8 (8.4)	
Splenic flexure	6 (6.4)	10 (10.5)	
Transverse colon	3 (3.2)	2 (2.1)	
CRP	4.2 (0.4–195.1)	11.7 (0.6–254.2)	<0.001**[c]
Hemoglobin gr/dL	11.5 ± 1.8	11.3 ± 1.8	0.290[b]
Albumin gr/dL	4.1 (3.0–5.3)	4.0 (2.2–5.2)	0.040*[c]
Neutrophil mm^3/L	3.76 (1.75–9.6)	4.83 (0.1–14.7)	0.002*[c]
Lymphocyte mm^3/L	1.79 (0.71–4.12)	1.39 (0.38–5.31)	<0.001**[c]
Platelets mm^3/L	269,000 (58,000–660,000)	303,000 (45,000–756,000)	0.230[c]
CEA	2.08 (0.53–5.57)	8.27 (1.53–805.0)	<0.001**[c]
Ca 19.9	8.85 (2.0–97.1)	13.9 (2.0–245.0)	0.014*[c]

CRP, C-reactive protein; CEA, carcinoembryonic antigen, SD, standard deviation; Ca 19.9, carbohydrate antigen 19.9.

* $p < 0.05$, ** $p < 0.001$, a: Chi-square, b: Student's *t*-test, c: Mann Whitney U test.

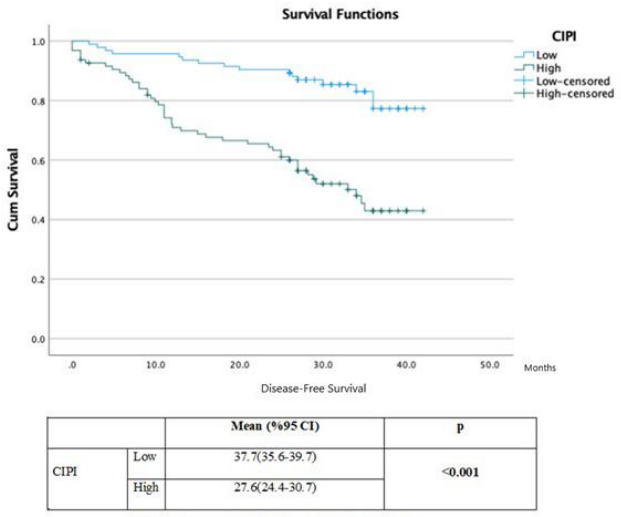

Fig. 2. Disease free survival by CIPI groups.

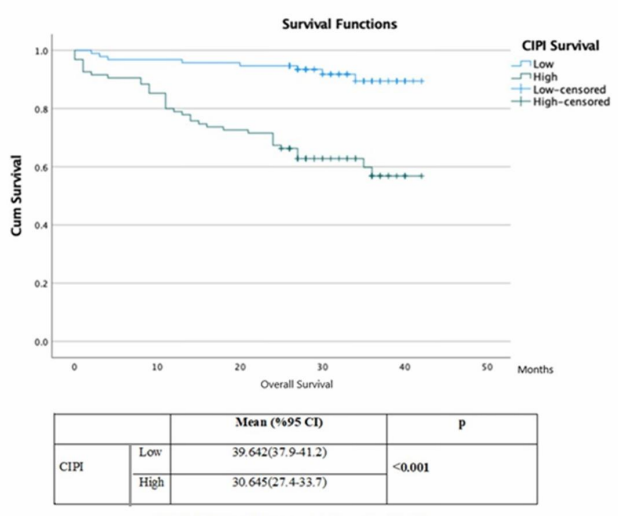

Fig. 3. Overall survival by CIPI groups.

Table 3. Operative data.

	Group 1 low CIPI	Group 2 high CIPI	*p*
Operation (n (%))			
Anterior resection	10 (10.6)	8 (8.4)	0.147[a]
APR	5 (5.3)	13 (13.7)	
Low anterior resection	45 (47.9)	34 (35.8)	
Right hemicolectomy	19 (20.2)	24 (25.3)	
Left hemicolectomy	7 (7.4)	10 (10.5)	
Subtotal colectomy	5 (5.3)	6 (6.3)	
Total colectomy	3 (3.2)	0	
Operation type (n (%))			
Open	47 (50)	61 (64.2)	0.132[a]
Laparoscopic	27 (28.7)	18 (18.9)	
Robotic	20 (21.3)	16 (16.8)	
Length of stay (day)	6 (2–35)	7 (3–31)	0.508[b]

APR, abdominopelvic resection; a: Chi-square; b: Student's *t*-test.

0.002). Other factors, including gender, neoadjuvant treatment, type of admission, lymphovascular invasion, tumor size, tumor differentiation, T and N stages, operation type and CEA levels, did not significantly impact overall survival in multivariate analysis.

In the multivariate Cox regression analysis for disease-free survival, a high CIPI score again stood out as a critical prognostic factor (HR = 3.280, 95% CI: 1.695–6.347, $p < 0.001$), indicating a substantially elevated risk of recurrence (Table 6). Among the remaining variables, MSI (HR = 0.202, $p < 0.001$), neoadjuvant treatment (HR = 0.476, $p = 0.038$), and Ca 19.9 (HR = 1.009, $p = 0.002$) were significant. Other variables, such as age, gender, admission type, lymphovascular and perineural invasion, tumor size, tumor differentiation, operation type, and T and N stages, did not reach statistical significance.

Discussion

In this study, which explored the prognostic significance of the (CIPI) in stages 1–3 colorectal cancer following curative surgical treatment, and its relationship with microsatellite instability and tumor budding, we found no association between the CIPI index and either MSI or tumor budding. However, a high CIPI index was correlated with adverse histopathological features and reduced survival times.

Cancer is widely acknowledged as a chronic inflammatory condition, characterized by a complex interaction between various circulating blood cells, chemokines, stromal cells, and metabolic factors [16]. Inflammatory cells within the tumor microenvironment significantly impact tumor development. Neutrophilia emerges during systemic inflammation, and lymphopenia is an indicator of suppressed cell-mediated immunity. The neutrophil-to-lymphocyte ratio has been proposed as a simple index of systemic inflammatory response. The prognostic significance of NLR in malignancy might be attributed to the contribution of tumor-derived neutrophils to high tumor angiogenesis activity, the number of lymphocytes related to the severity of the disease, and immune evasion by tumor cells from infiltrating lymphocytes [5,17].

CEA, a member of the immunoglobulin supergene family expressed in normal mucosal cells, plays a role in cell recognition and adhesion mechanisms. It also serves as an important tumor marker in colorectal cancer, with elevated CEA levels being associated with a worse prognosis [18,19]. Based on these evidences, researchers have developed new composite indices by combining inflammatory markers with tumor markers to provide clearer prognoses, with the most recent being the CIPI index based on neutrophil, lymphocyte, and CEA levels.

The inaugural study on the CIPI index by Su *et al.* [12] included 106 patients in the study cohort and 250 in the validation cohort. In the study cohort, patients with a CIPI $\geq$300 compared to those with <300 had median average survival times of 3.8 and 9.0 months, respectively (hazard ratio (HR) 2.78, 95% confidence interval (CI) 1.82–4.23; $p < 0.0001$), demonstrating the new scoring system's efficacy in classifying patient survival risk [12].

A year after this initial study, You *et al.* [20] investigated this new index in patients with stages 1–3 colorectal cancer who underwent curative surgery. Their study included 12,000 patients and identified a CIPI cut-off value of 8. They found that a high CIPI index was associated with more advanced tumor stages, including T stage ($p < 0.001$), N stage ($p < 0.001$), histological type ($p < 0.001$), and histological differentiation ($p < 0.001$). CIPI was also linked to obstruction ($p < 0.001$), perforation ($p < 0.001$), and levels of hemoglobin ($p < 0.001$) and albumin ($p < 0.001$). For short-term outcomes, preoperative high CIPI groups had higher postoperative 30-day morbidity and mortality rates compared to the low CIPI group; $p < 0.001$. Regarding long-term outcomes, the high CIPI group exhibited significantly higher recurrence rates (30.6% vs. 16.0%, $p < 0.001$) and worse relapse-free survival (RFS) and OS ($p < 0.001$). When considering three-year, five-year, and ten-year survival, the high CIPI group consistently showed worse survival rates compared to the low CIPI group [20].

Similarly, Xie *et al.* [11] investigated the CIPI index in 1304 patients with stages 1–3 colorectal cancer, identifying a cut-off value of 11. They found that high CIPI was significantly associated with male gender, advanced T stage, advanced N stage, advanced TNM stage, colon cancer, larger tumor size, high neutrophil count, low lymphocyte count, and high CEA levels. Furthermore, the overall mortality in the high CIPI group was 16.2% higher than in the low CIPI group. Patients with high CIPI had a lower 5-year disease-free survival (DFS) (53.0% vs. 68.5%, $p < 0.001$). OS rate for patients with high CIPI was significantly lower than for those with low CIPI (55.5% vs. 71.7%, $p < 0.001$), and this trend of lower survival with high CIPI persisted across subgroups when patients were divided by stages [11].

Table 4. Pathological data.

	Group 1 low CIPI N (%)	Group 2 high CIPI N (%)	*p*
MSI-H	8 (8.5)	6 (6.3)	0.565[a]
Tumor budding	63 (67.0)	74 (77.9)	0.094[a]
Tumor budding grade (n = 137)			
Low	37 (58.7)	42 (56.8)	0.950[a]
Medium	18 (28.6)	23 (31.1)	
High	8 (12.7)	9 (12.2)	
Mucinous hystology	17 (18.1)	14 (14.7)	0.534[a]
Mixed type pathology	8 (8.5)	7 (7.4)	0.771[a]
Grade			
Low	9 (9.6)	6 (6.3)	0.703[a]
Medium	76 (80.9)	79 (83.2)	
High	9 (9.6)	10 (10.5)	
T staging			
1	7 (7.4)	1 (1.1)	
2	13 (13.8)	5 (5.3)	
3	53 (56.4)	53 (55.8)	
4A	20 (21.3)	27 (28.4)	0.004*[a]
4B	1 (1.1)	9 (9.5)	
N staging			
0	57 (60.6)	38 (40)	
1a	16 (17)	20 (21.1)	
1b	8 (8.5)	20 (21.1)	0.058[a]
1c	1 (1.1)	3 (3.2)	
2a	6 (6.4)	6 (6.3)	
2b	6 (6.4)	8 (8.4)	
Lymphovascular invasion	54 (57.4)	68 (71.6)	0.042*[a]
Perineural invasion	31 (33.0)	54 (56.8)	<0.001**[a]
Crohn-like lymphoid reaction	6 (6.4)	8 (8.4)	0.593[a]
Tumor perforation	5 (5.3)	18 (18.9)	0.004*[a]
Tumor diameter	3.00 (0.1–7.8)	3.8 (0.3–10.3)	0.001*[b]
Total no lymph nodes	25 (1–198)	27 (6–113)	0.483[b]
Number of malign lymph nodes	0 (0–24)	1 (0–44)	0.008*[b]

MSI-H, microsatellite instability high. * $p < 0.05$, ** $p < 0.001$, a: Chi-square, b: Mann Whitney U test.

Consistent with the literature, our series included stages 1–3 colorectal patients who underwent curative resection. Using ROC curves, we found our cut-off value to be 8.54, and in our series, a high CIPI level was associated with tumor localization, inflammatory cell counts, and adverse histopathological features such as increased lymphovascular and perineural invasion, diameter, and tumor perforation. Our findings support the common view in the literature that both disease-free and overall survival times were reduced at high CIPI levels. A possible explanation for the relationship between CIPI and CRC prognosis is that CIPI reflects a combination of systemic inflammation and tumor burden in CRC patients.

It is believed that MSI tumors are more immunogenic, leading to a lymphocytic response that restricts the tumor at an early stage and prevents distant metastasis. The positive impact of microsatellite instability on prognosis is thought to be based on the immunological reaction against the tumor. With the progression of the disease stage, immune evasion mechanisms emerge, diminishing the positive effect of MSI on prognosis [21,22]. Numerous studies have reported tumor budding as an independent prognostic factor associated with lymph node metastasis, local recurrence, and survival. Guidelines from the European Society for Medical Oncology and the ITBCC include tumor budding as a criterion for identifying high-risk patient groups [15,23–26].

There is limited evidence in the literature regarding the relationship between the CIPI index, MSI status, and tumor budding. Only one study found no association between MSI status and CIPI, and other studies did not examine these pa-

Table 5. Multivariate Cox proportional hazards regression analysis of overall survival.

Variable	B	SE	Wald	df	*p*-value	Exp (B)	95% CI for Exp (B)
Age (years)	0.035	0.015	5.381	1	0.020*	1.035	1.005–1.066
Gender (male vs. female)	–0.068	0.346	0.039	1	0.843	0.934	0.474–1.838
Neoadjuvant treatment	–0.135	0.504	0.072	1	0.788	0.874	0.326–2.343
Emergency vs. elective	0.482	0.635	0.577	1	0.448	1.620	0.467–5.624
Lymphovascular invasion	0.500	0.388	1.666	1	0.197	1.650	0.771–3.527
Perineural invasion	–0.945	0.406	5.417	1	0.020*	0.389	0.175–0.861
MSI (stable vs. high)	–1.582	0.524	9.124	1	0.003*	0.206	0.074–0.574
T stage (T3–4 vs. T1–2)	1.047	1.069	0.958	1	0.328	2.848	0.350–23.161
N stage (N1–2 vs. N0)	0.084	0.393	0.046	1	0.831	1.088	0.503–2.352
Tumor differentiation			2.191	2	0.334		
Low vs good	0.882	0.793	1.237	1	0.266	2.416	0.510–11.443
Low vs moderate	–0.196	1.310	0.022	1	0.881	0.822	0.063–10.725
Tumor size	0.005	0.112	0.002	1	0.962	1.005	0.807–1.253
Operation type (MIS vs. open)	–0.816	0.439	3.451	1	0.063	0.442	0.187–1.046
CEA	–0.002	0.002	1.485	1	0.223	0.998	0.994–1.001
Ca 19.9	0.010	0.003	9.923	1	0.002*	1.010	1.004–1.016
CIPI (high vs. low)	1.219	0.434	7.882	1	0.005*	3.383	1.445–7.921

SE, standard error; MIS, minimally invasive surgery. * $p < 0.05$.

Table 6. Multivariate Cox proportional hazards regression analysis of disease free survival.

Variable	B	SE	Wald	df	*p*-value	Exp (B)	95% CI for Exp (B)
Age (years)	0.022	0.011	3.623	1	0.057	1.022	0.999–1.045
Gender (male vs. female)	0.101	0.280	0.131	1	0.718	1.107	0.639–1.917
Neoadjuvant treatment	–0.741	0.357	4.321	1	0.038*	0.476	0.237–0.959
Emergency vs. elective	0.238	0.555	0.185	1	0.668	1.269	0.428–3.766
Lymphovascular invasion	0.327	0.324	1.019	1	0.313	1.386	0.735–2.614
Perineural invasion	–0.407	0.338	1.451	1	0.228	0.665	0.343–1.291
MSI (stable vs. high)	–1.599	0.458	12.189	1	<0.001*	0.202	0.082–0.496
T stage (T3–4 vs. T1–2)	0.495	0.582	0.723	1	0.395	1.641	0.524–5.136
N stage (N1–2 vs. N0)	0.319	0.329	0.943	1	0.332	1.376	0.723–2.620
Tumor differentiation							
Low vs good	–0.201	0.751	0.072	1	0.788	0.818	0.188–3.561
Low vs moderate	0.161	0.513	0.098	1	0.754	1.174	0.430–3.211
Tumor size	0.016	0.098	0.028	1	0.867	1.017	0.838–1.232
Operation type (MIS vs. open)	0.042	0.330	0.016	1	0.899	1.043	0.546–1.992
CEA	–0.001	0.001	0.851	1	0.356	0.999	0.996–1.001
Ca 19.9	0.009	0.003	9.503	1	0.002*	1.009	1.003–1.015
CIPI (high vs. low)	1.188	0.337	12.429	1	<0.001*	3.280	1.695–6.347

* $p < 0.05$.

rameters [12]. In our series, we did not show a relationship between MSI status and CIPI, nor between the presence and degree of tumor budding. This could be due to several reasons, including the limited number of patients with MSI status, making it statistically inconclusive. The lack of association with tumor budding may be attributed to our exclusion of patients with initial metastatic disease.

The limitations of our study include its retrospective nature and single-center design. However, given the scarcity of literature on the CIPI index, we believe our study contributes valuable insights.

Conclusions

A high pre-treatment CIPI score is associated with a poorer prognosis in patients with colorectal cancer (CRC). The CIPI is also closely related to clinicopathological factors. As easily accessible and cost-effective biomarkers, CIPI levels hold potential as independent prognostic factors in CRC, necessitating further research to establish their utility and optimal threshold values. Future studies focused on developing prognostic tools and surveillance programs for treatment strategy and personalized cancer care are essential. Our findings suggest that CIPI, derived from CEA and NLR, is a promising prognostic tool for patients with colorectal cancer after curative resection.

This index can guide us especially in the decision-making process about adjuvant chemotherapy. Especially in stage 2 colorectal cancer, the high level of this index can predict the possibility of an aggressive tumor and direct adjuvant treatment. For patients with high CIPI values, consideration of closer monitoring or more aggressive treatment strategies to improve prognosis may be warranted.

Availability of Data and Materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

UT – Conceptualization and design, drafting the article, final approval. SY – Conceptualization, analysis and interpretation of data, drafting the article, final approval. MZŞ – Data analysis, revising the article, final approval. RD – Conceptualization, design, revising the article, final approval. EK – Conceptualization, drafting the article, final approval. ZT – Supervision, acquisition of data, final approval. HB – Conceptualization, analysis, revising the article, final approval. All authors have been involved in revising it critically for important intellectual content. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This study is approved by Ethics Committee of Basaksehir Çam and Sakura City Hospital, Istanbul, Turkey dated 13 March 2024 with decision (Number 194). The patient's informed consent has been obtained for this study and a statement that this study was conducted in accordance with the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

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