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Evaluation of Inflammatory Markers in the Blood of Colorectal Cancer Patients

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Abstract

The incidence of colorectal cancer (CRC) is rising globally, accompanied by a high mortality rate. Systemic inflammation is believed to significantly contribute to CRC development, highlighting the need for accessible, reliable, and cost-effective tools to assess patients' inflammatory status. This study aimed to evaluate liver and renal functions and the changes in blood cell-based inflammatory markers related to CRC. This cross-sectional case-control study included 60 colorectal cancer (CRC) patients and 30 healthy controls. Complete blood counts were performed using an automated analyzer. The blood cell-based inflammatory markers include the platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and neutrophil × platelet/lymphocyte × hemoglobin ratio (NP/LHB). SII and NP/LHB were significantly elevated in patients with CRC compared with controls (probability [p] = 0.029 and 0.043), while NLR and PLR showed no significant differences (p = 0.486 and 0.39). Tumor stage, grade, and site, along with disease duration, may impact the levels of PLR, NLR, SII, and NP/LHB. The levels of liver function parameters alanine transaminase (ALT) and aspartate transaminase (AST) were significantly higher in patients than in controls (p = 0.013 and 0.019, respectively), while alkaline phosphatase levels showed non-significant differences (p = 0.197). The renal function parameter serum creatinine showed significantly elevated levels in patients compared to controls (p = 0.048), while the levels of blood urea nitrogen were not significantly different (p = 0.39). Changes in the level of these blood-cell-based inflammatory indicators may be influenced by tumor stage, tumor grade, disease duration, and tumor site. Significantly elevated levels of ALT, AST, and creatinine were also associated with CRC.

Keywords: Colorectal cancer; Inflammation; Neutrophil-to-lymphocyte ratio; Platelet-to-lymphocyte ratio; systemic immune-inflammation index.

تقييم العلامات الالتهابية في دم مرضى سرطان القولون والمستقيم

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الخلاصة

تزايدت نسبة الإصابة بسرطان القولون والمستقيم (CRC) على مستوى العالم، مع ارتفاع معدل الوفيات المرتبط به. يُعتقد أن الالتهاب يسهم بشكل كبير في تطور سرطان القولون والمستقيم، مما يبرز الحاجة إلى أدوات متاحة وموثوقة وفعالة من حيث التكلفة لتقييم الحالة الالتهابية للمرضى. هدفت هذه الدراسة إلى تقييم وظائف الكبد والكلى والتغيرات في مؤشرات الالتهاب المستندة إلى الخلايا الدموية المتعلقة بسرطان القولون والمستقيم. تم إجراء هذه الدراسة الحالية ذات المجموعتين (حالة وضابطة) وشملت ستين مريضًا بسرطان القولون والمستقيم وثلاثين شخصًا سليمًا. تم إحالة المرضى إلى مستشفى الأورام التعليمي (مدينة الطب، بغداد، العراق) خلال الفترة من أكتوبر إلى ديسمبر عام ٢٠٢٢. تم إجراء فحوصات تعداد الدم الكامل باستخدام جهاز آلي. تم تقييم مؤشرات الالتهاب المستندة إلى الخلايا الدموية بما في ذلك نسبة الصفائح الدموية إلى الخلايا اللمفاوية(PLR) ، ونسبة العدلات إلى الخلايا اللمفاوية(NLR) ، ومؤشر الالتهاب المناعي النظامي(SII) ، ونسبة العدلات×الصفائح الدموية/الخلايا اللمفاوية×الهيموغلوبين .(NP/LHB) كانت مستويات SII و NP/LHBمرتفعة بشكل كبير في المرضى المصابين بسرطان القولون والمستقيم مقارنةً بالمجموعة الضابطة) احتمالية = [p] ٠.٠٢٩ و٠.٠٤٣)، في حين أن NLR و PLRلم يظهر عليهما اختلافات ذات دلالة إحصائية = p) ٠.٤٨٦ و٠.٣٩ .(قد تؤثر مرحلة الورم، ودرجته، وموقعه، بالإضافة إلى مدة المرض، على مستويات PLR و NLRو SIIو NP/LHB. كانت مستويات معلمات وظائف الكبد مثل الألانين ترانس أمينار (ALT) والأسبارتات ترانس أمينار (AST) مرتفعة بشكل كبير في المرضى مقارنةً بالضوابط = p) ٠.٠١٣ و٠.٠١٩ على التوالي(، في حين أن مستويات الفوسفاتاز القلوية لم تظهر اختلافات ذات دلالة إحصائية = p) ٠.١٩٧ .(كانت مستويات مقياس وظائف الكلى مثل الكرياتينين في الدم مرتفعة بشكل كبير في المرضى مقارنةً بالأصحاء = p) ٠.٠٤٨)، في حين أن مستويات نيتروجين اليوريا في الدم لم تُظهر اختلافات ذات دلالة إحصائية = p) ٠.٣٩ .(قد تتأثر التغيرات في مستوى هذه المؤشرات الالتهابية المستندة إلى الخلايا الدموية بمرحلة الورم، ودرجته، ومدة المرض، وموقع الورم. كما كانت مستويات ALT و ASTوالكرياتينين المرتفعة بشكل كبير مرتبطة بسرطان القولون والمستقيم.

1. Introduction

Colorectal cancer (CRC) is described by abnormal cell growth in the appendix, rectum, or colon[1, 2]. Between 2000 and 2019, the proportion of colorectal cancer (CRC) cases relative to all other cancer types in Iraq demonstrated an upward trend, increasing from 3.69% to 6.5%. This rise corresponds to an average Annual Percentage Change (APC) of 3.54%, indicating a consistent year-on-year increase[2]. Increasing evidence suggests that CRC is driven by systemic inflammation in which blood cells, including platelets and white blood cells (WBCs), especially neutrophils and lymphocytes, are functionally involved through the ability to produce pro-inflammatory cytokines [3]. Therefore, ongoing research has been attempting to establish CRC-associated markers based on the number of relevant types of blood cells, with the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) being the main focus [4]. Routinely performed peripheral blood examinations can easily provide reliable counts of neutrophils, lymphocytes, monocytes, and platelets, all of which show an association with systemic inflammatory responses [5]. Numerical changes in these cells, which are located in close proximity to the tumor microenvironment, may provide a clear reflection of the aggressiveness of the disease [6]. It has been noted that a high NLR indicates a poor prognosis of CRC [7]. Another peripheral blood marker, known as the systemic immune-inflammation index (SII), only takes into account the number of lymphocytes, neutrophils, and platelets [8]. The original purpose of this index was to stratify hepatocellular carcinoma patients, especially in terms of prognosis [9], while its potential use for following up CRC metastasis was later reported [10]. A new blood cell-based marker that combines SII and hemoglobin (Hb) concentration, namely the

NP/LHB ratio (neutrophil × platelet/lymphocyte × Hb), has recently been proposed as a tool for the early diagnosis of CRC [11].

Due to the significant association of hepatic metastases with a notable proportion of colorectal cancer (CRC)-related mortality, there has been considerable conjecture concerning a potential correlation between the pathogenesis of this neoplastic disease and hepatic functionality[12]. Recent developments in transplantation methodologies have amplified scholarly interest in the application of liver transplantation for patients diagnosed with liver-limited stage IV colorectal cancer (CRC) [13]. Promising data from small studies indicate a 5-year overall survival (OS) rate of 50% to 83% among transplant patients, thus highlighting the role of liver transplantation in CRC [14]. In addition, serum changes in the concentrations of creatinine and blood urea nitrogen (BUN) are used as parameters to evaluate kidney function [15].

This study aimed to identify potential alterations in the blood cell-based inflammatory markers PLR, NLR, SII, and NP/LHB's levels in relation to colorectal cancer (CRC). It was also assessed how these markers related to the site, grade, and tumor stage. Furthermore, the study aimed to assess kidney function by measuring serum creatinine and blood urea nitrogen (BUN) and liver function tests like alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) by using a fully automated device.

2. Materials and Methods

2.1 sample collection

The current cross-sectional, case-control study was conducted on 60 CRC patients and 30 healthy individuals as a control group. Patients were referred to the Oncology Teaching Hospital (Baghdad Medical Complex, Baghdad, Iraq) during the period from October to December 2022. The NIH and Helsinki Declaration protocols were followed. Six patients (10%) were newly diagnosed, while 54 patients (90%) underwent oncologic surgery (both elective and emergency surgery) and were under treatment with 5-fluorouracil. The diagnosis of CRC and determination of tumor stage, grade, and location were performed by oncologists after sigmoidoscopy and colonoscopy examinations. Data on patients' demographic and clinical characteristics, such as age, sex, family history, body mass index (BMI), disease duration, TNM stage, tumor grade, and tumor site, were collected from hospital records. The control group included blood donors and health workers without chronic diseases.

2.2 Ethical Approval

The ethical approval was issued by the Ethics Committee in the Iraqi Ministry of Health and Environment; Reference No. 51895, Dec 7, 2022. Written consent was provided by all participants.

2.3. Inclusion and Exclusion Criteria

The patients included were adults of both sexes who met the CRC diagnostic criteria and consented to participate in the study. Excluded patients were those with inflammatory bowel disease, thyroid disease, diabetes, or other types of cancer.

2.4 Laboratory assessments

Five milliliters of blood were drawn from each participant and distributed into a plain tube (3 ml) and an EDTA tube (2 ml). Plain tube blood was centrifuged (3000 rpm for 10 min) after clotting, and the resulting serum was kept frozen at −20°C until needed. Assessment of ALT, AST, ALP, creatinine, and BUN was measured using assay kits (Thermo Scientific,

USA), and a fully automated biochemical analyzer (Thermo Scientific, USA) was performed based on the manufacturer protocol. EDTA blood was used to determine Hb concentration and the count of white blood cells (WBCs), including neutrophils, lymphocytes, and platelets, using a fully automated hematology analyzer (Sysmex Corporation, Japan). Targeted blood-cell-based inflammatory markers were calculated using the following equations as previously described [11].

$$\text{NLR (Neutrophil-to-Lymphocyte ratio)} = \frac{Absolute\ number\ of\ Neutrophils}{Absolute\ number\ of\ Lymphocytes}$$

$$\text{PLR (Platelet-to-Lymphocyte Ratio)} = \frac{Absolute\ number\ of\ Platelets}{Absolute\ number\ of\ Lymphocytes}$$

$$\text{SII (Systemic Immune Inflammation Index)} = \frac{Absolute\ number\ of\ Neutrophil\ x\ Absolute\ number\ of\ Platelets}{Absolute\ number\ of\ Lymphocytes}$$

$$\text{NP/LHB ratio} = \frac{Absolute\ number\ of\ Neutrophils\ x\ Absolute\ number\ of\ Platelets}{Absolute\ number\ of\ Lymphocytes\ x\ Hemoglobin\ concentration\ g/dL}$$

2.5 Statistical Analysis

Categorical variables were given as numbers and percentages, and significant differences were assessed using the Fisher exact test. Parametric variables were expressed in terms of mean ± standard deviation (M ± SD), and statistically significant differences were determined by one-way analysis of variance (ANOVA) test. Non-parametric variables were expressed as median and interquartile range (IQR: 25–75%), and statistically significant differences were detected using the Mann-Whitney U test. Receiver operating characteristic (ROC) curve analysis was applied to evaluate the discriminatory performance of the markers studied. Through this analysis, the area under the curve (AUC), cut-off point, sensitivity, and specificity were calculated. Spearman's rank-order correlation analysis was performed to evaluate pairwise correlation between variables. The results were presented as a heat map matrix of the correlation coefficient (r_s). Probability (p) < 0.05 was chosen to indicate statistical significance. GraphPad Prism version 9.5.1 (San Diego, CA, USA) was used to accomplish statistical analysis G*Power software version 3.1.9.7 was used to calculate sample size power [16].

3. Results and Discussion

3.1 Power of sample size

G*Power software was used to calculate sample power with the following inputs: 60 CRC patients, 30 controls, a one-tailed *p-value* of 0.05, and an effect size *p-value* of 0.5. The calculated power for the sample size was 0.71, which is less than the recommended 0.8. The most common reason for power being less than 0.8 is insufficient sample size.

3.2 Demographic and clinical features

Demographic and clinical features of CRC patients and controls are shown in Table 1. Patients and controls were relatively near in age (58.1 ± 13.1 *and*. 59.7 ± 11.2 years; p = 0.429) and male and female, respectively (males: 58.3 *vs*. 53.3%; females: 41.7 *vs*. 46.7%; p = 0.625). BMI showed no significant difference between patients and controls (25.83 ± 5.73 and 26.19 ± 3.37; p = 0.574), respectively. It was observed that 36.7% of CRC patients had a family history of cancer, and this may indicate the role of genetic factors in the etiology of the disease [17]. Most CRC cases were in TNM stages III (40%) and IV (36.7%) of the disease, whereas stages I and II occurred in only 14 patients (23.3%). Based on the histopathological grade (tumor differentiation), most cases were grade II (moderately differentiated; 73.3%), whereas 12 cases (20.2%) were grade III, and only 4 cases (6.7%) were grade I. The results of the tumor site analysis showed colon involvement in 24 cases

(70%) and rectum involvement in 18 cases (30%). The predominance of colon involvement (70%) over rectal involvement (30%) is supported by previous studies and can be attributed to anatomical, genetic, dietary, and screening-related factors [18].

Table 1: Demographic and clinical features.

Characteristics; mean ± SD or n (%)		Patients; n = 60	Controls; n = 30	*p*-value
Age (years)		58.1 ± 13.1	59.7 ± 11.2	NA
Male		35 (58.3)	16 (53.3)	NA
Female		25 (41.7)	14 (46.7)	
Duration of disease (months)		8.1 ± 8.3	NA	NA
BMI (Kg/m$^{2)}$		25.83 ± 5.73	26.19 ± 3.37	NA
Family history	Yes	22 (36.7)	NA	NA
	No	38 (63.7)		
TNM stage	I/II	14 (23.3)	NA	NA
	III	24 (40)		
	IV	22 (36.7)		
Grade	I	4 (6.7)	NA	NA
	II	44 (73.3)		
	III	12 (20.2)		
Tumor site	Colon	42 (70.0)	NA	NA
	Rectum	18 (30.0)		

SD: Standard deviation; BMI: Body mass index; NA: Not applicable; *p*: probability of ANOVA test or Fisher exact test.

3.3 Laboratory data

As presented in Table 2, the estimated Hb concentration in patients and control was 12.12 ± 1.53 and 12.36 ± 1.74 g/dL; $p = 0.507$, respectively, WBC count in patients and control (7.05 ± 2.32 and 7.98 ± 2.79 $\times 10^3$ µ/L; $p = 0.099$), lymphocyte count (2.13 ± 0.94 and. 2.19 ± 0.66 $\times 10^3$ µ/L; $p = 0.743$, respectively), and neutrophil count in patients and control (4.57 ± 2.60 and 4.42 ± 1.11 $\times 10^3$ µ/L; $p = 0.756$), respectively, showed no significant differences between CRC patients and controls. With respect to platelets, the count was significantly increased in patients compared to controls (290.32 ± 138.49 and 204.43 ± 63.46 × 10^3 µ/L; $p = 0.002$). The discussion has been expanded to include a deeper analysis of all relevant findings rather than focusing on a single result. It has been noted that elevated platelet counts are associated with increased mortality rates in various cancers, as platelets contribute to inflammation, tumor growth, and metastasis [19].

Based on these findings, platelet count alone may not be sufficient as a prognostic indicator; instead, it should be evaluated alongside other inflammatory and immune markers. Therefore, this study recommends further research to explore the mechanisms linking platelets to tumor progression and their combined predictive value with other biomarkers.

The results of renal function parameters revealed non-significant differences in BUN concentrations in CRC patients and control 30.52 ± 15.07 and 30.02 ± 6.80 mg/dL; p = 0.39, respectively, while serum creatinine concentrations were significantly decreased in patients compared to controls 0.83 ± 0.19 and 0.92 ± 0.21 mg/dL; $p = 0.048$, respectively, as seen in Table 2. BUN levels may remain stable because they depend not only on renal function but

also on protein metabolism and hydration status [20]. Since BUN is influenced by multiple factors, including protein intake and liver function, the non-significant difference may suggest that nitrogen metabolism is not severely altered in CRC patients or that compensatory mechanisms maintain stable levels [21]. Studies have shown that creatinine levels tend to decrease in cancer patients due to muscle wasting (cachexia) and malnutrition, both common in CRC patients [22].

Serum creatinine is mainly derived from the non-enzymatic conversion of creatinine and phosphocreatine, and insufficient creatinine production in CRC patients can be attributed to low muscle mass and inadequate nutrition [23]. Besides, it has recently been reported that low and high serum creatinine concentrations are more associated with reduced survival in patients with CRC [24].

In colorectal cancer (CRC) patients, liver function enzyme levels show notable differences compared to healthy controls. Serum ALT levels were significantly higher in CRC patients (12.56 ± 5.49 IU/L) than in controls (9.63 ± 4.32 IU/L; p = 0.013). Similarly, AST levels were significantly elevated in CRC patients (24.61 ± 11.11 IU/L) compared to controls (19.41 ± 6.02 IU/L; p = 0.019). Although ALP levels were also higher in CRC patients (83.25 ± 25.52 IU/L) than in controls (76.67 ± 15.17 IU/L), the difference did not reach statistical significance (p = 0.197) (Table 2). The observed elevation of ALT and AST in CRC patients can be attributed to multiple factors. CRC progression is often associated with systemic inflammation and metabolic disturbances, which can contribute to hepatic dysfunction. Secondly, liver metastases, a common occurrence in CRC, can lead to hepatocyte damage and enzyme leakage, further exacerbating ALT and AST elevations [25]. ALP is often associated with liver or bone metastases, its mild elevation in non-metastatic CRC could be due to systemic inflammation or changes in bone turnover [26]. The study findings indicate significantly higher ALT and AST levels in CRC patients than in healthy controls, suggesting mild hepatic involvement or systemic metabolic alterations. However, ALP levels did not significantly differ, implying that biliary function remains largely unaffected in early CRC stages. These enzyme changes may serve as early biomarkers for CRC progression and warrant further clinical evaluation to assess their prognostic and diagnostic value.

Table 2; Measurements of laboratory markers in CRC patients and the healthy control group.

Parameters; mean ± SD	Patients; n = 60	Controls; n = 30	*p*-value
Hemoglobin (g/dL)	12.12 ± 1.53	12.36 ± 1.74	NA
WBC ($\times 10^3$ μ/L)	7.052 ± 2.32	7.98 ± 2.79	NA
Lymphocyte ($\times 10^3$ μ/L)	2.13 ± 0.94	2.19 ± 0.66	NA
Neutrophil ($\times 10^3$ μ/L)	4.57 ± 2.60	4.42 ± 1.11	NA
Platelets count ($\times 10^3$ μ/L)	290.32 ± 138.49	204.43 ± 63.46	0.002
Blood urea nitrogen (mg/dL)	30.52 ± 15.07	30.02 ± 6.80	NA
Serum creatinine (mg/dL)	0.83 ± 0.19	0.92 ± 0.21	0.048
ALT (IU/L)	12.56 ± 5.49	9.63 ± 4.32	0.013
AST (IU/L)	24.61 ±11.11	19.41 ± 6.02	0.019
ALP (IU/L)	83.25 ± 25.52	76.67 ± 15.17	NA

SD: Standard deviation; WBC: White blood cell; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; *p*: probability of ANOVA test (significant p-value is indicated in bold).NA: Not applicable.

3.4 Blood-cell-based inflammatory markers

The analysis of inflammatory markers in CRC patients and healthy controls revealed that Platelet-to-Lymphocyte Ratio (PLR) and Neutrophil-to-Lymphocyte Ratio (NLR) did not show significant differences between the two groups. The median (IQR) of PLR was 146.7 (99.49–183.3) in CRC patients and 129.1 (91.73–183.6) in controls ($p = 0.486$; Figure 1A). Similarly, NLR values were 1.67 (1.43–2.33) in CRC patients and 1.92 (1.43–2.71) in controls ($p = 0.39$; Figure 1B). In contrast, the Systemic Immune-Inflammation Index (SII) and Neutrophil-to-Platelet/Lymphocyte-to-Hemoglobin Ratio (NP/LHB) were significantly elevated in CRC patients. The SII levels were 479.2 (305.3–928.4) in CRC patients compared to 371.2 (298.3–506.8) in controls ($p = 0.029$; Figure 1C). Additionally, NP/LHB was 38.47 (25.08–77.57) in CRC patients, significantly higher than 28.58 (21.60–47.80) in controls ($p = 0.043$; Figure 1D).

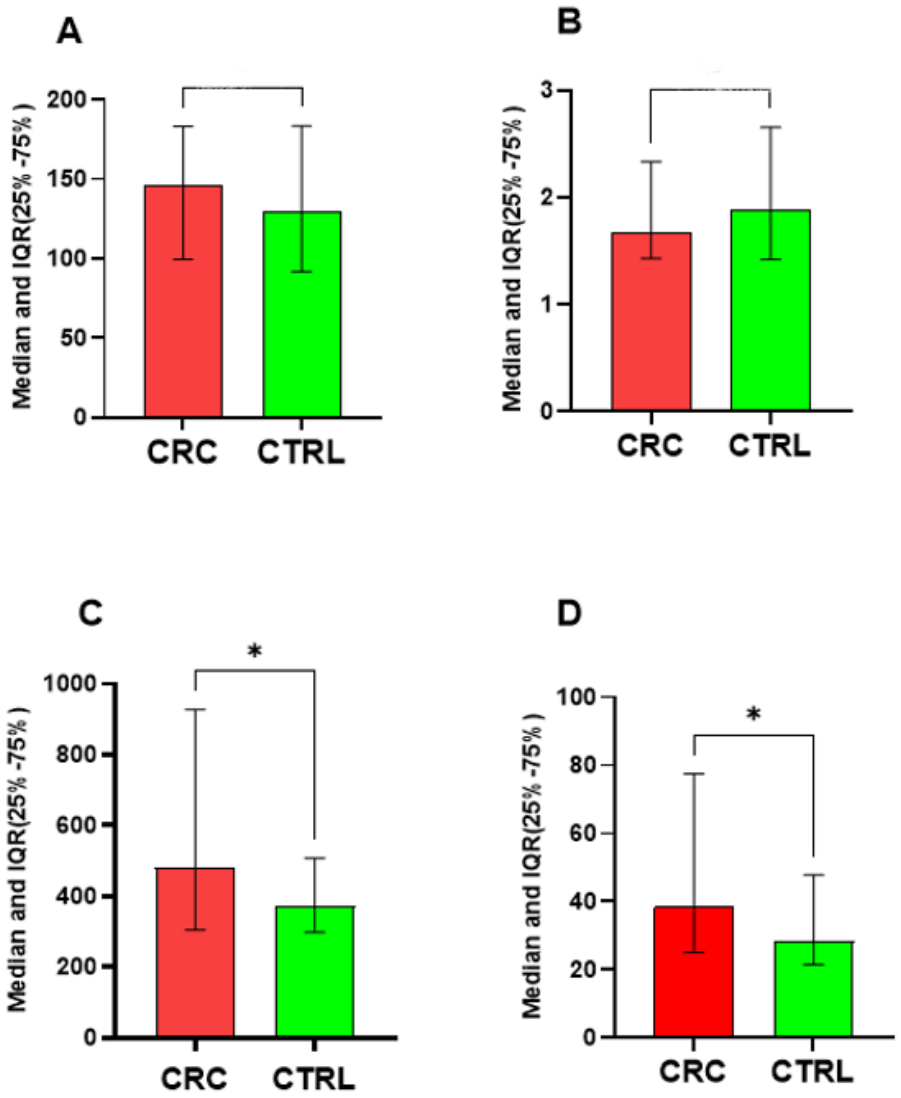

Figure 1: Comparison of inflammatory markers between colorectal cancer (CRC) patients and controls (CTRL). SII and NP/LHB were significantly elevated in CRC patients, while PLR and NLR showed no significant differences. (Mann-Whitney U test; $p < 0.05$ considered significant). [A] PLR (Platelet-to-Lymphocyte Ratio) ($p = 0.486$), [B] NLR (Neutrophil-to-Lymphocyte Ratio ($p = 0.39$), [C] SII (Systemic Immune-Inflammation Index) ($p = 0.029$), [D] NP/LHB (Neutrophil × Platelet/Lymphocyte × Hemoglobin Ratio) ($p = 0.043$).

The lack of significant differences in PLR and NLR in this study contrasts with previous reports that identified these markers as prognostic indicators in CRC [27]. One possible explanation for this discrepancy is the small sample size, which may have limited statistical power. Additionally, prior treatment exposure (such as chemotherapy or anti-inflammatory medications) in some CRC patients may have altered systemic inflammation, affecting PLR and NLR values.

While the existing results do not substantiate the diagnostic efficacy of PLR and NLR in CRC, they underscore the necessity for extensive studies to evaluate these biomarkers across diverse clinical environments further. Subsequent investigations should also take into account pre-treatment as opposed to post-treatment levels to ascertain whether therapeutic interventions affect their diagnostic and prognostic significance. Nevertheless, the current study revealed that SII and NP/LHB values were markedly elevated in CRC patients compared to the healthy control group. Regarding SII, the correlation between this biomarker and survival outcomes has been elucidated in various forms of solid tumors [28]. A prior investigation demonstrated that the SII exhibited a more pronounced correlation with the predisposition to the onset of CRC, as well as malignancies of the kidney, liver, and lung, in addition to lymphoma and myeloma, in comparison to alternative markers of inflammation [29]. Events during which DNA is damaged, apoptosis is inhibited, and angiogenesis is developed, which result mainly from elevated levels of the characteristic mediators of systemic inflammation: cytokines and chemokines. These conditions lead to the growth and development of cancer cells, as well as metastases [30]. Prior meta-analyses have demonstrated a correlation between the SII and numerous clinical determinants in CRC, with ramifications that encompass an augmented likelihood of cancer onset. Consequently, an elevated SII has been regarded as an indicator of unfavorable prognosis in CRC [31]. According to various researchers, the development and progression of CRC are strongly influenced by prolonged inflammation [32]. SII, known for its high objectivity as a tumor marker, effectively reflects the host's inflammatory response. Similarly, NP/LHB is a newly identified blood cell-based inflammatory marker, with existing evidence suggesting its potential role in distinguishing CRC patients from healthy controls [11].

3.5 ROC curve analysis

As shown in Figure 2, the ROC curve demonstrated the poor performance of PLR (AUC = 0.545; 95% CI = 0.418-0.673; p = 0.482; cut-off point = 131.1; sensitivity = 53.3%; specificity = 56.6%), NLR (AUC = 0.556; 95% CI = 0.432-0.681; p = 0.387; cut-off point = 1.70; sensitivity = 57%; specificity = 55%), SII (AUC = 0.62; 95% CI = 0.505-0.742; p = 0.056; cut-off point = 401.3; sensitivity = 60.0%; specificity = 63.3%), and NP/LHB (AUC = 0.613; 95% CI = 0.494-0.734; p = 0.079; cut-off point = 33.52%; sensitivity = 60%; specificity = 63.3%) in distinguishing between patients with CRC and controls.

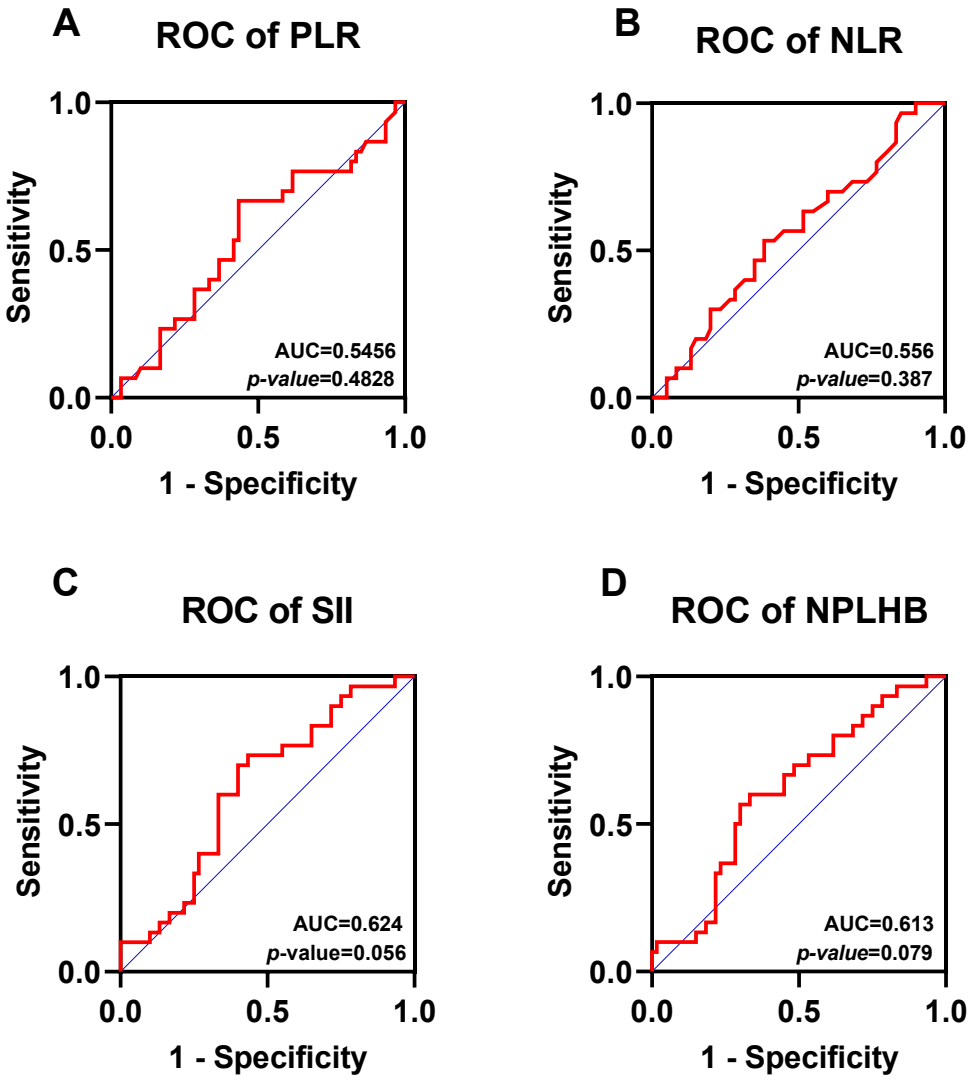

Figure 2: Receiver operating characteristic (ROC) curve analysis of inflammatory markers for distinguishing colorectal cancer (CRC) patients from controls. .[A] PLR (Platelet-to-Lymphocyte Ratio): Showed limited diagnostic performance in differentiating CRC from controls. [B] NLR (Neutrophil-to-Lymphocyte Ratio): Demonstrated low discriminatory ability in identifying CRC patients. [C] SII (Systemic Immune-Inflammation Index): Exhibited strong diagnostic potential, with a higher area under the curve (AUC). [D] NP/LHB (Neutrophil × Platelet/Lymphocyte × Hemoglobin Ratio): Displayed significant predictive accuracy for CRC detection.

3.6 Associations between blood-cell-based inflammatory markers and CRC-related variables

PLR, NLR, SII, and NP/LHB were assessed concerning TNM staging. No statistically significant differences were observed across stages I/II, III, and IV for PLR (Figure 3A), SII (Figure 3C), and NP/LHB (Figure 3D). However, NLR (Figure 3B) was significantly higher in early-stage CRC I/II (2.33) compared to stage III (1.52) ($p = 0.025$), whereas the difference between stages I/II and IV (1.55) was not significant. Although PLR levels tended to rise in advanced stages (III and IV), this increase did not reach statistical significance. These findings support previous evidence indicating that PLR lacks predictive value for CRC staging, whereas NLR may serve as a more reliable marker in this context [33].

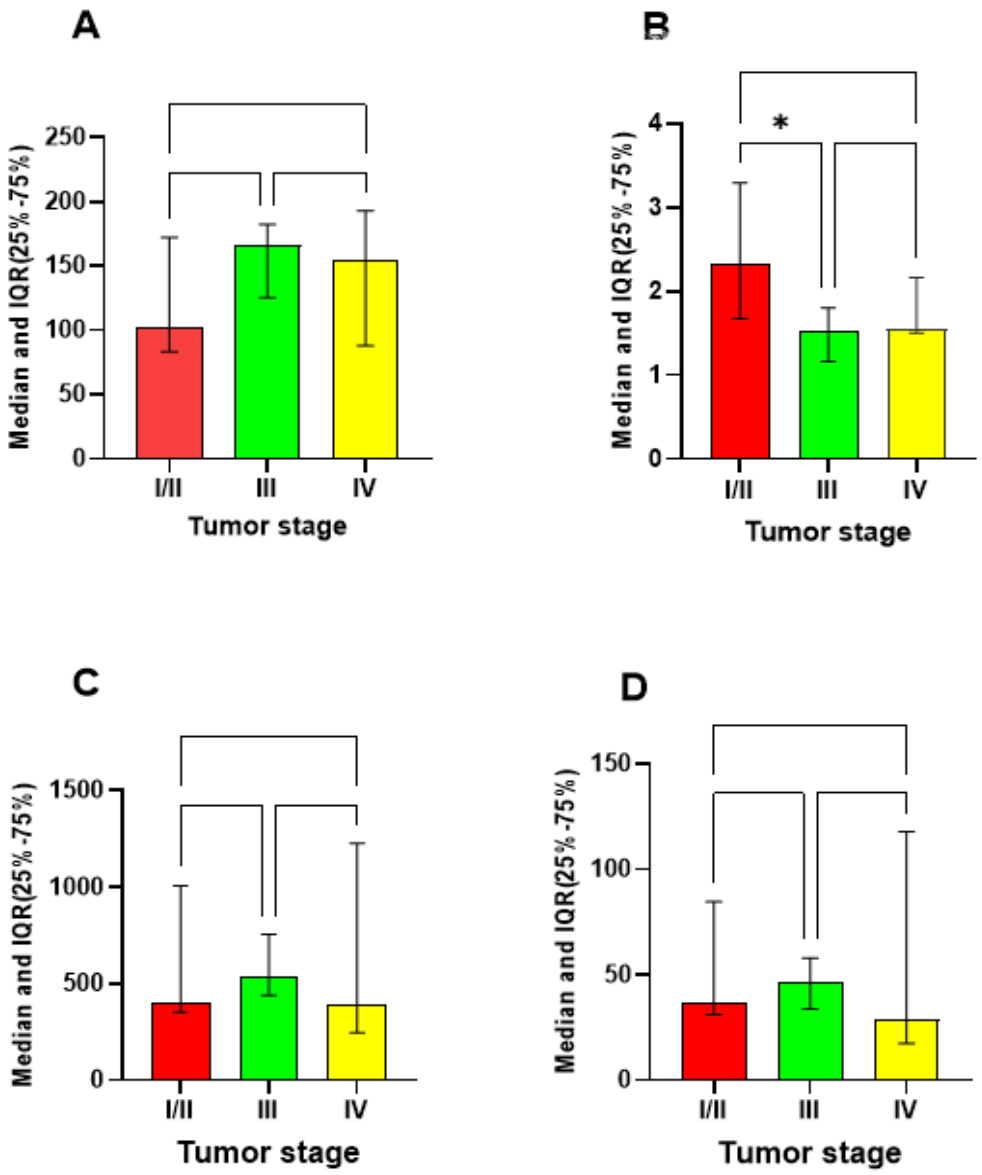

Figure 3: Column-bar plots showing the distribution of inflammatory markers in colorectal cancer (CRC) patients across different tumor stages. Median values are represented by columns and interquartile ranges (IQR) by bars. Statistical significance was determined using the Mann-Whitney U test (*p < 0.05; ns: not significant). [A] PLR: No significant difference was observed between tumor stages. [B] NLR: No significant variation was detected across tumor stages. [C] SII: Significantly elevated in advanced tumor stages (*p < 0.05). [D] NP/LHB: Higher levels were observed in advanced stages with significant differences (*p < 0.05).

Only SII and NP/LHB were significantly elevated in grade II (G2) compared to grade III (G3) tumors (SII: 540.1 [364.8-948.6] vs. 257.3 [224.8-480.1], p = 0.038; NP/LHB: 46.99 [31.71-77.57] vs. 18.39 [17.59-33.89], p = 0.0104). These results suggest a complex relationship between inflammation and tumor progression, where higher inflammatory markers are associated with G2 rather than G3. This may indicate immune evasion mechanisms in higher-grade tumors [34]. The findings highlight the potential of SII and NP/LHB as biomarkers for tumor differentiation, warranting further investigation into their clinical significance. According to tumor grade, the current results indicate that SII and NP/LHB show significant variations between grades II and III. Findings reported by other

groups are inconsistent with our current results, as they observed that SII and NP/LHB values were associated with poor histological differentiation (grade III) [11]. Regarding PLR and NLR, a study conducted by Turhan and his colleagues reported similar findings in that PLR and NLR showed no correlation with tumor histopathological grades [33]. In addition, no variations in NLR and PLR have been reported in relation to tumor grading in patients with colon cancer [35].

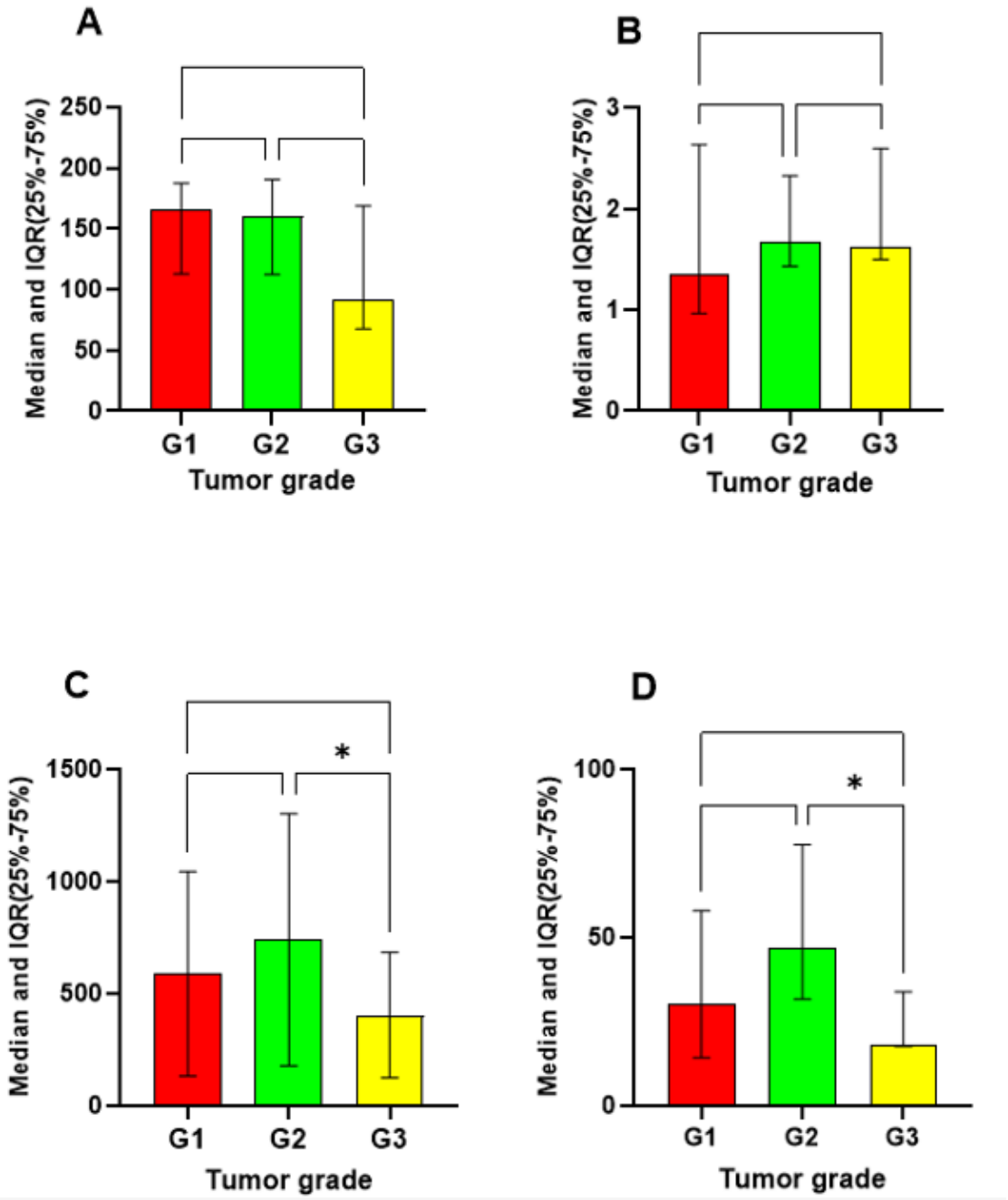

Figure 4: Column-bar plots showing the distribution of inflammatory markers in colorectal cancer (CRC) patients based on tumor grade. Median values are represented by columns and interquartile ranges (IQR) by bars. Statistical significance was determined using the Mann-Whitney U test (*p < 0.05; ns: not significant). [A] PLR: No significant difference was observed between tumor grades.[B] NLR: No significant variation detected across tumor grades. [C] SII: Significantly elevated in grade II compared to grade III (*p < 0.05). [D] NP/LHB: Higher levels in grade II than in grade III with significant differences (*p < 0.05).

The next association analysis was between PLR, NLR, SII, and NP/LHB and disease duration, in which CRC patients were divided into two groups, ≤ 6 and > 6 months (Figure 5). Only SII (597.3 (352.6-1007.0) *vs*. 406.0 (251.8-690.7); p = 0.047; Figure 5C) and NP/LHB (57.71 (26.63-84.59) *vs*. 33.89 (17.99-50.32); p = 0.019; Figure 5D). These results indicate that CRC patients diagnosed in less than 6 months showed an increase in SII and NP/LHB, and as the disease progressed, a gradual decrease in both markers was observed. It is possible to attribute this decrease to the effect of the chemotherapy 5-fluorouracil, which affects the cancer cells and thus reduces inflammation, leading to a decrease in NP/LHB levels. These findings have been previously observed in CRC after 6 months of treatment with 5-fluorouracil, where more than 50% of patients revealed decreased levels of assessed inflammatory markers [36].

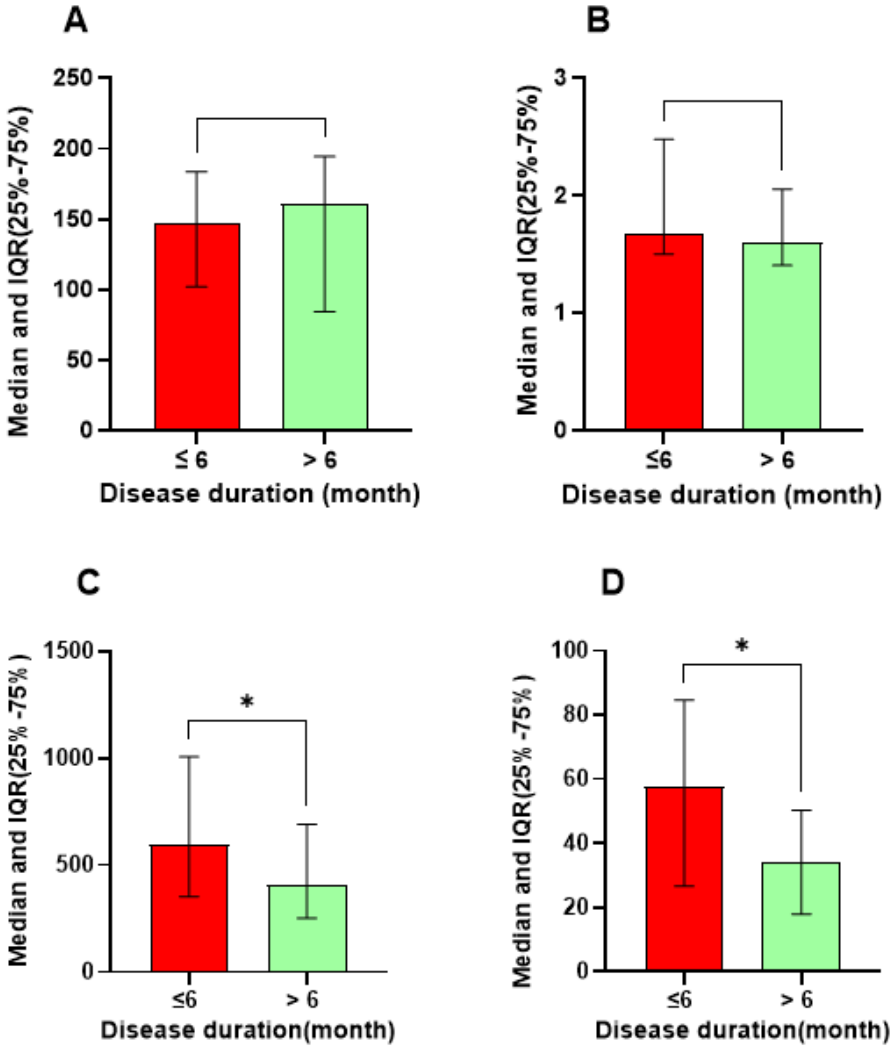

Figure 5: Comparison of inflammatory markers among colorectal cancer (CRC) patients classified by disease duration. SII and NP/LHB were significantly elevated in specific disease duration groups, while PLR and NLR showed no significant differences. (Mann-Whitney U test; p < 0.05 considered significant). [A] PLR (Platelet-to-Lymphocyte Ratio) (p = 0.486), [B] NLR (Neutrophil-to-Lymphocyte Ratio) (p = 0.39), [C] SII (Systemic Immune-Inflammation Index) (p = 0.029), [D] NP/LHB (Neutrophil × Platelet/Lymphocyte × Hemoglobin Ratio) (p = 0.043).

The final evaluation was an association of PLR, NLR, SII, and NP/LHB with the tumor site (Figure 6). Accordingly, CRC patients were divided into two groups: the colon site and the rectum site. NLR showed no significant differences between the two groups of patients (p = 0.8761; Figure 6B). While PLR (166.0 (109.9-192.9) *vs*. 120.7 (69.42-165.40; p = 0.0319; Figure 6A), SII (597.3 (353.8-1007) *vs*. 374.6 (240.9-717.5; p = 0.0264; Figure 6 C), and NP/LHB (49.28 (32.36-84.59) *vs*. 31.23 (19.13-52.95; p = 0.0287; Figure 6 D) were significantly elevated in patients with a colon site compared to patients with a rectum site.

The results observed in our study are consistent with those reported by another study, which revealed that higher levels of PLR, SII, and NP/LHB were associated with the colon site compared with the rectum site [11]. In contrast to our findings, another study showed no significant differences in the values of these indices about tumor location [33].

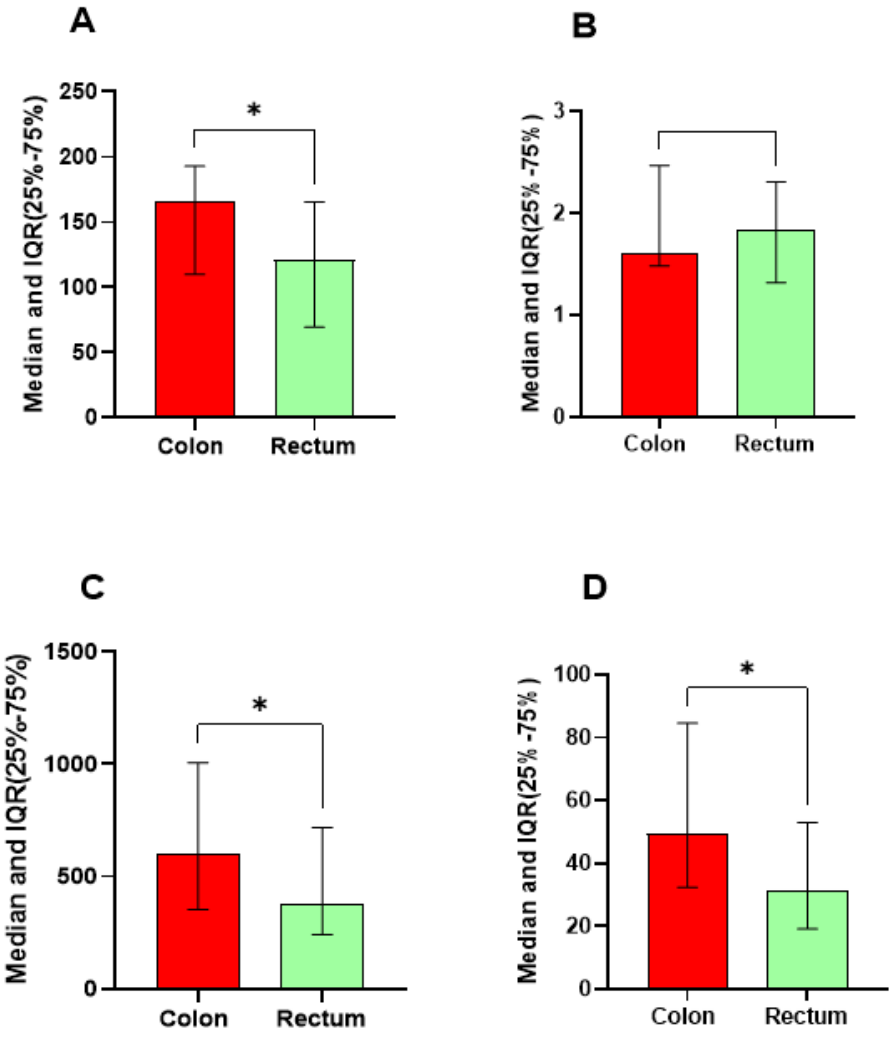

Figure 6: Column-bar plots of [A] PLR (platelet-to-lymphocyte ratio), [B] NLR (neutrophil-to-lymphocyte ratio), [C] SII (systemic immune-inflammation index), and [D] NP/LHB (neutrophils × platelets/lymphocytes × hemoglobin ratio) in colorectal cancer (CRC) patients and controls (CTRL) classified by tumor site. SII and NP/LHB were significantly elevated in specific tumor site groups, while PLR and NLR showed no significant differences. Columns indicate median values and bars represent interquartile range (IQR). Significance was determined using the Mann-Whitney U test (*p < 0.05; ns: not significant).

4. Correlation analysis

Spearman rank-order correlation analysis was conducted to assess the relationships among the blood cell-based inflammatory markers: PLR, NLR, SII, and NP/LHB values. A strong positive correlation was found specifically between SII and NP/LHB (rs = 0.97; p = 0.003) (see Figure 7). This study examined variations in these four inflammatory markers and their associations with colorectal cancer (CRC), with particular attention to tumor stage, grade, site, and disease duration. Significant findings were noted, particularly regarding SII and NP/LHB.

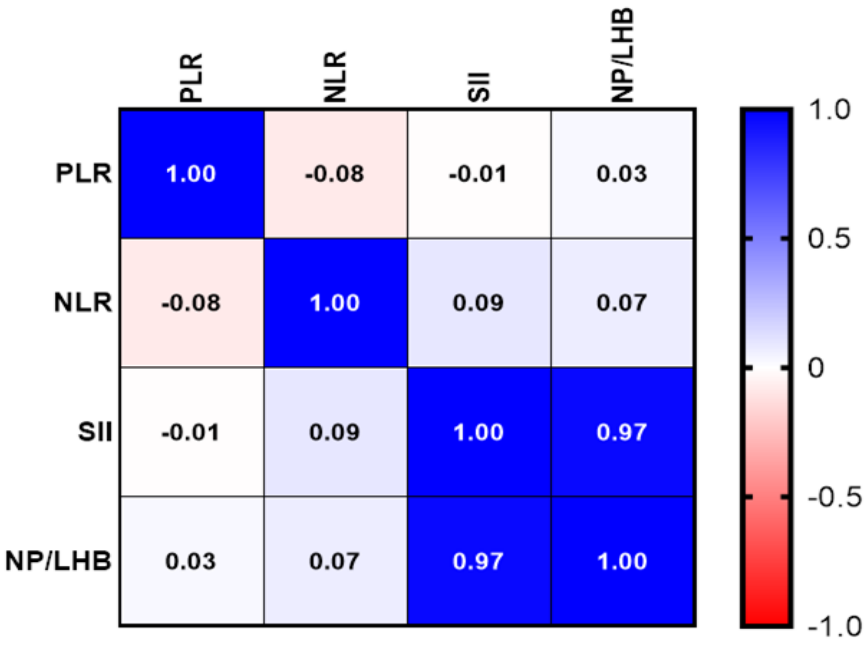

Figure 7: Heat-map matrix of Spearmans rank-order correlation analysis between PLR, NLR, SII, and NP/LHB. Values inside the boxes indicate the correlation coefficient. Blue: positive correlation. Red: negative

5. Study limitations

This study has several limitations. Firstly, the number of participants was low. Additionally, the parameters PLR, NLR, SII, and NP/LHB may be considered non-specific markers for distinguishing inflammation associated with colorectal cancer (CRC) from inflammation caused by other conditions. To address these limitations, To overcome these limitations, larger multi-center studies are needed to validate these findings, along with longitudinal research to assess their predictive value. Mechanistic studies should explore the role of SII and NP/LHB in tumor-immune interactions, while integrating these markers with genetic profiling could enhance their clinical utility for tumor grading and personalized treatment.

6. Conclusions

Our findings highlight the potential role of blood cell-based inflammatory markers in colorectal cancer (CRC) assessment. While SII and NP/LHB were significantly elevated in CRC patients, their limited discriminatory ability suggests they may be more useful as supplementary rather than primary diagnostic tools. Additionally, their association with tumor characteristics, such as stage and grade, underscores their potential prognostic value. Elevated liver and kidney function markers further support the systemic impact of CRC. Future research should focus on refining these markers' clinical utility and integrating them with existing diagnostic strategies to enhance early detection and patient management.

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Data Sharing Statement

All datasets used and/or analyzed are presented in the current study.

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Disclosure

The author has declared that no competing interests exist.

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