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Diagnostic value of peripheral blood inflammatory indices for clinicopathological profile of colorectal cancer: a retrospective observational study

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Abstract

Background Colorectal cancer (CRC) ranks as the third most prevalent cancer globally and the second leading cause of cancer-related mortality. This study investigates the diagnostic value of peripheral blood inflammatory indices, including the Cancer-Inflammation Prognostic Index (CIPI), Systemic Inflammation Response Index (SIRI), Hemoglobin-Albumin-Lymphocyte-Platelet (HALP) index, Neutrophil-to-Lymphocyte Ratio (NLR), and Platelet-to-Lymphocyte Ratio (PLR), in the early diagnosis of clinicopathological characteristics of CRC.

Method This retrospective observational study involved 224 patients with CRC aged over 45, admitted to Rasoul-Akram Hospital from September 2019 to 2023, undergoing elective CRC surgery. Key demographic and clinicopathological data were collected alongside blood samples to derive inflammatory indices. Univariate and multivariate analyses were applied to determine metastasis and stage predictors. A receiver operating characteristic (ROC) analysis was performed to evaluate the SIRI diagnostic value in differentiating tumors with and without metastasis and the CIPI diagnostic value in differentiating tumors with high and low stage.

Results The study identified a significant association between elevated SIRI levels and metastasis in univariate analysis (OR = 2.79, CI = 1.12–6.94). Multivariate analysis shows CIPI is associated with advanced tumor stages (OR = 1.97, CI = 1.14–3.38). According to the ROC curve, the optimal cut-off value of SIRI and CIPI was 1.376 (sensitivity 52.6%, specificity 60.8%, AUC = 61.5%) for diagnosing the metastasis and 7.114 (sensitivity 59.8%, specificity 57%, AUC = 57.9%) for diagnosing the tumor stage, respectively.

Discussion The findings show that a higher SIRI value is associated with a higher chance of metastasis and a higher CIPI value is associated with a higher chance of advanced stages. Furthermore, the study advocates for the integration of these inflammatory indices into clinical practice to facilitate personalized treatment strategies and early diagnosis, enhancing the prognosis and survival in CRC.

Keywords Colorectal cancer, Peripheral blood inflammatory indices, Tumor biomarkers, Combined immune prognostic index, Cancer inflammation diagnostic indices

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Introduction

Colorectal cancer (CRC) is the third most common form of cancer globally. It holds the position of the second-highest contributor to cancer-related deaths, with an annual death rate of 0.6 million [1, 2]. According to studies, by 2035 there will be 2.5 million additional instances of CRC worldwide [3, 4]. CRC was the fourth-leading cause of cancer death in both men and women younger than 50 years in the late 1990s but is now first in men and second in women, according to the American Cancer Society, Cancer Facts & Figs. 2024 [5].

The clinicopathological profile of CRC affects the prognosis and survival of the patients. The survival rates for disease recurrence, mortality without recurrence, and mortality after recurrence were all better for early-stage colon cancer than for other stages [6]. Emergency surgery-required CRCs generally show a more advanced stage than elective cases, leading to a rapidly rising mortality rate [7]. Additionally, the 5-year overall survival following metastases was 16.6% higher for primary CRC tumors identified by screening [8]. These results emphasize that early diagnosis of the tumors and their clinicopathological profile has the potential to provide precise treatment and improve the overall prognosis of CRC.

The complex tumor microenvironment is made up of immune-inflammatory cells with different characteristics, which play pivotal roles in tumorigenesis and progression [9]. Inflammatory processes may contribute to systemic inflammation and are related to tumor clinicopathological characteristics such as metastasis and stage [10]. There is growing evidence that the severity of local immune inflammation in the tumor microenvironment is reflected in peripheral blood inflammatory indices [11, 12]. These indicators could help patients with cancer receive personalized treatment.

As a result of their accessibility, reproducibility, non-invasiveness, and cost-effectiveness, the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have gained popularity in the diagnosis, treatment, follow-up management, and prognosis prediction of a variety of solid tumors, including gastric cancer [13], breast cancer [14], lung cancer [15], ovarian cancer [16], as well as CRC [17]. For patients with metastatic CRC receiving regorafenib, a new prognostic index known as the cancer-inflammation prognostic index (CIPI), which is based on CEA and NLR, was recently presented as a promising novel prognostic marker [18]. The systemic inflammation response index (SIRI), another innovative inflammatory index based on the number of peripheral neutrophils, monocytes, and lymphocytes, demonstrated universal prognostic and diagnostic biomarkers in most malignant tumors, including CRC [19–21]. The SIRI In 2016, Jiang et al. showed the prognostic value of the hemoglobin-albumin-lymphocyte-platelet (HALP) index, which utilized preoperative hemoglobin, albumin, lymphocyte, and platelet levels in CRC [22].

This study was designed to explore the association of novel peripheral blood inflammatory indices, including CIPI, SIRI, HALP, NLR, and PLR, with the clinicopathological profile of CRC. To our knowledge, this is the first study to propose a diagnostic model for stage and metastasis of CRC based on these indices.

Materials and methods

This study was conducted as a retrospective observational study and was approved by the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.REC.1403.558). The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for observational studies.

Sample size calculation

The sample size in this study was computed using Power and Sample software version 3.1.2 by William D. Dupont and Walton D. Plummer for two independent groups. The study from Hilmi Yazici et al. was adopted as it has the most similar method and objectives to this study [21]. With 80% study power, a two-sided α of 0.05, and expected proportions (prevalence of higher stages, including 3 and 4) in high and low SIRI values (≤ 1.38 vs. >1.38 in the mentioned study) of 0.607 and 0.354, at least 76 patients were required for the investigation. Based on the anticipated amount of missing and excluded data, the number of 224 patients was determined as the selected sample size.

Study participants

All patients admitted to Rasoul-Akram Hospital for elective CRC surgery from September 2019 to 2023 and over 45 years old were included in the study.

The inclusion criteria were as follows: 1. All primary tumors localized from cecum to rectum 2. All the chosen patients underwent elective CRC surgery.

The exclusion criteria were as follows: 1. patients with a history of any neoplastic disease; 2. patients with any infections and hematologic diseases; 3. patients on antiplatelet or steroid therapy; 4. combination of other primary tumors; 5. the patients who did undergo radiotherapy and chemotherapy before surgery.

Sampling and data collection procedure

Parameters that were recorded from 224 patients with CRC included demographic profile and past medical history, including diabetes and hypertension. CRC stage (according to PTNM AJCC 8th edition), tumor location (proximal, distal, rectosigmoid, and total, which means

Table 1 Inflammatory indices formulas

Index	Calculation formula
combined immune prognostic index (CIPI)	CEA level (ng/L) × platelet count (/L)
systemic inflammation response index (SIRI)	Neutrophil (/L) × Monocyte (/L)/ lymphocyte (/L)
hemoglobin-albumin-lympho-cyte-platelet (HALP)	hemoglobin (g/L) × albumin (g/L) × lymphocytes (/L) /platelets count (/L)
Neutrophil-to-lymphocyte ratio (NLR)	Neutrophil (/L)/lymphocyte (/L)
Platelet-lymphocyte ratio (PLR)	platelet count (/L)/lymphocyte (/L)

being in more than 2 of the 3 locations mentioned), grade of the tumor (well differentiated, moderately differentiated, and poorly differentiated), and distant metastasis were selected as the clinicopathological profile of the tumor according to colonoscopy findings and biopsy reports.

Blood samples were collected 1 week before biopsy, and 5 inflammatory indices were calculated based on patients' blood samples (Table 1). The association between the indices and the tumor metastasis, PTNM stage, and tumor anatomical site was analyzed. The flow chart of the sampling and data collection procedure is shown in Fig. 1.

Statistical analysis

Continuous variables with non-normal distributions were expressed as median and interquartile range (IQR).

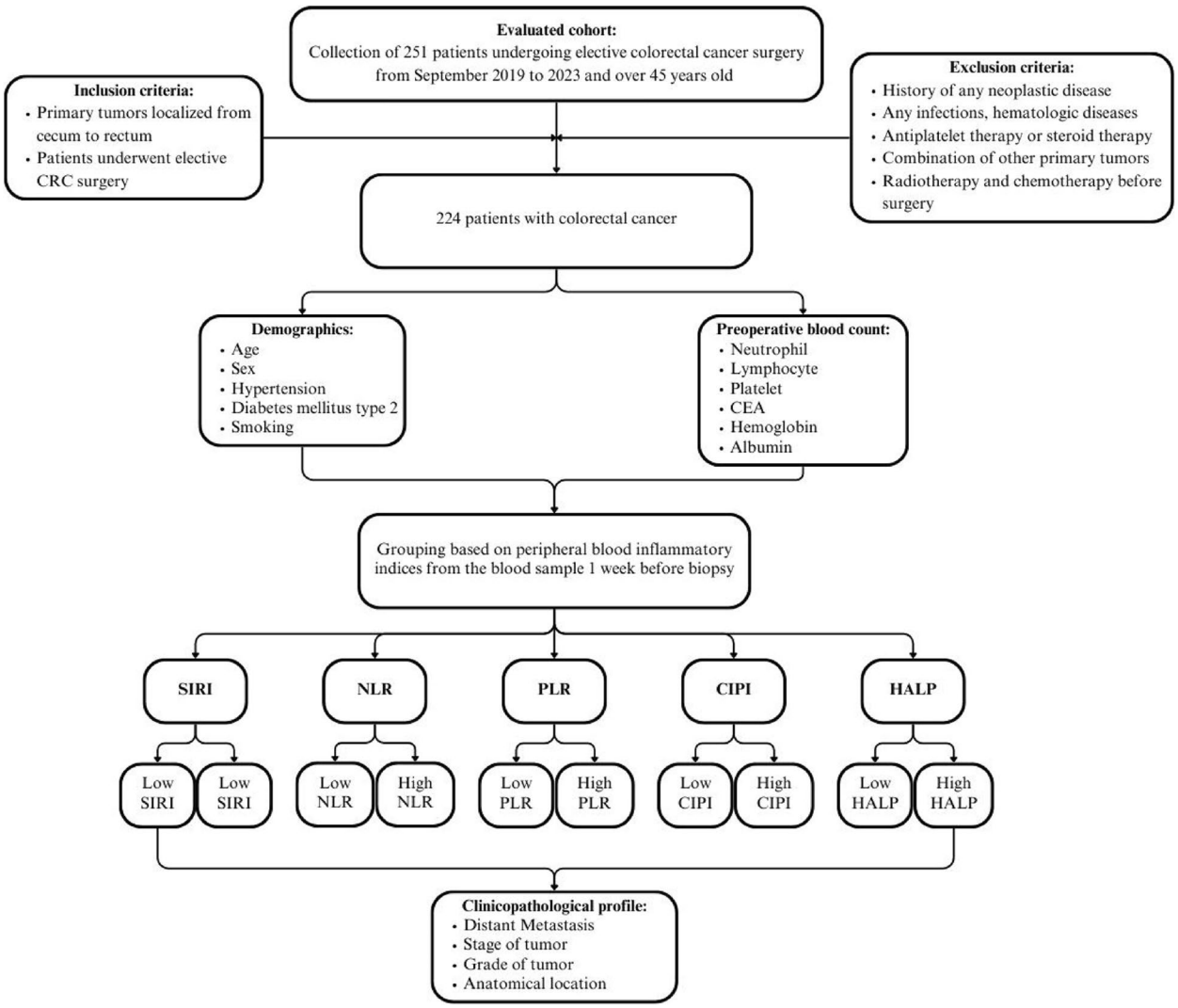


Fig. 1 Flow chart of the sampling and data collection procedure

Qualitative variables were expressed as numbers and percentages. The Spearman correlation was used to present the relationship between inflammatory indices. Pearson's chi-square test was used to determine the association of indices with clinicopathological characteristics. Logistic regression models were applied for univariate and multivariate analyses of metastasis and stage predictors. Candidate variables with $P<0.05$ in univariate analysis were subsequently entered into multivariable models, and those resulting variables with $P<0.05$ were considered independent predictors.

A receiver operating characteristic (ROC) curve was generated for indices with $P<0.05$ in univariate and multivariate analyses, and the area under the curve, sensitivity, and specificity values of the diagnostic model were calculated. The ROC curve was used to determine the cutoff value of SIRI in differentiating between metastatic and non-metastatic groups. All statistical analyses were performed using SPSS version 27.0 (IBM). Two-tailed significance values were used, and $P<0.05$ and 95% confidence intervals (CIs) were considered statistically significant.

Results

Clinicopathological characteristics of the patients

This study included 224 patients undergoing tumor excision and final histological investigation. Table 2 represents the clinicopathological characteristics of patients with CRC. The median age (range) of patients was 63 (45–95), the majority of them were male (56.3%) and between the ages of 56 and 65.

Of the patients, 22.8% and 33.5% had diabetes and hypertension, respectively. More than half of the tumors were found in the rectosigmoid location (52.2%) and had a moderately differentiated grade (47.8%). The most common tumor stage was stage 2 (39.7%), and the rarest stage was 1 (8%); also, 21.4% of tumors were in stage 4, of which 17.0% had distant metastasis.

Correlation between peripheral blood inflammation indices

The results of the correlation analysis showed that all peripheral blood inflammatory indices were significantly negatively correlated with the HALP index ($P<0.001$(. A significant positive correlation was identified between all other peripheral blood inflammatory indices ($P<0.001$) except between CIPI and NLR (P-value$=0.82$). The correlations between each inflammatory index are shown in Table 3.

Relationship between peripheral blood inflammation indices and clinicopathological characteristics

Table 4 shows the correlation between inflammatory indices and clinicopathological characteristics of CRC. Since no validated CIPI, SIRI, HALP, NLR, or PLR cut-off

Table 2 Clinicopathological characteristics of all 224 patients with colorectal cancer

Characteristics	Patients (n)	Percentage (%)
Age (years)		
45–55	51	22.8
56–65	79	35.3
66–75	64	28.6
≥ 75	30	13.4
Sex		
Male	126	56.3
Female	98	43.8
Type 2 diabetes mellitus		
No	173	77.2
Yes	51	22.8
Hypertension		
No	149	66.5
Yes	75	33.5
Smoking		
No	179	79.9
Yes	45	20.1
Distant Metastasis		
No	186	83.0
Yes	38	17.0
Stage		
1	18	8.0
2	89	39.7
3	69	30.8
4	48	21.4
Grade of tumor		
Well	86	38.4
Moderate	107	47.8
poor	31	13.8
Anatomical location		
Proximal	57	25.4
Distal	24	10.7
Rectosigmoid	117	52.2
overall	26	11.6
Blood parameters (median, IQR)		
Neutrophil count	5.29 (3.16–8.01)	
Lymphocyte count	1.28 (4.80–10.60)	
White blood cell count	7.5 (4.80–10.60)	
Platelet count	210 (142.50–281.75)	
CEA level	40.42 (2.70–87.30)	
Hemoglobin level	10.4 (8.90–11.90)	
Albumin	3.52 (3.10–4.00)	
SIRI	1.39 (0.65–2.72)	
NLR	3.38 (2.39–5.95)	
PLR	151.55 (102.53–220.58)	
CIPI	13.66 (4.94–19.97)	
HALP	22.99 (12.58–38.04)	

Table 3 The correlation between preoperative inflammatory indices in patients with colorectal cancer

Inflammatory indices	HALP	CIPI	PLR	NLR
SIRI	R* = -0.403	R* = 0.491	R* = 0.288	R* = 0.755
	P-value > 0.001	*P*-value > 0.001	*P*-value > 0.001	*P*-value > 0.001
NLR	R* = -0.584	R* = 0.116	R* = 0.509	
	P-value > 0.001	*P*-value = 0.82	*P*-value > 0.001	
PLR	R* = -0.885	R* = 0.255		
	P-value > 0.001	*P*-value > 0.001		
CIPI	R* = -0.255			
	P-value > 0.001			

values have been reported in the literature, and the AUC obtained from the ROC curve for most indices was undesirably less than 60%, the medians of the peripheral blood inflammation indices were chosen as cut-off values for grouping: CIPI (≤13.66 vs. > 13.66), SIRI (≤1.39 vs. > 1.39), HALP (≤23.00 vs. > 23.00), NLR (≤3.38 vs. > 3.38), and PLR (≤151.55 vs. > 151.55). Patients were categorized into either low or high groups.

Among the peripheral blood inflammation indices, all had a significant relationship with age groups, except SIRI (p-value = 0.102). It is also possible to see a trend in the parallel increase of indices and age. Also, values higher than the indices cut-off become more prevalent with increasing age. For instance, the prevalence of high PLR (> 151.55) shows an increasing trend with increasing age (45–55 yrs., 37.3%; 56–65 yrs., 46.8%; 66–75 yrs., 56.3%; ≥ 75 yrs., 70.0%). On the other hand, only SIRI had a significant relationship with gender; thus, in high values of SIRI (> 1.39), the prevalence of men (56.3%) is higher. SIRI has also been associated with metastasis, which shows that the prevalence of metastasis in high values of SIRI (> 1.39) is more than two times its prevalence in low values of SIRI (≤ 1.39).

There is no correlation between diabetes mellitus, hypertension, smoking, and stage with any of the indices. Among the indices, only HALP had a significant relationship with tumor grade; in high values of HALP (> 23.00), the prevalence of moderately differentiated is lower than low values of HALP (≤ 23.00).

Only PLR has been associated with the anatomical location of the tumor; in high PLR values (> 151.55), a lower prevalence of tumor in distal (25.0) and overall (38.5) locations was observed compared to low PLR values (≤ 151.55).

Diagnostic value of peripheral blood inflammatory indices for metastasis and stage of CRC

Table 5 shows the univariate analyses of metastasis predictors. The results of univariate analysis show that age, gender, smoking, diabetes, blood pressure, and none of the peripheral blood inflammation indices have any effect on the chance of metastasis except SIRI, which indicates an increase in the chance of detecting metastasis in high SIRI values (> 1.39).

Table 6 shows the univariate and multivariate analyses of stage predictors. The results of univariate analysis show that females have a lower chance of being diagnosed with higher stages (3 and 4) (OR = 0.56, CI = 0.33, 0.96). Also, a high value of CIPI (> 13.66) significantly increases the chance of diagnosing a tumor with stages 3 and 4 (OR = 1.89, CI = 1.11, 3.22). After multivariate analyses, the effect of CIPI value and sex on the chance of detecting higher stages remained significant (OR = 1.97, CI = 1.14–3.38; OR = 0.54, CI = 0.31–0.93, respectively). Figure 2 illustrates the results of univariate and multivariate analyses for metastasis and stage.

Potential of SIRI for metastasis diagnosis in CRC patients

In univariate analyses, the only significant index in predicting metastasis of tumors was SIRI; receiver operating characteristic (ROC) analyzes were performed on SIRI. Figure 3 shows ROC analyses pertaining to the SIRI-based diagnostic model. SIRI's best cut-off value for metastasis diagnosis was estimated to be 1.376 (sensitivity 52.6%, specificity 60.8%, AUC = 61.5%).

Potential of SIRI for metastasis diagnosis in CRC patients

CIPI was the only significant index in both univariate and multivariate analyses that could predict the stage of tumors; receiver operating characteristic (ROC) analyses were conducted on CIPI. ROC analysis for the CIPI-based diagnostic model is displayed in Fig. 4. For the diagnosis of metastases, the optimal cut-off value for CIPI was calculated to be 7.114 (sensitivity 59.8%, specificity 57%, AUC = 57.9%).

Discussion

This study highlights the diagnostic value of peripheral blood inflammatory indices in CRC. Among the indices analyzed, the SIRI and CIPI demonstrated significant

Table 4 The Correlation Between Preoperative inflammatory indices and clinicopathological characteristics of colorectal cancer

Characteristics	SIRI [n, (%)]			NLR [n, (%)]			PLR [n, (%)]			CIPI [n, (%)]			HALP [n, (%)]		
	≤1.39	>1.39	*P* value	≤3.38	>3.38	*P* value	≤151.55	>151.55	*P* value	≤13.66	>13.66	*P* value	≤23.00	>23.00	*P* value
Age (years)			0.102			**0.009**			**0.024**			**0.010**			**0.006**
45–55	33 (64.7)	18 (35.3)		26 (51.0)	25 (49.0)		32 (62.7)	19 (37.3)		33 (64.7)	18 (35.3)		17 (33.3)	34 (66.7)	
56–65	35 (44.3)	44 (55.7)		19 (24.1)	60 (75.9)		42 (53.2)	37 (46.8)		29 (36.7)	50 (63.3)		39 (49.4)	40 (50.6)	
66–75	30 (46.9)	34 (53.1)		18 (28.1)	46 (71.9)		28 (43.8)	36 (56.3)		32 (50.0)	32 (50.0)		34 (53.1)	30 (46.9)	
≥75	13 (43.3)	17 (56.7)		8 (26.7)	22 (73.3)		9 (30.0)	21 (70.0)		11 (36.7)	19 (63.3)		22 (73.3)	8 (26.7)	
Sex			**0.045**			0.086			0.354			0.578			0.178
Male	55 (43.7)	71 (56.3)		34 (27.0)	92 (73.0)		59 (46.8)	67 (53.2)		57 (45.2)	69 (54.8)		68 (54.0)	58 (46.0)	
Female	56 (57.1)	42 (42.9)		37 (37.8)	61 (62.2)		52 (53.1)	46 (46.9)		48 (49.0)	50 (51.0)		44 (44.9)	54 (55.1)	
Type 2 diabetes mellitus			0.599			0.660			0.578			0.525			0.549
No	85 (49.4)	87 (50.6)		53 (30.8)	119 (69.2)		84 (48.8)	88 (51.2)		79 (45.9)	93 (54.1)		85 (49.4)	87 (50.6)	
Yes	26 (51.0)	25 (49.0)		18 (35.3)	33 (54.7)		26 (51.0)	25 (49.0)		25 (49.0)	26 (51.0)		27 (52.9)	24 (47.1)	
Hypertension			0.491			0.597			0.600			0.321			0.913
No	76 (51.4)	72 (48.6)		46 (31.3)	101 (68.7)		73 (49.3)	75 (50.7)		72 (49.0)	75 (51.0)		75 (51.0)	72 (49.0)	
Yes	35 (46.7)	40 (53.3)		25 (33.3)	50 (66.7)		37 (49.3)	38 (50.7)		33 (44.0)	42 (56.0)		36 (48.0)	39 (52.0)	
Smoking			0.605			0.707			0.500			0.491			0.525
No	89 (50.0)	89 (50.0)		58 (32.6)	120 (67.4)		86 (48.3)	92 (51.7)		86 (48.3)	92 (51.7)		91 (51.1)	87 (48.9)	
Yes	22 (48.9)	23 (51.1)		13 (28.9)	32 (71.1)		24 (53.3)	21 (46.7)		19 (42.2)	26 (57.8)		21 (46.7)	24 (53.3)	
Distant Metastasis			**0.015**			0.244			0.259			0.174			0.476
No	99 (53.2)	87 (46.8)		62 (33.3)	124 (66.7)		89 (47.8)	97 (52.2)		91 (48.9)	95 (51.1)		91 (48.9)	95 (51.1)	
Yes	12 (31.6)	26 (68.4)		9 (23.7)	29 (76.3)		22 (57.9)	16 (42.1)		14 (36.8)	24 (63.2)		21 (55.3)	17 (44.7)	
Stage			0.173			0.092			0.569			0.093			0.483
1	12 (66.7)	6 (33.3)		10 (55.6)	8 (44.4)		11 (61.1)	7 (38.9)		11 (61.1)	7 (38.9)		6 (33.3)	12 (66.7)	

Table 4 (continued)

Characteristics	SIRI [n, (%)]			NLR [n, (%)]			PLR [n, (%)]			CIPI [n, (%)]			HALP [n, (%)]		
	≤ 1.39	> 1.39	*P* value	≤ 3.38	> 3.38	*P* value	≤ 151.55	> 151.55	*P* value	≤ 13.66	> 13.66	*P* value	≤ 23.00	> 23.00	*P* value
2	48 (53.9)	41 (46.1)		30 (33.7)	59 (66.3)		43 (48.3)	46 (51.7)		48 (53.9)	41 (46.1)		44 (49.4)	45 (50.6)	
3	32 (46.4)	37 (53.6)		19 (27.5)	50 (72.5)		31 (44.9)	38 (55.1)		29 (42.0)	40 (58.0)		37 (53.6)	32 (46.4)	
4	19 (39.6)	29 (60.4)		12 (25.0)	36 (75.0)		26 (54.2)	22 (45.8)		17 (35.4)	31 (64.6)		25 (52.1)	23 (47.9)	
Grade of tumor			0.277			0.372			0.162			0.613			**0.019**
Well	38 (44.2)	48 (55.8)		31 (36.0)	55 (64.0)		47 (54.7)	39 (45.3)		41 (47.7)	45 (52.3)		35 (40.7)	51 (59.3)	
Moderate	59 (55.1)	48 (44.9)		33 (30.8)	74 (69.2)		46 (43.0)	61 (57.0)		52 (48.6)	55 (51.4)		64 (59.8)	43 (40.2)	
Poor	14 (45.2)	17 (54.8)		7 (22.6)	24 (77.4)		18 (58.1)	13 (41.9)		12 (38.7)	19 (61.3)		13 (41.9)	18 (58.1)	
Anatomical location			0.982			0.395			**0.022**			0.887			0.189
Proximal	28 (49.1)	29 (50.9)		18 (31.6)	39 (68.4)		25 (43.9)	32 (56.1)		27 (47.4)	30 (52.6)		33 (57.9)	24 (42.1)	
Distal	11 (45.8)	13 (54.2)		11 (45.8)	13 (54.2)		18 (75.0)	6 (25.0)		13 (54.2)	11 (45.8)		8 (33.3)	16 (66.7)	
Rectosigmoid	59 (50.4)	58 (49.6)		33 (28.2)	84 (71.8)		52 (44.4)	65 (55.6)		53 (45.3)	64 (54.7)		60 (51.3)	57 (48.7)	
overall	13 (50)	13 (50)		9 (34.6)	17 (65.4)		16 (61.5)	10 (38.5)		12 (46.2)	14 (53.8)		11 (42.3)	15 (57.7)	

Table 5 Results of logistic regression to identify **metastasis** (never vs. ever) predictors

Variable		Unadjusted. OR (95% CI)	*P* value
Age (years)			
	45–55	Reference	
	56–65	1.18 (0.47, 2.93)	0.713
	66–75	0.86 (0.32, 2.31)	0.772
	≥ 75	0.51 (0.12, 2.08)	0.356
Sex			
	Male	Reference	
	Female	0.57 (0.28, 1.15)	0.119
Type 2 diabetes mellitus			
	No	Reference	
	Yes	1.48 (0.67, 3.25)	0.321
Hypertension			
	No	Reference	
	Yes	0.77 (0.36, 1.66)	0.516
Smoking			
	No	Reference	
	Yes	0.55 (0.20, 1.50)	0.247
SIRI			
	No	Reference	
	Yes	2.46 (1.17, 5.17)	**0.017**
NLR			
	No	Reference	
	yes	1.61 (0.71, 3.61)	0.247
PLR			
	No	Reference	
	yes	0.66 (0.33, 1.35)	0.261
CIPI			
	No	Reference	
	yes	1.64 (0.80, 3.37)	0.176
HALP			
	No	Reference	
	yes	0.77 (0.38, 1.56)	0.477

Data are adjusted for age, sex (male vs. female), type 2 diabetes mellitus (never vs. ever), hypertension (never vs. ever), Smoking (never vs. ever), SIRI (≤ 1.39 vs > 1.39), NLR (≤ 3.38 vs > 3.38), PLR (≤ 151.55 vs > 151.55), CIPI (≤ 13.66 vs > 13.66), HALP (≤ 23.00 vs > 23.00)

In each of the variables, one of the subgroups is considered as a reference category, and the odds ratio of the subgroup/other subgroups is calculated. OR value higher than one is considered as a risk factor and less than one as a protective factor. OR = Odds Ratio, CI = 95% Confidence Interval

diagnostic value for metastasis and tumor stage, respectively. However, CIPI shows undesirably lower AUC values in the ROC curve (57.9% compared to 61.5%). Higher SIRI and CIPI values were associated with metastasis and advanced disease stages, supporting the role of systemic inflammation in driving CRC progression and their potential as a diagnostic marker. Although the NLR and PLR have been widely studied, their association with metastasis was not statistically significant in this study.

Our findings align with previous studies that emphasize the significance of systemic inflammatory markers in CRC. Shen et al. (2024) demonstrated that SIRI, NLR, and PLR are associated with metastasis and poor survival in metastatic CRC, with AUC values for these indices ranging from 0.6 to 0.7. These results align with the AUC of 61.5% observed in our study, though differences in populations and cut-off values might explain slight discrepancies [23]. Also, Menyhart et al. (2024) performed a comprehensive meta-analysis, highlighting that elevated SIRI levels were strongly associated with poor overall survival (OS) and progression-free survival (PFS) in CRC and other malignancies [24].

CIPI, while less frequently studied than SIRI, showed a strong correlation with advanced tumor stages in our study. These results are supported by Yu et al. (2022) [25], who reported that high CIPI levels were associated with advanced tumor stages and poor disease-free survival. However, as emphasized by Yu et al. and Xie et al. (2023) [26], the utility of CIPI remains underexplored, and further research is needed to validate its diagnostic significance in patients with CRC.

The results of the studies also emphasize the role of inflammatory markers in clinical decision-making, early screening, and personalized treatment. Hao Cai et al. (2023) show that the preoperative CEA and SIRI were significantly associated with overall survival in patients with CRC, which supports more accurate risk assessment and personalized treatment [27]. SIRI can also be considered a practical biomarker to diagnose the prognosis of patients with CRC, including tumor stage and invasion [28]. Another study shows the high-CIPI with the cutoff value of 8 is significantly associated with stage, histologic type, and grade of CRC tumors [29].

The association between high SIRI values and metastasis underscores the role of systemic inflammation in CRC progression. Elevated neutrophil and monocyte counts foster an inflammatory microenvironment that promotes tumor growth, immune evasion, and angiogenesis. Neutrophils promote each step of the metastatic cascade, including premetastatic niche formation, tumor cell migration, intravasation, and extravasation [30]. monocytes recruit regulatory T cells and reduce CD8 + T cell infiltration, further suppressing anti-tumor immunity. At the same time, reduced lymphocyte counts reflect impaired cytotoxic activity and immune surveillance, shifting the immune balance toward a pro-tumor state that supports metastasis and tumor progression [31]. The association between high CIPI values and advanced tumor staging is primarily linked to CEA, a glycoprotein strongly tied to CRC progression and aggressiveness. Elevated preoperative CEA levels are indicative of more advanced disease stages, as they reflect increased

Table 6 Results of logistic regression to identify **stage** (1&2 vs. 3&4) predictors

Variable		Unadjusted. OR (95% CI)	*P* value	Adjusted. OR (95% CI)	*P* value
Age (years)					
	45–55	Reference			
	56–65	1.93 (0.94, 3.95)	0.069		
	66–75	1.49 (0.71, 3.13)	0.288		
	≥ 75	1.15 (0.46, 2.85)	0.758		
Sex					
	Male	Reference		Reference	
	Female	0.56 (0.33, 0.96)	**0.036**	0.54 (0.31, 0.93)	**0.028**
Type 2 diabetes mellitus					
	No	Reference			
	Yes	0.93 (0.50, 1.75)	0.839		
Hypertension					
	No	Reference			
	Yes	0.71 (0.41, 1.24)	0.237		
Smoking					
	No	Reference			
	Yes	0.94 (0.49, 1.81)	0.866		
SIRI					
	No	Reference	0.063		
	Yes	1.65 (0.97, 2.80)			
NLR					
	No	Reference			
	Yes	1.65 (0.93, 2.92)	0.081		
PLR					
	No	Reference			
	Yes	1.07 (0.63, 1.81)	0.794		
CIPI					
	No	Reference		Reference	
	Yes	1.89 (1.11, 3.22)	**0.018**	1.97 (1.14, 3.38)	**0.014**
HALP					
	No	Reference			
	Yes	0.77 (0.46, 1.31)	0.349		

Data are adjusted for age, sex (male vs. female), type 2 diabetes mellitus (never vs. ever), hypertension (never vs. ever), Smoking (never vs. ever), SIRI (≤ 1.39 vs > 1.39), NLR (≤ 3.38 vs > 3.38), PLR (≤ 151.55 vs > 151.55), CIPI (≤ 13.66 vs > 13.66), HALP (≤ 23.00 vs > 23.00)

In each of the variables, one of the subgroups is considered as a reference category, and the odds ratio of the subgroup/other subgroups is calculated. OR value higher than one is considered as a risk factor and less than one as a protective factor. OR = Odds Ratio, CI = 95% Confidence Interval

tumor burden and aggressiveness [32]. CEA also plays a critical role in assessing prognosis and diagnosis, with higher levels correlating with reduced overall survival and a higher likelihood of metastasis [33]. This relationship underscores the utility of CIPI in stratifying patients based on disease severity and its potential to guide therapeutic decision-making in CRC management [34].

The non-significant findings for NLR and PLR in metastasis diagnosis in this study contrast with the results of several studies, including those by Cao et al. (2023) [20] and Nakamoto et al. (2023) [35], who identified these indices as independent prognostic markers. These differences could be attributed to population heterogeneity, varying cut-off values, or differences in statistical power across studies. Future research should address these discrepancies through multicenter studies and standardized methodologies.

The SIRI reflects the interplay between tumor-promoting and anti-tumor immune mechanisms in CRC. Lymphocytes play a crucial role in anti-tumor immunity by inducing cytotoxicity and inhibiting tumor cell proliferation. However, decreased lymphocyte levels,

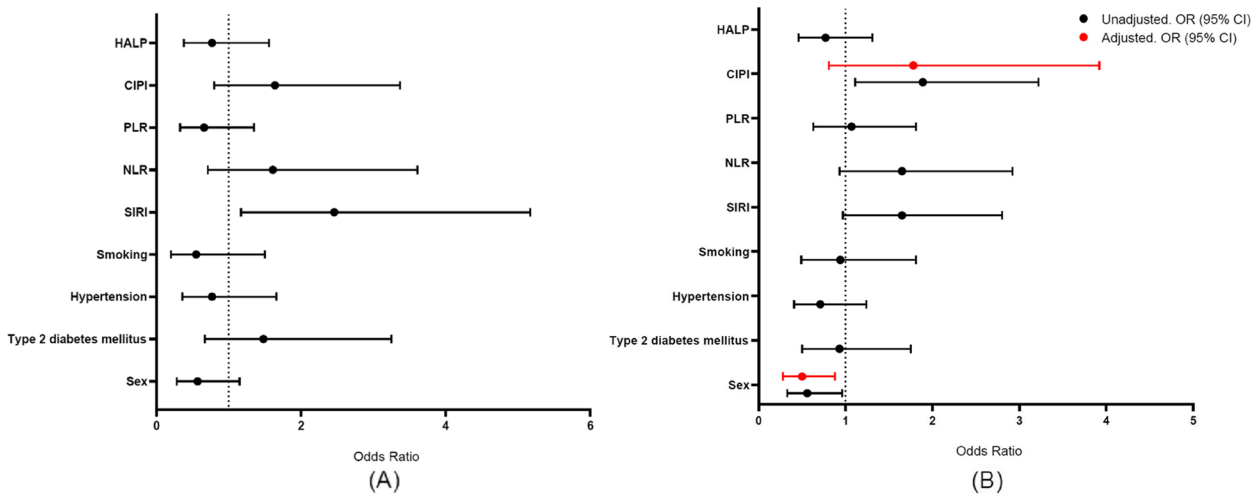
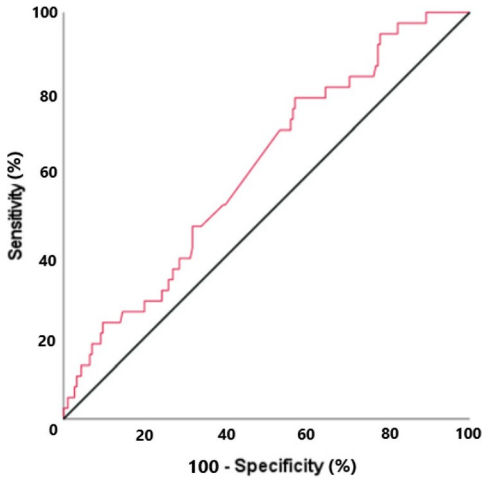


Fig. 2 Forest plot of Univariate and multivariate analysis of sex, type 2 diabetes mellitus, hypertension, Smoking, SIRI, NLR, PLR, CIPI, HALP as the predictors of metastasis (A) and tumor stage (B)

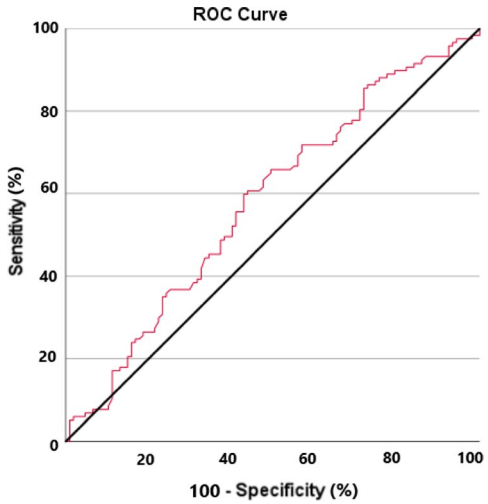


Area under the curve	p-value	Confidence interval	Cut off	Sensitivity	Specificity
61.5%	0.026	0.52-0.78	1.376	52.6%	60.8%

Fig. 3 Receiver operating characteristic (ROC) curve analysis of the SIRI for metastasis of colorectal cancer

often observed in CRC patients, impair the host immune response, facilitating tumor progression. In contrast, tumor-associated macrophages (TAMs) and tumor-associated neutrophils (TANs) are recruited to the tumor microenvironment (TME) via chemokine signaling pathways such as CCL2-CCR2 and CXCL1/2/5-CXCR2, respectively [33]. These cells contribute to angiogenesis, immune suppression, and tumor invasion through the release of growth factors and cytokines. By integrating neutrophil, monocyte, and lymphocyte counts, SIRI serves as a comprehensive marker of systemic immune dysregulation, reflecting the inflammatory state and its association with tumor aggressiveness and prognosis in CRC [36].

This study comprehensively evaluates the diagnostic role of multiple systemic inflammatory indices, including SIRI and CIPI, in a well-structured retrospective setting, offering valuable insights into their correlation with tumor staging and metastasis. By utilizing routine, accessible laboratory data, it highlights the potential for integrating



Area under the curve	p-value	Confidence interval	Cut off	Sensitivity	Specificity
57.9%	0.041	0.50-0.65	7.114	59.8%	57%

Fig. 4 Receiver operating characteristic (ROC) curve analysis of the CIPI for stage of colorectal cancer

these indices into clinical workflows for personalized CRC management. However, several limitations must be acknowledged. The retrospective nature of the study introduces selection bias, and its single-center design limits the generalizability of the findings. Furthermore, the absence of standardized cut-off values for indices such as SIRI and CIPI complicates comparisons with other studies. As highlighted by Cao et al. (2023) [20], inconsistent cut-offs can influence statistical results, underscoring the need for consensus in future research. Additionally, this study did not assess longitudinal changes in inflammatory indices, which could provide valuable insights into treatment response and disease progression. Furthermore, other potential confounding factors, such as physical activity level, BMI, and dietary habits, that could influence the observed association were not available. The results of this study might apply to other populations with comparable demographic and lifestyle traits, even though it concentrated on the Iranian population. Nevertheless, care should be used when extrapolating the findings to groups with significantly diverse genetic backgrounds and environmental exposures.

The findings of this study support the integration of inflammatory indices such as SIRI and CIPI into routine clinical practice for CRC. These indices offer a cost-effective, minimally invasive means of stratifying patients based on their risk of metastasis and. Standardizing cut-off values for inflammatory indices would facilitate their incorporation into predictive models, enhancing clinical decision-making. Furthermore, combining inflammatory indices with molecular biomarkers could provide a more comprehensive understanding of CRC biology and improve diagnostic accuracy. In future studies, authors can observe the association of SIRI and CIPI with cancer prognosis, such as overall survival and progression-free survival. This approach can help validate SIRI's predictive value in clinical settings. For instance, previous research has shown that SIRI can be a reliable predictor of prognosis in various cancers, including CRC [37, 38]. By analyzing how SIRI correlates with OS and PFS, researchers can better understand its utility in predicting patient outcomes and tumor metastasis.

Conclusion

In conclusion, this study underscores the significant diagnostic value of peripheral blood inflammatory indices, particularly the SIRI, in diagnosing metastasis and tumor staging in CRC patients. The findings suggest that elevated SIRI levels are closely associated with metastatic disease, highlighting that higher SIRI values are associated with a higher chance of detecting metastasis during CRC diagnosis. Although other indices like CIPI also show potential, their implications warrant further exploration. By integrating these easily accessible inflammatory markers into clinical practice, healthcare providers can enhance personalized treatment strategies for CRC, ultimately improving patient outcomes. Future multicenter studies are essential to validate these results and standardize cut-off values for broader application.

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Authors' contributions
All authors have made significant contributions to this study. M.R designed the work, collected some data, performed the statistical analyses, and prepared the final manuscript. H.R Supervised the implementation of the plan. A.K collected some data, and wrote a part of the main manuscript text. R.G.P Collected some data and wrote a part of the main manuscript text. B.S.A supervised the implementation of the plan and edited the main manuscript text. S.N wrote a part of the main manuscript text. A.N Supervised the implementation of the plan.

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

Declarations

Ethics approval and consent to participate
Ethical approval for this study (Ethical code: IR.IUMS.REC.1403.558) was provided by the.
Research Ethics Committee of Iran university of medical sciences, Tehran, Iran on 2024–09-22.
This study is approved by the Iran University of Medical Sciences research ethics committee with the ethics code: IR.IUMS.REC.1403.558.
It is hereby announced that informed consent has been obtained from all the participants to conduct the study and the personal information of the patients will not be disclosed in any way.
The patient consent form is the official form of Rasool Akram Hospitals and is available for all patients.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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