Prognostic Value of Systemic Inflammatory Markers and Scoring Systems in Predicting Postoperative 30-Day Complications and Mortality in Colorectal Cancer Surgery: A Retrospective Cross-Sectional Analysis

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AIM: Cancer-related systemic inflammation causes the increase of proinflammatory markers and acute phase proteins. Activation of systemic inflammatory response has been linked to poorer prognosis in colorectal cancer. This study aims to evaluate the prognostic value of preoperative systemic inflammatory markers and inflammation/nutrition scoring systems in predicting the postoperative early period (first 30 days) complications and mortality outcomes of patients who underwent curative surgery for colorectal cancer in our clinic.
METHODS: This study was designed as a retrospective single-arm cross-sectional study. In this study, 300 patients older than 18 years of age who underwent open and laparoscopic surgery for colorectal cancer were included. Demographic characteristics of the patients, preoperative hemogram and biochemical values, operation characteristics, postoperative tumor pathologies and disease stages were recorded.
RESULTS: Neoadjuvant chemoradiotherapy, Systemic Inflammation Score, Modified Glasgow Prognostic Score, Naples Prognostic Score and Prognostic Nutritional Index had a significant effect on the first 30-day mortality (*p*-values: <0.001, 0.007, <0.001, <0.001, <0.001, respectively).
CONCLUSIONS: The results suggest that certain preoperative inflammation and nutrition scores might serve as indicators for potential early postoperative adverse outcomes in colorectal cancer surgery.

Keywords: colorectal cancer; inflammation; morbidity; mortality

Introduction

Colorectal (CRC) cancers are the third most common type of cancer globally [1]. The relationship between inflammation and cancer was first discovered in the 19th century by Rudolf Virchow, who proposed a hypothesis in 1863 that immune cells infiltrating the tissue reflect the site where inflammatory cells appear in cancer lesions in inflamed tissue [2]. The accurate treatment and prognosis of CRC primarily depend on pathological staging [3,4]. However, recent studies have also associated the patient's immune and nutritional status with short and long-term outcomes in CRC and other cancers [5,6]. Evidence suggests that the presence of a systemic inflammatory response in CRC is a significant factor for poor prognosis. Additionally, there is a close relationship between malignant disease and inflammation, as cancer itself may induce local or systemic inflammation mediated by the activation and production of transcription factors. The number of major inflammatory cytokines that can affect cell proliferation, cell survival, angiogenesis, tumor cell migration, tumor invasion, tumor metastasis, and inhibition of adaptive immunity is associated with prognosis. The close relationship between CRC and inflammation can also be explained by inflammatory bowel diseases being premalignant conditions for CRC. Furthermore, cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory drugs have reduced the incidence of colorectal adenomas and CRC [5,7].

Due to the multiple roles of inflammation in CRC, various inflammation-based parameters and hematologic indices have been proposed as prognostic or predictive biomarkers. Cancer-related inflammation encompasses tumor-derived and host-derived cytokines, immune cells, and inflammatory protein mediators, and it is determined by levels of acute-phase proteins, such as serum leukocytes, neutrophils, lymphocytes, platelets, and C-Reactive protein [4,5,6,8]. Recently, combinations of these systemic inflammation parameters, including the neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), and platelet-lymphocyte ratio (PLR), have been reported as prognostic factors in some malignant solid tumors [9,10,11].

In addition to the individual use of hematologic markers, the combined use of these markers in scoring systems with various formulas plays a significant role in determining prognosis. The Naples Prognostic Score (NPS), Modified Glasgow Prognostic Score (mGPS), Systemic Inflam-

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mation Score (SIS), and Onodera's Prognostic Nutritional Index (PNI) systems, calculated using the patient's systemic inflammation and hematologic markers, are among the most commonly used [11,12,13,14].

This study aims to measure the prognostic value of preoperative systemic inflammatory markers and inflammation/nutrition scoring systems in predicting postoperative early-term (first 30 days) complications and mortality outcomes in patients undergoing curative surgery for CRC in our clinic.

Materials and Methods

Patient Selection

The study commenced with the approval of the Clinical Research Ethics Committee of Kocaeli Derince Training and Research Hospital under decision number 2022/135. Records of patients treated surgically for CRC in the Department of General Surgery at Kocaeli Derince Training and Research Hospital were retrospectively examined using the hospital database between January 2015 and December 2022. The enrollment criteria were as follows: (1) CRC underwent curative resection, (2) pathological biopsy proven adenocarcinoma, (3) older than 18 years old. The exclusion criteria were as follows: (1) emergency surgery due to mechanical obstruction, perforation or bleeding, (2) patients underwent palliative surgery,(3) recurrent colorectal disease, (4) patients with the diagnosis of any inflammatory disease or other malignancies, (5) missing hematological or biochemical data, (6) missing pathological data. Finally, 300 patients who underwent laparoscopic or open surgery for CRC were enrolled in this study.

Data Collection

Following demographic characteristics, clinical features and pathological findings were retrospectively gathered: sex, age, tumor characteristics, Tumor-Node-Metastasis (TNM) stage, serum albumin and C-Reactive protein levels, plasma cholesterol levels, hematological parameters, including total counts of neutrophils, lymphocytes and monocytes, NLR, PLR and LMR. The blood samples collected no later than three days before the surgery were used for hematologic and biochemical parameters. Postoperative complications were classified according to the Clavien-Dindo Classification [15,16].

The mGPS were calculated as follows: it gives 1 point for albumin <3.5 g/dL and 1 point for C reactive protein (CRP) ≥ 10 mg/L, resulting in scores of low risk (0 points), intermediate risk (1 point), and high risk (2 points) [17]. The NPS was calculated based on four parameters: serum albumin (normal range: ≥ 4 g/dL), total cholesterol (normal range: >180 mg/dL), NLR (normal range: >4.44) and LMR (normal range: ≤ 2.96) [13]. The Onodera's PNI was calculated according to the following formula: $10\times$ serum albumin (g/dL) + $0.005 \times$ total lymphocyte count (per mm^3) [18]. The SIS values were determined using the combination of the LMR and the serum albumin concentration: patients with LMR >4.44 and albumin level >4.0

Table 1. Demographic characteristics, comorbidities, cancer features, and Clavien-Dindo Classification of the patients.

	All patients
	N = 300 (%)
Sex	
Female	114 (38.0)
Male	186 (62.0)
Age	
≤60	91 (30.3)
>60	209 (69.7)
Resection type	
Right hemicolectomy	125 (41.7)
Low anterior resection	64 (21.3)
Abdominoperineal resection	47 (15.7)
Left hemicolectomy	35 (11.7)
Anterior resection	29 (9.7)
Operation type	
Open	177 (59.0)
Laparoscopic	123 (41.0)
Comorbidities (yes)	
Hypertension	107 (35.7)
Coronary artery disease	57 (19.0)
Diabetes	46 (15.3)
Chronic obstructive pulmonary disease	16 (5.3)
Chronic renal disease	7 (2.3)
Other malignancy	4 (1.3)
Length of hospital stay (day, median)	7.00 [6.0;45.0]
Neoadjuvant therapy (yes)	74 (24.7)
ASA class	
1	31 (10.3)
2	225 (75.0)
3	44 (14.7)
Clavien-Dindo Classification	
Class 0 (No complication)	43 (14.3)
Class 1	149 (49.7)
Class 2	44 (14.7)
Class 3	33 (11.0)
Class 4	10 (3.3)
Class 5	21 (7.0)
Cancer stage (TNM)	
Stage 1	98 (32.7)
Stage 2	73 (24.3)
Stage 3	95 (31.7)
Stage 4	34 (11.3)
Tumor location	
Ascending colon/cecum	125 (41.7)
Rectum	51 (17.0)
Sigmoid colon	38 (12.7)
Descending colon	35 (11.7)
Anal canal	28 (9.3)
Rectosigmoid junction	23 (7.7)

ASA, American Society of Anesthesiologists Classification; TNM, Tumor-Node-Metastasis.

Table 2. The ROC analysis results of inflammatory markers.

	AUC (95% CI)	Cut-off value	Sensitivity	Specificity	PPD	NPD
NLR	0.56 (50–63)	2.41	81	39	42	78
LMR	50 (43–57)	2.94	48	58	39	67
PLR	57 (50–64)	195.60	58	55	42	70
PNI score	63 (56–70)	32.10	52	75	53	73

AUC, Area under the curve; CI, Confidence interval; PPD, Positive predictive value; NPD, Negative predictive value; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; PLR, platelet-lymphocyte ratio; PNI, Prognostic Nutritional Index; ROC, Receiver operating characteristic.

g/dL were given score 0; patients with LMR ≤4.44 or albumin level ≤4.0 g/dL were given score 1; patients with LMR ≤4.4 and 4 albumin level ≤4.0 g/dL were given score 2 [19].

Statistical Analyses

Number and percentage for categorical variables, mean ± standard deviation or median (minimum-maximum value) for continuous variables were provided. The presence of normal distribution was assessed using histograms, quantile-quantile plot plots, and normal distribution tests (Kolmogorov-Smirnov or Shapiro-Wilk). Receiver operating characteristic (ROC) analysis was conducted to determine the best cutoff point for laboratory values according to the Clavien-Dindo Classification. The optimal cut-off point was determined based on the Youden index, and laboratory variables were categorized for this point. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test in cases where assumptions were not met. The Fisher-Freeman-Halton test was used for tables larger than 2×2 when the number of expected values was <5. Independent groups were compared using *t*-tests or Mann-Whitney U tests depending on the normal distribution of continuous variables. Kaplan-Meier survival curves were created for mortality, and group survival times were compared using the log-rank test. Factors influencing mortality in 30 days were investigated. Cases with a two-sided *p*-value: < 0.05 were considered statistically significant. R version 4.2.3 (https://www.r-project.org/) was used for data analysis and visualization.

Results

Demographic Characteristics

In this study, 300 patients were included, with a mean age of 65.93 (91 (30.3%) patients under 60 years; 209 (69.7%) patients aged 60 and over). Of these, 114 (38.0%) were female, and 186 (62.0%) were male. Right hemicolectomy was performed on 125 (41.7%) patients with colon/cecum tumors, and175 (58.3%) patients with left-sided tumors underwent 64 (21.3%) lower anterior resection, 29 (9.7 %) anterior resection, 35 (11.7%) left hemicolectomy, and 47 (15.7%) abdominoperineal resection surgeries (Table 1).

ROC Analyses for Cut-off Values

The cut-off values for NLR, PLR, LMR, and PNI scores were calculated using ROC analysis with the Clavien-Dindo Classification as the endpoint (Table 2). Patients were divided into two groups for each inflammatory marker [NLR ≤2.41 (low) and NLR >2.41 (high); LMR ≤2.94 (low) and LMR >2.94 (high); PLR ≤195.60 (low) and NLR >195.60 (high); PNI ≤32.10 (low) and PNI >32.10 (high)].

Analysis of Patients Based on NLR, PLR, and LMR Values

Patients were analyzed by dividing them into two groups based on the cut-off values of NLR, PLR, and LMR (Table 3). Age, gender and operation type did not show significant differences between low and high groups. Length of hospital stay was significantly longer in the high PLR group (*p*-value: 0.013). Patients with the Clavien-Dindo Classification two or higher had significantly higher NLR and PLR (*p*-values: <0.001, 0.024, respectively). Patients with stage three or higher disease had a significantly higher NLR value (*p*-value: 0.006). Patients with high NLR and PLR values required more perioperative transfusions (*p*-values: 0.019, <0.001, respectively).

Analysis Based on Scoring Systems

Patients were compared based on the scores for SIS, NPS, and mGPS and the calculated cut-off values for PNI (Table 4). There was no significant difference in gender among patients in scoring systems. Patients with high SIS score and PNI value were more frequently in the 60 years and older group (*p*-values: 0.040, 0.009, respectively). Patients with low PNI values were significantly in Clavien-Dindo groups two and above (*p*-value: <0.001). Patients who received neoadjuvant chemoradiotherapy had a significantly higher PNI value (*p*-value: <0.001). Patients showing lymphovascular invasion had significantly higher scores, but no significant difference was found regarding differentiation and disease stage. Patients with a tumor diameter of five and below had significantly lower SIS and NPS scores (*p*-values: 0.003, <0.001, respectively).

Table 3. Comparison of patients based on NLR, PLR, and LMR values.

	NLR				PLR				LMR			
	≤2.41	>2.41	χ^2	*p*	≤195.60	>195.60	χ^2	*p*	≤2.94	>2.94	χ^2	*p*
	N = 95	N = 205			N = 151	N = 149			N = 168	N = 132		
Sex			0.55	0.458			0.0008	0.928			3.53	0.060
Female	39 (41.1)	75 (36.6)			57 (37.7)	57 (38.3)			56 (33.3)	58 (43.9)		
Male	56 (58.9)	130 (63.4)			94 (62.3)	92 (61.7)			112 (66.7)	74 (56.1)		
Age			1.28	0.260			1.11	0.293			2.27	0.132
≤60	33 (34.7)	58 (28.3)			50 (33.1)	41 (27.5)			45 (26.8)	46 (34.8)		
>60	62 (65.3)	147 (71.7)			101 (66.9)	108 (72.5)			123 (73.2)	86 (65.2)		
Length of hospital stay	7 [1;25]	7 [1;45]	-	0.521	7 [1;15]	8 [2;45]	-	0.013	7 [1;45]	7 [1;25]	-	0.084
Clavien-Dindo Classification			11.65	<0.001			5.07	0.024			1.18	0.279
Class 0/1	74 (77.9)	118 (57.6)			106 (70.2)	86 (57.7)			112 (66.7)	80 (60.6)		
Class 2/3/4/5	21 (22.1)	87 (42.4)			45 (29.8)	63 (42.3)			56 (33.3)	52 (39.4)		
Clavien-Dindo Classification			12.27	0.031			7.65	0.177			4.10	0.535
Class 0	16 (16.8)	27 (13.2)			24 (15.9)	19 (12.8)			29 (17.3)	14 (10.6)		
Class 1	58 (61.1)	91 (44.4)			82 (54.3)	67 (45.0)			83 (49.4)	66 (50.0)		
Class 2	8 (8.4)	36 (17.6)			18 (11.9)	26 (17.4)			23 (13.7)	21 (15.9)		
Class 3	6 (6.3)	27 (13.2)			11 (7.3)	22 (14.8)			15 (8.9)	18 (13.6)		
Class 4	3 (3.2)	7 (3.4)			6 (3.97)	4 (2.7)			6 (3.6)	4 (3.0)		
Class 5	4 (4.2)	17 (8.3)			10 (6.6)	11 (7.4)			12 (7.1)	9 (6.8)		
T stage			7.34	0.062			5.89	0.117			5.87	0.118
1	5 (5.3)	11 (5.4)			10 (6.6)	6 (4.0)			13 (7.7)	3 (2.3)		
2	20 (21.1)	27 (13.2)			24 (15.9)	23 (15.4)			22 (13.1)	25 (18.9)		
3	60 (63.2)	122 (59.5)			97 (64.2)	85 (57.0)			101 (60.1)	81 (61.4)		
4	10 (10.5)	45 (22.0)			20 (13.2)	35 (23.5)			32 (19.0)	23 (17.4)		
N stage			6.48	0.090			1.53	0.677			0.29	0.961
0	65 (68.4)	111 (54.1)			93 (61.6)	83 (55.7)			100 (59.5)	76 (57.6)		
1	18 (18.9)	59 (28.8)			35 (23.2)	42 (28.2)			42 (25.0)	35 (26.5)		
2	12 (12.6)	32 (15.6)			22 (14.6)	22 (14.8)			24 (14.3)	20 (15.2)		
3	0 (0.0)	3 (1.5)			1 (0.7)	2 (1.34)			2 (1.19)	1 (0.76)		
M stage (presence; yes/no)			4.65	0.031			0.80	0.371			0.14	0.709
Yes	93 (97.9)	187 (91.2)			139 (92.1)	141 (94.6)			156 (92.9)	124 (93.9)		
No	2 (2.1)	18 (8.8)			12 (8.0)	8 (5.37)			12 (7.1)	8 (6.1)		

Table 3. Continued.

	NLR				PLR				LMR			
	≤2.41	>2.41	χ^2	*p*	≤195.60	>195.60	χ^2	*p*	≤2.94	>2.94	χ^2	*p*
	N = 95	N = 205			N = 151	N = 149			N = 168	N = 132		
Cancer stage			7.40	0.006			1.91	0.167			0.003	0.955
Stage 1/2	65 (68.4)	106 (51.7)			92 (60.9)	79 (53.0)			96 (57.1)	75 (56.8)		
Stage 3/4	30 (31.6)	99 (48.3)			59 (39.1)	70 (47.0)			72 (42.9)	57 (43.2)		
Differentiation			2.95	0.086			0.008	0.927			0.06	0.897
Well differentiated	65 (68.4)	119 (58.0)			93 (61.6)	91 (61.1)			102 (60.7)	82 (62.1)		
Poor differentiated	30 (31.6)	86 (42.0)			58 (38.4)	58 (38.9)			66 (39.3)	50 (37.9)		
Vascular invasion			1.27	0.261			0.85	0.356			2.49	0.114
No	63 (66.3)	122 (59.5)			97 (64.2)	88 (59.1)			97 (57.7)	88 (66.7)		
Yes	32 (33.7)	83 (40.5)			54 (35.8)	61 (40.9)			71 (42.3)	44 (33.3)		
Lymphatic invasion			1.12	0.291			0.06	0.801			0.83	0.361
No	59 (62.1)	114 (55.6)			86 (57.0)	87 (58.4)			93 (55.4)	80 (60.6)		
Yes	36 (37.9)	91 (44.4)			65 (43.0)	62 (41.6)			75 (44.6)	52 (39.4)		
Perineural invasion			0.42	0.516			0.47	0.420			2.83	0.090
No	63 (66.3)	128 (62.4)			99 (65.6)	92 (61.7)			100 (59.5)	91 (68.9)		
Yes	32 (33.7)	77 (37.6)			52 (34.4)	57 (38.3)			68 (40.5)	41 (31.1)		
Tumor size			1.98	0.159			2.15	0.143			0.045	0.831
≤5 cm	72 (75.8)	139 (67.8)			112 (74.2)	99 (66.4)			119 (70.8)	92 (69.7)		
>5 cm	23 (24.2)	66 (32.2)			39 (25.8)	50 (33.6)			49 (29.2)	40 (30.3)		
Perioperative blood transfusion			5.49	0.019			13.3	<0.001			1.19	0.276
No	89 (93.7)	172 (83.9)			142 (94.0)	119 (79.9)			143 (85.1)	118 (89.4)		
Yes	6 (6.3)	33 (16.1)			9 (6.0)	30 (20.1)			25 (14.9)	14 (10.6)		

NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; PLR, platelet-lymphocyte ratio; T, Tumor; N, Node; M, Metastasis. χ^2, Chi-square value.

Table 4. Comparison of patients based on SIS, NPS, mGPS, and PNI scores.

	SIS					NPS					mGPS					PNI			
	0	1	2	χ^2	p	0	1–2	3–4	χ^2	p	0	1	2	χ^2	p	≤32.10	>32.10	χ^2	p
	N = 15	N = 96	N = 189			N = 12	N = 145	N = 143			N = 86	N = 90	N = 124			N = 105	N = 195		
Sex				2.14	0.343				0.15	0.940				1.40	0.497			1.62	0.204
Female	7 (46.7)	41 (42.7)	66 (34.9)			5 (41.7)	56 (38.6)	53 (37.1)			30 (34.9)	32 (35.6)	52 (41.9)			45 (42.9)	69 (35.4)		
Male	8 (53.3)	55 (57.3)	123 (65.1)			7 (58.3)	89 (61.4)	90 (62.9)			56 (65.1)	58 (64.4)	72 (58.1)			60 (57.1)	126 (64.6)		
Age				6.40	0.040				5.74	0.057				5.00	0.082			6.72	0.009
≤60	7 (46.7)	36 (37.5)	48 (25.4)			5 (41.7)	52 (35.9)	34 (23.8)			29 (33.7)	33 (36.7)	29 (23.4)			22 (21.0)	69 (35.4)		
>60	8 (53.3)	60 (62.5)	141 (74.6)			7 (58.3)	93 (64.1)	109 (76.2)			57 (66.3)	57 (63.3)	95 (76.6)			83 (79.0)	126 (64.6)		
Neoadjuvant therapy				2.37	0.306				1.00	0.608				3.39	0.184			9.72	0.002
No	9 (60.0)	71 (74.0)	146 (77.2)			10 (83.3)	106 (73.1)	110 (76.9)			71 (82.6)	65 (72.2)	90 (72.6)			68 (64.8)	158 (81.0)		
Yes	6 (40.0)	25 (26.0)	43 (22.8)			2 (16.7)	39 (26.9)	33 (23.1)			15 (17.4)	25 (27.8)	34 (27.4)			37 (35.2)	37 (19.0)		
Clavien-Dindo Classification				1.05	0.593				0.87	0.649				1.47	0.481			21.06	<0.001
Class 0/1	8 (53.3)	60 (62.5)	124 (65.6)			9 (75.0)	94 (64.8)	89 (62.2)			59 (68.6)	58 (64.4)	75 (60.5)			49 (46.7)	143 (73.3)		
Class 2/3/4/5	7 (46.7)	36 (37.5)	65 (34.4)			3 (25.0)	51 (35.2)	54 (37.8)			27 (31.4)	32 (35.6)	49 (39.5)			56 (53.3)	52 (26.7)		
T stage				5.07	0.535				5.75	0.452				15.64	0.020			7.86	0.049
1	0 (0.0)	7 (7.3)	9 (4.8)			0 (0.00)	8 (5.52)	8 (5.59)			8 (9.30)	3 (3.33)	5 (4.03)			5 (4.76)	11 (5.64)		
2	4 (26.7)	17 (17.7)	26 (13.8)			2 (16.7)	28 (19.3)	17 (11.9)			16 (18.6)	12 (13.3)	19 (15.3)			13 (12.4)	34 (17.4)		
3	10 (66.7)	55 (57.3)	117 (61.9)			8 (66.7)	88 (60.7)	86 (60.1)			55 (64.0)	60 (66.7)	67 (54.0)			59 (56.2)	123 (63.1)		
4	1 (6.7)	17 (17.7)	37 (19.6)			2 (16.7)	21 (14.5)	32 (22.4)			7 (8.1)	15 (16.7)	33 (26.6)			28 (26.7)	27 (13.8)		
N stage				5.80	0.446				8.65	0.195				7.52	0.275			5.18	0.160
0	9 (60.0)	58 (60.4)	109 (57.7)			10 (83.3)	90 (62.1)	76 (53.1)			59 (68.6)	51 (56.7)	66 (53.2)			58 (55.2)	118 (60.5)		
1	6 (40.0)	22 (22.9)	49 (25.9)			2 (16.7)	35 (24.1)	40 (28.0)			17 (19.8)	27 (30.0)	33 (26.6)			24 (22.9)	53 (27.2)		
2	0 (0.00)	16 (16.7)	28 (14.8)			0 (0.0)	20 (13.8)	24 (16.8)			10 (11.6)	11 (12.2)	23 (18.5)			22 (21.0)	22 (11.3)		
3	0 (0.0)	0 (0.0)	3 (1.6)			0 (0.0)	0 (0.0)	3 (2.1)			0 (0.0)	1 (1.1)	2 (1.6)			1 (1.0)	2 (1.0)		
M stage (presence; yes/no)				0.04	0.980				5.69	0.058				3.08	0.214			3.77	0.052
No	14 (93.3)	90 (93.8)	176 (93.1)			10 (83.3)	140 (96.6)	130 (90.9)			82 (95.3)	86 (95.6)	112 (90.3)			94 (89.5)	186 (95.4)		
Yes	1 (6.7)	6 (6.3)	13 (6.9)			2 (16.7)	5 (3.45)	13 (9.09)			4 (4.65)	4 (4.44)	12 (9.68)			11 (10.5)	9 (4.62)		
Cancer stage				0.07	0.966				4.00	0.135				4.32	0.115			1.41	0.236
Stage 0–2	9 (60.0)	55 (57.3)	107 (56.6)			9 (75.0)	88 (60.7)	74 (51.7)			57 (66.3)	49 (54.4)	65 (52.4)			55 (52.4)	116 (59.5)		
Stage 3–4	6 (40.0)	41 (42.7)	82 (43.4)			3 (25.0)	57 (39.3)	69 (48.3)			29 (33.7)	41 (45.6)	59 (47.6)			50 (47.6)	79 (40.5)		

Table 4. Continued.

	SIS					NPS					mGPS					PNI			
	0	1	2	χ^2	p	0	1–2	3–4	χ^2	p	0	1	2	χ^2	p	≤32.10	>32.10	χ^2	p
	N = 15	N = 96	N = 189			N = 12	N = 145	N = 143			N = 86	N = 90	N = 124			N = 105	N = 195		
Differentiation				1.60	0.450				0.48	0.785				0.10	0.951			0.80	0.371
Well differentiated	10 (66.7)	54 (56.2)	120 (63.5)			8 (66.7)	91 (62.8)	85 (59.4)			53 (61.6)	54 (60.0)	77 (62.1)			68 (64.8)	116 (59.5)		
Poor differentiated	5 (33.3)	42 (43.8)	69 (36.5)			4 (33.3)	54 (37.2)	58 (40.6)			33 (38.4)	36 (40.0)	47 (37.9)			37 (35.2)	79 (40.5)		
Vascular invasion				6.77	0.034				11.47	0.003				6.41	0.041			10.08	0.002
No	11 (73.3)	68 (70.8)	106 (56.1)			9 (75.0)	102 (70.3)	74 (51.7)			62 (72.1)	55 (61.1)	68 (54.8)			52 (49.5)	133 (68.2)		
Yes	4 (26.7)	28 (29.2)	83 (43.9)			3 (25.0)	43 (29.7)	69 (48.3)			24 (27.9)	35 (38.9)	56 (45.2)			53 (50.5)	62 (31.8)		
Lymphatic invasion				6.16	0.046				11.8	0.003				8.18	0.017			6.68	0.010
No	11 (73.3)	63 (65.6)	99 (52.4)			9 (75.0)	96 (66.2)	68 (47.6)			60 (69.8)	51 (56.7)	62 (50.0)			50 (47.6)	123 (63.1)		
Yes	4 (26.7)	33 (34.4)	90 (47.6)			3 (25.0)	49 (33.8)	75 (52.4)			26 (30.2)	39 (43.3)	62 (50.0)			55 (52.4)	72 (36.9)		
Perineural invasion				1.86	0.396				4.93	0.085				6.23	0.044			4.96	0.026
No	12 (80.0)	61 (63.5)	118 (62.4)			10 (83.3)	98 (67.6)	83 (58.0)			63 (73.3)	58 (64.4)	70 (56.5)			58 (55.2)	133 (68.2)		
Yes	3 (20.0)	35 (36.5)	71 (37.6)			2 (16.7)	47 (32.4)	60 (42.0)			23 (26.7)	32 (35.6)	54 (43.5)			47 (44.8)	62 (31.8)		
Tumor size				11.64	0.003				16.35	<0.001				5.78	0.056			1.65	0.199
≤5 cm	13 (86.7)	78 (81.2)	120 (63.5)			11 (91.7)	115 (79.3)	85 (59.4)			68 (79.1)	64 (71.1)	79 (63.7)			69 (65.7)	142 (72.8)		
>5 cm	2 (13.3)	18 (18.8)	69 (36.5)			1 (8.3)	30 (20.7)	58 (40.6)			18 (20.9)	26 (28.9)	45 (36.3)			36 (34.3)	53 (27.2)		
Perioperative blood transfusion				0.30	0.861				4.86	0.088				3.87	0.144			5.22	0.022
No	13 (86.7)	85 (88.5)	163 (86.2)			11 (91.7)	132 (91.0)	118 (82.5)			75 (87.2)	83 (92.2)	103 (83.1)			85 (81.0)	176 (90.3)		
Yes	2 (13.3)	11 (11.5)	26 (13.8)			1 (8.3)	13 (9.0)	25 (17.5)			11 (12.8)	7 (7.78)	21 (16.9)			20 (19.0)	19 (9.74)		

NPS, Naples Prognostic Score; mGPS, Modified Glasgow Prognostic Score; SIS, Systemic Inflammation Score; PNI, Prognostic Nutritional Index.

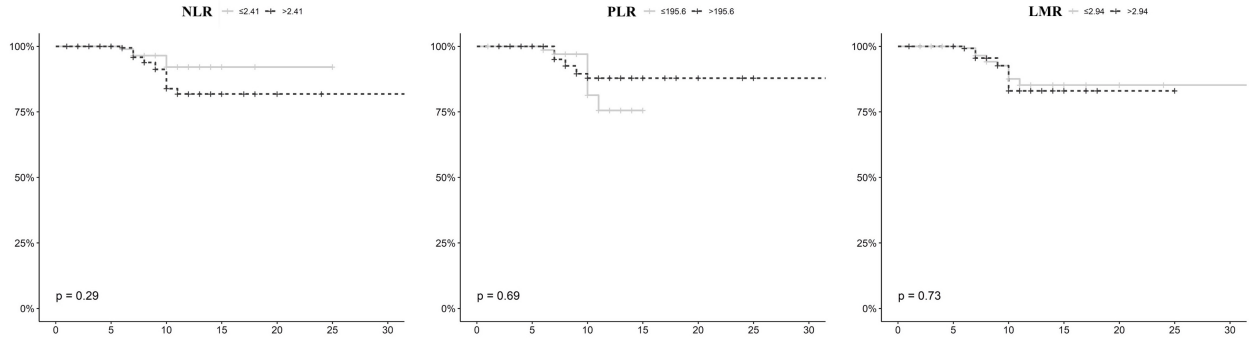

Fig. 1. Kaplan-Meier analyses for the length of hospital stay based on neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio (LMR) values (x-axis: percent survival; y-axis: days).

Prognostic Value of NLR, PLR, LMR, SIS, NPS, mGPS, and PNI

Analyses of the postoperative first 30-day length of stay in the hospital are shown in Figs. 1,2. There was no significant difference in Kaplan-Meier curves between groups based on cut-off values for NLR, PLR, and LMR (*p*-values: 0.29, 0.69, and 0.73, respectively). In analyses for SIS, mGPS, and PNI scores, patients with low scores were significantly discharged earlier (*p*-values: 0.0073, <0.0001, and <0.0001, respectively). No significant difference was found for PNI score (*p*-value: 0.61).

Mortality

In the first 30-day survival, no significant differences were found in age and gender. Disease stage, NLR, PLR, and LMR had no impact on the first 30-day survival. Additionally, neoadjuvant chemoradiotherapy, SIS, mGPS, NPS, and PNI scores had a significant impact on the first 30-day survival (Table 5).

Discussion

The relationship between cancer and inflammation has become clearer, with a study showing the presence of inflammatory cells in samples taken from tumor cells and the development of tumors in chronic inflammation areas [20]. The connection between malnutrition, carcinogenesis, tumor growth, and cancer progression with systemic inflammation has been shown in many cancers, including CRC. This has led to the exploration of biomarkers and the development of a formulation for prognostic scoring systems [17,20,21]. Inflammation associated with cancer and cell-mediated immune responses play vital roles in the development and progression of cancer. These processes are largely dependent on neutrophils, lymphocytes, and monocytes. Neutrophilia, monocytosis, and lymphopenia are non-specific responses to cancer-related inflammation and immune reactions, and they are associated with poor survival in malignancies. Neutrophils primarily interact with tumor cells by producing cytokines and chemokines, thereby regulating tumor cell proliferation, angiogenesis, and metastasis [22].

NLR is considered a balance between the inflammatory state of the tumor and the anti-tumor immune status. Studies showed that NLR is a significant prognostic indicator in colon cancer and a vital determinant indicating the likelihood of recurrence [23,24]. A study showed that right and left colon cancers are different from each other and that NLR can be considered a predictive factor in right colon cancer, while it may not be a predictive factor in left colon cancer and concluded that NLR is higher in stage II compared to stage I [25]. This result suggests that preoperatively low NLR in the early stages may contribute to the patient's treatment plan. Platelets facilitate tumor growth by separating the tumor from the primary site and hiding tumor cells from the immune system, thereby promoting tumor proliferation and contributing to distant metastasis [10,26]. Additionally, leukocytes infiltrating the tumor, including neutrophils and monocytes, play a significant role in tumor development and progression [27]. In a previous study, in patients with stage II colon cancer undergoing curative resection, LMR is a prognostic indicator and increased LMR is associated with improved survival [28]. In our study, NLR and PLR values were significantly higher in patients with the Clavien-Dindo Classification of two or higher points, while no significant difference was observed in LMR values. There was no significant difference in postoperative 30-day mortality among groups for NLR, PLR, and LMR.

Both CRP and albumin are acute-phase proteins and with an inflammatory stimulus, CRP levels increase, while albumin levels decrease in response to inflammation [29]. The independence of GPS as a prognostic factor has been shown in a study conducted on both operable and inoperable cancer patients in unselected cohorts [30]. In our study, a significant association was found between a low mGPS and shorter postoperative hospital stay. Additionally, a significant relationship was observed between a high mGPS score and mortality within the first 30 days.

This study shows a correlation between NPS and poorer prognosis. Despite being an excellent indicator of systemic inflammation and malnutrition, serum albumin lev-

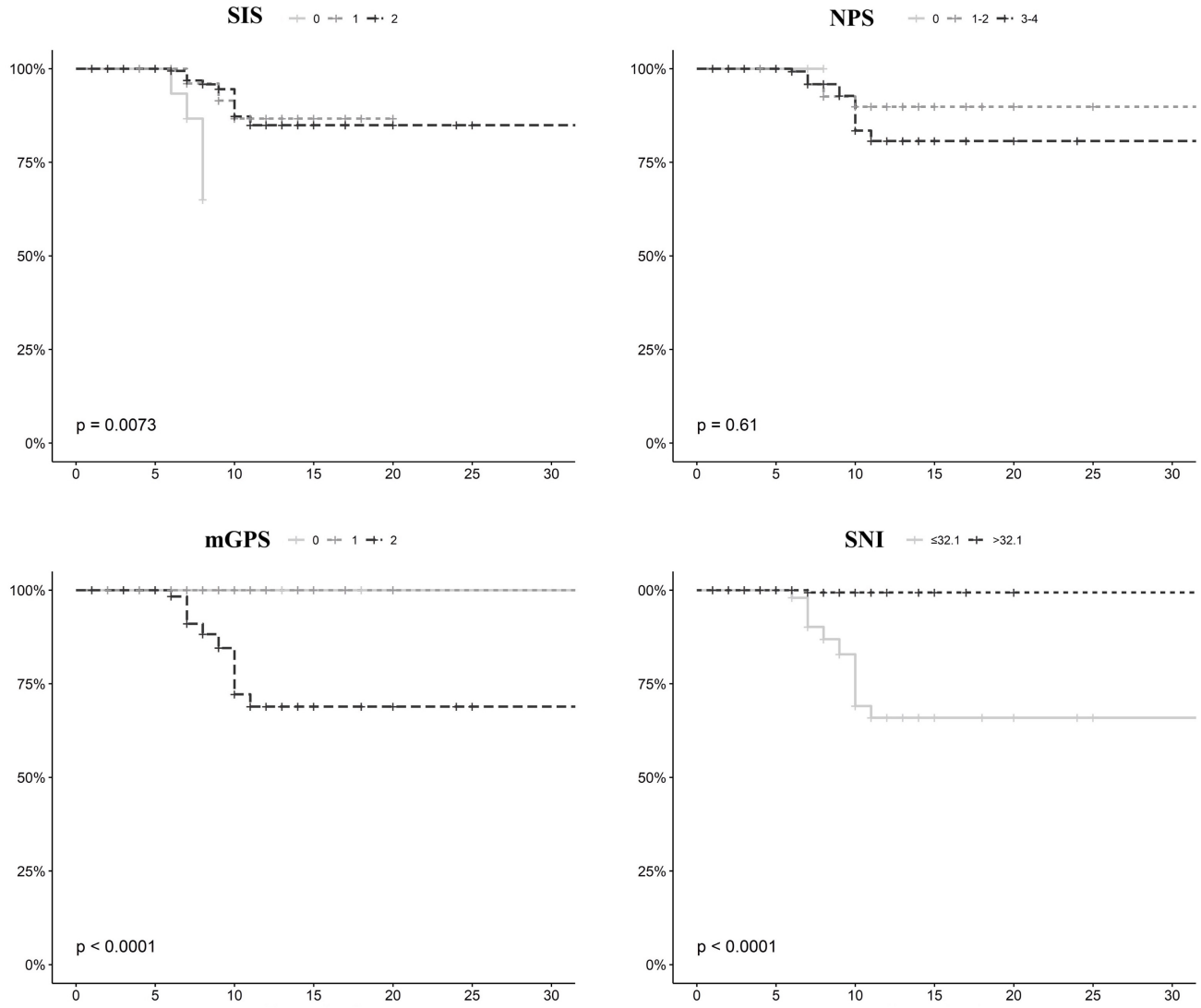

Fig. 2. Kaplan-Meier analyses for the length of hospital stay based on PNI, Naples Prognostic Score (NPS), Modified Glasgow Prognostic Score (mGPS) and SIS values (x-axis: percent survival; y-axis: days).

els are known to be influenced by liver functions, despite being utilized by many scoring systems [5,8]. Hypocholesterolemia affects mobility of cell surface receptors and their capacity to transmit transmembrane signals, and additionally low cholesterol levels have been reported to correlate with poorer prognosis in solid tumors [13,14]. NPS is an independent indicator of severe postoperative complications, and its relation to tumor recurrence and disease-free survival has also been reported [13].

A novel prognostic score, SIS, is a robust prognostic indicator for clear cell renal cell carcinoma and colorectal CRC [21]. However, the lack of widely accepted cut-off values has limited its acceptance. Therefore, it is necessary to determine the optimal cut-off value for serum albumin concentration and LMR, which is most closely associated with prognosis, depending on the characteristics of the target, such as cancer type and stage. The optimal threshold value for SIS should be investigated in advanced studies that include a broad composite population of cancer types, stages, and treatments. In our study, a low SIS was associated with a shorter postoperative hospital stay, while a high SIS was associated with increased mortality.

The initial purpose of PNI was to assess the nutritional and immunological status to predict short-term postoperative outcomes in patients with gastrointestinal malignancies. Increasing evidence indicates that PNI has a prognostic impact on the long-term survival outcomes of malignant carcinoma patients. Impaired PNI score an independent factor has been linked to worse median overall survival time and aggressive histopathological features [18]. In our study, a low PNI was associated with a shorter postoperative hospital stay, while a high PNI was associated with increased mortality.

This study has some limitations. First, this was a single center retrospective study with rather small sample size. Second, the inclusion of both colon and rectal cancer patients

Table 5. Prognostic parameters for postoperative mortality in the first 30 days.

	Mortality		χ^2	p
	No	Yes		
	N = 279	N = 21		
Sex			0.21	0.648
Female	107 (38.4)	7 (33.3)		
Male	172 (61.6)	14 (66.7)		
Age			0.033	0.855
≤60	85 (30.5)	6 (28.6)		
>60	194 (69.5)	15 (71.4)		
Neoadjuvant therapy			21.44	<0.001
No	219 (78.5)	7 (33.3)		
Yes	60 (21.5)	14 (66.7)		
SIS			5.86	0.007
0	12 (4.3)	3 (14.3)		
1	91 (32.6)	5 (23.8)		
2	176 (63.1)	13 (61.9)		
NPS			31.97	<0.001
0	12 (4.3)	0 (0.0)		
1	50 (17.9)	1 (4.8)		
2	87 (31.2)	7 (33.3)		
3	94 (33.7)	1 (4.8)		
4	36 (12.9)	12 (57.1)		
mGPS			32.05	<0.001
0	86 (30.8)	0 (0.0)		
1	90 (32.3)	0 (0.0)		
2	103 (36.9)	21 (100)		
PNI			36.02	<0.001
≤32.10	85 (30.5)	20 (95.2)		
>32.10	194 (69.5)	1 (4.8)		
Clavien-Dindo Classification			40.14	<0.001
Class 0–1	192 (64.0)	0 (0.00)		
Class 2–5	87 (36.0)	21 (100.0)		
Cancer stage			0.0002	0.989
Stage 1/2	159 (57.0)	12 (57.1)		
Stage 3/4	120 (43.0)	9 (42.9)		
NLR			1.66	0.198
≤2.41	91 (32.6)	4 (19.0)		
>2.41	188 (67.4)	17 (81.0)		
LMR			0.01	0.913
≤2.94	156 (55.9)	12 (57.1)		
>2.94	123 (44.1)	9 (42.9)		
PLR			0.07	0.796
≤195.60	141 (50.5)	10 (47.6)		
>195.60	138 (49.5)	11 (52.4)		

NPS, Naples Prognostic Score; mGPS, Modified Glasgow Prognostic Score; SIS, Systemic Inflammation Score; PNI, Prognostic Nutritional Index; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; PLR, platelet-lymphocyte ratio, χ^2, Chi-square value.

may show different prognostic features since rectal tumor location has been shown as an independent prognostic factor for worse disease-free survival [13].

Conclusions

In conclusion, in this study it appears that our new method may offer improvements over existing models in terms of efficiency and accuracy. Further research will be essential to fully ascertain the potential and scope of these advancements in the field of computational biology.

Availability of Data and Materials

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

Author Contributions

CA, NCA and AG designed the study, CA and NCA conducted the data collection, CA, NCA and AG analyzed the data, CA and NCA conducted the manuscript writing, AG provided supervision. All authors revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and ethical approval was obtained. The study commenced with the approval of the Clinical Research Ethics Committee of Kocaeli Derince Training and Research Hospital under decision number 2022/135. Written content was waived with the approval of the Clinical Research Ethics Committee of Kocaeli Derince Training and Research Hospital.

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Conflict of Interest

The authors declare no conflict of interest.

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