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Significance of preoperative blood tests in the prognosis of colorectal cancer: A prospective, multicenter study from Hungary

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Abstract

Background: The focus of this study was to analyze the prognostic value of different combinations of inflammatory and coagulation factors using preoperative blood and to appraise the clinical importance of these biomarkers in colorectal cancer patients.

Methods: A prospective, multicenter study included patients undergoing radical colorectal surgery in three county hospitals. Inflammatory and coagulation markers were analyzed preoperatively.

Results: Two hundred and one patients were included. We examined patients based on their tumor localization. Colon cancer group involved patients with the tumor localized in the colon ($n = 105$, 52.24%) and rectal cancer group the patients with the tumor in the rectum ($n = 96$, 47.76%). Examining coagulation factors, univariate Cox analysis of colon cancer patients showed that activated partial thromboplastin time ($p = 0.020$) was significantly associated with overall survival, but we could not prove it in multivariate analysis. In colon cancer patients, neutrophil-to-lymphocyte ratio (NLR, $p < 0.001$) was positively correlated with tumor size and had significant association ($\chi^2 = 5.48$, $p = 0.019$, df = 1) with perineural invasion. Univariate and multivariate Cox analysis of colon cancer patients showed that NLR ($p = 0.011$ and $p = 0.048$) was significantly associated with disease-free survival (DFS).

Conclusion: NLR was proved to be an independent prognostic factor for DFS in patients with non-metastatic colon cancer. NLR might help to recognize the high-risk patients between patients with the same tumor-node-metastasis stage and could help with the decision on adjuvant chemotherapy. Since the biomarkers in preoperative blood tests are habitually evaluated, NLR could be an inexpensive prognostic marker that can be easily assessed in clinical practice.

KEYWORDS
biomarker, colorectal cancer, laboratory, leukocyte, neutrophil, prognostic, survival

1 | INTRODUCTION

Colorectal cancer (CRC) is one of the main causes of cancer-related mortality worldwide, with increasing incidence and mortality and has the highest incidence rate in Europe.[1] In Hungary, CRC is the second source of cancer-related death in both males and females.[2] To decrease mortality rates, there have been numerous advancements in therapy procedures in the past few years, but CRC survival remained unsatisfactory. With regard to the frequency and mortality of this disease, it is necessary to find new prognostic factors that will assist to improve clinical outcomes with individualized treatment.

Surgical resection is deemed the only curative therapy for CRC. Laparoscopic surgery has significant role in the treatment of CRC. With the developing laparoscopic skills, this technique has comparable oncological outcomes in both colon and rectum cancer besides the well-known benefits of laparoscopy, such as lower morbidity rate and shorter hospital stay.[3,4] Tumor-node-metastasis (TNM) staging system is a commonly used staging system to predict prognosis for patients with CRC.[5] However, even if patients who are in the same stage and the same treatments are used, survival outcomes differ widely. It would be suitable to use a better system to identify the high-risk subgroups to predict the prognosis and optimize therapeutic strategies for patients undergoing curative resection of CRC.

In the past few years, it has appeared that blood biomarkers are associated with the prognosis of CRC. These biomarkers are effortlessly obtained from a preoperative routine blood test, so they have gained attention. It is known that inflammation plays an important role in carcinogenesis; neutrophils, lymphocytes, platelets, and monocytes are involved in tumor progression.[6,7] Lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and Glasgow prognostic score (GPS) represent systematic inflammatory responses and have great influence on clinical outcomes in CRC.[6–13] LMR can be calculated as the lymphocyte count divided by the monocyte count, and NLR and PLR can be calculated as the neutrophil count or platelet count divided by the lymphocyte count.[14] GPS can be calculated as score 2, when the patient has both an elevated level of C-reactive protein (CRP >5.0 mg/L) and hypoalbuminemia (<34 g/L), score 1, when the patient has only one of the above, and when the patient has neither of these two abnormalities, the score is 0. Besides the inflammatory parameters, we also investigated the relationship between coagulation factors and survival. Although it is well-known since 1865 that there is an association between malignancies and hypercoagulability, this research topic still has a great importance.[15] The relationship between coagulation factors and the tumor may play a significant role in either tumor prevention and treatment or can help predict recurrence and prognosis in patients with CRC.[16–18]

The objective of our prospective, multicenter study was to analyze the prognostic values of inflammatory and coagulation markers in CRC patients—who underwent radical resection—and to identify an accurate prognostic indicator to predict clinical outcomes and optimize therapeutic strategies.

2 | MATERIALS AND METHODS

2.1 | Study design

We prospectively analyzed 201 patients with colorectal adenocarcinoma who underwent radical surgeries at our institutions between 01 of September 2017 and 15 December 2020. The three county hospitals were the following: Department of Surgery, Moritz Kaposi General Hospital, Kaposvár, Hungary, Department of General Surgery, University of Debrecen, Kenézy Gyula Teaching Hospital, Debrecen, Hungary and Department of Surgery, Borsod-Abaúj-Zemplén County Hospital, and University Teaching Hospital, Miskolc, Hungary.

2.2 | Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) patients were older than 18 years, (2) patients had histopathologically confirmed CRC, and (3) laboratory tests, computed tomography, magnetic resonance imaging (MRI, in case of rectal cancer), and colonoscopy were achieved before surgery.

The exclusion criteria were as follows: (1) patients with distant metastasis, (2) patients who received anti-inflammatory medicine (including antibiotics) or immunosuppressive treatment (including steroids) within 3 months before surgery, or who had chronic inflammatory disorder including infection and autoimmune diseases, (3) history of thrombosis or embolism, (4) history of recurrence or other malignant tumors or hematological disorder, (5) patients who received oral anti-thrombotic drugs, (6) unresectable tumor was revealed under surgery, or (7) patients lost to follow-up.

2.3 | Clinical and laboratory assessment and follow-up

The preoperative routine blood test data achieved within 1 month before surgery included leukocyte count (G/L), neutrophils (G/L), lymphocytes (G/L), monocytes (G/L), platelet count (G/L), NLR, LMR, and PLR. D-dimer (μg/L), prothrombin time (PT) international normalized ratio (INR), fibrinogen (g/L), activated partial thromboplastin time (aPTT, s), total protein (g/L), and albumin (g/L) were also obtained. In addition, CRP (mg/L) and GPS were investigated. The resected CRCs were histopathologically classified following the eighth edition of the TNM classification. Besides the laboratory and histological results, we also investigated tumor size, body mass index (BMI, kg/m^2), smoking habits, type of surgery (laparoscopic or open), type of anastomosis (hand-sewn or instrumental), operating time, the integrity of the mesorectum following total mesorectal excision and the integrity of mesocolon following complete mesocolic excision, postoperative complications, and oncological therapies. Patients were followed-up every 6 months.

2.4 | Statistical analysis

Categorical variables were presented as a frequency or rate and were compared using the Chi-square test. Mann-Whitney *U* test or Student's *t* test was applied to compare and analyze the quantitative data of two groups. One-way ANOVA or the Kruskal-Wallis *H* test was used to compare the variables of more than two groups. The Spearman's rank correlation coefficient was applied to evaluate the correlation between two variables. The Kaplan-Meier estimate method with a log-rank test was used to accomplish univariate analysis. The hazard ratio and 95% confidence intervals estimated from the univariate and multivariate Cox regression analysis were detailed. Disease-free survival (DFS) was determined as the time from the date of surgery to the date of the detection of recurrence, death, or last follow-up. Overall survival (OS) was determined as the time from the date of surgery to the date of death or last follow-up. Intercooled Stata v 13.0 was used for all statistical analyses. The *p*-value equal or less than 0.05 was considered statistically significant.

2.5 | Ethics approval

The study protocol was approved by the Ethics Review Committee of Moritz Kaposi General Hospital, the Ethics Review Committee of University of Debrecen, Kenézy Gyula Teaching Hospital, and the Ethics Review Committee of Borsod-Abaúj-Zemplén County Hospital and University Teaching Hospital. All procedures performed were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

2.6 | Consent to participate

Oral and written informed consent was obtained from all patients.

3 | RESULTS

201 patients were enrolled in our prospective study (Figure). Baseline characteristics of the patients are demonstrated in Table 1. There were 119 (59.20%) males and 82 (40.80%) females, with a median age of 66 years (range 35–91). The median follow-up period was 24 months (range 7–40). During the follow-up period, 8 (3.98%) patients died. 12 (5.97%) patients experienced tumor spreading during the follow-up period. Patients with TNM stages I, II, and III accounted for 24.21%, 42.11%, and 33.68%, respectively. Of all the patients, 105 (52.24%) tumors were located in the colon, and 96 (47.76%) tumors were located in the

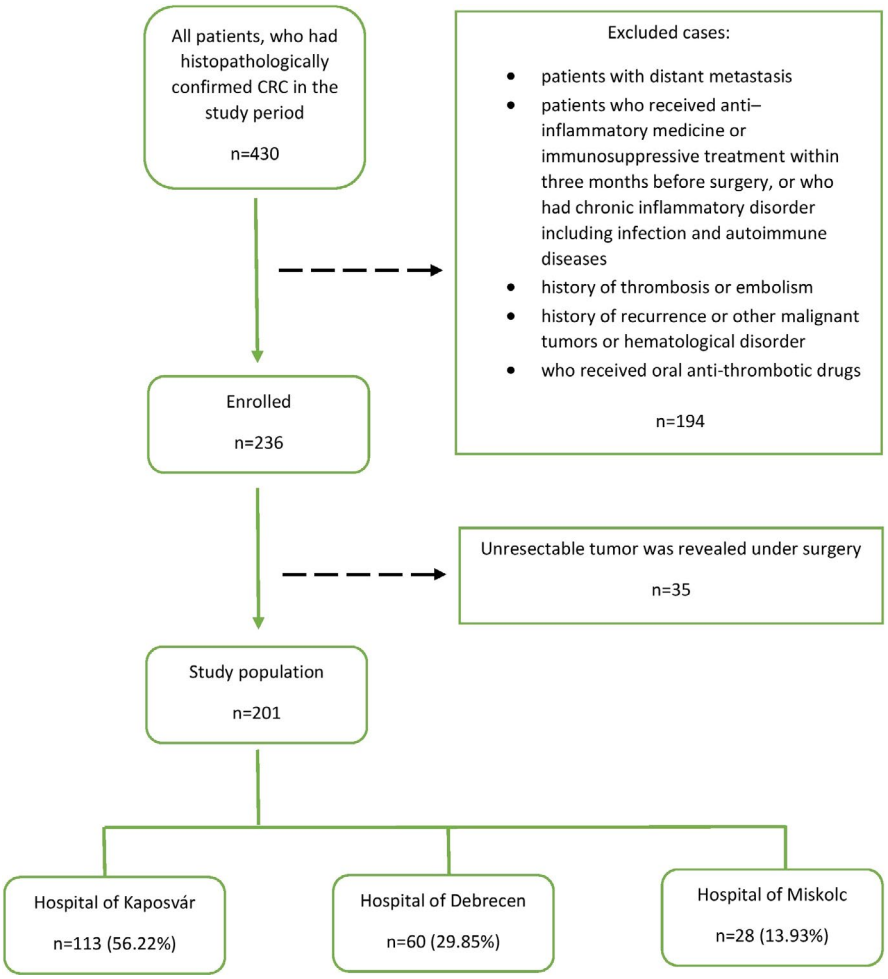

FIGURE 1 Flow chart of the multicentre study population from Hungary

TABLE 1 Patients demographics

Age	66 years	35–91
Sex		
Male	119	59.20%
Female	82	40.80%
BMI (kg)	27	16–42
Smoking		
Yes	40	19.90%
No	161	80.10%
Type of surgery		
Open	114	56.72%
Laparoscopic	87	43.28%
Operating time (min)	151.35	55–415
Type of anastomosis		
Hand-sawn	60	36.59%
Instrumental	104	63.41%
Tumor location		
Colon	105	52.24%
Rectum	96	47.76%
Histological grade		
I (well differentiated)	36	18.95%
II (moderately differentiated)	117	61.58%
III (poorly differentiated)	16	8.42%
Other	21	11.05%
T		
1	15	7.46%
2	41	21.47%
3	110	57.59%
4	25	13.09%
N		
0	129	66.49%
1	43	22.16%
2	22	11.34%
Stage		
I	46	24.21%
II	80	42.11%
III	64	33.68%
Preoperative laboratory data		
Leukocyte count (G/L)	6.97	3.13–18.76
Neutrophil count (G/L)	4.61	1.75–15.24
Lymphocyte count (G/L)	1.42	0.36–4.12
Monocyte count (G/L)	0.56	0.11–1.60
Platelet count (G/L)	276.00	58–723
NLR	3.28	0.59–20.09
LMR	2.43	0.87–8.86
PLR	194.09	61.70–1042.65
D-dimer (μg/L)	500.00	110–10,000
PT (INR)	1.01	0.83–1.21
Fibrinogen (g/L)	3.60	1.83–7.75
aPTT (s)	29.00	20–45
Total protein (g/L)	71.00	52–99
Albumin (g/L)	44.00	25–53
CRP (mg/L)	4.00	0.30–253
GPS	0	0–2
Postoperative complications	36	17.91%
Anastomosis insufficiency	5	3.05%
Neoadjuvant oncological therapy	83	41.29%
Adjuvant oncological therapy	122	60.70%

Abbreviations: aPTT, activated partial thromboplastin time; BMI, body mass index; CRP, C-reactive protein; GPS, Glasgow prognostic score; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PT, prothrombin time.

rectum. The mean values of LMR were 2.43 (0.87–8.86), NLR 3.28 (0.59–20.09), PLR 194.09 (61.70–1042.65), lymphocyte count 1.42 G/L (0.36–4.12), monocyte count 0.56 G/L (0.11–1.60), neutrophil count 4.61 G/L (1.75–15.24), aPTT 29 s (20–45), and D-dimer levels were 500 μg/L (110–10,000), respectively. Of the 201 patients included in the current study, 83 (41.29%) and 122 (60.70%) underwent neoadjuvant or adjuvant chemotherapy with 5-fluorouracil (5-FU)-based regimens, such as 5-FU plus leucovorin (de Gramont), 5-FU plus leucovorin with oxaliplatin (FOLFOX), or irinotecan (FOLFIRI).

The LMR, NLR, and PLR optimal cutoff levels were calculated with receiver operating characteristic curve analysis as the maximal Youden Index for both DFS (3.21, 3.96, 206.62) and OS (3.61, 3.06, 176.82). For other laboratory parameters, the reference value between normal and abnormal data was chosen as cutoff points, for non-laboratory parameters it was the median.

We examined our patients based on their tumor localization. Colon cancer group involved the patients with the tumor localized in the colon ($n = 105$, 52.24%) and rectal cancer group involved the patients with the tumor in the rectum ($n = 96$, 47.76%). In terms of colon cancer patients, NLR ($p < 0.001$), PLR ($p < 0.001$), aPTT ($p = 0.007$), fibrinogen ($p < 0.001$) levels, and GPS ($p < 0.001$) were all positively correlated with tumor size. LMR ($p = 0.003$) and albumin ($p < 0.001$) were negatively correlated with tumor size. In the rectal cancer group, LMR ($p = 0.016$) and fibrinogen ($p = 0.007$) were positively correlated with tumor size. There were no statistically significant correlation between PT (INR) or D-dimer and tumor size in either group; however, D-dimer levels were positively correlated with age both in the colon ($p < 0.001$) and the rectal cancer group ($p = 0.005$).

Examining patients with colon cancer, the Kruskal-Wallis H test showed significant association of NLR ($\chi^2 = 5.48$, $p = 0.019$, df = 1), GPS ($\chi^2 = 6.41$, $p = 0.011$, df = 1), and aPTT ($\chi^2 = 13.88$, $p < 0.001$, df = 1) with perineural invasion. Significant association was revealed between CRP and T stage ($\chi^2 = 12.41$, $p = 0.006$, df = 3). Albumin had significant effect on T stage ($\chi^2 = 17.08$, $p < 0.001$,

TABLE 2 Univariate and multivariate analysis of prognostic factors for DFS in colon cancer group using Cox proportional hazard model

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Age (≤65/>65 years)	1.01 (0.91–1.11)	0.916	—	—
Tumor size (≤3.3/>3.3 cm)	0.95 (0.57–1.58)	0.832	—	—
T stage (Tis–2/T3–4)	12.83 (1.41–117.05)	**0.024**	39.72 (0.99–1579.95)	**0.050**
N stage (−/+)	2.08 (0.63–6.85)	0.230	—	—
Vascular invasion (−/+)	2.66 (0.37–18.89)	0.328	—	—
Perineural invasion (−/+)	4.20 (0.59–29.86)	0.151	—	—
Lymphocyte count (≤5/>5 G/L)	0.37 (0.05–2.64)	0.318	—	—
Monocyte count (≤1/>1 G/L)	1.54 (0.02–114.56)	0.843	—	—
Neutrophil count (≤8.5/>8.5 G/L)	1.50 (1.07–2.10)	**0.018**	—	—
NLR (≤3.96/>3.96)	1.24 (1.05–1.46)	**0.011**	1.35 (1.00–1.81)	**0.048**
PLR (≤206.62/>206.62)	1.00 (0.99–1.01)	0.089	—	—
GPS (≤1/>1)	2.72 (0.58–12.68)	0.203	—	—
CRP (≤5/>5 mg/L)	1.00 (0.97–1.03)	0.915	—	—
aPTT (≤29/>29 s)	1.09 (0.92–1.29)	0.340	—	—
Fibrinogen (≤3/>3 g/L)	1.68 (0.88–3.21)	0.114	—	—
D-dimer (≤500/>500 μg/L)	1.00 (0.99–1.00)	0.460	—	—
Albumin (≤48/>48 g/L)	0.85 (0.74–0.98)	**0.021**	0.88 (0.71–1.08)	0.228
Adjuvant therapy (−/+)	3.03 (0.32–29.21)	0.337	—	—

Note: Bold values indicate significant differences ($p \leq 0.05$).

Abbreviations: aPTT, activated partial thromboplastin time; CI, confidence interval; CRP, C-reactive protein; DFS, disease-free survival; GPS, Glasgow prognostic score; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

df = 3) as well. CRP ($\chi^2 = 7.16$, $p = 0.028$, df = 2), aPTT ($\chi^2 = 6.78$, $p = 0.034$, df = 2), D-dimer ($\chi^2 = 8.78$, $p = 0.012$, df = 2), and albumin ($\chi^2 = 10.27$, $p = 0.006$, df = 2) were significantly associated with grade in the colon cancer group.

In terms of patients with rectal cancer, the Kruskal-Wallis H test showed significant association of D-dimer ($\chi^2 = 4.52$, $p = 0.033$, df = 1) with vascular invasion. There was significant association between platelet count ($\chi^2 = 11.14$, $p = 0.011$, df = 3), CRP ($\chi^2 = 14.05$, $p = 0.003$, df = 3), albumin ($\chi^2 = 10.69$, $p = 0.014$, df = 3), GPS ($\chi^2 = 15.95$, $p = 0.001$, df = 3), and T stage. APTT ($\chi^2 = 10.37$, $p = 0.006$, df = 2) and albumin ($\chi^2 = 7.37$, $p = 0.025$, df = 2) were significantly associated with grade in the rectal cancer group. We have not found significant correlation between D-dimer and N stage neither in the colon cancer group ($p = 0.230$), nor in the rectal cancer group ($p = 0.278$).

We examined DFS and OS in the two groups separately. In the colon cancer group, we performed univariate and multivariate Cox regression analysis for DFS (Table 2). NLR ($p < 0.001$) was significantly associated with DFS also in Kaplan-Meier log-rank analysis (Figure 2). The results of OS univariate and multivariate Cox regression analysis in colon cancer group were presented in Table 3. In multivariate analysis, none of the variables were significantly associated with OS.

The results of DFS and OS univariate Cox regression analysis in rectal cancer group were presented in Table 4. None of the variables were significant.

4 | DISCUSSION

In terms of coagulation factors, our multicenter, prospective study showed that fibrinogen levels in both groups and aPTT levels in the colon cancer group were positively correlated with tumor size. Current studies have revealed that elevated plasma fibrinogen plays a significant role in malignant behaviors of several tumors through inhibiting the elimination of cancer cells mediated by natural killer cells or cytotoxic cells.[19–21] As our results show, D-dimer levels were positively correlated with age in CRC patients. In colon cancer patients, D-dimer levels were significantly correlated with grade, and in terms of rectal cancer, D-dimer levels were associated with vascular invasion. Lee et al. examined the significance of coagulation factors such as PT, aPTT, fibrinogen, and D-dimer. Higher fibrinogen,

PT, or platelet count meant larger tumor sizes, and their study also emphasized that elongated PT and high D-dimer levels meant worse survival.[22] Much research has been conducted concerning the correlation between D-dimer levels and survival, even prospective ones.[23–27] Oya et al. and Lu et al. also reported that higher preoperative D-dimer levels meant significantly shorter postoperative survival even after curative resection, but we could not prove that.[28,29]

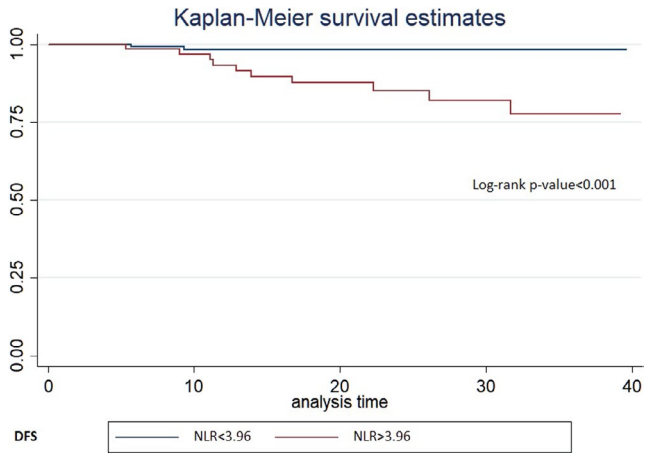

FIGURE 2 Kaplan-Meier curve for disease-free survival in colon cancer group

In terms of inflammatory factors, the GPS was positively correlated with tumor size and was associated with perineural invasion in our colon cancer patients. In rectal cancer patients, GPS was not correlated with tumor size, but was significantly associated with T stage. According to Choi et al., GPS was also significantly correlated with tumor size, as we experienced in our colon cancer patients, but they could not prove the significance with TNM stage, as we demonstrated in terms of T stage in rectal cancer patients.[13]

Few studies have been published in correlation of CRC and LMR, even less prospective ones. Stotz et al. reported that LMR with low lymphocyte and high monocyte count indicates insufficient antitumor immune response. They also found that low LMR patients did not benefit from 5-FU-based adjuvant chemotherapy.[30] While our results showed significant association between tumor size and LMR in CRC patients, we excluded LMR from further statistical analysis due to inconsistency between the two groups.

TABLE 3 Univariate and multivariate analysis of prognostic factors for OS in colon cancer group using Cox proportional hazard model

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Age (≤65/>65 years)	1.01 (0.93–1.09)	0.776	—	—
Gender (male/female)	0.65 (0.12–3.57)	0.623	—	—
Tumor size (≤3.3/>3.3 cm)	0.65 (0.37–1.17)	0.150	—	—
T stage (Tis–2/T3–4)	0.82 (0.29–2.24)	0.694	—	—
N stage (−/+)	0.26 (0.04–1.82)	0.175	—	—
Vascular invasion (−/+)	0.53 (0.62–4.52)	0.559	—	—
Lymphovascular invasion (−/+)	0.45 (0.05–3.83)	0.462	—	—
Perineural invasion (−/+)	0.64 (0.07–5.55)	0.689	—	—
Lymphocyte count (≤5/>5 G/L)	2.65 (1.01–6.99)	**0.048**	1.59 (0.57–4.46)	0.379
Monocyte count (≤1/>1 G/L)	72.07 (2.67–1942.26)	**0.011**	16.45 (0.42–639.38)	0.134
Neutrophil count (≤8.5/>8.5 G/L)	0.93 (0.56–1.56)	0.786	—	—
NLR (≤3.06/>3.06)	0.57 (0.25–1.31)	0.185	—	—
PLR (≤176.82/>176.82)	0.96 (0.97–1.00)	0.114	—	—
GPS (≤1/>1)	0.43 (0.09–2.11)	0.296	—	—
CRP (≤5/>5 mg/L)	0.88 (0.71–1.10)	0.268	—	—
aPTT (≤29/>29 s)	0.75 (0.59–0.96)	**0.020**	0.78 (0.59–1.01)	0.059
Fibrinogen (≤3/>3 g/L)	1.08 (0.53–2.24)	0.826	—	—
D-dimer (≤500/>500 μg/L)	0.99 (0.99–1.00)	0.772	—	—
Albumin (≤48/>48 g/L)	1.04 (0.88–1.22)	0.657		
Adjuvant therapy (−/+)	0.86 (0.17–4.32)	0.859	—	—

Note: Bold values indicate significant differences ($p \leq 0.05$).

Abbreviations: aPTT, activated partial thromboplastin time; CI, confidence interval; CRP, C-reactive protein; GPS, Glasgow prognostic score; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PLR, platelet-to-lymphocyte ratio.

TABLE 4 Univariate analysis of prognostic factors for DFS and OS in rectal cancer group using Cox proportional hazard model

	Univariate analysis DFS		Univariate analysis OS	
Variables	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Age (≤65/>65 years)	0.98 (0.91–1.04)	0.447	1.32 (0.99–1.76)	0.054
Tumor size (≤3.3/>3.3 cm)	1.02 (0.72–1.45)	0.898	0.93 (0.40–2.13)	0.860
T stage (Tis–2/T3–4)	2.18 (0.74–6.47)	0.160	2.49 (0.27–22.64)	0.419
N stage (–/+)	1.60 (0.60–4.24)	0.349	1.43 (0.20–10.10)	0.720
Vascular invasion (–/+)	1.24 (0.25–6.15)	0.794	3.42 (0.21–54.76)	0.384
Lymphocyte count (≤5/>5 G/L)	0.83 (0.26–2.63)	0.749	0.59 (0.04–7.96)	0.693
Monocyte count (≤1/>1 G/L)	4.05 (0.40–40.54)	0.234	8.94 (0.19–411.02)	0.262
Neutrophil count (≤8.5/>8.5 G/L)	1.22 (0.85–1.75)	0.279	0.98 (0.43–2.25)	0.971
NLR (OS: ≤3.06/>3.06; DFS: ≤3.96/>3.96)	1.14 (0.84–1.55)	0.403	1.19 (0.65–2.17)	0.565
PLR (OS: ≤176.82/>176.82; DFS: ≤206.62/>206.62)	0.99 (0.99–1.00)	0.823	0.99 (0.96–1.01)	0.673
CRP (≤5/>5 mg/L)	0.97 (0.85–1.11)	0.641	0.94 (0.68–1.30)	0.719
aPTT (≤29/>29 s)	0.90 (0.75–1.09)	0.279	0.54 (0.28–1.06)	0.073
Fibrinogen (≤3/>3 g/L)	1.00 (0.43–2.35)	0.993	1.73 (0.50–5.98)	0.384
D-dimer (≤500/>500 μg/L)	0.99 (0.99–1.00)	0.092	0.99 (0.99–1.00)	0.889
Albumin (≤48/>48 g/L)	1.02 (0.87–1.18)	0.847	1.00 (0.74–1.35)	0.992
Neoadjuvant therapy (–/+)	—	—	0.32 (0.02–5.09)	0.417
Adjuvant therapy (–/+)	1.37 (0.17–11.20)	0.768	0.22 (0.01–3.65)	0.294

Abbreviations: aPTT, activated partial thromboplastin time; CI, confidence interval; CRP, C-reactive protein; DFS, disease-free survival; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PLR, platelet-to-lymphocyte ratio.

NLR was an independent prognostic factor for DFS in patients with colon cancer and showed significant association with tumor size and perineural invasion. The study of Kim et al. supports our investigation, and they found that high NLR (≥3.0) is a useful prognostic factor to predict long-term outcomes in patients with stage III and IV colon cancer, similarly to Mizuno et al., examining stage II and III colon cancer patients.[31,32] According to the meta-analysis of Li et al., preoperative high NLR was connected with worse prognosis in patients who underwent surgery for CRC.[33] In our multicenter study, NLR was not significant for OS, presumably due to the short follow-up time.

The inflammatory and coagulation parameters and ratios have their own significance similarly to the prognostic parameters published before. The benefits of these are that it can be easily attained in everyday practice, it is relatively cheap, and easy to use in routine work. The present study showed that in colon cancer patients, NLR was the most important prognostic factor among the preoperative blood cell markers. NLR is an independent prognostic factor, which could be used together with the well-known factors and tumor markers. This biomarker could be a powerful tool for predicting survival outcome in patients with colon cancer. It might help to recognize the high-risk patients between patients with the same TNM stage and, in the future, could help with the decision on adjuvant chemotherapy.

The limitation of our study is the relatively small sample size and short follow-up time; therefore, we aim to continue this prospective study and report the long-term results. The novelty of this study is that this is the first multicenter, prospective study among the Hungarian population examining these preoperative biomarkers in CRC patients in three county hospital across the country. It is extremely important to find new, relevant prognostic factors for our patients to improve clinical outcomes with individualized treatment due to the increasing incidence of CRC in both males and females.

In conclusion, NLR was proved to be an independent prognostic factor for DFS in patients with non-metastatic colon cancer. NLR might help to recognize the high-risk patients between patients with the same TNM stage and could help with the decision on adjuvant chemotherapy. Since the biomarkers in preoperative blood tests are habitually evaluated, NLR could be an inexpensive prognostic marker that can be easily assessed in clinical practice.

CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception of the work, drafted the work, approved the final version to be published, and agreed to be accountable for all aspects of the work. In detail, Adrienn Biró involved in conceptualization, methodology, data curation, original draft preparation, writing, reviewing, editing, and visualization. Péter Kolozsi involved in data curation, writing, reviewing, and editing. Attila Nagy involved in formal analysis and validation. Zsolt Varga involved in data curation, writing, reviewing, and editing. Zsolt Káposztás involved in writing, reviewing, and editing. Dezső Tóth involved in conceptualization, methodology, writing, reviewing, and editing.

DATA AVAILABILITY STATEMENT

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

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