

# Neutrophil-to-lymphocyte ratio has limited predictive value for determining outcomes in perforated colon cancer: a propensity score analysis.

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## Research Article

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# Abstract

**Background:** The neutrophil-to-lymphocyte ratio is a significant prognostic marker in resectable colorectal cancer; however, there are no equivalent findings for perforated colon cancer. Using our colorectal cancer database, we retrospectively analyzed the data from 1995 to 2015 to determine whether the preoperative neutrophil-to-lymphocyte ratio is associated with survival outcomes in patients with perforated colon cancer.

**Methods:** One-to-one propensity score matching was applied to minimize the difference between the high (>5) and low ( $\leq 5$ ) neutrophil-to-lymphocyte ratio groups. Clinicopathological factors, long-term overall survival, and disease-free survival were analyzed and compared between the two groups. The primary outcomes were overall survival and disease-free survival.

**Results:** Before propensity score matching, the high neutrophil-to-lymphocyte ratio group had a significantly higher prevalence of leukocytosis (low vs. high neutrophil-to-lymphocyte ratio groups: 12 [12.9%] vs. 46 [59.7%],  $p < 0.001$ ), lower serum albumin levels (low vs. high neutrophil-to-lymphocyte ratio groups: 30 [32.3%] vs. 42 [54.5%],  $p = 0.003$ ), and a higher emergent operation rate (low vs. high neutrophil-to-lymphocyte ratio groups: 5 [5.4%] vs. 20 [26.0%],  $p < 0.001$ ). After one-to-one propensity score matching, the groups comprised 41 patients each; none of the parameters were significantly different between the two groups. The mean follow-up period was 76.3 months. The 5-year overall survival ( $p = 0.637$ ) and disease-free survival ( $p = 0.827$ ) rates were not significantly different between the high and low neutrophil-to-lymphocyte ratio groups.

**Conclusions:** The neutrophil-to-lymphocyte ratio has limited predictive value for determining outcomes in patients with perforated colon cancer.

## Background

Colon cancer is one of the most common causes of cancer-related deaths worldwide, with an estimated 551,269 deaths and 1,096,601 new colon cancer cases diagnosed annually [1]. Although current cancer treatments have improved outcomes, long-term survival remains unsatisfactory. An increasing number of reports have shown that systemic inflammatory reactions increase the risk of developing cancer [2, 3]. Several studies have focused on inflammation-based prognostic factors, such as C-reactive protein and albumin levels, platelet-to-lymphocyte ratio, and neutrophil-to-lymphocyte ratio (NLR), to identify patients at a high risk of colorectal cancer recurrence after primary surgery [4-7].

The NLR is a significant prognostic marker in patients with resectable colorectal cancer. The NLR is considered not only a marker of the inflammatory tumor environment but also an indicator of anti-tumor host immunity. A high preoperative NLR (>5) has been associated with poor overall survival (OS) [8-10].

The preoperative NLR has been shown to influence disease-free survival (DFS) in patients with stage I to III colorectal cancer; an elevated NLR (estimated cutoff value >3) is also associated with worse outcomes

(5-year DFS: 66.3% vs. 78.9% for colon cancer; 60.5% vs. 66.2% for rectal cancer) [11].

However, there is lack of evidence on the association between perforated colon cancer and the NLR. Therefore, we aimed to determine the associations between the preoperative NLR, clinicopathological factors, and survival outcomes in patients with perforated colon cancer.

## Materials And Methods

The medical records of a total of 240 patients with pathologically confirmed perforated colon cancer who underwent surgical treatment at Chang Gung Memorial Hospital, Linkou, Taiwan, between January 1, 1995 and December 31, 2015, were reviewed. All data were retrospectively reviewed from a prospectively maintained database after obtaining institutional review board approval. The definition of perforated colon was based on the pathology reports mentioning gross or microscopic perforation. We excluded patients with post-polypectomy perforation, those with short-term mortality (<30 days postoperatively), and those who had preoperative distal metastasis. Preoperative evaluation and postoperative follow-up data were collected for analysis. Data on the date of diagnosis and surgery, tumor stage and location, treatment, and cause of death (recurrence vs. second primary cancer) were also collected.

The preoperative demographic characteristics included age, sex, comorbidities (hepatitis, diabetes, and liver cirrhosis), serum albumin levels, carcinoembryonic antigen levels, hemoglobin levels, white blood cell (WBC) counts, and the NLR. Perioperative factors included tumor location and whether the patient underwent an emergent operation. Tumor–node–metastasis (TNM) stage, histology, and pathological findings were also reviewed.

The NLR was calculated by dividing the number of neutrophils by the number of lymphocytes. The preoperative NLR was calculated using the latest preoperative data, either at the emergency department or during admission. The cutoff value for the NLR in this study was set at 5, which was equal to that seen in most reviewed articles.

The primary study outcomes were OS and DFS. The cause of death was recorded as an event. Patients were recorded as alive at last follow-up, regardless of their disease status. Survival was measured from the date of surgery to the date of death or last known follow-up.

Propensity scores were calculated using the following covariates: WBC count, albumin level, and emergent surgery. The propensity scores were used for one-to-one patient matching between the high and low NLR groups; the matching tolerance was set at 0.05.

### *Statistical analyses*

Statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA), and p-values <0.05 were considered statistically significant. Pearson's chi-square test was used to determine differences in clinicopathological factors between the high and low NLR groups. Kaplan-Meier survival curves were used to assess survival in the different subgroups. The Cox proportional hazards model was

used for univariate and multivariate analyses; variables with  $p < 0.05$  in the univariate analysis were evaluated further in the multivariate analysis to determine independent risk factors for survival.

## Results

All 240 patients underwent surgical treatment with curative intent, including laparoscopic colectomy, traditional (open) colectomy, and emergent exploratory laparotomy. Patients were excluded if they had (1) undergone polypectomy and surgery within 24 hours ( $n=5$ ), (2) early mortality ( $<30$  days postoperatively,  $n=4$ ), or (3) confirmed distal metastasis ( $n=61$ ; **Fig. 1**). A total of 170 patients were ultimately enrolled in this study. There were 93 (54.7%) patients with a low NLR and 77 (45.3%) patients with a high NLR. The mean follow-up period was 76.3 months, ranging from 1.7 to 135.7 months.

Initial clinicopathological factors were compared between the high and low NLR groups (**Table 1**). In the high NLR group, there was a higher prevalence of leukocytosis (WBC count  $>12000/\mu\text{L}$ ) (low vs. high NLR groups: 12 [12.9%] vs. 46 [59.7%],  $p < 0.001$ ), a lower mean serum albumin level ( $<3.5$  g/dL) (low vs. high NLR groups: 30 [32.3%] vs. 42 [54.5%],  $p = 0.003$ ), and a higher likelihood of undergoing emergent surgery (low vs. high NLR groups: 5 [5.4%] vs. 20 [26.0%],  $p < 0.001$ ).

[Table 1]

After one-to-one propensity score matching, none of the clinicopathological factors were significantly different between the high and low NLR groups (**Table 1**). In patients with stage I to III perforated colon cancer, the 3- and 5-year OS rates were 75% and 61%, respectively, in the low NLR group, whereas those of the high NLR group were 80% and 67%, respectively. We also analyzed the 3- and 5-year OS rates in the subgroups of patients with stage II and III perforated colon cancer. We found that in patients with stage II perforated colon cancer, the 3- and 5-year OS rates were 90% and 84% in the low NLR group, respectively, whereas those of the high NLR group were 87% and 74%, respectively. Patients with stage III perforated colon cancer had 3- and 5-year OS rates of 60% and 41% in the low NLR group, respectively, whereas those of the high NLR group were 69% and 55%, respectively. The difference in OS rates between the high and low NLR groups in each subgroup comparison was not significant ( $p = 0.637$  for stages I to III,  $p = 0.512$  for stage II, and  $p = 0.500$  for stage III; **Fig. 2**).

DFS rates were also not significantly different between the high and low NLR groups. In patients with stage I to III perforated colon cancer, the 3- and 5-year DFS rates were both 70% in the low NLR group, whereas those of the high NLR group were 69% and 63%, respectively. In patients with stage II perforated colon cancer, the 3- and 5-year DFS rates were both 84% in the low NLR group, whereas those of the high NLR group were 74% and 69%, respectively. In patients with stage III perforated colon cancer, the 3- and 5-year DFS rates were both 55% in the low NLR group, whereas the corresponding values in the high NLR group were 58% and 50%, respectively ( $p = 0.827$  for stage I to III,  $p = 0.296$  for stage II, and  $p = 0.785$  for stage III; **Fig. 3**).

## Discussion

Chronic inflammation-induced carcinogenesis is a commonly accepted mechanism for several malignancies [3]. In colon cancer, systemic inflammation not only affects cytokines, but also promotes angiogenesis and metastasis formation [12]. Therefore, several systemic inflammatory-associated markers, such as C-reactive protein, lymphocyte-to-monocyte ratio, platelet-to-lymphocyte ratio, and NLR, have been used as outcome predictors [4-7].

Tumor-associated cytokines and growth factors enter the circulation causing a systemic response. These factors, which cause tumor angiogenesis and possibly neoplasm progression, may lead to an increase in neutrophil count [13]. Alternatively, the absolute lymphocyte count is considered to reflect the immune response of patients with cancer; lymphopenia is also correlated with worse outcomes in patients with colorectal cancer [14]. Therefore, the NLR can be considered a parameter that reflects the relationship between pro-tumor inflammatory and antitumor immune factors.

Multiple studies have focused on the association between the preoperative NLR and colon cancer outcomes. A normal NLR is considered to range between 0.78 and 3.53 [15]. A high NLR (>5) has been identified as a prognostic factor for poor OS and early recurrence [9, 10, 16]; however, in our study, patients with perforated colon cancer and a high NLR showed no significant differences in OS ( $p=0.637$ ) and DFS ( $p=0.827$ ).

A high NLR has also been associated with a higher T and N stage and a higher incidence of extramural venous invasion [17]; however, in our study, T and N staging was not associated with a high NLR. In patients with perforated colon cancer, regardless of whether they are showing clinical signs of peritonitis, perforation-related infection or inflammation is difficult to detect. Therefore, in these patients, the elevated neutrophil level associated with infection may be higher than the normal preoperative NLR. Consequently, the preoperative NLR may not reflect the balance between cancer-related inflammation and the immune response in patients with perforated colon cancer.

We reexamined the 12 enrolled patients with pT3 perforated colon cancer and classified them according to the cause of perforation. Among them, six had recorded perforation with abscess formation, four had proximal perforation (perforation site proximal to the primary tumor: 3.5, 2.3, and 3.7 cm; one patient had cecal perforation and ischemic change), and two had walled-off abscess with adhesion to the lateral abdominal sidewall.

Approximately 1% of colon cancer patients have perforation at the proximal site of the cancer [18]. These patients may have obstructive signs and a higher operative mortality rate than those with obstruction only.

Although abscess formation is rare, occurring in approximately 0.3 to 4% of colon cancer patients, it represents the second most common presentation of perforated lesions [19]. The pathological definition of an abscess is a localized collection of neutrophils near the tumor in the resected specimen. However,

when it comes to T stage, this can vary according to the version of the American Joint Committee on Cancer (AJCC) guidelines and the pathologist's opinion. For example, if a specimen showed perforation of the tumor in which the tumor cells are continuous with the serosal surface through inflammation, then the patient would have pT4a disease according to the AJCC 8th edition. However, according to the AJCC 7th edition, the patient would have pT3 disease, because of a lack of tumor cells on the serosa[20, 21]. In this study, patients were enrolled since 1995. Some patients with perforated colon cancer and abscess formation would have been diagnosed with pT3 disease according to the AJCC 7th or previous editions; however, today our pathologists would be more likely to impress these patients with pT4a disease according to the latest version of the AJCC guidelines.

Walled-off abscess formation is more likely to be clinically or surgically diagnosed, usually with localized abscess formation and adhesion to adjacent organs. Our pathologists also classified these as perforation. According to a literature review [22], there was no statistically significant difference in prognosis between patients with walled-off abscess formation and those with free perforation.

This study has several limitations. First, this was a single-center retrospective study involving a small number of patients. Second, preoperative data were collected using the latest data point before surgery, either in the emergency room or during admission, if elective surgery was performed. Third, the definition of perforation was based on pathology reports. Some patients who may have initially presented with local abscess formation and no peritoneal signs could have been enrolled in our study and undergone further elective surgery, rather than emergent surgery. Therefore, the results may not reflect equivalent clinical conditions among patients. Further larger studies are required to validate our findings.

## Conclusions

A high NLR (>5) is a well-known risk factor for survival in patients with resectable colon cancer. However, in patients with stage I to III perforated colon cancer, a high NLR did not correlate with poor outcomes, which limits its use for predicting survival outcomes.

## List Of Abbreviations

AJCC, American Joint Committee on Cancer; DFS, disease-free survival; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; WBC, white blood cell.

## Declarations

**Ethics approval and consent to participate:** This study was reviewed and approved by Chang Gung Memorial Hospital's Institutional Review Board (IRB) (IRB approval number: 202000133B0). The IRB waived the requirement for obtaining informed consent from the participants.

**Consent for publication:** Not applicable.

**Availability of data and materials:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interest:** The authors declare that they have no competing interests.

**Funding:** Not applicable.

**Authors' contributions:** All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by C-YW. The first draft of the manuscript was written by C-YW and was supervised by J-MC. All authors commented on previous versions of the manuscript and read and approved the final manuscript.

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2. We have revised our title, and the previous title was "Neutrophil-to-lymphocyte ratio has limited predictive value for determining outcomes in perforated colon cancer: a retrospective study."

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## Table

**Table 1. Patients’ characteristics before and after propensity score matching**

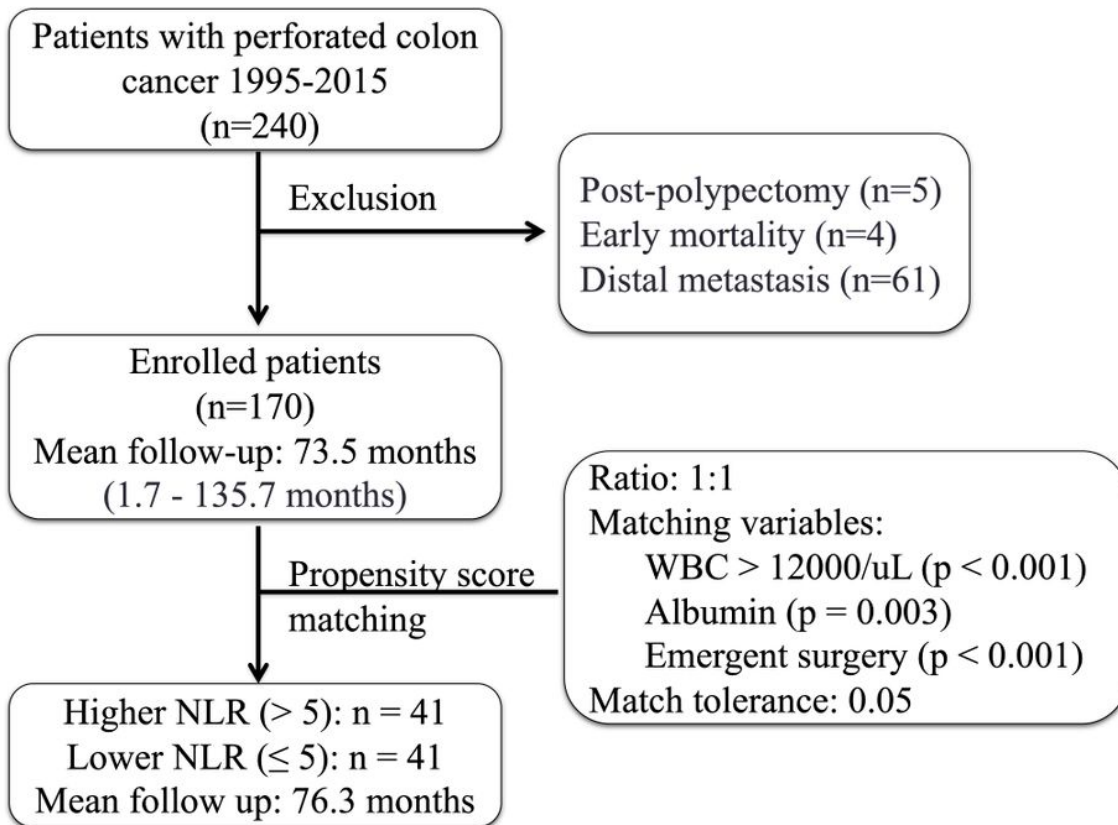
Characteristic		Before propensity score matching				After propensity score matching			
		Total (n=170)	NLR ≤5 (n=93)	NLR >5 (n=77)	p- value	Total (n=82)	NLR ≤5 (n=41)	NLR >5 (n=41)	p- value
Age (years)	≤65	99 (58.2%)	56 (60.2%)	43 (55.8%)	0.565	49 (59.8%)	24 (58.5%)	25 (61.0%)	0.822
	>65	71 (41.8%)	37 (39.8%)	34 (44.2%)		33 (40.2%)	17 (41.5%)	16 (39.0%)	
Sex	female	77 (45.3%)	47 (50.5%)	30 (39.0%)	0.131	35 (42.7%)	20 (48.8%)	15 (36.6%)	0.264
	male	93(54.7%)	46 (49.5%)	47 (61.0%)		47 (57.3%)	21 (51.2%)	26 (63.4%)	
Hb (g/dL)	≤10	75 (44.1%)	38 (40.9%)	37 (48.1%)	0.347	32 (39.0%)	16 (39.0%)	16 (39.0%)	1.000
	>10	95 (55.9%)	55 (59.1%)	40 (51.9%)		50 (61.0%)	25 (61.0%)	25 (61.0%)	
WBC count (/μL)	≤12000	112 (65.9%)	81 (87.1%)	31 (40.3%)	<0.001	58 (70.7%)	29 (70.7%)	29 (70.7%)	1.000
	>12000	58 (34.1%)	12 (12.9%)	46 (59.7%)		24 (29.3%)	12 (29.3%)	12 (29.3%)	
CEA (ng/mL)	≤5	70 (41.2%)	41 (44.1%)	29 (37.7%)	0.397	30 (36.6%)	15 (40.5%)	15 (41.7%)	0.922
	>5	100 (58.8%)	52 (55.9%)	48 (62.3%)		43 (52.4%)	22 (59.5%)	21 (58.3%)	
Albumin (g/dL)	≤3.5	72 (42.4%)	30 (32.3%)	42 (54.5%)	0.003	38 (46.3%)	19 (54.3%)	19 (54.3%)	1.000
	>3.5	98 (57.6%)	63 (67.7%)	35 (45.5%)		32 (39.0%)	16 (45.7%)	16 (45.7%)	
DM	no	146	82	64	0.346	65	35	30	0.173

		(58.9%)	(88.2%)	(83.1%)		(79.3%)	(85.4%)	(73.2%)	
	yes	24 (14.1%)	11 (11.8%)	13 (16.9%)		17 (20.7%)	6 (14.6%)	11 (26.8%)	
Hepatitis	no	165 (97.1%)	90 (96.8%)	75 (97.4%)	0.809	79 (96.3%)	39 (95.1%)	40 (97.6%)	0.556
	yes	5 (2.9%)	3 (3.2%)	2 (2.6%)		3 (3.7%)	2 (4.9%)	1 (2.4%)	
Liver cirrhosis	no	168 (98.8%)	92 (98.9%)	76 (98.7%)	0.893	81 (98.8%)	41 (100.0%)	40 (97.6%)	0.314
	yes	2 (1.2%)	1 (1.13%)	1 (1.3%)		1 (1.2%)	0 (0.00%)	1 (1.4%)	
Location	right	63 (37.1%)	32 (34.4%)	31 (40.3%)	0.432	30 (36.6%)	13 (31.7%)	17 (41.5%)	0.359
	left	107 (62.9%)	61 (65.6%)	46 (59.7%)		52 (63.4%)	28 (68.3%)	24 (58.5%)	
Emergent surgery	no	142 (85.3%)	88 (94.6%)	57 (74.0%)	<0.001	72 (87.8%)	36 (87.8%)	36 (87.8%)	1.000
	yes	25 (14.7%)	5 (5.4%)	20 (26.0%)		10 (12.2%)	5 (12.2%)	5 (12.2%)	
Histological type	adenocarcinoma	146 (85.9%)	78 (83.9%)	68 (88.3%)	0.408	67 (81.7%)	34 (82.9%)	33 (80.5%)	0.775
	mucinous carcinoma	24 (14.1%)	15 (16.1%)	9 (11.7%)		15 (18.3%)	7 (17.1%)	8 (19.5%)	
Histological grade	well differentiated	11 (6.5%)	9 (9.7%)	2 (2.6%)	0.166	3 (3.7%)	1 (2.4%)	2 (4.9%)	0.446
	moderate	133 (78.2%)	71 (76.3%)	62 (80.5%)		65 (79.3%)	31 (75.6%)	30 (82.9%)	
	poor	26 (15.3%)	13 (14.0%)	13 (16.9%)		14 (17.1%)	9 (22.0%)	5 (12.2%)	

T stage	2	1 (0.6%)	0 (0%)	1 (1.3%)	0.338	1 (1.2%)	0 (0%)	1 (2.4%)	0.602
	3	24 (14.1%)	11 (11.8%)	13 (16.9%)		12 (14.6%)	6 (14.6%)	6 (14.6%)	
	4	145 (85.3%)	82 (88.2%)	63 (81.8%)		69 (84.1%)	35 (85.4%)	34 (82.9%)	
N stage	0	89 (52.4%)	49 (52.7%)	40 (51.9%)	0.268	45 (54.9%)	21 (51.2%)	24 (58.5%)	0.174
	1	54 (31.8%)	33 (35.5%)	21 (27.3%)		25 (30.5%)	16 (39.0%)	9 (22.0%)	
	2	27 (15.9%)	11 (11.9%)	16 (20.8%)		12 (14.6%)	4 (9.8%)	8 (19.5%)	

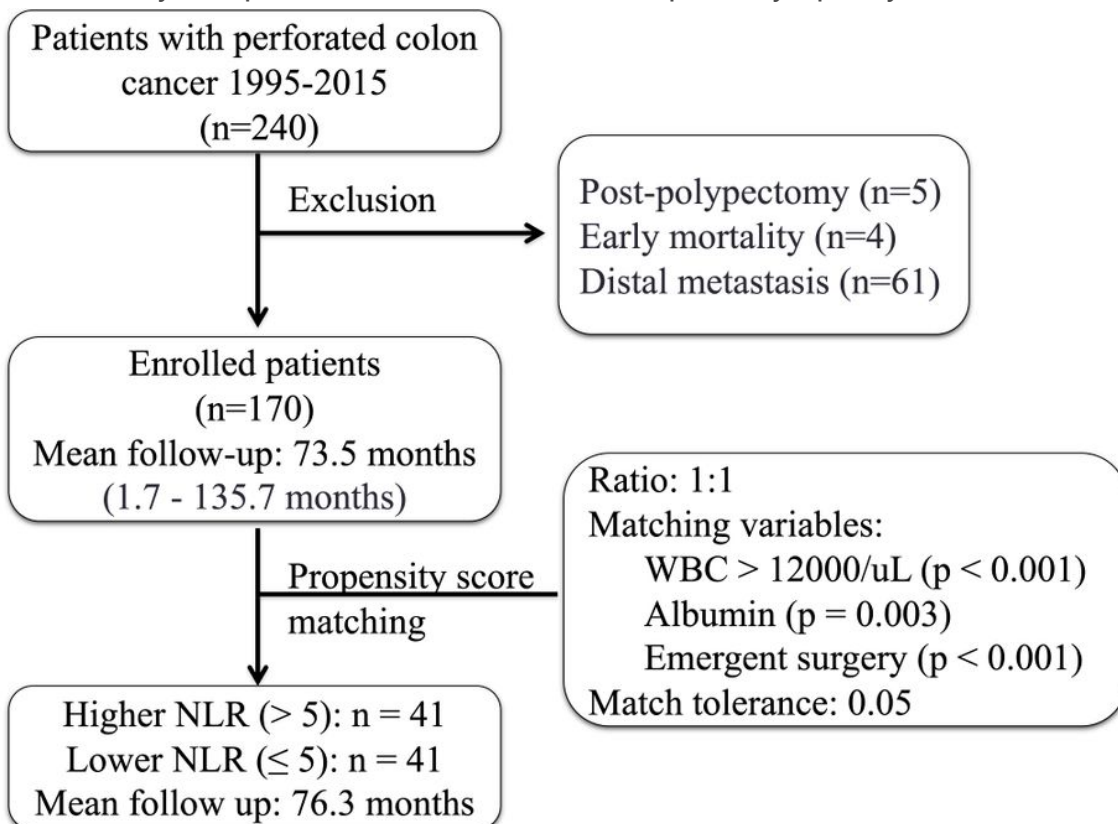
Abbreviations: CEA, carcinoembryonic antigen; DM, diabetes mellitus; Hb, hemoglobin; NLR, neutrophil-to-lymphocyte ratio; WBC, white blood cell.

## Figures



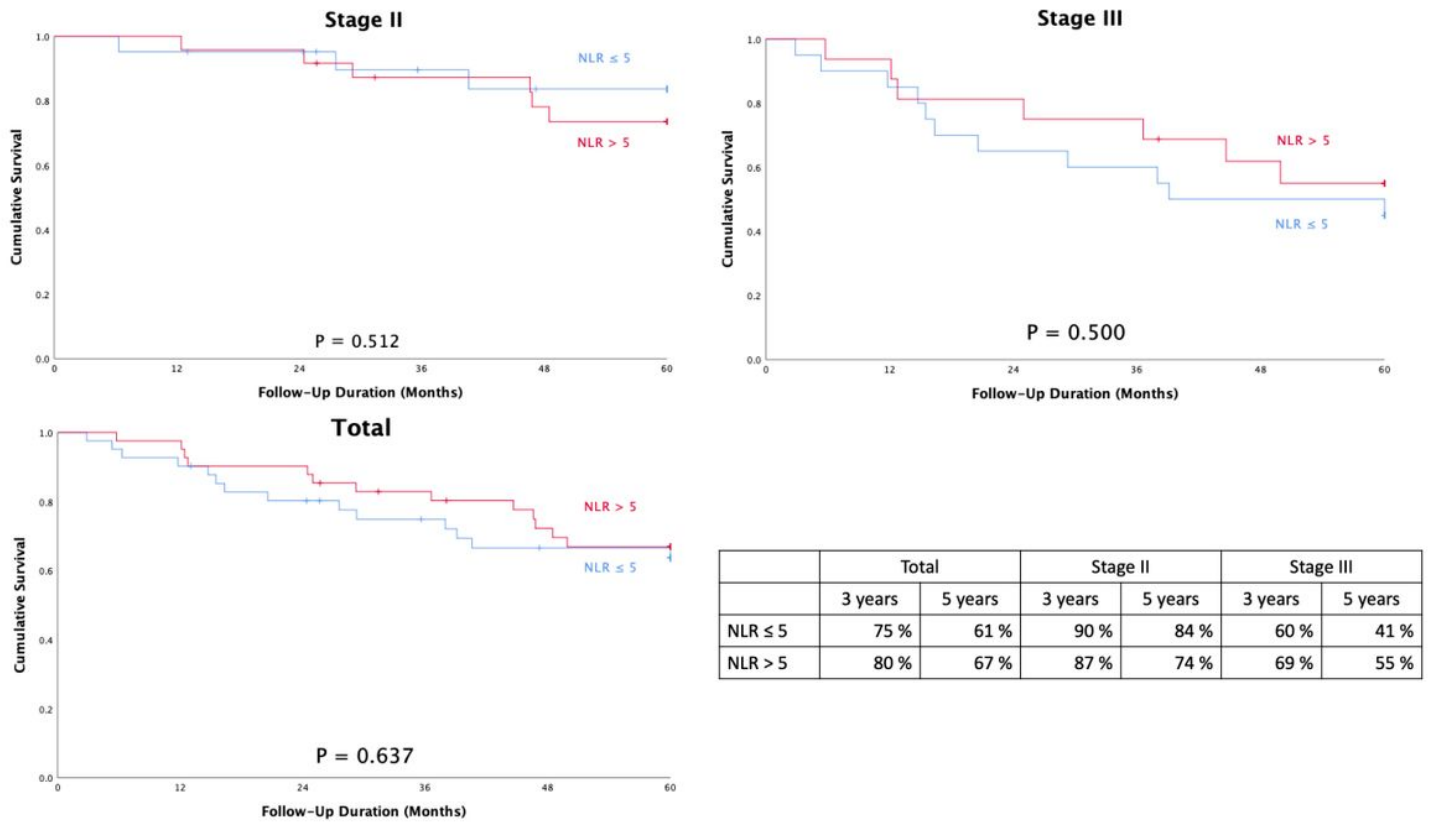
**Figure 1**

Flow chart of the study sample Abbreviations: NLR, neutrophil-to-lymphocyte ratio; WBC, white blood cell



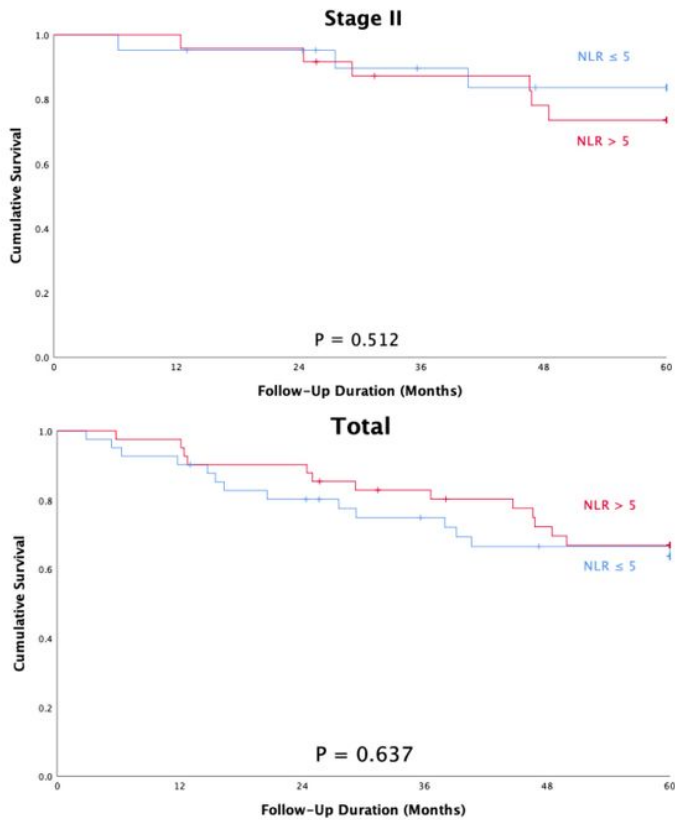
**Figure 1**

Flow chart of the study sample Abbreviations: NLR, neutrophil-to-lymphocyte ratio; WBC, white blood cell



**Figure 2**

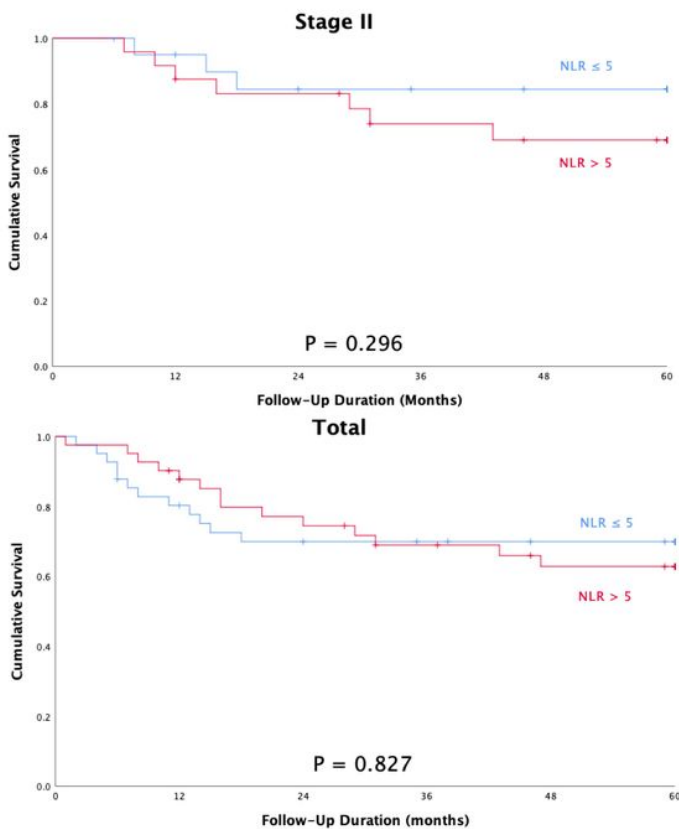
OS rates between patients in the high and low NLR groups Abbreviations: NLR, neutrophil-to-lymphocyte ratio; OS, overall survival



	Total		Stage II		Stage III	
	3 years	5 years	3 years	5 years	3 years	5 years
NLR ≤ 5	75 %	61 %	90 %	84 %	60 %	41 %
NLR > 5	80 %	67 %	87 %	74 %	69 %	55 %

**Figure 2**

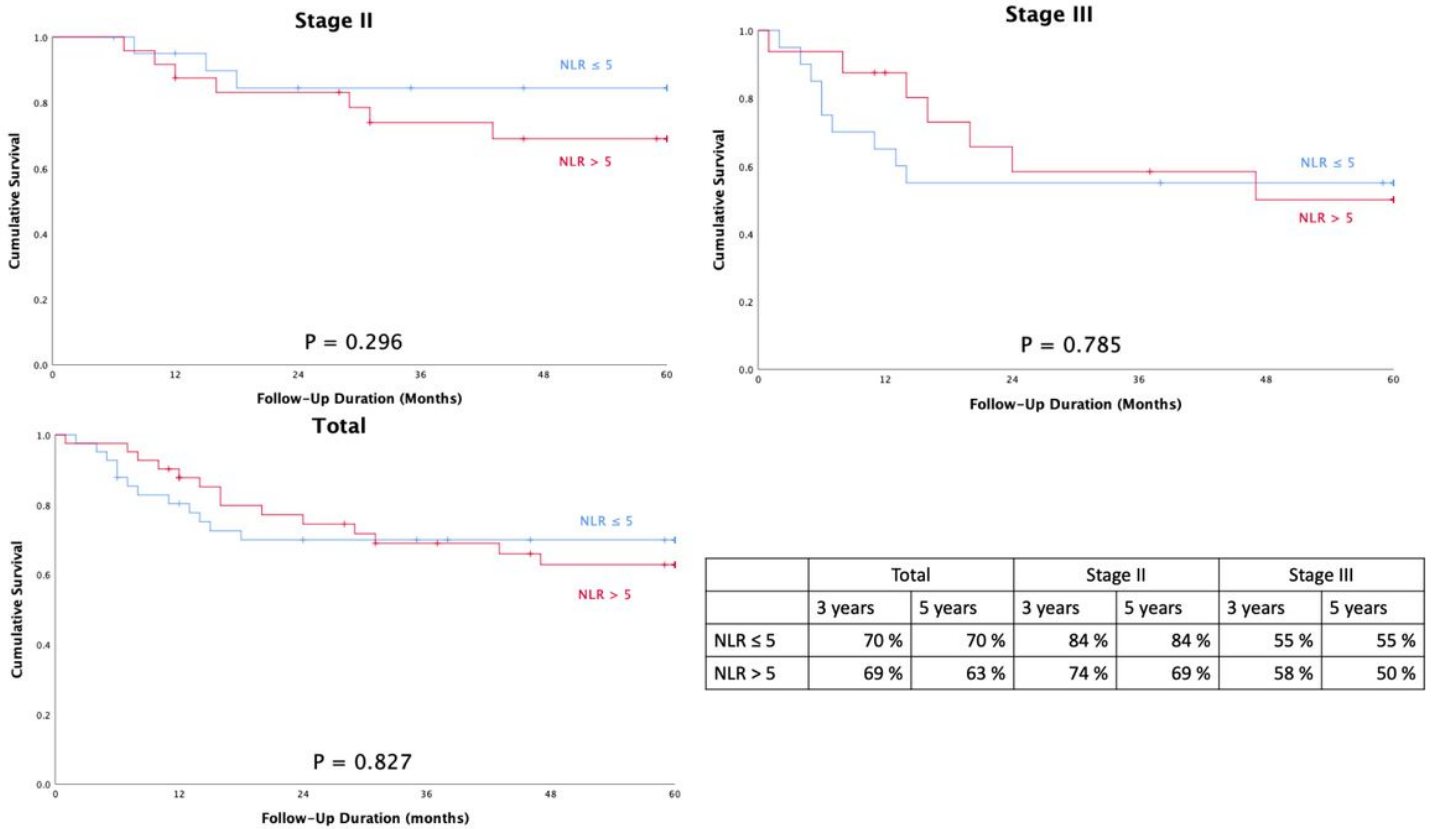
OS rates between patients in the high and low NLR groups Abbreviations: NLR, neutrophil-to-lymphocyte ratio; OS, overall survival



	Total		Stage II		Stage III	
	3 years	5 years	3 years	5 years	3 years	5 years
NLR ≤ 5	70 %	70 %	84 %	84 %	55 %	55 %
NLR > 5	69 %	63 %	74 %	69 %	58 %	50 %

**Figure 3**

DFS rates between patients in the high and low NLR groups Abbreviations: DFS, disease-free survival; NLR, neutrophil-to-lymphocyte ratio



**Figure 3**

DFS rates between patients in the high and low NLR groups Abbreviations: DFS, disease-free survival; NLR, neutrophil-to-lymphocyte ratio